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Liangbing Fu Date

EXPANDING THE SCOPE OF REACTIONS AND APPLICATIONS OF

DONOR/ACCEPTOR METALLOCARBENES

By

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Doctor of Philosophy

Chemistry

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EXPANDING THE SCOPE OF REACTIONS AND APPLICATIONS OF DONOR/ACCEPTOR METALLOCARBENES

By

Liangbing Fu

M.Sc., Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences

2011

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An abstract of

A dissertation submitted to the Faculty of the

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Abstract

EXPANDING THE SCOPE OF REACTIONS AND APPLICATIONS OF DONOR/ACCEPTOR METALLOCARBENES
By Liangbing Fu

The chemistry of rhodium-bound donor/acceptor carbenes has been extensively investigated and has given birth to a variety of useful transformations, among which C–H insertion reactions are of particular interest because it provides a unique strategy for the functionalization of unactivated C–H bonds. This dissertation is centered on expanding the scope of reactions and applications of donor/acceptor metallocarbenes by developing novel, efficient and selective transformations.

The first part of this dissertation describes the role of *ortho*-substituents on the donor group in rhodium-catalyzed asymmetric synthesis of *β*-lactones by intramolecular C–H insertion reactions of aryldiazoacetates. A systematic optimization of the reaction conditions including catalyst, solvent, reaction temperature was first conducted, followed by exploration of the substrate scope of the transformation. It was demonstrated that a proper substituent at the 2-position of the aryldiazoacetates was critical to the *β*-lactone formation, especially for the insertion into the less reactive primary C–H bonds.

The second part of the dissertation describes a rhodium(II)-catalyzed C–H functionalization of electron-deficient methyl groups. The combination of sterically demanding dirhodium triarylcyclopropane carboxylate catalysts and 2,2,2-trichloroethyl (TCE) aryldiazoacetates was shown to be critical to the success of the functionalizing challenging substrates such as ethyl crotonate. This reaction provides an alternative disconnection strategy for the asymmetric construction of 1,6-dicarbonyls.

The third part of the dissertation describes the development of a novel approach for the synthesis of 2,2,2-trichloroethyl aryl- and vinyldiazoacetates by a palladium-catalyzed cross-coupling reaction. This method uses commercially readily available aryl iodides as the starting materials and circumvents the problems due to the requisite use of the more dangerous diazo transfer reagent *o*-nitrobenzenesulfonyl azide in diazo transfer reactions, and allows for rapid construction of a library of useful diazo compounds.

The fourth part of the dissertation describes divergent reactions of indolyl- and pyrrolyl-tethered *N*-sulfonyl-1,2,3-triazoles for the efficient synthesis of polycyclic spiroindolines and tetrahydrocarbolines by rhodium(II)-catalyzed intramolecular annulations. It was shown that the product distribution of the reaction was highly dependent on the electronic and structural properties of the substrates.

The last part first describes the exploration of vinylogous reactivity of ethyl (3*E*,5*E*)-2-diazo-6-phenylhexa-3,5-dienoate. The vinylogous O–H insertion reaction can be combined with an intramolecular Diels-Alder reaction to afford cyclic ether products. Efforts towards the formal total synthesis of ephedradine will then be described. A four-fold C–H functionalization strategy was designed and executed to afford the dihydrobenzofuran core structure of ephedradine A. Lastly, systematic optimization studies for the reaction of a trichloroethyl aryldiazoacetate and isopropyl acetate will be presented.

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When things are going to completion, they tend to seem easy. However, one sometimes won't fully appreciate the challenges until they have to accomplish from the beginning. To obtain a PhD degree is just like this process as it is challenging but also rewarding. It was also great to meet with a group of intelligent people during this experience. The experience in the Davies group has definitely become one of the most exciting and valuable experiences in my life. Looking back on the five years, there are so many people who are worthy my sincere thanks.

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To my family

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List of abbreviations

Ac	acetyl
APCI	atmospheric pressure chemical ionization
Ar	aryl
Bn	benzyl
Bu	butyl
Bs	*p*-bromobenzenesulfonyl
B.O.	bond order
brsm	based on recovered starting material
c.a.	approximately
Cbz	carboxybenzyl
Cy	cyclohexyl
dba	bis(dibenzylideneacetone)
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane

DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	*N*,*N*-4-(dimethylamino)pyridine
DMA	dimethylacetamide
DMB	2,2-dimethylbutane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
Et	ethyl
equiv.	equivalents
eq.	equation
ESI	electrospray ionization
EWG	electron-withdrawing group

HMPU	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
Imid.	Imidazole
IR	infrared spectroscopy
L	ligand
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
min	minute
mmol	millimoles
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
N.R.	no reaction
N.O.	not observed
NSI	nanospray ionization

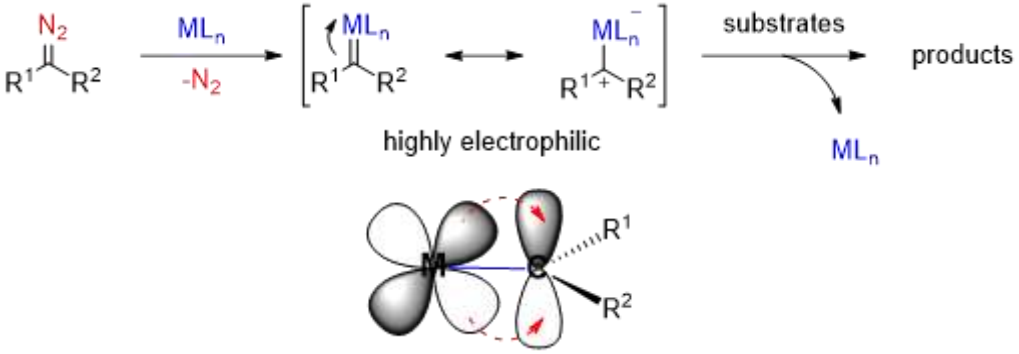
***o*-NBSA**	*ortho*-nitrobenzenesulfonyl azide
***p*-ABSA**	*para*-acetamidobenzenesulfonyl azide
Ph	phenyl
Piv	pivaloyl
por	porphyrin
Pr	propyl
rt	room temperature
r.r.	regioisomeric ratio
TBAF	tetrabutylammonium fluoride
TBATB	tetrabutylammonium tribromide
TBS	*tert*-butyldimethylsilyl
TBE	2,2,2-tribromoethyl
TCE	2,2,2-trichloroethyl
TEA	triethylamine
temp	temperature
Tf	trifluoromethanesulfonyl
TFE	2,2,2-trifluoroethyl

THF	tetrahydrofuran
TLC	thin layer chromatography
EDA	ethylenediamine
TMS	trimethylsilyl
TMSE	2-(trimethylsilyl)ethyl
Ts	tosyl

Chapter 1 Introduction

1.1 Metallocarbene chemistry

The quest for the development of more efficient, selective, and environmentally benign reactions is a continuous challenge in organic chemistry. As highly reactive species in organic chemistry, carbenes provide a powerful and versatile platform for the development of new reactions and synthetic strategies.[1-5] Free carbenes are so reactive that they often undergo non-selective reactions; however, their reactivity and selectivity can be modulated by tuning the properties of the substituents and the transition-metal bound to the carbene center.[2] One of the most commonly used methods for the generation of metallocarbenes is the transition-metal-catalyzed decomposition of diazo compounds.[3,4] The metallocarbenes thus generated can be stabilized by back-bonding from the transition metal (Scheme 1.1).[5] In these metallocarbenes, the transition-metal catalyst can bind to the carbene center through strong σ-bonding and weak π back-donation. This binding mode stabilizes the carbene to some extent but still ensures that the carbene retains high electrophilicity.[5]



Scheme 1.1 Generation of metallocarbenes from diazo compounds and back-bonding interaction

The reactivity profile of metallocarbenes is dependent on the carbene structure: the nature of substituents on the carbene carbon center and the properties of the transition metal catalyst.[3-5] Based on the electronic properties of the substituents on the carbene structures, diazo compounds derived metallocarbenes can be divided into three major classes: acceptor only[4], acceptor/acceptor,[5,6] and donor/acceptor[5,7,8] (Figure 1.1). The "acceptor" group, namely an electron-withdrawing group, enhances the electrophilicity of the metallocarbenes, and thus increases their reactivity. The "donor" group, which means electron-donating group, stabilizes the metallocarbenes and attenuates their reactivity by donation of electrons, and thus enhances the selectivity of metallocarbenes. As a consequence, donor/acceptor-substituted carbenes are generally more chemoselective than carbenes that are substituted with only acceptor groups or acceptor/acceptor groups.[5]

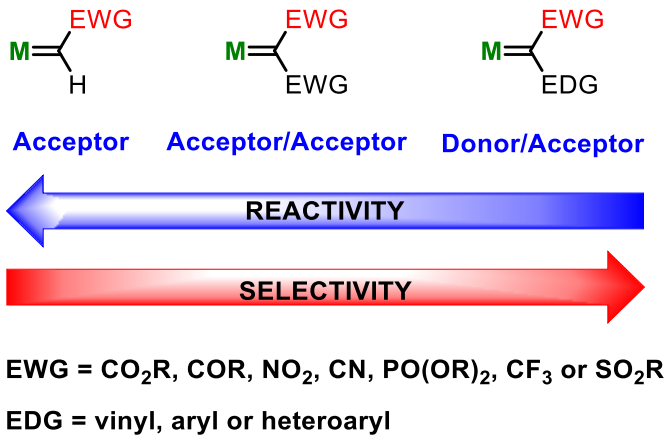


Figure 1.1 Three major classes of metallocarbenes derived from diazo compounds

The nature of transition metals also influences the reactivity of the carbene intermediate.[4,5] Different kinds of transition metals have been used in metallocarbene chemistry.[3] For example, with the vinyl-substituted metallocarbenes, the use of different transition metals may give different reactivity because vinylcarbenes also possess electrophilic character at the vinylogous position (Figure 1.2). With dirhodium carboxylate

catalysts, carbenoid reactivity dominates, while more electron-deficient catalysts were found to be able to enhance the vinylogous reactivity.[9] On the other hand, the properties of the transition-metal catalyst can be further finely tuned by the ligands attached to the metal center.[10]

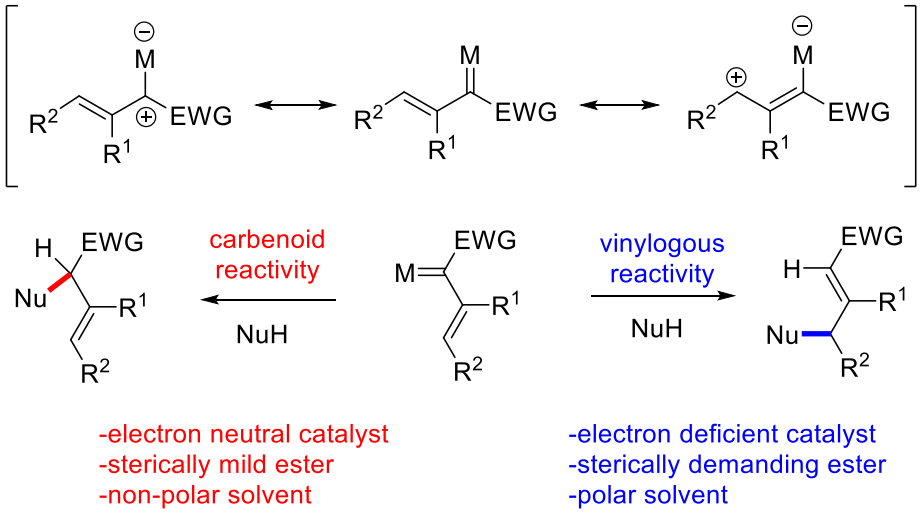


Figure 1.2 Reactivity of vinylcarbenes

1.2 Dirhodium catalysts for metallocarbene chemistry

While different kinds of metals such as copper[3,11], palladium,[12] silver[13] and gold[14] have been used in metallocarbene chemistry for the decomposition of carbene precursors to generate metallocarbenes, the development of rhodium catalysts for the decomposition of diazo compounds greatly enhanced the scope of transformations by metallocarbenes.[10] Rhodium(II) catalysts can be classified into four major types according to the structure of the ligands: rhodium carboxylates, rhodium carboxamidates, rhodium phosphates and *ortho*-metalated aryl phosphine rhodium complexes (Figure 1.3).[5] Rhodium catalysts used in metallocarbene chemistry are usually dirhodium complexes. Only one of the two rhodium atoms binds to the carbene center and the other one serves as the electron sink.[5]

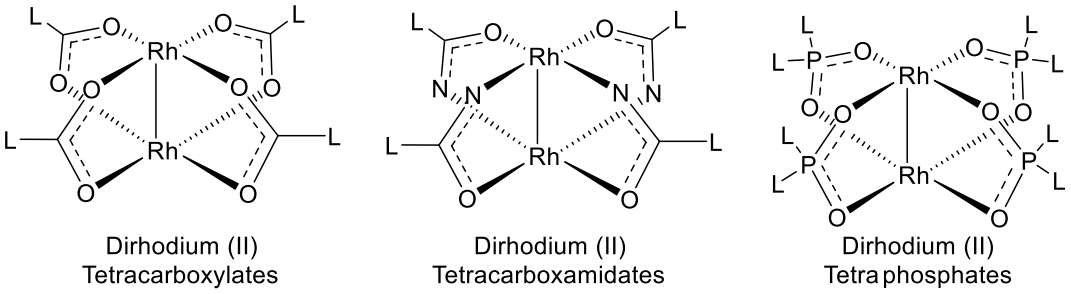


Figure 1.3 Types of rhodium(II) catalysts

Rhodium carboxamidates developed by the Doyle group are effective catalysts for the decomposition of diazo compounds.[15a] Representative catalysts in this class contain pyrrolidinones, oxazolidinones, imidazolidinones and azetidinones ligands. A number of dirhodium carboxamidate catalysts were shown to be particularly effective in transformations with acceptor-substituted carbenes derived from α-diazoesters and α-diazoamides.[3,15] Chiral rhodium phosphates catalysts, which are derived from C_2-symmetric binaphthyl phosphonate ligand. These catalysts were originally developed independently by McKervey and Pirrung in 1992.[16] So far, the application of rhodium phosphates catalysts in carbene C–H functionalization chemistry has been limited.[16]

Rhodium (II) carboxylates are highly effective catalysts for the decomposition of diazo compounds.[5] The prototypical dirhodium carboxylate catalyst dirhodium tetraacetate ($Rh_2(OAc)_4$)[17] has four bridging acetate ligands that are positioned symmetrically around the two rhodium atoms to give a dimeric "paddlewheel" complex with an overall D_{4h} symmetry (Figure 1.4).[5] Furthermore, by replacing the simple acetate ligand in dirhodium tetraacetate with chiral, non-racemic ligands, a sense of asymmetric induction can be imparted on the reactions of the rhodium carbene species.

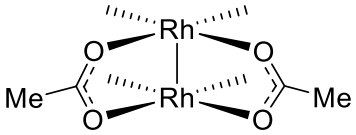
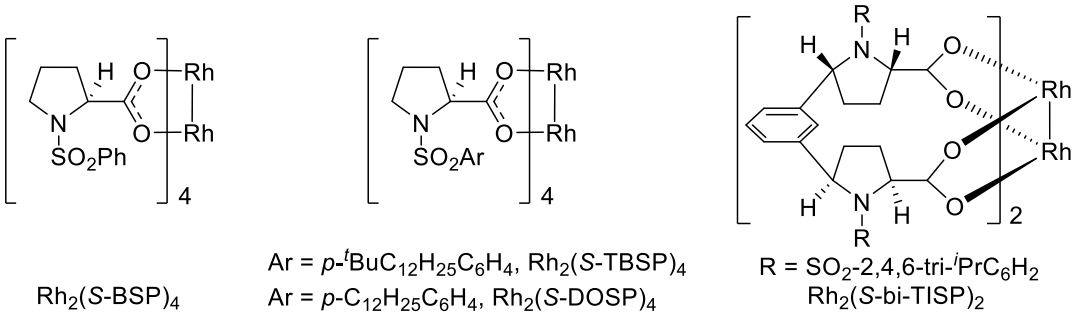


Figure 1.4 Dirhodium tetraacetate "paddlewheel"

The first class of rhodium catalysts for donor/acceptor carbenes is the arylsulfonylprolinates, first developed by McKervey and co-workers.[18-20] A typical catalyst in this class is Rh_2(*S*-BSP)$_4$ (Figure 1.5). Later, the scope of these catalysts were expanded by Davies to the more hydrocarbon soluble Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-DOSP)$_4$,[21] which were shown to be exceptional catalysts in carbene C–H chemistry.[5] The reason for the enhanced stereocontrol in hydrocarbon solvents was proposed to be solvent-induced orientation of the ligands to an overall D_2 symmetry. Rh_2(*S*-bi-TISP)$_4$ is a second generation catalyst that possessed a rigid bridging structure and could give high asymmetric induction even in non-hydrocarbon solvents.[22]



Rh_2(*S*-BSP)$_4$

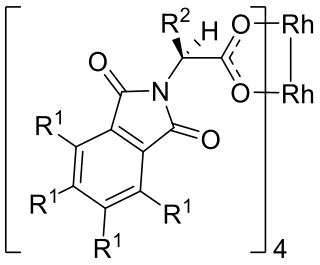
Ar = *p*-^{t}BuC$_{12}$H$_{25}$C$_6$H$_4$, Rh_2(*S*-TBSP)$_4$
Ar = *p*-C$_{12}$H$_{25}$C$_6$H$_4$, Rh_2(*S*-DOSP)$_4$

R = SO$_2$-2,4,6-tri-^{i}PrC$_6$H$_2$
Rh_2(*S*-bi-TISP)$_2$

Figure 1.5 Representative dirhodium catalysts derived from prolinates

A second class of dirhodium catalysts, ligated with the *N*-phthalimidyl amino acids, was first developed by Hashimoto.[23-25] The most well-known catalyst of this class is Rh_2(*S*-PTTL)$_4$ (Figure 1.6). A second related catalyst in this family, Rh_2(*S*-PTAD)$_4$, was reported by the Davies group and features an adamantyl group instead of a *tert*-butyl group.[26a] The introduction of *N*-phthalimidyl amino acid-ligated dirhodium catalysts expanded the scope

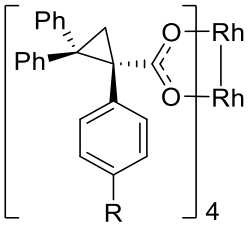
of diazoacetates to other esters than methyl esters, to diazo ketoesters, diazo ketones, diazophosphonate, or 1-aryl-2,2,2-trifluorodiazoethanes, and even to C–H amination reactions.[23-24,26]



R^1 = H, R^2 = ^{t}Bu	Rh_2(*S*-PTTL)$_4$
R^1 = H, R^2 = adamantyl	Rh_2(*S*-PTAD)$_4$
R^1 = Br, R^2 = ^{t}Bu	Rh_2(*S*-TBPTTL)$_4$
R^1 = Cl, R^2 = ^{t}Bu	Rh_2(*S*-TCPTTL)$_4$
R^1 = Cl, R_2 = adamantyl	Rh_2(*S*-TCPTAD)$_4$

Figure 1.6 Representative *N*-phthalimidyl amino acids derived dirhodium catalysts

A third class of catalysts is based on a chiral cyclopropane carboxylate ligand that was synthesized by rhodium-catalyzed cyclopropanation reactions (Figure 1.7).[27] The first example of this family of catalysts is Rh_2(*R*-*p*-BrTPCP)$_4$,[27] and the catalyst library was subsequently expanded to include functionalized version Rh_2(*R*-*p*-PhTPCP)$_4$ and the core structure Rh_2(*R*-TPCP)$_4$.[28,29] These dirhodium triarylcyclopropane carboxylate catalysts are exceptionally sterically demanding and have been shown to give results in reactions such as C–H insertions that differ significantly from Rh_2(DOSP)$_4$ and Rh_2(PTAD)$_4$.[28-30]

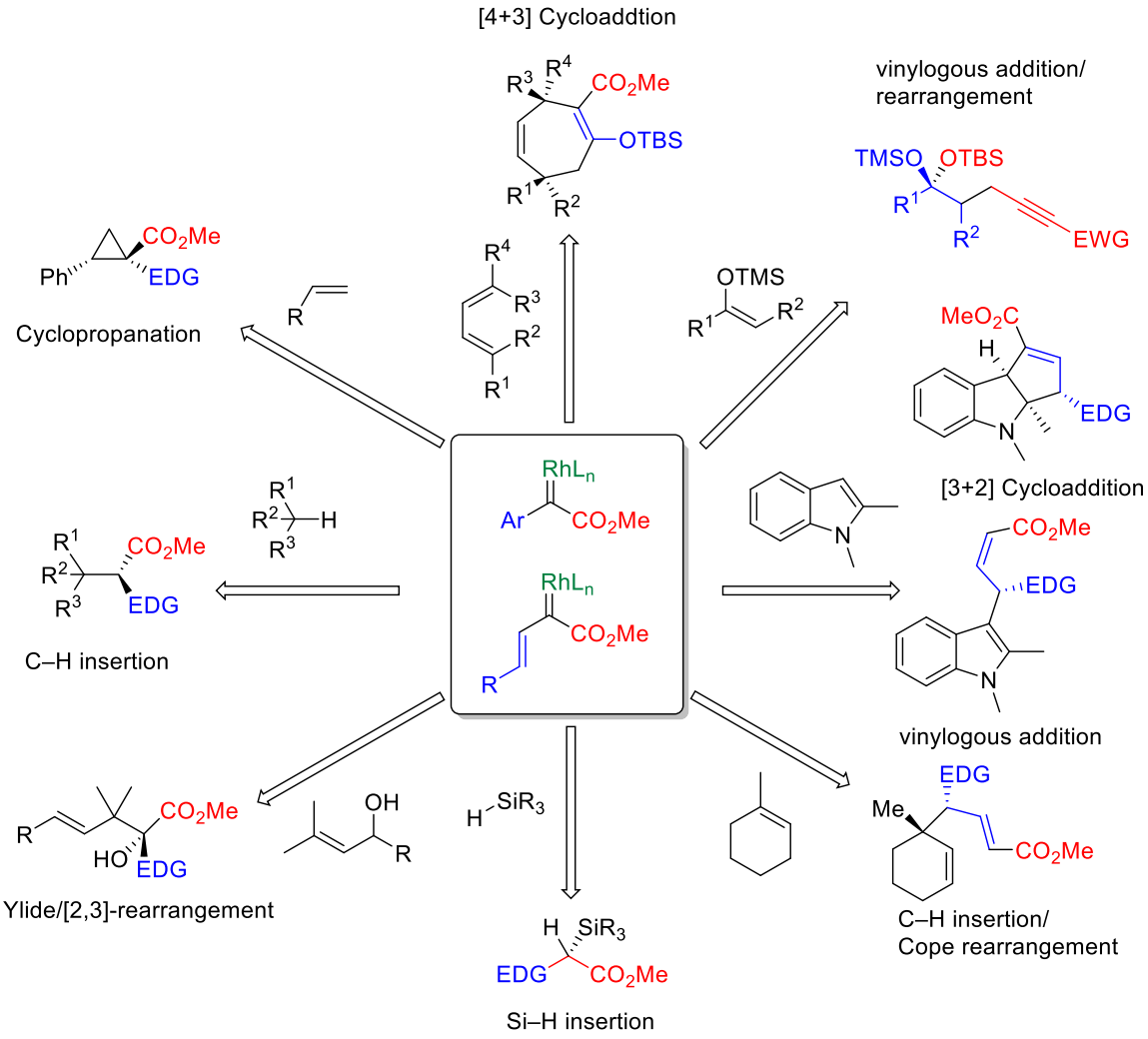


R = Br	Rh_2(*R*-*p*-BrTPCP)$_4$
R = Ph	Rh_2(*R*-*p*-PhTPCP)$_4$
R = H	Rh_2(*R*-TPCP)$_4$

Figure 1.7 Representative dirhodium triarylcyclopropane carboxylate catalysts

Rhodium-bound donor/acceptor carbenes have advanced the chemistry of metallocarbenes and have enabled various useful transformations, especially in intermolecular carbene reactions (Scheme 1.2).[5,7] These transformations include not only classic carbene transformations, such as cyclopropanation[31-33] and C–H insertion,[3,5] but

also cycloaddition,[34-36] ylide formation,[37-39] and vinylogous reactivity[28,36,40] to generate useful scaffolds and building blocks for further diversification. Rhodium-bound donor/acceptor carbenes also enabled intermolecular asymmetric C–H insertions that were not achieved with other types of metallocarbenes.[4,5] The chemistry of metallocarbenes have also been showcased in the total synthesis of natural products and biologically active compounds.[41-45]

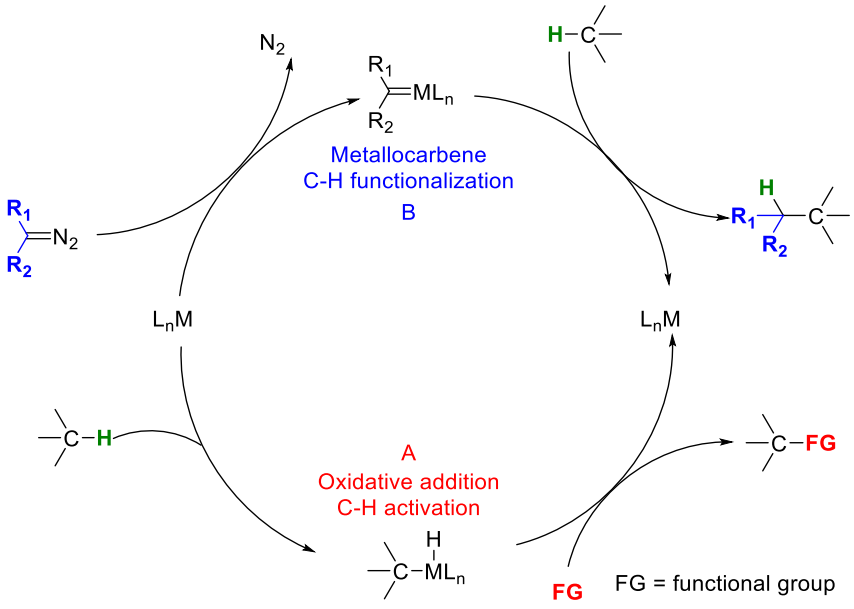


Scheme 1.2 Reactivity of donor/acceptor rhodium carbenes

1.3 Carbene induced C–H insertion reactions

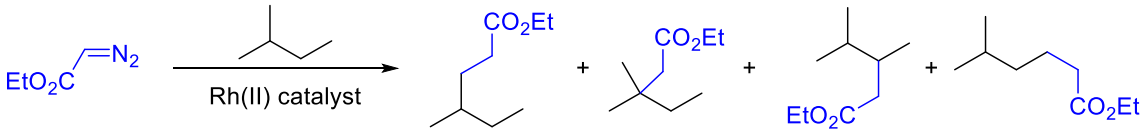
The development of efficient ways to synthesize natural products and complex biologically active compounds is one of the main focal points of organic chemists. As a novel strategy, the direct functionalization of unactivated C–H bonds offers unique opportunities for rapid access to complex molecules as it does not require the use of functional groups in the substrate.[46]

Two distinctive approaches exist for C–H functionalization. The more traditional approach requires a formal oxidative activation step, namely, the insertion of a transition metal into the C–H bond to be functionalized to generate a transition metal hydride intermediate (Scheme 1.3, A).[47,48] Alternatively, C–H functionalization can be achieved by concerted insertion of a metallocarbene into a C–H bond (Scheme 1.3, B).[4, 5] *In situ* generation of the metallocarbenes by decomposition of diazo compounds with chiral transition metal complexes has made asymmetric C–H functionalization an efficient and very promising method in synthetic chemistry.[5]

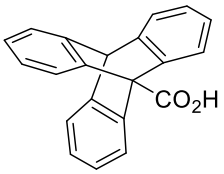


Scheme 1.3 Two complementary approaches for C–H functionalization

The selectivity and reactivity of carbene C–H insertion reactions are controlled by the structure of carbene, the nature of C–H substrate, and the properties of the catalyst. The more traditional acceptor-only and acceptor-acceptor metallocarbenes are so reactive that the selectivity is often very poor, and for this reason they are broadly used only in intramolecular C–H insertion reactions.[5] For example, in the functionalization of 2-methylbutane with acceptor-only diazo compound ethyl diazoacetate **1.1** (Scheme 1.4),[50] when $Rh_2(OAc)_4$ was used as the catalyst, a mixture of products was formed, with product **1.4** resulting from insertion into the secondary position being formed as the major product. When the catalyst was switched to a bulky $Rh_2(9\text{-trp})_4$, an increase in the ratio of primary C–H insertion products **1.2** and **1.5** was observed. Finally, with the use of the electron-deficient catalyst $Rh_2(TFA)_4$, the more electron rich tertiary (**1.3**) and secondary (**1.4**) products are formed as the major products. A general preference for the methylene C–H insertion was observed, but the regioselectivity was poor even though the effect of catalysts on site-selectivity was seen in these reactions.



1.1



9-triptycenecarboxylic acid (9-trp)

	1.2	**1.3**	**1.4**	**1.5**
$Rh_2(OAc)_4$	1	8	90	1
$Rh_2(9\text{-trp})_4$	18	18	27	37
$Rh_2(TFA)_4$	2	25	66	4

Scheme 1.4 Reaction of ethyl diazoacetate with 2-methylbutane

The intermolecular C–H insertion reactions did not become synthetically useful until the advent of rhodium-bound donor/acceptor carbenes introduced by the Davies group.[5]

The attenuated reactivity of donor/acceptor carbenes enables highly selective intermolecular C–H insertion reactions to occur with a broad range of substrates.[5] The C–H insertion event is considered to be initiated by a hydride transfer-type event that ultimately leads to the formation of a new C–C bond (Figure 1.8).[49] This has been supported by theoretical studies by Davies and co-workers where the calculated transition states for C–H insertion showed evidence for considerable hydride transfer during the C–H insertion event.

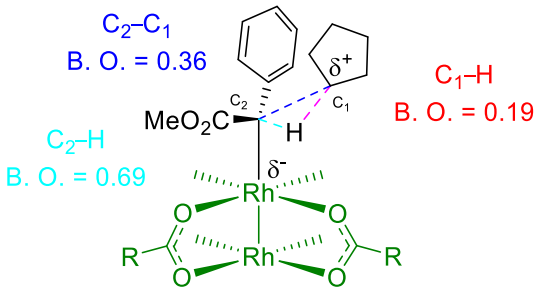


Figure 1.8 Calculated hydride transfer in rhodium carbene C–H insertion

The factors influencing selectivity in rhodium carbene C–H insertion reactions have been thoroughly reviewed.[51] The electronic nature of the C–H bond is critical due to the concerted asynchronous hydride transfer during the C–H insertion events. The C–H bond that leads to the best stabilization of a carbocation in the transition state is thus the most reactive (Figure 1.9). As such, considering electronic effects, the order of reactivity from highest to lowest is tertiary > secondary > primary C–H bonds. On the other hand, donor/acceptor rhodium carbenes are sterically demanding complexes. Therefore, the steric environment of the C–H bond also influences the selectivity. From the point of view of sterics, the reactivity decreases from primary to secondary to tertiary. These two factors are in effect at the same time, and C–H insertion reaction typically takes place preferentially at secondary C–H sites as a balance of the two effects.

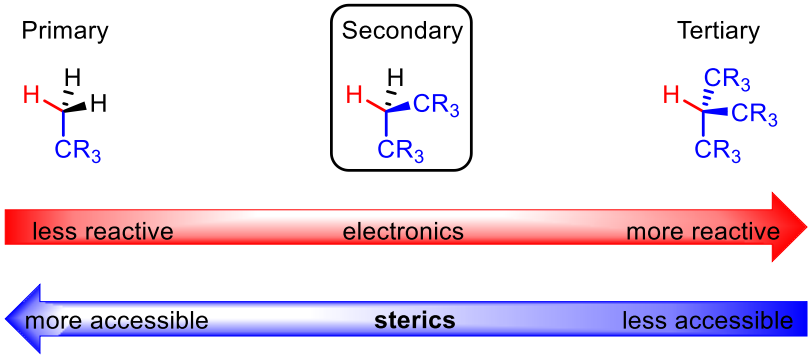
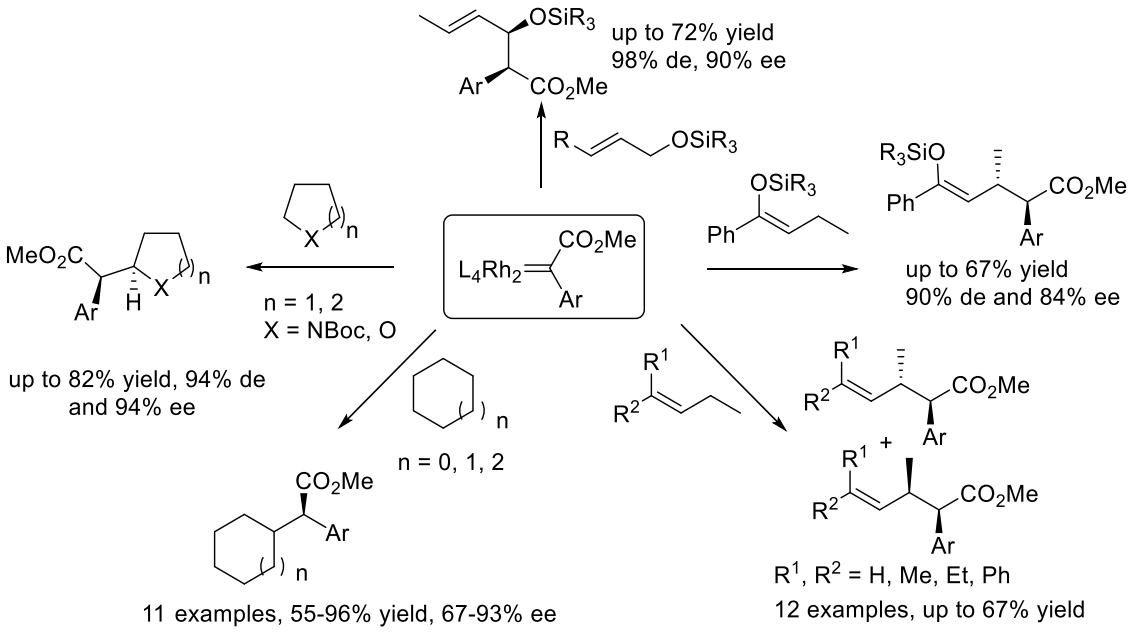


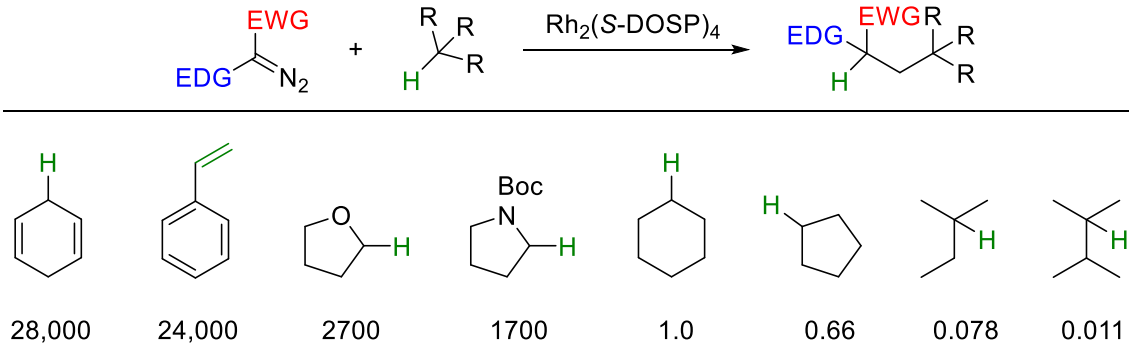
Figure 1.9 Electronic vs steric effects of C–H bonds in C–H insertion reactions

As described above, rhodium carbenes preferentially insert into C–H bonds that stabilize positive charge, rhodium carbene induced C–H functionalization is enhanced by electron-donating groups adjacent to the site of C–H activation as they can stabilize carbocation-like intermediates through resonance.[5] These electron-donating groups include alkoxy, nitrogen and vinyl groups since there is positive charge build-up on the reacting carbon (Scheme 1.5). Besides electronic and steric effects, conformational factors also influence the reactivity and selectivity.[5]



Scheme 1.5 Typical C–H insertion reactions with donor/acceptor rhodium carbenes

Relative rates of insertion into various C–H bonds have been determined by competition studies between styrene and different substrates (Scheme 1.6).[52] The reactivity-enhancing effect of a vinyl or heteroatom group to the C–H bond to be functionalized can be clearly seen. Furthermore, steric effects can also be observed by comparing the reaction rates of cyclohexane and cyclopentane to 2-methylbutane and 2,3-dimethylbutane. For steric reasons, functionalization of the less electronically activated secondary C–H bonds in the cyclic hydrocarbon substrates is preferred to the more electronically activated tertiary positions of the acyclic compounds.

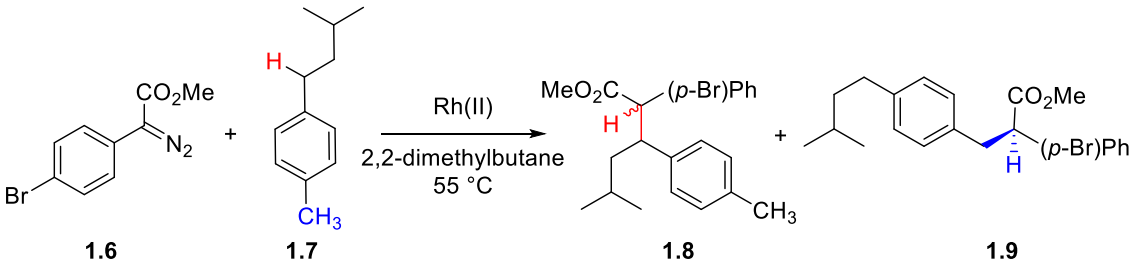


Scheme 1.6 Relative rates of C–H insertion with donor/acceptor rhodium carbenes

However, these general trends can be changed by tuning the steric environment of the catalyst. Drastic changes in the selectivity were observed using the bulky triarylcyclopropane carboxylate catalysts. A recent discovery from the Davies group disclosed that with these catalysts, the functionalization of less reactive but more sterically accessible primary methyl groups can be effected.[29,53] Specifically, for the functionalization of substrate **1.7** that contains competing secondary and primary C–H bonds, when Rh_2(*S*-DOSP)$_4$ was used as the catalyst, the secondary C–H insertion product **1.8** was formed as the major product (Table 1.1, entry 1).[54] In contrast, by using the bulkier

catalyst Rh_2(*S*-*p*-PhTPCP)$_4$, products **1.9** was formed exclusively with high enantioselectivity (94%) (entry 2).[29]

Table 1.1 Selective functionalization of a substrate that contains competing secondary and primary C–H bonds



1.6 **1.7** **1.8** **1.9**

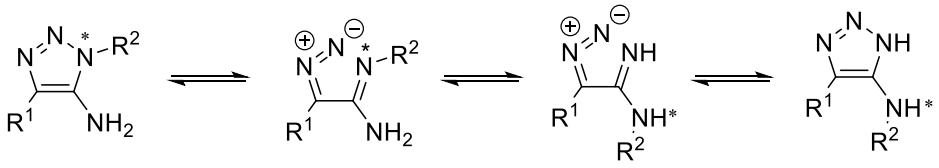
entry	catalyst	yield (%)	**1.8** : **1.9**	ee for **1.9**
1	Rh_2(S-DOSP)$_4$	70%[a]	1.7:1	77%
2	Rh_2(S-*p*-PhTPCP)$_4$	90%[b]	1:>20	94%

[a]Combined yield for **1.8** and **1.9**.[b]Yield for **1.9**.

1.4 Use of *N*-sulfonyl-1,2,3-triazoles alternative carbene precursors

Traditionally, *α*-diazocarbonyls are the most commonly used precursors for the generation of metallocarbenes. Recently, *N*-sulfonyl triazoles have also emerged as an alternative source of carbene precursors. The basic premise of the chemistry relies on the Dimroth rearrangement, in which 1,2,3-triazoles-5-amines can undergo a ring-opening/ring-closing sequence to afford the isomeric amino triazoles (eq. 1.1).[55]

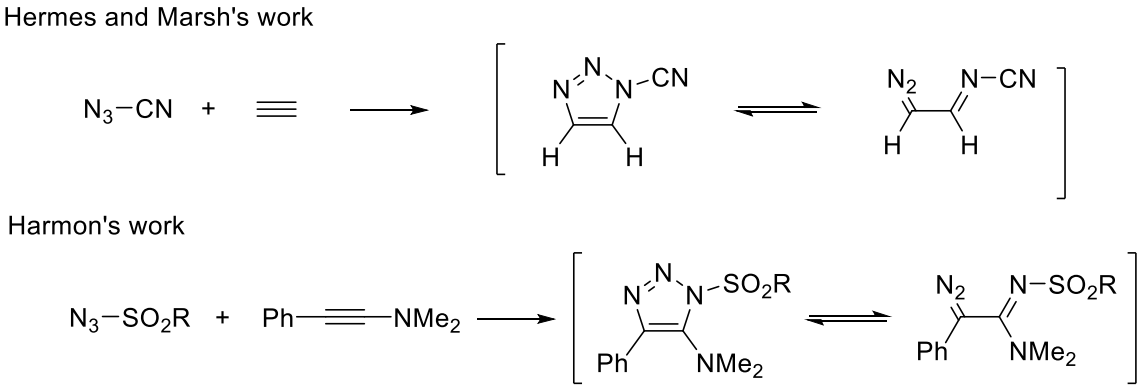
Dimroth Rearrangement



(eq. 1.1)

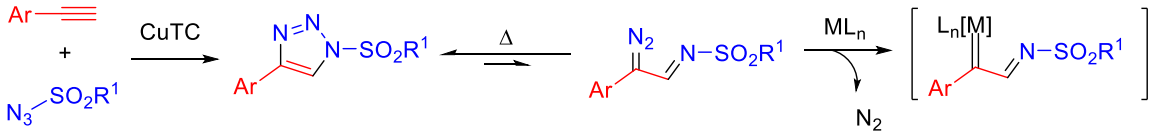
Typically, the equilibrium favors the ring-closed form due to aromaticity, however, when a strong electron-withdrawing group is present at the N-1 position, the ring-open form could exist in a more significant amount (Scheme 1.7). In 1967, Hermes and Marsh

reported that at slightly elevated temperature, closed-ring and open-ring isomers of 1-cyano-1,2,3-triazole existed as an isomeric mixture in a 1:1 ratio.[56] Later in 1970, Harmon reported that *N*-sulfonyl-1,2,3-triazoles with an amino group at the C-5 position also existed as an isomeric mixture of open and closed-chain isomers.[57]



Scheme 1.7 Triazole rearrangements/ring-chain isomerization

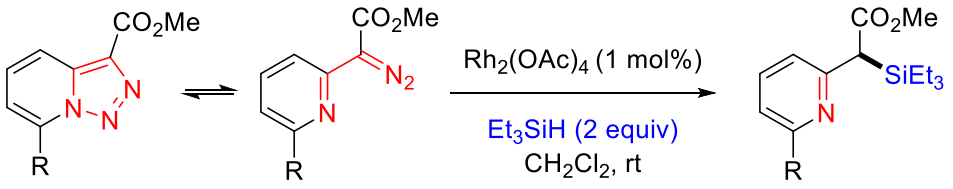
Recently, it was shown that 1,2,3-triazoles bearing a strong electron-withdrawing sulfonyl group at N-1 position can act as masked diazo compounds.[58,59] *N*-sulfonyl-1,2,3-triazoles are capable of undergoing a 'ring-to-chain isomerization' to expose the diazo moiety, and in the presence of a suitable catalyst, metallocarbenes can be generated (Scheme 1.8). Many of the catalysts developed for diazo decomposition can also be used in rhodium catalyzed decomposition of triazoles to generate metallocarbenes.[60]



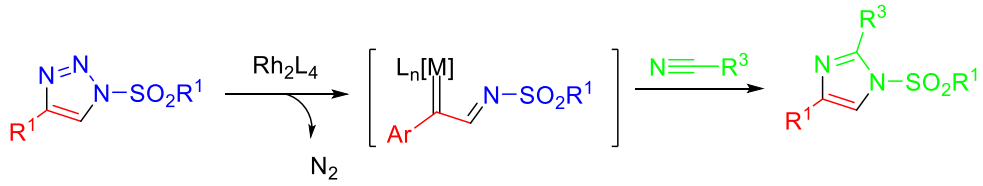
Scheme 1.8 Generation of metallocarbenes from *N*-sulfonyl-1,2,3-triazoles

The early examples of using *N*-sulfonyl-1,2,3-triazoles as carbene precursors were reported by Gevorgyan and Fokin.[59,60] In 2007, Gevorgyan reported that 7-chloro-

substituted pyridotriazole was decomposed in the presence of a rhodium(II) catalyst to reveal a transient rhodium carbenoid, which was then confirmed by inserting into the Si–H bond of triethylsilane (eq. 1.2). Fokin in 2008 demonstrated that rhodium(II)-catalyzed reactions between *N*-sulfonyl-1,2,3-triazoles and nitriles can undergo transannulation to afford the corresponding imidazoles. Rhodium iminocarbenes are proposed to be the intermediates.[59]

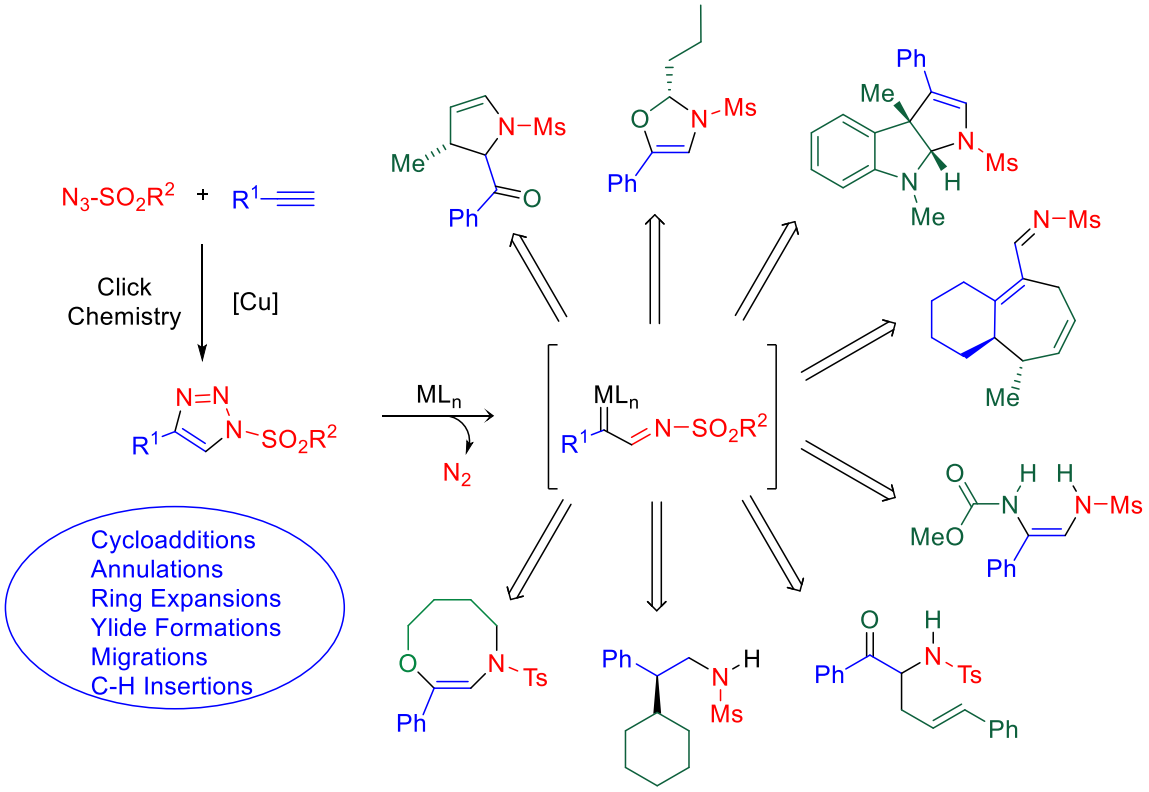


(eq. 1.2)



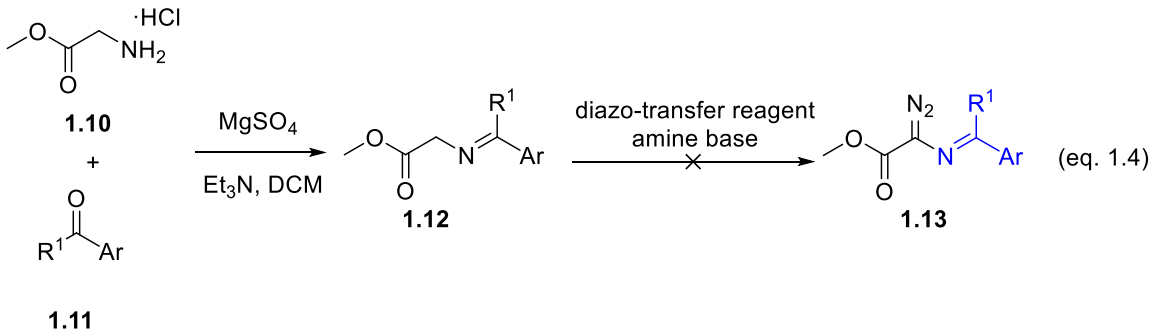
(eq. 1.3)

A distinctive feature of using *N*-sulfonyl triazoles is that the generated metallocarbenes have a pendant sulfonyl imine group, which exhibits higher nucleophilicity than their counterparts derived from α-diazo esters.[60] This increased nucleophilicity enables the *α*-imino group to further react or cyclize in reactions involving zwitterionic intermediates.[59,61-63] Numerous studies have demonstrated the application of *N*-sulfonyltriazoles as viable precursors in both classic reactions including enantioselective cyclopropanation[64-65] and C–H insertion reactions[66] and novel transformations such as transannulation for direct heterocycle formation,[59,67-70] unusual reactivity,[71-72] and ylide formation followed by sequential rearrangement[73-76] (Scheme 1.9). Work in this field has been documented and reviewed by the Davies and other groups.[60]



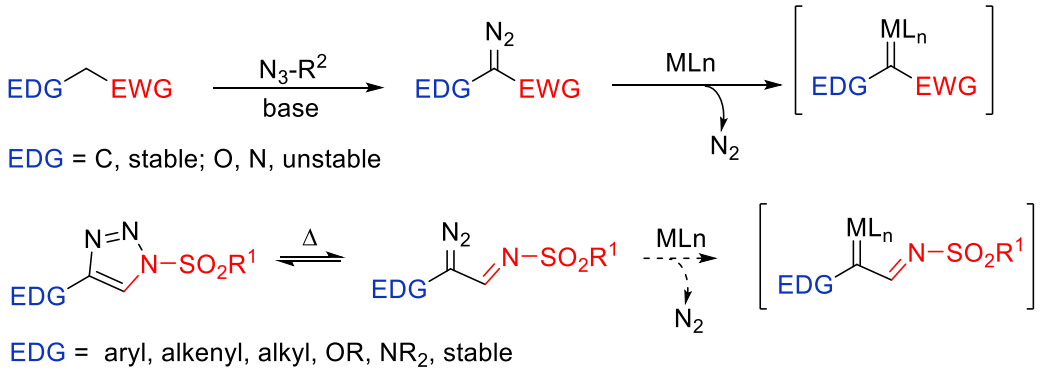
Scheme 1.9 Representative rhodium catalyzed triazole reactions

The Davies group has been particularly interested in using *N*-sulfonyl-1,2,3-triazoles to expand the scope of donor groups that can be incorporated into donor/acceptor carbenes.[77,78] Previously, donor/acceptor diazo compounds with oxygen and nitrogen as the donor groups were inaccessible as all the attempts for their preparation had largely met with failure. For example, the attempts to prepare amino-diazo compound **1.13** were unsuccessful as rapid evolution of dinitrogen during their attempted synthesis was observed, suggesting that diazo compounds **1.12** were decomposing as they were being formed (eq. 1.4).

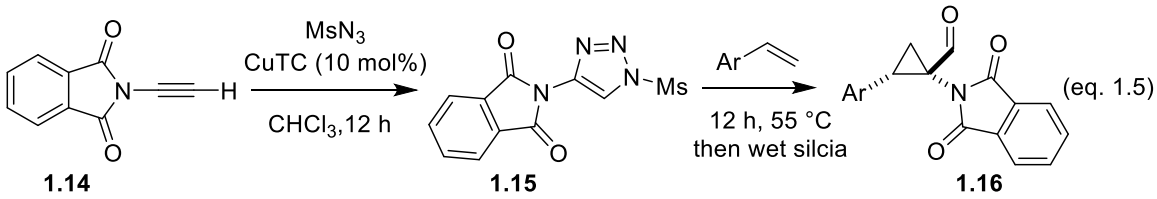


R^1 = H, Me, OMe, Ph, CF_3; R^2 = EDG and/or EWG

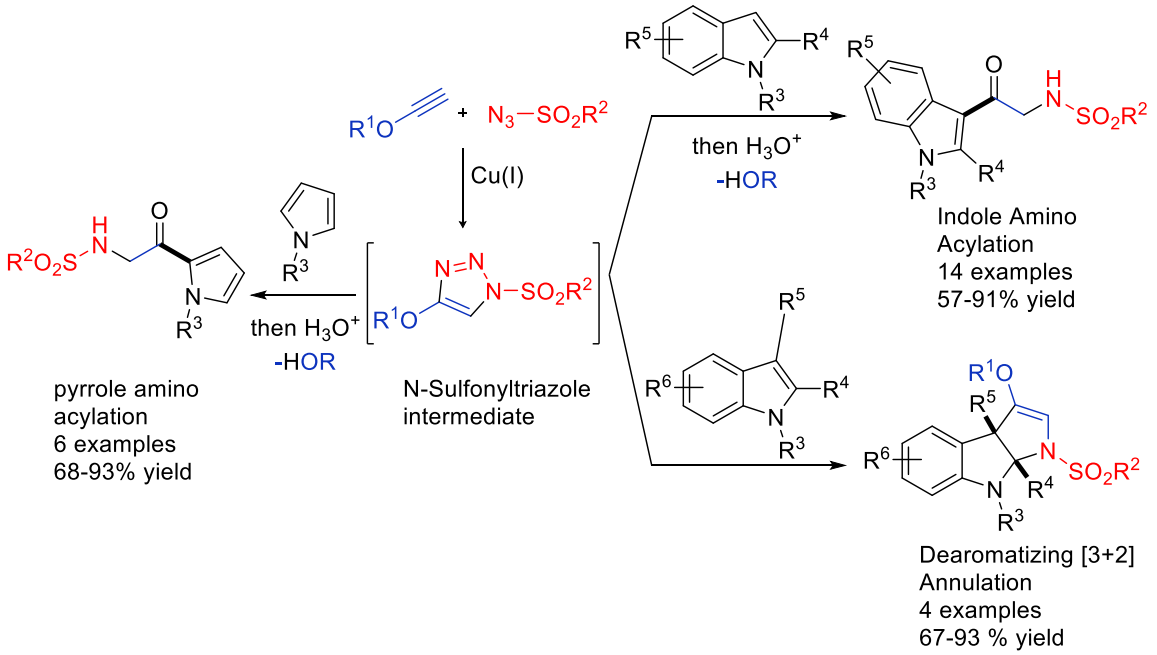
In 2012, a breakthrough in heteroatom-substituted donor/acceptor diazo compounds was achieved by the Davies group that realized the incorporation of nitrogen and oxygen as the donor groups into donor/acceptor carbenes (Scheme 1.10).[77] By using 'click' chemistry, these amino-substituted diazo compounds were prepared as masked triazoles (eq. 1.5). Under thermal conditions, 4-phthalimido-*N*-methanesulfonyl-1,2,3-triazole **1.15** readily generated a donor/ acceptor carbene, in which the donor group is the phthalimidyl group. This carbene can be trapped by a range of alkenes and allows for rapid access to a variety of cyclopropyl *α*-amino acids **1.16** with high levels of diasteroselectivity.[40] Attempts to render this cyclopropanation reaction enantioselective have not yet been successful so far.



Scheme 1.10 Expansion of the donor group using *N*-sulfonyl-1,2,3-triazoles



The Davies group subsequently developed an efficient method for the aminoacylation of indoles and pyrroles using 4-alkoxy *N*-sulfonyltriazoles.[78] The oxo-tryptamine and oxo-pyrroloethanamine products are synthesized in a multicomponent one-pot cascade reaction. As previously observed with amino-substituted triazoles, the alkoxy-substituted triazoles also undergo nitrogen extrusion under relatively mild conditions without requiring the use of a dirhodium catalyst.



Scheme 1.11 Aminoacylation of indoles and pyrroles derivatives with 4-alkoxy *N*-sulfonyltriazoles

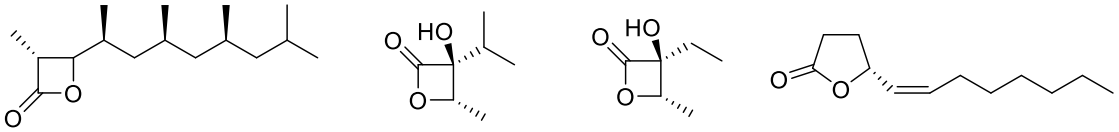
1.5 Conclusions

To summarize, the chemistry of rhodium-bound donor/acceptor carbenes has been extensively investigated and given birth to a variety of valuable transformations. C–H insertion is of particular interest because it provides a novel strategy for the functionalization of unactivated C_{sp3}–H bonds. Typically, diazo compounds are the primary source for the generation of donor/acceptor carbenes. Recently, *N*-sulfonyl 1,2,3-triazoles have emerged as alternative precursors for the generation of donor/acceptor carbenes. The major theme of this thesis is to expand the scope of reactions of donor/acceptor carbenes by developing novel, efficient and selective transformations. The aims are as follows: 1) To expand the scope of site-selective C–H functionalization; 2) To develop efficient methods for the preparation of useful synthetic building blocks; 3) To apply the metallocarbene chemistry to the total synthesis of natural products and biologically active compounds.

Chapter 2 Rhodium-catalyzed asymmetric synthesis of *β*-lactones by intramolecular C–H insertions of *ortho*-substituted aryldiazoacetates

2.1 Introduction

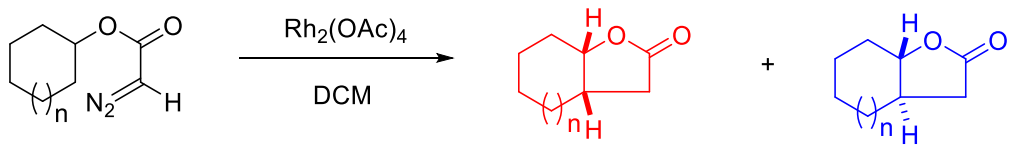
Lactones are important intermediates and structural motifs in organic chemistry and natural products and biologically active compounds.[79-81] Some representative lactones in drugs and biologically active compounds include *β*- and *γ*-lactones such as vittatalactone, viridiflorine-*β*–lactone and norviridiflorine-*β*-lactone, and buibuilactone (Figure 2.1).[82]



vittatalactone viridiflorine-*β*-lactone norviridiflorine-*β*-lactone buibuilactone

Figure 2.1 Representative lactones in drugs and biologically active compounds

Carbene-induced C–H insertion has been used for the synthesis of lactones; however, the formation of *γ*–lactones is generally preferred.[83,84] For example, in the reaction of a diazoester compound **2.1** with competing secondary and tertiary C–H bonds present in the molecule, the *γ*-lactone was preferentially formed (Scheme 2.1).



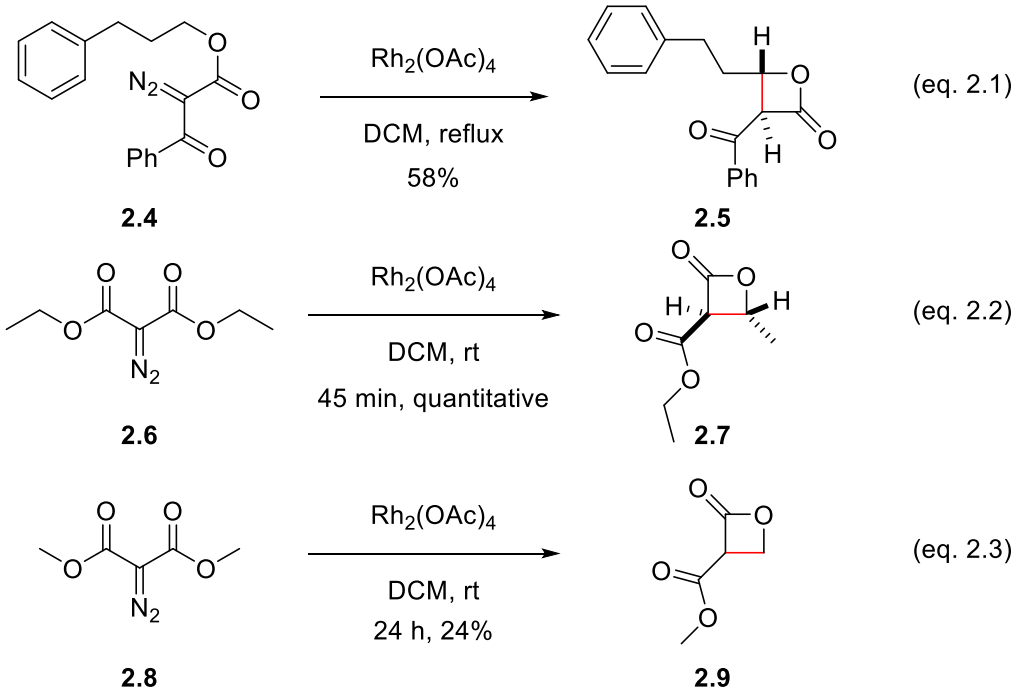
n = 1, **2.1a**
n = 2, **2.1b**
n = 3, **2.1ac**

2.2a-c **2.3a-c**

2.2a:**2.3a** = 40:60
2.2b:**2.3b** = 30:70
2.2c:**2.3c** = 29:71

Scheme 2.1 *γ*–Lactone formation in the reaction of cyclic alkyl diazoacetates

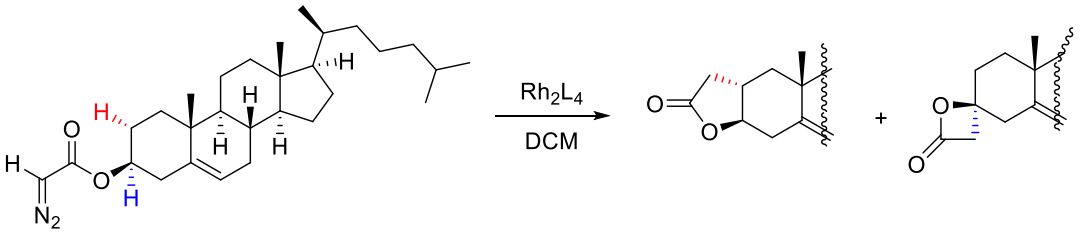
Although four-membered *β*–lactones are more strained, examples of *β*–lactone formation through intramolecular C–H functionalization have also been documented (Scheme 2.2).[85-87] For α-diazo-β-keto acetates, the intramolecular C–H insertion reactions under the catalysis of $Rh_2(OAc)_4$ gave exclusively the corresponding *β*–lactone products (eq. 2.1). This was also the case for dialkyl α-diazo malonates (eq. 2.2). *Trans*-stereoisomers were preferentially formed in cases where diastereomers were expected to be formed. One rare example of intramolecular C–H insertion into the methyl ester group was also reported for the more reactive acceptor/acceptor diazo compound in a racemic reaction (eq. 2.3). However, this intramolecular C–H insertion was slow. Due to the lower reactivity of primary C–H bonds in carbene C–H insertion reactions, under the catalysis of $Rh_2(OAc)_4$, the starting material was only consumed after 24 h and gave the lactone product in low yield (24%).



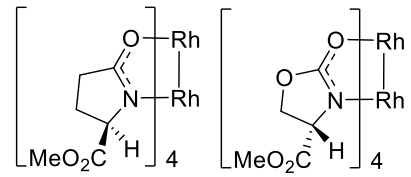
Scheme 2.2 *β*–Lactone formation through intramolecular C–H functionalization

The stereoselective version of *β*–lactone synthesis by carbene C–H insertion approach was also explored. In 2001, the Doyle group reported a selective synthesis of five or four-membered lactone products in a steroidal framework (Table 2.1).[88] With the *R*-enantiomer of selected catalysts, *γ*-lactone **2.11** was formed as the major product from the reaction of diazo compound **2.10**. The highest selectivity was obtained when the reaction was catalyzed by Rh_2(5*R*-MEPY)$_4$ (entry 1). By switching to the catalyst to Rh_2(5*S*-MEPY)$_4$ or Rh_2(4*S*-MEOX)$_4$, selective synthesis of *β*-lactone **2.12** was preferentially formed instead. The best selectivity for this product was obtained when the reaction was catalyzed by Rh_2(4*S*-MEOX)$_4$ (entry 4). Interestingly, the authors reported that no product was generated from C–H insertion at the allylic secondary site.

Table 2.1 Selective formation of *β*- and *γ*-lactones through intramolecular C–H functionalization

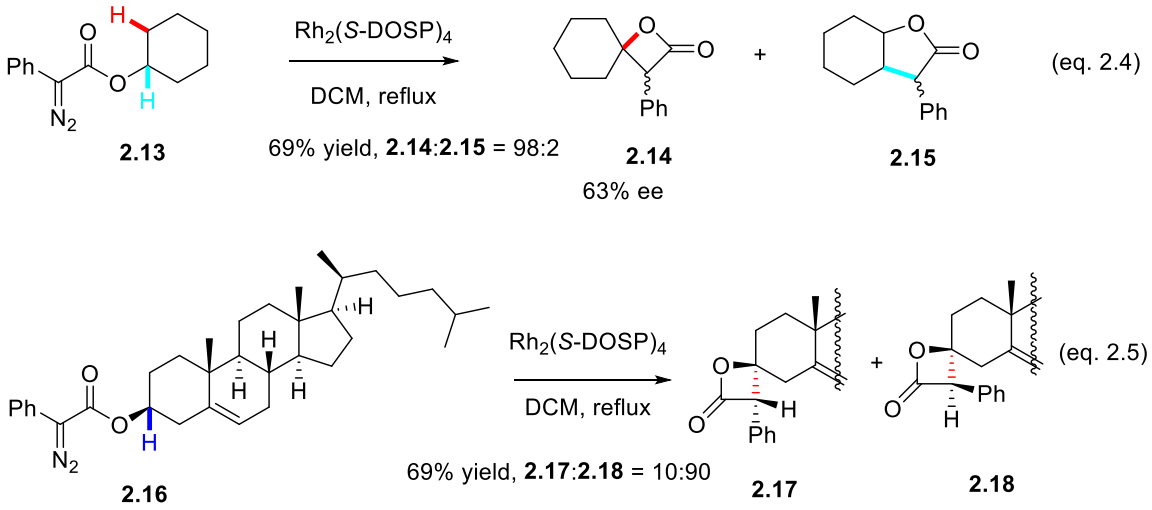


entry	catalyst	yield (%)	**2.11**:**2.12**
1	Rh_2(5*R*-MEPY)$_4$	81	94:6
2	Rh_2(4*R*-MEOX)$_4$	81	89:11
3	Rh_2(5*S*-MEPY)$_4$	74	33:67
4	Rh_2(4*S*-MEOX)$_4$	80	10:90



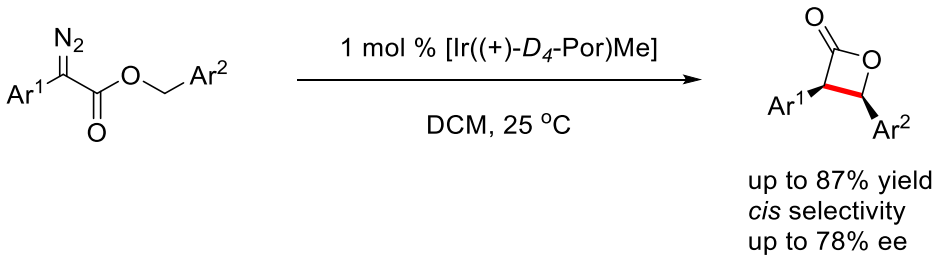
The Doyle group further showed that with a donor/acceptor carbenes, selective *β*-lactone can be achieved by intramolecular C–H insertions of a cyclohexyl phenyldiazoacetate **2.13** (Scheme 2.3).[88-89] In this system, both tertiary and secondary C–H bonds are present, and insertions into these C–H sites can lead to the formation of *β*- and

γ-lactones respectively. However, the Doyle group showed that reaction of diazo compound **2.13** preferred formation of *β*-lactone **2.14** instead of *γ*-lactone **2.15**. The highest enantioselectivity for **2.14** was 63% when the reaction was performed in refluxing DCM with Rh_2(*S*-DOSP)$_4$ as the catalyst (eq. 2.4).[89] The preference for the formation of *β*-lactones was also observed in a more complex steroidal substrate **2.16**. When Rh_2(*S*-DOSP)$_4$ was used as the catalyst, the reaction gave exclusively *β*-lactone products **2.17** and **2.18** in 69% yield with 10:90 diastereomeric ratio (eq. 2.5).[88]



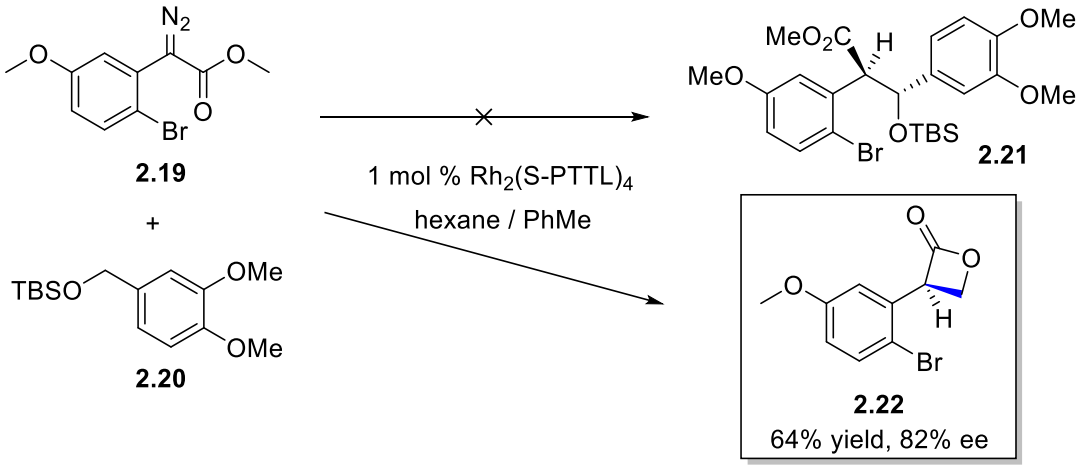
Scheme 2.3 Intramolecular C–H insertion with tertiary esters

The Che group recently developed an iridium-catalyzed intramolecular C–H insertion into saturated benzylic C−H bonds of α-diazoesters for the synthesis of *cis-β*–lactones (Scheme 2.4).[90] The substrate of the transformation was broad and a variety of α-diazoesters with saturated benzylic C−H bonds were tolerated. The products were obtained in up to 87% yield with high levels of *cis* diastereoselectivity and up to 78% ee.



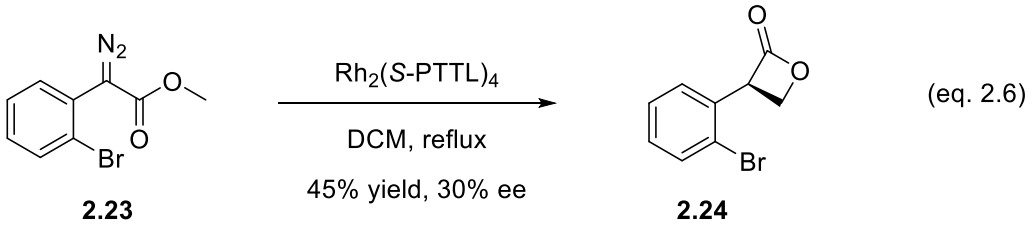
Scheme 2.4 Che's iridium-catalyzed *β*–lactone synthesis

Though the synthesis of *β*–lactone *via* intramolecular C–H insertion of tertiary and secondary C–H bonds were previously studied by the Doyle and Che groups independently, the enantioselectivity was low, leaving room for further development of this type of transformation. During the exploration of C–H insertion at benzylic position, a former graduate student Dr. Hengbin Wang discovered that in the Rh_2(*S*-PTTL)$_4$ catalyzed reaction of diazo compound **2.19** and the silyl benzyl ether **2.20**, no expected C–H insertion product **2.21** was observed.[91] Instead, only the *β*-lactone product **2.22** was isolated in good yield and ee (Scheme 2.5). This was the first time that formation of *β*-lactone via asymmetric intramolecular primary C–H bond insertion was achieved. The absolute conformation of **2.22** was obtained by X-ray crystallography.



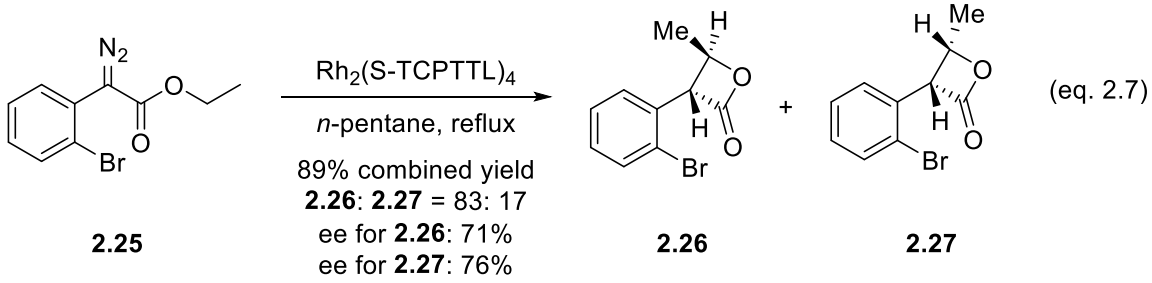
Scheme 2.5 Discovery of the *β*–lactone formation by primary C–H bond insertion

Dr. Wang also explored the intramolecular primary C–H insertion reaction with substrate **2.23** (eq. 2.6). The reaction conditions with respect to the solvent were briefly optimized using Rh_2(*S*-PTTL)$_4$ as the catalyst. Various solvents, such as hexanes, 2,2-dimethylbutane, toluene, dichloromethane, dichloromethane and trifluorotoluene were examined and the best conditions employed dichloromethane as the solvent. The *β*–lactone product **2.24** was obtained in 45% yield and 30% ee when **2.23** was treated with Rh_2(*S*-PTTL)$_4$ in refluxing dichloromethane.[91]

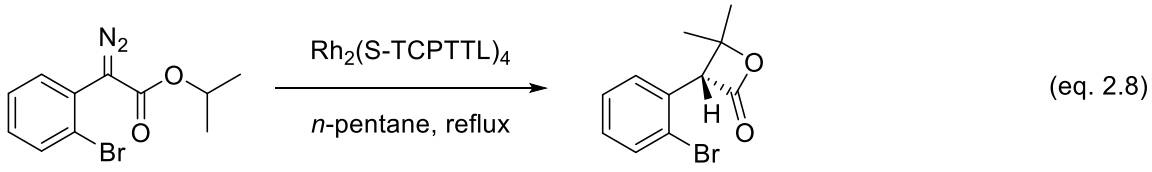


2.23 **2.24** (eq. 2.6)

Dr. Wang also screened some commonly used chiral dirhodium catalysts for synthesizing *β*–lactone through secondary and tertiary C–H insertions using dichloromethane as the solvent (eq. 2.7).[91] Among the catalysts (Rh_2(*S*-PTAD)$_4$, Rh_2(*S*-BTPCP)$_4$, Rh_2(*S*-TCPTTL)$_4$, Rh_2(*S*-NTTL)$_4$, Rh_2(*S*-TCPTV)$_4$) Rh_2(*S*-TCPTAD)$_4$ screened, Rh_2(*S*-TCPTTL)$_4$ showed best catalytic reactivity for this reaction. When the reaction was performed in refluxing *n*-pentane under the catalysis of Rh_2(*S*-TCPTTL)$_4$, the *β*–lactone products were obtained in 89% combined yield with 83:17 of diastereoselectivity in favor of the *trans* product **2.26**. The ee for products **2.26** and **2.27** were 71 % and 76 % ee respectively. For tertiary C–H insertion, the reaction of **2.28** under the catalysis of Rh_2(S-TCPTTL)$_4$ in refluxing pentane gave the lactone product **2.29** in excellent yield (90%), but only moderate ee (45%) (eq. 2.8).



2.25 **2.26** **2.27** (eq. 2.7)



2.28 **2.29** (eq. 2.8)

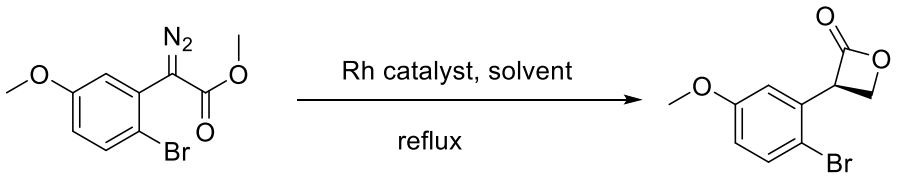
The initial discovery and results from Dr. Hengbin Wang suggested a promising and interesting opportunity for *β*−lactone formation by rhodium carbene chemsitry, but the transformation needed further systematic investigations with respect to the reaction conditions and substrate scope. My work on this project was focused first on systematic optimization of the reaction conditions with the aim of further improving the yield and stereoselectivity of the transformation and on the substrate scope of the transformation with the aim of probing the key factors that influence the efficiency of the transformation.

2.2 Results and discussion

At the outset of the exploration, systematic optimization of the reaction conditions was conducted using methyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **2.19** as the model substrate (Table 2.2). Rh_2(*S*-DOSP)$_4$, a well-known catalyst for donor/acceptor carbene C−H insertion reactions, was first examined. It was found that the reaction performed in dichloromethane gave the *β*−lactone product **2.22** in 31% yield with moderate enantiomeric induction (51%), while hydrocarbon solvent *n*-pentane gave essentially no *β*−lactone product (Table 2.2, entries 1 and 2). It was proposed that the more structurally

bulky catalyst might force the C–H insertion to happen *via* the intramolecular pathway and the reduce the intermolecular C–H insertions and dimerizations. To this end, the bulkier achiral catalyst $Rh_2(TPA)_4$ and triarylcyclopropane carboxylate catalyst Rh_2(*S*-*p*-BrTPCP)$_4$ were tested in refluxing dichloromethane. To our delight, the reaction with $Rh_2(TPA)_4$ afforded the desired product in higher yield than that with Rh_2(*S*-DOSP)$_4$ (Table 2.2, entry 3). Rh_2(*S*-*p*-BrTPCP)$_4$ gave even higher yield and similar enantioselectivity to that with Rh_2(*S*-DOSP)$_4$, and interestingly, with opposite enantioinduction (Table 2.2, entry 4).

Table 2.2 Optimization of the reaction conditions: screening of catalysts



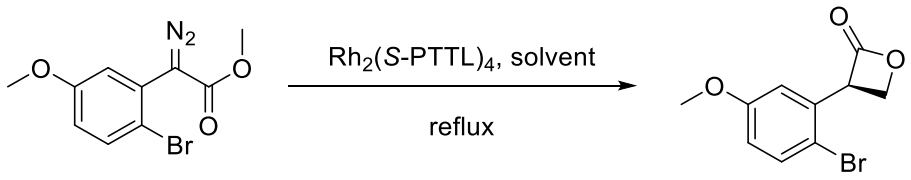
2.19 **2.22**

entry	catalyst	solvent	yield (%)	ee (%)
1	Rh_2(*S*-DOSP)$_4$	DCM	31	51
2	Rh_2(*S*-DOSP)$_4$	*n*-pentane	not observed	---
3	$Rh_2(TPA)_4$	DCM	47	---
4	Rh_2(*S*-*p*-BrTPCP)$_4$	DCM	70	-50

With these results in hand, the *N*-phthalimidyl catalyst Rh_2(*S*-PTTL)$_4$, which was initially used in the discovery of the *β*-lactone formation, was tested in different solvents (Table 2.3). In refluxing *n*-hexane, the reaction provided the product **2.22** in 53% yield and with 70% ee (Table 2.3, entry 1). The combination of *n*-hexane and toluene as the reaction media was also tested in order to improve the solubility of the reaction partners. The isolated yield essentially remained the same while the ee increased slightly (Table 2.3, entry 2). Next, the reaction was performed in *n*-pentane, which is also hydrocarbon solvent

with lower boiling point than *n*-hexane. The yield dropped slightly while the ee increased to 83% (Table 2.3, entry 3). Halogenated solvents were also tested (Table 2.3, entries 4 and 5). When the reaction was performed in refluxing dichloromethane, the desired product was obtained in 45% yield and 77% ee. However, no desired product was obtained when the reaction was performed in α,α,α-trifluorotoluene at 40 °C. Based on the data, we concluded that *N*-phthalimidyl catalyst Rh_2(*S*-PTTL)$_4$ gave best performance compared to Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-*p*-BrTPCP)$_4$, when the reaction was performed in either hydrocarbon solvent or dichloromethane.

Table 2.3 Optimization of the reaction conditions: screening of solvents



2.19 **2.22**

entry	solvent	yield (%)	ee (%)
1	*n*-hexane	53	70
2	*n*-hexane/toluene (20 :1)	54	75
3	*n*-pentane	44	83
4	DCM	45	77
5	TFT[a] (40 °C)	not observed	---

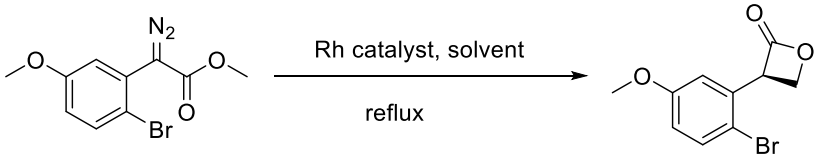
[a]TFT = *a,a,a*-trifluorotoluene

Based on the promising results obtained with of Rh_2(*S*-PTTL)$_4$, we turned our attention to the examination of other rhodium catalysts having the same phthalimidyl *tert*-leucine core structure as Rh_2(*S*-PTTL)$_4$ (Table 2.4). With halogenated Rh_2(*S*-TBPTTL)$_4$ as the catalyst, the reaction of the diazo compound **2.19** in refluxing *n*-pentane gave product **2.22** in decent yield (50%) and enantioinduction (72%) (entry 1). Higher yield (70%) and enantioselectivity (83%) were obtained when the same reaction was performed in refluxing DCM (entry 2). To improve the enantioselectivity, reactions were performed at lower

temperature. By lowering the reaction temperature to room temperature, the reaction performed with Rh_2(*S*-TBPTTL)$_4$ in dichloromethane did not generate the *β*–lactone product (entry 3). Rh_2(*S*-TCPTTL)$_4$ was also tested and the reaction gave the product in essentially similar yield (73%) and ee (84%) (entry 4) within experimental error to entry 2.

Inspired by the good result with *N*-phthalimidyl catalyst, another type of *N*-phthalimidyl catalyst, Rh_2(*S*-PTAD)$_4$, was also tested for this reaction (Table 2.4). When the Rh_2(*S*-PTAD)$_4$ catalyzed reaction was performed in refluxing dichloromethane, lactone **2.22** was obtained in 23% yield and 57% ee (entry 5). Based on previous results with Rh_2(*S*-PTTL)$_4$ showing that halogenated catalysts gave superior results as compared to non-halogenated ones, tetrachlorinated version Rh_2(*S*-TCPTAD)$_4$ was tested. To our delight, 72 % yield and high ee (86%) were obtained by switching the catalyst to Rh_2(*S*-TCPTAD)$_4$ (entry 6).

Table 2.4 Optimization of the reaction conditions: comparison of *N*-phthalimidyl catalysts



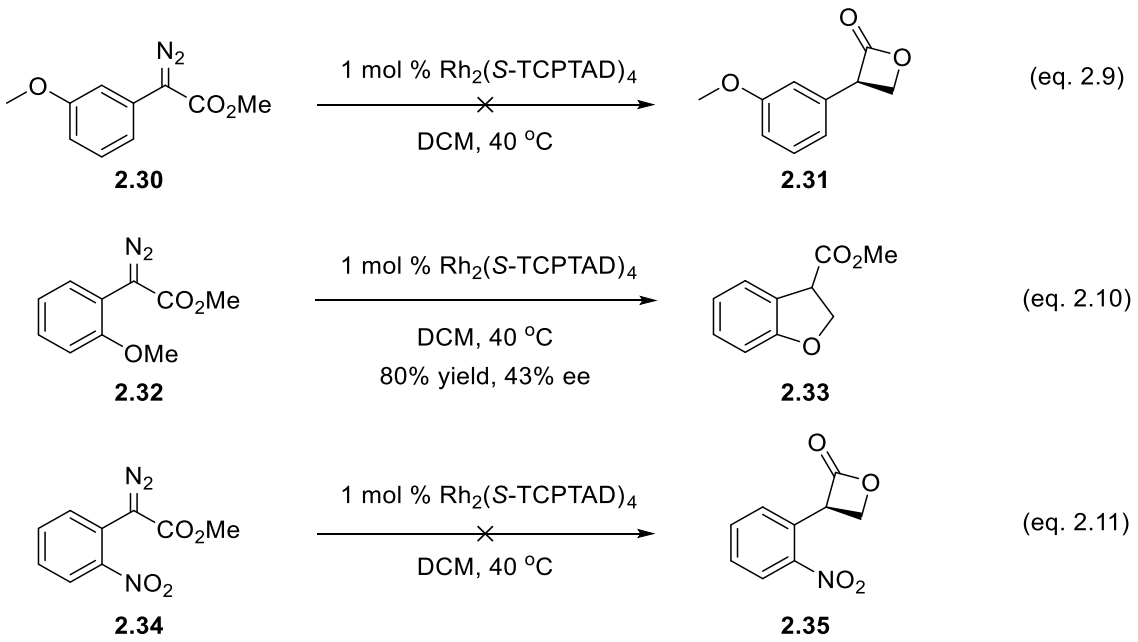
2.19 **2.22**

entry	catalyst	solvent	yield (%)	ee (%)
1	Rh_2(*S*-TBPTTL)$_4$	*n*-pentane	50	72
2	Rh_2(*S*-TBPTTL)$_4$	DCM	70	83
3	Rh_2(*S*-TBPTTL)$_4$	DCM (rt)	<5	---
4	**Rh_2(*S*-TCPTTL)$_4$**	**DCM**	**73**	**84**
5	Rh_2(*S*-PTAD)$_4$	DCM	23	57
6	**Rh_2(*S*-TCPTAD)$_4$**	**DCM**	**72**	**86**

As a brief summary of the optimization, the results showed that the efficiency of the *β*−lactone formation reaction was highly dependent on the nature of the catalyst, the solvent and the temperature, with Rh_2(*S*-TBPTTL)$_4$ and Rh_2(*S*-TCPTAD)$_4$ in refluxing dichloromethane giving similar results. The best reaction conditions obtained will be used in further studies.

After the optimized reaction conditions were obtained, the substrate scope of the transformation was explored. Thus, various substituted methyl phenyldiazoacetates were reacted under the catalysis of Rh_2(*S*-TCPTAD)$_4$ in refluxing dichloromethane. The first goal was to determine and understand the elements that governed the formation of the *β*−lactone product.

The influence of substitution patterns on the phenyl ring was first examined (Scheme 2.6). Control experiments showed that the presence of an *ortho*-substituent was required, since the reaction of methyl 2-diazo-2-(3-methoxyphenyl)acetate **2.30** under the standard conditions did not give the *β*-lactone product (eq. 2.9). An *ortho*-methoxy substituent was not tolerated in the *β*-lactone formation reaction as it resulted in the formation of the dihydrobenzofuran product derived from the insertion into the 2-methoxy group (eq. 2.10).[92a] Similarly, an *ortho*-nitro group was not tolerated either as this reaction tended to undergo oxygen atom transfer (eq. 2.11).[92b] These control experiment indicated that a suitable substituent such as bromo at 2-position was essential to this transformation, and a 5-methoxy group was beneficial.

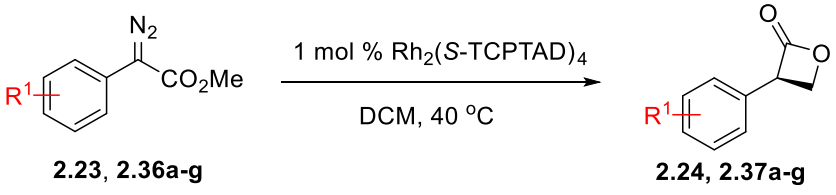


Scheme 2.6 Control experiments

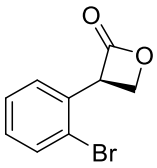
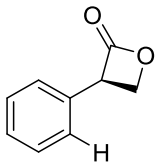
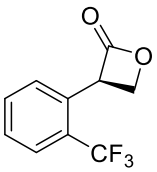
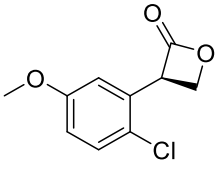
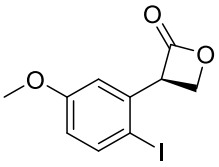
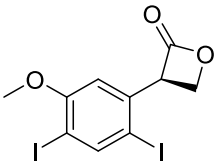
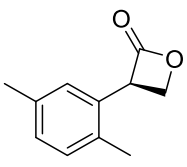
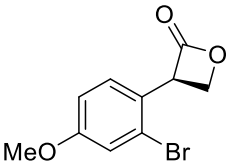
The scope of the intramolecular methyl C−H insertion reaction was then studied using the standard reaction conditions (Rh_2(*S*-TCPTAD)$_4$ in refluxing dichloromethane) (Table 2.5). The influence of substituents on the phenyl ring was first examined. Compared to the standard diazo compound **2.19**, the reaction of diazo compound **2.23** with only an *ortho*-bromo group gave the lactone product **2.24** in decreased yield and enantioselectivity, which again emphasized the importance of substitution patterns on the phenyl ring. The reaction of phenyldiazoacetate **2.36a**, lacking an *ortho*-substituent, was very informative. None of the *β*-lactone **2.37a** was observed, further demonstrating the importance of *ortho*-substitution to enhance intramolecular C−H insertions. These control experiments indicate that a suitable 2-substituent is essential to the success of this transformation, and a 5-methoxy group is beneficial. Consequently, the influence of other *ortho*-substituents was examined. The reaction of diazoacetate **2.36b** with an *ortho*-CF_3 group did not yield the *β*-lactone product as the diazo compound was not efficiently decomposed, presumably due

to lower reactivity in the presence of a strong electron-withdrawing group. With *ortho*-chloro and iodo groups, lactones **2.37c** and **2.37d** were synthesized in good yields and with high levels of enantioselectivity. With an additional iodo group at the *para*-position, compound **2.37e** was obtained in decreased yield and enantioselectivity. When diazo compound **2.36f** with 2,5-dimethyl was used as the substrate, the desired product was obtained, though in low yield (25%) and moderate ee (56%). The position of the methoxy substitution also influenced the results of this transformation as the reaction of substrate **2.36g** with a methoxy group *para* to the diazo functionality gave only trace amount of the desired product. The absolute configurations of *β*-lactone products were tentatively assigned to be the same as **2.22** by analogy.

Table 2.5 Exploration of the substrate scope: primary C−H insertion



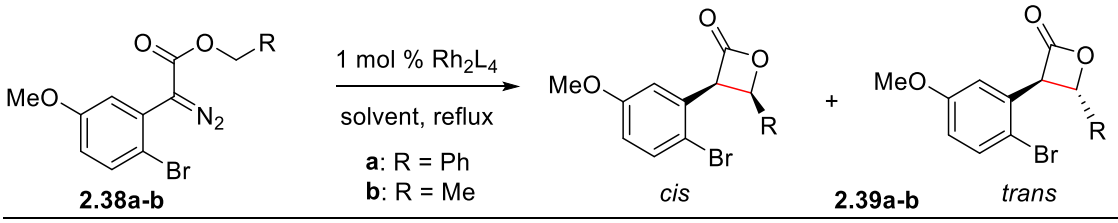
2.23, **2.36a-g** → **2.24, 2.37a-g**

 **2.24** 53% yield, 61% ee	 **2.37a** N.O.[a]	 **2.37b** N.O.[a,b]	 **2.37c** 65% yield, 84% ee
 **2.37d** 67% yield, 92% ee	 **2.37e** 43% yield, 68% ee	 **2.37f** 25% yield, 56% ee[c]	 **2.37g** trace[c]

[a]N.O.: The product was not observed. [b]The diazo compound was not efficiently decomposed.
[c]Rh_2(*S*-TBPTTL)$_4$as the catalyst.

The exploration was then extended to insertions into methylene C−H bonds. Benzyl aryldiazoacetate **2.38a** and ethyl aryldiazoacetate **2.38b** were used for the optimization studies (Table 2.6). In the presence of Rh_2(*S*-TCPTAD)$_4$, the reaction of benzyl ester **2.38a** produced *cis*-**2.39a** in good yield with 96% ee and 10:1 dr (entry 1). Further studies revealed that the diastereoselectivity can be improved by using Rh_2(*S*-TCPTTL)$_4$. With Rh_2(*S*-TCPTTL)$_4$ as the catalyst, *cis*-**2.39a** was obtained in similar yield and enantioselectivity but with increased dr (>19:1) (entry 2). Similar improvement of the diastereoselectivity was observed for the reaction of ethyl aryldiazoacetate **2.38b**. The diastereoselectivity of lactone **2.39** was improved from 4:1 to 8.3:1 in favor of the *trans*-product when the catalyst was changed from Rh_2(*S*-TCPTAD)$_4$ to Rh_2(*S*-TCPTTL)$_4$ (entries 4 and 6). Interestingly, the reaction of the benzyl ester **2.38a** preferentially formed the *cis*-*β*-lactone *cis*-**2.39a**, whereas the reaction of the ethyl ester **2.38b** preferentially formed the *trans*-*β*-lactone *trans*-**2.39b**. The absolute configurations for the major diastereomers *cis*-**2.39a** and *trans*-**2.39b** were unambiguously assigned by X-ray crystallographic analysis (Figure 2.2). The methylene C−H bonds are more reactive than the methyl C−H bond, so hydrocarbon solvents can be used without competing intermolecular insertions into the solvent. Slightly higher enantioselectivity for *trans*-**2.39b** was observed when the reaction of **2.38b** was performed in refluxing pentane (entry 7).

Table 2.6 Exploration of secondary C−H insertion: reaction condition optimization



entry	R^2	Rh_2L_4	solvent	*cis:trans*[a]	yield	ee[b]
1	Ph	Rh_2(*S*-TCPTAD)$_4$	DCM	10:1	73%	96%
2	Ph	Rh_2(*S*-TBPTTL)$_4$	DCM	**>19:1**	60%	96%
3	**Ph**	**Rh_2(*S*-TCPTTL)$_4$**	**DCM**	**>19:1**	**72%**	**97%**
4	Me	Rh_2(*S*-TCPTAD)$_4$	DCM	1:4.0	77%[c]	82%
5	Me	Rh_2(*S*-TBPTTL)$_4$	DCM	1:5.6	65%[c]	74%
6	Me	Rh_2(*S*-TCPTTL)$_4$	DCM	1:8.3	78%[c]	90%
7	Me	**Rh_2(*S*-TCPTTL)$_4$**	***n*-pentane**	**1:8.3**	**79%[c]**	**94%**

[a]Determined by ^{1}H NMR analysis. [b]Refers to that of the major diastereomer. [c]Combined yield.

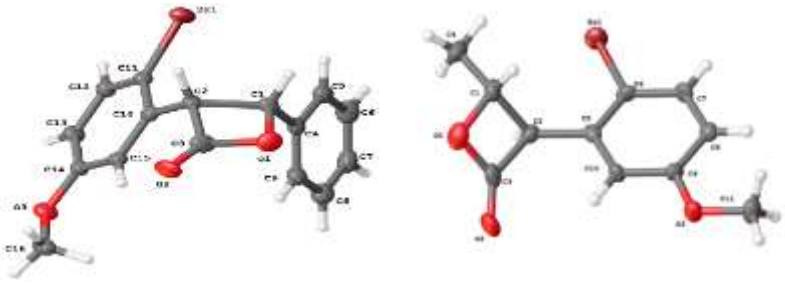
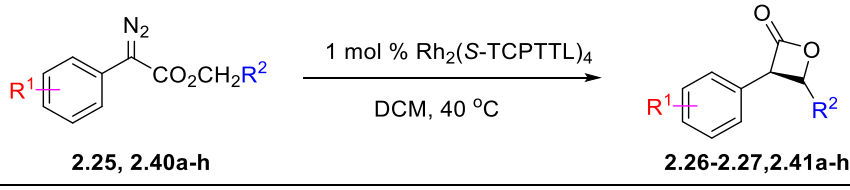


Figure 2.2 X-ray crystal structures for *cis*-**2.39a** and *trans*-**2.39b**

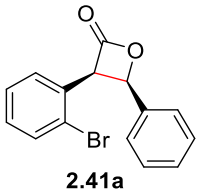
The scope of the methylene C−H insertions was then explored (Table 2.7). The added ability to stabilize positive charge built up during the C−H insertion step renders these substrates more reactive. It was quickly found that for these more reactive substrates, the influence of the *ortho*-substituent was less pronounced in these reactions. The reactions generally proceeded in higher yields and levels of enantioselectivity compared to the primary methyl C−H insertion reactions. Benzyl aryldiazoacetates with an *ortho*-substituent are exceptional substrates, generating the *β*-lactones with >19:1 dr and 97−99% ee. Most notable is the observation that the unsubstituted phenyldiazoacetate **2.40b** is

capable of forming the *β*-lactone **2.41b** in moderate yield with 64% ee. Bromo, ester, and nitro substituent at the *para*-position of the benzyl ester were all tolerated (**2.40e, g, h**). Substrate **2.40f** with an *ortho*-bromo substituent on the benzyl ester was exceptional substrate, and the reaction afford the lactone product **2.41f** in 91% yield with 99% ee. For these more reactive substrates with secondary C−H bonds, an *ortho*-trifluoromethyl substituent was also highly favorable (**2.40c and 2.40d**). For instance, the reaction of benzyl aryldiazoacetae **2.40c**, the *β*−lactone **2.41c** was formed in 60% yield and in 99% ee.

Table 2.7 Exploration of the substrate scope: secondary C−H insertion

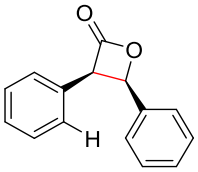


2.25, 2.40a-h → **2.26-2.27,2.41a-h**



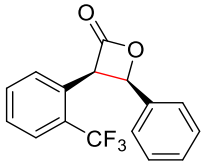
2.41a

63% yield, >19:1 dr
84% ee (*cis*)



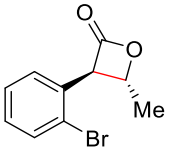
2.41b

51% yield, >19:1 dr
64% ee (*cis*)



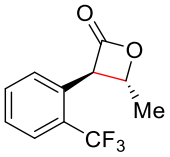
2.41c

60% yield, >19:1 dr
99% ee (*cis*)



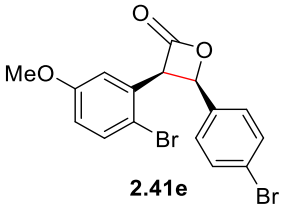
2.26-2.27

80% combined yield[a]
trans:*cis* = 7.9:1, 71% ee (*trans*)



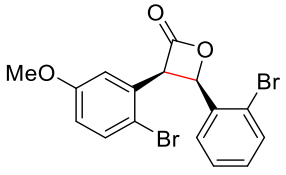
2.41d

83 % combined yield[a]
trans:*cis* = 11.1:1, 95 % ee (*trans*)



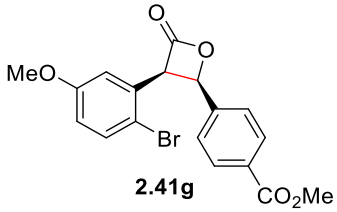
2.41e

73% yield, >19:1 dr, 97% ee (*cis*)



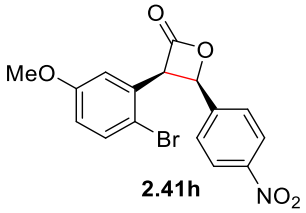
2.41f

91% yield, >19:1 dr, 99% ee (*cis*)



2.41g

78% yield, >19:1 dr, >99% ee (*cis*)

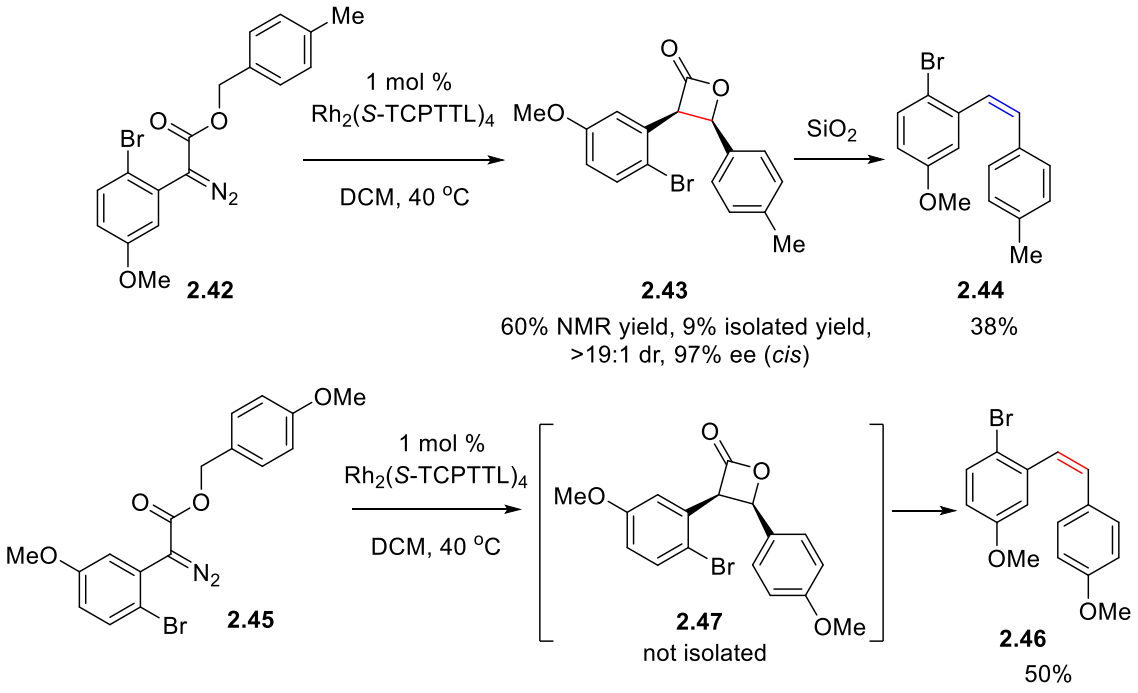


2.41h

71% yield, 16:1 dr, >99% ee (*cis*)

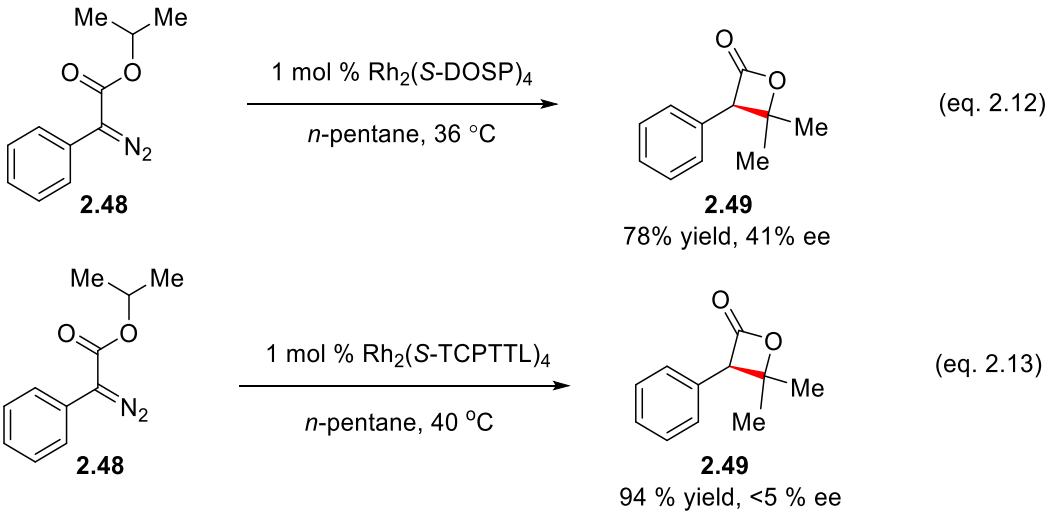
[a] *n*-Pentane was used as the solvent.

The reactions of substrates with electron-donating groups on the benzyl ester gave unexpected results. When a methyl group was placed at the *para*-position of the benzyl ester (**2.42**), the desired C−H insertion product **2.43** was isolated in low yield (60% NMR yield). This is because lactone **2.43** readily underwent CO_2 extrusion to form the olefin **2.44** upon column chromatography in a stereospecific fashion (Scheme 2.7). Similar CO_2 extrusion reactions of *β*-silylethyl aryldiazoacetates for the synthesis of *Z*-olefins were previously reported by our group.[92c] Analysis of the ^{1}H NMR of the crude reaction mixture and chiral HPLC analysis indicated that the diastereoselectivity (>19:1 favoring the *cis* diastereomer) and enantioselectivity (97% ee) of lactone **2.43** were still very high. When the *para*-position of the benzyl ester bears an even stronger electron-donating a methoxy group (**2.45**), the *β*-lactone **2.47** was not observed in the ^{1}H NMR of the crude reaction mixture. Instead, the olefin **2.46** was isolated in 50% yield.



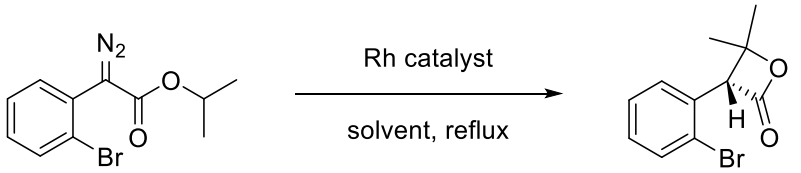
Scheme 2.7 Olefin formation with electron-rich diazo esters

The intramolecular insertion into methine C−H bonds of unsubstituted isopropyl phenyldiazoacetate **2.48** has been previously reported by the Doyle group.[89] The *β*-lactone product **2.49** was obtained in 78% yield with 41% ee when the reaction was performed in refluxing pentane with Rh_2(*S*-DOSP)$_4$ as the catalyst (eq. 2.12). Interestingly, the use of Rh_2(*S*-TCPTTL)$_4$ for this same substrate without 2-bromo substituent gave inferior result compared to Rh_2(*S*-DOSP) catalysis (eq. 2.13). The reaction only gave the *β*-lactone product **2.49** in 94% yield with <5% ee when the reaction was performed in refluxing pentane with Rh_2(*S*-TCPTTL)$_4$ as the catalyst.



However, in our system, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of *ortho*-bromo derivative **2.28** provided the lactone product **2.29** with only 13% ee (Table 2.8). Consistent with the methyl and methylene C−H insertions, higher enantioselectivity (45% ee) was observed when Rh_2(*S*-TCPTTL)$_4$ was used as the catalyst. Consistent with the result with primary and secondary C−H insertion reactions described earlier, by adding a *meta*-methoxy group on the phenyl group (**2.50**) improved the yield and enantioselectivity (Table 2.9). When the reaction was performed in refluxing pentane with Rh_2(*S*-TCPTTL)$_4$ as the catalyst, the lactone product **2.51** was produced in 95% yield and 93% ee.

Table 2.8 Tertiary C−H insertion: reaction condition optimization screening for **2.28**

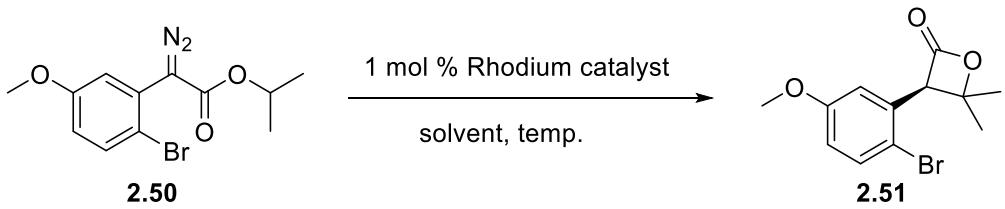


2.28 **2.29**

entry	catalyst	solvent	yield	ee
1[a]	Rh_2(*S*-TCPTTL)$_4$	*n*-pentane	90%	43%
2[a]	Rh_2(*S*-TCPTTL)$_4$	*n*-pentane (0°C)	50%	48%
3[a]	Rh_2(S-DOSP)$_4$	*n*-pentane	89%	13%
4	Rh_2(*S*-TCPTTL)$_4$	DCM	89%	17%

[a] Results obtained by Dr. Hengbin Wang

Table 2.9 Tertiary C−H insertion: reaction condition optimization screening for **2.50**



2.50 **2.51**

entry	catalyst	solvent	temp.	yield[a]	ee
1	Rh_2(*S*-TCPTTL)$_4$	DCM	40 °C	95%	81%
2	Rh_2(*S*-TCPTTL)$_4$	*n*-Pentane	40 °C	95%	93%
3	Rh_2(*S*-DOSP)$_4$	*n*-Pentane	40 °C	93%	17%
4	Rh_2(*S*-TCPTTL)$_4$	*n*-Pentane	0 °C	trace	/

[a] Isolated yield.

2.3 Summary

In conclusion, the introduction of an *ortho*-substituent on aryldiazoacetates interferes with intermolecular reactions and promotes intramolecular C−H insertions to form *β*-lactones. With proper substitution, even methyl aryldiazoacetates are capable substrates in the formation of *β*-lactones. These results suggest that the possibility of competing *β*-

lactone formation needs to be taken into account when designing intermolecular C–H insertion reactions, and less reactive esters need to be designed to maximize the potential of aryldiazoacetates in intermolecular C−H insertion reactions.

Chapter 3 Rhodium(II)-catalyzed asymmetric C–H functionalization of electron-deficient methyl groups

3.1 Introduction

The development of new methods for the chemo-, regio- and stereoselective functionalization of inert C–H bonds has long been a challenge in organic chemistry.[93-95] While the more established and widely utilized C–H functionalization methods either rely on the use of directing groups[96-99] or involve radical reactions,[100-102] carbene-induced C–H insertion reactions have in recent years been shown to be the most versatile method for enantioselective C–H functionalization.[3,5,103-105] Even though intramolecular versions of carbene-induced C–H insertions were developed in the 1980's, intermolecular C–H insertion had not been demonstrated to be synthetically useful until the advent of donor/acceptor rhodium carbenes.

One challenge and direction of carbene C–H insertion chemistry is to expand its scope to substrates that have not been used before to allow for novel disconnection strategies. A possible approach to achieve this would be to use the catalyst/reagent control, which is being developed in the Davies group. To this end, a systematic study was conducted to determine whether crotonate derivatives could be used in rhodium carbene chemistry to achieve an asymmetric synthesis of 1,6-dicarbonyl compounds (Figure 3.1). Expectedly, the successful realization of this hypothesis will provide a novel disconnection strategy for the synthesis of 1,6-dicarbonyl compounds, in a highly asymmetric manner.

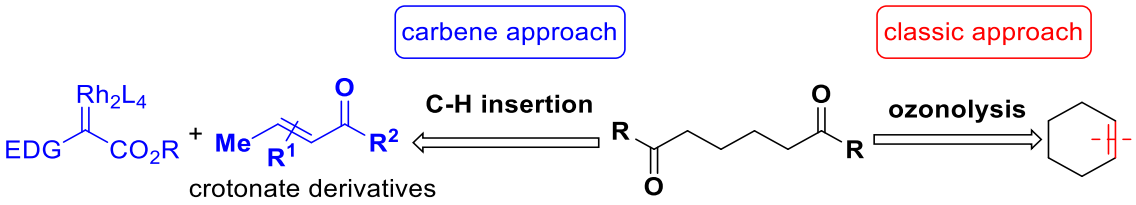
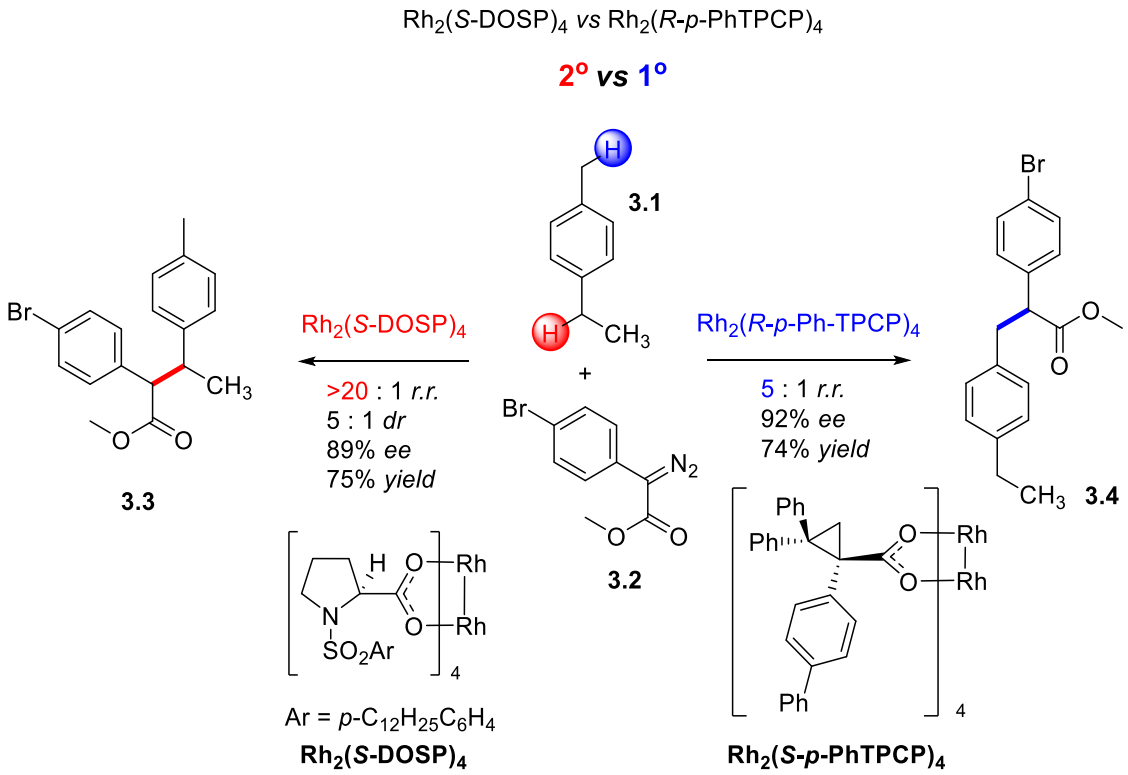


Figure 3.1 Conceptual design of carbene C–H functionalization for 1,6-dicarbonyl synthesis

Donor/acceptor rhodium carbenes behave as highly electrophilic intermediates and undergo C–H functionalization in a concerted asynchronous manner, characterized by positive charge build-up at carbon.[49] Hence, electron rich allylic and benzylic C–H bonds, secondary C–H bonds, or those α to oxygen or nitrogen are activated toward carbene insertion.[5]

Recently, the Davies group is devoted to the development of a toolbox to achieve control of selectivity in C–H functionalization and has achieved promising results. One breakthrough was the development of a new class of dirhodium catalysts ligated with triphenylcyclopropane carboxylate (TPCP).[27] These dirhodium catalyst are sterically demanding and tend to favor functionalization of less crowded C–H bonds. A typical example to illustrate this point is the functionalization of 1-ethyl-4-methylbenzene, which contains competing primary and secondary benzylic C–H bonds (Scheme 3.1).[29] With the classical Rh_2(*S*-DOSP)$_4$ as the catalyst, the more reactive but also more sterically hindered secondary C–H bonds were exclusively functionalized with >20:1 regioisomeric ratio (r.r.), 5:1 diastereomeric ratio, and 89% enantioselectivity for the major diastereomer. In contrast, when a more sterically demanding Rh_2(*R*-*p*-PhTPCP)$_4$ catalyst was utilized, steric factor dominated, and the less reactive but sterically more accessible primary C–H bonds

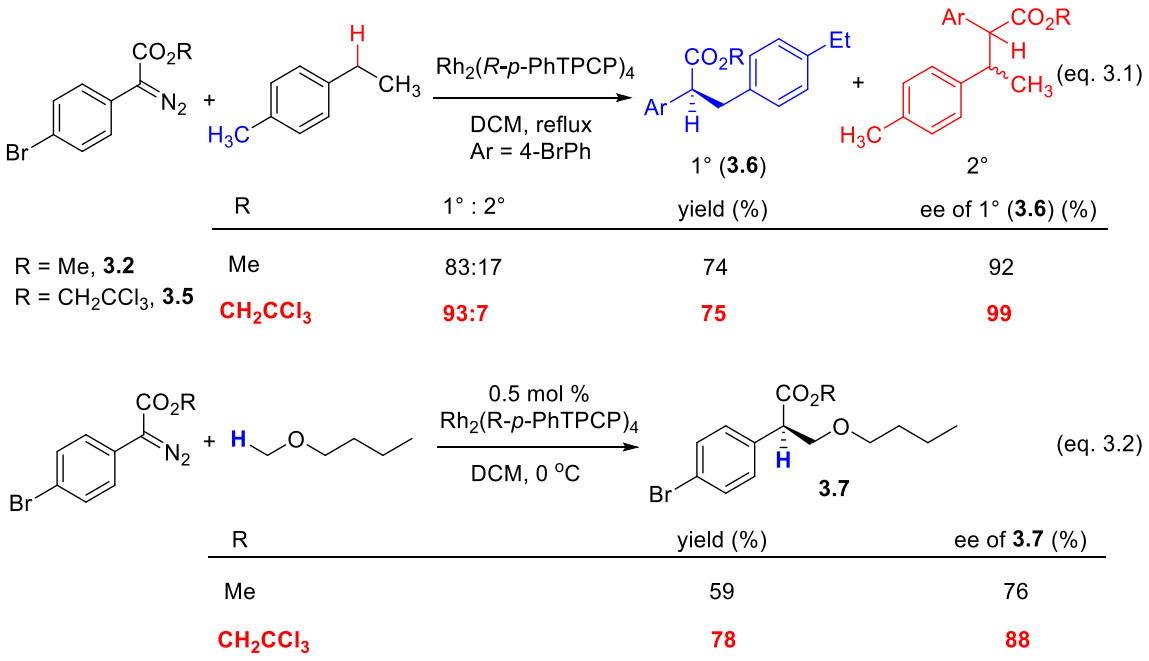
were preferentially functionalized with good regioselectivity (5:1) and high level of enantioselectivity (92%) for the major product **3.4**.



Scheme 3.1 Site selective C–H insertion with Rh_2(*S*-DOSP)$_4$ and Rh_2(*R*-*p*-PhTPCP)$_4$

A further advancement was the design and development of 2,2,2-trichloroethyl aryldiazoacetates as a new class of robust reagents for rhodium carbene chemistry.[53,106] It was observed that the reactions with the 2,2,2-trichloroethyl aryldiazoacetates gave cleaner reactions than their methyl counterparts. It was postulated that the corresponding carbenes are more robust, and therefore are less prone to side reactions, including carbene dimerizations, azine formation, and -lactone formation. The use of 2,2,2-trichloroethyl aryldiazoacetates has been demonstrated to offer several advantages.[53] First of all, compared to their methyl ester analogues, 2,2,2-trichloroethyl aryldiazoacetates can improve both the regioselectivity and enantioselectivity of the C–H functionalization

(Scheme 3.2). Again, this is illustrated by the functionalization of 1-ethyl-4-methylbenzene. Under the same reaction conditions (Rh_2(*R*-*p*-PhTPCP)$_4$ in refluxing dichloromethane), the use of 2,2,2-trichloroethyl aryldiazoacetate instead of its methyl counterpart enhanced the site selectivity for primary C–H bond and the product **3.6** was obtained in improved enantioselectivity (eq. 3.1). Yet another example is the functionalization of methyl butyl ether. By using Rh_2(*R*-*p*-PhTPCP)$_4$ as the catalyst, the primary C–H bond was preferentially functionalized, and both the yield and the enantioselectivity of the transformation were significantly improved (eq. 3.2).



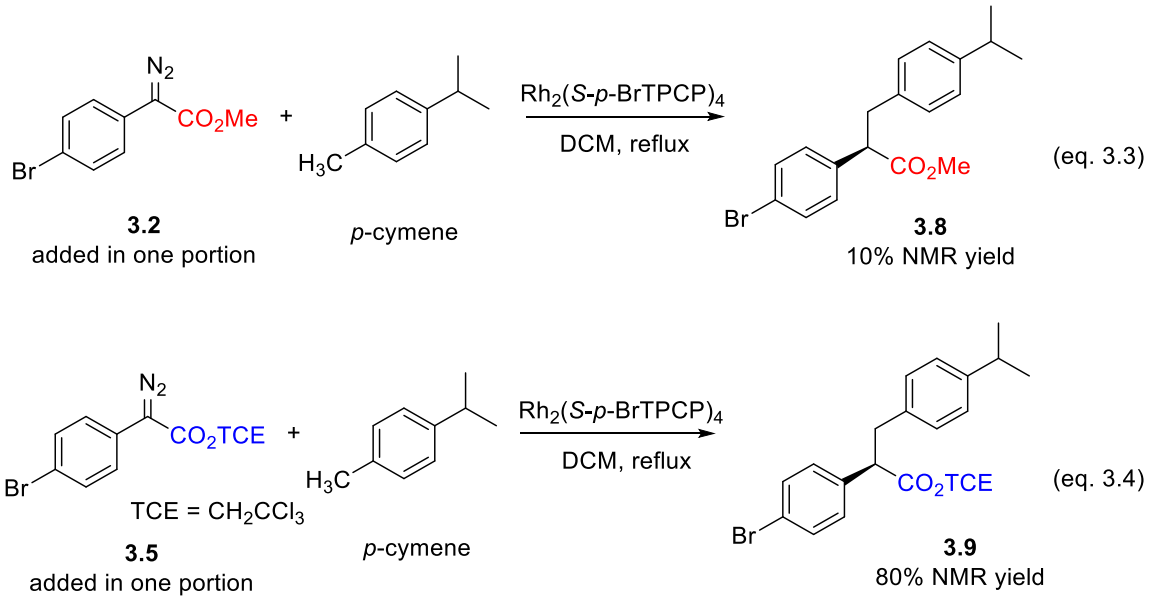
R	1° : 2°	yield (%)	ee of 1° (**3.6**) (%)
R = Me, **3.2** R = CH_2CCl_3, **3.5**			
Me	83:17	74	92
CH_2CCl_3	**93:7**	**75**	**99**

R	yield (%)	ee of **3.7** (%)
Me	59	76
CH_2CCl_3	**78**	**88**

Scheme 3.2 Control of regioselective C–H functionalization with TCE diazoacetates

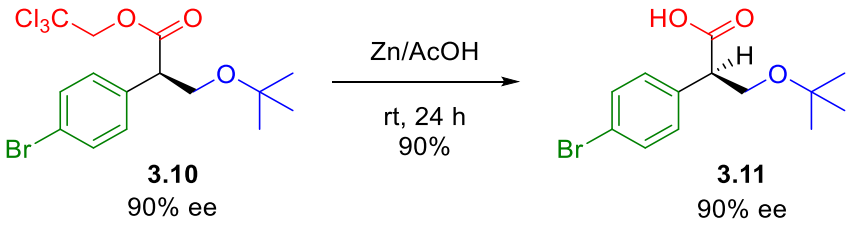
Another advantage of 2,2,2-trichloroethyl aryldiazoacetate reagents is that unlike conventional alkyl aryldiazoacetates, these reagents can be added in one portion.[53] In rhodium carbene chemistry, diazo compounds are often added slowly with a syringe pump to the catalyst/substrate solution. This way a low concentration of diazo compounds is maintained to safely prevent carbene dimerizations. Control reactions of direct one portion

addition of both methyl and 2,2,2-trichloroethyl diazo compound supported the superiority of the trichloroethyl diazo over the methyl diazo compound (Scheme 3.3). Under the same reaction conditions (Rh_2(*S*-*p*-PhTPCP)$_4$, refluxing dichlorormethane), the reaction of methyl aryldiazoacetate **3.2** with *p*-cymene resulted in a low 10% NMR yield of the C–H insertion product and carbene dimerizations dominated (eq. 3.3). In contrast, when this reaction was performed with diazo compound **3.5**, the desired product was formed in 80% yield as determined by NMR (eq. 3.4). These results clearly demonstrate the improved efficiency of the trichloroethyl diazoacetate over the methyl diazoacetate due to a lower propensity for dimerization.



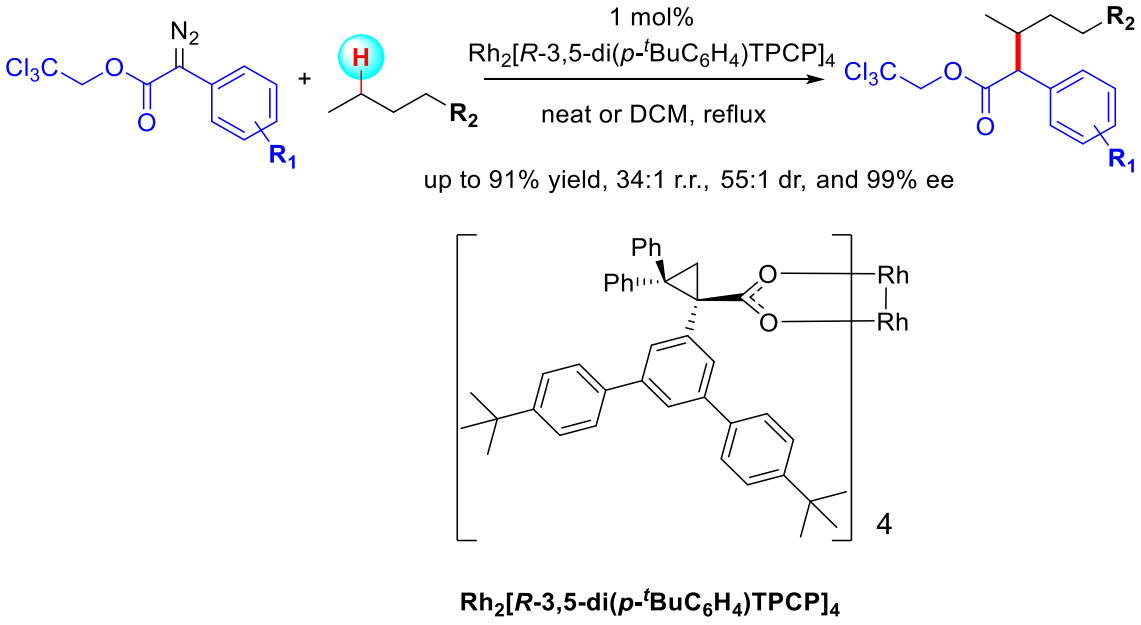
Scheme 3.3 Comparing Me and TCE diazo compounds in one portion addition

A further advantage of the trichloroethyl ester is its ease of removal under mild conditions.[53] This can be demonstrated in the cleavage of the *tert*-butyl ether in the C–H functionalization product **3.10**. Treatment of **3.10** with Zn/AcOH at room temperature for 24 h afforded the carboxylic acid **3.11** in 90% yield with complete retention of the enantioselectivity (eq. 3.5).



(eq. 3.5)

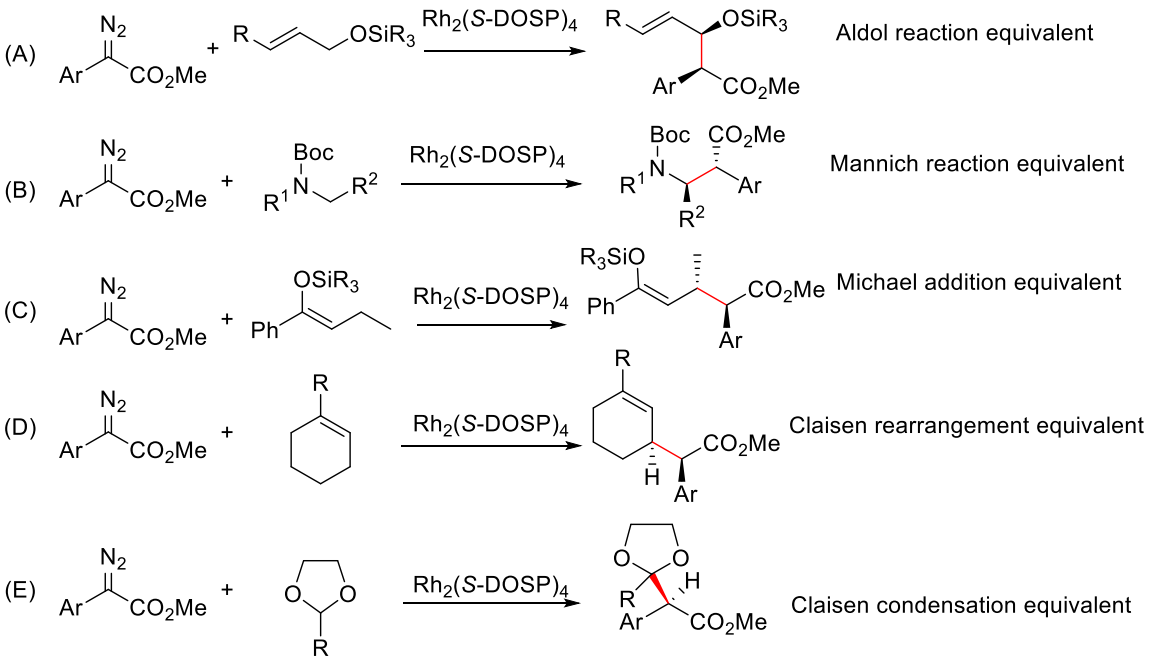
Furthermore, the combination of dirhodium triarylcyclopropane carboxylate catalysts and the trichloroethyl esters of donor/acceptor carbenes enables the functionalization of substrates that were considered to be too unreactive for effective C–H functionalization. A breakthrough was made by the Davies group that catalyst/reagent combination made possible the regio- and stereoselective functionalization of simple *n*-alkanes at C2 by using a trichloroethyl diazoacetates and a newly designed dirhodium triarylcyclopropane carboxylate catalyst Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$.[107]



Scheme 3.4 Selective C–H functionalization of simple *n*-alkanes at C2

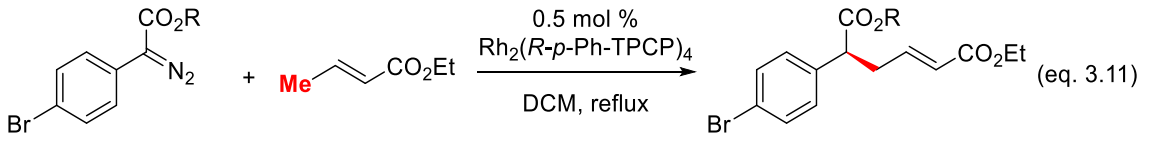
The advances of site selective C–H functionalization reactions with rhodium(II)-carbenes allow one to develop complementary approaches to classic synthetic transformations (Scheme 3.5). For example, *β*-hydroxy esters, products of classic aldol

reaction, can be thought of as arising from C–H insertion into substrates containing C–H bonds α to oxygen.[108-110] Moreover, β-amino esters, which are classically prepared by the Mannich reaction, can arise from carbene insertion into C–H bonds α to nitrogen.[111-113] Allylic C−H functionalization of silyl vinyl ethers generates protected 1,5-dicarbonyl compounds, and this reaction can be considered as a Michael addition reaction surrogate.[114] β,γ–Unsaturated esters, which are usually prepared *via* the Claisen rearrangement, can be accessed via allylic C–H insertion reactions.[115] The C–H functionalization reaction of tertiary C–H bonds of dioxalanes form protected β-keto esters in high chemo- and stereoselectivity,[116] and this transformation can be considered as a surrogate for the Claisen condensation reaction. Furthermore, the 'carbene insertion Claisen reaction' is beneficial because stereo-control is challenging in the standard Claisen condensation due to epimerization of the unprotected β-keto esters under basic conditions. All of these examples demonstrate that carbene C–H insertion reaction can be used as surrogates for classic strategic reactions, often in a highly stereo-selective manner. Thus these methods begin to change the way one thinks of constructing functional arrays.



Scheme 3.5 Representative carbene C–H insertions as surrogates for classic reactions

Studies initiated by a former graduate student Dr. David M. Guptill in the Davies group successfully showed the functionalization of ethyl crotonate **3.12** by using 2,2,2-trichloroethyl aryldiazoacetate with Rh_2(*R*-*p*-PhTPCP)$_4$ as the catalysis (eq. 3.11).[117] Brief optimization of the reaction conditions with regards to the choice of aryldiazacetates, the relative concentration, and addition time were conducted. Under Dr. David M. Guptill's basic conditions, the C–H insertion product was obtained in 86% NMR yield with 95% ee.



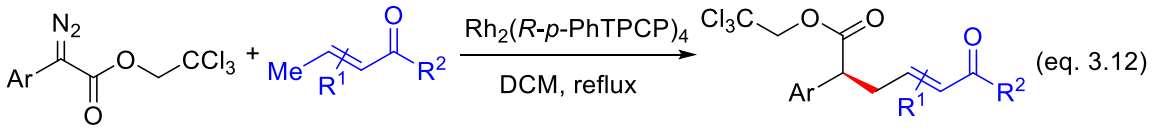
R= CH_2CCl_3 (TCE), **3.5**
R = Me, **3.2**

3.12
2 equiv.

R= TCE, **3.13**, 86% NMR yield, 95% ee
R = Me, **3.14**, 15% NMR yield

These studies provided proof of principle that the combination of Rh_2(*R*-*p*-PhTPCP)$_4$ and 2,2,2-trichloroethyl aryldiazoacetates could open up the possibility of the functionalization of relatively electron-deficient substrates. This result prompted us to fully

explore their potential to functionalize challenging substrates such as ethyl crotonate and its analogues. Expectedly, this transformation can provide an alternative disconnection strategy for the asymmetric construction of 1,6-dicarbonyls (eq. 3.12). To further understand the controlling factors, substrate scope and utilities of the transformation, we performed systematic studies.



(eq. 3.12)

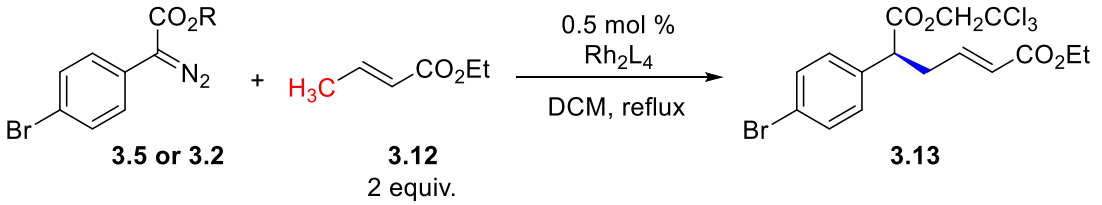
-1,6-dicarbonyl formation

-primary methyl functionalization

3.2 Results and discussion

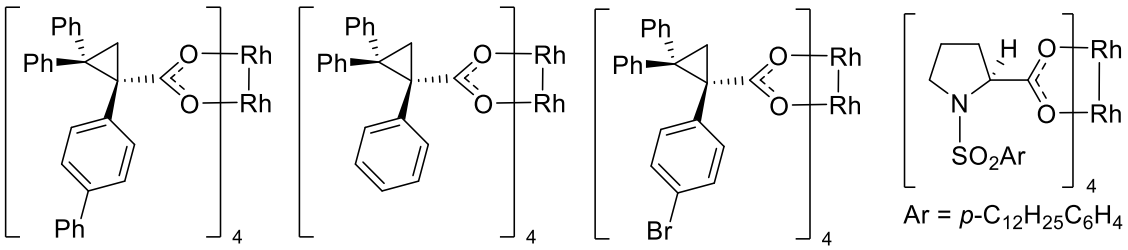
With the results from Dr. David M. Guptill that 2,2,2-trichloroethyl aryldiazoacetate was much superior to its methyl counterpart, further optimization and exploration were initiated by comparing several related catalysts in the reaction of the 2,2,2-trichloroethyl ester **3.5** with ethyl crotonate (Table 3.1). The related catalysts, Rh_2(*R*-TPCP)$_4$ and Rh_2(*R*-*p*-BrTPCP)$_4$ gave similar but slightly inferior results compared to Rh_2(*R*-*p*-PhTPCP)$_4$ (entries 1-3). Further comparison of the classical catalyst Rh_2(*S*-DOSP)$_4$ indicated that this catalyst was inferior in this challenging reaction (entry 4), even when methyl aryldiazoacetate or trichloroethyl aryldiazoacetate was used (entry 5).

Table 3.1 Optimization studies of the reaction between aryldiazoacetate and ethyl crotonate



entry	R	Rh_2L_4	yield (%)	ee (%)
1	**TCE**	**Rh_2(*R*-*p*-PhTPCP)$_4$**	**74**	**95**
2	TCE	Rh_2(*R*-TPCP)$_4$	71	89
3	TCE	Rh_2(*R*-*p*-BrTPCP)$_4$	65	91
4	TCE	Rh_2(*S*-DOSP)$_4$	12[a]	/
5	Me	Rh_2(*S*-DOSP)$_4$	-[b]	/

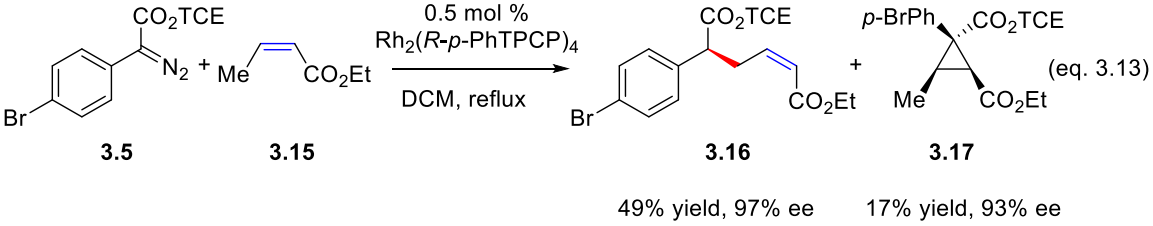
[a]Yield determined by ^{1}H NMR using trichloroethylene as the internal standard.[b]The product was not observed.



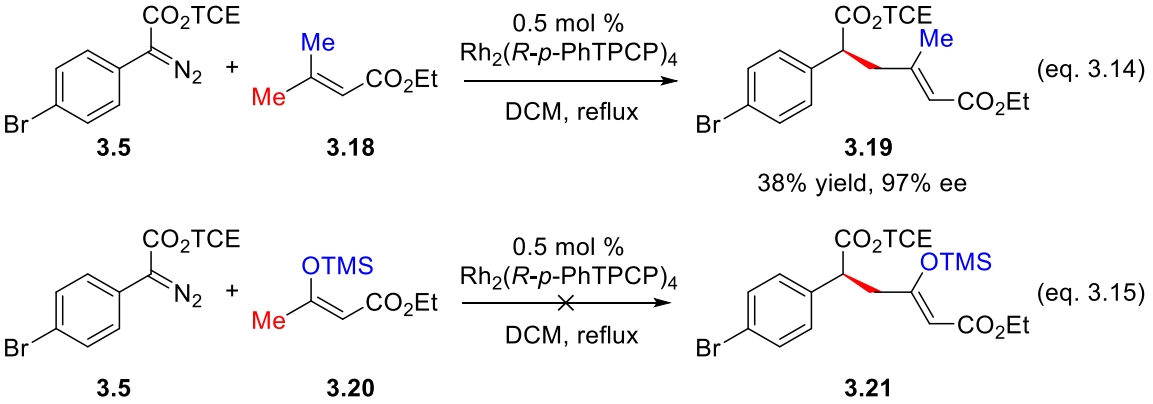
Rh_2(*R*-*p*-PhTPCP)$_4$ Rh_2(*R*-TPCP)$_4$ Rh_2(*R*-*p*-BrTPCP)$_4$ Rh_2(*S*-DOSP)$_4$

Previous studies demonstrated that rhodium carbene-induced C–H functionalization reactions at electron rich allylic positions are sensitive to steric effects.[5] To further examine this effectin this system, differentially substituted crotonate derivatives with varying steric environment and alkene geometry were tested. Compared to the reaction with standard substrate *E*-crotonate **3.12**, the reaction of ethyl (*Z*)-but-2-enoate **3.15** with *Z*-geometry at the olefin double bond gave the C–H insertion product **3.16** as the *Z* isomer, in 49% yield and 97% ee. Along with the isolation of the desired product, cyclopropanation by-product **3.17** was also formed, in 17% yield with 93% ee, and its stereochemistry was assigned by

analogy to that of products in a similar reaction[33b] (eq. 3.13). This result is consistent with previous studies and further showed that the delicate balance between C–H functionalization and cyclopropanation is dependent on alkene geometry.[5]

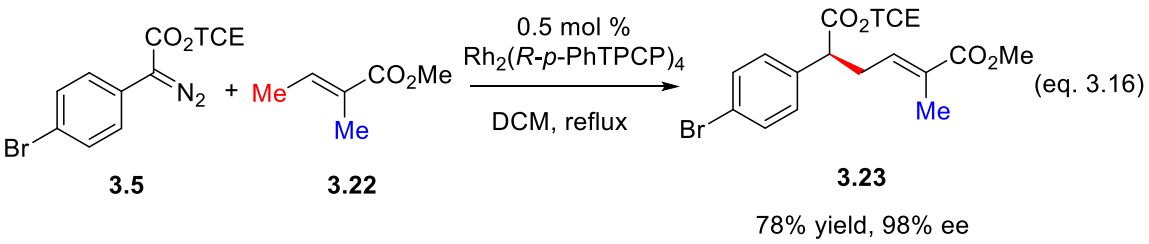


For substrate ethyl 3-methylbut-2-enoate **3.18** that contains two competing primary C–H bonds at the terminal position, the more accessible methyl group was functionalized preferentially to afford the product **3.19** with a high level of enantioselectivity (97%). Compared the standard reaction with ethyl crotonate **3.12**, the yield for this reaction was lower (38%), presumably because of steric interference between the rhodium carbene and the additional methyl group on the substrate (eq. 3.14). This point was further reinforced by the test of substrate **3.20**, which contains a bulkier siloxy group (eq. 3.15). The reaction under the standard conditions did not yield any of the desired C–H insertion product, and carbene dimerizations dominated.



Methyl (*E*)-2-methylbut-2-enoate **3.22** is another substrate that contains two competing primary methyl groups. When this substrate was used, the more accessible primary methyl

group was again preferentially functionalized to form **3.23** in good yield and high level of enantioselectivity (78% yield, 98% ee) (eq. 3.16). The improved yield can be rationalized by the electron-donation from the additional methyl group.



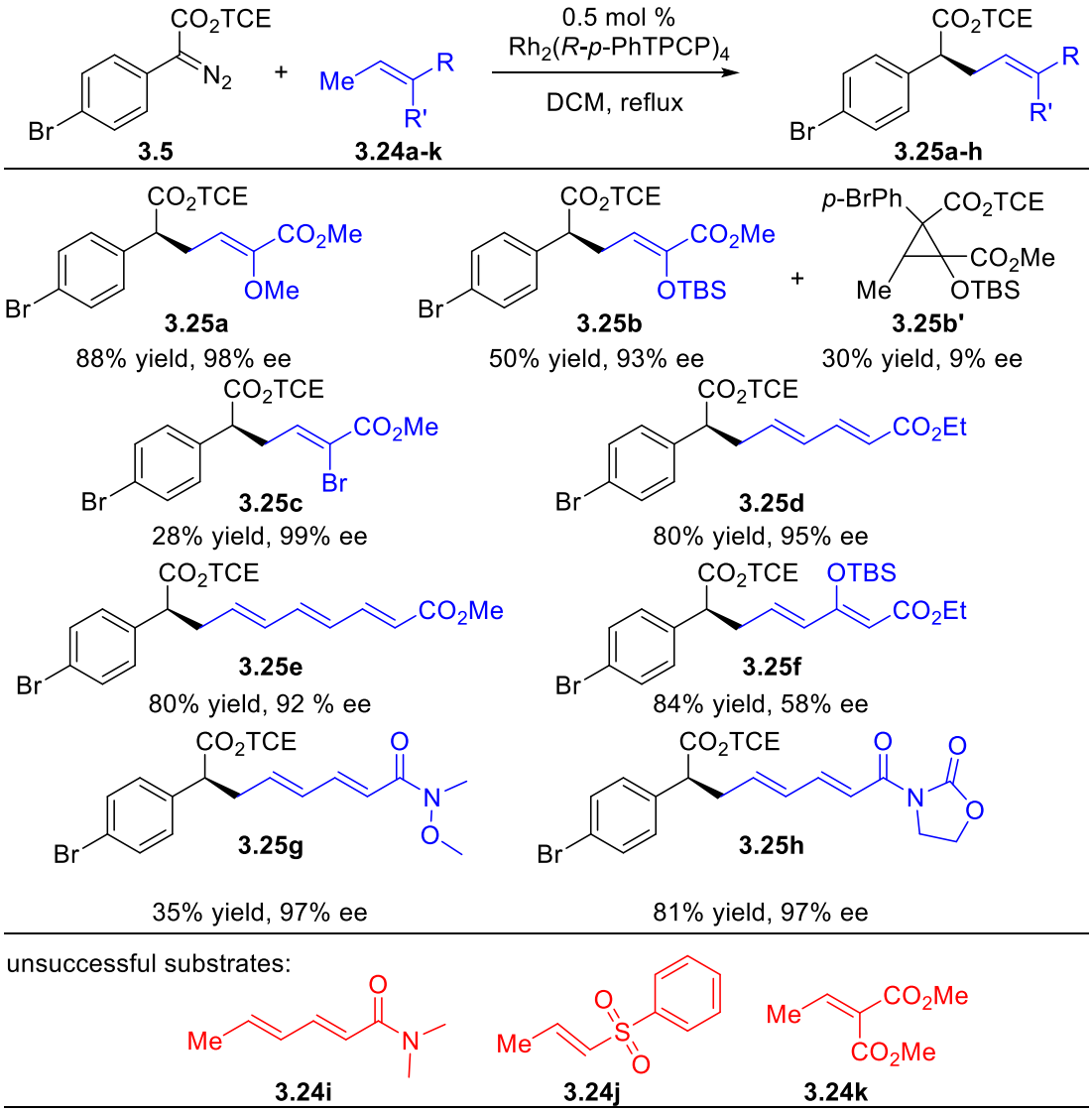
3.5 **3.22** **3.23**

78% yield, 98% ee

The scope of the reaction was then explored with more elaborate substrates with the idea of probing the limit of electron-deficiency in mind (Table 3.2). Different crotonate derivatives with various internal substituents were competent substrates, though to varying degrees. The reactions afforded **3.25a-c** with high levels of enantioselectivity (93-99% ee), but the overall yield was greatly influenced by the nature of the internal substituent. Similar to the methyl derivative **3.22** (eq. 3.16), a methoxy group was well tolerated and **3.25a** was efficiently formed (88%). However, in the case of the siloxy derivative **3.24b**, the C−H functionalization product **3.25b** was isolated in a lower 50% yield, due to the occurrence of a competing cyclopropanation product (**3.25b'**, isolated in 30% yield with 9% ee). For the bromo derivative **3.25c**, the yield of the C–H functionalization product was low, presumably because the methyl site is no longer sufficiently reactive. The reaction was compatible with more highly conjugated substrates, as illustrated by the formation of **3.25d-h**. Again the levels of enantioselectivity were high (92-97% ee), except for the case of the 3-siloxy derivative **3.25f** (58% ee). The reaction is also compatible with other electron-withdrawing groups such as the Weinreb amide (**3.24g**) and oxazolidinone (**3.24h**) though the isolated yield of the Weinreb amide product **3.25g** was relatively low (35%). So far, the transformation using the standard reaction conditions is limited to the indicated

unsaturated carbonyl systems. An unsaturated *N*,*N*-dimethyl amide or phenylsulfone did not give the desired product. A substrate that contained an additional electron-withdrawing group was not a competent substrate in this transformation, presumably due to the highly reduced reactivity of the methyl groups.

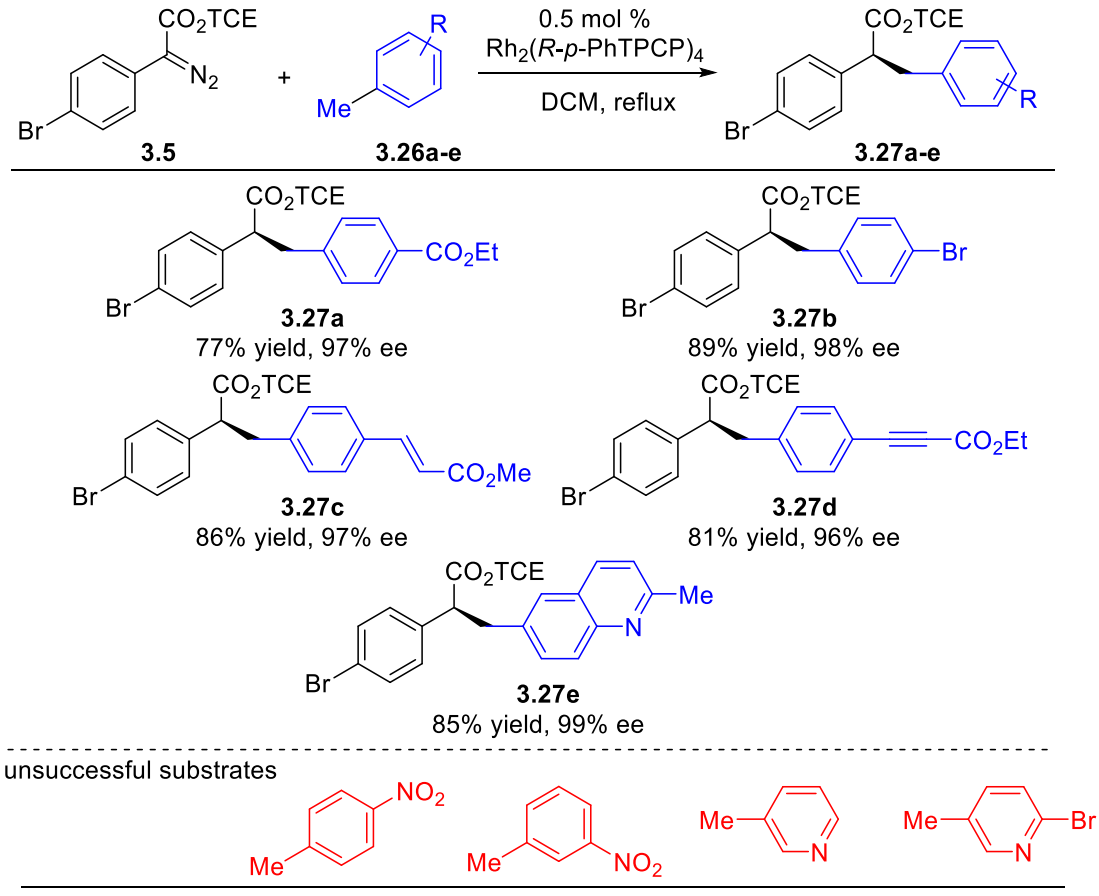
Table 3.2 C–H functionalization of electron-deficient methyl groups



Substrates containing electron-deficient benzylic methyl groups (**13**) were also evaluated in order to further explore the influence of electron withdrawing groups on C–H

insertion reactions (Table 3.3). Toluene derivatives with *p*-ethoxycarbonyl, *p*-bromo, *p*-methoxycarboalkenyl and *p*-ethoxycarboalkynyl groups were all good substrates, undergoing C–H functionalization in high yields (77-89%) and with high levels of enantioselectivity (96-98% ee). The functionalization of 2,6-dimethylquinoline **3.26e** occurred exclusively at the relatively more electron-rich methyl site and the product **3.26e** was obtained in excellent yield and ee. Exceptions were nitro-substituted toluene and pyridine derivatives, whose reactions failed to give rise to the desired product, presumably because they are too electron deficient.

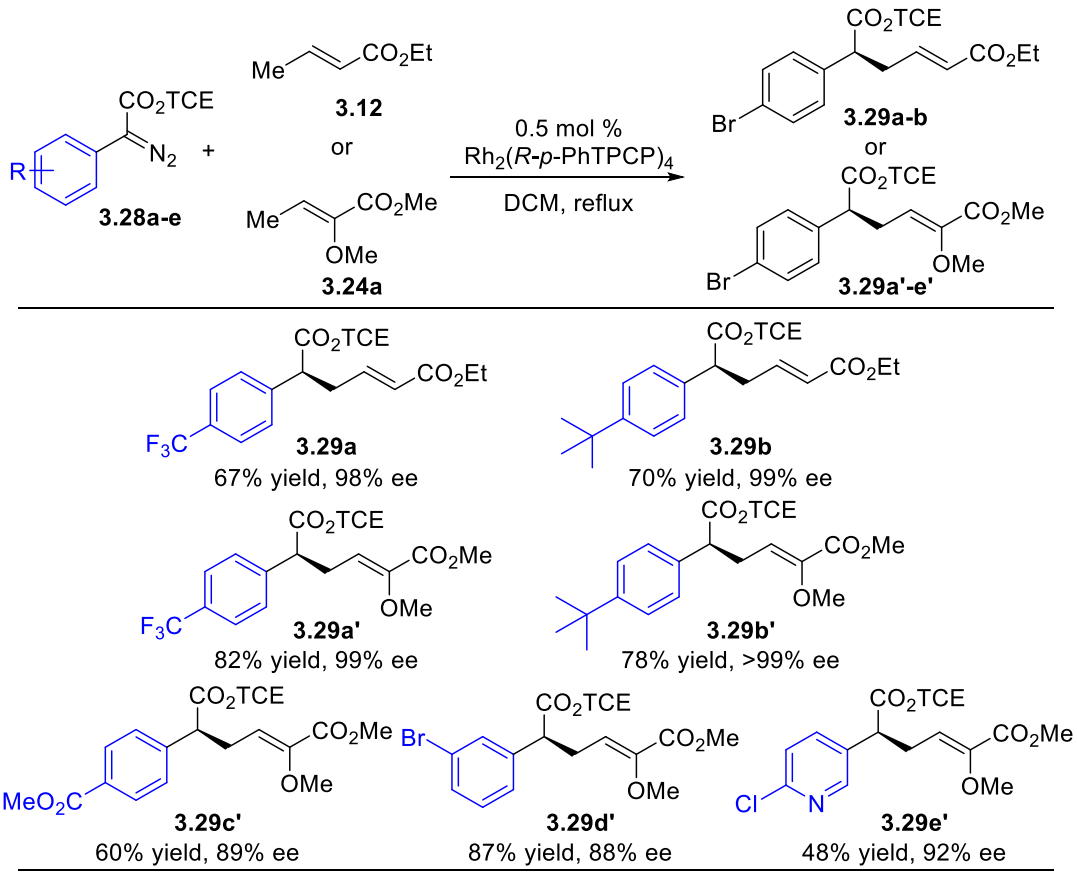
Table 3.3 Functionalization of electron-deficient aromatic methyl groups



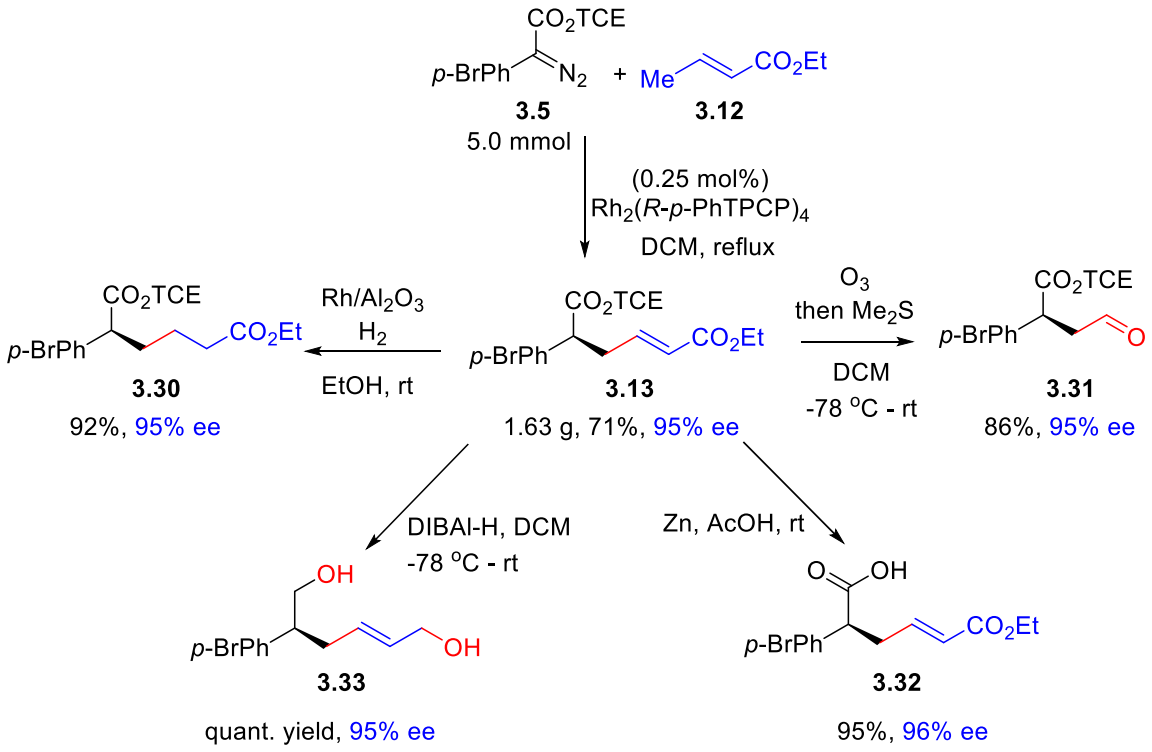
The reaction is applicable to a variety of aryldiazoacetates as illustrated in Table 3.4. When TCE arydiazoacetates bearing *p*-^{t}Bu or *p*-CF_3 were tested, again, **3.24a** turned out to

be a better behaving substrate compared to ethyl crotonate **3.12** (**3.29a**, **b vs 3.29a', b'**). To fully explore the potential of the scope of arydiazoacetates, substrate **3.24a** was used to react with a variety of other diazo acetates. Both electron-rich and electron-deficient *para*-substituents on the phenyl ring were compatible, generating **3.29a'-c'** in 60-82% yield and high levels of enantioselectivity (89->99% ee). The *meta*-bromo substituent was also tolerated and **3.29d'** was formed in 87% yield and 88% ee. TCE aryldiazoacetate bearing an *ortho*-bromo on the phenyl ring gave only trace amount of the product, presumably because it is sterically more hindered, and interferes with intermolecular C-H insertion. Notably, the C–H functionalization reaction could be carried out with the pyridyl derivative **3.28e** to form **3.29e'** in 48% yield and 92% ee.

Table 3.4 Scope of TCE aryldiazoacetates



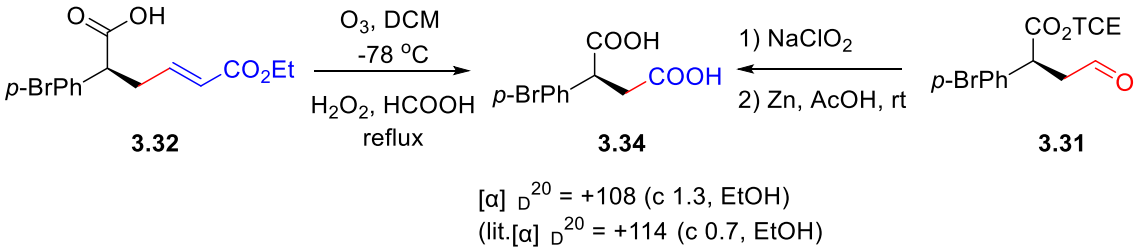
The utility of the C–H functionalization reaction was demonstrated by the synthesis of **3.13** on a gram scale with a reduced catalyst loading of 0.25 mol % (Scheme 3.6). The product **3.13** is quite versatile and was easily manipulated in a variety of ways to give products with oxygen functionality in a 1,6- or 1,4-relationship. Selective hydrogenation of **3.13** generated the saturated product **3.30** in 92% yield. Ozonolysis of **3.13** generated the aldehyde **3.31** in 86% yield. The TCE ester could be selectively deprotected with zinc in acetic acid at room temperature to form the acid **3.32** in 95% yield, or the two ester groups could be reduced to the diol **3.33** in essentially quantitative yield.



Scheme 3.6 Synthetic utilities of the C–H functionalization

One of the challenges associated this project was the determination of the absolute configuration of the C–H functionalization products. All attempts at obtained crystalline material of the methyl ester products were unsuccessful. Ozonolysis of **3.32** followed by oxidative work-up, or Pinnick-Lindgren-Kraus oxidation of **3.31** followed by carboxylic

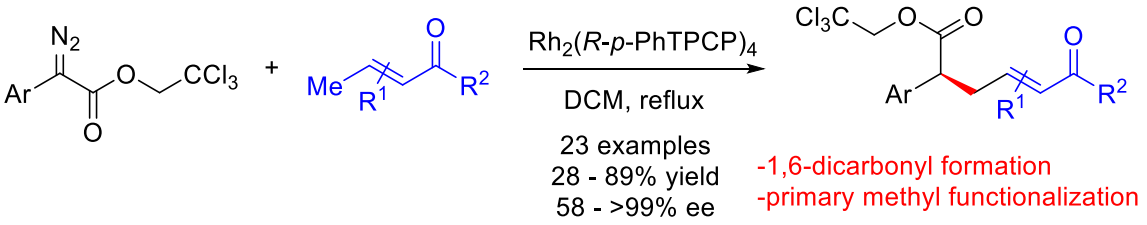
acid deprotection generated the known succinic acid derivative **3.34**. This compound was used to determine the absolute configuration of **3.34** by comparison of its optical rotation with the reported value (Scheme 3.7).[118]



Scheme 3.7 Determination of the absolute configuration

3.3 Summary

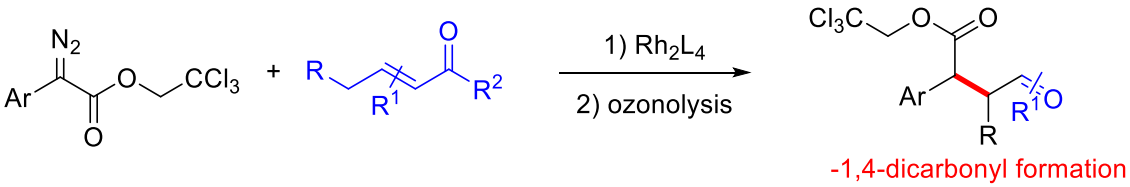
In conclusion, the enantioselective C–H functionalization of relatively electron-deficient methyl sites was achieved by using the combination of 2,2,2-trichloroethyl (TCE) aryldiazoacetates and the sterically demanding dirhodium triarylcyclopropane carboxylate catalyst (Scheme 3.8). The substrate scope of the transformation was relatively broad, and various 1,6-dicarbonyl derivatives were readily furnished. These studies further demonstrate that rhodium carbene induced C–H insertion reactions can be used as key disconnection strategies for some classic reactions.



Scheme 3.8 Summary for the C–H functionalization reaction of electron-deficient methyl groups

3.4 Future directions

One of the potential direction of the project is based on the illustration that upon ozololysis of the product, 1,4-dicarbonyl compounds could be synthesized (Scheme 3.9). This can provide possibilities of developing carbene version of Stetter reaction for 1,4-dicarbonyl compound synthesis. One could imagine that with more elaborate substrates, differently substituted 1,4-dicarbonyl compound with defined stereochemistry can be synthesized. Systematic optimization will be necessary since secondary and tertiary C–H bonds would need to be used to maximize the potential applications of the proposed transformation.



Scheme 3.9 Future directions: rhodium carbene approach for 1,4-dicarbonyl compound synthesis

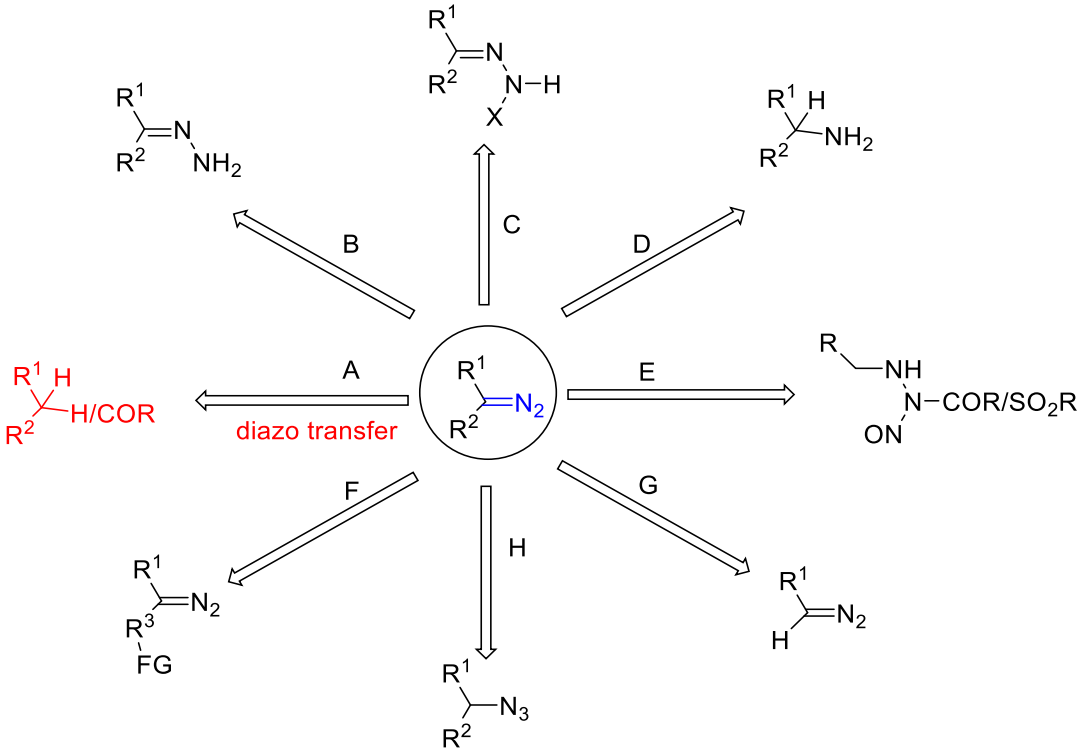
Chapter 4 Synthesis of 2,2,2-trichloroethyl aryl- and vinyldiazoacetates by palladium-catalyzed cross-coupling reactions

4.1 Introduction

α-Diazocarbonyls are widely recognized as useful building blocks and versatile reagents in organic chemistry.[3,118,119] One useful and important application of diazo compounds is their utility in carbene chemistry. Under photochemical or thermal conditions, diazo compounds can undergo extrusion of dinitrogen to provide facile access to free carbenes. However, due to their high reactivity, the reactions of free carbenes often lack selectivity.[120] Transition metal-catalyzed diazo decomposition gives rise to highly reactive, yet stabilized, transient metallocarbene complexes, which can undergo a variety of valuable transformations that often feature an extraordinary level of chemo-, regio-, and stereoselectivity.[5,121] This has resulted in major advances in metallocarbene chemistry.[5]

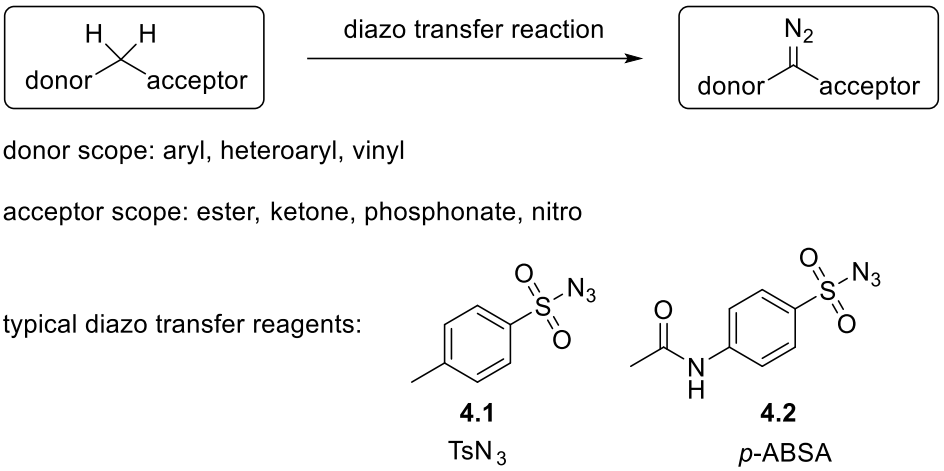
To date, several methods have been developed for the synthesis of diazo compounds (Scheme 4.1).[3,122-124] The methods most often used are: A) diazo-group transfer onto activated methylene or methane compounds; B) dehydrogenation of hydrazones, C) base promoted elimination of sulfonylhyrazones; D) diazotization of α-acceptor-substituted primary aliphatic amines; E) alkaline cleavage of *N*-alkyl-*N*-nitroso sulfonamides, carboxamides, and ureas; F) modification of substituents on existing diazo compound; G) substitution an diazomethyl compounds; H) phosphine-mediated conversion of azides into

diazo compounds. Most of these methods focus on the introduction of the diazo functionality or conversion of other functional groups to the diazo moiety (Scheme 4.1).



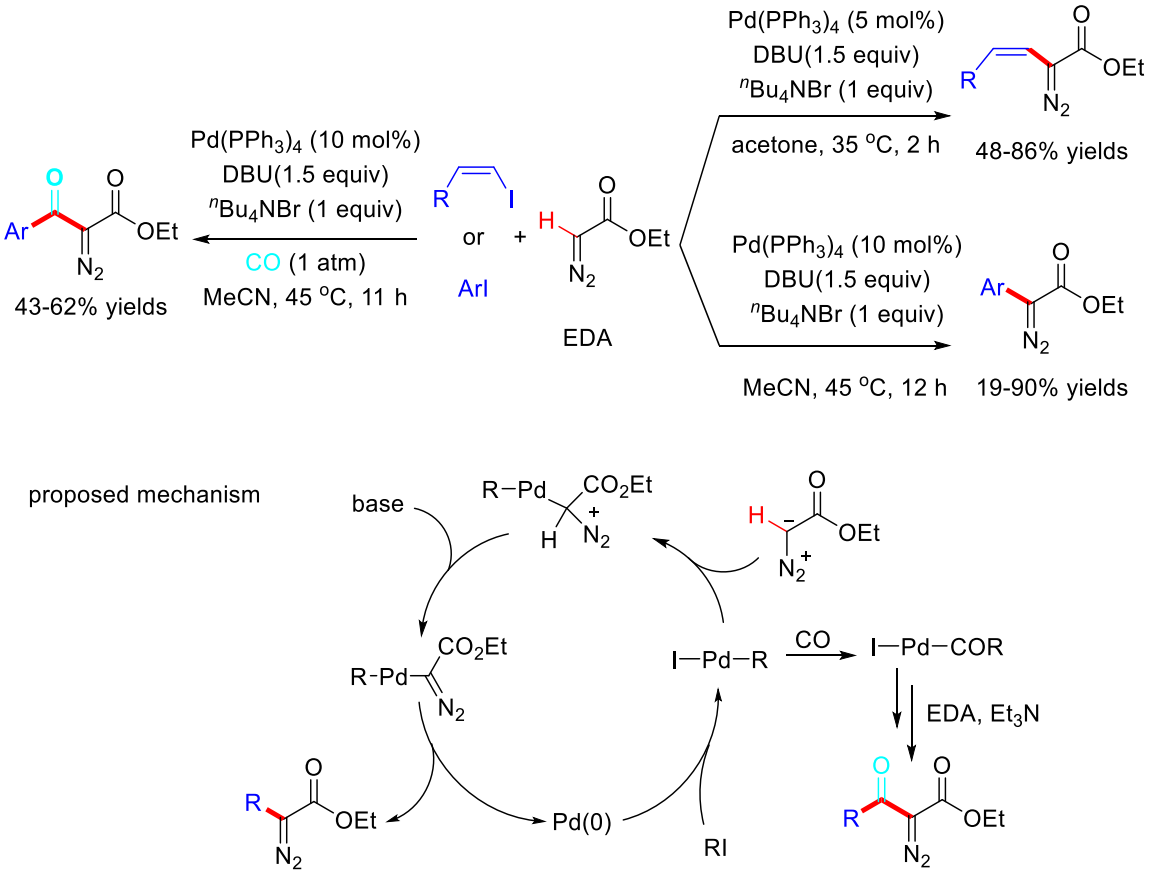
Scheme 4.1 Major synthetic methods for the generation of diazo compounds

The most commonly used method to access donor/acceptor diazo compounds, however, has been by means of the Regitz diazo transfer reaction (Scheme 4.2).[3,123] This method utilizes substrates that contain suitable acidic protons and uses sulfonyl azides as the diazo transfer reagents. Initially, tosyl azide (**4.1**) was used as the diazo transfer regent. Later, however, the *p*-acetamidobenzenesulfonyl azide (**4.2**)[125] was developed by the Davies group as a safer reagent for diazo transfer reactions and has been used as a routine diazo transfer reagent ever since.



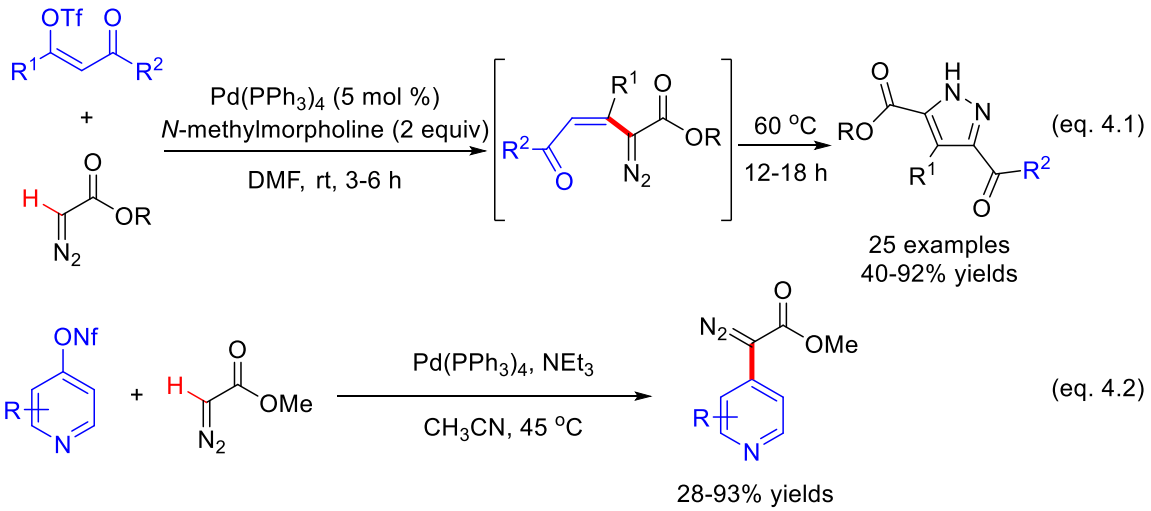
Scheme 4.2 Regitz diazo transfer reaction for diazo compound synthesis

Recently, cross-coupling methodology was developed as an alternative to the Regitz diazo transfer reaction for the synthesis of aryldiazoacetates. These methods use simple ethyl diazoacetate (EDA) and can be considered as formal transition-metal-catalyzed C−H functionalization of EDA. The first example of this approach was reported by the Wang group in 2007 (Scheme 4.3).[126] In their report, Wang and coworkers showed that ethyl diazoacetate (EDA) can undergo efficient palladium-catalyzed cross-coupling reactions with aryl or vinyl iodides. Moreover, under an atmosphere of carbon monoxide (CO), carbonylation occurred prior to the cross-coupling reaction to afford *β*-keto-*α*-diazoesters. One limitation of this method is that the vinyl iodide was limited to cross-coupling partners bearing electron-withdrawing groups EDA was the only diazo carbonyl substrate reported.



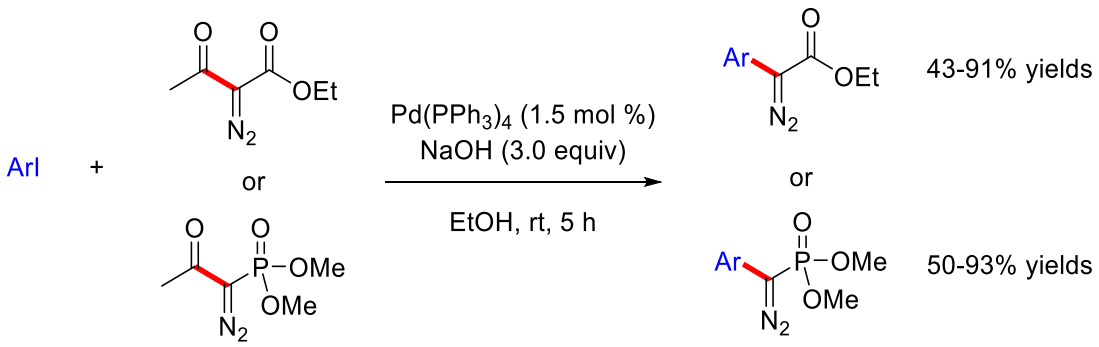
Scheme 4.3 Wang's work on the synthesis of diazoacetates by cross-coupling

Following the disclosure of Wang's seminal work, the coupling partners were subsequently extended to triflates and pyrid-4-yl nonaflates (Scheme 4.4). The Frantz group reported a tandem catalytic cross-coupling/electrocyclization of enol triflates and diazoacetates for the synthesis of 3,4,5-trisubstituted pyrazoles (eq. 4.1).[127] Additionally, the Reissig group developed a palladium-catalyzed coupling of pyrid-4-yl nonaflates as the coupling partners with diazoacetates to afford a fairly broad range of pyrid-4-yl-substituted methyl diazoacetates in generally high yields (eq. 4.2).[128]



Scheme 4.4 Frantz's and Reissig's work on the synthesis of diazo compounds

The Wang group also developed a deacylative cross-coupling method for the synthesis of acyldiazocarbonyl compounds and aryldiazophosphates (Scheme 4.5). This coupling reaction uses readily available starting materials and proceeds at room temperature. A variety of functional groups were tolerated and the diazo products were obtained in moderate to excellent yields.[129]

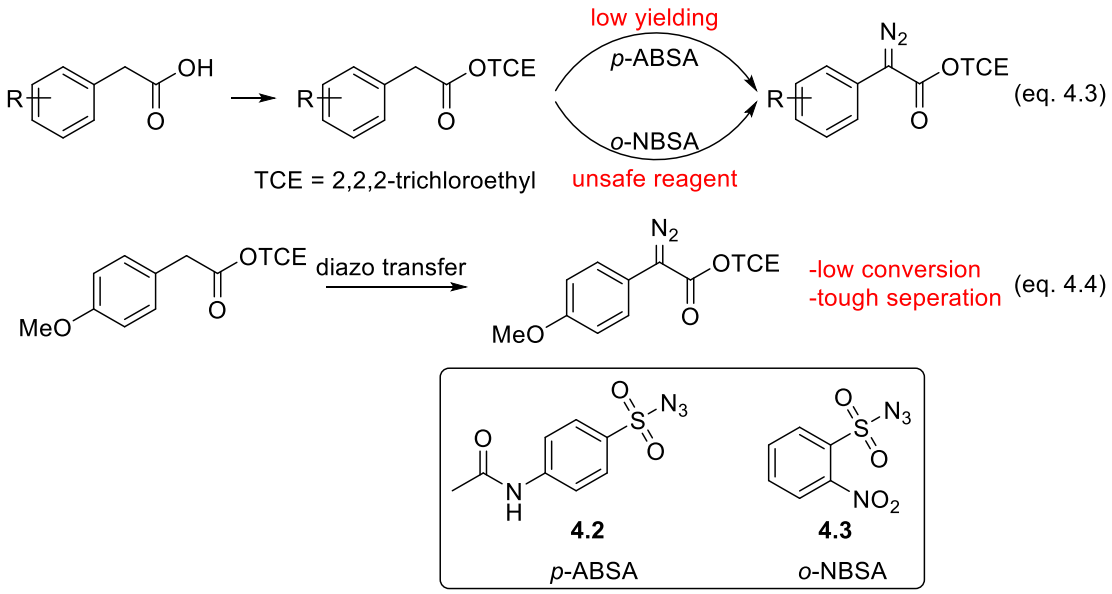


Scheme 4.5 Wang's deacylative cross-coupling for the synthesis of diazo compounds

Recently, the trichloroethyl (TCE) aryldiazoacetates have emerged as versatile reagents in rhodium carbene chemistry as the resulting metallocarbenes tend to give cleaner reactions, improved the selectivity and enabled the functionalization of substrates that were not considered to be reactive in carbene chemistry.[53,107] Furthermore, it offers opportunities

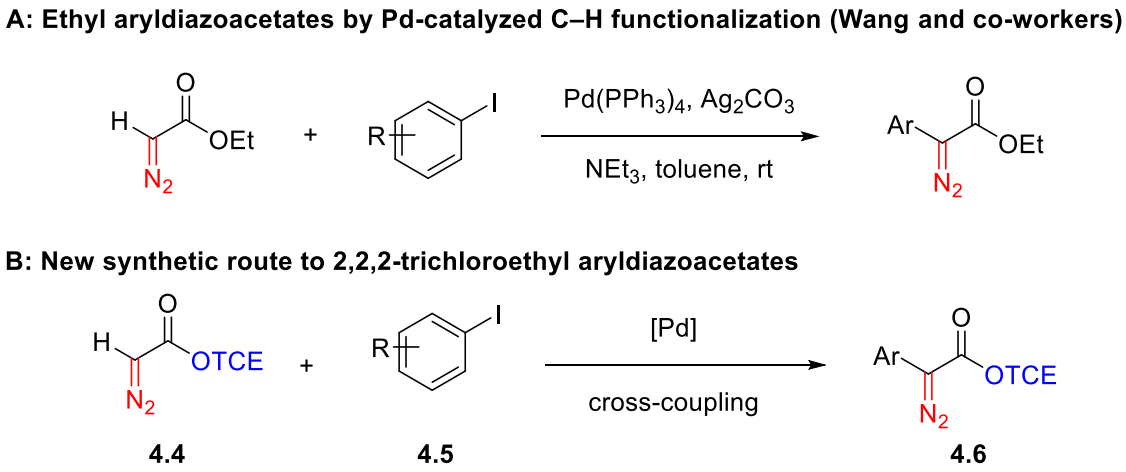
for orthogonal deprotection strategies to remove the trichloroethyl esters to obtain the corresponding carboxylic acids than methyl ester derivatives, and the reaction conditions are generally milder (Zn/AcOH, rt), allowing for the retention of stereochemistry.[53]

With the recently demonstrated greater utility of trichloroethyl (TCE) diazoacetates and more evidence that they are robust reagents in rhodium carbene chemistry, a general and efficient route for their synthesis is desirable (Scheme 4.6). The classic method for the synthesis of aryldiazoacetates uses the Regitz diazo transfer reaction (Scheme 1, A).[130,131] In the case of the formation of TCE diazoacetates, the safe diazo transfer reagent, *p*-acetamidobenzenesulfonyl azide (*p*-ABSA), did not give good yields, and instead, the more reactive and less stable *o*-nitrobenzenelsulfonyl azide must be used (eq. 4.3).[53] Furthermore, if the aryl group has electron-donating substituents such as methoxy, the diazo transfer reaction is ineffective even with the more reactive diazo transfer reagent *o*-nitrobenzenesulfonyl azide (eq. 4.3).[132]



Scheme 4.6 Synthesis of TCE aryldiazoacetates by traditional diazo transfer reaction

The Wang group most recently disclosed a palladium-catalyzed C–H functionalization strategy for the synthesis of ethyl aryldiazoacetates from aryl iodides and ethyl diazoacetate. This work was demonstrated to have a broader substrate scope as compared to their previous report (Scheme 4.7, A).[133] Inspired by this work, we hypothesized that a similar strategy could also be applied to the synthesis of trichloroethyl (TCE) aryldiazoacetates and thus, circumvent the problems of the diazo transfer reactions for generating these compounds (Scheme 4.7, B).



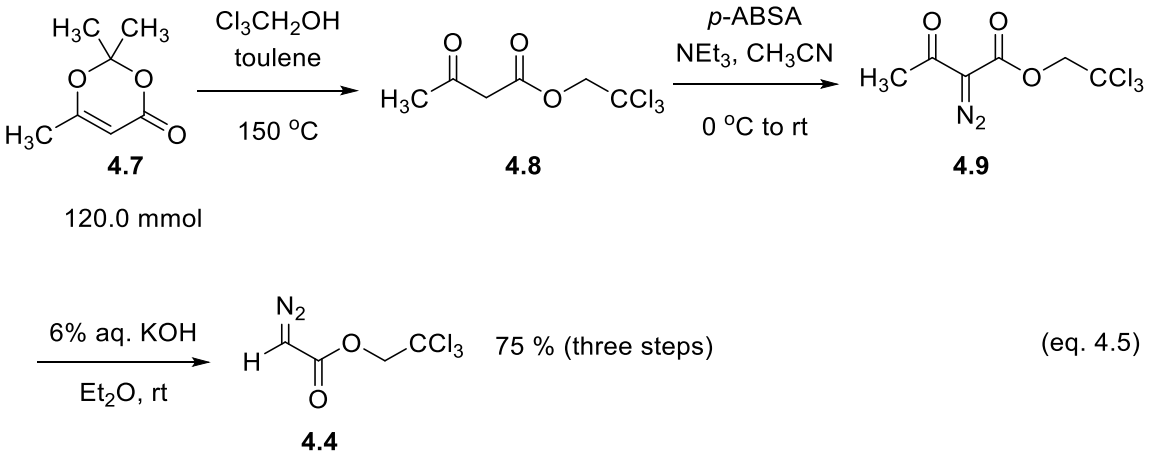
Scheme 4.7 Synthesis of trichloroethyl aryldiazoacetates by palladium-catalyzed cross-coupling

4.2 Results and discussion

Note: this work was conducted in collaboration with Dr. Jeffrey D. Mighion. Reactions performed by him will be stated.

At the outset of the exploration, a practical method would be needed to access the staring material, trichloroethyl (TCE) diazoacetate **4.4**. The known procedure for its preparation is not amenable to large-scale synthesis.[134] An efficient synthesis of **4.4** was achieved by adapting a reported procedure for the synthesis of 2,2,2-trifluoroethyl

diazoacetate.[135] Condensation of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**4.7**) with trichloroethanol formed the acetoacetate **4.8**, followed by diazo transfer reactions with *p*-ABSA to form **4.9**. Hydrolysis/decarboxylation of **4.9** generated **4.4** in 75% overall yield over three steps (eq. 4.5). This reaction was carried out at up to 120 mmol scale with only one column purification needed.

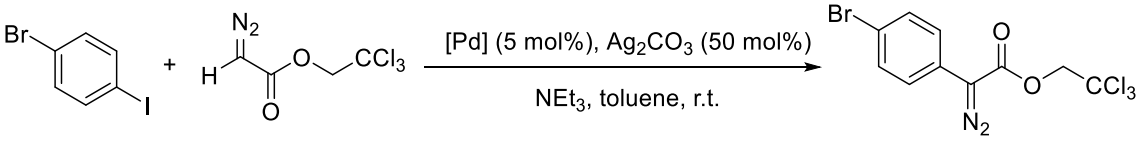


With **4.4** in hand, the optimal conditions for the cross-coupling were first explored using 1-bromo-4-iodobenzene **4.5a** as the standard substrate, coupled with trichloroethyl (TCE) diazoacetate under palladium catalysis. Under the reaction conditions reported by Wang and co-workers ($Pd(PPh_3)_4$ (5 mol %)/Ag_2CO_3 (10 mol %)), variable yields (42-83%) of the coupling product **4.6a** were obtained. Attempts at using other palladium and ligand combinations such as $Pd_2(dba)_3$ with dppe, Sphos, and PCy_3 were unsuccessful. In Wang's standard reaction conditions, both palladium and silver salts were used. We recognized that both of these metal salts could potentially catalyze the decomposition of diazo compounds, especially the more electron-deficient trichloroethyl aryldiazoacetate.[136-138]

The possibility that the variable yields were caused by product decomposition was investigated by means of ReactIR experiments, by monitoring the characteristic resonance

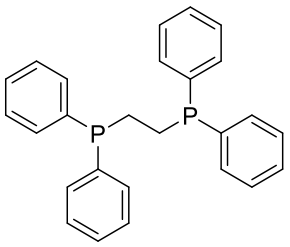
signals of the diazo functionality at 2097 cm^{-1} (Figure 4.1). When the diazo product **4.6a** was treated with palladium tetrakis(triphenylphosphine) (5 mol %) for 4 h, it underwent significant decomposition. After an induction period of about 2 h, **4.6a** decomposed rapidly and was virtually all consumed after 4 h. In contrast, when an additional 10 mol % of triphenylphosphine was added to the mixture, the decomposition of **4.6a** was greatly retarded. Consequently, the cross coupling reactions were repeated using an additional 10 mol % of triphenylphosphine and under these conditions, **4.6a** was generated in 89% yield and was consistent in yields between runs.

Table 4.1 Optimization of the reaction conditions

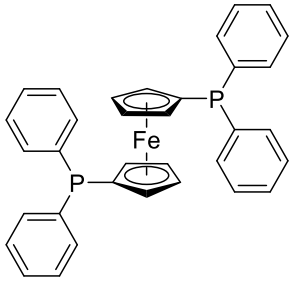


4.5a **4.4** **4.6a**

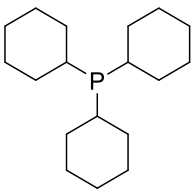
entry	[Pd]	additional Ligand	yield (%)
1	$Pd(PPh_3)_4$	-	42-83
2	$Pd_2(dba)_3$	dppe	<5
3	$Pd_2(dba)_3$	Sphos	<5
4	$Pd_2(dba)_3$	PCy_3	<5
5	$Pd(PPh_3)_4$	PPh_3	89



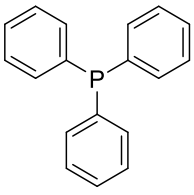
dppe



dppf



PCy_3



PPh_3

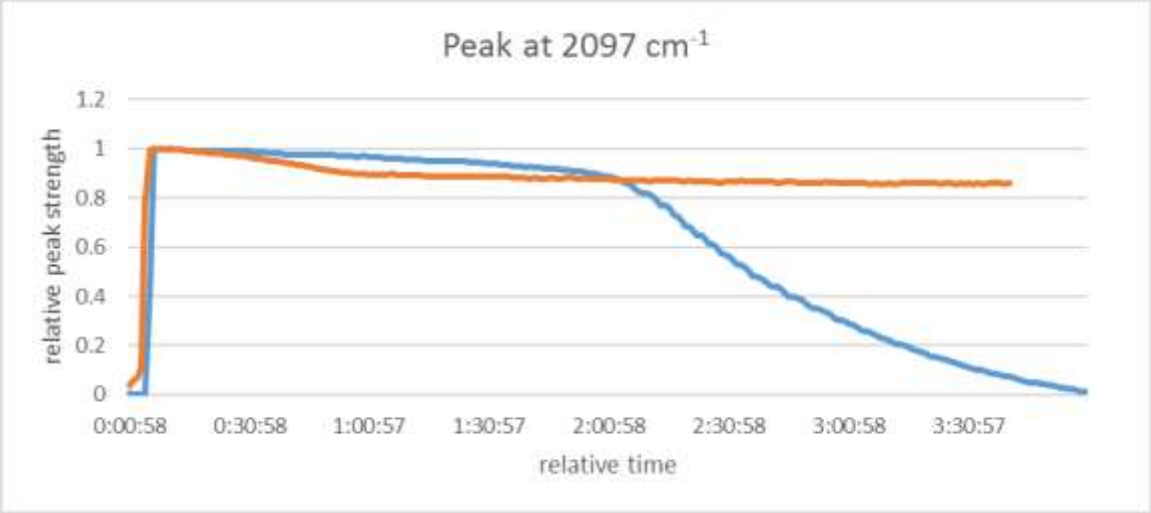
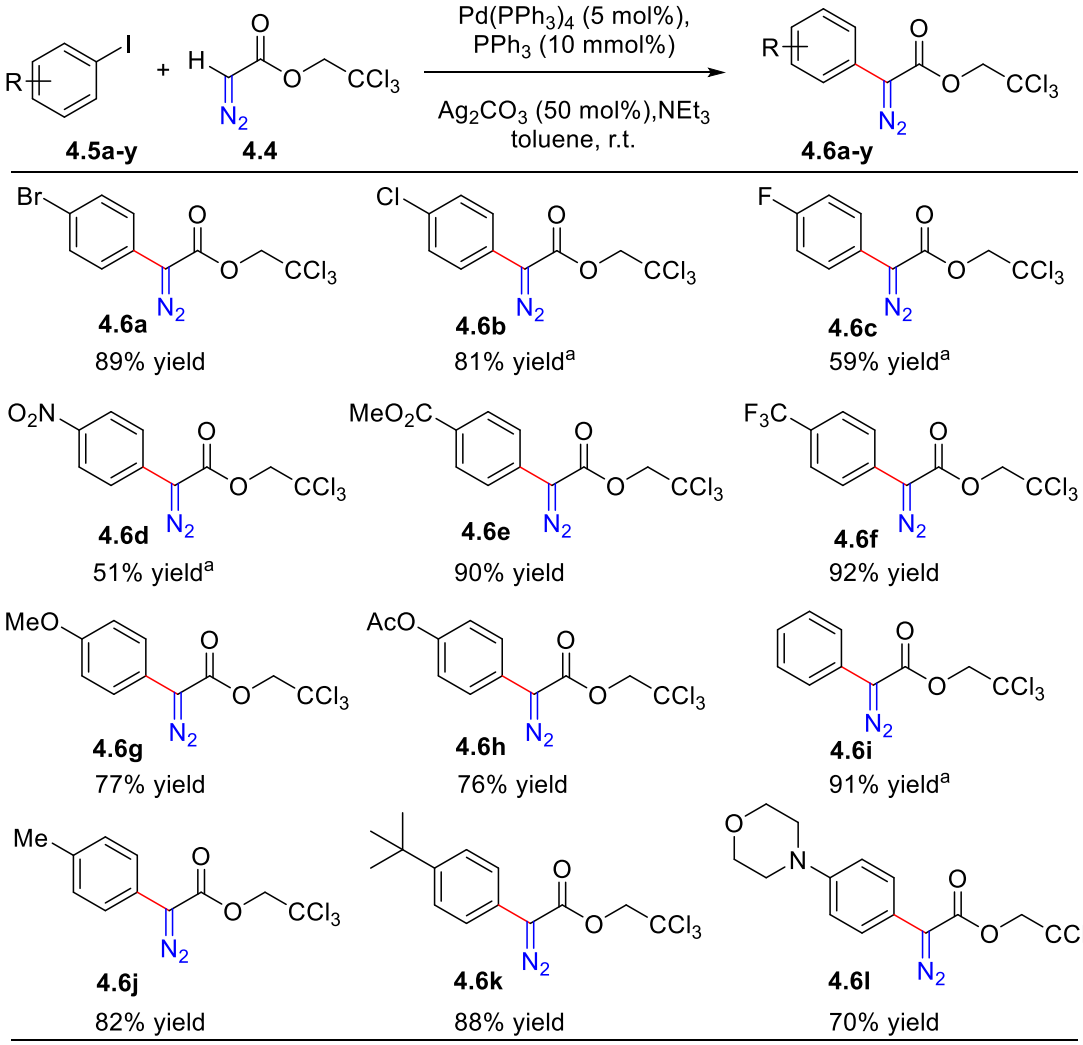


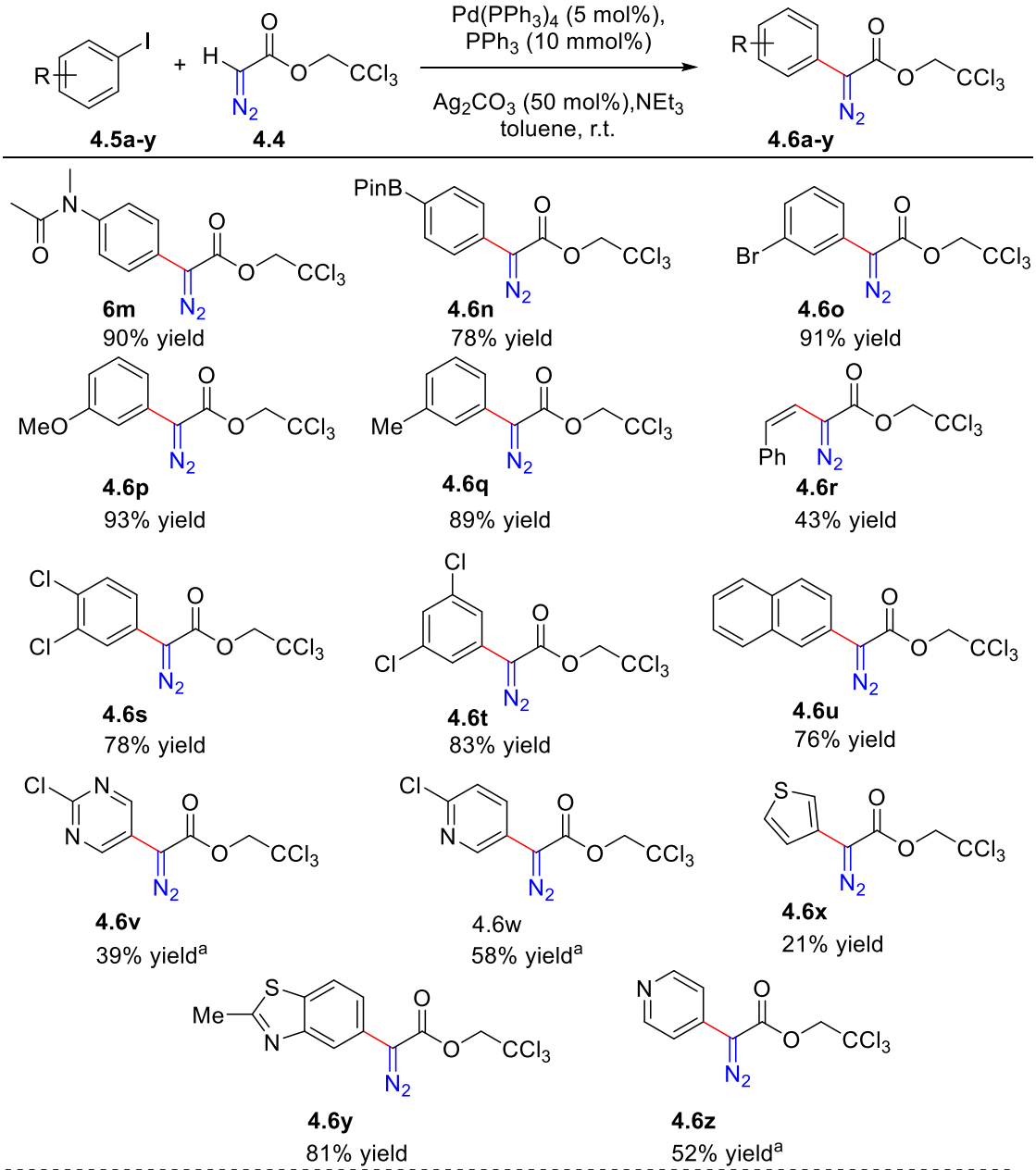
Figure 4.1 ReactIR experiments for the studies of product stability. (Blue): **4.6a** in the presence of $Pd(PPh_3)_4$ (5 mol%); (Red): **4.6a** in the presence of $Pd(PPh_3)_4$ (5 mol%) and PPh_3 (10 mol%).

With the reliable procedure in hand, the substrate scope of the cross-coupling reaction was then explored (Table 4.2). A range of *p*-substituted phenyl iodide derivatives with both electron-withdrawing and electron-donating groups were tolerated (**4.6a-m**). The other groups such as pinacolate boron is compatible with this chemistry, generating **4.6n**, which contains a useful synthetic handle for further manipulation. Particularly noteworthy is the ready access to the methoxy, amino, and acetamido derivatives (**4.6g**, **4.6l** and **4.6m**) as the methoxy derivative **4.6g** was not effectively formed in a diazo transfer reaction and amino derivatives have not been extensively utilized in the chemistry of donor/acceptor carbenes due to their inefficient synthesis. *meta*-Substituents such as halogen, methyl, and methoxy were also well tolerated (**4.6o-q**). Trichloroethyl (*Z*)-styryldiazoacetate could also be synthesized by this method (**4.6r**). Both 3,5- and 3,4-disubstituted substrates were also compatible with this method (**4.6s-t**). Moreover, heterocyclic TCE diazoacetates could also be synthesized as illustrated by the thiophene-, benzothiazole-, pyridine-, and pyrimidine-

diazoacetates (**4.6v-z**), with the pyridine and pyrimidine systems requiring longer reactions times. Some substrates that did not perform in the system include the *ortho*-substituted phenyl iodide derivatives and an unprotected phenol. The fact that *ortho*-substituted derivatives could not be prepared by this cross-coupling method suggested that the reaction is sensitive to steric effects under the reaction conditions. The reaction of 4-iodophenol with trichloroethyl (TCE) diazoacetate led to a complex mixture, probably due to the coordination of the substrate to the palladium catalyst.

Table 4.2 Scope of aryl- and vinyl iodides

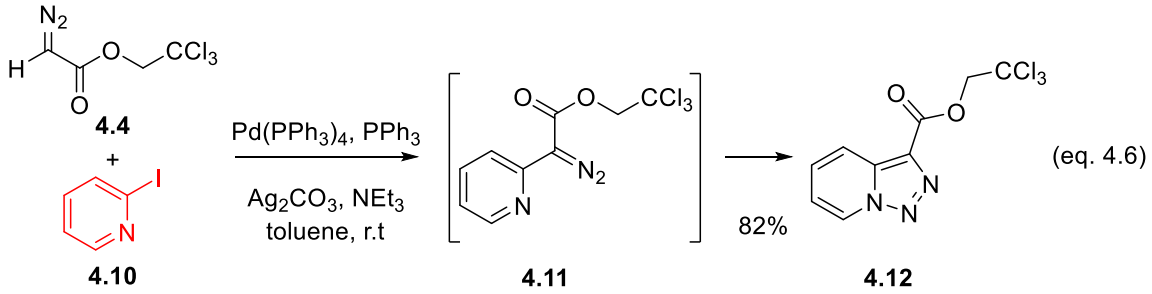




[a]The reaction was performed by Dr. Jeffrey D. Mighion.

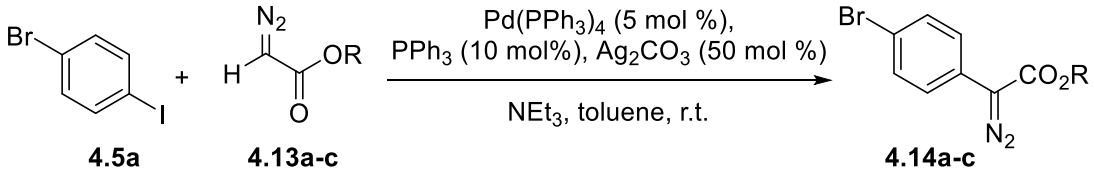
Interestingly, the cross-coupling reaction of 2-iodopyridine **4.10** gave a cyclic pyridotriazole product **4.12** instead of isolation of the diazo product **4.11** (eq. 4.6). The formation of cyclized product **4.12** was proposed to go through the initial formation of

cross-coupled diazo compound **4.11**, followed by a ring closing cyclization process. This ring opened/closed equilibrium of pyridotriazoles was utilized in a Rh-catalyzed transannulation reaction by Gevorgyan and co-workers,[58b] and the observation that this cross-coupling reaction can form this type of product provides an alternative method for the preparation of pyridotriazoles.



The palladium-catalyzed cross-coupling process could be applied to other ester derivatives that are useful in rhodium carbene chemistry (Table 4.3). Specifically, besides 2,2,2-trichloroethyl, 2,2,2-trifluoro (TFE), 2,2,2-tribromo (TBE), and trimethylsilylethyl (TMSE) aryldiazoacetate could also be synthesized with this cross-coupling strategy (Table 2).[106,107,139] The reactions with TBE and TFE diazoacetates gave lower conversion as compared to TCE and TMSE diazoacetates, and these reactions were not further optimized.

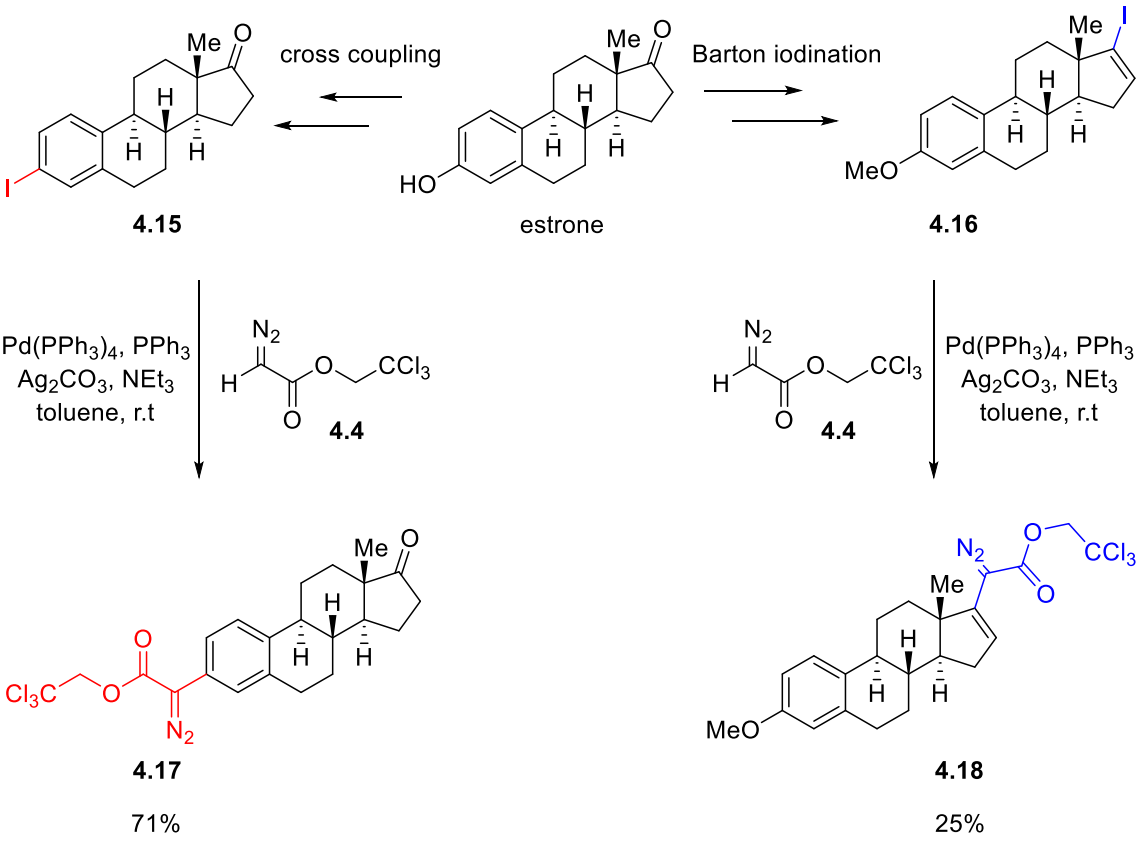
Table 4.3 Expansion to other aryldiazoacetates



4.5a **4.13a-c** **4.14a-c**

entry	R	product	yield
1	TCE	**4.6a**	89%
2	TFE	**4.14a**	58%
3	TBE	**4.14b**	53%
4	TMSE	**4.14c**	87%

The synthetic utility of the transformation was further demonstrated by functionalizing estrone derivatives (Scheme 4.8). Aryl iodides **4.15** is a known compound[129] and was synthesized from estrone according to the literature procedure. Alternatively, vinyl iodide **4.16** was synthesized from estrone by Barton iodination method. The reactions of **4.15** and **4.16** under the standard reaction conditions afforded the corresponding cross-coupling products **4.17** and **4.18** in 71% and 25% yield respectively. The relatively low yield (25%) for the generation of **4.18** is presumably another indication that the cross-coupling reaction is not very tolerant of sterically demanding iodides.

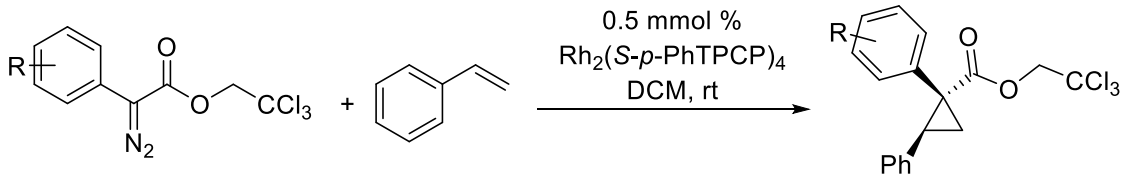


Scheme 4.8 Application of the cross-coupling methodology to estrone derivatives

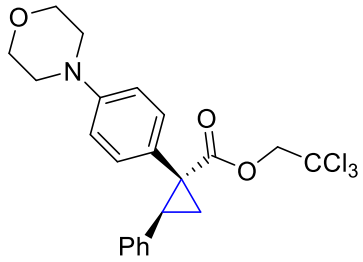
The cross-coupling reaction generated a number of novel trichloroethyl (TCE) diazo compounds that had not been previously applied to enantioselective rhodium-catalyzed

reactions. Therefore, some of the most interesting ones were evaluated in the cyclopropanation of styrene. The standard reaction condition (Rh_2(*S*-*p*-PhTPCP)$_4$ in dichloromethane at room temperature) was chosen from similar reaction that was published recently by our group (Scheme 4.9).[106] The reactions of TCE aryldiazoacetates with *p*-morpholine and *p*-Bpin on the phenyl ring gave the desired cyclopropanation in good yields with high levels of enantioselectivity (**4.20a-b**). The 3,5-dichloro-substituted TCE diazoacetate yielded the cyclopropane in 85% yield with 85% ee (**4.20c**). Additionally, heterocycles such as benzothiazole, thiophene and pyrimidine were tolerated as the aryl group of the TCE diazoacetates (**4.20d-f**). Cyclopropanes were obtained in good yields (85-65%) with excellent levels of enantioselectivity (99-85%). The asymmetric induction with the heterocyclic diazo esters is much improved over previous results of cyclopropanation with the corresponding methyl esters using Rh_2(*S*-DOSP)$_4$ as the catalyst as noted by **4.20e**.[140] The absolute configuration of the cyclopropanation products were assigned by analogy to that of the products from the literature.[106]

Table 4.4 Test of new diazo compounds in cyclopropanation reactions

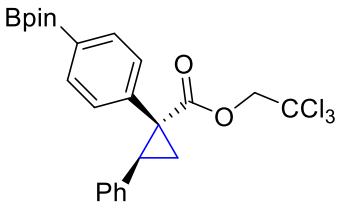


4.6 **4.19** **4.20a-f**



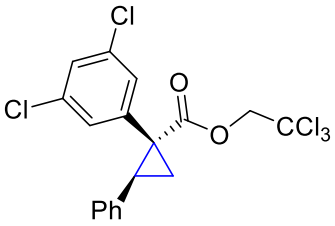
4.20a

71%, 98% ee



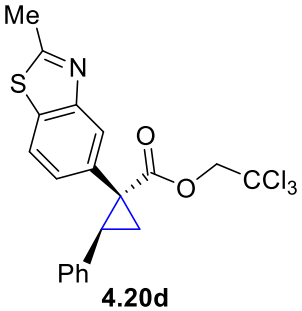
4.20b

74%, 95% ee



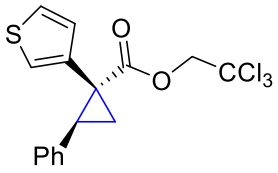
4.20c

85%, 85% ee



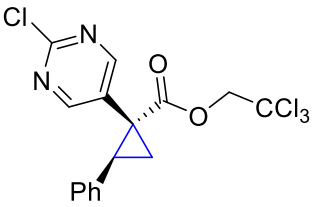
4.20d

65%, 98% ee



4.20e

70%, 99% ee



4.20f

80%, 88% ee[a]

[a]The reaction was performed by Dr. Jeffrey D. Mighion.

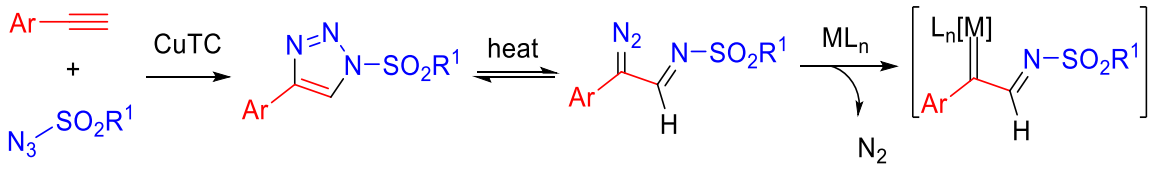
4.3 Summary

In conclusion, a general and efficient route for the synthesis of 2,2,2-trichloroethyl (TCE) aryl-, heteroaryl-, and vinyldiazoacetates was achieved by palladium-catalyzed cross-coupling of the corresponding iodides and diazoacetate. The successful development of this process required addition of further phosphine ligand to the reaction mixture to avoid decomposition of the diazo product. The ready access of the diazo compounds will enhance the range and flexibility of the donor/acceptor metallocarbene chemistry.

Chapter 5 Divergent reactions of indolyl- and pyrrolyl-tethered *N*-sulfonyl-1,2,3-triazoles: efficient synthesis of polycyclic spiroindolines and tetrahydrocarbolines by rhodium(II)-catalyzed intramolecular annulations

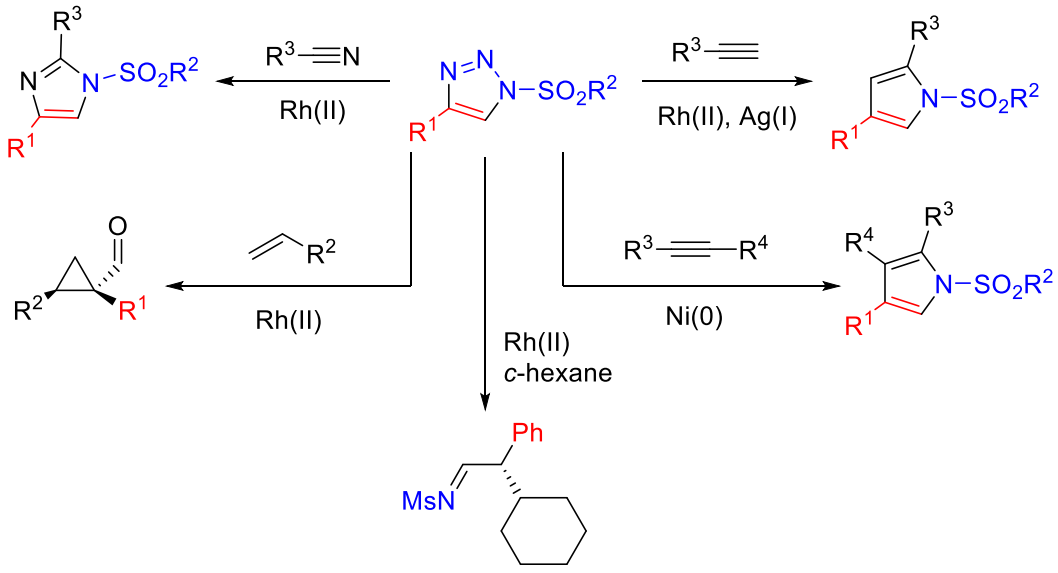
5.1 Introduction

Transition-metal bound-carbenes are valuable intermediates in organic synthesis, especially in C–C bond forming reactions, as they display a diverse array of elaborate transformations.[5,121] A variety of useful synthetic transformations have been developed with metal-stabilized carbenes. Traditionally, metallocarbenes can be generated from the metal-catalyzed decomposition of α-diazo carbonyls.[3,121] Recently, *N*-sulfonyl 1,2,3-triazoles have emerged as alternative precursors for the generation of donor/acceptor carbenes because they server as a latent source of diazo compounds (Scheme 5.1).[60] Chuprakov and Gevorgyan first showed that 1,2,3-triazoles bearing a strong electron-withdrawing group at *N*-1 position, which are capable of undergoing ring-to-chain isomerization to expose the diazo moiety, can act as masked diazo compounds, thus serving as an alternate source of carbene precursors.[58,59]



Scheme 5.1 Triazole ring-chain isomerization to generate *α*-imino metallocarbenes

So far, the choices of catalyst for triazole-derived carbene chemistry has somewhat been limited to dirhodium tetracarboxylate catalysts. In a rare case, nickel catalysis was also utilized.[141] In the presence of dirhodium tetracarboxylate, the metal stabilized donor/acceptor carbene intermediate was generated from the *α*-diazo imine which is isomerized from *N*-sulfonyl-1,2,3-triazoles. A number of groups have demonstrated the synthetic utility of *N*-sulfonyltriazoles as viable precursors in both classic and novel rhodium carbene reactivity (Scheme 5.2).[60] Moreover, the pendent sulfonyl imine group in the zwitterionic intermediate is more nucleophilic than esters and can cyclize to form heterocycles. Since these initial reports, the Fokin, Gevorgyan, Davies, Murakami, and other groups have extensively demonstrated the synthetic potentials of triazoles as carbene precursors for the development of useful transformations, including transannulations for the facile synthesis of heterocycles.[60,67-70]



Scheme 5.2 Typical transformation of triazoles

The Davies group has been interested in using 1,2,3-triazoles for the development of new reactions and to expand the scope of donor groups in donor/acceptor carbenes. To this

end, the Davies group reported that 4-amido-1-sulfonyl-1,2,3-triazoles can be used to introduce a *N*-phthalimido donor group, which enabled an expedited synthesis of cyclopropyl amino acids.[77] The Davies group also described a series of transformations using *N*-sulfonyltriazoles as carbene precursors, for instance, formal [4+3] cycloaddition reactions with diene[142], formal [3+2] cycloaddition reactions with indoles[143], formation of trisubstituted pyrroles[69] and formation of 2,3-fused pyrroles and indoles.[62]

Nitrogen-containing heterocycles are present in a wide variety of natural products and pharmaceutical compounds. Among these polycyclic spiroindolines, azepino[4,5-*b*]indoles, and *β*-carbolines are of significant importance (Figure 5.1).[144-149] As a result, a variety of methods have been developed to synthesize these classes of compounds.[150-155] These methods include palladium-catalyzed cascade cyclisation,[150] Cu(II)-catalyzed intramolecular [3+2] annulation reactions between donor–acceptor cyclopropanes and indoles,[152] and gold-catalyzed reactions of *α*-(2-indolyl) propargylic alcohols with imines.[154] However, direct, simple and effective approaches to the synthesis of these classes of compounds still remains relatively challenging and the development of general and divergent methods for their synthesis is highly desirable.

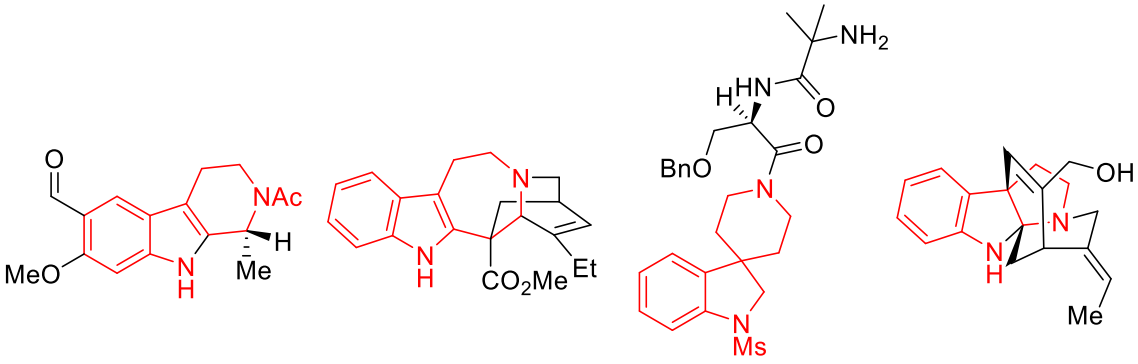
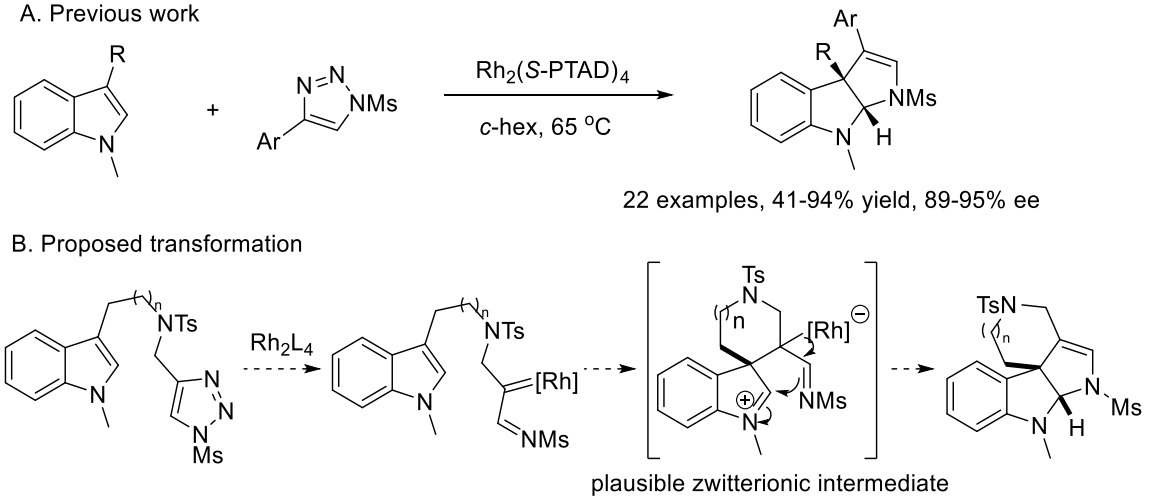
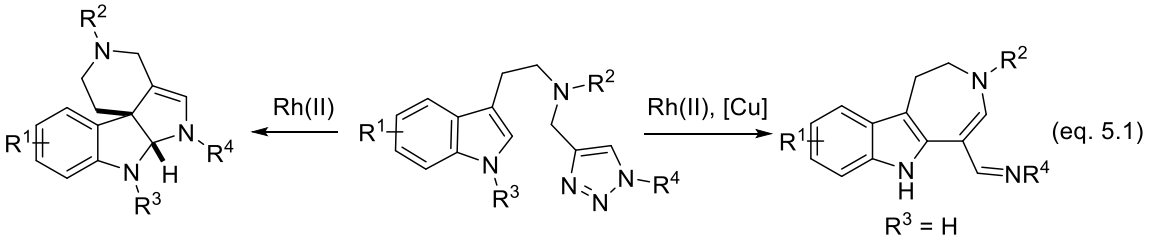


Figure 5. 1 Spiroindoline and *β*-carboline containing natural products

Previously we developed an enantioselective synthesis of pyrroloindolines via formal [3+2] cycloaddition reaction of 3-substituted indoles with 4-aryl-1-sulfonyl-1,2,3-triazoles (Scheme 5.3, A).[143] Given the ability of *N*-sulfonyl-1,2,3-triazoles to undergo transannulation reactions, we were interested in exploring whether *N*-sulfonyl-1,2,3-triazoles could provide opportunities for the development of a general approach for the synthesis of polycyclic spiroindolines. We hypothesized that by tethering the triazole to the indole ring, initial intramolecular attack would generate a zwitterionic intermediate, which can then cyclize to give the polycyclic spiroindolines product by virtue of the tether (Scheme 5.3, B). Concurrent with our work, the Shi group published similar work that polycyclic pyrroloindolines and azepino[4,5-*b*]indoles could be formed with indolyltriazoles as the substrates (eq. 5.1).[156] This chapter details our efforts towards the divergent synthesis of not only polycyclic spiroindolines, and azepino[4,5-*b*]indoles, but also *β*-carbolines. Furthermore, polycyclic spiroindolines with different ring sizes and tethers were tolerated. This work also showed that pyrrolyltriazoles could be used as substrates in the system.



Scheme 5.3 Proposed transformation for the synthesis of polycyclic spiroindolines

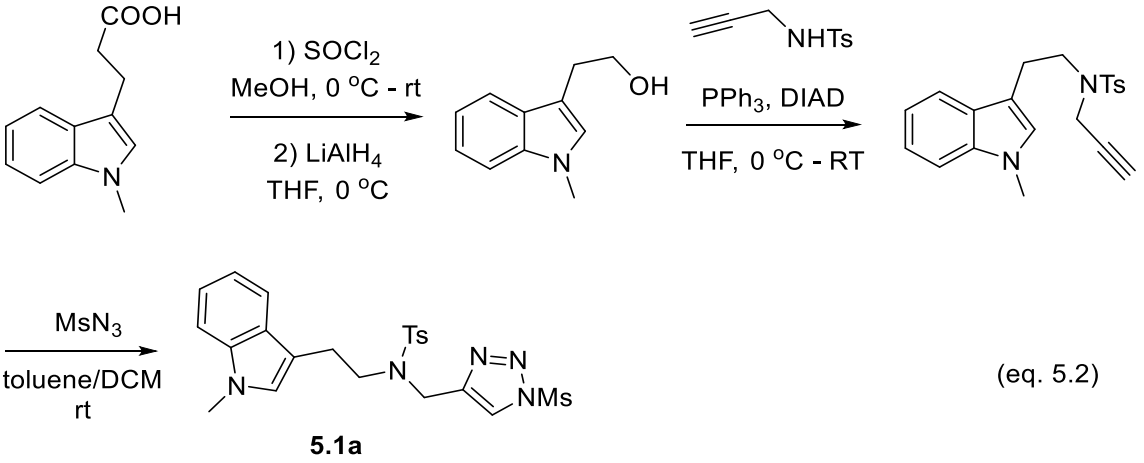


5.2 Results and discussion

We began to test the hypothesis by using a tethered-indolyl triazole **5.1a** as the model substrate in the initial exploration (Table 5.1). The triazole substrate **5.1a** was synthesized by sequential esterification, reduction, Mitsunobu reaction, and click reaction, starting from commercially available 3-(1-methyl-1*H*-indol-3-yl)propanoic acid (eq. 5.2). To our delight, the reaction of triazole **5.1a** using catalytic $Rh_2(OOct)_4$ in 1,2-dichloroethane (DCE) at 80 °C gave the expected product **5.2a** in 62% yield with high diastereoselectivity (entry 1). Optimization of the reaction conditions was next conducted. The efficiency of the reaction was found to be dependent on the nature of the dirhodium catalyst and the solvent. Ethyl acetate, which was not commonly used in metallocarbene transformations, was found to be the optimal solvent for the transformation, (entries 2-5). After systematic explorations of the dirhodium catalysts for the reaction, $Rh_2(OOct)_4$ was found to be optimal among all the achiral catalysts (entries 6-8), but inferior to the best chiral catalyst Rh_2(*S*-PTTL)$_4$. With this catalyst, the reaction of **5.1a** gave the product **5.2a** in 87% yield, but with only mediocre enantioselectivity (31%). The diastereoselectivity of this intramolecular reaction was routinely high (> 19:1) and only single diastereomer was observed, but the enantioselectivity of the reaction remains to be optimized.

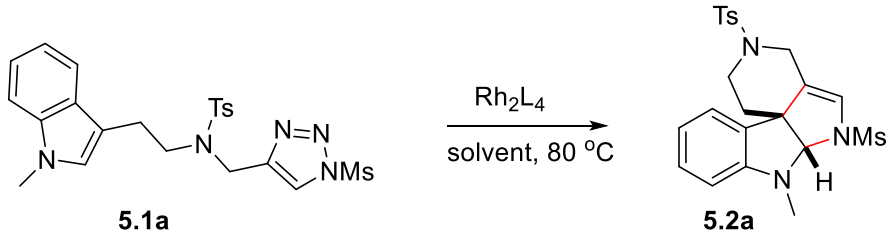
The next step was to improve the enantioselectivity for the transformation (Table 5.2). Various types of chiral catalyst, including prolinate catalysts, phthalimidyl catalyst, and

triarylcyclopropane carboxylate catalyst, were tested, and the phthalimido catalyst Rh_2(*S*-PTAD)$_4$ and Rh_2(*S*-PTTL)$_4$ gave superior results (entries 1-6). Lowering the reaction temperature led to significantly lower yield but did not improve the enantioinduction (entries 7-8). Screening the different solvents showed that ethyl acetate performed best (entries 9-13). Comparison of Rh_2(*S*-PTAD)$_4$, Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-NTTL)$_4$ indicated that Rh_2(*S*-PTTL)$_4$ was superior (entries 14-15). Switching the sulfonyl group from mesyl to tosyl did not help (entry 16). The only moderate enantioselectivity of the transformation after extensive screening was presumably due to the fact that the rhodium carbene generated from triazole compound **5.1a** is not a typical donor/acceptor carbene.[5]



(eq. 5.2)

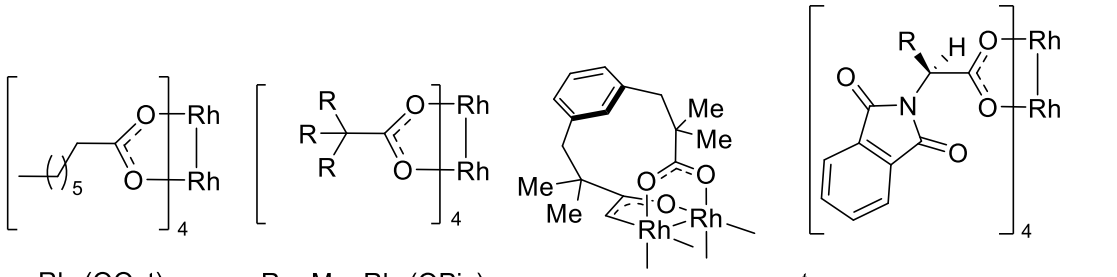
Table 5.1 Optimization of the reaction conditions



5.1a **5.2a**

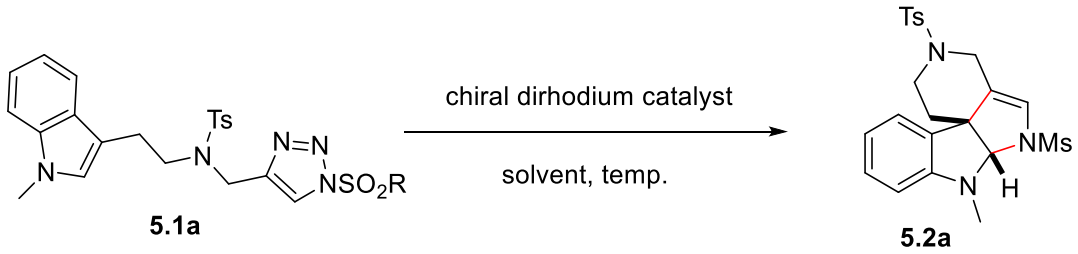
entry	catalyst	solvent	yield (%)[a]
1	$Rh_2(OOct)_4$	DCE	62
2	$Rh_2(OOct)_4$	toluene	48
3	$Rh_2(OOct)_4$	$CHCl_3$	63
4	$Rh_2(OOct)_4$	*c*-hex	<5
5	$Rh_2(OOct)_4$	EtOAc	65
6	$Rh_2(TPA)_4$	EtOAc	60
7	$Rh_2(OPiv)_4$	EtOAc	58
8	$Rh_2(esp)_2$	EtOAc	55
9	**Rh_2(*S*-PTTL)$_2$**	**EtOAc**	**87[b]**
10	Rh_2(*S*-PTAD)$_2$	EtOAc	86

[a]Isolated yield. [b]ee was 31% as determined by chiral HPLC analysis.



$Rh_2(OOct)_4$ R = Me, $Rh_2(OPiv)_4$ R = Ph, $Rh_2(TPA)_4$ $Rh_2(esp)_2$ R = ^{t}Bu, Rh_2(*S*-PTTL)$_4$ R = Adamantyl, Rh_2(*S*-PTAD)$_4$

Table 5.2 Screening of chiral catalysts



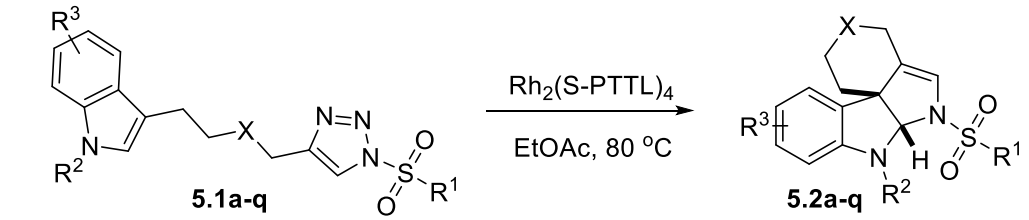
5.1a **5.2a**

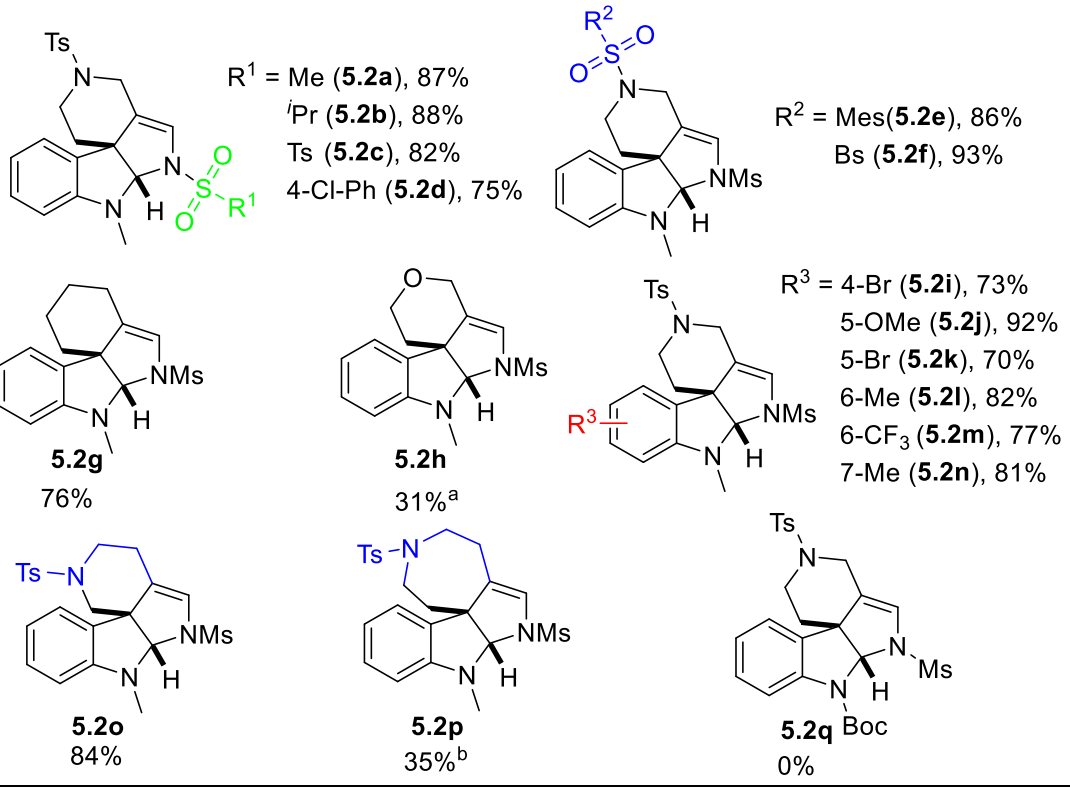
entry	catalyst	SO_2R	solvent	temp.	yield (%)	ee (%)[b]
1	Rh_2(*S*-DOSP)$_4$	Ms	DCE	80	48	<5
2	Rh_2(*S*-PTAD)$_4$	Ms	DCE	80	72	26
3	Rh_2(*S*-PTTL)$_4$	Ms	DCE	80	75	27
4	Rh_2(*S*-NTTL)$_4$	Ms	DCE	80	56	10
5	Rh_2(*S*-BTPCP)$_4$	Ms	DCE	80	45	<1
6	Rh_2(*S*-TCPTAD)$_4$	Ms	DCE	80	35	9
7	Rh_2(*S*-PTAD)$_4$	Ms	DCE	65	33	28
8	Rh_2(*S*-PTAD)$_4$	Ms	DCE	rt	NR[a]	/
9	Rh_2(*S*-NTTL)$_4$	Ms	DCE	80	26	4
10	Rh_2(*S*-PTAD)$_4$	Ms	$CHCl_3$	80	74	30
11	Rh_2(*S*-NTTL)$_4$	Ms	toluene	80	76	23
12	Rh_2(*S*-NTTL)$_4$	Ms	*c*-hex	80	43	16
13	Rh_2(*S*-PTAD)$_4$	Ms	EA	80	86	30
14	**Rh_2(*S*-PTTL)$_4$**	**Ms**	**EA**	**80**	**87**	**31**
15	Rh_2(*S*-NTTL)$_4$	Ms	EA	80	76	6
16	Rh_2(*S*-PTTL)$_4$	Ts	EA	80	52	26

[a]No reaction. [b]Determined by chiral HPLC analysis.

Having established the optimized conditions (Rh_2(*S*-PTTL)$_4$ in ethyl acetate at 80 °C) for the transformation, the scope of this reaction was subsequently explored, and to our delight, it turned out to be very general (Table 5.3). A variety of sulfonyl groups on the triazole ring including tosyl, mesyl, isopropyl sulfonyl, and *para*-chlorobenzenesulfonyl, were all tolerated (**5.2a**-**d**). Also, reactions of substrates with different *N*-sulfonyl groups on the substrate tether: X = NTs, NMes, and NBs all proceeded smoothly to afford the corresponding products (**5.2a**, **5.2e** and **5.2f**). Tethering atoms other than nitrogen were also examined: a carbon-tethered substrate also gave the desired product in good yield (**5.2g**). The oxygen-tethered analogue gave low yield, with the observation of 1,2-hydride shift byproduct (**5.2h**). A similar 1,2-hydride shift byproduct was also observed by Shi and coworkers in their intramolecular annulations.[10e] Different types of substitutions on the indole ring were all tolerated, and the desired products were obtained in good to excellent yields regardless of the electronic nature of the substitutions (**5.2i**-**n**).[14] A substrate with the position of the nitrogen-tether moved closer to the indole ring performed as well (**5.2o**). A substrate with the tether homologated by one carbon was also tolerated, but higher temperature was required for the transformation. In this case, the corresponding 7-membered ring product was obtained in diminished yield (**5.2p**). We found that the substituent on the indole nitrogen has significant influence on the reactivity. For example, *N*-Boc substituted substrate did not give the desired product presumably because the presence of an electron-withdrawing group on the indole *N* atom led to significant decrease of the nucleophilicity of C3 (**5.2q**). The structure of **5.2l** was confirmed by X-ray crystallography, and the other structures were tentatively assigned to be the same as **5.2l** by analogy (Figure 5.2).

Table 5.3 Substrate scope of the intramolecular annulations





[a]Formation of byproduct derived from 1,2-hydride shift was observed. [b]Performed at 120 °C.

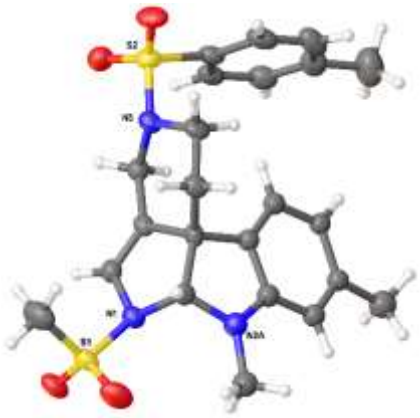
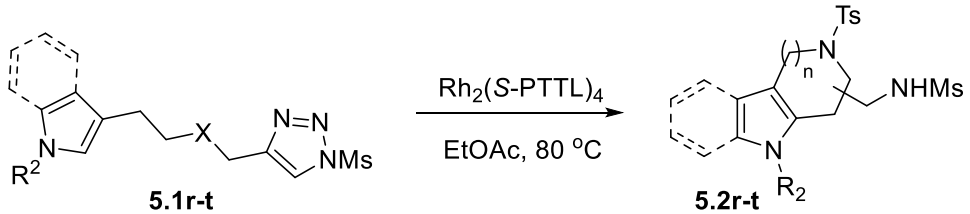


Figure 5.2 X-ray crystallography structure of **5.2l**

Interestingly, the substrate with unprotected nitrogen atom on the indole gave the formal C–H functionalization product (**5.2r**) (Table 5.4). This formal C–H functionalization was also observed with the more electron-rich pyrrole-tethered substrate and the substrate with one carbon shorter in the tether (**5.2s** and **5.2t**). In the latter case, the annulated products were obtained as a mixture of *Z/E* isomers, which could be reduced smoothly to the corresponding sulfonyl amides when treated with $NaBH_3CN$.[157]

Table 5.4 Observation of formal C−H functionalization products with *N*-sulfonyl-1,2,3-triazoles

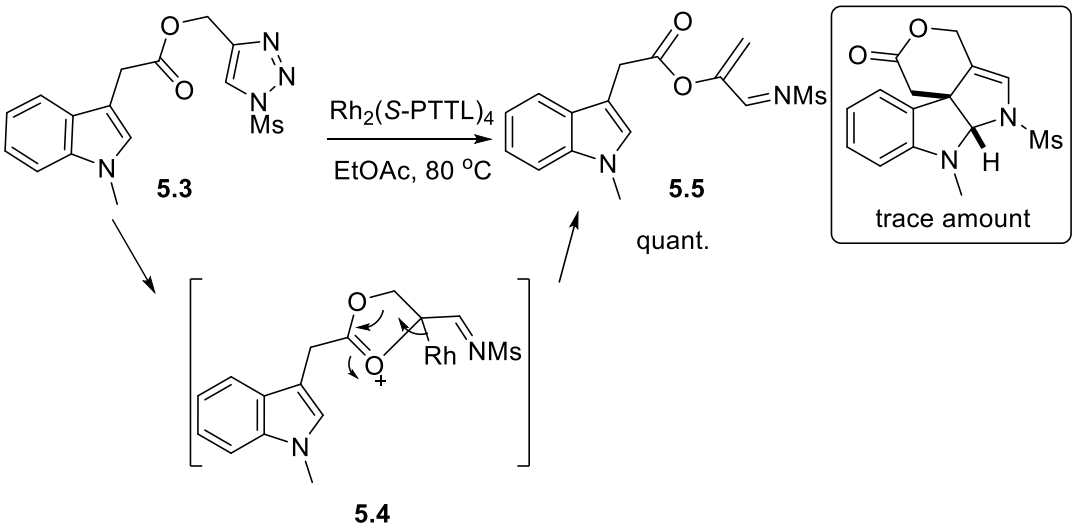


5.1r-t → **5.2r-t**

5.2r	**5.2s**	**5.2t**
53%[a]	56%	30%[a]

[a]After reduction by $NaBH_3CN$.

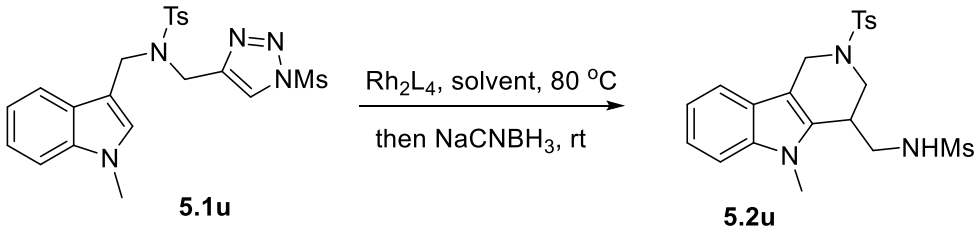
The reaction with an ester tethered substrate led to unexpected result (Scheme 5.4). Only trace amount of the desired product was observed based on crude ^1H NMR analysis. Instead, the product **5.5**, proposed to be derived from rearrangement of the zwitterionic intermediate **5.4** that was generated by nucleophilic attack of the oxygen lone pair of the ester toward the electrophilic rhodium carbene, was formed in nearly quantitative yield.



Scheme 5.4 Test of substrate with an ester as the tether

After exploration of the synthesis of spiroindolines, we aimed to expand the methodology to the synthesis of tetrahydrocarbolines. Optimization of the reaction conditions was conducted, and the combination of $Rh_2(OOct)_4$ and DCE was found to be the optimal combination (Table 5.5, entry 1). Specifically, other achiral catalysts $Rh_2(TPA)_4$, $Rh_2(esp)_2$, $Rh_2(OPiv)_4$, and $Rh_2(OAc)_4$ proved less effective compared to $Rh_2(OOct)_4$ (entries 2-5). Screening of the solvent revealed that the less polar solvents toluene and *c*-hexane were less effective for the system. Chloroform also worked in the reaction, but was not as effective as dichloroethane (entries 6-8).

Table 5.5 Optimization of the reaction conditions for tetrahydrocarbolines formation

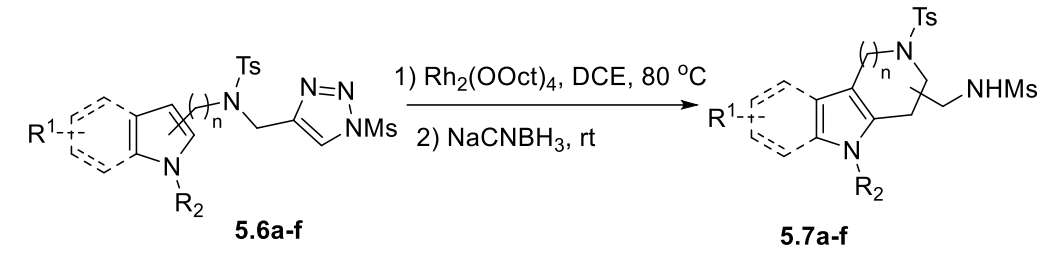


5.1u **5.2u**

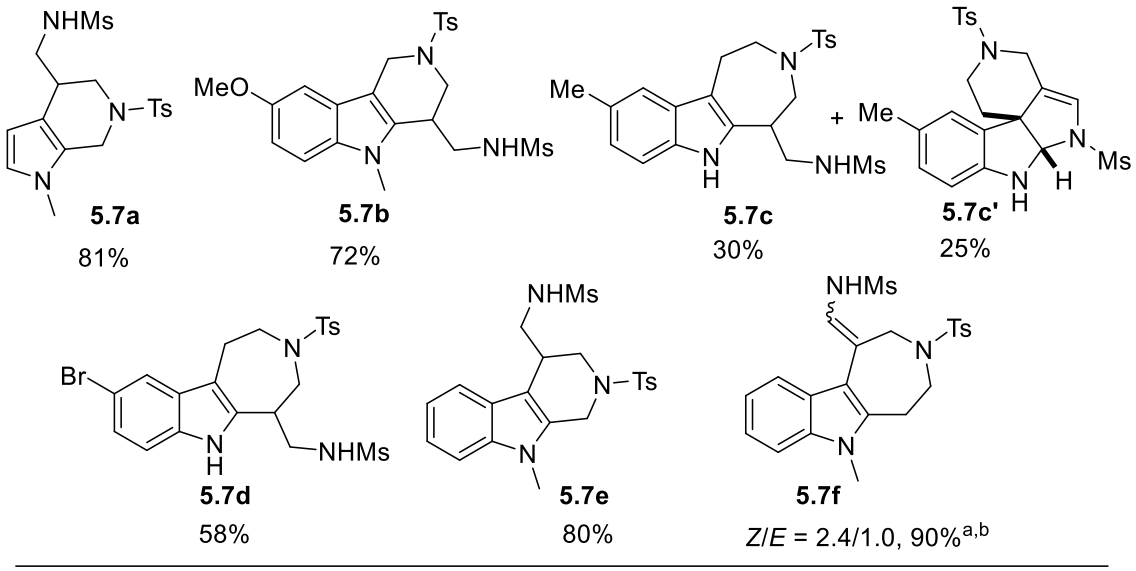
entry	catalyst	solvent	yield (%)
1	**$Rh_2(OOct)_4$**	**DCE**	**81**
2	$Rh_2(TPA)_4$	DCE	48
3	$Rh_2(OPiv)_4$	DCE	76
4	$Rh_2(OAc)_4$	DCE	70
5	$Rh_2(esp)_2$	DCE	71
6	$Rh_2(OOct)_4$	toluene	38
7	$Rh_2(OOct)_4$	$CHCl_3$	60
8	$Rh_2(OOct)_4$	*c*-hex	<5

The substrate scope for this reactivity was then examined under the optimized reaction conditions (Table 5.6). A variety of carboline-type products could be synthesized. Pyrrole-tethered triazole also gave the desired tetrahydropyrrolopyridine product in excellent yield after reduction (**5.7a**). Methoxy substitution was also tolerated (**5.7b**). Notably, substrate with an electron donating methyl group at the 5-position gave a mixture of the spiroindoline and tetrahydrocarboline products (**5.7c** and **7c'**) while substrate bearing an electron withdrawing bromo substituent at this position gave exclusively tetrahydrocarboline product (**5.7d**), suggesting that the distribution of products is dependent on the subtle balances of both electronic and conformational effects. The modularity of the transformation was further demonstrated by using substrates with the tethers at C2-position of the indole, in which case, the product containing *β*-tetrahydrocarboline and *β*-azepine cores could be efficiently synthesized (**5.7e** and **5.7f**).

Table 5.6 Substrate scope for the intramolecular formal C−H functionalization with *N*-sulfonyl-1,2,3-triazoles



5.6a-f **5.7a-f**



5.7a 81%

5.7b 72%

5.7c 30% + **5.7c'** 25%

5.7d 58%

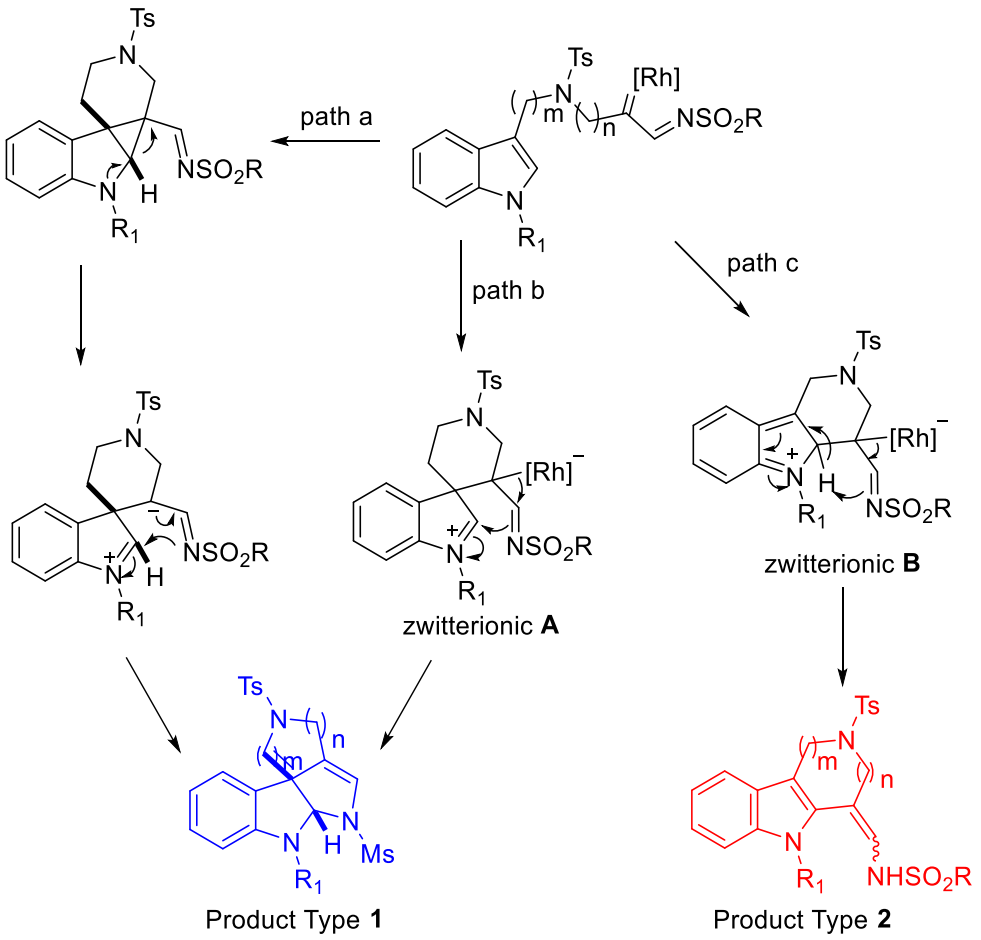
5.7e 80%

5.7f *Z*/*E* = 2.4/1.0, 90%[a,b]

[a]The products were not reduced with $NaBH_3CN$. [b]Combined yield of two stereoisomers.

Plausible mechanistic pathways are outlined in Scheme 5.5. For the annulation reactivity, one possible reaction pathway involves initial cyclopropanation of the C2–C3 double bond of the indole followed by subsequent ring-opening and recombination (path a). However, considering that *N*-Boc indoles which are reported to undergo concerted cyclopropanations with Rh(II) carbenes to afford isolable cyclopropylindolines did not work under the reaction conditions, and the presence of solvent effects in the reaction, we suggest that zwitterionic pathways resulting from substantial polarization of the C2–C3 double bond are also possible (path b). On the other hand, when the tether is one carbon shorter, or with N–H free indoles, a Friedel-Crafts-type reaction takes place. In this case,

reaction occurs at C2 *via* zwitterionic intermediate **B**, giving the formal C–H functionalization products (path c).

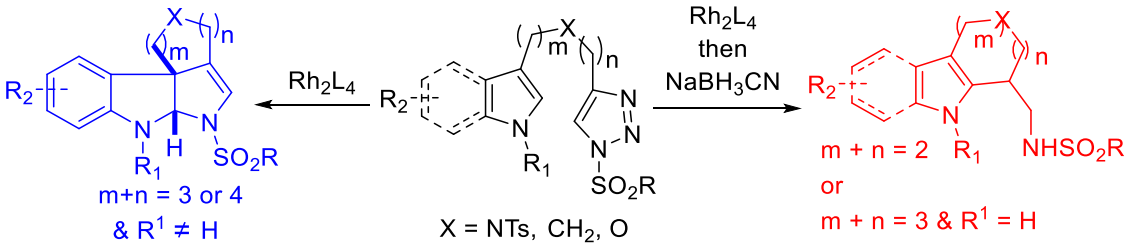


Scheme 5.5 Proposed mechanistic pathways

5.3 Summary

In conclusion, a synthesis of polycyclic spiroindolines by rhodium(II)-catalyzed intramolecular annulations of indolyl-tethered 1-sulfonyl-1,2,3-triazoles was achieved. During the course of this study we found that by tuning electronic and structural factors, tetrahydrocarbolines could be also be synthesized (Scheme 5.6). This method features intramolecular reactions of indolyl- and pyrrolyl-tethered triazoles, allowing for divergent

synthesis of a variety of nitrogen-containing heterocycles including spiroindolines, tetrahydrocarbolines, tetrahydropyrrolopyridine, and azepine-containing scaffolds.



Scheme 5.6 Summary of the divergent transformations of the tethered 1-sulfonyl-1,2,3-triazoles

Chapter 6 Miscellaneous studies

The chemistry of donor/acceptor carbenes has found extensive applications in organic chemistry and it still provides a platform for the discovery and development of new reactions.[3-5,121] The reaction systems involving rhodium donor/acceptor carbenes not only allow for chemists to improve and advance the chemistry that already exists, but also enable opportunities for reactions that are completely unexpected. Arguably, one challenge or goal of C–H functionalization is the application of the chemistry in a more complex setting. This chapter describes work on the efforts towards the expansion of the vinylogous reactivity of rhodium carbenes to an extended conjugation system, the application of sequential C–H functionalization to the total synthesis of a class of natural products, and the optimization of reaction conditions for a serendipitously discovered reaction.

6.1 Vinylogous reactivity of ethyl (3*E*,5*E*)-2-diazo-6-phenylhexa-3,5-dienoate

6.1.1 Introduction

Transition metal bound-vinylcarbenes are valuable intermediates in organic synthesis as they display a diverse array of elaborate transformations in addition to standard reactions at the carbene carbon site (carbenoid reactivity).[158] Furthermore, vinylcarbenes possess electrophilic character at the vinylogous position, permitting vinylogous reactivity (Figure 6.1.1).[36,159-164] These studies showed that the vinylogous reactivity of rhodium carbenes was favored when the vinylogous position of the vinylcarbenes is unsubstituted. Other factors found to favor vinylogous reactivity include the use of polar solvents, and sterically

demanding esters on the vinylcarbenes. In addition, the use of more electron-deficient catalysts such as some dimolybdenum, diruthenium catalysts that bears electron-withdrawing ligands enhanced the vinylogous reactivity.[165,166]

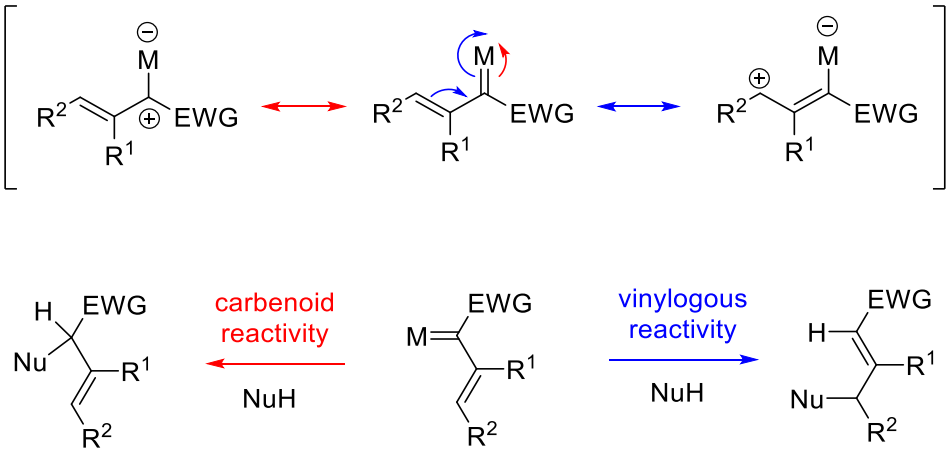
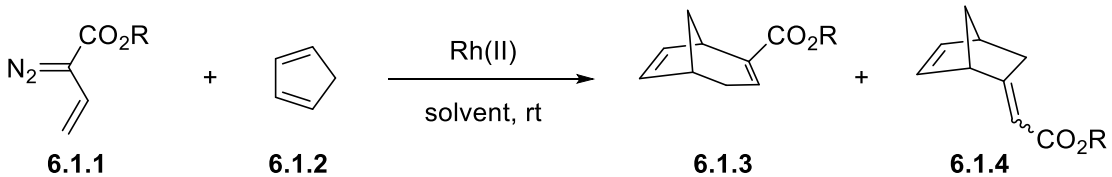


Figure 6.1.1 Reactivity of vinylcarbenes

Seminal work on vinylogous reactivity was disclosed in 1990 by the Davies group during the exploration of the reaction between vinyldiazoacetate **6.1.1** and cyclopentadiene **6.1.2** (Table 6.1.1).[159] Besides the observation of a formal [4+3] product **6.1.3**, a six-membered ring-containing bicyclic product **6.1.4** was also identified. The formation of product **6.1.4** was proposed to be derived from initial attack of the nucleophile at the vinylogous position. Further control studies suggested that the solvent, electronic nature of dirhodium catalyst, and size of the ester group influenced the pathway of the reaction. When more polar dichloromethane was used as the solvent, for example, the reaction shifted to favor the formation of product **6.1.4**. A more electron-deficient catalyst also favored the vinylogous reactivity. Increasing of the size of the ester group further shifted the reactivity towards the vinylogous position. Additional studies were disclosed by the Davies group describing the guiding principles for carbenoid versus vinylogous reactivity of rhodium(II)-stabilized vinylcarbenes.[160]

Table 6.1.1 Early studies of transformations of rhodium-vinylcarbenes with cyclopentadiene

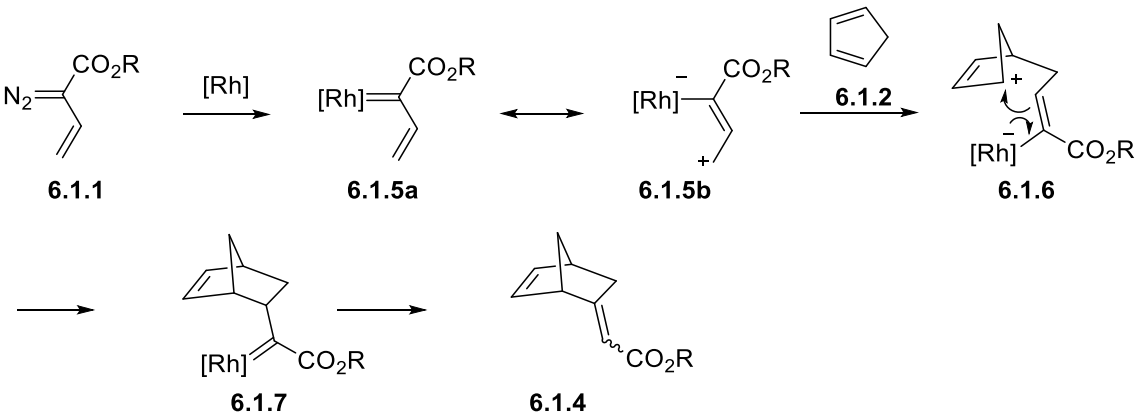


6.1.1 **6.1.2** **6.1.3** **6.1.4**

entry	catalyst	solvent	R	**6.1.3**:**6.1.4**
1	$Rh_2(OAc)_4$	pentane	Me	95:5
2	$Rh_2(OAc)_4$	CH_2Cl_2	Me	67:33
3	$Rh_2(TFA)_4$	CH_2Cl_2	Me	32:68
4	$Rh_2(OAc)_4$	CH_2Cl_2	BHT	0:100

[a]BHT: 2,6-di(*tert*-Bu)-4-methylbenzene.

The proposed mechanistic pathway for the formation of the vinylogous product is outlined (Scheme 6.1.1).[159] Upon decomposition of vinyldiazoaceatate **6.1.1**, one can rationalize the reactivity of vinylcarbene **6.1.5a** through its charge-separated form **6.1.5b**. Upon reaction with cyclopentadiene **6.1.2**, zwitterionic intermediate **6.1.6** could be generated, which can then undergo efficient ring closure to afford metallocarbene **6.1.7**. Lastly, metallocarbene **6.1.7** undergoes a 1,2-hydride shift to provide bicycloadduct **6.1.4**.



6.1.1 **6.1.5a** **6.1.5b** **6.1.6** **6.1.7** **6.1.4**

Scheme 6.1.1 Mechanistic rationale for product **6.1.4** formation

Results from recent studies on rhodium-bound vinylcarbene showed that the divergent reactivity is also dependent on the conformation of the vinylcarbenes.[36,163] Generally, the *s-trans* conformation favors vinylogous reactivity, and the reactivity can be controlled by elements that can influence the conformation of the vinylcarbenes (Figure 6.1.2). These factors include the geometry of the alkenyl about the vinylcarbenes and the nature of the catalyst. A vinylcarbene with *Z*-geometry about the vinyl group can interfere with the ligands around rhodium catalyst in the *s-cis* conformation and thus the *s-trans* conformation is favored. For similar reasons, in the presence of a sterically demanding catalyst, the vinylcarbene tends to exist preferentially in the *s-trans* conformation.

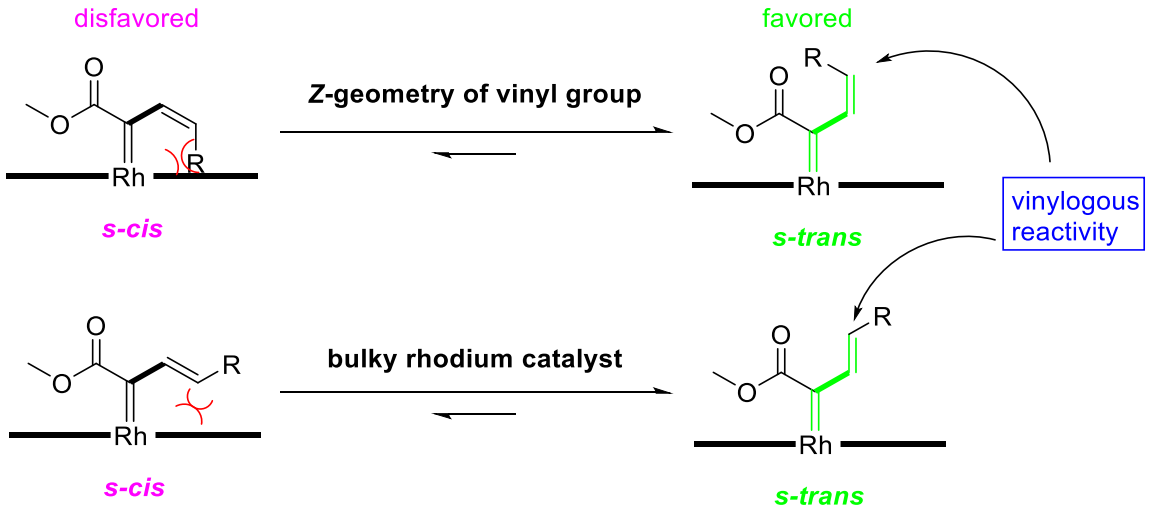
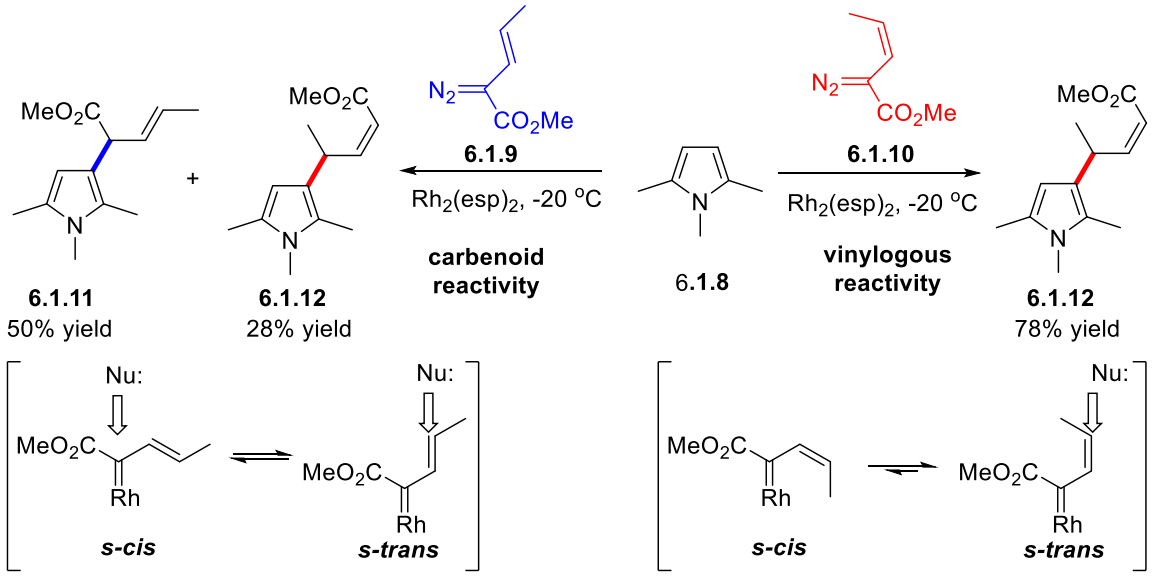


Figure 6.1.2 Factors that influence the conformation of rhodium vinylcarbenes

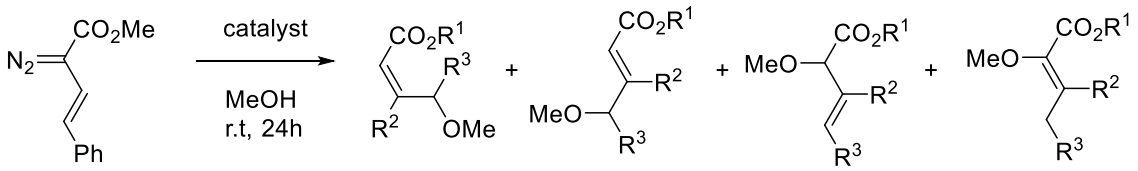
A recent example by the Davies group illustrated that the *s-trans* conformation can enhance the vinylogous reactivity (Scheme 6.1.2).[36] The reaction of a sterically hindered pyrrole derivative **6.1.8** with *E*-vinyldiazoacetate **6.1.9** gave a mixture of the vinylogous alkylation product **6.1.11** and **6.1.12**. In contrast, the reaction of **6.1.8** with *Z*-vinyldiazoacetate **6.1.10** exclusively the vinylogous alkylation product **6.1.12** in 78% yield).



Scheme 6.1.2 Enhancement of vinylogous reactivity with *Z*-vinyldiazoacetate

A more relevant example is the O−H insertion reaction between styryl diazo compound and methanol.[165,166] The reactivity profile of vinyldiazoacetate **6.1.13** was found to be dependent on the nature of the catalyst used: the more electron-deficient ruthenium and molybdenum catalysts favored vinylogous reactivity and so did AgOTf (Table 6.1.2). When Rh_2(*S*-TBSP)$_4$ was used as the catalyst, the reaction of diazo **6.1.13** with methanol gave exclusive carbenoid reactivity products. In contrast, when silver was used as the catalyst, the reaction of diazo compound **6.1.13** with methanol gave 89:5:6 ration of ***Z*-6.1.14**:***E*-6.1.14**:**6.1.15** in favor of the vinylogous reactivity product. The general trend is that the use of more electron-deficient catalyst favors the vinylogous reactivity.

Table 6.1.2 O−H insertion of methyl (*E*)-2-diazo-4-phenylbut-3-enoate (**6.1.13**)



catalyst	combined yield	***Z*-6.1.14:*E*-6.1.14:6.1.15:6.1.16**
Rh_2(*S*-TBSP)$_4$	86	0:0:89:11
$Mo(CO)_6$/*S*-TBSP-H	93	34:17:40:9
$Ru_2(TFA)_2(CO)_5$	45	11:75:14:0
AgOTf	95	89:5:6:0

With vinylogous reactivity in mind, it was of interest to explore the reactivity profile of ethyl (3*E*,5*E*)-2-diazo-6-phenylhexa-3,5-dienoate[167]. A component of further consideration in this system is if vinylogous reactivity is favored, which vinylogous site will be preferred (Figure 6.1.3). As a result, systematic studies were undertaken to explore the system.

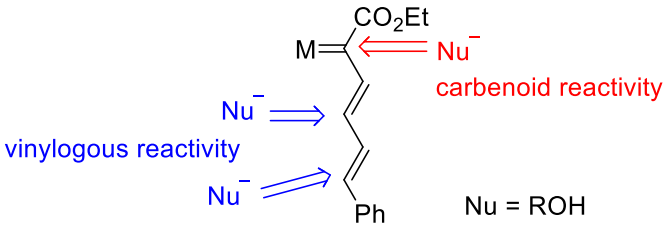


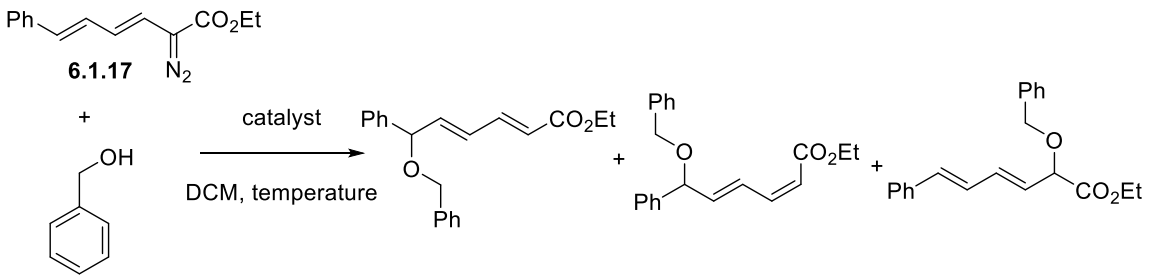
Figure 6.1.3 System to be studied for vinylogous reactivity

6.1.2 Results and Discussion

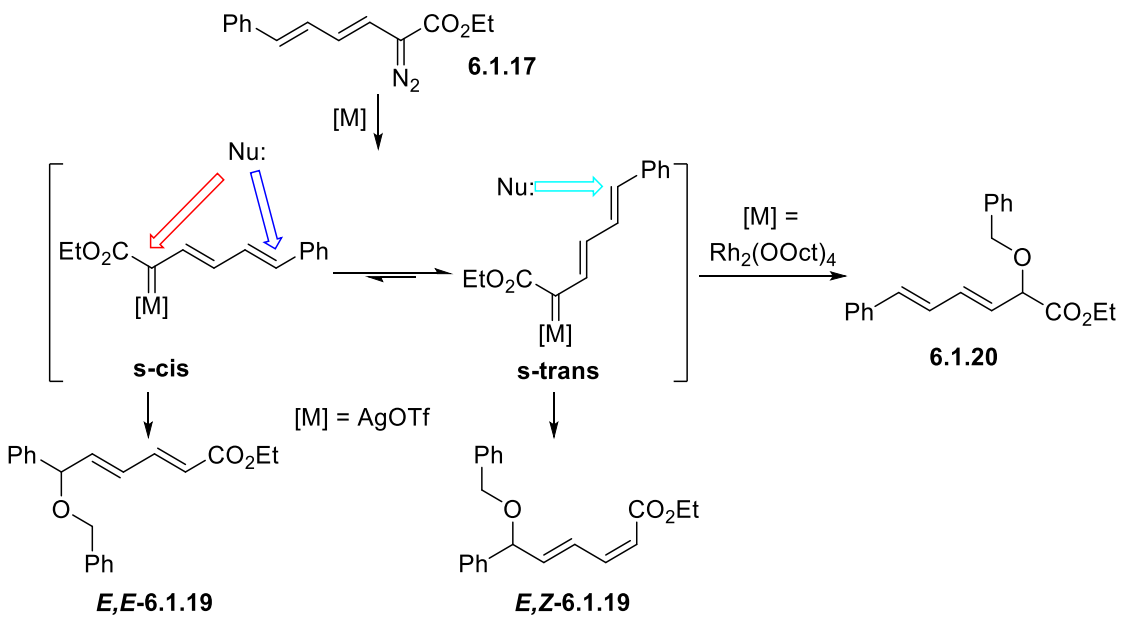
An initial test was performed using ethyl (3*E*,5*E*)-2-diazo-6-phenylhexa-3,5-dienoate (**6.1.17**) and benzyl alcohol (**6.1.18**) (Table 6.1.3). As expected, the reaction of diazo compound **6.1.17** with benzyl alcohol under the catalysis of a dirhodium catalyst $Rh_2(OOct)_4$ gave exclusively carbenoid reactivity product **6.1.20** (Table 6.1.3, entry 1). With the more electron-deficient catalyst AgOTf, the products derived from vinylogous

reactivity were preferentially formed with 15.7:1.5:1 ratio of ***E,E*-6.1.19**:***E,Z*-6.1.19**:**6.1.20**, and interestingly, at the remote vinylogous site exclusively (Table 6.1.3, entry 2). Increasing the temperature led to slight decrease of ratio of ***E,E*-6.1.19**:***E,Z*-6.1.19**, and the vinylogous reactivity mainly dominated (Table 6.1.3, entries 3-4). The mechanism for the product distribution is that with a dirhodium catalyst, carbenoid reactivity dominated, and the product **6.1.20** was the major product. On the contrary, when AgOTf was used as the catalyst, vinylogous reactivity was favored. Furthermore, similar to the AgOTf-catalyzed O−H insertion reaction with methyl (*E*)-2-diazo-4-phenylbut-3-enoate, ***E,E*-6.1.19** derived from the *s-cis* conformation was formed as the major product.[165]

Table 6.1.3 Reactivity profile of ethyl (3*E*,5*E*)-2-diazo-6-phenylhexa-3,5-dienoate diazo (**6.1.17**)



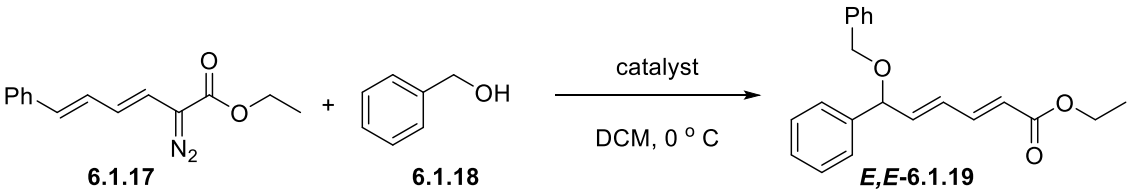
entry	catalyst	temperature	yield of major product	*E,E*-**6.1.19**:*E,Z*-**6.1.19**:***6.1.20***
1	$Rh_2(OOct)_4$	0 °C	76%	<1::1:19
2	AgOTf	0 °C	74%	15.7:1.5:1
3	AgOTf	rt	68%	10:1.1:1
4	AgOTf	reflux	60%	7.1:0.7:1



Scheme 6.1.3 Rationale for product distribution

With these results in hand, the next step was to explore the possibility of asymmetric O−H insertion (Table 6.1.4). A combination of silver triflate and chiral phosphine ligand (*S*)-Tol-BINAP only gave trace amount of product with incomplete decomposition of the staring diazo compound (entry 1). We then turned our attention to the gold catalysis[14b,32,168] in the hope that this approach would give better results, as gold-carbenes were demonstrated to be effective in other carbene transformations. A series of combinations of catalysts and ligands were tested and the vinylogous reactivity was favored. However, essentially these conditinos did not give enantioinduction (entries 2-7).

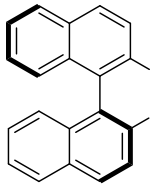
Table 6.1.4 Exploration of an asymmetric version of the vinylogous O−H insertion reaction



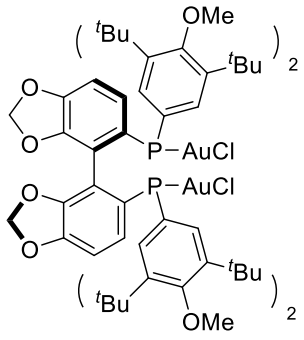
6.1.17 **6.1.18** ***E,E*-6.1.19**

entry	catalyst	yield	ee
1	AgOTf/(*S*)-Tol-BINAP	< 5%[a]	/
2	$AgSbF_6$/(*S*)-Xylyl-BINAP$(AuCl)_2$	41%	< 5%
3	$AgSbF_6$/(*R*)-DTBM-SEGPHOS$(AuCl)_2$	22%	< 5%
4	AgOTf/(*R*)-DTBM-SEGPHOS$(AuCl)_2$	39%	< 5%
5	AgOTf/(*S*)-Tol-BINAP$(AuCl)_2$	45%	8%
6	AgOTf/(*S*)-BINAP$(AuCl)_2$	42%	< 5%
7	AgOTf/(*S*)-MonoPhos(AuCl)	55%	< 5%

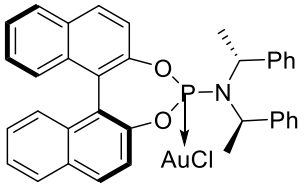
[a]Diazo compound was not completely decomposed.



R = Tol: (*S*)-Tol-BINAP
R = Xylyl: (*S*)-Tol-BINAP
R = H: (*S*)-BINAP

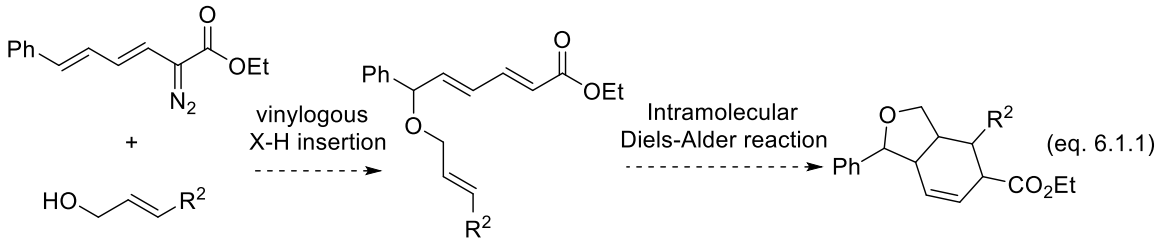


(*R*)-DTBM-SEGPHOS$(AuCl)_2$



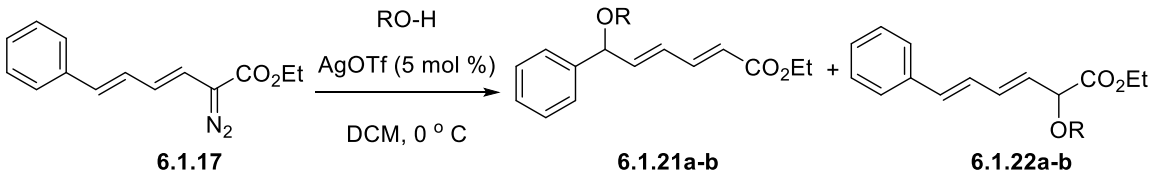
(*S*)-MonoPhos(AuCl)

We imagined that the carbene O−H insertion reaction might be combined with an intramolecular Diels−Alder reaction (eq. 6.1.1). If that is the case, then cascade reactions would allow the construction of more complex structures from simple substrates. To this end, an allylic alcohol would need to be used.

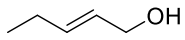
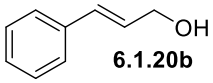


First, we attempted to extend the O−H insertion chemistry to allylic alcohol **6.1.20** (Table 6.1.5). Similar to the results obtained with benzyl alcohol, the dirhodium catalyst gave exclusively carbenoid reactivity, while the reaction preferred vinylogous reactivity with AgOTf as the catalyst. The products **6.1.21-6.1.22** obtained in these reactions set the stage for the exploration of the intramolecular Diels−Alder reaction.

Table 6.1.5 Extension of the reactions to allylic alcohols



6.1.17 **6.1.21a-b** **6.1.22a-b**

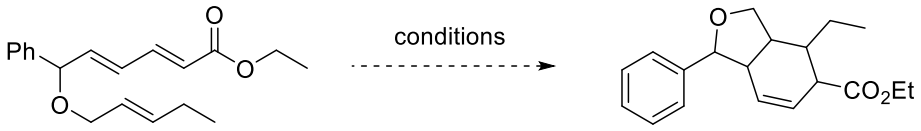
RO-H	catalyst	**6.1.21**:**6.1.22**[a]	yield[b]
 **6.1.20a**	AgOTf	>95:5	70%
	$Rh_2(OOct)_4$	<5:95	75%
 **6.1.20b**	AgOTf	94:6	75%
	$Rh_2(OOct)_4$	<5:95	52%

[a]analysis based on crude ^{1}H NMR. [b]isolated yield of the major product.

With the product **6.1.21a-b** in hand, we then turned to explore the intramolecular Diels−Alder reaction. The possibility with product **6.1.21a** was explored first (Table 6.1.6). Unfortunately, under the several conditions that were employed, the desired Diels−Alder reaction did not take place. When the reaction was performed under refluxing toluene, starting material remained. This was also the case when the temperature was elevated to 150 ℃ and 200 ℃ under microwave heating. Attempts to promote a Lewis acid-catalyzed

Diels−Alder reaction were met with little success. When **6.1.21a** was treated with $AlCl_3$ at 0 °C, the starting material was decomposed, but the products were still not obtained.

Table 6.1.6 Exploration of Diels−Alder reaction with **6.1.21a**

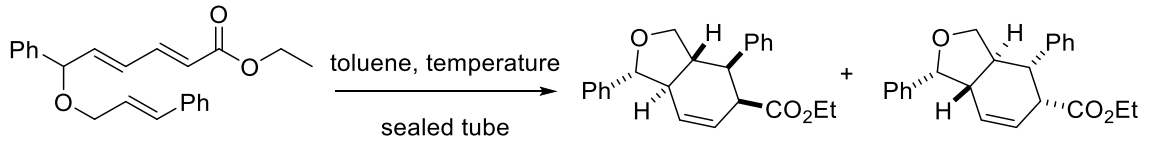


6.1.21a **6.1.23**

condition	result
toluene, reflux, 12 h	no desired product, recovery of starting material
Microwave, toluene, 150 °C, 30 min	no desired product, recovery of starting material
Microwave, toluene, 200 °C, 30 min	no desired product, recovery of starting material
$AlCl_3$ (20 mol %), DCM, 0 °C	no desired product, starting material was decomposed

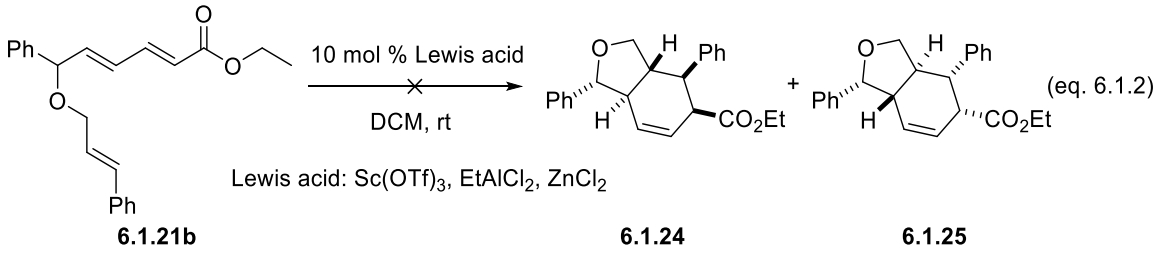
We hypothesized that because the ethyl group is not strongly electron-donating for inverse electron-demand Diels−Alder reaction. As a result, we tried the Diels−Alder reaction with product **6.1.21b** featuring an electron-rich dienophile (Table 6.1.7). To our delight, the desired products **6.1.24** and **6.1.25** were obtained in 4:1 dr and in high yield at 150 °C in toluene (sealed vessel) (entries 1-3). Further screening of solvents suggested that trifluorotoluene and dichloroethane also worked well (entries 4-5). The structure of the major diastereomer was confirmed by X-ray crystallography (Figure 6.1.4). Lewis acid conditions were still ineffective in this system with substrate **6.1.21b** (eq. 6.1.2).

Table 6.1.7 Exploration of Diels−Alder reaction with **6.1.21b**



6.1.21b **6.1.24** **6.1.25**

entry	solvent	temperature	**6.1.24**:**6.1.25**	combined yield
1	toluene	110 °C	/	no reaction, recovery of **6.1.21b**
2	toluene	150 °C	4:1	92%
3	toluene	180 °C	/	decomposition
4	TFT	150 °C	4:1	91%
5	DCE	150 °C	4:1	89%



6.1.21b **6.1.24** **6.1.25**

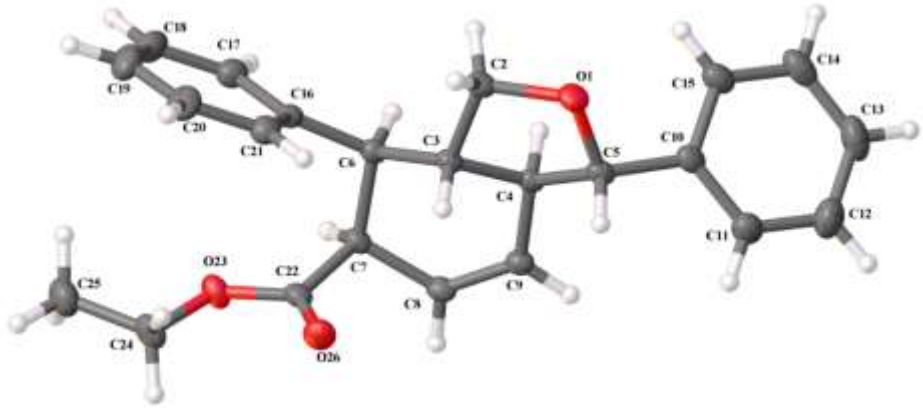
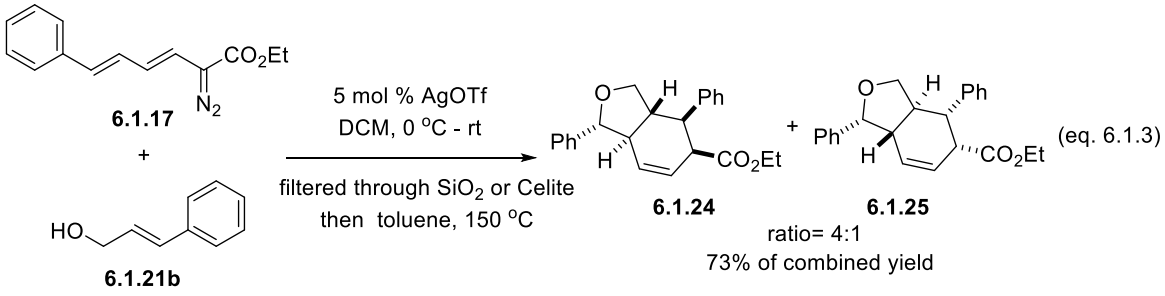


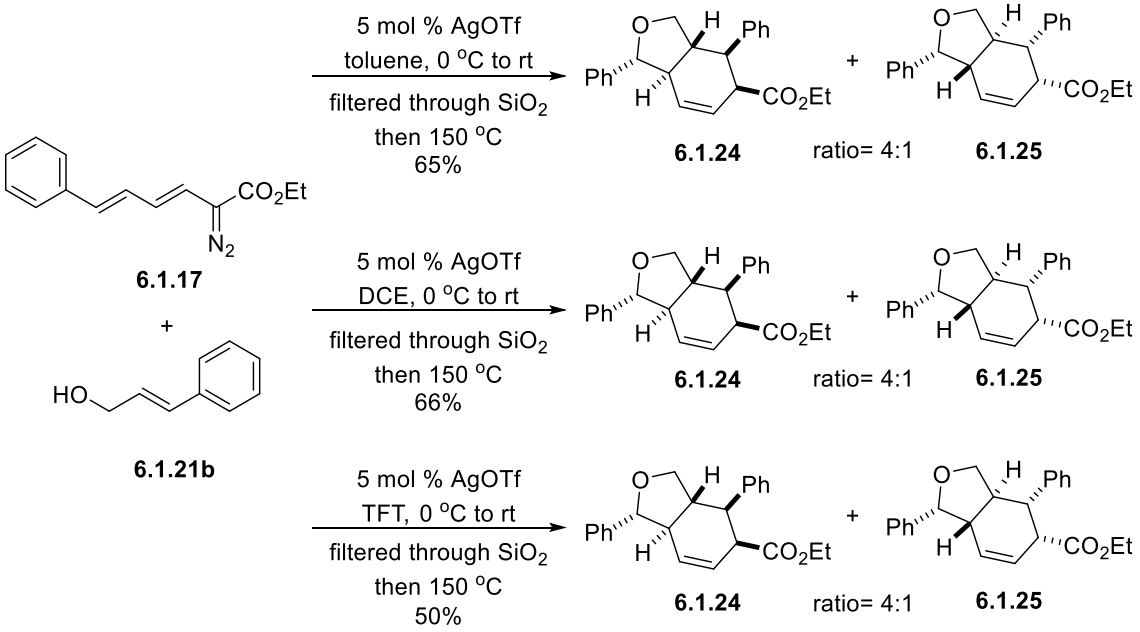
Figure 6.1.4 X-ray crystal structure of the DA product (major diastereomer **6.1.24**)

We then turned our attention to the development of a sequential O−H insertion/Diels−Alder reaction procedure (eq. 6.1.3). After the first step was complete, removal of the silver salt by either SiO_2 or Celite® and evaporation of the solvent and then subjecting the system to Diels−Alder conditions afforded the desired prodcts in good yield.

This procedured avoided the need to purify the starting material for the cycloaddition reaction.



A one-pot, two-step, single-solvent procedure with one filtration was further successfully developed. Toluene or dichloroethane could be used as a single solvent in the cascade reactions to afford the cyclic products **6.1.24** and **6.1.25** in similarly good yield and diastereomeric ratio, while the use of α,α,α-trifluorotoluene (TFT) as the solvent lead to slightly lower yield (Scheme 6.1.4).



Scheme 6.1.4 Development of a sequential two-step procedure with single solvent

6.1.3 Summary

1. Silver catalysis favors the vinylogous reactivity while rhodium catalyst favors carbenoid reactivity for vinylcarbenes with extended conjugation.

2. The combination of O−H insertion and intramolecular Diels−Alder reaction is possible, leading to the formation of bicyclic structures form simple substrate.

3. Thus far, an asymmetric version of the transformation is still not successful, suggesting that further exploration is required.

6.2 Efforts towards the formal total synthesis of ephedradine *via* sequential C−H functionalization strategy

6.2.1 Introduction

Ephedradine A-D (Figure 6.2.1) are complex macrocyclic spermine alkaloids isolated by Hikino and co-workers in 1979.[169] They are used as one of the components in traditional Chinese medicine. The structure consists of a unique framework of substituted dihydrobenzofuran core, bridged across a seventeen-membered lactam ring containing a spermine unit. The first racemic synthesis of ephedradine A was reported by Wasserman and coworkers in 1985.[170] The first enantioselective total synthesis of (−) ephedradine A was accomplished by Fukuyama in 2003 using a linear approach.[171] In this approach, a diastereoselective Rh_2(*S*-DOSP)$_4$ catalyzed intramolecular C−H insertion reaction was used to construct the dihydrobenzofuran ring.

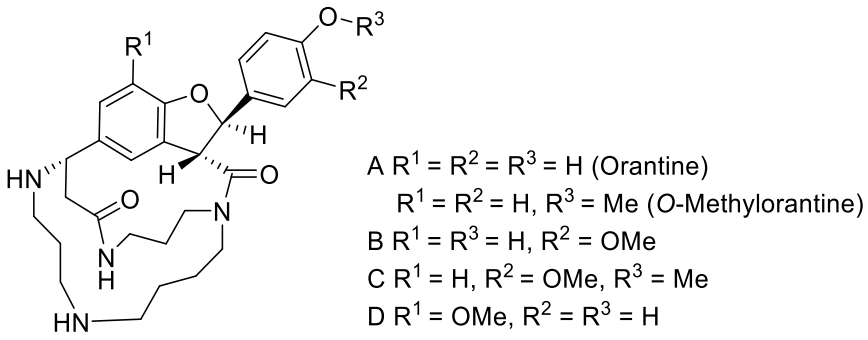


Figure 6.2.1 Ephedradine family of natural products

As part of a collaborative project between the Davies, Jin-Quan Yu, Justin DuBois, and Simon Blakey group, it was hypothesized that the synthesis of ephedradine can be achieved using sequential C−H functionalization strategies (Figure 6.2.2). Specifically, we envisioned that sequential C−H amination,[172] C−H oxidative/cyclization[173-174] and carbene C−H insertion[173,175] can be applied to expedite the total synthesis of ephedradine. This strategy was first conceived by former postdoctoral scholar Dr. Jillian E. Spengler, and was explored in more detail by Dr. Sandeep Raikar.

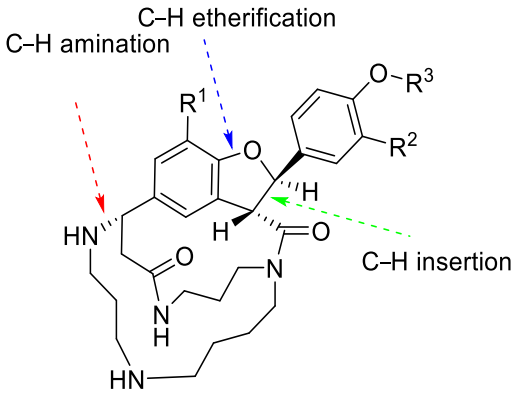
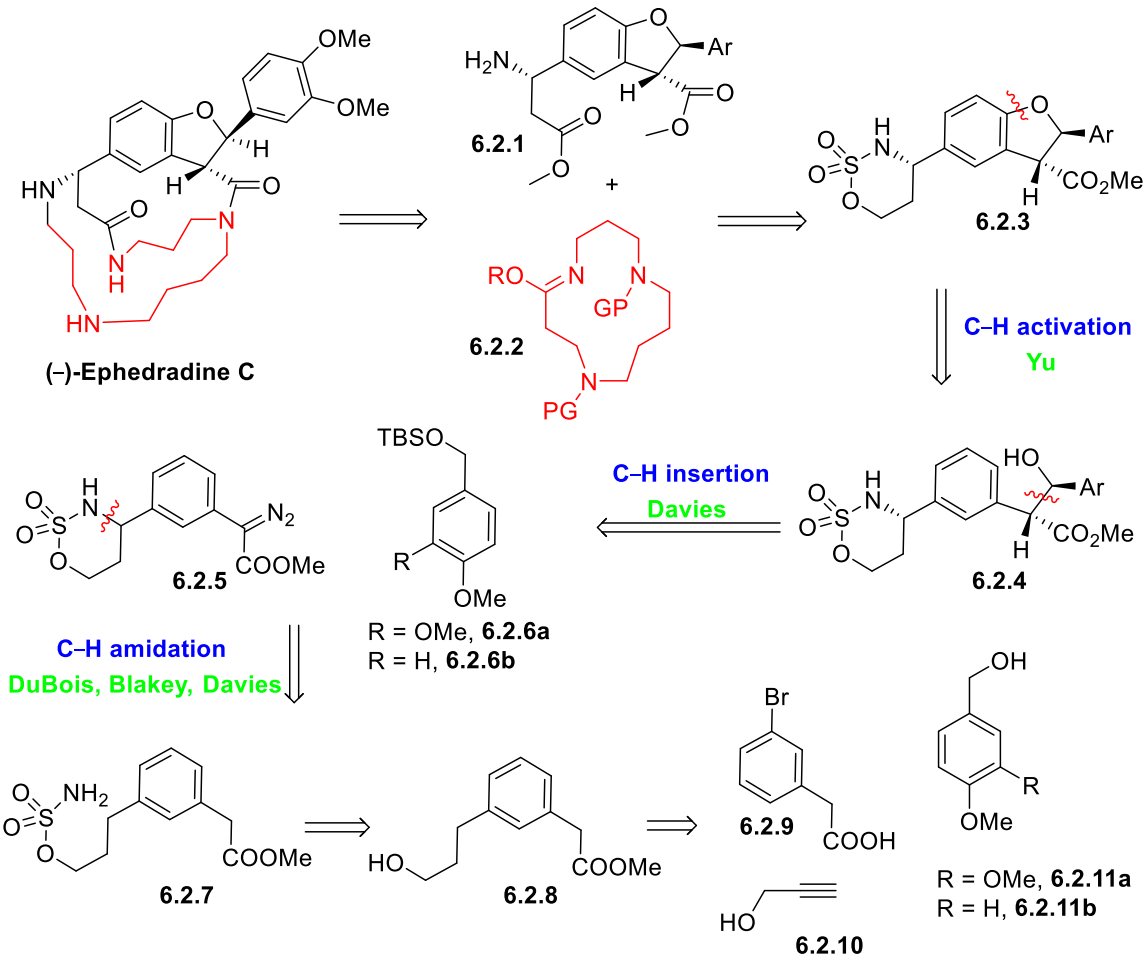


Figure 6.2.2 Key disconnections in the synthesis of ephedradine

From the perspective of retrosynthesis, ephedradine can be broken down into two halves, the dihydrobenzofuran **6.2.1** core and the macrocycle **6.2.2**. The coupling of two fragments was previously reported by Wasserman.[170] Our focus was on the

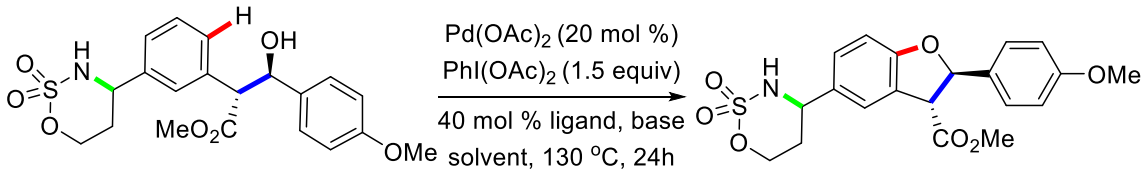
enantioselective synthesis of the dihydrobenzofuran core **6.2.1**, aiming to accomplish a formal total synthesis. Inspired by research from the DuBois group,[172] we envisioned that the *β*-amino ester could be masked as oxathiazinane dioxide **6.2.3**. The dihydrobenzofuran core could be prepared by a palladium-catalyzed intramolecular C−H oxidation/cyclization from compound **6.2.4** using Yu's chemistry.[173-174] An intermolecular asymmetric carbene C−H carbene insertion[173,175] between **6.2.5** and **6.2.6** could assemble the dihydrobenzofuran compound **6.2.4**. The cyclic oxathiazinane dioxide in **6.2.5** could be installed *via* an intramolecular C−H amidation of **6.2.3** using Rh(II)-catalysis developed by the DuBois or the Blakey research groups.



Scheme 6.2.1 Retrosynthetic analysis of ephedradine

Former postdoctoral scholar Dr. Sandeep Raikar did extensive investigations into this strategy and showed that this strategy was initially very promising. However, for this strategy to be practical, one key challenge needs to be addressed. The C–H oxidation/cyclization step was low-yielding (the highest yield was 10%). In either the later stage of the synthetic sequence (Table 6.2.1), or the earlier stage (Table 6.2.2), the C–H oxidation/cyclization step was problematic because of the low yielding of the reaction after extensive optimization.

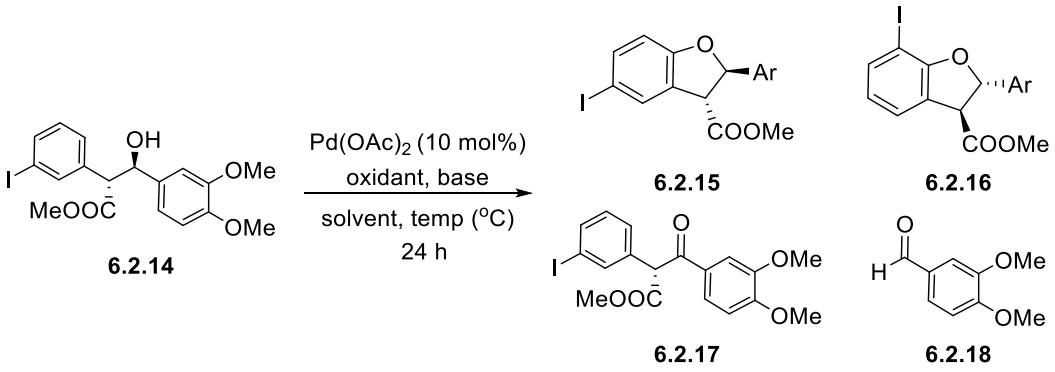
Table 6.2.1 Optimization of the C–H oxidation/cyclization with **6.2.12**



6.2.12 **6.2.13**

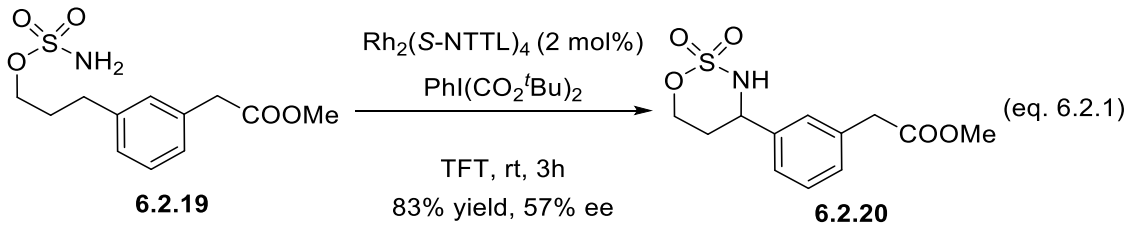
entry	solvent	base	ligand	yield
1	DCE	Li_2CO_3	none	0
2	PhMe	Li_2CO_3	none	0
3	$PhCF_3$	Li_2CO_3	none	0
4	C_6F_6	Li_2CO_3	none	0
5	HFIP	Li_2CO_3	none	0
6	EtOAc	Li_2CO_3	none	0
7	tAmylOH	Li_2CO_3	none	0
8	PhMe	Na_2HPO_4	none	0
9	$PhCF_3$	Na_2HPO_4	none	0
10	C_6F_6	Na_2HPO_4	none	10
11	C_6F_6	Li_2CO_3	Ac-Leu-OH	0
12	C_6F_6	Li_2CO_3	Ac-Leu-OH	0

Table 6.2.2 Optimization of the C–H oxidation/cyclization with **6.2.14**



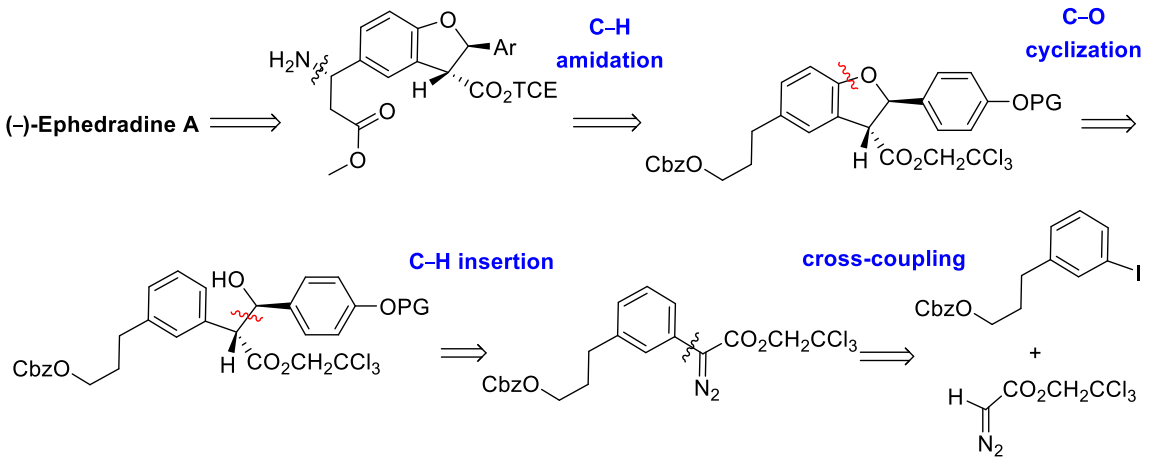
entry	solvent	oxidant	base	temp (°C)	result
1	C_6F_6/DCE	$PhI(OAc)_2$	Li_2CO_3	100	traces of **6.2.15** + unreacted **6.2.14**
2	C_6F_6/DCE	NFSI	Li_2CO_3	100	0% of **6.2.15**
3	DCE	NFSI	Li_2CO_3	100	0% of **6.2.15**

Furthermore, the nitrene C–H insertion was not highly stereoselective. The highest ee for the nitrene C–H insertion was 57% in an intramolecular C–H amination reaction after extensive optimization. When the intramolecular C–H amination reaction of substrate **6.2.16** was performed with Rh_2(*S*-NTTL)$_4$ as the catalyst and $PhI(CO_2{}^tBu)_2$ as the oxidant, the product **6.2.20** was obtained in 83% yield with 57% ee (eq. 6.2.1).



These studies showed that this strategy was promising; however, the two aforementioned problems needed to be solved. To solve the problems, we envisioned that the unsatisfactory C–H oxidation/cyclization step might be better addressed by using an electron-withdrawing group on the aryl ring. By doing so, we could potentially suppress the retro-aldol and oxidation side-reactions that competed with the C–H

oxidation/cyclization (Table 6.2.2). Additionally, one possible approach to solve or circumvent the low stereoselectivity in C–H amination might be to use chiral auxiliary for the C–H amination reaction. The new disconnection strategy is outlined in Scheme 6.2.2. This strategy uses the cross-coupling reaction that was described in Chapter 4 for the preparation of trichloroethyl aryldiazoacetates and thus highlights another formal C–H functionalization reaction. The use of trichloroethyl aryldiazoacetates tend to give improved reactions with regards to yield and enantioselectivity for C–H insertion reaction. Furthermore, reactions involving trichloroethyl aryldiazoacetates can be conducted in dichloromethane and thus might avoid the poor solubility of some substrates in hydrocarbon solvent that we used for the proposed carbene C–H insertion reaction.[173,175]

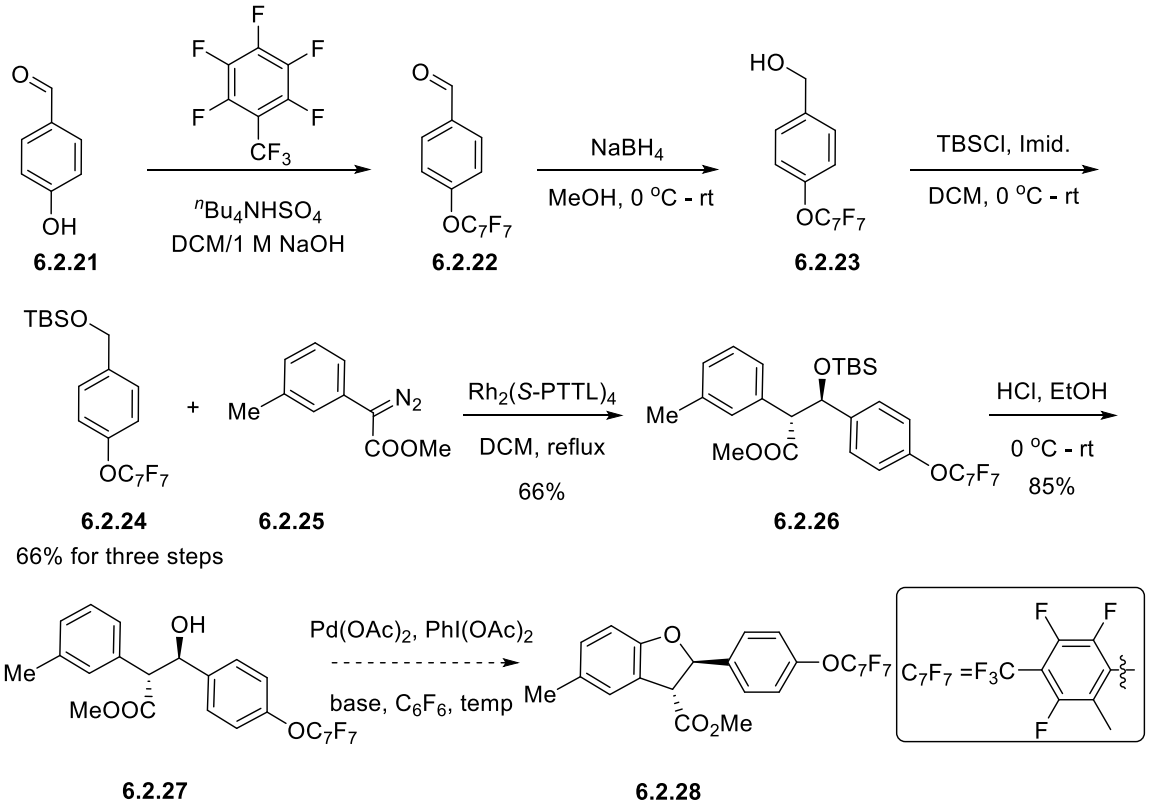


Scheme 6.2.2 New retrosynthetic strategy outlining the synthesis of ephedradine A

6.2.2 Results and discussion

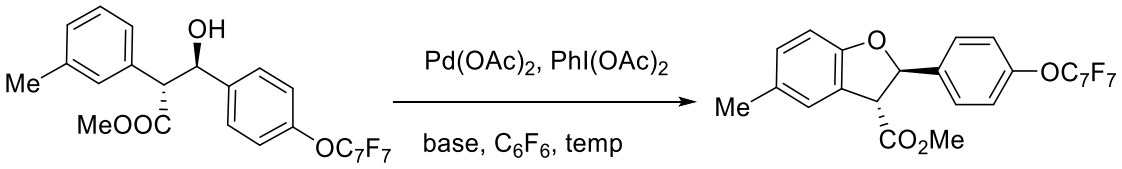
To test the hypothesis, model studies were first performed (Scheme 6.2.3). The precursor for the key C–H oxidation/cyclization step was quickly synthesized. Benzyl silyl ether **6.2.24** that contained a heptafluoryl tolyl protecting group[176] for the phenolic hydroxyl was prepared in three steps from 4-hydroxybenzaldehyde **6.2.21** in 66% overall

yield. Following a precedent C–H insertion reaction between benzyl silyl ether and aryldiazoacetates by the Davies group,[173,175] the reaction of **6.2.24** with **6.2.25** afforded carbene C–H insertion product **6.2.26**, which was then hydrolyzed to give the alcohol **6.2.27**. With the cyclization precursor **6.2.27** in hand, it was tested under some typical conditions. To our delight, the C–H oxidation/cyclization reaction worked reasonably well and the desired cyclization product **6.2.28** was obtained in 36% yield. Examination of another base Na_2HPO_4 gave similar result, while elevation of reaction temperature to 120 ℃ led to decomposition of starting material.



Scheme 6.2.3 Model studies for ephedradine C–H functionalization

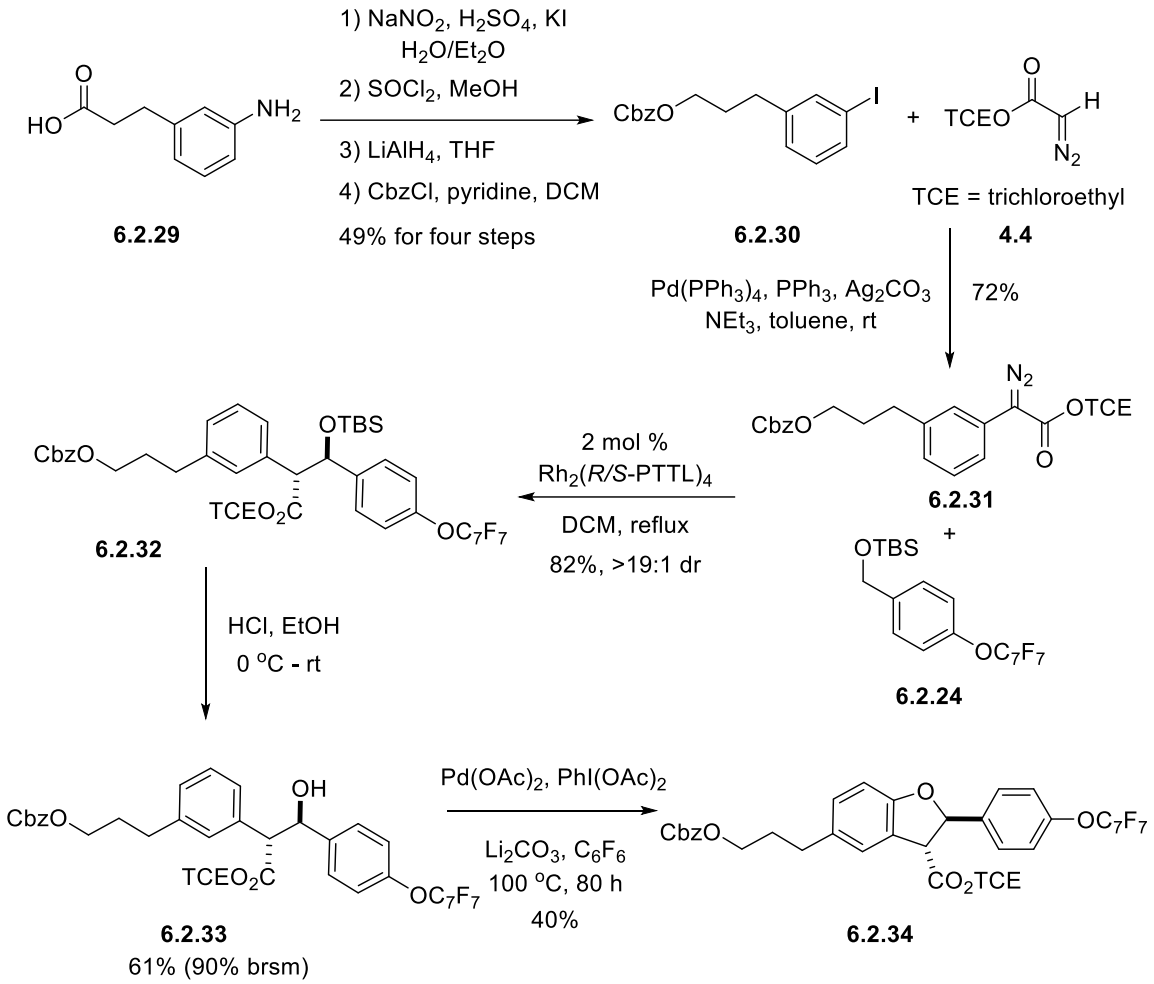
Table 6.2.3 Optimization studies for the intramolecular C–H oxidation/cyclization reaction in model studies



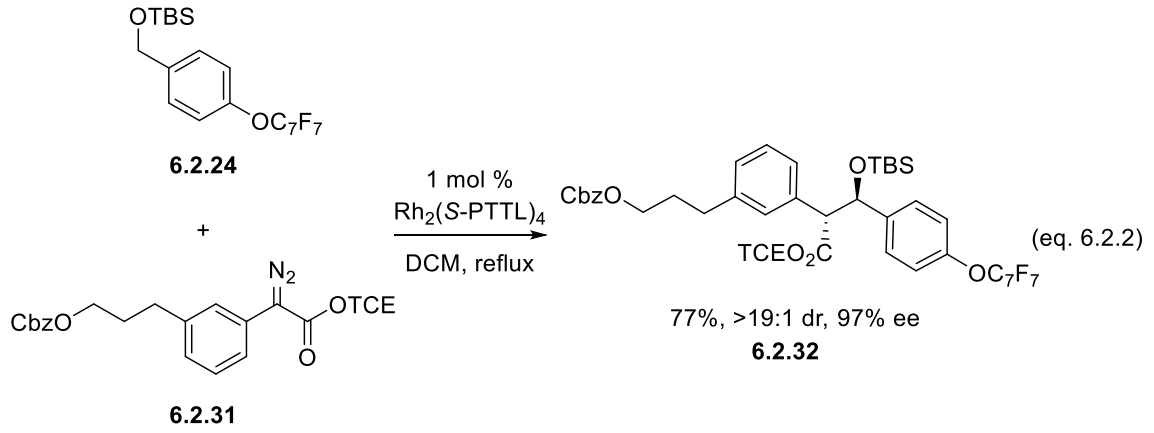
6.2.27 **6.2.28**

entry	base	temp (^{o}C)	yield (%)
1	Li_2CO_3	100	36
2	Na_2HPO_4	100	35
3	Li_2CO_3	120	decomposition

With this promising result, the forward synthesis of the core structure of ephedradine A was explored (Scheme 6.2.4). The cross coupling precursor **6.2.30** was synthesized from 3-(3-aminophenyl)propanoic acid (**6.2.29**) in four steps in 49% overall yield. The cross-coupling reaction between **6.2.30** and 2,2,2-trichloroethyl diazoacetate (**4.4**) efficiently gave the diazo product **6.2.31**, which underwent an effective carbene C–H insertion reaction to afford **6.2.32** in 77% yield in high diastereomeric ratio with high enantioselectivity (97%) (eq. 6.2.2). Hydrolysis of the carbene C–H insertion reaction product **6.2.32** gave the cyclization precursor **6.2.33** in 61% yield (90% based on recovered staring material). Gratifyingly, the C–H oxidation/cyclization reaction successfully afforded the desire product **6.2.34** in 40% yield after 80 h at 100 ℃. With these results in hand, the core dihydrobenzofuran structure of ephedradine was obtained.



Scheme 6.2.4 Forward synthesis of the core structure of ephedradine A

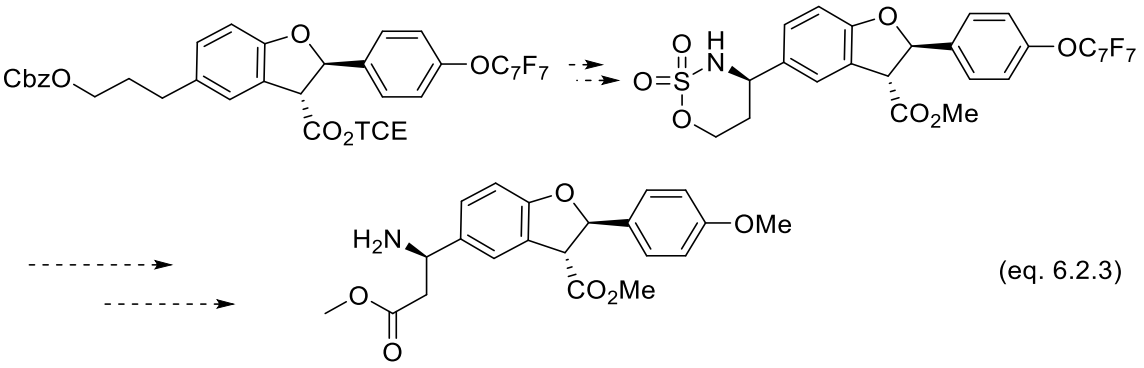


6.2.3 Summary

A four-fold C–H functionalization strategy involving C–H amination, carbene C–H insertion, C–H oxidation/cyclization, and cross-coupling reactions was designed for the synthesis of the core structure of ephedradine. The carbene C–H insertion reaction with trichloroethyl aryldiazoacetates was conducted in dichloromethane and gave high level of enantioselectivity. By introducing an electron-withdrawing heptafluoryl tolyl protecting group for the phenolic hydroxyl group, the C–H oxidation/cyclization proceeded in synthetically useful yield, affording the dihydrobenzofuran core structure of ephedradine.

6.2.3 Future direction

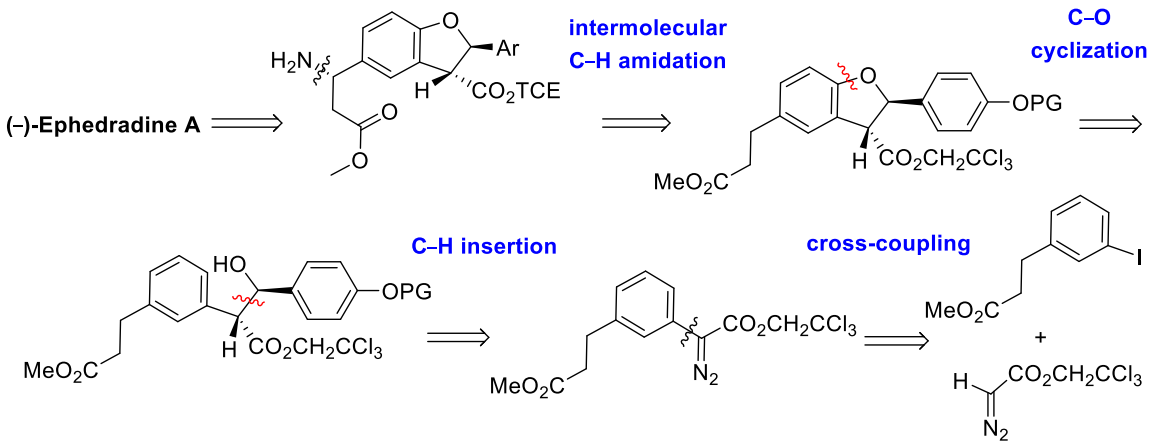
1. The first direction would be to push the core structure of ephedradine further and arrive at a formal total synthesis of *O*-methylorantine (eq. 6.2.3).



(eq. 6.2.3)

common intermediate for the formal total synthesis

2. Another direction is to use a revised synthetic plan relying on an intermolecular C–H amination reaction (Scheme 6.2.5). This approach might be able to avoid manipulation of the oxidation state of the side chain and to utilize the auxiliary-assisted intermolecular C–H amination.

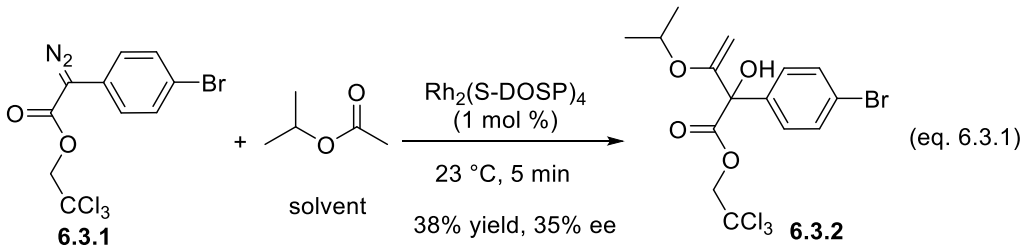


Scheme 6.2.5 Another new retrosynthetic strategy for the synthesis of ephedradine

6.3 Exploration of the formation of a tertiary carbinol *via* a rhodium(II)-catalyzed reaction with isopropyl acetate

6.3.1 Introduction

Recently, Dr. Cecilia Tortoreto in the Davies group discovered a reaction while exploring the used of novel catalysts in carbene C–H insertion reactions. Dr. Tortoreto noticed an unprecedented side reaction occurring in some reactions when isopropyl acetate was used as the solvent. With isopropyl acetate as the solvent, the reaction of a trichloroethyl aryldiazoacetate gave an unknown product in 38% yield with 35% enantioselectivity (eq. 6.3.1). Early ^{1}H NMR analysis of the unknown compound led to the suggestion that a unique quaternary hydroxyl-enoate was formed.



(eq. 6.3.1)

This initial result provides a good starting point to further explore the new reactivity. This chapter describes studies to further optimize reaction conditions, and to obtain a consistent procedure for transformation. The aims of the studies are: 1) to resolve and confirm the structure of the product; 2) to optimize the reaction conditions for the reactions with the hope of achieving high enantioselectivity; 3) to investigate into the scope and utilities of the reaction.

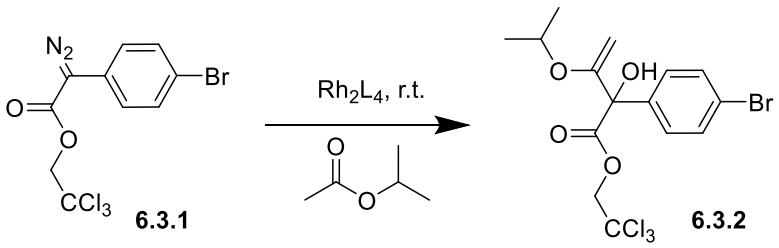
6.3.2 Results and discussion

Note: this work was conducted closely together with Mr. Kevin Hoang, a pre-graduate student, and Mr. Cameron Pratt, a summer rotation student, whom I mentored during their time in the Davies group. Reactions were performed by them unless otherwise stated.

The optimization of reactions was conducted with the standard substrate **6.3.1** using isopropyl acetate as the solvent (Table 6.3.1). The method of addition of diazo compound was first examined, and it turned out that one batch addition is superior to slow addition of the aryldiazoacetate **6.3.1** (entry 1-2). Different types of catalysts, including the prolinate (entry 1-2), phthalimidyl (entries 3-7), phosphinate (entry 8), triarylcyclopropane (entries 9-14), and the diarylcyclopropane (entry 15) catalysts were tested. Dichloromethane was known to be a good solvent for reactions with Rh_2(*S*-*p*-BrTPCP)$_4$.[28,53,107] However, when the reaction was performed under the catalysis of Rh_2(*S*-*p*-BrTPCP)$_4$, the reaction was not effective even when dichloromethane was employed as the solvent (entry 10). Among these catalysts examined, the best result with respect to the yield obtain was with Rh_2(*S*-DOSP)$_4$, and the product **6.3.2** was afforded in 58% yield but with low ee (29%). With Rh_2(*R*-

2Cl,4Br-TPCP)$_4$ as the catalyst, the reaction gave the product in high ee (87%) but with low yield (25%).

Table 6.3.1 Screening of chiral non-racemic catalysts[a]



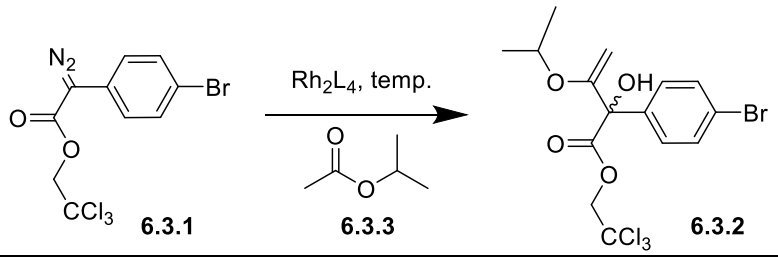
entry	catalyst	yield (%)	ee (%)
1	**Rh$_2$(*S*-DOSP)$_4$**	**56**	**29**
2[b]	Rh$_2$(*S*-DOSP)$_4$	17	10
3	Rh$_2$(*S*-PTAD)$_4$	57	-5
4	Rh$_2$(*S*-TCPTAD)$_4$	39	-19
5	Rh$_2$(*S*-NTTL)$_4$	27	-42
6	Rh$_2$(*S*-TBPTTL)$_4$	46	-50
7	Rh$_2$(*S*-TFPTTL)$_4$	10	-8
8	Rh$_2$(*R*-BNP)$_4$	/	/
9	Rh$_2$(*S*-*p*-BrTPCP)$_4$	7	26
10	Rh$_2$(*S*-*p*-BrTPCP)$_4$	<5[c]	/
11	Rh$_2$(*S*-*p*-PhTPCP)$_4$	13	<5
12	Rh$_2$(*S*-*o*-2Cl-TPCP)$_4$	10	51
13	Rh$_2$(*S*-*o*-2Cl,5Br-TPCP)$_4$	32	24
14	**Rh$_2$(*S*-*o*-2Cl,4Br-TPCP)$_4$**	**25**	**87**
15	Rh$_2$(*S*-DPCP)$_4$	26	-6

[a]Reaction conditions: **6.3.1** (0.3 mmol) was added in one portion to the catalyst (1 mol %) in 2 mL isopropylacetate at room temperature. [b]The diazo in 2 mL isopropylacetate was added with a syringe pump. [c]Dichloromethane was used as the solvent with 10 equivalents of isopropyl acetate as the substrate.

We then focused on improving the yield of the reaction (Table 6.3.2). Achiral catalysts were first examined and $Rh_2(OOct)_4$ worked best, but it was still inferior to Rh_2(*S*-DOSP)$_4$ (entries 1-6). Further optimization of solvent and concentration of the materials with Rh_2(*S*-DOSP)$_4$ as the catalyst showed that they are critical factors (entries 7-8). When the reaction was performed in a mixed solvent of dichloromethane and isopropyl acetate (0.5 mL/0.5 mL) at room temperature, the product **6.3.2** was obtained in 61% yield. Further increasing the temperature to 40 ℃ outcompeted side dimerization reactions and **6.3.2** was obtained in 71% yield, while performing the reaction at 60 ℃ with achiral catalyst was not beneficial (entries 9-10). With this optimized solvent combination, concentration and temperature, two achiral catalysts that worked best in this transformation, $Rh_2(OOct)_4$ and $Rh_2(OAc)_4$, were further examined. The reactions led to similarly improved yield (entries 11-12) and with $Rh_2(OOct)_4$ as the catalyst, the reaction afforded the product in 68% yield (entry 11). The structure of product **6.3.2** has been confirmed by X-ray crystallography (Figure 6.3.1).

A possible mechanistic pathway for the formation of product **6.3.2** is outlined in Scheme 6.3.1. Decomposition of the trichloroethyl aryldiazoacetate **6.3.1** by dirhodium catalyst generates a rhodium-bound carbene. Following the formation this rhodium carbene, the carbonyl group of the isopropyl acetate can attack the carbene to form a carbonyl ylide intermediate **6.3.3**. This step has largely been thought to be reversible; however, in this scenario, the ylide collapses to form an epoxide **6.3.4**. Rearrangement of **6.3.4** then occur with the assistance of the lone pair on the isopropyl group to form an intermediate **6.3.5**, which then undergoes an intramolecular proton abstraction to give the product **6.3.2**.

Table 6.3.2 Optimization of the yield of the reaction[a]



entry	catalyst	solvent (**6.3.3**/DCM)	temp. (°C)	yield (%)
1	$Rh_2(OAc)_4$	2mL/0mL	rt[b]	48
2	$Rh_2(OPiv)_4$	2mL/0mL	rt[b]	5
3	$Rh_2(TPA)_4$	2mL/0mL	rt[b]	16
4	$Rh_2(TFA)_4$	2mL/0mL	rt[b]	10
5	$Rh_2(OOct)_4$	2mL/0mL	rt[b]	36
6	$Rh_2(esp)_2$	2mL/0mL	rt[b]	10
7	$Rh_2(S\text{-DOSP})_4$	1mL/1mL	rt	40
8	$Rh_2(S\text{-DOSP})_4$	0.5mL/0.5mL	rt	56
9	**$Rh_2(S\text{-DOSP})_4$**	**0.5mL/0.5mL**	**40**	**71**
10	$Rh_2(S\text{-DOSP})_4$	0.5mL/0.5mL	60	45
11	**$Rh_2(OOct)_4$**	**0.5mL/0.5mL**	**40[a]**	**68**
12	$Rh_2(OAc)_4$	0.5mL/0.5mL	40[a]	64

[a]Reaction conditions: **6.3.1** (0.3 mmol) was added in one portion to the catalyst (1 mol %) in 2 mL isopropylacetate at room temperature. [b]Reactions were performed by myself (Liangbing Fu)

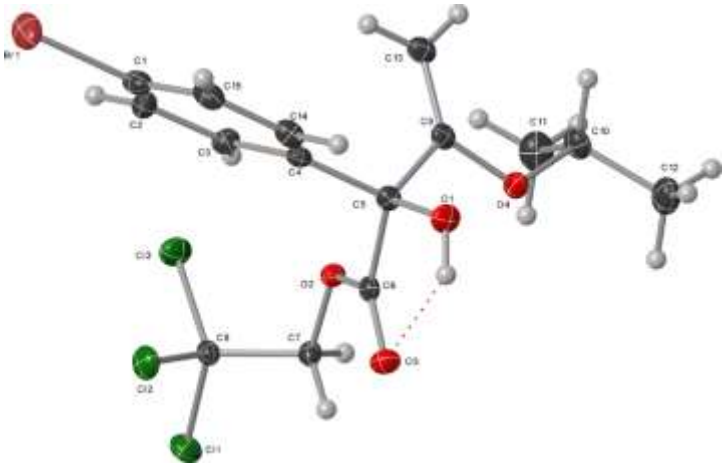
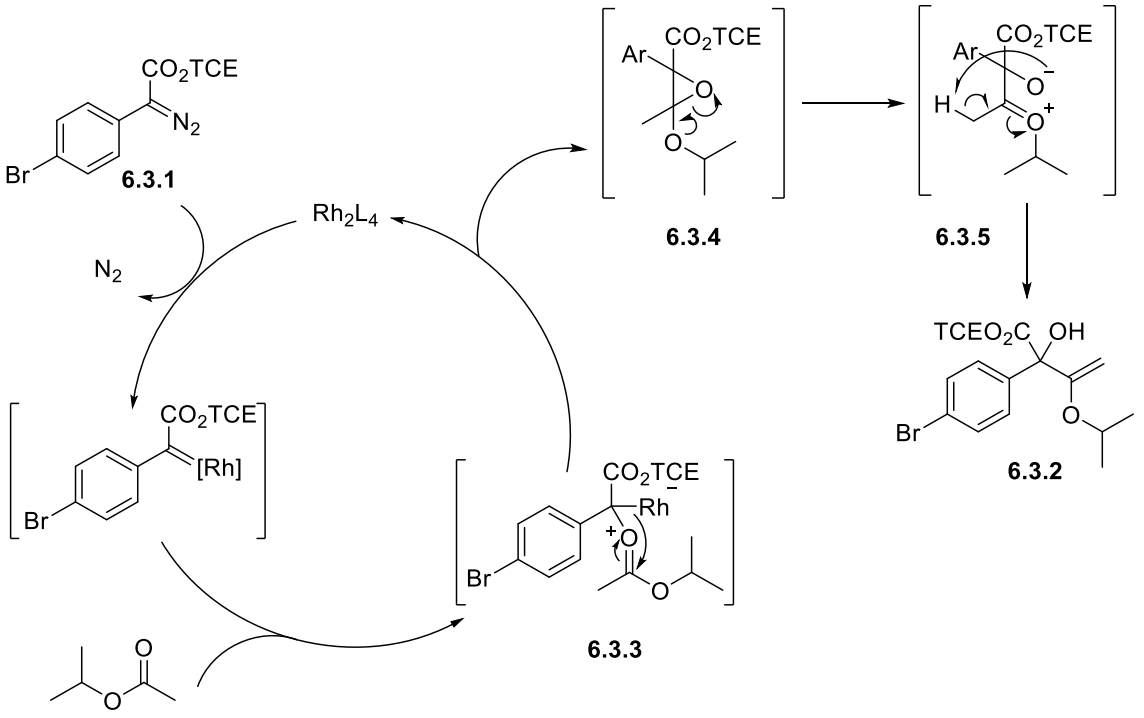


Figure 6.3.1 X-ray structure of product **6.3.2**



Scheme 6.3.1 Proposed mechanism for the formation of **6.3.2**

6.3.3 Summary

Systematic optimization studies of a rhodium(II)-catalyzed reaction with between isopropyl acetate and a diazo compound were conducted. With $Rh_2(OOct)_4$ as the catalyst, the reaction afforded the product **6.3.2** in 68% yield. The structure of the product was confirmed by X-ray crystallography. With these results, the groundwork has been laid for further studies and for the expansion of the chemistry to a variety of substrates.

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Experimental Section

General Methods:

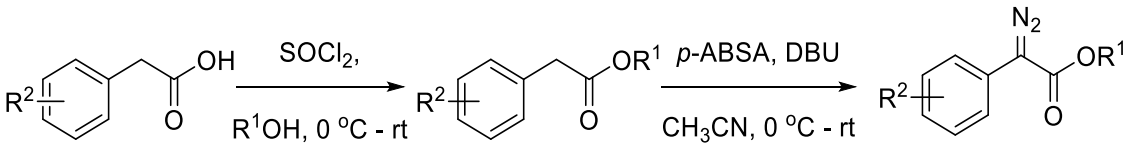
^{1}H Nuclear Magnetic Resonance (^{1}H NMR) and ^{13}C Nuclear Magnetic Resonance (^{13}C NMR) spectra were recorded on Varian INOVA 400, VNMR 400, INOVA 500, INOVA 600 or UNITY 600 MHz. NMR spectra were recorded in deuterated chloroform ($CDCl_3$) at room temperature unless otherwise stated. The NMR data were presented as follows: chemical shift in ppm with tetramethylsilane (TMS, $\delta = 0.00$ ppm) for ^{1}H NMR and the residual of chloroform ($\delta = 77.0$ ppm) for ^{13}C NMR as internal standards, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br. = broad), coupling constant (*J*/Hz), integration. IR spectra were collected on a Nicolet iS10 from Thermo Scientific and reported in unit of cm^{-1}. Mass spectra were recorded on a Finnigan LTQ FTMS mass spectrometer. Optical rotations were measured on a Jasco polarimeters (concentration in g/100mL). Enantiomeric excess was determined by anatylical enantioselective chromatographies on Varian Prostar instruments using HPLC grade hexanes/isopropanol as gradient solvents. Melting points were measured on a MEL-TEMP of Electrothermal (uncorrected). All reactions were performed under argon atmosphere in oven or flame dried glassware. Acetonitrile, dichloromethane, toluene and *n*-pentane were dried by a solvent purification system (passed through activated alumina columns). Analytical TLC was performed on silica gel plates using UV light or phosphomolybdic acid stain. Flash column chromatography was performed on silica gel 60Å (230-400 mesh) from Sorbent Technologies. Unless otherwise noted, all other chemical reagents were obtained from commercial sources and used as received. The procedure for the preparation of and the

characterization data for all new compounds and key intermediates will be described in each chapter.

Experimental section for chapter 2: Rhodium-catalyzed asymmetric synthesis of *β*-lactones by intramolecular C–H insertions of *ortho*-substituted aryldiazoacetates

General procedures for the synthesis of diazo substrates

Typical procedure A:

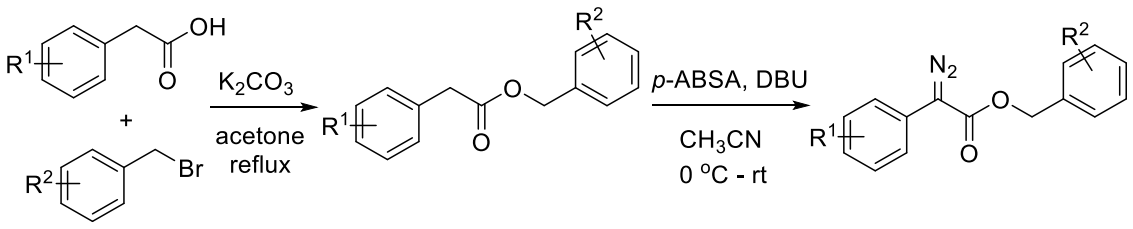


A solution of carboxylic acid (5.0 mmol, 1.0 equiv) in methanol or ethanol (20 mL) was cooled to 0 °C in an ice bath. Thionyl chloride (12.5 mmol, 2.5 equiv) was then added slowly. The reaction mixture was warmed to room temperature gradually and stirred overnight before it was concentrated *in vacuo*. The remaining residue was washed with 30 mL of saturated aqueous sodium bicarbonate ($NaHCO_3$) and extracted with 2 × 40 mL of diethyl ether. The combined organics were dried over anhydrous magnesium sulfate and concentrated to give the crude ester which was directly used in the next step.

To a stirred solution of the ester obtained in the previous step (1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.3 equiv) in acetonitrile, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 equiv) was added dropwise at 0 °C. The

reaction mixture was allowed to warm to room temperature and stirred overnight before it was quenched with 30 mL of saturated aqueous ammonium chloride. The crude mixture was extracted with diethyl ether (2 × 40 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified through silica gel chromatography (eluting hexanes: diethyl ether) to afford the diazo compounds.

Typical Procedure B:

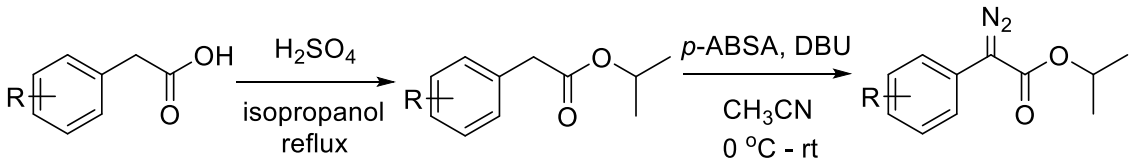


A mixture of carboxylic acid (5.0 mmol, 1.0 equiv), benzyl bromide (5.5 mmol, 1.1 equiv) and potassium carbonate (5.5 mmol, 1.1 equiv) in acetone (20 mL, 0.25 M) was refluxed overnight before it was cooled to room temperature. The mixture was filtered and the residue was washed with another volume of acetone. The filtrates were concentrated to give the crude ester which was directly used in the diazo transfer step.

To a stirred solution of the ester obtained previously (1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.3 equiv) in acetonitrile, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight before it was quenched with 30 mL of saturated aqueous ammonium chloride. The crude mixture was extracted with diethyl ether (2 × 40 mL), dried over anhydrous $MgSO_4$,

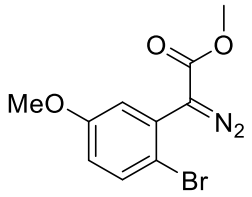
concentrated *in vacuo*, and purified through silica gel chromatography (eluting hexanes: diethyl ether) to afford the corresponding diazo compounds.

Typical Procedure C:



A solution of carboxylic acid (5.0 mmol, 1.0 equiv) and sulfuric acid (2.5 mmol, 0.5 equiv) in isopropanol (20 mL, 0.25 M) was refluxed overnight before it was cooled to room temperature and concentrated. The residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and concentrated to give the crude ester which was directly used in the next step.

To a stirred solution of the ester obtained previously (1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.3 equiv) in acetonitrile, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.5 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight before it was quenched with 30 mL of saturated aqueous ammonium chloride. The crude mixture was extracted with diethyl ether (2 × 40 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified through silica gel chromatography (eluting hexanes: diethyl ether) to afford the corresponding diazo compounds.



2.29

Methyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.29): Prepared according to general procedure A using 2-(2-bromo-5-methoxyphenyl)acetic acid[1] (1.17 g, 4.8 mol, 1.0 equiv) and methanol (20 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 10/1 to 15/2) to afford a yellow solid (1.21 g, 94% yield); m.p. 59-62 °C, R_f = 0.20 (hexanes: diethyl ether = 10: 1).

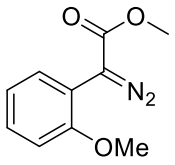
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 (d, *J* = 9.0 Hz, 1H), 7.02 (d, *J* = 3.0 Hz, 1H), 6.72 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.0, 159.2, 134.0, 126.5, 117.9, 116.7, 114.7, 55.8, 52.5, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2953, 2853, 2098, 1703, 1590, 1567, 1471, 1435, 1339, 1283, 1235, 1192, 1154, 1074, 1036, 1015 cm^{-1}.

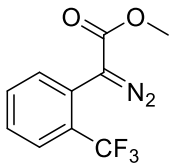
HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{10}O_3N_2Br$ 284.9869 found 284.9870.

[1] Adams, H.; Gilmore, N. J.; Jones, S.; Muldowney, M. P.; von Reuss, S. H.; Vemula, R. *Org. Lett.* **2008**, *10*, 1457.



2.32

Methyl 2-diazo-2-(2-methoxyphenyl)acetate (**2.32**): Prepared according to general procedure A using 2-(2-methoxyphenyl)acetic acid (0.83 g, 5.0 mmol, 1.0 equiv) and methanol (15 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 10/1) to afford an orange solid (0.87 g, 85% yield); m.p. 34-36 °C, R_f = 0.33 (hexanes: diethyl ether = 10: 1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.6, Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H). Data matched that from literature.[2]



2.36b

Methyl 2-diazo-2-(2-(trifluoromethyl)phenyl)acetate (**2.36b**): Prepared according to general procedure A using 2-(2-(trifluoromethyl)phenyl)acetic acid (1.63 g, 8.0 mmol, 1.0 equiv) and methanol (32 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 10/1) to afford a yellow oil (1.95 g, 85% yield); R_f = 0.23 (hexanes: diethyl ether = 10: 1).

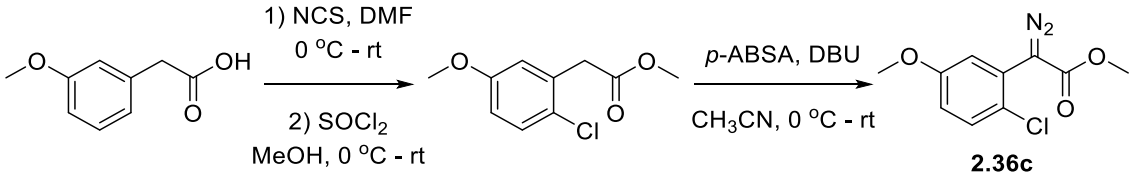
[2] Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.63-7.58 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 134.4, 132.4, 129.9 (q, *J* = 30.1 Hz), 129.4, 126.8 (q, *J* = 5.3 Hz), 123.8 (q, *J* = 271.5 Hz), 123.5 (q, *J* = 1.8 Hz), 52.3, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2957, 2096, 1703, 1496, 1437, 1313, 1285, 1254, 1176, 1154, 1123, 1072, 1033, 767, 680 cm^{-1}.

HRMS (NSI) calcd. for $C_{10}H_8O_2N_2F_3$ $(M+H)^+$ 245.0532 found 245.0535.



Methyl 2-(2-chloro-5-methoxyphenyl)-2-diazoacetate (2.36c): Prepared according to general procedure A:

2-(2-chloro-5-methoxyphenyl)acetic acid was prepared as follows:[3] To a stirred solution of 2-(3-methoxyphenyl)acetic acid (5.00 g, 30.0 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (DMF) (20 mL) was added a solution of *N*-chlorosuccinimide (NCS) (4.42 g, 33.0 mmol, 1.1 equiv) in DMF (22 mL) dropwise. The reaction mixture was warmed to room temperature gradually and stirred for 24 h before it was diluted with water

[3] PCT Int. Appl., 2004096781, 11 Nov 2004.

(80 mL) and extracted with EtOAc (2 × 80 mL). The combined organics were dried over Na_2SO_4, concentrated, and concentrated to give the crude 2-(2-chloro-5-methoxyphenyl)acetic acid. This acid was dissolved in methanol (75 mL) was cooled to 0 °C in an ice bath. Thionyl chloride (5.5 mL, 75.0 mmol, 2.5 equiv) was then added slowly. The reaction mixture was warmed to room temperature gradually and stirred overnight before it was concentrated *in vacuo*. The remaining residue was diluted with 100 mL of diethyl ether and washed with 30 mL of saturated aqueous sodium bicarbonate (2 × 50 mL), dried over anhydrous magnesium sulfate, and purified by flash column chromatography (silica gel, hexanes/diethyl ether = 20/1 to 10/1) to afford the methyl ester (6.0 g).

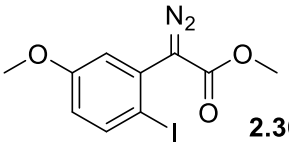
To a stirred solution of the ester obtained in the previous step (3.27 g, *c.a.* 15.0 mmol, 1.0 equiv) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (5.40 g, 22.5 mmol, 1.3 equiv) in acetonitrile (50 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4.53 mmol, 30.0 mmol, 1.5 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight before it was quenched with 50 mL of saturated aqueous ammonium chloride. The crude mixture was extracted with diethyl ether (2 × 50 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (silica gel, hexanes/diethyl ether = 20/1 to 10/1) to afford a yellow solid (3.0 g, 75% yield for three steps); m.p. 66-69 °C, R_f = 0.25 (hexanes: diethyl ether = 8: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 3.2 Hz, 1H), 6.81 (dd, *J* = 8.8, 3.2 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 158.6, 130.8, 125.1, 124.7, 116.9, 116.2, 55.9, 52.5, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2954, 2924, 2853, 2099, 1704, 1594, 1486, 1340, 1236, 1153, 1036, 812, 742cm^{-1}.

HRMS (NSI) calcd. for $C_{10}H_9O_3N_2ClNa$ $(M+Na)^+$ 263.0194 found 263.0193.



2.36d

Methyl 2-diazo-2-(2-iodo-5-methoxyphenyl)acetate (2.36d): Prepared according to general procedure A using 2-(2-iodo-5-methoxyphenyl)acetic acid[4] (1.61 g, 6.15 mmol, 1.0 equiv) and methanol (30 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 12/1 to 8/1) to afford a yellow solid (0.94 g, 46% yield). m.p. 85-87°C, R_f = 0.30 (hexanes: diethyl ether 10: 1).

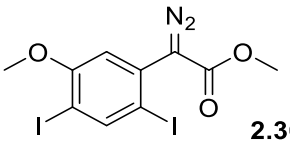
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 2.8 Hz, 1H), 6. 65 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 160.2, 140.4, 130.4, 118.7, 117.4, 89.3, 55.7, 52.6, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2952, 2094, 1698, 1584, 1465, 1231, 1191, 1032, 774, 740 cm^{-1}.

HRMS (NSI) calcd. for $C_{10}H_9O_3N_2INa$ $(M+Na)^+$ 354.9550 found 354.9548.

[4] Eur. Pat. Appl., 145361, 19 Jun 1985.



2.36e

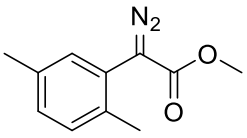
Methyl 2-diazo-2-(2,4-diiodo-5-methoxyphenyl)acetate (2.36e): Prepared according to general procedure A using 2-(2,4-diiodo-5-methoxyphenyl)acetic acid[4] (2.09 g, 5.0 mmol, 1.0 equiv) and methanol (20 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 10/1 to 7/1) to afford a yellow solid (1.5 g, 66% yield for two steps); m.p. 94-98°C, R_f = 0.28 (hexanes: diethyl ether 7: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 6.89 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 158.5, 148.2, 130.3, 114.6, 89.2, 88.1, 66.3, 56.5, 52.3.

IR (neat): 2949, 2847, 2092, 1694, 1568, 1459, 1309, 1271, 1156, 1072, 879, 741 cm^{-1}.

HRMS (NSI) calcd. for $C_{10}H_8O_3N_2I_2Na$ $(M+Na)^+$ 480.8517 found 480.8515.



2.36f

Methyl 2-diazo-2-(2,5-dimethylphenyl)acetate (2.36f): Prepared according to general procedure A using 2-(2,5-dimethylphenyl)acetic acid (1.97 g, 12.0 mmol, 1.0 equiv) and methanol (30 mL) in the first step. Purified by flash column chromatography (silica gel,

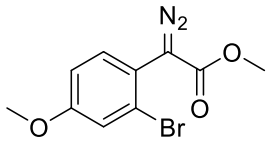
hexanes/diethyl ether = 12/1) to afford a brown oil (1.78 g, 73% yield for two steps); R_f = 0.30 (hexanes: diethyl ether = 10:1).

^{1}H NMR (400 MHz, CDCl3) δ 7.20 (s, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 3.82 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (100 MHz, CDCl3): 166.9, 136.3, 134.8, 131.6, 130.9, 130.0, 124.0, 52.4, 21.1, 19.7, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2952, 2085, 1710, 1503, 1436, 1337, 1257, 1188, 1050, 815 cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_9IN_2O_3Na$ $(M+Na)^+$ 227.0791 found 227.0793.



2.36g

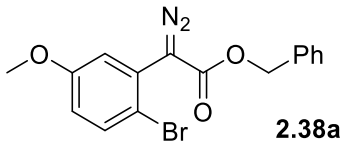
Methyl 2-(2-bromo-4-methoxyphenyl)-2-diazoacetate (2.36g): Prepared according to general procedure A using 2-(2-bromo-4-methoxyphenyl)acetic acid (1.09 g, 4.45 mmol, 1.0 equiv) and methanol (12 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 12/1) to afford a yellow oil (0.92 g, 72% yield for two steps), R_f = 0.26 (hexanes: diethyl ether = 10:1).

^{1}H NMR (400 MHz, CDCl3) δ 7.36 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 2.8 Hz, 1H), 6. 90 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (150 MHz, CDCl3): 166.6, 160.8, 134.0, 126.0, 118.4, 117.8, 114.4, 55.9, 52.4, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2951, 2841, 2094, 1698, 1600, 1496, 1261, 1193, 1033, 848, 742 cm^{-1}.

HRMS (ESI) calc. for $C_{10}H_9BrN_2O_3Na$ $(M+Na)^+$ 306.9689 found 306.9690.



2.38a

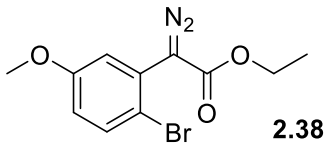
Benzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.38a): Prepared according to general procedure B using 2-(2-bromo-5-methoxyphenyl)acetic acid (0.86 g, 3.5 mmol, 1.0 equiv) and benzyl bromide (0.66 g, 3.85 mmol, 1.1 equiv) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 8/1) to afford a yellow solid (0.75 g, 80% yield); m.p. 45-47°C, R_f = 0.25 (hexanes: diethyl ether = 8: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.35-7.40 (m, 5H), 7.11 (d, *J* = 2.8 Hz, 1H), 6. 78 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.32 (s, 2H), 3.75 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 159.3, 136.1, 134.1, 128.9, 128.6, 128.4, 126.5, 117.9, 117.0, 114.8, 67.1, 55.8, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2937, 2093, 1698, 1589, 1470, 1378, 1276, 1182, 1028, 911, 768, 739 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{13}O_3N_2BrNa$ $(M+Na)^+$ 383.0002 found 383.0004.



2.38b

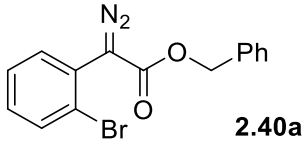
Ethyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.38b): Prepared according to general procedure A using 2-(2-bromo-5-methoxyphenyl)acetic acid (0.86 g, 3.5 mmol, 1.0 equiv) and ethanol (15 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 8/1) to afford a yellow solid (0.78 g, 84% yield); m.p. 75-78°C, R_f = 0.22 (hexanes: diethyl ether = 8: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.0 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 1H), 6. 74 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 165.6, 159.2, 134.0, 126.7, 117.8, 116.8, 114.7, 61.5, 55.8, 14.7, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2924, 2853, 2090, 1698, 1589, 1465, 1277, 1152, 1095, 806, 741 cm^{-1}.

HRMS (NSI) calcd. for $C_{11}H_{11}O_3N_2BrNa$ $(M+Na)^+$ 320.9845 found 320.9844.



2.40a

Benzyl 2-(2-bromophenyl)-2-diazoacetate (2.40a): Prepared according to general procedure B using 2-(2-bromophenyl)acetic acid (1.29 g, 6.0 mmol, 1.0 equiv) and benzyl bromide (1.13 g, 6.6 mmol, 1.1 equiv) in the first step. Purified by flash column

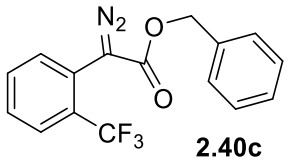
chromatography (silica gel, hexanes/diethyl ether = 10/1) to afford a yellow oil (1.94 g, 88% yield), R_f = 0.30 (hexanes: diethyl ether = 9: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (t, *J* = 8.4 Hz, 2H), 7.45-7.33 (m, 6H), 7.17 (td, *J* = 8.0, 1.6 Hz, 1H), 5.35 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 136.3, 133.7, 133.3, 130.5, 129.0, 128.6, 128.5, 128.1, 126.0, 124.7, 67.1, the resonance resulting from the diazo carbon was not detected.

IR (neat): 3034, 2096, 1703, 1497, 1476, 1379, 1283, 1240, 1154, 1062, 1011, 754, 697 cm^{-1}.

HRMS (NSI) calcd. For $C_{15}H_{11}O_2N_2BrNa$ $(M+Na)^+$ 352.9896 found 352.9897.



2.40c

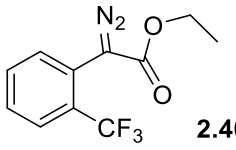
Benzyl 2-diazo-2-(2-(trifluoromethyl)phenyl)acetate (2.40c): Prepared according to general procedure B using 2-(2-(trifluoromethyl)phenyl)acetic acid (1.63 g, 8.0 mmol, 1.0 equiv) and benzyl bromide (1.51 g, 8.8 mmol, 1.1 equiv) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 12/1) to afford a yellow oil (2.3 g, 90% yield), R_f = 0.25 (hexanes: diethyl ether = 12: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.62-7.59 (m, 2H), 7.52-7.47 (m, 1H), 7.36-7.31 (m, 5H), 5.29 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 136.1, 134.7, 132.5, 130.2 (q, *J* = 30.0 Hz), 129.7, 128.8, 128.5, 128.2, 127.1, 124.1 (q, *J* = 272.0 Hz), 123.7, 67.1, the resonance resulting from the diazo carbon was not detected.

IR (neat): 3036, 2097, 1699, 1602, 1314, 1281, 1150, 1125, 1015, 767, 740 cm^{-1}.

HRMS (NSI) calcd. For $C_{16}H_{11}O_2N_2F_3Na$ $(M+Na)^+$ 343.0665 found 343.0663.



2.40d

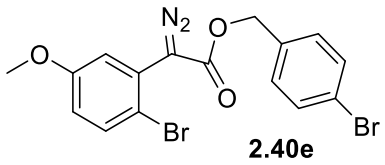
Ethyl 2-diazo-2-(2-(trifluoromethyl)phenyl)acetate (2.40d): Prepared according to general procedure A using 2-(2-(trifluoromethyl)phenyl)acetic acid (1.43 g, 7.0 mmol, 1.0 equiv) and ethanol (25 mL) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 12/1) to afford a yellow oil (1.54 g, 85% yield); R_f = 0.25 (hexanes: diethyl ether = 12: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.59-7.55 (m, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 165.8, 134.3, 132.1, 129.9 (q, *J* = 29.7 Hz), 129.3, 126.8, 123.8 (q, *J* = 271.5 Hz), 123.6, 61.3, 14.3, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2985, 2096, 1700, 1342, 1314, 1284, 1154, 1125, 1035, 768 cm^{-1}.

HRMS (NSI) calcd. for $C_{11}H_9O_2N_2F_3Na$ $(M+Na)^+$ 281.0508 found 281.0506.



2.40e

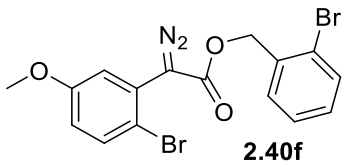
4-bromobenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.40e): Prepared according to general procedure B using 2-(2-bromo-5-methoxyphenyl)acetic acid (1.23 g, 5.0 mmol, 1.0 equiv) and 1-bromo-4-(bromomethyl)benzene (1.37 g, 5.5 mmol, 1.1 equiv) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 20/1 to 10/1) to afford a yellow solid (0.55 g, 30% yield); m.p. 92-95 °C, R_f = 0.26 (hexanes: diethyl ether = 8: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7. 50-7.46 (m, 3H), 7.26-7.24 (m, 2H), 7.04 (d, *J* = 2.8 Hz, 1H), 6.78 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.22 (s, 2H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 159.2, 135.1, 134.1, 132.0, 130.1, 126.3, 122.6, 117.9, 117.0, 114.9, 66.2, 55.8, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2935, 2094, 1697, 1483, 1277, 1231, 1148, 1069, 1030, 1011, 802, 739 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{13}O_3N_2Br_2$ $(M+H)^+$ 438.9298 found 438.9305.



2.40f

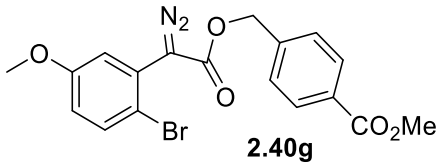
2-bromobenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.40f): Prepared according to general procedure B using 2-(2-bromo-5-methoxyphenyl)acetic acid (1.23 g, 5.0 mmol, 1.0 equiv) and 1-bromo-2-(bromomethyl)benzene (1.37 g, 5.5 mmol, 1.1 equiv) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 10/1) to afford a yellow solid (1.95 g, 89% yield); m.p. 106-108 °C, R_f = 0.25 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7. 30 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7. 07 (d, *J* = 2.4 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.35 (s, 2H), 3.76 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 158.9, 135.1, 133.82, 133.79, 132.8, 129.7, 127.5, 126.1, 123.6, 117.5, 116.8, 114.5, 66.3, 55.8, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2935, 2836, 2094, 1699, 1589, 1471, 1276, 1232, 1182, 1149, 1027, 750 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{12}O_3N_2Br_2Na$ $(M+Na)^+$ 460.9107 found 460.9109.



2.40g

Methyl 4-((2-(2-bromo-5-methoxyphenyl)-2-diazoacetoxy)methyl)benzoate (2.40g): Prepared according to general procedure B using 2-(2-bromo-5-methoxyphenyl)acetic acid (1.23 g, 5.0 mmol, 1.0 equiv) and methyl 4-(bromomethyl)benzoate (1.26 g, 5.5 mmol, 1.1

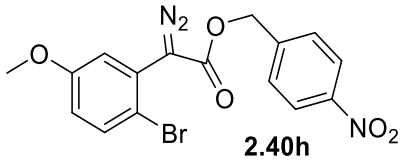
equiv). Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 15/2) to afford a yellow solid (1.67 g, 80% yield); m.p. 74-77 °C, R_f = 0.20 (hexanes: diethyl ether = 8:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.43-7.37 (m, 3H), 7.03 (d, *J* = 2.8 Hz, 1H), 6.73 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.28 (s, 2H), 3.86 (s, 3H), 3.71 (s, 3H), the resonance resulting from the diazo carbon was not detected.

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 165.2, 159.2, 141.1, 134.1, 130.2, 130.1, 127.8, 126.3, 117.9, 116.9, 114.9, 66.2, 55.8, 52.4.

IR (neat): 2951, 2839, 2096, 1699, 1589, 1470, 1435, 1274, 1232, 1149, 1108, 1031, 809, 754 cm^{-1}.

HRMS (NSI) calcd for $C_{18}H_{16}O_5N_2Br$ $(M+H)^+$ 419.0237 found 419.0235.



2.40h

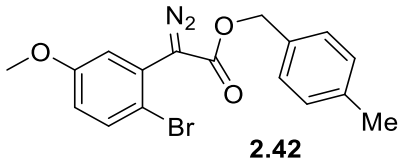
4-nitrobenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.40h): Prepared according to general procedure B using 2-(2-bromo-5-methoxyphenyl)acetic acid (1.23 g, 5.0 mmol, 1.0 equiv) and 1-(bromomethyl)-4-nitrobenzene (1.19 g, 5.5 mmol, 1.1 equiv) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 5/1) to afford a yellow solid (0.41 g, 21% yield); m.p. 125-127 °C, R_f = 0.22 (hexanes: diethyl ether = 5: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.6 Hz, 2H), 7.52-7.47 (m, 3H), 7.03 (d, *J* = 2.8 Hz, 1H), 6.78 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.35 (s, 2H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 159.0, 147.7, 143.0, 133.9, 128.3, 125.8, 123.8, 117.8, 116.7, 114.8, 65.2, 55.6, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2936, 2852, 2098, 1701, 1606, 1520, 1470, 1346, 1235, 1072, 1031, 1014, 857, 739 cm^{-1}.

HRMS (NSI) calcd for $C_{16}H_{13}O_5N_3Br$ $(M+H)^+$ 406.0033 found 406.0037.



2.42

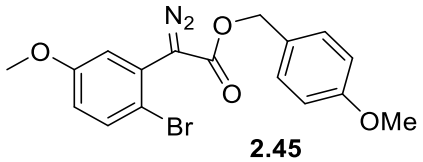
4-methylbenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.42): Prepared according to general procedure B using 2-(2-bromo-5-methoxyphenyl)acetic acid (1.23 g, 5.0 mmol, 1.0 equiv) and 1-(bromomethyl)-4-methylbenzene (1.02 g, 5.5 mmol, 1.1 equiv) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 20/1) to afford a yellow solid (1.19 g, 53% yield); m.p. 55-58 °C, R_f = 0.30 (hexanes: diethyl ether = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 7. 10 (d, *J* = 2.0 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.0 Hz, 1H), 5.28 (s, 2H), 3.76 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 159.0, 138.2, 133.82, 132.79, 129.3, 128.4, 126.3, 117.6, 116.7, 114.5, 66.9, 55.6, 21.3, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2956, 2095, 1698, 1589, 1469, 1376, 1277, 1232, 1150, 1030, 805, 739 cm^{-1}.

HRMS (NSI) calcd. for $C_{17}H_{15}O_3N_2BrNa$ $(M+Na)^+$ 397.0158 found 397.0162.



2.45

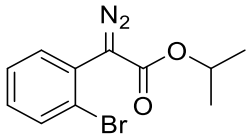
4-methoxybenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.45): Prepared according to general procedure B using 2-(2-bromo-5-methoxyphenyl)acetic acid (1.23 g, 5.0 mmol, 1.0 equiv) and 1-(bromomethyl)-4-methoxybenzene (1.1 g, 5.5 mmol, 1.1 equiv) in the first step. Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 10/1) to afford a yellow solid (1.66 g, 85% yield); m.p. 34-37 °C, R_f = 0.22 (hexanes: diethyl ether = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 2.8 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.75 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.22 (s, 2H), 3.79 (s, 3H), 3.75 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 159.9, 159.2, 134.1, 130.3, 128.2, 126.6, 117.8, 116.9, 114.8, 114.2, 66.9, 55.8, 55.5, the resonance resulting from the diazo carbon was not detected.

IR (neat): 2957, 2836, 2093, 1694, 1514, 1464, 1231, 1149, 1028, 1010, 819, 738 cm^{-1}.

HRMS (NSI) calcd for $C_{17}H_{15}O_4N_2BrNa$ $(M+Na)^+$ 413.0107 found 413.0111.



2.28

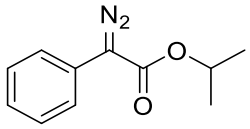
Isopropyl 2-(2-bromophenyl)-2-diazoacetate (2.28): Prepared according to general procedure C using 2-bromophenylacetic acid (3.30 g, 15.0 mmol, 1.0 equiv) to afford a yellow oil (3.73 g, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.53 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.6, 1.7 Hz, 1H), 5.17 (sep, *J* = 6.4 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 133.1, 132.6, 129.7, 127.4, 125.7, 124.0, 68.7, 21.8, the resonance resulting from the diazo carbon was not detected.

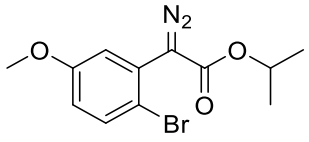
IR (neat): 2980, 2090, 1694, 1475, 1386, 1240, 1103, 1005, 752 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{12}O_2N_2Br$ 283.0077 found 283.0076.



2.48

Isopropyl 2-diazo-2-phenylacetate (2.48): Prepared according to general procedure C using phenylacetic acid (1.36 g, 10.0 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 30/1) to afford an orange oil to afford a yellow oil (1.80 g, 90% yield); **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 5.20 (sep, *J* = 6.6 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 6H). Data matches that from the literature.[5]



2.50

Isopropyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (2.50): Prepared according to general procedure C using 2-(2-bromo-5-methoxyphenyl)acetic acid (1.65 g, 6.7 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes/diethyl ether = 12/1) to afford a yellow solid (1.81 g, 87% yield); m.p. 46-49 °C, R_f = 0.40 (hexanes: diethyl ether = 9: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.8 Hz, 1H), 6.99 (d, *J* = 2.8 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.07 (sep, *J* = 5.2 Hz, 1H), 3.64 (s, 3H), 1.20 (d, *J* = 5.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 159.1, 133.9, 126.7, 117.8, 116.5, 114.4, 69.1, 55.6, 22.2, the resonance resulting from the diazo carbon was not detected.

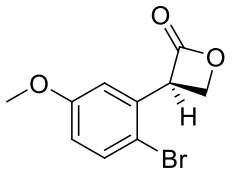
IR (neat): 2928, 2854, 2092, 1698, 1590, 1467, 1374, 1236, 1182, 1106, 1030, 743 cm^{-1}.

[5] Doyle, M. P.; May, E. J. *Synlett* **2001**, 967.

HRMS (NSI) calcd. for $C_{12}H_{13}O_3N_2BrNa$ $(M+Na)^+$ 335.0002 found 335.0001.

General procedure for enantioselective intramolecular C–H insertion:

Under argon atmosphere, to a solution of rhodium catalyst (0.0050 mmol, 0.01 equiv) in solvent (5 ml) at reflux was added a solution of diazo compound (0.50 mmol, 1.0 equiv) in the corresponding solvent (5 ml) over 3 hours. After stirring an additional two hours at reflux, the reaction was cooled to room temperature and concentrated *in vacuo*. The crude residue was analyzed by ^{1}H NMR with $CDCl_3$ as the solvent and purified by flash chromatography (silica gel, hexanes/diethyl ether) to afford the pure *β*-lactones.



2.22

(*R*)-3-(2-bromo-5-methoxyphenyl)oxetan-2-one (2.22): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.19)** (143 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTAD)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 15/1) to afford **2.22** as a white solid (92 mg, 72% yield); m.p. 58-60 °C, R_f = 0.25 (hexanes: diethyl ether = 10:1).

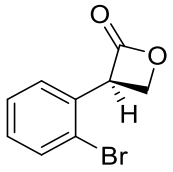
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 3.2 Hz, 1H), 6.76 (dd, *J* = 8.8, 3.2 Hz, 1H), 5.12 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.76 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.22 (dd, *J* = 5.2, 4.8 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6, 159.3, 133.7, 133.5, 115.7, 113.7, 113.4, 66.7, 56.6, 55.6.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{10}O_3Br$ 256.9808 found 256.9807.

IR (neat): 2939, 2838, 1819, 1594, 1572, 1471, 1417, 1332, 1295, 1241, 1168, 1108, 1063, 1017 cm^{-1}.

HPLC analysis: 86% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 17.45 min, minor; t_R = 21.34 min, major). **$[\alpha]_D^{20}$** -150.2° (c = 1.27, $CHCl_3$, 99% ee, obtained by recrystallization from hot hexanes).



2.24

(*R*)-3-(2-bromophenyl)oxetan-2-one (2.24): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 2-(2-bromophenyl)-2-diazoacetate **(2.23)** (64 mg, 0.25 mmol, 1.0 equiv), Rh_2(*S*-TCPTAD)$_4$ (5.5 mg, 0.0025 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl

ether = 12/1) to afford **2.24** as a colorless oil (60 mg, 53% yield). R_f = 0. 53 (hexanes: diethyl ether = 5: 1).

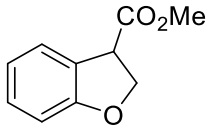
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.54 (m, 2H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.24 (td, *J* = 7.7, 1.7 Hz, 1H), 5.19 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.79 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.24 (dd, *J* = 5.2, 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 132.95, 132.9, 129.8, 128.2, 128.0, 123.4, 66.6, 56.7.

IR (neat): 2981, 1816, 1474, 1438, 1331, 1296, 1180, 1124, 1104, 1051, 1024 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_9H_8O_2Br$ 226.9702 found 226.9700.

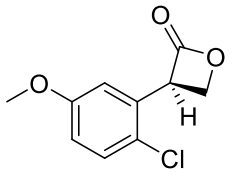
HPLC analysis: 61% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 12.30 min, major; t_R = 12.94 min, minor); **$[\alpha]_D^{20}$** -41.3^o (c = 1.73, $CHCl_3$).



2.33

Methyl 2,3-dihydrobenzofuran-3-carboxylate (**2.33**): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 2-diazo-2-(2-methoxyphenyl)acetate (**2.32**) (41 mg, 0.2 mmol, 1.0 equiv), Rh_2(*S*-TCPTAD)$_4$ (4.2 mg, 0.002 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/

diethyl ether = 12/1) to afford **2.33** as a clear oil (28.5 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.92 (dd, *J* = 9.6, 6.4 Hz, 1H), 4.65 (app t, *J* = 9.6 Hz, 1H), 4.32 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.76 (s, 3H). Data matched that from the literature.[2] **HPLC** analysis: 43% ee (OD, 0.5% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 10.30 min, minor; t_R = 14.15 min, major).



2.37c

(*R*)-3-(2-chloro-5-methoxyphenyl)oxetan-2-one (2.37c): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 2-(2-chloro-5-methoxyphenyl)-2-diazoacetate **(2.36c)** (121 mg, 0.5 mmol, 1 equiv), Rh_2(*S*-TCPTAD)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 12/1) to afford **2.37c** as a white solid (69 mg, 65% yield); m.p. 68-70 °C, R_f = 0.25 (hexanes: diethyl ether = 10: 1).

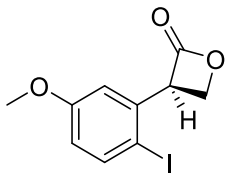
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.12 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.73 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.25 (app t, *J* = 5.2 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6, 158.7, 131.8, 130.3, 124.3, 115.2, 113.4, 66.4, 55.6, 54.7.

IR (neat): 2939, 2839, 1818, 1599, 1576, 1475, 1296, 1241, 1107, 1024, 945, 892, 870, 811 cm^{-1}.

HRMS (NSI) calcd. for $C_{10}H_9O_3ClNa$ $(M+Na)^+$ 235.0132 found 235.0136.

HPLC analysis: 84% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 16.85 min, minor; t_R = 21.97 min, major); **$[\alpha]_D^{20}$** -78.3° (c = 1.60, $CHCl_3$).



2.37d

(*R*)-3-(2-iodo-5-methoxyphenyl)oxetan-2-one (2.37d): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 2-(2-iodo-5-methoxyphenyl)-2-diazoacetate **(2.36d)** (166 mg, 0.5 mmol, 1 equiv), Rh_2(*S*-TCPTAD)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 12/1) to afford **2.37d** as a white solid (102 mg, 67% yield); m.p. 65-68 °C. R_f = 0.30 (hexanes: diethyl ether = 8: 1).

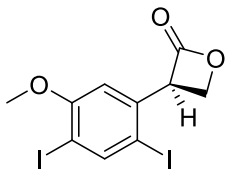
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68(d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.05 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.79 (dd, *J* = 7.2, 5.2 Hz, 1H), 4.15 (app t, *J* = 5.2 Hz, 1H), 3.78 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.7, 160.3, 140.0, 137.5, 116.0, 113.9, 86.9, 67.1, 60.4, 55.5.

IR (neat): 2937, 2837, 1817, 1589, 1567, 1465, 1293, 1169, 1106, 1058, 1009, 943, 890, 867, 809 cm^{-1}.

HRMS (NSI) calcd. for $C_{10}H_9O_3INa$ $(M+Na)^+$ 326.9489 found 326.9487.

HPLC analysis: 92% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 18.94 min, minor; t_R = 20.54 min, major); **$[\alpha]_D^{20}$** -1.86° (c = 1.30, $CHCl_3$).



2.37e

(*R*)-3-(2,4-diiodo-5-methoxyphenyl)oxetan-2-one (2.37e): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 2-diazo-2-(2,4-diiodo-5-methoxyphenyl)acetate **(2.36e)** (161 mg, 0.35 mmol, 1 equiv), Rh_2(*S*-TCPTAD)$_4$ (7.4 mg, 0.0035 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography

(silica gel, hexanes/ diethyl ether = 12/1) to afford **2.37e** as a white solid (65 mg, 43% yield); m.p. 100-102 °C. R_f = 0.30 (hexanes: diethyl ether = 8: 1).

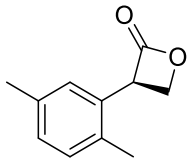
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17(s, 1H), 7.00 (s, 1H), 5.04 (dd, J = 6.9, 5.1 Hz, 1H), 4.84 (dd, J = 6.9, 5.1 Hz, 1H), 4.18 (app t, J = 5.1 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 159.2, 148.2, 138.1, 110.6, 87.7, 87.0, 67.2, 60.2, 56.8.

IR (neat): 2935, 2847, 1819, 1573, 1545, 1459, 1358, 1243, 1110, 1048, 1033, 944, 898, 876, 731, 687 cm^{-1}.

HRMS (NSI) calcd. for $C_{10}H_8O_3I_2Na$ $(M+Na)^+$ 452.8455 found 452.8454.

HPLC analysis: 68% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 19.32 min, major; t_R = 21.83 min, minor); **$[\alpha]_D^{20}$** -45.2^o (c = 1.80, $CHCl_3$).



2.37f

(*R*)-3-(2,5-dimethylphenyl)oxetan-2-one (2.37f): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 2-diazo-2-(2,5-dimethylphenyl)acetate **(2.36f)** (102 mg, 0.5 mmol, 1 equiv), Rh_2(*S*-TBPTTL)$_4$ (12.6 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/

ethyl acetate = 10/1) to afford **2.37f** as a colorless oil colorless oil (22 mg, 25 % yield); R_f = 0.25 (hexanes: diethyl ether = 10: 1).

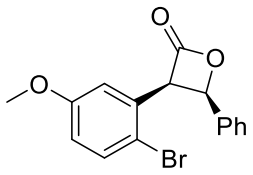
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19(s, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 5.04 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.66 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.23 (app t, *J* = 6.8 Hz, 1H), 2.31 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (100 MHz, CDCl3): δ 170.1, 136.6, 132.8, 131.2, 130.8, 129.2, 127.2, 66.5, 54.9, 21.2, 19.2.

IR (neat): 2921, 1817, 1505, 1104, 942, 878 cm^{-1}.

HRMS (ESI) calc. for $C_{11}H_{13}O_2$ $(M+H)^+$ 177.0910 found 177.0909.

HPLC: (SS_WHELK_H, 3% isopropanol in hexanes, 1.0 mL/min) retention times of 18.2 min (major) and 20.2 min (minor), 56% ee; **[α]$_D^{20}$** -77.6 ° (*c* 1.40, $CHCl_3$).



2.39a

(3*R*,4*R*)-3-(2-bromo-5-methoxyphenyl)-4-phenyloxetan-2-one (2.39a): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using benzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.38a)** (181 mg, 0.50 mmol, 1 equiv), Rh_2(*S*-TCPTTL)$_4$ (9.0 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 15/1) to afford **2.39a** as a white solid (120 mg, 72% yield); m.p. 59-61 °C. R_f = 0.30 (hexanes: diethyl ether = 9: 1).

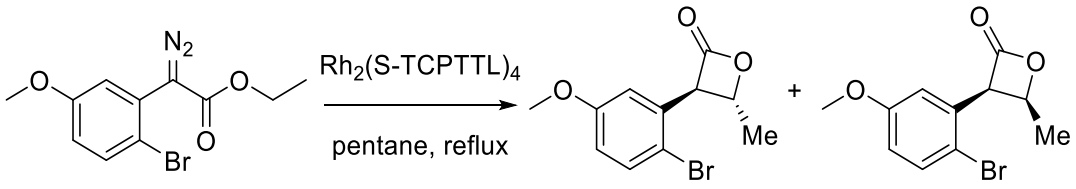
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16-7.22(m, 6H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.54 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.95 (d, *J* = 6.8 Hz, 1H), 5.57 (d, *J* = 6.8 Hz, 1H), 3.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 158.9, 133.7, 133.2, 131.7, 128.9, 128.2, 126.8, 115.8, 115.7, 114.1, 76.9, 61.8, 55.7.

IR (neat): 2936, 2838, 1822, 1593, 1573, 1475, 1455, 1295, 1240, 1226, 1118, 1018, 958, 857, 760, 696 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{13}O_3BrNa$ $(M+Na)^+$ 354.9940 found 354.9939.

HPLC analysis: 97% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 21.78 min, major; t_R = 25.73 min, minor); **$[\alpha]_D^{20}$** -62.6° (c = 1.71, $CHCl_3$).



2.38b ***trans*-2.39b** ***cis*-2.39b**

(3*R*,4*R*)-3-(2-bromo-5-methoxyphenyl)-4-methyloxetan-2-one (*trans*-2.39b): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using ethyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.38b)** (299 mg, 1.0 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (18.0 mg, 0.01 mmol, 0.01 equiv) as the catalyst and *n*-pentane as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 20/1) to afford the products **2.39b** (225

mg, 83% combined yield). The major diastereomer ***trans*-2.39b** was isolated as a white solid: m.p. 42-44 °C. R_f = 0.25 (hexanes: diethyl ether = 10: 1).

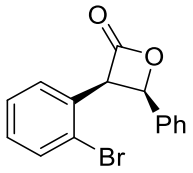
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.74 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.67 (d, *J* = 4.4 Hz, 1H), 4.54 (qd, *J* = 6.0, 4.4 Hz, 1H), 3.77 (s, 3H), 1.80 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 159.6, 133.9, 133.8, 115.9, 114.3, 114.0, 77.1, 62.5, 55.8, 21.0.

IR (neat): 2936, 2839, 1816, 1593, 1573, 1472, 1384, 1294, 1130, 1017, 828 cm^{-1}.

HRMS (ESI) calcd for $C_{11}H_{11}O_3BrNa$ $(M+Na)^+$ 292.9789 found 292.9784.

HPLC analysis: 94% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 19.10 min, minor; t_R = 24.21 min, major); **$[\alpha]_D^{20}$** -74.1° (c = 1.86, $CHCl_3$).



2.41a

(3*R*,4*R*)-3-(2-bromophenyl)-4-phenyloxetan-2-one (2.41a): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using benzyl 2-(2-bromophenyl)-2-diazoacetate **(2.40a)** (166 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (9.0 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel,

hexanes/ diethyl ether = 20/1) to afford **2.41a** as a white solid (95 mg, 63% yield); m.p. 91-93 °C. R_f = 0.28 (hexanes: diethyl ether = 10: 1).

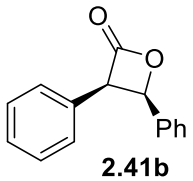
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.21-7.12 (m, 6H), 6.98 (td, *J* = 7.6, 1.6 Hz, 1H), 5.96 (d, *J* = 6.8 Hz, 1H), 5.62 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 133.8, 132.7, 130.9, 130.3, 129.9, 128.9, 128.2, 127.7, 126.8, 123.9, 77.0, 61.9.

IR (neat): 2924, 1828, 1475, 1455, 1440, 1255, 1124, 1026, 958, 758, 698 cm^{-1}.

HRMS (NSI) calcd. for $C_{15}H_{12}O_2Br$ $(M+H)^+$ 303.0015 found 303.0015.

HPLC analysis: 84% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 12.93 min, major; t_R = 16.00 min, minor); **$[\alpha]_D^{20}$** -99.8^o (c = 2.10, $CHCl_3$).



2.41b

(3*R*,4*R*)-3,4-diphenyloxetan-2-one (2.41b): Prepared according to the general procedure for enantioselective intramolecualr C–H insertion using benzyl 2-diazo-2-phenylacetate **(2.40b)** (126 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (9.0 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 20/1 to

10/1) to afford **2.41b** as a white solid (58 mg, 51% yield); m.p. 115-117 °C. R_f = 0.21 (hexanes: diethyl ether = 10: 1).

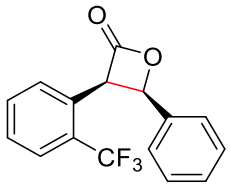
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.16 (m, 3H), 7.11-7.10 (m, 5H), 6.97-6.95 (m, 2H), 5.89 (d, *J* = 6.8 Hz, 1H), 5.35 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 134.1, 130.2, 128.5, 128.4, 128.2, 127.8, 126.2, 76.7, 61.3.

IR (neat): 3029, 2915, 1820, 1802, 1602, 1496, 1457, 1448, 1283, 1260, 1125, 1075, 955, 857, 805, 768, 756, 728, 695 cm^{-1}.

HRMS (NSI) calcd. for $C_{15}H_{13}O_2$ $(M+H)^+$ 225.0910 found 225.0915.

HPLC analysis: 64% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 22.19 min, minor; t_R = 23.84 min, major); **$[\alpha]_D^{20}$** -27.4° (c = 1.33, $CHCl_3$).



2.41c

(3*R*,4*R*)-4-phenyl-3-(2-(trifluoromethyl)phenyl)oxetan-2-one (2.41c): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using benzyl 2-diazo-2-(2-(trifluoromethyl)phenyl)acetate **(2.40c)** (160 mg, 0.50 mmol, 1 equiv), Rh_2(*S*-TCPTTL)$_4$ (9.0 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography

(silica gel, hexanes/ diethyl ether = 45/1) to afford **2.41c** as a colorless oil (88 mg, 60% yield). R_f = 0.25 (hexanes: diethyl ether = 8: 1).

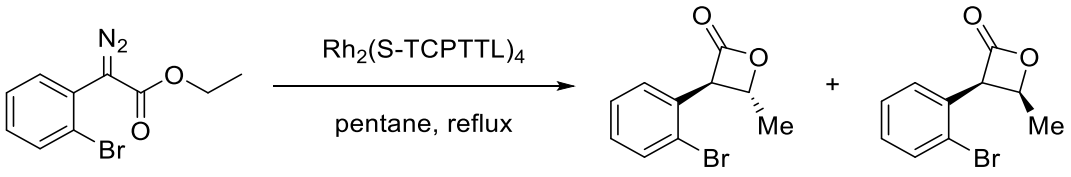
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.27-7.24 (m, 2H), 7.19-7.09 (m, 5H), 5.91 (d, *J* = 6.8 Hz, 1H), 5.70 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 133.4, 131.8, 130.9, 128.6, 128.4, 128.1, 126.2, 123.9 (q, *J* = 271.5 Hz), 77.4, 59.0.

IR (neat): 2923, 1829, 1608, 1586, 1455, 1314, 1257, 1154, 1110, 1038, 961, 881, 765, 699 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{11}O_2F_3Na$ $(M+Na)^+$ 315.0603 found 315.0602.

HPLC analysis: 99% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 9.88 min, major; t_R = 12.00 min, minor); **$[\alpha]_D^{20}$** -73.7 ^{o} (c = 2.40, $CHCl_3$).



2.25 **2.26** **2.27**

(3*R*,4*R*)-3-(2-bromophenyl)-4-methyloxetan-2-one (2.26): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using ethyl 2-(2-bromophenyl)-2-diazoacetate (**2.25**) (135 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (9.0 mg, 0.005 mmol, 0.01 equiv) as the catalyst and *n*-pentane as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash chromatography (silica gel,

hexanes: diethyl ether = 20:1) to afford the products **2.26** and **2.27** (97 mg, 80% combined yield). The major diastereomer **2.26** was isolated as a white solid: R_f = 0.32 (hexanes: ethyl acetate = 10: 1).

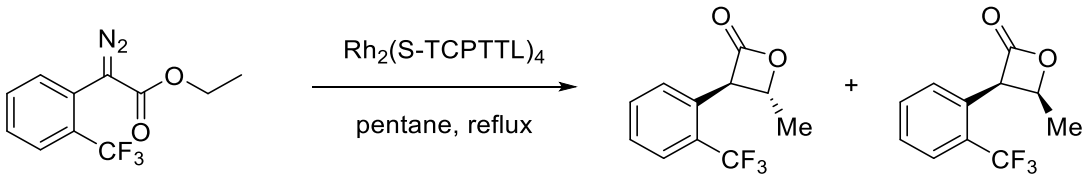
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.22 (td, *J* = 7.7, 1.7 Hz, 1H), 4.75 (d, *J* = 4.2 Hz, 1H), 4.56 (qd, *J* = 6.1, 4.2 Hz, 1H), 1.83 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (C), 133.1 (CH), 132.9 (C), 129.9 (CH), 128.6 (CH), 128.2 (CH), 123.7 (C), 76.8 (CH), 62.3 (CH_2), 20.7 (CH_3).

IR (neat): 2981, 1814, 1473, 1440, 1384, 1354, 1314, 1278, 1256, 1181, 1130, 1087, 1022 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{10}O_2Br$ 240.9859 found 240.9857.

HPLC analysis: 76% ee (AD-H, 0.5% *i*Pr-OH in hexanes, 1.0 mL/min, λ = 230 nm, t_R = 20.60 min, major; t_R = 48.59 min, minor); **[α]$_D^{20}$** -63.2^o (c = 2.06, $CHCl_3$).



2.40d ***trans*-2.41d** ***cis*-2.41d**

(3*R*,4*R*)-4-methyl-3-(2-(trifluoromethyl)phenyl)oxetan-2-one (*trans*-2.41d): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using ethyl 2-diazo-2-(2-(trifluoromethyl)phenyl)acetate **(2.40d)** (129 mg, 0.50 mmol, 1.0 equiv),

Rh_2(*S*-TCPTTL)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and *n*-pentane as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (hexanes/ diethyl ether = 25/1) to afford the products (95 mg, 83% combined yield): ***trans*-2.41d** (53 mg) and a mixture of ***trans*-2.41d** and ***cis*-2.41d** (42 mg). The major diastereomer ***trans*-2.41d** was isolated as a colorless oil: R_f = 0.25 (silica gel, hexanes: diethyl ether = 8: 1).

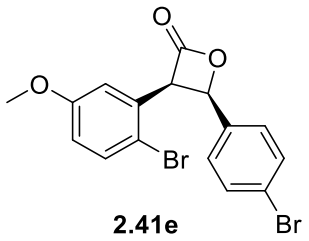
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 4.0 Hz, 1H), 4.53 (qd, *J* = 6.4, 4.0 Hz, 1H), 1.68 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 132.9, 131.1, 128.7, 128.5, 128.2, 126.4 (q, *J* = 6.0 Hz), 123.9 (q, *J* =272.0 Hz), 77.8, 59.5, 19.7.

IR (neat): 2986, 1823, 1609, 1586, 1502, 1454, 1388, 1316, 1285, 1261, 1162, 1119, 1038, 979, 834, 768, 748 cm^{-1}.

HRMS (NSI) calcd. for $C_{11}H_9O_2F_3Na$ $(M+Na)^+$ 253.0447 found 253.0457.

HPLC analysis: 95% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 7.27 min, major; t_R = 15.01 min, minor); **$[\alpha]_D^{20}$** -41.0^o (c = 2.15, $CHCl_3$).



2.41e

(3*R*,4*R*)-3-(2-bromo-5-methoxyphenyl)-4-(4-bromophenyl)oxetan-2-one (2.41e): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using 4-bromobenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.40e)** (88 mg, 0.20 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (3.6 mg, 0.002 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 12/1) to afford **2.41e** as a white solid (61 mg, 73% yield); m.p. 129-132 °C. R_f = 0.30 (hexanes: diethyl ether = 10: 1).

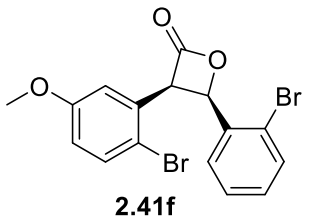
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 2.8 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.88 (d, *J* = 6.8 Hz, 1H), 5.55 (d, *J* = 6.8 Hz, 1H), 3.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 158.8, 133.2, 132.6, 131.2, 131.1, 128.3, 122.9, 115.7, 115.5, 113.7, 76.1, 61.6, 55.5.

IR (neat): 2937, 2837, 1828, 1594, 1574, 1475, 1417, 1296, 1241, 1227, 1121, 1073, 1019, 959, 810, 720 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{13}O_3Br_2$ $(M+H)^+$ 410.9226 found 410.9227.

HPLC analysis: 97% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 45 min, t_R = 27.35 min, major; t_R = 31.65 min, minor); **[α]$_D^{20}$** -35.7° (c = 1.82, $CHCl_3$).



2.41f

(3*R*,4*R*)-3-(2-bromo-5-methoxyphenyl)-4-(2-bromophenyl)oxetan-2-one (2.41f): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using 2-bromobenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.40f)** (220 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 15/1) to afford **2.41f** as a white solid (186 mg, 91% yield); m.p. 148-150 °C. R_f = 0.25 (hexanes: diethyl ether = 10: 1).

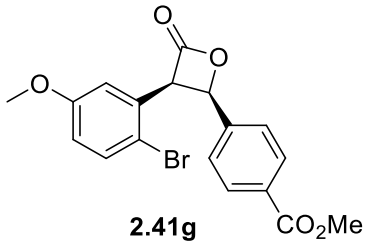
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.31-7.27 (m, 2H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 6.58 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.42 (d, *J* = 2.8 Hz, 1H), 6.16 (d, *J* = 6.8 Hz, 1H), 5.85 (d, *J* = 6.8 Hz, 1H), 3.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 158.5, 133.7, 133.6, 133.0, 130.7, 130.4, 128.4, 127.2, 122.4, 116.8, 116.0, 115.6, 76.6, 61.6, 55.6.

IR (neat): 2937, 2836, 1828, 1593, 1570, 1473, 1440, 1436, 1293, 1235, 1109, 1018, 954, 893, 865, 852, 756, 737 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{13}O_3Br_2$ $(M+H)^+$ 410.9226 found 410.9228.

HPLC analysis: >99% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 40 min, t_R = 26.65 min, minor; t_R = 28.87 min, major); **$[\alpha]_D^{20}$** 11.2° (c = 1.26, $CHCl_3$).



2.41g

Methyl 4-((2*R*,3*R*)-3-(2-bromo-5-methoxyphenyl)-4-oxooxetan-2-yl)benzoate (2.41g): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using methyl 4-((2-(2-bromo-5-methoxyphenyl)-2-diazoacetoxy)methyl)benzoate **(2.40g)** (210 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 5/1) to afford **2.41g** as a white solid (153 mg, 78% yield); m.p. 150-153 °C. R_f = 0.30 (hexanes: diethyl ether = 6: 1).

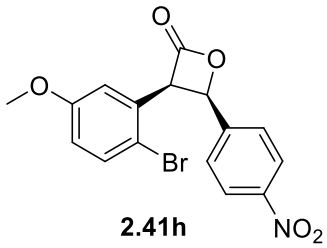
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.51 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.96 (d, *J* = 6.8 Hz, 1H), 5.60 (d, *J* = 6.8 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 166.4, 158.8, 138.6, 133.1, 131.0, 130.3, 129.2, 126.5, 115.6, 115.5, 113.7, 76.0, 61.9, 55.5, 52.2.

IR (neat): 2951, 1828, 1720, 1594, 1574, 1475, 1435, 1419, 1279, 1241, 1227, 1109, 1018, 958, 870, 769, 711 cm^{-1}.

HRMS (NSI) calcd. for $C_{18}H_{16}O_5Br$ $(M+H)^+$ 391.0176 found 391.0178.

HPLC analysis: >99% ee (AD-H, 2% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 60 min, t_R = 41.92 min, major; t_R = 44.04 min, minor); **$[\alpha]_D^{20}$** -45.2° (c = 1.95, $CHCl_3$).



2.41h

(3*R*,4*R*)-3-(2-bromo-5-methoxyphenyl)-4-(4-nitrophenyl)oxetan-2-one (2.41h): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using 4-nitrobenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.40h)** (56 mg, 0.138 mmol, 1 equiv), Rh_2(*S*-TCPTTL)$_4$ (2.5 mg, 0.0014 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 3/1) to afford **2.41h** as a light yellow solid (38 mg, 78% yield); m.p. 151-153 °C. R_f = 0.25 (hexanes: diethyl ether = 3: 1).

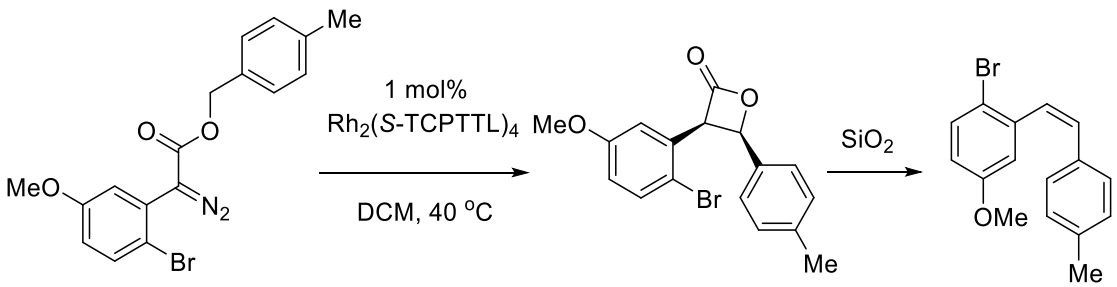
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.56 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.01 (d, *J* = 6.8 Hz, 1H), 5.66 (d, *J* = 6.8 Hz, 1H), 3.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 158.9, 147.9, 140.8, 133.4, 130.6, 127.5, 123.2, 115.8, 115.5, 113.5, 75.3, 62.3, 55.5.

IR (neat): 2939, 1831, 1594, 1573, 1519, 1475, 1417, 1346, 1295, 1240, 1227, 1108, 1018, 956, 870, 855, 824, 708 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{12}O_5NBrNa$ $(M+Na)^+$ 399.9791 found 399.9794.

HPLC analysis: >99% ee (AD-H, 2% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 60 min, t_R = 42.88 min, major; t_R = 49.78 min, minor); **$[\alpha]_D^{20}$** -18.1° (c = 1.93, $CHCl_3$).



2.42 **2.43** **2.44**

(3*R*,4*R*)-3-(2-bromo-5-methoxyphenyl)-4-(*p*-tolyl)oxetan-2-one (2.43): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using 4-methylbenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.42)** (188 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The NMR yield of the desired product was determined to be 60% by ^{1}H NMR analysis with dibromomethane as the internal standard. Purification of the crude residue by flash column chromatography (silica gel, hexanes/ diethyl ether = 12/1) afforded the

desired C-H insertion product **2.43** as a white solid (16 mg, 9% yield); m.p. 108-110 °C. R_f = 0.26 (silica gel, hexanes: diethyl ether = 8: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, *J* = 9.2, 1.2 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 2.8 Hz, 1H), 6.56 (dd, *J* = 9.2, 2.8 Hz, 1H), 5.91 (d, *J* = 6.8 Hz, 1H), 5.53 (d, *J* = 6.8 Hz, 1H), 3.70 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 169.2, 158.7, 138.6, 133.0, 131.7, 130.4, 128.6, 126.7, 115.6, 115.5, 113.0, 76.9, 61.4, 55.5, 21.1

IR (neat): 2936, 1823, 1593, 1574, 1475, 1419, 1295, 1240, 1227, 1171, 1112, 1018, 960, 859, 807 cm^{-1}.

HRMS (NSI) calcd. for $C_{17}H_{16}O_3Br$ $(M+H)^+$ 347.0277 found 347.0281.

HPLC analysis: 97% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 40 min, t_R = 22.81 min, major; t_R = 25.16 min, minor); **$[\alpha]_D^{20}$** 1.6° (c = 0.92, $CHCl_3$).

(*Z*)-1-bromo-4-methoxy-2-(4-methylstyryl)benzene (**2.44)**:

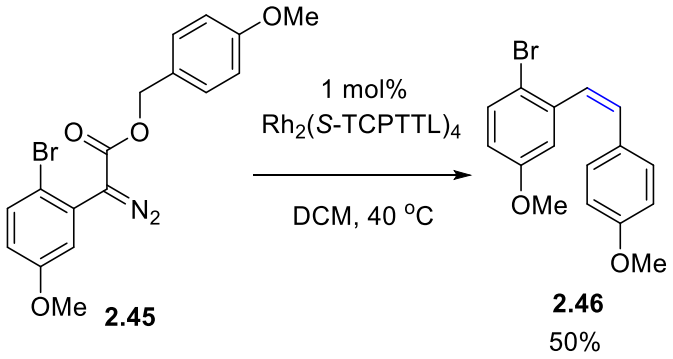
The lactone **2.43** readily underwent CO_2 extrusion and concomitant double bond formation upon silica gel column chromatography to give the corresponding olefin **(*Z*)-1-bromo-4-methoxy-2-(4-methylstyryl)benzene 2.44** as a colorless oil (60 mg, 38% yield). R_f = 0.30 (hexanes: diethyl ether = 12: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.76 (d, *J* = 3.2 Hz, 1H), 6.68-6.64 (m, 2H), 6.54 (d, *J* = 12.0 Hz, 1H), 3.54 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 138.9, 137.4, 133.6, 133.5, 133.4, 131.7, 129.1, 128.8, 115.7, 115.7, 114.6, 55.5, 21.5.

IR (neat): 3010, 2922, 2853, 1590, 1566, 1462, 1417, 1301, 1236, 1175, 1123, 1112, 1055, 1017, 871, 812 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{16}OBr$ $(M+H)^+$ 303.0379 found 303.0376.



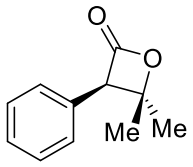
(*Z*)-1-bromo-4-methoxy-2-(4-methoxystyryl)benzene (2.46): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using 4-methoxybenzyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate **(2.45)** (196 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 25/1) to afford **2.46** as a colorless oil (80 mg, 50% yield); R_f = 0.32 (hexanes: diethyl ether = 12: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 2.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.66 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.61 (d, *J* = 12.0 Hz, 1H), 6.48 (d, *J* = 12.0 Hz, 1H), 3.75 (s, 3H), 3.56 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.1, 158.7, 139.1, 133.5, 131.2, 130.6, 129.0, 127.9, 115.7, 115.6, 114.7, 113.8, 55.5, 55.4.

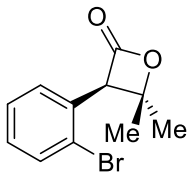
IR (neat): 3003, 2933, 2834, 1606, 1589, 1565, 1509, 1462, 1421, 1301, 1290, 1276, 1251, 1236, 1174, 1033, 1016, 870. 835, 810 cm^{-1}.

HRMS (NSI) calcd. for $C_{16}H_{16}O_2Br$ $(M+H)^+$ 319.0339 found 319.0335.



2.49

4,4-Dimethyl-3-phenyloxetan-2-one (**2.49**): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using isopropyl 2-diazo-2-phenylacetate (**2.48**) (41 mg, 0.2 mmol, 1.0 equiv), Rh_2(*S*-TCPTAD)$_4$ (4.2 mg, 0.002 mmol, 0.01 equiv) as the catalyst and DCM as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 12/1) to afford **2.33** as a clear oil (33 mg, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41-7.31 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.63 (s, 1H), 1.77 (s, 3H), 1.22 (s, 3H). Data matched that from the literature.[5] **HPLC** analysis: <5% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 30 min, t_R = 16.79 min, major; t_R = 26.28 min, minor).



2.29

(*R*)-3-(2-bromophenyl)-4,4-dimethyloxetan-2-one (2.29): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using isopropyl 2-(2-bromophenyl)-2-diazoacetate **(2.28)** (142 mg, 0.5 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (9.0 mg, 0.005 mmol, 0.01 equiv) as the catalyst and *n*-pentane as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 20/1 to 15/1) to afford the product **2.29** as a white solid (114 mg, 90% yield); m.p. 38-41 °C. R_f = 0.28 (hexanes: diethyl ether = 10: 1).

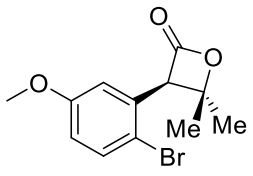
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.32 (td, *J* = 7.8, 1.2 Hz, 1H), 7.19 (td, *J* = 7.8, 1.2 Hz, 1H), 4.83 (s, 1H), 1.87 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6, 133.0, 132.9, 132.1, 129.8, 127.9, 123.9, 82.1, 63.9, 27.7, 22.7.

IR (neat): 2978, 2932, 1809, 1472, 1439, 1387, 1378, 1262, 1241, 1213, 1118, 1133, 1071, 1024, 969, 804, 747, 718 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{12}O_2Br$ 255.0015 found 255.0020.

HPLC analysis: 43% ee (*SS*-Whelk, 1% isopropanol in hexanes, 1.0 mL/min, 30 min, λ = 210 nm, t_R = 11.20 min, major; t_R = 15.01 min, minor); **$[\alpha]_D^{20}$** -49.7^o (c = 2.03, $CHCl_3$).



2.51

(*R*)-3-(2-bromo-5-methoxyphenyl)-4,4-dimethyloxetan-2-one (2.51): Prepared according to the general procedure for enantioselective intramolecular C–H insertion using isopropyl 2-(2-bromo-5-methoxyphenyl)-2-diazoacetate (**2.50**) (157 mg, 0.50 mmol, 1.0 equiv), Rh_2(*S*-TCPTTL)$_4$ (11 mg, 0.005 mmol, 0.01 equiv) as the catalyst and *n*-pentane as the solvent. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ diethyl ether = 15/1) to afford **2.51** as a white solid (136 mg, 95% yield); m.p. 67-69°C. R_f = 0.25 (hexanes: diethyl ether = 9: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 3.0 Hz, 1H), 6.74 (dd, *J* = 9.0, 3.0 Hz, 1H), 4.78 (s, 1H), 3.76 (s, 3H), 1.87 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6, 159.2, 133.6, 133.0, 115.6, 115.4, 114.0, 82.2, 63.9, 55.5, 27.7, 22.6.

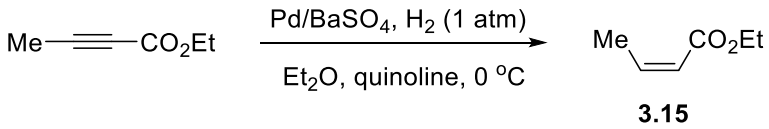
IR (neat): 2977, 2935, 1811, 1592, 1573, 1474, 1416, 1387, 1378, 1295, 1246, 1211, 1168, 1073, 1059, 1017, 972, 804, 684 cm^{-1}.

HRMS (NSI) calcd. for $C_{12}H_{14}O_3Br$ $(M+H)^+$ 285.0121 found 285.0121.

HPLC analysis: 93% ee (AD-H, 1% isopropanol in hexanes, 1.0 mL/min, λ = 230 nm, 45 min, t_R = 17.66 min, major; t_R = 19.68 min, minor); **$[\alpha]_D^{20}$** -112.7° (c = 1.95, $CHCl_3$).

Experimental section for chapter 3: Rhodium(II)-catalyzed asymmetric C–H functionalization of electron-deficient methyl groups

Preparation of starting materials:

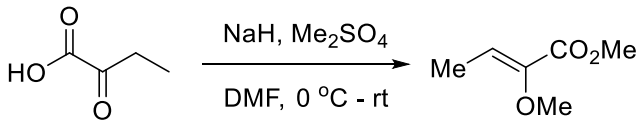


3.15

Ethyl (*Z*)-but-2-enoate (**3.13)**:

This compound was prepared according to a literature procedure:[6] A solution of ethyl but-2-ynoate (3.36 g, 30.0 mmol, 1.0 equiv) in 30 mL of anhydrous diethyl ether was stirred with 5% palladium on barium sulfate (60 mg, 0.54 mmol, 1.8 mmol %), 60 mg of quinoline under an atmosphere of hydrogen (balloon) at 0 °C for 36 h. The progress of the reaction was monitored by removing aliquots that are concentrated and analyzed by ^{1}H NMR, monitoring the disappearance of the methyl singlet at δ 1.95. After hydrogenation is complete, the catalyst is removed by filtration through a Celite® pad. The diethyl ether is removed with a rotary evaporator, and the product was purified by distillation at atmospheric pressure at 143–145°C (bath temperature) to give a clear liquid (3.01 g, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.30 (dq, *J* = 11.6, 7.2 Hz, 1H), 5.76 (dq, *J* = 11.6, 2.0 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.11 (dd, *J* = 7.3, 2.0 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).

[6] Taschner, M. J.; Rosen, T.; Heathcock, C. H. *Org. Synth.* **1986**, *64*, 108.



3.24a

Methyl (*Z*)-2-methoxybut-2-enoate (3.24a):

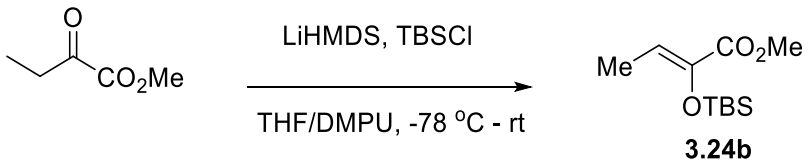
This compound was prepared according to a literature procedure: To NaH (5.14 g, 128.5 mmol, 5.0 equiv) in *N*,*N*-dimethylformamide (30 mL) was added a solution of 2-oxobutanoic acid (2.65 g, 25.7 mmol, 1.0 equiv) in 10 mL of *N*,*N*-dimethylformamide dropwise. The resulting foam was stirred for 90 min at rt. Then the solution was cooled to 0 °C and dimethyl sulfate (12.2 mL, 128.5 mmol, 5.0 equiv) was added over 60 min by syringe pump. The reaction was stirred at rt for 3 h before it was quenched with H_2O (30 mL), and the aqueous layer was extracted with diethyl ether (2x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated at rt. The residue was purified by flash chromatography (hexanes: diethyl ether = 10: 1) to afford **3.24a** as a colorless oil (900 mg, 27%); R_f = 0.25 (hexanes: diethyl ether = 8: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.30 (q, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 1.75 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 146.8, 124.1, 59.8, 51.8, 11.0.

IR (neat): 2957, 2927, 2857, 1727, 1600, 1464, 1325, 1276, 1148, 1069, 811, 721 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_6H_{11}O_3$ 131.0703; found 131.0703.



3.24b

Methyl (*Z*)-2-((*tert*-butyldimethylsilyl)oxy)but-2-enoate (3.24b):

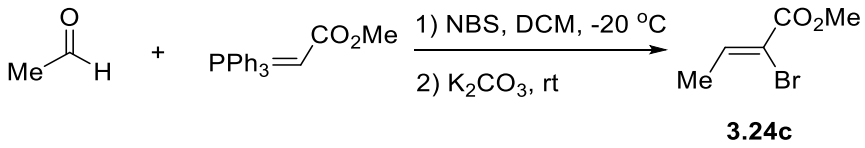
To a solution of LiHMDS (1 M in THF, 24.0 mL, 24.0 mmol, 1.2 equiv) at -78 °C was added a solution of methyl 2-oxobutanoate (2.32 g, 20.0 mmol, 1.0 equiv) in 10 mL of THF. After stirring at -78 °C for 30 min, DMPU (6 mL, 2.5 equiv) was added. The reaction was then stirred for 5 min before a solution of TBSCl (4.52 g, 30.0 mmol, 1.5 equiv) in 5 mL of THF was added dropwise. The reaction was then stirred for 5 h at rt before it was quenched with saturated aqueous NH_4Cl (20 mL), extracted with diethyl ether (30 mL × 2). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: diethyl ether (60: 1 to 30: 1) to give methyl (*Z*)-2-((*tert*-butyldimethylsilyl)oxy)but-2-enoate (**3.24b**) as a yellow oil (1.74 g, 38%); R_f = 0.63 (hexanes: ethyl acetate = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 6.09 (q, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 1.71 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 9H), 0.13 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 141.4, 117.9, 51.7, 25.8, 18.5, 11.4, -4.4.

IR (neat): 2957, 2931, 2858, 1729, 1651, 1260, 1142, 1090, 1036, 839, 808, 784 cm^{-1}.

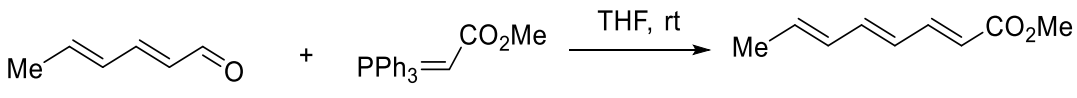
HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{23}O_3Si$ 231.1411; found 231.1411.



3.24c

Methyl (*Z*)-2-bromobut-2-enoate (**3.24c**):

This compound was prepared according to a literature procedure:[7] NBS (1.96 g, 11.0 mmol, 1.1 equiv) was added portionwise under nitrogen atmosphere to a solution of methyl (triphenylphosphoranylidene)-acetate (3.34 g, 10.0 mmol, 1.0 equiv) in dichloromethane (30 mL) at -20 °C. The mixture was stirred at -20 °C for 1 h and then allowed to warm to rt. Acetaldehyde (0.44 g, 10.0 mmol, 1.0 equiv) and K_2CO_3 (3.45 g, 25.0 mmol, 2.5 equiv) were added to the mixture which was stirred for 16 h. The reaction mixture was poured into 30 mL of H_2O. The organic phase was washed with brine (30 mL), dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1) to give **3.24c** as a colorless oil (1.14 g, 64%); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.37 (q, *J* = 6.8 Hz, 1H), 3.80 (s, 3H), 1.93 (d, *J* = 6.8 Hz, 3H).

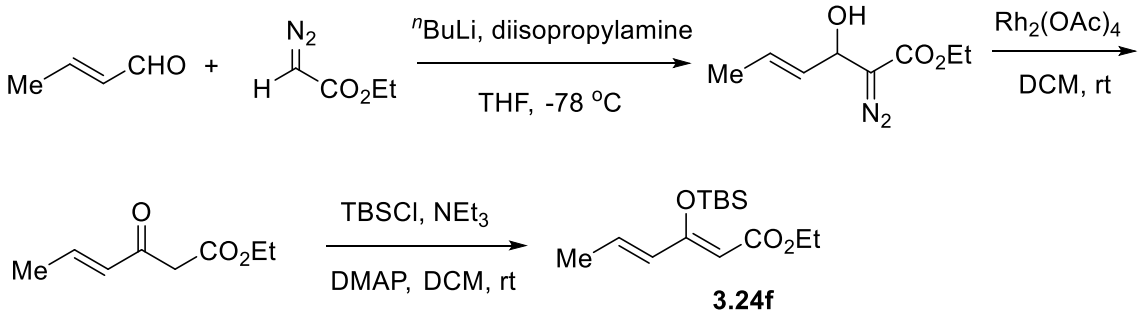


3.24e

Methyl (2*E*,4*E*,6*E*)-octa-2,4,6-trienoate (**3.24e**):

[7] Brenna, E.; Gatti, F. G.; Manfredi, A.; Monti, D.; Parmeggiani, F. *Org. Process Res. Dev.* **2012**, *16*, 262.

This compound was prepared according to a literature procedure[8]: To a solution of methyl (triphenylphosphoranylidene)acetate (2.52 g, 7.5 mmol, 1.0 equiv) in dry THF (20 mL) at rt was added (2*E*,4*E*)-hexa-2,4-dienal (0.56 g, 5.8 mmol). The mixture was stirred at rt under nitrogen, for 48 h, after which the solvent was evaporated and the residue was dissolved in a minimal amount of dichloromethane. Hexanes was added to the stirred solution to precipitate triphenylphosphine oxide. The precipitate was separated by filtration and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluting with hexanes: diethyl ether = 40: 1) to give **3.24e** as a white solid (0.66 g, 75%); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.27 (dd, *J* = 15.6, 11.6 Hz, 1H), 6.49 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.25–6.06 (m, 2H), 5.91 (dq, *J* = 14.8, 6.8 Hz, 1H), 5.81 (d, *J* = 15.2 Hz, 1H), 3.71 (s, 3H), 1.80 (dd, *J* = 6.8, 1.2 Hz, 3H).



Ethyl (2*Z*,4*E*)-3-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienoate (3.24f):

^{n}BuLi (2.5 M in hexanes, 15.0 mL, 37.5 mmol, 1.43 equiv) was added to a solution of diisopropylamine (3.60 g, 35.6 mmol, 1.36 equiv) at -78 °C dropwise under argon. The

[8] Pandey, R. K.; Lindeman, S.; Donaldson, W. A. *ARKIVOC* **2010**, 4, 25.

solution was then stirred at -78 °C for 30 min to give a light yellow lithium diisopropylamide (LDA) solution that was used directly.

The LDA solution prepared above was then added dropwise to a solution of (*E*)-but-2-enal (4.2 g, 4.9 mL, 59.4 mmol, 2.26 equiv) was added ethyl 2-diazoacetate (3.0 g, 26.3 mmol, 1.00 equiv) at -78 °C. After stirring at -78 °C for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (40 mL), and was extracted with diethyl ether (100 mL × 2). The combined organics were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: diethyl ether (4 :1) to give ethyl (*E*)-2-diazo-3-hydroxyhex-4-enoate as a yellow oil (4.6 g, *c.a.* 95% purity) that was used in the next step without further purification.

To a solution of $Rh_2(OAc)_4$ (56 mg, 0.5 mol %) in dry dichloromethane (10 mL) was added the diazo compound (*E*)-2-diazo-3-hydroxyhex-4-enoate (4.6 g, *c.a.* 25 mmol) dropwise. The reaction mixture was stirred at rt for 2 h. Then the solvent was removed under reduced pressure to give crude ethyl (*E*)-3-oxohex-4-enoate, which was used directly in the next step.

To a solution of crude ethyl (*E*)-3-oxohex-4-enoate in dry dichloromethane (75 mL) was added TBSCl (4.1 g, 27.5 mmol, 1.0 equiv), NEt_3 (4.3 mL, 30.0 mmol, 1.1 equiv), and DMAP (154 mg, 1.25 mmol, 5 mol %) sequentially at rt. The reaction mixture was stirred at rt for 24 h before it was concentrated. The residue was extracted with diethyl ether (100 mL × 2). The combined organics were washed with saturated aqueous NH_4Cl (50 mL), brine (50 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography

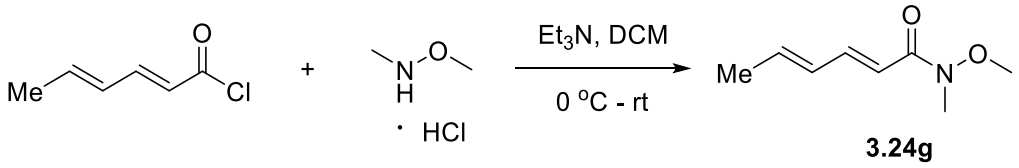
on silica gel eluting with hexanes: diethyl ether (50: 1 to 25: 1) to give ethyl (2*Z*,4*E*)-3-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienoate (**3.24f**) as a colorless oil (3.5 g, 49% for three steps); R_f = 0.40 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34 (dq, *J* = 15.2, 1.6 Hz, 1H), 6.44 (dq, *J* = 15.2, 7.2 Hz, 1H), 5.03 (s, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 1.83 (dd, *J* = 7.2, 1.6 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.93 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 163.8, 134.9, 125.6, 98.7, 59.4, 25.6, 18.3, 18.3, 14.4, -4.6.

IR (neat): 2957, 2931, 2859, 1707, 1648, 1582, 1293, 1257, 1131, 1051, 911, 823, 808, 781 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{27}O_3Si$ 271.1724; found 271.1721.

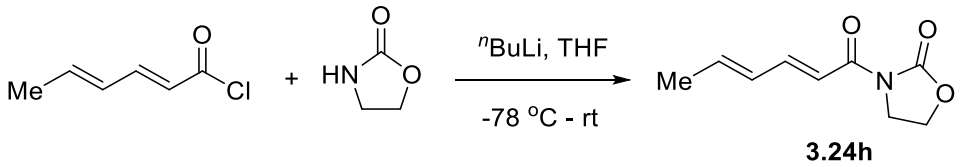


3.24g

(2*E*,4*E*)-*N*-methoxy-*N*-methylhexa-2,4-dienamide (**3.24g**):

To a mixture of *N*,*O*-dimethylhydroxylamine hydrochloride (1.67 g, 17.14 mmol, 1.05 equiv) and triethylamine (4.95 mL, 35.90 mmol, 2.2 equiv) in dry dichloromethane (50 mL) was added (2*E*,4*E*)-hexa-2,4-dienoyl chloride (2.13 g, 16.32 mmol, 1.0 equiv) at 0 °C. The resulting mixture was stirred overnight at rt, then was diluted with diethyl ether (100 mL), washed sequentially with HCl (1 M, 50 mL) and brine (50 mL), dried over $MgSO_4$,

concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (4: 1 to 2: 1) to give **3.24g** as a light yellow oil (1.70 g, 67%). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.28 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.35 (d, *J* = 15.2 Hz, 1H), 6.23 (ddq, *J* = 15.2, 10.8, 0.8 Hz, 1H), 6.12 (dq, *J* = 15.2, 6.8 Hz, 1H), 3.68 (s, 3H), 3.23 (s, 3H), 1.84 (dd, *J* = 6.8, 0.8 Hz, 3H). Data matched that of literature.[9]



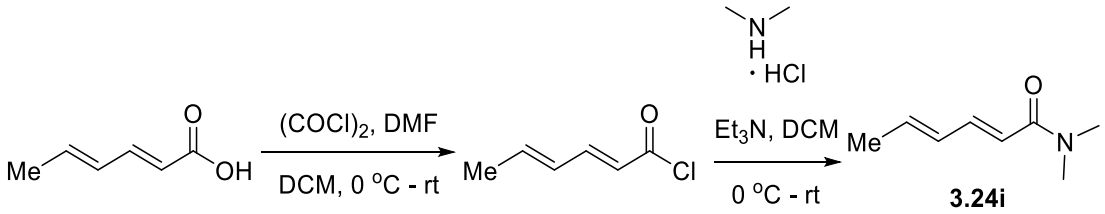
3.24h

3-((2*E*,4*E*)-hexa-2,4-dienoyl)oxazolidin-2-one (3.24h):

^{n}BuLi (1.6 M in hexanes, 1.40 mL, 22.0 mmol, 1.1 equiv) was added to a stirred solution of oxazolidin-2-one (1.74 g, 20.0 mmol, 1.0 equiv) in 30 mL of THF at −78 °C over 10 min. Then (2*E*,4*E*)-hexa-2,4-dienoyl chloride (2.87 g, 22.0 mmol, 1.1 equiv) was added and the resultant mixture was stirred for a further 30 min at −78 °C, after which time the reaction mixture was allowed to warm to rt and sat. aq. NH_4Cl solution (50 mL) was added. The organic material was extracted twice with ethyl acetate (50 mL), and the combined organic extracts were washed sequentially with sat. aq. $NaHCO_3$ solution (50 mL) and brine (50 mL). The organics were then dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (2: 1) to give **3.24h** as a white solid (1.30 g, 36%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 15.2, 10.8 Hz, 1H), 7.16 (d, *J* = 15.2 Hz, 1H), 6.35–

[9] Ley, S. V.; Cox, L. R.; Meek, G.; Metten, K.-H.; Piqué, C.; Worrall, J. M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 3299.

6.25 (m, 1H), 6.20 (dq, *J* = 15.2, 6.4 Hz, 1H), 4.39 (t, *J* = 8.0 Hz, 2H), 4.05 (t, *J* = 8.0 Hz, 2H), 1.85 (d, *J* = 6.4 Hz, 3H). Data matched that of literature.[10]



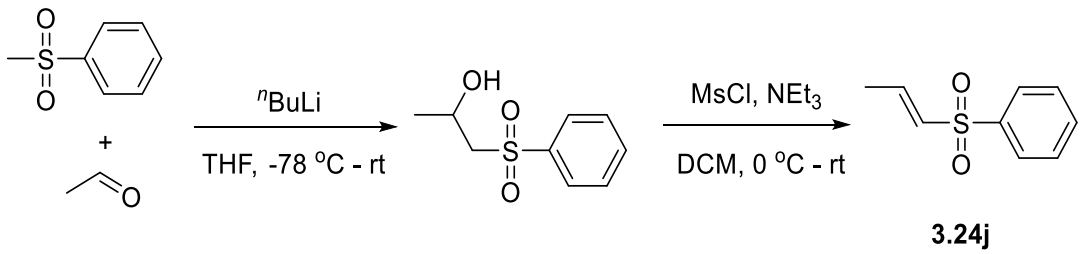
(2*E*,4*E*)-*N*,*N*-dimethylhexa-2,4-dienamide (**3.24i**):

To a mixture of (2*E*,4*E*)-hexa-2,4-dienoic acid (1.12 g, 10.0 mmol, 1.0 equiv) in dry dichloromethane (40 mL) was added oxalyl chloride (1.72 mL, 20.0 mmol, 2.0 equiv) at 0 °C. Then several drops of dimethylformamide (DMF) was added. The resulting mixture was stirred at rt for 2 h before it was concentrated to give (2*E*,4*E*)-hexa-2,4-dienoyl chloride that was used directly in the next step.

To a mixture of dimethylamine hydrochloride (1.23 g, 15.0 mmol, 1.5 equiv) and triethylamine (4.17 mL, 15.0 mmol, 3.0 equiv) in dry dichloromethane (40 mL) was added the above obtained (2*E*,4*E*)-hexa-2,4-dienoyl chloride at 0 °C. The resulting mixture was stirred overnight at rt, then was diluted with diethyl ether (100 mL), washed sequentially with HCl (1 M, 50 mL) and brine (50 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (4: 1 to 2: 1) to give **3.24i** (0.90 g, 65%). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.22 (dd, *J* = 15.2, 10.8 Hz,

[10] Zhang, J.; Hong, S. H. *Org. Lett.* 2012, *14*, 4646.

1H), 6.19 (d, *J* = 15.2 Hz, 1H), 6.21-6.02 (m, 3H), 3.04 (s, 3H), 2.98 (s, 3H), 1.80 (d, *J* = 6.4 Hz, 3H). Data matched that of literature.[11]



3.24j

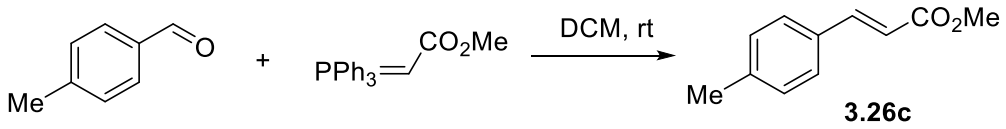
(*E*)-(prop-1-en-1-ylsulfonyl)benzene (**3.24j**):

To a solution of (methylsulfonyl)benzene (1.25 g, 8.01 mmol, 1.00 equiv) in THF (40 mL) was added ^{n}BuLi (1.6 M in hexanes, 5.50 mL, 8.80 mmol, 1.10 equiv) at −78 °C under argon. The resulting mixture was stirred at 0 °C for 30 mins and was cooled to −78 °C before acetaldehyde (0.49 mL, 8.81 mmol, 1.10 equiv) was added. The reaction mixture was allowed to warm to rt and stirred for 2 h. Then sat. aq. NH_4Cl solution (30 mL) was added. The organic material was extracted twice with diethyl ether (50 mL each time), and the combined organic extracts were dried over $MgSO_4$, and concentrated to give an alcohol intermediate that was used directly in the next step.

The material obtained from the previous step was dissolved in DCM (25 mL) and cooled to 0 °C. Then triethylamine (11.2 mL, 80.0 mmol, 10.0 equiv) and MsCl (0.93 mL, 12.0 mmol, 1.5 equiv) were added sequentially. The reaction was stirred at room temperature for 1.5 h, at which point it was quenched with sat. aq. NH_4Cl solution (30 mL)

[11] Parker, K. A.; J. Petraitis, J. J.; Kosley, R. W.; Buchwald, S. L. *J. Org. Chem.* **1982**, *47*, 389.

was added. Layers were separated and the aqueous layer was extracted twice with dichloromethane (30 mL). The combined organic extracts were dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (6: 1 to 3: 1) to give **3.24j** (1.11 g, 76%). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.87-7.83 (m, 2H), 7.61-7.49 (m, 3H), 6.99 (dq, *J* = 15.2, 6.8 Hz, 1H), 6.35 (dq, *J* = 15.2, 1.6 Hz, 1H), 1.91 (dd, *J* = 6.8, 1.6 Hz, 3H). Data matched that of literature.[12]

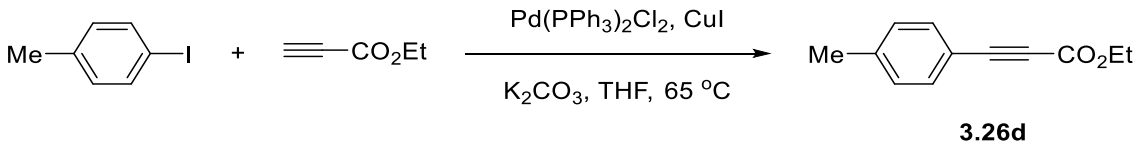


3.26c

Methyl (*E*)-3-(*p*-tolyl)acrylate (**3.26c**):

This compound was prepared according to a literature procedure:[13] To a solution of 4-methylbenzaldehyde (2.0 g, 16.6 mmol, 1.0 equiv) in dichloromethane (65 mL) was added methyl(triphenylphosphoranylidene)acetate (6.66 g, 19.9 mmol, 1.2 equiv) in one portion. The mixture was stirred at rt for 3 days and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexanes: diethyl ether (40: 1 to 20: 1) to give **3.26c** as a white solid (2.80 g, 89%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 16.0 Hz, 1H), 3.78 (s, 3H), 2.35 (s, 3H).

[12] Mauleón, P.; Alonso, I.; Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924.
[13] Zhdanko, A.; Schmauder, A.; Ma, C. I.; L. Sibley, D.; Sept, D.; Sasse, F.; Maier, M. E. *Chem. Eur. J.* **2011**, *17*, 13349



3.26d

Ethyl 3-(*p*-tolyl)propiolate (**3.26d**):

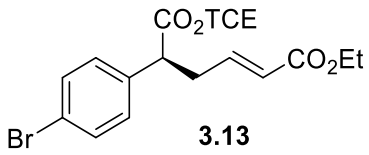
This compound was prepared according to a literature procedure:[14] To a solution of 1-iodo-4-methylbenzene (1.64 g, 7.5 mmol, 1.5 equiv), ethyl propiolate (490 mg, 5.0 mmol, 1.0 equiv) and K_2CO_3 (2.07 g, 15.0 mmol, 3.0 equiv) in THF (40 mL) was added $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol, 2 mol %) and CuI (38 mg, 0.2 mmol, 4 mol %). The resulting mixture was then heated under an argon atmosphere at 65 °C for 12 h. The reaction was monitored by TLC to establish the consumption of starting material. After the mixture was cooled to rt, the solids were removed by filtration. Then the filtrate was treated with H_2O (50 mL) and extracted with ethyl acetate (2 × 50 mL), and the combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to give **3.26d** as a colorless oil (395 mg, 42%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

General Procedure for the C-H functionalization reaction:

To an oven-dried, 10 mL round-bottomed flask, equipped with a reflux condenser and magnetic stir bar, was cooled to rt under argon before it was added with rhodium (II)

[14] Li, J.; Zhang, J.; Tan, H.; Wang, D. Z. *Org. Lett.* **2015**, *17*, 2522.

catalyst (0.5 mol %) and substrate (2.0 equiv), followed by dry dichloromethane (0.5 mL). The solution was heated to reflux under argon. Then a solution of the diazo compound was dissolved in 1.2 mL dichloromethane under argon and added dropwise to the reaction mixture over 3 h by a syringe pump. The flask used to dissolve the diazo and the needle/syringe were rinsed with 0.5 mL of dichloromethane, which was added to the reaction over 30 min. The solution was stirred at reflux for 1 h and then was cooled to rt. The solvent was removed *in vacuo* and the crude reside was purified by column chromatography.



3.13

1-ethyl 6-(2,2,2-trichloroethyl) (*S*,*E*)-5-(4-bromophenyl)hex-2-enedioate (3.13):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl (*E*)-but-2-enoate (**3.12**) (182 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (12: 1 to 6: 1) to afford **3.13** as a colorless oil (270 mg, 74% isolated yield); R_f = 0.25 (hexanes: diethyl ether = 5: 1).

^{1}H NMR (600 MHz; $CDCl_3$) δ 7.51-7.45 (m, 2H), 7.25-7.19 (m, 2H), 6.83 (app dt, *J* = 15.6, 7.1 Hz, 1H), 5.88 (app dt, *J* = 15.6, 1.5 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.83 (dd, *J* = 8.2, 7.1 Hz, 1H), 3.03 (dddd, *J* =

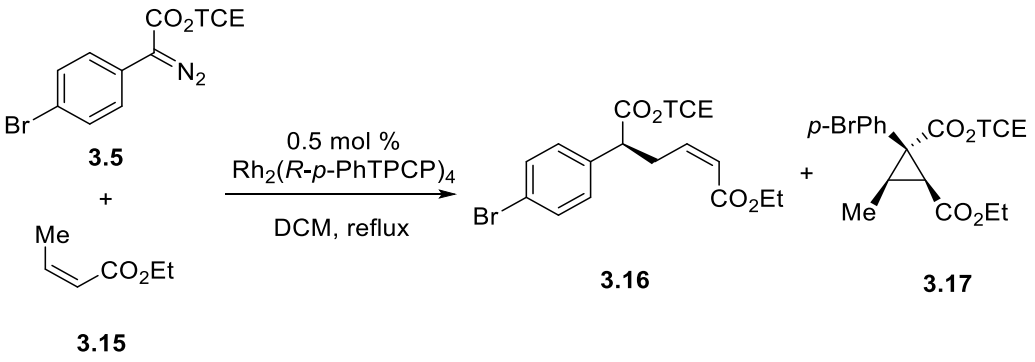
15.5, 8.5, 7.1, 1.5 Hz, 1H), 2.71 (app dtd, *J* = 15.3, 7.1, 1.5 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 166.1, 143.9, 135.9, 132.2, 129.9, 124.4, 122.3, 94.7, 74.4, 60.6, 49.9, 35.4, 14.4.

IR (neat): 2981, 1750, 1716, 1139 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{16}O_4Cl_3BrNa$ 478.9190; found 478.9199.

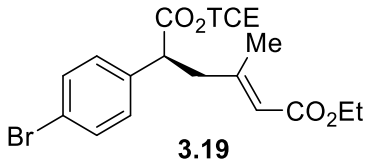
HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 23.02 min, Minor: 20.38 min, 95% ee; **[α]$^{20}_D$**: +43° (c 1.7, $CHCl_3$).



The reaction was performed according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl (*Z*)-but-2-enoate (**3.15**) (182 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (8: 1 to 6: 1) to afford the C–H insertion product (**3.16**) and cyclopropanation product (**3.17**).

1-ethyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-5-(4-bromophenyl)hex-2-enedioate (3.16): a colorless oil (180 mg, 49%); R_f = 0.17 (hexanes : diethyl ether = 10 : 1); **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.08 (app dt, *J* = 11.4, 7.8 Hz, 1H), 5.79 (app dt, *J* = 11.4, 1.8 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.83 (app t, *J* = 7.8 Hz, 1H), 3.34 (app dtd, *J* = 15.0, 7.8, 1.8 Hz, 1H), 3.26 (app dtd, *J* = 15.0, 7.8, 1.8 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.0, 165.8, 144.7, 136.0, 131.8, 129.9, 122.3, 121.8, 94.6, 74.1, 60.1, 50.3, 31.7, 14.2; **IR** (neat): 2981, 1750, 1714, 1645, 1488, 1371, 1192, 1139, 1011, 820, 761, 717 cm^{-1}; **HRMS** (NSI) *m/z*: $[M+Cl]^-$ calcd for $C_{16}H_{16}O_4BrCl_4$ 490.8992; found 490.8997; **HPLC**: SS-WHELK column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 13.08 min, Minor: 11.84 min, 97% ee. **$[\alpha]^{20}_D$**: +13° (c 2.6, $CHCl_3$).

2-ethyl 1-(2,2,2-trichloroethyl) (1*S*,2*S*,3*R*)-1-(4-bromophenyl)-3-methylcyclopropane-1,2-dicarboxylate (**3.17)**: a colorless oil (62 mg, 17%); R_f = 0.20 (hexanes : diethyl ether = 10 : 1); **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 4.61 (s, 2H), 4.35 – 3.88 (m, 2H), 2.79 (d, *J* = 9.6 Hz, 1H), 2.31 (dq, *J* = 9.6, 6.6 Hz, 1H), 1.33 (d, *J* = 6.6 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.0, 168.3, 133.4, 131.2, 130.3, 122.1, 94.5, 74.6, 60.8, 38.7, 31.6, 27.8, 14.1, 10.2; **IR** (neat): 2959, 1732, 1490, 1224, 1176, 1035, 1012, 830, 809, 787, 766, 717 cm^{-1}; **HRMS** (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{17}O_4BrCl_3$ 456.9370; found 456.9378; **HPLC**: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 6.14 min, Minor: 7.57 min, 93% ee. **$[\alpha]^{20}_D$**: +29° (c 2.3, $CHCl_3$).



3.19

1-ethyl 6-(2,2,2-trichloroethyl) (*S*,*E*)-5-(4-bromophenyl)-3-methylhex-2-enedioate (3.19):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl 3-methylbut-2-enoate (**3.18**) (205 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1 to 10: 1) to afford **3.19** as a colorless oil (144 mg, 38%); R_f = 0.33 (hexanes: diethyl ether = 8: 1).

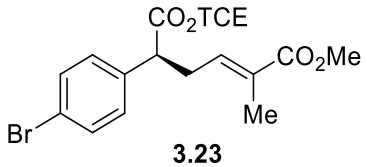
^{1}H NMR (600 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.65 (q, *J* = 1.2 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.93 (dd, *J* = 9.0, 6.6 Hz, 1H), 2.97 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.57 (dd, *J* = 14.4, 6.6 Hz, 1H), 2.14 (d, *J* = 1.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 166.1, 154.4, 135.9, 132.0, 129.6, 122.0, 118.2, 94.5, 74.2, 59.7, 48.8, 43.6, 18.7, 14.2.

IR (neat): 2980, 1752, 1714, 1651, 1488, 1369, 1222, 1147, 1012, 836, 800, 755, 720 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{19}O_4BrCl_3$ 470.9527; found 470.9533.

HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 9.11 min, Minor: 10.12 min, 97% ee; **$[\alpha]^{20}_D$**: +27° (c 1.0, $CHCl_3$).



3.23

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*E*)-5-(4-bromophenyl)-2-methylhex-2-enedioate (3.23):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), methyl (*E*)-2-methylbut-2-enoate (**3.22**) (182 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (8: 1) to afford **3.23** as a colorless oil (286 mg, 78%); R_f = 0.25 (hexanes: diethyl ether = 6: 1).

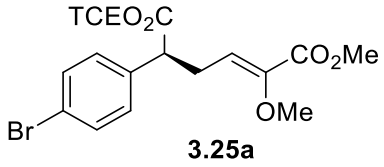
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.61 (app tq, *J* = 7.6, 1.6 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 3.77 (app t, *J* = 7.6 Hz, 1H), 3.68 (s, 3H), 2.97 (app dtd, *J* = 15.2, 7.6, 0.8 Hz, 1H), 2.67 (app dtd, *J* = 15.2, 7.6, 0.8 Hz, 1H), 1.80 (d, *J* = 1.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 168.0, 137.0, 135.9, 132.0, 130.2, 129.7, 122.0, 94.6, 74.1, 51.9, 49.9, 32.0, 12.6.

IR (neat): 2951, 1750, 1712, 1652, 1488, 1435, 1372, 1265, 1191, 1124, 1074, 1011, 902, 826, 755, 717 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{17}O_4BrCl_3$ 456.9370; found 456.9374.

HPLC: OJ-H column, 1 mL/min, 2 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 15.44 min, Minor: 21.99 min, 98% ee; **[α]$^{20}_{D}$**: +42° (c 2.1, $CHCl_3$).



3.25a

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-5-(4-bromophenyl)-2-methoxyhex-2-enedioate (**3.25a**):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), methyl (*Z*)-2-methoxybut-2-enoate (**3.24a**) (208 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1 to 15: 1) to afford **3.25a** as a colorless oil (334 mg, 88%); R_f = 0.64 (hexanes: diethyl ether = 6: 1).

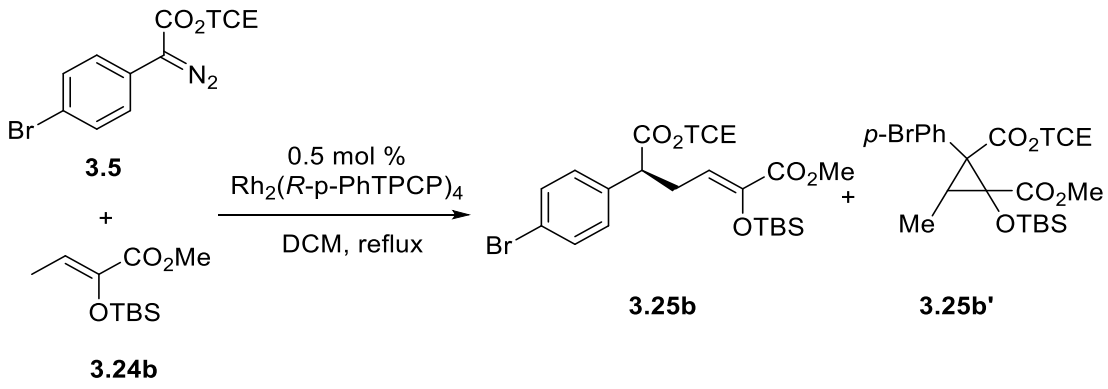
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.07 (app t, *J* = 7.6 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 3.75 (app t, *J* = 7.6 Hz, 1H), 3.72 (s, 3H), 3.59 (s, 3H), 2.97 (app dt, *J* = 15.2, 7.6 Hz, 1H), 2.77 (app dt, *J* = 15.2, 7.6 Hz, 1H).

^{3}C NMR (100 MHz, $CDCl_3$) δ 171.0, 163.6, 147.6, 136.0, 131.9, 129.8, 123.3, 121.9, 94.6, 74.1, 59.9, 52.0, 49.9, 28.8.

IR (neat): 2951, 2844, 1750, 1724, 1652, 1488, 1435, 1372, 1252, 1201, 1141, 1115, 1072, 1011, 943, 827, 799, 769, 716 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{17}O_5BrCl_3$ 472.9320; found 472.9324.

HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 11.88 min, Minor: 13.34 min, 98% ee; **$[\alpha]^{20}_D$**: +43° (c 2.5, $CHCl_3$).

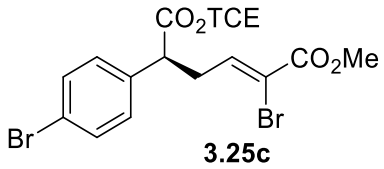


Performed according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), methyl (*Z*)-2-((*tert*-butyldimethylsilyl)oxy)but-2-enoate (**3.24b**) (368 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1 to 15: 1) to afford the products **3.25b** and **3.25b'**.

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-5-(4-bromophenyl)-2-((*tert*-butyldimethylsilyl)oxy)hex-2-enedioate (3.25b): a colorless oil (228 mg, 50%); R_f = 0.64

(hexanes : diethyl ether = 6 : 1); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.83 (app t, *J* = 7.2 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 3.75 (t, *J* = 7.6 Hz, 1H), 3.68 (s, 3H), 2.96 (dt, *J* = 15.2, 7.6 Hz, 1H), 2.75 (dt, *J* = 15.2, 7.6 Hz, 1H), 0.93 (s, 9H), 0.14 (s, 3H), 0.14 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.1, 164.7, 142.2, 136.0, 131.9, 129.8, 121.9, 117.4, 94.6, 74.1, 52.0, 49.9, 28.9, 25.8, 18.6, -4.2, -4.3; **IR** (neat): 2953, 2930, 2857, 1754, 1728, 1647, 1489, 1371, 1252, 1136, 1012, 840, 785, 720 cm^{-1}; **HRMS** (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{29}O_5BrCl_3Si$ 573.0028; found 573.0039; The ee was determined by chiral **HPLC**: SS-WHELK column, 1 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 9.62 min, Minor: 7.55 min, 93% ee. **$[\alpha]^{20}_D$**: +29° (c 2.0, $CHCl_3$).

2-methyl 1-(2,2,2-trichloroethyl) 1-(4-bromophenyl)-2-((*tert*-butyldimethylsilyl)oxy)-3-methylcyclopropane-1,2-dicarboxylate (3.25b') :obtained as a white solid (138 mg, 30%); m.p. 81-82 °C. R_f = 0.48 (hexanes : diethyl ether = 6 : 1); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.73 (s, 3H), 2.61 (q, *J* = 6.4 Hz, 1H), 1.08 (d, *J* = 6.4 Hz, 3H), 0.68 (s, 9H), 0.16 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 169.0, 134.2, 131.0, 129.8, 122.0, 94.5, 74.7, 66.4, 52.4, 42.8, 29.9, 25.8, 18.6, 10.1, -3.6, -3.7; **IR** (neat): 2953, 2930, 2857, 1747, 1489, 1252, 1207, 1153, 1050, 1013, 875, 839, 781, 768, 719 cm^{-1}; **HRMS** (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{29}O_5BrCl_3Si$ 573.0028; found 573.0034; The ee was determined by chiral **HPLC**: SS-WHELK column, 1 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 5.01 min, Minor: 5.44 min, 9% ee. **$[\alpha]^{20}_D$**: -5° (c 1.5, $CHCl_3$).



3.25c

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-2-bromo-5-(4-bromophenyl)hex-2-enedioate (3.25c):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), methyl (*Z*)-2-bromobut-2-enoate (**3.24c**) (285 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1 to 10: 1) to afford **3.25c** as a colorless oil (117 mg, 28%); R_f = 0.20 (hexanes: diethyl ether = 10: 1).

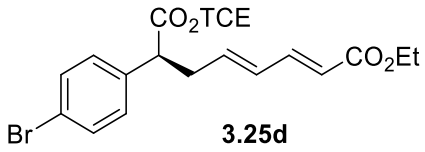
^{1}H NMR (600 MHz; $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.17 (app t, *J* = 7.2 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 3.87 (app t, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 3.07 (ddd, *J* = 15.0, 7.8, 6.6 Hz, 1H), 2.88 (app dt, *J* = 15.0, 7.2 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 162.4, 141.4, 135.4, 132.1, 129.7, 122.2, 118.4, 94.5, 74.2, 53.4, 48.9, 35.0.

IR (neat): 2953, 1750, 1731, 1627, 1488, 1408, 1372, 1261, 1144, 1174, 1035, 1011, 827, 799, 762, 718 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{14}O_4Br_2Cl_3$ 520.8319; found 520.8328.

HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 13.68 min, Minor: 15.02 min, 99% ee; **[α]$^{20}_{D}$**: +31° (c 0.3, $CHCl_3$).



3.25d

1-ethyl 8-(2,2,2-trichloroethyl) (*S*,2*E*,4*E*)-7-(4-bromophenyl)octa-2,4-dienedioate (3.25d):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl (2*E*,4*E*)-hexa-2,4-dienoate (**3.24d**) (224 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (9: 1) to afford **3.25d** as a colorless oil (310 mg, 80%); R_f = 0.27 (hexanes: diethyl ether = 8: 1).

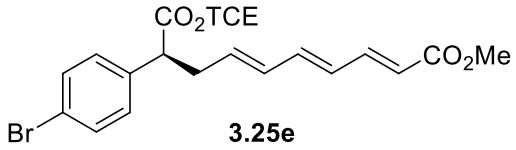
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.13 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.20 (dd, *J* = 15.2, 10.8 Hz, 1H), 5.95 (app dt, *J* = 15.2, 7.6 Hz, 1H), 5.77 (d, *J* = 15.2 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.76 (dd, *J* = 8.0, 7.6 Hz, 1H), 2.95 (app dt, *J* = 15.2, 8.0 Hz, 1H), 2.66 (app dt, *J* = 15.2, 7.6 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 166.9, 143.7, 138.4, 135.9, 131.9, 131.1, 129.7, 121.9, 121.0, 94.6, 74.1, 60.3, 50.4, 36.1, 14.3.

IR (neat): 2980, 1749, 1709, 1644, 1488, 1368, 1302, 1251, 1131, 1011, 823, 796, 756, 718 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{19}O_4BrCl_3$ 482.9527; found 482.9535.

HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 23.48 min, Minor: 18.58 min, 95% ee; **[α]$^{20}_D$**: +43° (c 1.9, $CHCl_3$).



3.25e

1-methyl 10-(2,2,2-trichloroethyl) (*S*,2*E*,4*E*,6*E*)-9-(4-bromophenyl)deca-2,4,6-trienedioate (3.25e):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl (2*E*,4*E*,6*E*)-octa-2,4,6-trienoate (**3.24e**) (243 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1 to 10: 1) to afford **3.25e** as a colorless oil (318 mg, 80%); R_f = 0.26 (hexanes: diethyl ether = 10: 1).

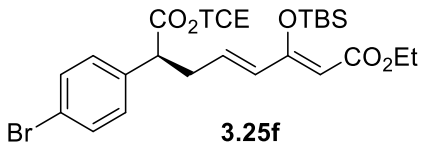
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.18 (m, 3H), 6.42 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.24-6.14 (m, 2H), 5.84 (d, *J* = 15.2 Hz, 1H), 5.77 (app dt, *J* = 15.2, 7.2 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 3.75 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.72 (s, 3H), 3.03 – 2.85 (m, 1H), 2.75 – 2.58 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 167.4, 144.5, 140.0, 136.0, 134.4, 132.6, 131.9, 129.7, 129.3, 121.9, 120.6, 94.6, 74.1, 51.5, 50.6, 36.2.

IR (neat): 2950, 1750, 1713, 1618, 1488, 1434, 1266, 1135, 1037, 1005, 825, 755, 718 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}O_4BrCl_3$ 494.9527; found 494.9531.

HPLC: AD-H column, 1 mL/min, 2 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 23.35 min, Minor: 21.54 min, 92% ee; **$[\alpha]^{20}_D$**: +64° (c 1.6, $CHCl_3$).



3.25f

1-ethyl 8-(2,2,2-trichloroethyl) (*S*,2*Z*,4*E*)-7-(4-bromophenyl)-3-((*tert*-butyldimethylsilyl)oxy)octa-2,4-dienedioate (3.25f):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl (2*Z*,4*E*)-3-((*tert*-butyldimethylsilyl)oxy)hexa-2,4-dienoate (**3.24f**) (432 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1 to 10: 1) to afford **3.25f** as a colorless oil (140 mg, 35%); R_f = 0.25 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.51 – 7.40 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.24 (app dt, *J* = 15.2, 7.6 Hz, 1H), 5.05 (s, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H),

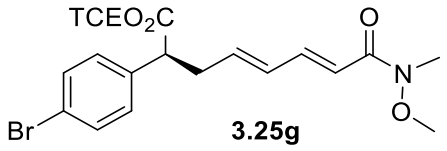
4.10 (q, *J* = 7.2 Hz, 2H), 3.77 (dd, *J* = 8.0, 7.6 Hz, 1H), 2.99 (app dtd, *J* = 14.8, 8.0, 6.8, 1.2 Hz, 1H), 2.75 (app dtd, *J* = 14.8, 8.0, 6.8, 1.2 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 167.1, 162.9, 135.9, 134.4, 131.9, 129.9, 126.9, 121.8, 100.0, 94.6, 74.1, 59.6, 50.5, 35.5, 25.5, 18.2, 14.4, -4.7, -4.7.

IR (neat): 2955, 2930, 2858, 1753, 1703, 1647, 1582, 1488, 1373, 1298, 1257, 1132, 1049, 1011, 824, 809, 783, 719 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{33}O_5BrCl_3Si$ 613.0341; found 613.0344.

HPLC: AD-H column, 1 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 9.21 min, Minor: 11.44 min, 58% ee; **[α]$^{20}_D$**: +25° (c 1.9, $CHCl_3$).



3.25g

2,2,2-trichloroethyl (*S*,4*E*,6*E*)-2-(4-bromophenyl)-8-(methoxy(methyl)amino)-8-oxoocta-4,6-dienoate (3.25g):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), (2*E*,4*E*)-*N*-methoxy-*N*-methylhexa-2,4-dienamide (**3.24g**) (248 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with

hexanes: ethyl acetate (4: 1 to 2: 1) to afford **3.25g** as a colorless oil (140 mg, 35%); R_f = 0.23 (hexanes: ethyl acetate = 2: 1).

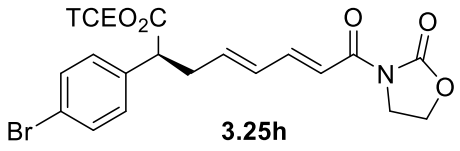
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.23 – 7.13 (m, 3H), 6.37 (d, *J* = 15.2 Hz, 1H), 6.26 (dd, *J* = 15.2, 11.0 Hz, 1H), 5.95 (app dt, *J* = 14.8, 7.1 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 3.77 (dd, *J* = 8.3, 7.0 Hz, 1H), 3.67 (s, 3H), 3.22 (s, 3H), 3.02 – 2.89 (m, 1H), 2.65 (app dtd, *J* = 14.3, 6.9, 1.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 167.0, 142.6, 137.7, 136.0, 131.9, 131.6, 129.7, 121.9, 118.6, 94.6, 74.1, 61.8, 50.4, 36.2, 32.4.

IR (neat): 2923, 2853, 1750, 1657, 1630, 1607, 1488, 1377, 1135, 1001, 818, 794, 756, 719 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{20}O_4NBrCl_3$ 497.9636; found 497.9643.

HPLC: AD-H column, 1 mL/min, 10 % ^{i}PrOH in hexanes, λ = 254 nm. t_R: Major: 15.83 min, Minor: 14.89 min, 97% ee; **[α]$^{20}_D$**: +38° (c 1.3, $CHCl_3$).



3.25h

2,2,2-trichloroethyl (*S*,4*E*,6*E*)-2-(4-bromophenyl)-8-oxo-8-(2-oxooxazolidin-3-yl)octa-4,6-dienoate (3.25h):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), 3-((2*E*,4*E*)-hexa-2,4-dienoyl)oxazolidin-2-one (**3.24h**) (290 mg, 1.6

mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether: dichloromethane (1: 1: 0 to 1: 1: 0.01) to afford **3.25h** as a colorless solid (340 mg, 81%); m.p. 76-78 °C; R_f = 0.22 (hexanes: diethyl ether = 1: 1).

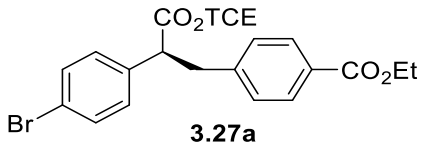
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 15.2, 10.8 Hz, 1H), 7.25 – 7.12 (m, 3H), 6.33 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.04 (app dt, *J* = 14.8, 7.6 Hz, 1H), 4.72 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.39 (t, *J* = 8.0 Hz, 2H), 4.04 (t, *J* = 8.0 Hz, 2H), 3.78 (app t, *J* = 7.6 Hz, 1H), 2.98 (app dt, *J* = 14.8, 7.6 Hz, 1H), 2.68 (app dt, *J* = 14.8, 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 165.3, 153.5, 145.5, 140.1, 135.8, 132.0, 131.6, 129.7, 121.9, 119.4, 94.6, 74.1, 62.0, 50.3, 42.7, 36.2.

IR (neat): 2921, 1770, 1749, 1675, 1632, 1603, 1488, 1385, 1361, 1270, 1136, 1031, 1009, 908, 825, 794, 756, 708 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{18}O_5NBrCl_3$ 523.9428; found 523.9435.

HPLC: AD-H column, 1 mL/min, 20 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 31.35 min, Minor: 35.56 min, 97% ee; **[α]$^{20}_D$**: +62° (c 2.8, $CHCl_3$).



3.27a

Ethyl (*S*)-4-(2-(4-bromophenyl)-3-oxo-3-(2,2,2-trichloroethoxy)propyl)benzoate (3.27a):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl 4-methylbenzoate (**3.26a**) (262 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (12: 1 to 6: 1) to afford **3.27a** as a colorless oil (311 mg, 77%); R_f = 0.23 (hexanes: diethyl ether = 6: 1).

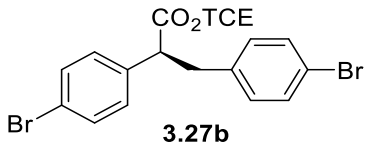
^{1}H NMR (600 MHz; $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.01 (app t, *J* = 7.8 Hz, 1H), 3.52 (dd, *J* = 13.8, 8.4 Hz, 1H), 3.16 (dd, *J* = 13.8, 7.2 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 166.3, 143.1, 136.0, 131.9, 129.8, 129.7, 129.0, 128.9, 121.9, 94.5, 74.1, 60.9, 52.4, 39.1, 14.3.

IR (neat): 2980, 1750, 1712, 1611, 1488, 1367, 1274, 1137, 1100, 1073, 1021, 1011, 908, 832, 798, 753, 718 cm^{-1}.

HRMS (APCI) *m/z*: $[M-H]^-$ calcd for $C_{20}H_{19}O_4BrCl_3$ 506.9527; found 506.9532.

HPLC: OJ-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 28.98 min, Minor: 34.51 min, 97% ee; **[α]$^{20}_D$**: +61° (c 2.3, $CHCl_3$).



3.27b

2,2,2-trichloroethyl (*S*)-2,3-bis(4-bromophenyl)propanoate (3.27b):

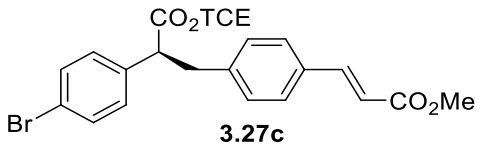
Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), 1-bromo-4-methylbenzene (**3.26b**) (274 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to afford **3.27b** as a colorless solid (366 mg, 88%); m.p. 74-75 °C, R_f = 0.70 (hexanes: diethyl ether = 5: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.91 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.38 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.02 (dd, *J* = 14.0, 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.9, 136.0, 131.9, 131.6, 130.7, 129.8, 121.9, 120.7, 94.5, 74.1, 52.6, 38.6; **IR** (neat): 2954, 1748, 1487, 1371, 1202, 1135, 1072, 1011, 812, 753, 716 cm^{-1}.

HRMS (APCI) *m/z*: [M-H]$^-$ calcd for $C_{17}H_{12}O_2Br_2Cl_3$ 510.8275; found 510.8266.

HPLC: AS-H column, 0.5 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 14.75 min, Minor: 18.39 min, 98% ee; **[α]$^{20}_D$**: +70° (c 2.0, $CHCl_3$).



3.27c

Methyl (*S*,*E*)-3-(4-(2-(4-bromophenyl)-3-oxo-3-(2,2,2-trichloroethoxy)propyl)phenyl)acrylate (3.27c):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), methyl (*E*)-3-(*p*-tolyl)acrylate (**3.26c**) (282 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (15: 1 to 15: 2) to afford **3.27c** as a colorless oil (368 mg, 86%); R_f = 0.21 (hexanes: diethyl ether = 8: 1).

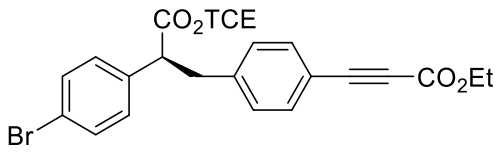
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.61 (d, *J* = 16.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.37 (d, *J* = 16.0 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.95 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.78 (s, 3H), 3.43 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.08 (dd, *J* = 14.0, 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 167.4, 144.4, 140.5, 136.1, 132.9, 131.9, 129.8, 129.5, 128.2, 121.9, 117.5, 94.5, 74.1, 52.5, 51.7, 39.1.

IR (neat): 2950, 1749, 1715, 1635, 1488, 1435, 1314, 1273, 1167, 1136, 1011, 982, 818, 797, 754, 717 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{19}O_4BrCl_3$ 518.9527; found 518.9533.

HPLC: AD-H column, 1 mL/min, 2 % ^{i}PrOH in hexanes, λ = 254 nm. t_R: Major: 32.01 min, Minor: 34.73 min, 97% ee; **[α]$^{20}_{D}$**: +100° (c 1.6, $CHCl_3$).



3.27d

Ethyl (*S*)-3-(4-(2-(4-bromophenyl)-3-oxo-3-(2,2,2-trichloroethoxy)propyl)phenyl)propiolate (3.27d):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), ethyl 3-(*p*-tolyl)propiolate (**3.26d**) (301 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1 to 10: 1) to afford **3.27d** as a colorless oil (345 mg, 81%); R_f = 0.20 (hexanes: diethyl ether = 12: 1).

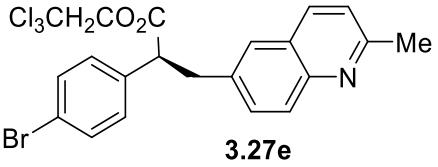
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.56 – 7.36 (m, 4H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.93 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.43 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.07 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 154.0, 141.0, 135.9, 133.1, 131.9, 129.8, 129.3, 122.0, 118.0, 94.5, 85.8, 80.8, 74.1, 62.1, 52.4, 39.2, 14.1.

IR (neat): 2928, 2235, 2209, 1751, 1704, 1488, 1368, 1290, 1194, 1176, 1140, 1011, 824, 720 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{19}O_4BrCl_3$ 530.9527; found 530.9532.

HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 254 nm. t_R: Major: 22.54 min, Minor: 20.12 min, 96% ee; **[α]$^{20}_D$**: +92° (c 2.2, $CHCl_3$).



3.27e

2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-3-(2-methylquinolin-6-yl)propanoate (3.27e):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (7.0 mg, 0.004 mmol, 0.5 mol %), 2,6-dimethylquinoline (**3.26e**) (251 mg, 1.6 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**3.5**) (298 mg, 0.8 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to afford **3.27b** as a colorless solid (341 mg, 85%); R_f = 0.33 (hexanes: diethyl ether = 1: 1).

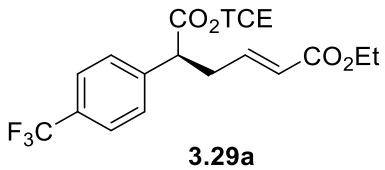
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.92–7.88 (m, 2H), 7.49–7.41 (m, 4H), 7.24-7.21 (m, 3H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.06 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.59 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.21 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.70 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 158.8, 146.9, 136.2, 135.8, 135.4, 131.9, 130.7, 129.8, 128.8, 127.1, 126.3, 122.2, 121.9, 94.5, 74.1, 52.6, 39.1, 25.3.

IR (neat): 2954, 1749, 1601, 1488, 1372, 1264, 1133, 1074, 1011, 907, 829, 753, 718 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{18}O_2NBrCl_3$ 499.9581; found 499.9594.

HPLC: AS-H column, 1 mL/min, 3 % ^{i}PrOH in hexanes, λ = 254 nm. t_R: Major: 11.19 min, Minor: 16.73 min, 99.9% ee; **$[\alpha]^{20}_D$**: +81° (c 1.4, $CHCl_3$).



3.29a

1-ethyl 6-(2,2,2-trichloroethyl) (*S*,*E*)-5-(4-(trifluoromethyl)phenyl)hex-2-enedioate (3.29a):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), ethyl (*E*)-but-2-enoate (**3.12**) (91 mg, 0.8 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (**3.28a**) (145 mg, 0.4 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (12: 1 to 6: 1) to afford **3.29a** as a colorless oil (120 mg, 67%); R_f = 0.20 (hexanes: diethyl ether = 5: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 6.82 (app dt, *J* = 15.6, 7.2 Hz, 1H), 5.87 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* =

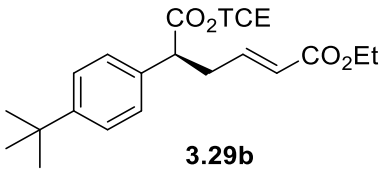
12.0 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.92 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.06 (app dtd, *J* = 15.2, 8.4, 1.2 Hz, 1H), 2.72 (app dtd, *J* = 15.2, 6.8, 1.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 165.8, 143.4, 140.6, 130.3 (q, *J* = 32 Hz), 128.4, 125.8 (q, *J* = 4 Hz), 123.9 (q, *J* = 271 Hz), 124.3, 94.4, 74.2, 60.4, 50.0, 35.1, 14.2.

IR (neat): 2984, 1753, 1717, 1324, 1267, 1162, 1125, 1068, 975, 842, 716 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{17}O_4Cl_3F_3$ 447.0139; found 447.0145.

HPLC: OJ-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 17.65 min, Minor: 24.57 min, 98% ee; **$[\alpha]^{20}_D$**: +38° (c 2.0, $CHCl_3$).



3.29b

1-ethyl 6-(2,2,2-trichloroethyl) (*S*,*E*)-5-(4-(tert-butyl)phenyl)hex-2-enedioate (3.29b):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), ethyl (*E*)-but-2-enoate (**3.12**) (92 mg, 0.8 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate (**3.28b**) (140 mg, 0.4 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1 to 10: 1) to afford **3.29b** as a colorless oil (122 mg, 70%); R_f = 0.31 (hexanes: diethyl ether = 10: 1).

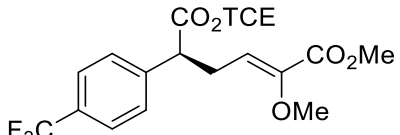
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.87 (ddd, *J* = 16.0, 8.4, 6.8 Hz, 1H), 5.89 (d, *J* = 16.0 Hz, 1H), 4.77 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.82 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.04 (app dt, *J* = 14.8, 8.4 Hz, 1H), 2.70 (app dt, *J* = 14.8, 6.8 Hz, 1H), 1.29 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 166.1, 150.9, 144.5, 133.7, 127.5, 125.8, 123.7, 94.7, 74.1, 60.3, 49.8, 35.4, 34.5, 31.3, 14.2.

IR (neat): 2961, 2870, 1751, 1718, 1656, 1367, 1266, 1136, 1038, 974, 833, 720 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{26}O_4Cl_3$ 435.0891; found 435.0893.

HPLC: OD-H column, 1 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 14.26 min, Minor: 23.45 min, 99% ee; **[α]$^{20}_D$**: +49° (c 1.9, $CHCl_3$).



3.29a'

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-2-methoxy-5-(4-(trifluoromethyl)phenyl)hex-2-enedioate (3.29a'):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), methyl (*Z*)-2-methoxybut-2-enoate (**3.24a**) (104 mg, 0.8 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (**3.28a**) (145 mg, 0.4 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with

hexanes: diethyl ether (12: 1 to 6: 1) to afford **3.29a'** as a colorless oil (152 mg, 82%); R_f = 0.30 (hexanes: diethyl ether = 6: 1).

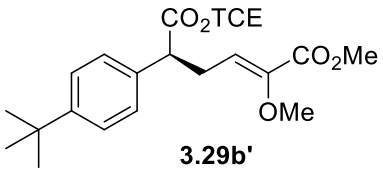
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 6.09 (app t, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 3.87 (app t, *J* = 7.6 Hz, 1H), 3.73 (s, 3H), 3.59 (s, 3H), 3.02 (app dt, *J* = 14.8, 7.6 Hz, 1H), 2.82 (app dt, *J* = 14.8, 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 163.5, 147.7, 140.9, 130.2 (q, *J* = 32 Hz), 128.5, 125.7 (q, *J* = 4 Hz), 123.9 (q, *J* = 271 Hz), 122.9, 94.5, 74.2, 59.9, 52.0, 50.2, 28.8.

IR (neat): 2954, 1752, 1726, 1323, 1269, 1163, 1116, 1068, 1018, 843, 779, 716 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{17}O_5Cl_3F_3$ 463.0088; found 463.0093.

HPLC: OD-H column, 1 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 7.84 min, Minor: 9.00 min, 99% ee; **$[\alpha]^{20}_D$**: +34° (c 1.5, $CHCl_3$).



3.29b'

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-5-(4-(*tert*-butyl)phenyl)-2-methoxyhex-2-enedioate (3.29b'):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), methyl (*Z*)-2-methoxybut-2-enoate (**3.24a**) (104 mg, 0.8 mmol, 2.0

equiv), and 2,2,2-trichloroethyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate (**3.28b**) (140 mg, 0.4 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (12: 1 to 8: 1) to afford **3.29b'** as a colorless oil (141 mg, 78%); R_f = 0.26 (hexanes: diethyl ether = 8: 1).

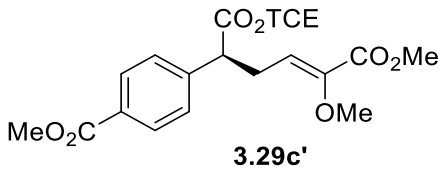
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.17 (app t, *J* = 7.6 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.77 (dd, *J* = 8.0, 7.6 Hz, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 3.01 (ddd, *J* = 14.8, 8.0, 7.6 Hz, 1H), 2.79 (app dt, *J* = 14.8, 7.6 Hz, 1H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 163.8, 150.8, 147.3, 134.0, 127.6, 125.7, 124.3, 94.7, 74.0, 59.9, 52.0, 50.0, 34.5, 31.3, 29.1.

IR (neat): 2957, 1751, 1727, 1435, 1365, 1269, 1202, 1138, 1109, 1034, 835, 800, 778, 720 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{26}O_5Cl_3$ 451.0840; found 451.0844.

HPLC: OD-H column, 1 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 11.47 min, Minor: 14.88 min, >99% ee; **$[\alpha]^{20}_D$**: +44° (c 2.2, $CHCl_3$).



3.29c'

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-2-methoxy-5-(4-(methoxycarbonyl)phenyl)hex-2-enedioate (3.29c'):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), methyl (*Z*)-2-methoxybut-2-enoate (**3.24a**) (104 mg, 0.8 mmol, 2.0 equiv), and methyl 4-(1-diazo-2-oxo-2-(2,2,2-trichloroethoxy)ethyl)benzoate (**3.28c**) (141 mg, 0.4 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (5: 1) to afford **3.29c'** as a colorless oil (102 mg, 56%); R_f = 0.25 (hexanes: diethyl ether = 5: 1).

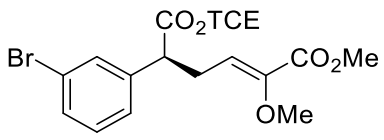
^{1}H NMR (500 MHz; $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.12 (app t, *J* = 7.5 Hz, 1H), 4.75 (s, 2H), 3.92 (s, 3H), 3.89 (app t, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 3.61 (s, 3H), 3.05 (app dt, *J* = 15.0, 7.5 Hz, 1H), 2.85 (app dt, *J* = 15.0, 7.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 166.6, 163.6, 147.6, 142.0, 130.1, 129.8, 128.2, 123.1, 94.6, 74.2, 59.9, 52.2, 52.0, 50.5, 28.8.

IR (neat): 2954, 1751, 1720, 1611, 1436, 1278, 1184, 1149, 1110, 1020, 965, 858, 747, 719 cm^{-1}.

HRMS (NSI) *m/z*: $[M-H]^-$ calcd for $C_{18}H_{18}O_7Cl_3$ 451.0124; found 451.0127.

HPLC: AS-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 210 nm, 230 nm. t_R: Major: 18.33 min, Minor: 21.94 min, 89% ee; **[α]$^{20}_D$**: +40° (c 0.9, $CHCl_3$).



3.29d'

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-5-(3-bromophenyl)-2-methoxyhex-2-enedioate (3.29d'):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), methyl (*Z*)-2-methoxybut-2-enoate (**3.24a**) (104 mg, 0.8 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2,2,2-trichloroethyl 2-(3-bromophenyl)-2-diazoacetate (**3.28d**) (149 mg, 0.4 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (15: 1 to 15: 2) to afford **3.29d'** as a colorless oil (165 mg, 87%); R_f = 0.21 (hexanes: diethyl ether = 8: 1).

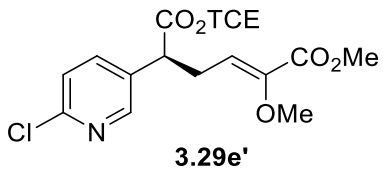
^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50 (t, *J* = 1.6 Hz, 1H), 7.42 – 7.40 (m, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.09 (app t, *J* = 7.6 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 3.77 – 3.73 (m, 4H), 3.60 (s, 3H), 2.99 (app dt, *J* = 15.2, 7.6 Hz, 1H), 2.79 (app dt, *J* = 14.8, 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 163.6, 147.6, 139.1, 131.1, 131.0, 130.3, 126.8, 123.2, 122.7, 94.6, 74.1, 59.9, 52.0, 50.1, 28.8.

IR (neat): 2951, 2846, 1750, 1724, 1651, 1434, 1315, 1265, 1200, 1141, 1114, 1033, 998, 804, 777, 717, 693 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{16}O_5BrCl_3Na$ 494.9139; found 494.9140.

HPLC: AS-H column, 0.5 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 16.19 min, Minor: 15.28 min, 88% ee. **[α]$^{20}_D$**: +30° (c 1.4, $CHCl_3$).



3.29e'

1-methyl 6-(2,2,2-trichloroethyl) (*S*,*Z*)-5-(6-chloropyridin-3-yl)-2-methoxyhex-2-enedioate (3.29e'):

Prepared according to general procedure using Rh_2(*R*-*p*-PhTPCP)$_4$ (3.5 mg, 0.002 mmol, 0.5 mol %), methyl (*Z*)-2-methoxybut-2-enoate (**3.24a**) (104 mg, 0.8 mmol, 2.0 equiv), and 2,2,2-trichloroethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate (**3.28e**) (132 mg, 0.4 mmol, 1.0 equiv). Purified by column chromatography on silica gel eluting with hexanes: diethyl ether (4: 1 to 2: 1) to afford **3.29e'** as a yellow oil (83 mg, 48%); R_f = 0.23 (hexanes: diethyl ether = 2: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.34 (d, *J* = 2.8 Hz, 1H), 7.67 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.04 (app t, *J* = 7.6 Hz, 1H), 4.72 (s, 2H), 3.83 (app t, *J* = 7.6 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 2.99 (app dt, *J* = 14.8, 7.6 Hz, 1H), 2.80 (app dt, *J* = 14.8, 7.6 Hz, 1H).

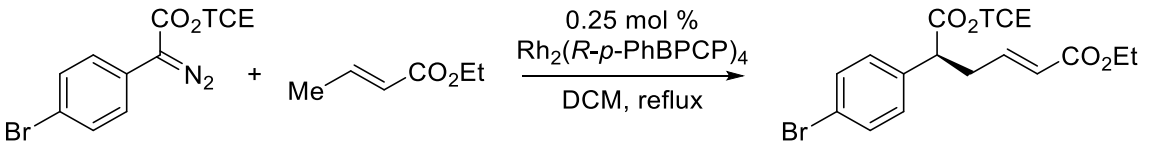
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 163.3, 151.1, 149.5, 147.9, 138.2, 131.7, 124.4, 122.0, 94.4, 74.2, 59.9, 52.1, 47.2, 28.6.

IR (neat): 2922, 1612, 1497, 1342, 1156, 1095, 999, 956, 914, 800, 751, 734, 666 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}O_5NCl_4$ 429.9777; found 429.9780.

HPLC: OD-H column, 1 mL/min, 5 % ^{i}PrOH in hexanes, λ = 254 nm. t_R: Major: 13.63 min, Minor: 16.49 min, 92% ee; **[α]$^{20}_D$**: +34° (c 1.5, $CHCl_3$).

Procedure for gram-scale preparation of 3.13



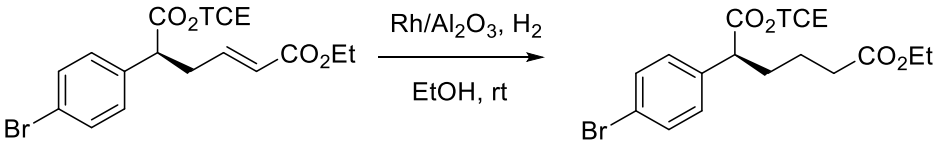
3.5
5.0 mmol

3.12

3.13
1.63 g, 71% yield, 95% ee

An oven-dried round-bottomed flask, equipped with a reflux condenser and magnetic stir bar was charged with Rh_2(*R*-*p*-PhTPCP)$_4$ (22.0 mg, 0.0125 mmol, 0.25 mol %), ethyl (*E*)-but-2-enoate (**3.12**) (1.14 g, 10.0 mmol), and dichloromethane (5 mL). The solution was heated to reflux. The diazo ester (**3.5**) (1.86 g, 5.0 mmol, 1.0 equiv) in 6 mL dichloromethane, was added dropwise over 3 h by a syringe pump. After the addition was complete, the needle nd syringe were rinsed with 2 mL dichloromethane, and was added to the reaction over 30 min. The solution was stirred for further refluxed for 3 h and then was cooled to rt. The solvent was removed *in vacuo* and the crude reside purified by column chromatography on silica gel eluting hexanes: diethyl ether = 6: 1 to give **3.13** as a colorless oil (1.63 g, 71% yield, 95% ee).

Selective hydrogenation of 3.13



3.13

3.30

6-ethyl 1-(2,2,2-trichloroethyl) (*S*)-2-(4-bromophenyl)hexanesdioate (3.30):

A solution of the ester (**3.13**) (92 mg, 0.20 mmol, 1.0 equiv) in 2 mL of ethanol was stirred with 10 mg of 5% rhodium on alumia under 1 atm of hydrogen (balloon) at rt for 3 h. Upon complete conversion of the starting material as indicated by TLC analysis, the solution was filtered through Celite®. The filtrate was concentrated and the reside was purified by column chromatography on silica gel eluting with hexanes: diethyl ether = 12: 1 to 6: 1 to give **3.30** as a colorless oil (85 mg, 92% yield). R_f = 0.24 (hexanes: diethyl ether = 5: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.68 (t, *J* = 7.5 Hz, 1H), 2.33 (td, *J* = 7.5, 3.0 Hz, 2H), 2.23 – 2.04 (m, 1H), 1.92 – 1.85 (m, 1H), 1.78 – 1.48 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H).

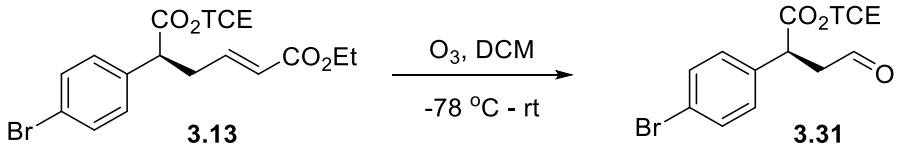
^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 171.6, 136.6, 131.9, 129.8, 121.7, 94.7, 74.1, 60.4, 50.7, 33.8, 32.3, 22.7, 14.2.

IR (neat): 2955, 1731, 1488, 1372, 1133, 1073, 1011, 916, 824, 761, 717 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}O_4BrCl_3$ 458.9527; found 458.9535.

HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 13.44 min, Minor: 11.28 min, 95% ee; **$[\alpha]^{20}_D$**: +17° (c 2.4, $CHCl_3$).

Ozonolysis of 3.13 with reductive work-up



2,2,2-trichloroethyl (*S*)-2-(4-bromophenyl)-4-oxobutanoate (3.31):

A solution of the ester (**3.13**) (46 mg, 0.10 mmol) in dichloromethane (1.2 mL) was cooled to -78 °C. Then ozone was passed through the solution until a blue color persisted. Excess ozone was purged from the system by bubbling oxygen through the reaction mixture for 15 min, followed by addition of dimethyl sulfide (0.10 mL). The reaction was warmed to rt, concentrated and the reside purified by column chromatography on silica gel eluting hexanes: diethyl ether = 6: 1 to 3: 1 to give **3.31** as a colorless oil (33.5 mg, 86% yield). R_f = 0.25 (hexanes: diethyl ether = 3: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 9.77 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.21 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.43 (dd, *J* = 18.8, 9.6 Hz, 1H), 2.88 (dd, *J* = 18.8, 4.8 Hz, 1H).

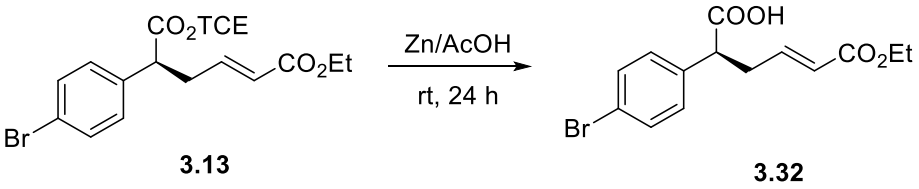
^{13}C NMR (100 MHz, $CDCl_3$) δ 198.5, 170.7, 135.5, 132.1, 129.7, 122.0, 94.5, 74.3, 46.5, 44.1.

IR (neat): 2924, 2849, 1751, 1723, 1489, 1376, 1220, 1150, 1074, 1011, 916, 828, 769, 718 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}O_3BrCl_3Na$ 408.8771; found 408.8775.

HPLC: AS-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 210 nm, 230 nm. t_R: Major: 15.11 min, Minor: 16.65 min, 95% ee; **[α]$^{20}_{D}$**: +52° (c 1.5, $CHCl_3$).

Deprotection of trichloroethyl ester



3.13 **3.32**

(*S*,*E*)-2-(4-bromophenyl)-6-ethoxy-6-oxohex-4-enoic acid (3.32):

The ester (**3.13**) (160 mg, 0.35 mmol, 1.0 equiv) was dissolved in 2 mL of glacial acetic acid, and zinc powder (137 mg, 2.1 mmol, 6.0 equiv) was added. The solution was allowed to stir at rt for 24 h. Upon complete conversion of the starting material as indicated by TLC analysis, the solution was diluted with H_2O (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated to give **3.32** as a colorless oil (109 mg, 95% yield).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.81 (app dt, *J* = 15.5, 7.0 Hz, 1H), 5.85 (d, *J* = 16.0 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 3.69 (app t, *J* = 7.5 Hz, 1H), 2.95 (app dt, *J* = 15.0, 7.5 Hz, 1H), 2.64 (app dt, *J* = 15.0, 7.5 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 3H).

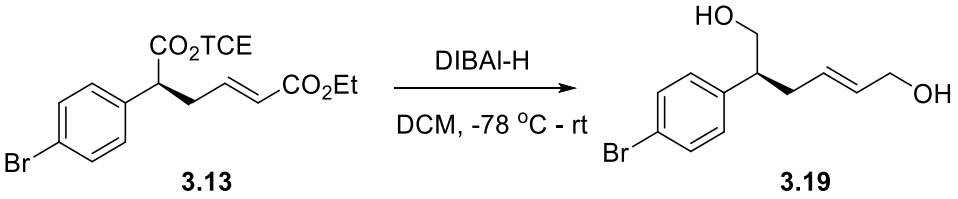
^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 166.2, 144.3, 136.1, 132.1, 129.7, 123.9, 122.0, 60.5, 49.8, 35.1, 14.2.

IR (neat): 2982, 1712, 1655, 1489, 1370, 1273, 1201, 11589, 1074, 1012, 824 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{16}O_4Br$ 327.0227; found 327.0229.

HPLC: OJ-H column, 1 mL/min, 10 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 11.25 min, Minor: 10.15 min, 96% ee; **[α]$^{20}_{D}$**: +70° (c 0.6, $CHCl_3$).

Reduction of 3.13 to diol



(*S*,*E*)-5-(4-bromophenyl)hex-2-ene-1,6-diol (3.19):

A solution of the ester (**3.13**) (46 mg, 0.10 mmol, 1.0 equiv) in 1 mL of dichloromethane was added dropwise to 0.42 mL of 1.0 M DIBAl-H in dichloromethane (0.42 mmol, 4.2 equiv) under argon at -78 °C. The solution was stirred overnight while warmed up to rt before it was quenched carefully with 0.5 mL of 2 M HCl and extracted with ethyl acetate (3 x 3 mL). The organic extracts were washed with brine (3 mL), dried over Na_2SO_4 and concentrated to give **3.19** as colorless oil (28 mg, quantitative yield). R_f = 0.15 (hexanes: ethyl acetate = 1: 2).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.65 (app dt, *J* = 15.0, 5.5 Hz, 1H), 5.57 (app dt, *J* = 15.0, 6.5 Hz, 1H), 4.03 (d, *J* = 5.5 Hz, 2H), 3.78 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.72 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.85 (app p, *J* = 7.0 Hz, 1H), 2.49 (app dt, *J* = 14.0, 7.0 Hz, 1H), 2.35 (app dt, *J* = 14.5, 7.0 Hz, 1H), 1.73 (br s, 2H).

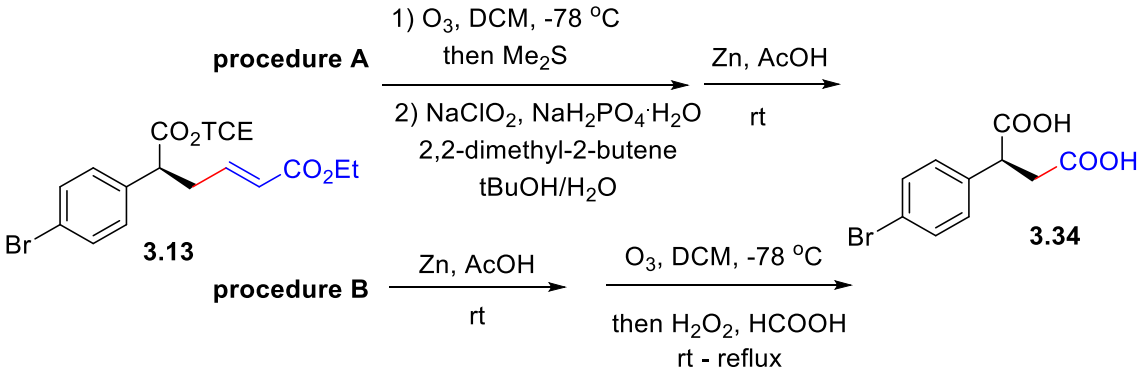
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 131.7, 131.2, 129.8, 129.8, 120.6, 66.6, 63.4, 47.7, 34.8.

IR (neat): 2955, 1754, 1727, 1652, 1619, 1437, 1325, 1271, 1165, 1119, 1069, 844, 718cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{16}O_2Br$ 271.0328; found 271.0332.

HPLC: OJ-H column, 1 mL/min, 10 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 13.79 min, Minor: 12.57 min, 95% ee; **[α]$^{20}_D$**: +26° (c 0.6, $CHCl_3$).

Conversion of 3.13 to a diacid and assignment of absolute configuration



Procedure A: A solution of the ester (**3.13**) (160 mg, 0.35 mmol) in dichloromethane (2 mL) was cooled to -78 °C. Ozone was then passed through the solution until a light blue color persisted. Excess ozone was purged from the system by bubbling oxygen through the reaction mixture for 15 min, followed by addition of methyl sulfide (0.10 mL). The reaction was warmed to rt and concentrated. The residue was suspended in ^{t}BuOH/H_2O (2 mL/2 mL), then $NaClO_2$ (317 mg, 3.50 mmol, 10.0 equiv), $NaH_2PO_4{\cdot}H_2O$ (483 mg, 3.50 mol,

10.0 equiv), 2,2-dimethyl-2-butene (0.62 mL, 5.35 mmol, 15.0 equiv) were added. The reaction was stirred at rt over night before it was quenched with 10 mL of H_2O, and acidified with 1 M HCl to pH 3. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The residue was dissolved in 2 mL of glacial acetic acid, and zinc powder (137 mg, 2.1 mmol, 6.0 equiv) was added. The solution was allowed to stir at rt for 24 h. Upon complete conversion of the starting material as indicated by TLC analysis, the solution was diluted with H_2O (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. The solids obtained were triturated with dichloromethane/hexanes (3/1 v/v, 4 mL) to give **3.34** as a white solid (72 mg, 75%).

Procedure B: The ester (**3.13**) (160 mg, 0.35 mmol, 1.0 equiv) was dissolved in 2 mL of glacial acetic acid, and zinc powder (137 mg, 2.1 mmol, 6.0 equiv) was added. The solution was allowed to stir at rt for 24 h. Upon complete conversion of the starting material as indicated by TLC analysis, the solution was diluted with H_2O (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated.

The residue in dichloromethane (4 mL) was cooled to -78 °C. Then ozone was passed through the solution until a blue color persisted. Excess ozone was purged from the system by bubbling oxygen through the reaction mixture for 15 min, followed by addition of methyl sulfide. The reaction was warmed to rt and concentrated. The residue was dissolved in 1 mL of formic acid, followed by addition of H_2O_2 (30% solution in H_2O, 0.3 mL). The mixture was stirred at rt for 2 h before it was refluxed for 1 h. Additional 1 mL of formic

acid was added and the reaction was heated to reflux for 2 h. The reaction was cooled rt, and 10 mL of H_2O was added. The organics were extracted with ethyl acetate (15 mL × 3), dried over Na_2SO_4, concentrated, and dried in *vacuo*. The solids were triturated with dichloromethane/hexanes (3/1 v/v, 4 mL) to give **3.34** as a white solid (44 mg, 46%).

(*S*)-2-(4-bromophenyl)succinic acid (3.34): obtained as a white solid, m.p. 197-198 °C (lit.,[12] m.p. 198-199 °C).

^{1}H NMR (500 MHz; acetone-d_6) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.09 (dd, *J* = 10.0, 5.5 Hz, 1H), **3.13** (dd, *J* = 17.0, 10.0 Hz, 1H), 2.70 (dd, *J* = 17.0, 5.5 Hz, 1H).

^{13}C NMR (125 MHz, acetone-d_6) δ 173.1, 171.8, 138.2, 131.7, 130.0, 120.8, 46.4, 36.9.

IR (neat): 2921, 1690, 1488, 1414, 1306, 1289, 1201, 1175, 1073, 1012, 927, 799, 748 cm^{-1}.

HRMS (NSI) *m/z*: $[M-H]^-$ calcd for $C_{10}H_8O_4Br$ 270.9611; found 270.9615; **$[\alpha]_D^{20}$**: +105 (c 1.3, EtOH) (lit.,[15] $[\alpha]_D^{20}$: +114 (c 0.7, EtOH)).

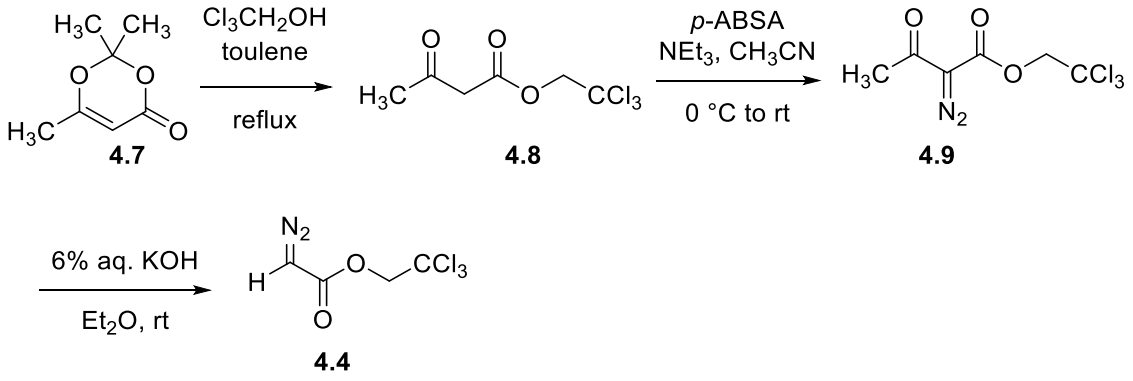
[15] Lawston, I. W.; Inch, T. D. *J. Chem. Soc. Perkin Trans. 1* **1983**, 2629.

Experimental section for chapter 4: Synthesis of 2,2,2-trichloroethyl aryl- and vinyldiazoacetates by palladium-catalyzed cross-coupling reactions

Procedure for ReactIR studies of product Stability

2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**4.6a**) were added to separate 10 mL volumetric flasks and diluted with toluene. A two-neck, 10 mL round-bottomed flask, was equipped with a magnetic stir bar and a rubber septum with an argon inlet adaptor. In addition, a glass joint was used to fix the ReactIR probe to the flask. Triphenylphosphine (5 mol %) and/or palladium(0)tetrakis(triphenylphosphine) (5 mol %) in 1mL toluene was added. After collecting background spectra for 5 scans (5 minutes), the 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**4.6a**) (2 mL) was added to the reaction flask and reaction progress was monitored with respect to the C=N stretching frequency observed for 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**4.6a**).

Procedures for the preparation of starting materials



2,2,2-trichloroethyl 2-diazoacetate (4.4):

Prepared according to procedures adapted from those for the preparation of similar compounds:[16] A solution of 2,2,2-trichloroethan-1-ol (17.92 g, 120.0 mmol, 1.0 equiv) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4- one (**4.7**) (17.04 g, 120.0 mmol, 1.0 equiv) in 24 mL of toluene in a flask was immersed in an oil bath that had been preheated to 150 °C, and the solution was vigorously stirred. The evolution of acetone became apparent within several minutes, heating was continued for a total of 6 hours. The reaction was cooled, and passed through a short plug of silica gel eluting with 20% ethyl acetate in hexanes (200 mL). The filtrate was concentrated to afford 2,2,2-trichloroethyl 3-oxobutanoate (**4.8**) as an oil which was directly in the next step.

2,2,2-trichloroethyl 3-oxobutanoate (**4.8**) obtained from the previous step was dissolved in CH_3CN (300 ml), followed by addition of 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (37.44 g, 156.0 mmol, 1.3 equiv). The reaction mixture was cooled in an ice bath and Et_3N (25.2 mL, 180.0 mmol, 1.5 equiv) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred over night, during which time a white precipitate crashed out. The solids were filtered off and were further washed with Et_2O (100 ml). The filtrates were concentrated, then diluted with diethyl ether (300 mL), and washed with 5% KOH (250 ml). The crude ether solution containing 2,2,2-trichloroethyl 2-diazo-3-oxobutanoate (**4.9**) was used directly in the next step.

To the crude ether solution of 2,2,2-trichloroethyl 2-diazo-3-oxobutanoate (**4.9**) obtained from the previous step was added 6% KOH (250 ml). The resulting biphasic mixture was stirred at room temperature for 6 h. The organic phase was separated, dried

[16] Mao, H.; Lin, A.; Shi, Y.; Mao, Z.; Zhu, X.; Li, W.; Hu, H.; Cheng, Y.; Zhu, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 6288.

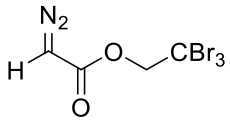
over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with hexanes: diethyl ether (40: 1 to 20: 1) gave 2,2,2-chloroethyl 2-diazoacetate (**4.4**) as a yellow liquid (19.46 g, 75% yield for three steps); R_f = 0.23 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 4.83 (m, 3H) (overlap of signals).

^{13}C NMR (125 MHz, $CDCl_3$) δ 95.0, 73.8, 46.6 (the resonance resulting from the carbonyl carbon in the 2,2,2-trichloroethyl ester was not detected).

IR (neat): 2113, 1699, 1385, 1349, 1220, 1146, 729, 704 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_4H_4O_2N_2Cl_3$ 216.9333; found 216.9333.



4.13b

2,2,2-tribromoethyl 2-diazoacetate (**4.13b**):

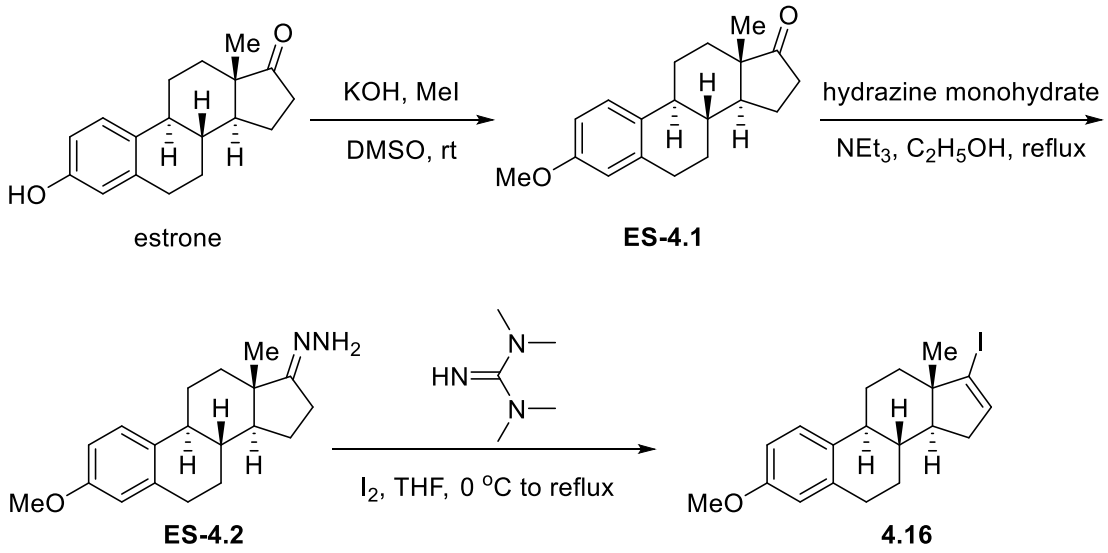
Prepared by the same procedure as that for the preparation of **4.4**.

^{1}H NMR (500 MHz; $CDCl_3$) δ 5.00 (m, 3H) (overlap of signals).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 165.1, 76.7, 47.0, 36.4.

IR (neat): 3119, 2942, 2112, 1692, 1435, 1382, 1344, 1217, 1144, 1077, 1043, 1006, 941, 857, 727, 703 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_4H_4Br_3N_2O_2$ 348.7817; found 348.7818.



(8*R*,9*S*,13*S*,14*S*)-17-iodo-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[*a*]phenanthrene (4.16):

Estrone (4.33 g, 16.0 mmol, 1.0 equiv) was added to a suspension of KOH (3.64 g, 64.0 mmol, 4.0 equiv) in 50 mL anhydrous dimethyl sulfoxide at rt. Then methyl iodide (4.54 g, 32.0 mmol, 2.0 equiv) was added. The reaction was stirred at room temperature overnight, and diluted with water (100 mL), extracted with ethyl acetate (2 X 120 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, and concentrated to afford **ES-4.1** as a white solid, which was used directly in the next step.

A mixture of **ES-4.1**, hydrazine monohydrate (3.2 mL, 64.0 mmol, 4.0 equiv) and NEt_3 (3.3 mL, 24.0 mmol, 1.5 equiv) in 45 mL ethanol was refluxed for 6 h before it was cooled to room temperature. The mixture was then concentrated under vacuum to afford **ES-4.2** as a white crystalline. This product was used directly in the next step.

Iodine (9.52 g, 37.5 mmol, 2.5 equiv) was dissolved in 20 mL tetrahydrofuran, followed by addition of 1,1,3,3-tetramethylguanidine (22.8 mL, 180.0 mmol, 12.0 equiv), then the reaction was cooled to 0 °C. A solution of **ES-4.2** obtained from the above in 20 mL tetrahydrofuran was added, and the reaction was stirred at 0 °C for 1 h before it was filtered. The residue was washed with tetrahydrofuran (30 mL), and the filtrates were concentrated to approximately 50 mL volume. This material was refluxed for 2 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL), diluted with ethyl acetate (2 X 50 mL). The combined organics were washed with brine (60 mL), dried over $MgSO_4$, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (25: 1) to give the (8*R*,9*S*,13*S*,14*S*)-17-iodo-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[*a*]phenanthrene (**4.16**) as a white solid (2.02 g, 32% for three steps); m.p. 132-134 °C; R_f = 0.50 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.71 (d, *J* = 3.0 Hz, 1H), 6.23 (dd, *J* = 3.0, 1.5 Hz, 1H), 3.84 (s, 3H), 3.02-2.90 (m, 2H), 2.48-2.43 (m, 1H), 2.34-2.28 (m, 2H), 2.11 (ddd, *J* = 14.5, 11.0, 1.5 Hz, 1H), 2.02-1.97 (m, 1H), 1.87–1.59 (m, 4H), 1.54-1.44 (m, 2H), 0.83 (s, 3H).

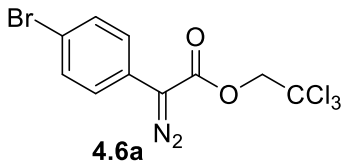
^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 137.8, 137.4, 132.5, 126.1, 113.9, 112.8, 111.5, 55.3, 54.1, 50.4, 44.2, 37.9, 36.4, 33.6, 29.8, 27.6, 26.5, 15.4.

IR (neat): 2928, 2852, 1608, 1499, 1453, 1281, 1256, 1247, 1154, 1048, 808 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{24}IO$ 395.0866; found 395.0867.

General Procedure A: for the palladium-catalyzed cross-coupling reaction:

$Pd(PPh_3)_4$ (231 mg, 0.2 mmol, 5 mol %), PPh_3 (106 mg, 0.4 mmol, 10 mol %), aryl iodide (4.0 mmol, 1.0 equiv), Ag_2CO_3 (550 mg, 2.0 mmol, 0.5 equiv) were suspended in toluene (16 mL) under argon, followed by addition of NEt_3 (0.73 mL, 5.2 mmol, 1.3 equiv) and 2,2,2-trichloroethyl 2-diazoacetate (1.13 g, 5.2 mmol, 1.3 equiv). The resulting reaction was stirred at room temperature for 4 h and then filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in vacuo and the residue was purified by column chromatography to give the products.

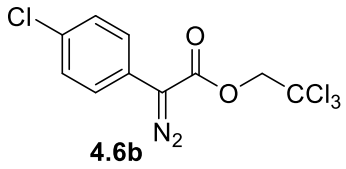


4.6a

2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**4.6a**)

Prepared according to **general procedure A** using 1-bromo-4-iodobenzene (**4.5a**) (1.13 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to give the product as an orange solid (1.32 g, 89%); R_f = 0.53 (hexanes: diethyl ether = 10: 1). This compound is a known compound.[17]

[17] a) Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 17718; b) Bess, E. N.; Guptill, D. M.; Davies, H. M. L.; Sigman, M. S. *Chem. Sci.* **2015**, *6*, 3057; c) Negretti, S.; Cohen, C. M.; Chang, J. J.; Guptill, D. M.; Davies, H. M. L. *Tetrahedron* **2015**, *71*, 7415.



4.6b

2,2,2-trichloroethyl 2-(4-chlorophenyl)-2-diazoacetate (**4.6b**)

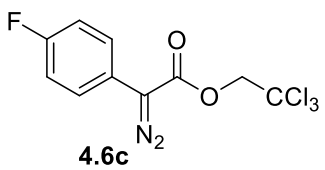
Prepared according to **general procedure A** using 1-chloro-4-iodobenzene (**4.55b**) (954 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with a gradient from hexanes to hexanes: diethyl ether (9: 1) to give the product as an orange amorphous solid (1.06 g, 81%). m.p. 46-49 °C; R_f = 0.68 (hexanes: diethyl ether = 9: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.44 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 4.91 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg of $Cr(acac)_3$) δ 163.1, 132.1, 129.3, 125.2, 123.3, 95.0, 74.0 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2954, 2091, 1707, 1494, 1374, 1341, 1276, 1237, 1139, 1097, 1044, 1011, 926, 825, 785, 730, 711 cm^{-1}.

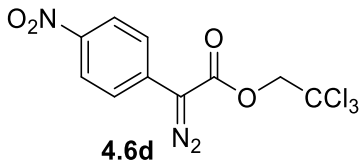
HRMS (NSI) *m/z*: $[M]^+$ calcd for $C_{10}H_6O_2N_2Cl_4$ 325.91779; found 325.91794.



4.6c

2,2,2-trichloroethyl 2-diazo-2-(4-fluorophenyl)acetate (**4.6c**)

Prepared according to **general procedure A** using 1-fluoro-4-iodobenzene (**4.5c**) (888 mg, 0.46 mL, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with a gradient from hexanes to hexanes: diethyl ether (9: 1) to give the product as an orange oil (731 mg, 59%). R_f = 0.63 (hexanes: diethyl ether = 9: 1). This compound is a known compound.[17]



4.6d

2,2,2-trichloroethyl 2-diazo-2-(4-nitrophenyl)acetate (**4.6d**)

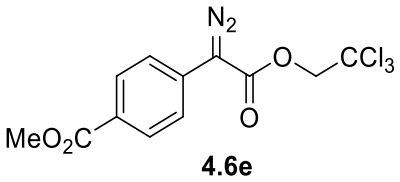
Prepared according to **general procedure A** using 1-iodo-4-nitrobenzene (**4.5d**) (996 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with a gradient from hexanes to hexanes: diethyl ether (4: 1) to give the product as a yellow solid (689 mg, 51%). m.p. 91-93 °C (decomposition); R_f = 0.41 (hexanes: diethyl ether = 4: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 9.1 Hz, 2H), 4.94 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 162.0, 145.5, 132.9, 124.5, 123.4, 94.7, 74.1 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2957, 2099, 1716, 1593, 1511, 1499, 1375, 1328, 1301, 1232, 1140, 1112, 1041, 929, 849, 785, 750, 715, 686 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_7O_4N_3Cl_3$ 337.94967; found 337.94974.



4.6e

Methyl 4-(1-diazo-2-oxo-2-(2,2,2-trichloroethoxy)ethyl)benzoate (4.6e):

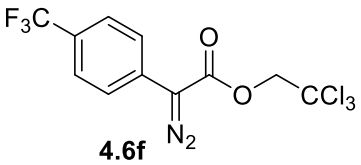
Prepared according to **general procedure A** using methyl 4-iodobenzoate (**4.5e**) (1.05 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (8: 1) to give the product as a yellow solid (1.27 g, 90%). m.p. 94-95 °C; R_f = 0.20 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 4.99 (s, 2H), 3.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 162.5, 130.2, 130.0, 127.5, 123.0, 94.8, 73.8, 52.1 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2956, 2094, 1705, 1609, 1318, 1236, 1114, 1050, 950 cm^{-1}.

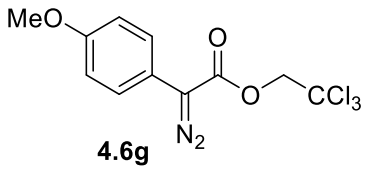
HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}O_4N_2Cl_3$ 350.9701; found 350.9703.



4.6f

2,2,2-trichloroethyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (**4.6f**)

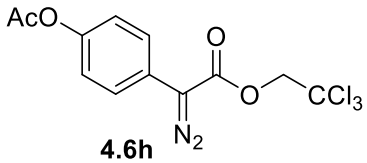
Prepared according to **general procedure A** using 1-iodo-4-(trifluoromethyl)benzene (**4.5f**) (1.09 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (25: 1) to give the product as an orange solid (1.33 g, 92%); R_f = 0.47 (hexanes: diethyl ether = 10: 1)). This compound is a known compound.[17]



4.6g

2,2,2-trichloroethyl 2-diazo-2-(4-methoxyphenyl)acetate (**4.6g**)

Prepared according to **general procedure A** using 1-iodo-4-methoxybenzene (**4.5g**) (936 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (24: 1) to give the product as an orange solid (0.99 g, 77%); R_f = 0.48 (hexanes: diethyl ether = 10: 1). This compound is a known compound.[17]



4.6h

2,2,2-trichloroethyl 2-(4-acetoxyphenyl)-2-diazoacetate (**4.6h**)

Prepared according to **general procedure A** using 4-iodophenyl acetate (**4.5h**) (1.05 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with

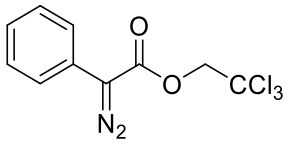
hexanes: diethyl ether (10: 1) to give the product as a yellow solid (1.07 g, 76%); m.p. 82-84 °C (decomposition); R_f = 0.25 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (600 MHz; $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.88 (s, 2H), 2.26 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 163.1, 148.9, 125.1, 122.3, 122.1, 95.0, 73.8, 21.1 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2966, 2089, 1752, 1702, 1506, 1421, 1373, 1340, 1286, 1277, 1237, 1193, 1169, 1138, 1075, 1050, 1033, 1011, 912, 849, 818, 802, 780, 732, 702, 678 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}Cl_3N_2O_4$ 350.9701; found 350.9703.



4.6i

2,2,2-trichloroethyl 2-diazo-2-phenylacetate (**4.6i**)

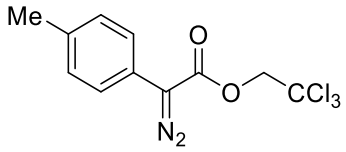
Prepared according to **general procedure A** using iodobenzene (**4.5i**) (816 mg, 0.45 mL, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with a gradient from hexanes to hexanes: diethyl ether (9: 1) to give the product as an orange solid (1.07 g, 91%). m.p. 57-59 °C; R_f = 0.63 (hexanes: diethyl ether = 9: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.24(d, *J* = 7.2 Hz, 1H), 4.92 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg of $Cr(acac)_3$) δ 163.4, 129.2, 128.8, 128.4, 124.7, 124.1, 95.1, 73.9.

IR (neat): 2953, 2089, 1708, 1598, 1498, 1374, 1334, 1238, 1135, 1084, 1048, 925, 822, 783, 752, 714, 689, 668 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd for $C_{10}H_7O_2N_2Cl_3$ 291.95676; found 291.95680.



4.6j

2,2,2-trichloroethyl 2-diazo-2-(*p*-tolyl)acetate (**4.6j**)

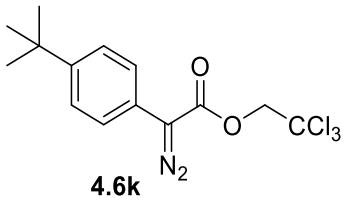
Prepared according to **general procedure A** using 1-iodo-4-methylbenzene (**4.5j**) (872 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (25: 1) to give the product as an orange solid (1.01 g, 82%); m.p. 59-60 °C; R_f = 0.50 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 2H), 4.93 (s, 2H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 136.3, 129.8, 124.2, 121.3, 95.1, 73.8, 21.1 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2953, 2090, 1711, 1515, 1375, 1339, 1285, 1241, 1138, 1047, 926, 810, 773, 729, 716 cm^{-1}.

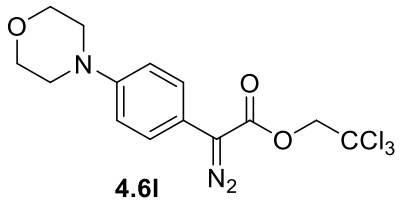
HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{10}Cl_3N_2O_2$ 306.9802; found 306.9801.



4.6k

2,2,2-trichloroethyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate (**4.6k**)

Prepared according to **general procedure A** using 1-(*tert*-butyl)-4-iodobenzene (**4.5k**) (1.04 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (25: 1) to give the product as an orange solid (1.23 g, 88%); R_f = 0.57 (hexanes: diethyl ether = 8: 1). This compound is a known compound.[17]



4.6l

2,2,2-trichloroethyl 2-diazo-2-(4-morpholinophenyl)acetate (**4.6l**)

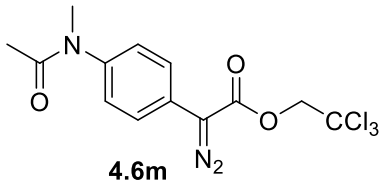
Prepared according to **general procedure A** using 4-(4-iodophenyl)morpholine (**4.5l**) (1.16 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (3: 1) to give the product as a red solid (1.06 g, 70%); m.p. 76-78 °C (decomposition); R_f = 0.23 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 4.92 (s, 2H), 3.88 (t, *J* = 5.0 Hz, 4H), 3.19 (t, *J* = 5.0 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 149.9, 125.8, 116.1, 114.6, 95.2, 73.8, 66.8, 49.0 (the resonances resulting from the carbonyl carbon in the 2,2,2-trichloroethyl ester and the diazo carbon were not detected).

IR (neat): 2960, 2856, 2088, 1709, 1610, 1518, 1450, 1376, 1339, 1291, 1235, 1142, 1123, 1052, 927, 822, 785, 731, 715, 659 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd for $C_{14}H_{14}Cl_3N_3O_3$ 377.0095; found 377.0093.



4.6m

2,2,2-trichloroethyl 2-diazo-2-(4-(*N*-methylacetamido)phenyl)acetate (**4.6m**)

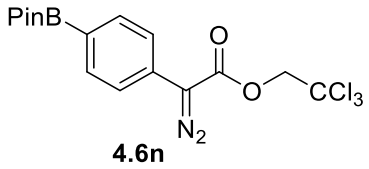
Prepared according to **general procedure A** using *N*-(4-iodophenyl)-*N*-methylacetamide (**4.5m**) (1.10 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (2: 1 to 1 :1) to give the product as a pale yellow solid (1.31 g, 90%); m.p. 96-98 °C (decomposition); R_f = 0.27 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.94 (s, 2H), 3.27 (s, 3H), 1.90 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 170.5, 163.0, 142.5, 127.8, 125.1, 124.4, 95.0, 73.9, 37.1, 22.4 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2954, 2094, 1713, 1656, 1604, 1510, 1436, 1374, 1341, 1278, 1237, 1138, 1088, 1043, 927, 843, 786, 713cm^{-1}.

HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{13}H_{13}Cl_3NO_3$ 335.9956; found 335.9958.



4.6n

2,2,2-trichloroethyl 2-diazo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (**4.6n**)

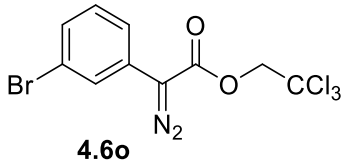
Prepared according to **general procedure A** using 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**4.5n**) (1.32 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (20: 1 to 10 :1) to give the product as a pale yellow solid (1.31 g, 78%); m.p.108-110 °C (decomposition); R_f = 0.24 (hexanes: ethyl acetate = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.91 (s, 2H), 1.36 (s, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 135.5, 127.7, 122.8, 95.0, 83.9, 73.9, 24.9 (the resonances resulting from and quaternary carbon attached to boron and the diazo carbon were not detected).

IR (neat): 2979, 2092, 1716, 1607, 1398, 1358, 1339, 1270, 1235, 1140, 1094, 1044, 1018, 961, 926, 824, 782, 715, 653 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}BCl_3N_2O_4$ 419.0498; found 419.0502.



4.6o

2,2,2-trichloroethyl 2-(3-bromophenyl)-2-diazoacetate (**4.6o**)

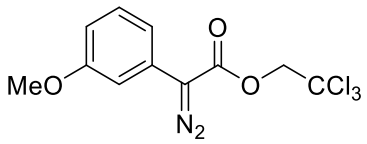
Prepared according to **general procedure A** using 1-bromo-3-iodobenzene (**4.5o**) (1.13 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to give the product as a yellow solid (1.36 g, 91%); R_f = 0.60 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (t, *J* = 1.9 Hz, 1H), 7.43-7.38 (m, 1H), 7.36-7.33 (m, 1H), 7.30-7.26 (m, 1H) and 4.92 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.75, 130.44, 129.20, 127.07, 126.64, 123.28, 122.16, 94.94, 73.92 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2094, 1710, 1479, 1237, 1139 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{10}H_7BrO_2Cl_3N_2^+$ 375.0316, observed 375.0320.



4.6p

2,2,2-trichloroethyl 2-diazo-2-(3-methoxyphenyl)acetate (**4.6p**)

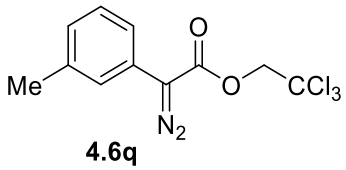
Prepared according to **general procedure A** using 1-iodo-3-methoxybenzene (**4.5p**) (936 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1) to give the product as an orange solid (1.20 g, 93%); m.p. 65-67 °C; R_f = 0.38 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.34 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.93 (s, 2H), 3.85 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 163.2, 160.2, 130.1, 126.1, 116.0, 112.0, 109.8, 95.1, 73.9, 55.4 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2954, 2092, 1713, 1600, 1578, 1494, 1376, 1249, 1178, 1136, 1042, 851, 771, 730, 716, 687 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{10}Cl_3N_2O_3$ 322.9752; found 322.9750.



4.6q

2,2,2-trichloroethyl 2-diazo-2-(*m*-tolyl)acetate (**4.6q**)

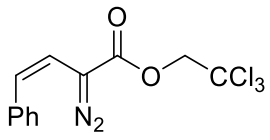
Prepared according to **general procedure A** using 1-iodo-3-methylbenzene (**4.5q**) (872 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to give the product as a yellow solid (1.10 g, 89%); m.p. 45-47 °C; R_f = 0.64 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.48–7.23 (m, 3H), 7.06 (d, *J* = 3.5 Hz, 1H), 4.94 (s, 2H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 163.4, 138.9, 129.1, 127.2, 124.7, 124.4, 121.2, 95.1, 73.8, 21.6 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2953, 2091, 1713, 1604, 1492, 1374, 1287, 1243, 1135, 1050, 849, 776, 716, 690 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{10}Cl_3N_2O_2$ 306.9802; found 306.9802.



4.6r

2,2,2-trichloroethyl (*Z*)-2-diazo-4-phenylbut-3-enoate (**4.6r**)

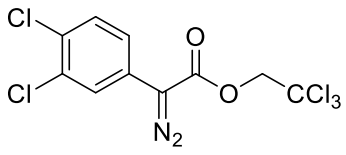
Prepared according to **general procedure A** using (*Z*)-(2-iodovinyl)benzene (**4.5r**) (920 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30 : 1) to give the product as an orange solid (550 mg, 43%); m.p. 49-51 °C; R_f = 0.42 (hexanes: diethyl ether = 15: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 2H), 6.64 (d, *J* = 11.5 Hz, 1H), 6.02 (d, *J* = 11.5 Hz, 1H), 4.90 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 128.5, 128.1, 127.4, 125.6, 111.2, 95.0, 74.1 (the resonances resulting from the carbonyl carbon in the 2,2,2-trichloroethyl ester and the diazo carbon were not detected).

IR (neat): 3027, 2093, 1705, 1619, 1447, 1408, 1371, 1264, 1217, 1110, 1056, 861, 785, 738, 714, 684 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{10}Cl_3N_2O_2$ 318.9802; found 318.9805.



4.6s

2,2,2-trichloroethyl 2-diazo-2-(3,4-dichlorophenyl)acetate (**4.6s**)

Prepared according to **general procedure A** using 1,2-dichloro-4-iodobenzene (**4.5s**) (1.09 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting

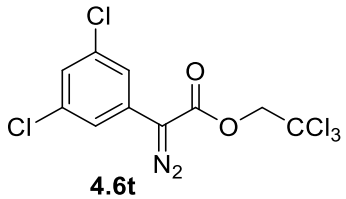
with hexanes: diethyl ether (24: 1) to give the product as a yellow solid (1.14 g, 78%); m.p. 58-59 °C; R_f = 0.44 (hexanes: diethyl ether = 12: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.64 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 4.89 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 162.6, 133.4, 130.8, 130.0, 125.4, 125.1, 122.7, 94.8, 73.9 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2956, 2099, 1712, 1479, 1373, 1341, 1276, 1239, 1147, 1048, 800, 716 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{10}H_6Cl_5O_2$ 332.8805; found 332.8805.



4.6t

2,2,2-trichloroethyl 2-diazo-2-(3,5-dichlorophenyl)acetate (**4.6t**)

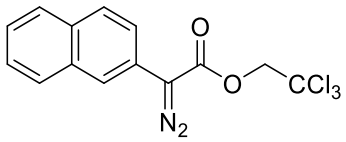
Prepared according to **general procedure A** using 1,3-dichloro-5-iodobenzene (**4.5t**) (1.09 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (25: 1) to give the product as a yellow solid (1.21 g, 83%); m.p. 90-91 °C; R_f = 0.48 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.42 (s, 2H), 7.20 (s, 1H), 4.93 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 162.3, 135.8, 128.4, 126.1, 121.7, 94.8, 74.0 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2955, 2099, 1717, 1588, 1560, 1447, 1372, 1335, 1261, 1233, 1153, 1094, 1051, 846, 800, 733, 713, 669 cm^{-1}.

HRMS (APCI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{10}H_6Cl_5O_2$ 332.8805; found 332.8805.



4.6u

2,2,2-trichloroethyl 2-diazo-2-(naphthalen-2-yl)acetate (**4.6u**)

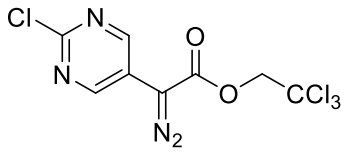
Prepared according to **general procedure A** using 2-iodonaphthalene (**4.5u**) (1.04 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether: dichloromethane (25: 1: 1) to give the product as a yellow solid (1.04 g, 76%). m.p. 107-108 °C (decomposition); R_f = 0.45 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.02 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.54-7.45 (m, 3H), 4.95 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 163.5, 133.5, 131.6, 128.9, 127.7, 127.7, 126.8, 126.1, 122.8, 121.7, 121.7, 95.1, 73.9 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2958, 2098, 1698, 1327, 1246, 1232, 1145, 1124, 1049, 852, 803, 727, 710 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{10}O_2N_2Cl_3$ 342.98024; found 342.98029.



4.6v

2,2,2-trichloroethyl 2-(2-chloropyrimidin-5-yl)-2-diazoacetate (**4.6v**)

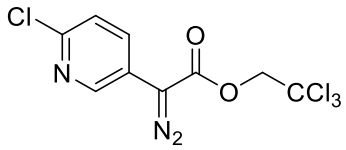
Prepared according to **general procedure A** using 2-chloro-5-iodopyrimidine (**4.5v**) (962 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with a gradient from hexanes to hexanes: diethyl ether (1: 1) to give the product as a yellow-brown solid (299 mg, 39%). m.p. 86-88 °C (decomposition); R_f = 0.32 (hexanes: diethyl ether = 3: 2).

^{1}H NMR (500 MHz; $CDCl_3$) δ 8.79 (s, 2H), 4.94 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg of $Cr(acac)_3$) δ 158.7, 153.8 119.9, 94.5, 74.3 (the resonances resulting from the carbonyl carbon in the 2,2,2-chloroethyl ester and the diazo carbon were not detected).

IR (neat): 2958, 2101, 1706, 1528, 1417, 1272, 1240, 1140, 1054, 926, 794, 757, 729, 714 cm^{-1}.

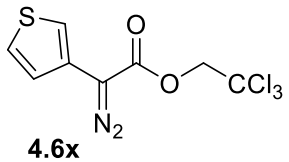
HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_8H_5O_2N_4Cl_4$ 328.91611; found 328.91637.



4.6w

2,2,2-trichloroethyl 2-(6-chloropyridin-3-yl)-2-diazoacetate (**4.6w**)

Prepared according to **general procedure A** using 2-chloro-5-iodopyridine (**4.5w**) (958 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with a gradient from hexanes to hexanes: diethyl ether (4: 1) to give the product as an orange solid (767 mg, 58%). m.p. 69-73 °C (decomposition); R_f = 0.34 (hexanes: diethyl ether = 4: 1). This compound is a known compound.[17]



4.6x

2,2,2-trichloroethyl 2-diazo-2-(thiophen-3-yl)acetate (**4.6x**)

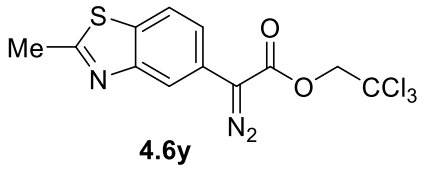
Prepared according to **general procedure A** using 3-iodothiophene (**4.5x**) (840 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to give the product as an orange solid (252 mg, 21%); m.p. 49-52 °C (decomposition); R_f = 0.60 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.45–7.35 (m, 2H), 7.06 (dd, *J* = 5.2, 1.6 Hz, 1H), 4.90 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$ with 3 mg $Cr(acac)_3$) δ 126.8, 123.6, 122.9, 118.4, 95.0, 74.0 (the resonances resulting from the carbonyl carbon in the 2,2,2-chloroethyl ester and the diazo carbon were not detected).

IR (neat): 3127, 2953, 2087, 1702, 1534, 1428, 1393, 1310, 1266, 1211, 1128, 1091, 1046, 857, 830, 798, 765, 711 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_8H_6Cl_3N_2O_2S$ 298.9210; found 298.9210.



4.6y

2,2,2-trichloroethyl 2-diazo-2-(2-methylbenzo[*d*]thiazol-5-yl)acetate (**4.6y**)

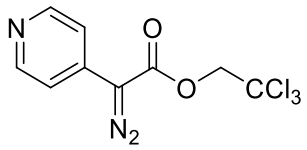
Prepared according to **general procedure A** using 5-iodo-2-methylbenzo[*d*]thiazole (**4.5y**) (1.10 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (12: 1 to 6: 1) to give the product as an orange solid (1.18 g, 81%); m.p. 107-108 °C (decomposition); R_f = 0.25 (hexanes: ethyl acetate = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.96 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.87 (s, 2H), 2.76 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 163.1, 153.9, 133.5, 122.7, 122.0, 120.9, 117.6, 95.0, 73.8, 20.2 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2953, 2089, 1710, 1523, 1463, 1374, 1342, 1279, 1251, 1168, 1129, 1084, 1066, 1042, 884, 814, 782, 730, 712 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_9Cl_3N_3O_2S$ 363.9476; found 363.9479.



4.6z

2,2,2-trichloroethyl 2-diazo-2-(pyridin-4-yl)acetate (**4.6z**)

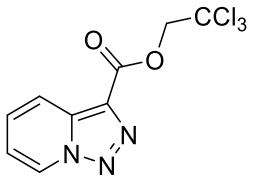
Prepared according to **general procedure A** using 4-iodopyridine (**4.5z**) (820 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with a gradient with hexanes: ethyl acetate (3: 2 to 2: 3) to give the product as a red amorphous solid (611 mg, 52%). m.p. 70-75 °C; R_f = 0.28 (hexanes: ethyl acetate = 3: 2).

^{1}H NMR (500 MHz; $CDCl_3$) δ 8.57 (d, *J* = 6.4 Hz, 2H), 7.43 (d, *J* = 6.5 Hz, 2H), 4.93.

^{13}C NMR (125 MHz, $CDCl_3$ with 3 mg of $Cr(acac)_3$) δ 161.8, 150.1, 134.7, 117.3, 94.8, 74.0 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2955, 2102, 1713, 1592, 1544, 1497, 1420, 1379, 1349, 1248, 1219, 1144, 1088, 1046, 991, 813, 786, 715, 670 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_9H_7O_2N_3Cl_3$ 293.95984; found 293.95981.



4.12

2,2,2-trichloroethyl [1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate (**4.12**)

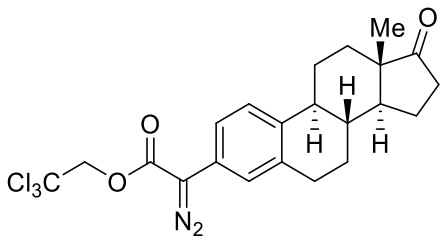
Prepared according to **general procedure A** using 2-iodopyridine (**4.10**) (820 mg, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (2: 1 to 1: 2) to give the product as a white solid (968 mg, 82%); m.p. 151-152 °C; R_f = 0.15 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 8.90 (d, *J* = 6.5 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 7.65 (dd, *J* = 8.5, 6.5 Hz, 1H), 7.24 (t, *J* = 6.5 Hz, 1H), 5.12 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 135.2, 130.3, 127.9, 126.3, 119.2, 116.9, 95.0, 74.1.

IR (neat): 3110, 2954, 1740, 1636, 1514, 1435, 1334, 1269, 1204, 1177, 1157, 1140, 1083, 1049, 779, 751, 713, 695, 678 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_9H_7Cl_3N_3O_2$ 293.9598; found 293.9596.



4.17

2,2,2-trichloroethyl 2-diazo-2-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)acetate (4.17)

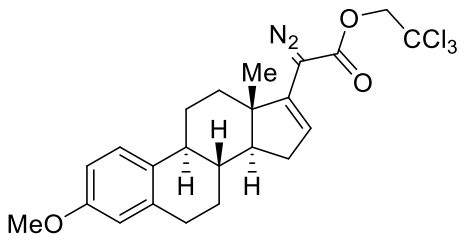
Prepared according to **general procedure A** using (8*R*,9*S*,13*S*,14*S*)-3-iodo-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[a]phenanthren-17-one (**4.15**) (1.52 g, 4.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (10: 1) to give the product as a yellow solid (1.33 g, 71%); m.p. 122-124 °C (decomposition); R_f = 0.25 (hexanes: ethyl acetate = 8: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 1H), 7.28-7.25 (m, 2H), 4.92 (s, 2H), 2.95 (dd, *J* = 9.0, 4.0 Hz, 2H), 2.53 (dd, *J* = 19.0, 9.0 Hz, 1H), 2.46-2.42 (m, 1H), 2.35-2.30 (m, 1H), 2.21–2.00 (m, 4H), 1.71-1.59 (m, 2H), 1.57-1.45 (m, 4H), 0.93 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 220.7, 163.6, 138.3, 137.5, 126.2, 124.8, 121.7, 121.7, 95.1, 73.8, 50.5, 48.0, 44.2, 38.1, 35.8, 31.6, 29.5, 26.4, 25.7, 21.6, 13.9 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2929, 2859, 2088, 1737, 1712, 1502, 1453, 1375, 1243, 1133, 1087, 1047, 1007, 808, 783, 730, 714 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{24}Cl_3N_2O_3$ 469.0852; found 469.0853.



4.18

2,2,2-trichloroethyl 2-diazo-2-((8*S*,9*S*,13*S*,14*S*)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)acetate (**4.18**)

Prepared according to **general procedure A** using (8*R*,9*S*,13*S*,14*S*)-17-iodo-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[*a*]phenanthrene (**4.16**) (1.57 g, 2.0 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: dichloromethane (10: 1 to 5: 1 to 2: 1) to give the product as a light yellow foam (482 mg, 25%); m.p. 66-68 °C (decomposition); R_f = 0.33 (hexanes: ethyl acetate = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 1H), 6.75 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 6.26 (dd, *J* = 3.0, 2.0 Hz, 1H), 4.91 (d, *J* = 12.0 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 3.81 (s, 3H), 2.99-2.88 (m, 2H), 2.43-2.31 (m, 3H), 2.09 (ddd, *J* = 15.5, 11.5, 2.0 Hz, 1H), 1.99-1.91 (m, 2H), 1.82-1.72 (m, 2H), 1.69–1.59 (m, 2H), 1.49 (qd, *J* = 12.0, 7.0 Hz, 1H), 0.99 (s, 3H).

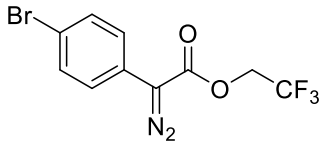
^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 157.6, 137.9, 133.4, 132.4, 127.4, 126.0, 113.9, 111.5, 95.1, 74.0, 56.0, 55.2, 48.3, 44.1, 37.1, 34.9, 31.6, 29.7, 27.6, 26.5, 16.5 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2929, 2856, 2086, 1719, 1609, 1500, 1453, 1376, 1252, 1237, 1142, 1114, 1048, 1035, 815, 716 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H-N_2]^+$ calcd for $C_{23}H_{26}Cl_3O_3$ 455.0947; found 455.0946.

General Procedure B: for the palladium-catalyzed cross-coupling reaction with different diazoesters:

$Pd(PPh_3)_4$ (116 mg, 0.1 mmol, 5 mol %), PPh_3 (53 mg, 0.2 mmol, 10 mol %), 1-bromo-4-iodobenzene (**4.5a**) (2.0 mmol, 1.0 equiv), Ag_2CO_3 (275 mg, 1.0 mmol, 0.5 equiv) were suspended in toluene (8 mL) under argon, followed by addition of NEt_3 (0.47 mL, 2.6 mmol, 1.3 equiv) and diazoacetates **4.13a-c** (2.6 mmol, 1.3 equiv). The resulting reaction was stirred at room temperature for 4 h and then filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in *vacuo* and the residue was purified by column chromatography to give the products.

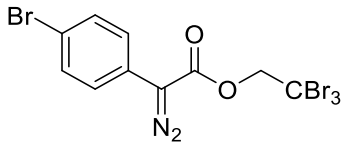


4.14a

2,2,2-trifluoroethyl 2-(4-bromophenyl)-2-diazoacetate (**4.14a**)

Prepared according to **general procedure B** using 2,2,2-trifluoroethyl 2-diazoacetate (**4.13a**) (437 mg, 2.6 mmol, 1.3 equiv); purified by column chromatography on silica gel

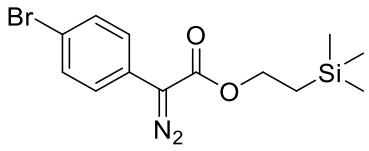
eluting with hexanes: diethyl ether (30: 1) to give the product as a yellow solid (265 mg, 41%); R_f = 0.58 (hexanes: diethyl ether = 10: 1). This compound is a known compound.[17]



4.14b

2,2,2-tribromoethyl 2-(4-bromophenyl)-2-diazoacetate (**4.14b**)

Prepared according to **general procedure B** using 2,2,2-tribromoethyl 2-diazoacetate (**4.13b**) (910 mg, 2.6 mmol, 1.3 equiv), 10 mol % of $Pd(PPh_3)_4$ (231 mg, 0.2 mmol) and 20 mol % of PPh_3 (105 mg, 0.4 mmol) were used; purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to give the product as a yellow solid (535 mg, 53%); R_f = 0.56 (hexanes: diethyl ether = 10: 1). This compound is a known compound.[17]



4.14c

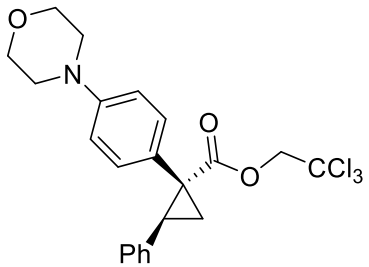
2-(trimethylsilyl)ethyl 2-(4-bromophenyl)-2-diazoacetate (**4.14c**)

Prepared according to **general procedure B** using 2-(trimethylsilyl)ethyl 2-diazoacetate (**4.13c**) (484 mg, 2.6 mmol, 1.3 equiv); purified by column chromatography

on silica gel eluting with hexanes: diethyl ether (30: 1) to give the product as an orange oil (593 mg, 87%); R_f = 0.52 (hexanes: diethyl ether = 10: 1). This compound is a known compound.[17]

General Procedure C: for the cyclopropanation reaction:

In an oven-dried, 10 mL round-bottomed flask, equipped with a magnetic stir bar, as solution of Rh_2(*S*-*p*-PhTPCP)$_4$ (3.5 mg, 0.5 mol %) and styrene (**4.19**) (pre-purified by passing through a pipette column) (0.1 mL, 0.8 mmol, 2.0 equiv) in dry dichloromethane (1.5 mL) at room temperature. Then a solution of the diazo compound (0.4 mmol, 1.0 equiv) was dissolved in 2.0 mL dichloromethane under argon and added dropwise to the reaction mixture over 2 h by a syringe pump. The flask used to dissolve the diazo and the needle/syringe were rinsed with 0.5 mL of dichloromethane, which was added to the reaction over 30 min. The solution was stirred for another 2 h at room temperature. The solvent was removed *in vacuo* and the crude reside was purified by column chromatography.



4.20a

2,2,2-trichloroethyl (1*R*,2*S*)-1-(4-morpholinophenyl)-2-phenylcyclopropane-1-carboxylate (**4.20a**)

Prepared according to **general procedure C** using 2,2,2-trichloroethyl 2-diazo-2-(4-morpholinophenyl)acetate (**4.6l**) (151 mg, 0.4 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting first with dichloromethane, then with hexanes: ethyl acetate (5: 1) to give the product as a colorless solid (130 mg, 71%); m.p. 101-103 °C; R_f = 0.27 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.09-7.05 (m, 3H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.81-6.77 (m, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.81 (t, *J* = 4.4 Hz, 4H), 3.16 (dd, *J* = 9.6, 7.6 Hz, 1H), 3.06 (t, *J* = 4.4 Hz, 4H), 2.25 (dd, *J* = 9.6, 4.8 Hz, 1H), 1.93 (dd, *J* = 7.6, 4.8 Hz, 1H).

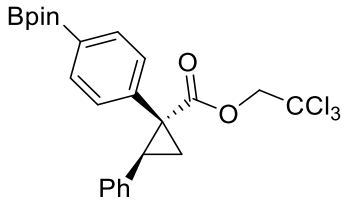
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 135.9, 135.9, 135.9, 132.7, 128.1, 127.8, 126.5, 114.9, 95.2, 74.2, 66.7, 49.2, 36.5, 33.9, 20.4.

IR (neat): 2958, 2854, 1732, 1613, 1519, 1450, 1379, 1234, 1210, 1151, 1122, 1097, 1052, 931, 825, 775, 713, 696 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{23}Cl_3NO_3$ 454.0738; found 454.0739.

$[\alpha]^{20}_D$: +21° (c 1.4, $CHCl_3$).

HPLC: SS-WHELK column, 1 mL/min, 4 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 40.37 min, Minor: 25.17 min, 98% ee.



4.20b

2,2,2-trichloroethyl (1*R*,2*S*)-2-phenyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxylate (**4.20b**)

Prepared according to **general procedure C** using 2,2,2-trichloroethyl 2-diazo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (**4.6n**) (168 mg, 0.4 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (15: 1 to 15: 2) to give the product as a colorless solid (147 mg, 74%); m.p. 97-98 °C; R_f = 0.18 (hexanes: ethyl acetate = 10: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.09–7.04 (m, 5H), 6.80-6.78 (m, 2H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.21 (dd, *J* = 9.6, 7.6 Hz, 1H), 2.27 (dd, *J* = 9.6, 5.2 Hz, 1H), 2.00 (dd, *J* = 7.6, 5.2 Hz, 1H), 1.30 (s, 12H).

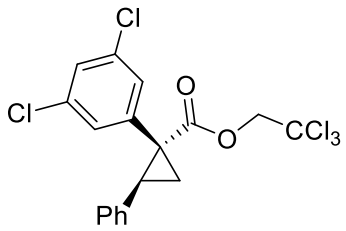
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 136.7, 135.5, 134.1, 131.3, 128.1, 127.9, 126.6, 110.0, 95.0, 83.7, 74.3, 37.3, 34.0, 24.9, 24.9, 20.2.

IR (neat): 2978, 1735, 1613, 1398, 1360, 1321, 1266, 1240, 1210, 1146, 1097, 1052, 1021, 963, 859, 807, 773, 714, 696, 658 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{27}BCl_3O_4$ 495.1063; found 495.1065.

$[\alpha]^{20}_D$: +3° (c 1.7, $CHCl_3$).

HPLC: SS-WHELK column, 1 mL/min, 1% ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 10.86 min, Minor: 9.15 min, 95% ee.



4.20c

2,2,2-trichloroethyl (1*R*,2*S*)-1-(3,5-dichlorophenyl)-2-phenylcyclopropane-1-carboxylate (**4.20c**)

Prepared according to **general procedure C** using 2,2,2-trichloroethyl 2-diazo-2-(3,5-dichlorophenyl)acetate (**4.6t**) (145 mg, 0.4 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (20: 1) to give the product as a colorless oil (150 mg, 85%); R_f = 0.45 (hexanes: diethyl ether = 8: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.14-7.11 (m, 4H), 6.94 (d, *J* = 2.0 Hz, 2H), 6.84-6.82 (m, 2H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.23 (dd, *J* = 9.6, 7.6 Hz, 1H), 2.26 (dd, *J* = 9.6, 5.6 Hz, 1H), 1.99 (dd, *J* = 7.6, 5.6 Hz, 1H).

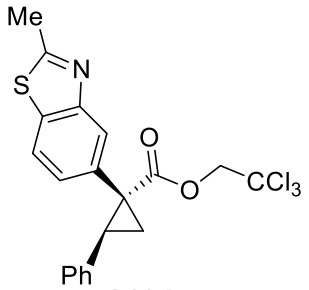
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 137.2, 134.5, 134.0, 130.5, 128.2, 128.0, 127.6, 127.2, 94.8, 74.5, 36.3, 34.2, 19.9.

IR (neat): 3032, 2954, 1737, 1589, 1565, 1432, 1416, 1378, 1250, 1233, 1209, 1159, 1128, 1112, 1157, 861, 817, 798, 720, 701 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{14}Cl_5O_2$ 436.9431; found 436.9436.

$[\alpha]^{20}_D$: -1° (c 1.5, $CHCl_3$).

HPLC: AS-H column, 0.25 mL/min, 0.25 % ^{i}PrOH in hexanes, λ = 210, 230 nm. t_R: Major: 26.19 min, Minor: 23.97 min, 85% ee.



4.20d

2,2,2-trichloroethyl (1*R*,2*S*)-1-(2-methylbenzo[*d*]thiazol-5-yl)-2-phenylcyclopropane-1-carboxylate (**4.20d**)

Prepared according to **general procedure C** using 2,2,2-trichloroethyl 2,2,2-trichloroethyl 2-diazo-2-(2-methylbenzo[*d*]thiazol-5-yl)acetate (**4.6y**) (146 mg, 0.4 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (6 : 1) to give the product as a colorless oil (115 mg, 65%); R_f = 0.23 (hexanes: ethyl acetate = 6: 1).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.75 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.03–7.01 (m, 3H), 6.97 (dd, *J* = 8.4, 1.76 Hz, 1H), 6.82-6.79 (m, 2H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 3.27 (dd, *J* = 9.6, 7.2 Hz, 1H), 2.76 (s, 3H), 2.33 (dd, *J* = 9.6, 5.2 Hz, 1H), 2.09 (dd, *J* = 7.2, 5.2 Hz, 1H).

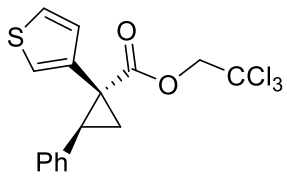
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 167.2, 153.1, 135.3, 134.6, 132.0, 129.1, 128.1, 127.9, 126.7, 125.3, 120.4, 95.0, 74.3, 37.1, 34.1, 20.4, 20.1.

IR (neat): 2923, 2853, 1731, 1604, 1525, 1456, 1432, 1417, 1376, 1242, 1204, 1145, 1092, 1064, 1051, 974, 816, 770, 757, 712, 695 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{17}Cl_3NO_2S$ 440.0040; found 440.0041.

$[\alpha]^{20}_D$: +50° (c 1.5, $CHCl_3$).

HPLC: OJ-H column, 1 mL/min, 3 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 13.23 min, Minor: 18.90 min, 98% ee.



4.20e

2,2,2-trichloroethyl (1R,2S)-2-phenyl-1-(thiophen-3-yl)cyclopropane-1-carboxylate (**4.20e**)

Prepared according to **general procedure C** using 2,2,2-trichloroethyl 2-diazo-2-(thiophen-3-yl)acetate (**4.6x**) (120 mg, 0.4 mmol, 1.0 equiv); purified by column chromatography on silica gel eluting with hexanes: diethyl ether (25: 1) to give the product as a colorless solid (106 mg, 70%); m.p. 74-76 °C; R_f = 0.47 (hexanes: diethyl ether = 10: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.15–7.13 (m, 3H), 7.05 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.00 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.93–6.91 (m, 2H), 6.78 (dd, *J* = 5.0, 1.5 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 3.20 (dd, *J* = 9.5, 7.5 Hz, 1H), 2.30 (dd, *J* = 9.5, 5.0 Hz, 1H), 2.05 (dd, *J* = 7.5, 5.0 Hz, 1H).

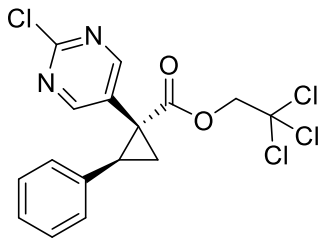
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 135.5, 134.6, 130.3, 128.1, 127.9, 126.8, 125.7, 124.5, 95.1, 74.4, 35.3, 32.3, 20.5.

IR (neat): 3031, 2953, 1733, 1499, 1456, 1433, 1378, 1248, 1213, 1197, 1148, 1096, 1056, 819, 799, 766, 709, 695 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{14}Cl_3O_2S$ 374.9775; found 374.9775.

$[\alpha]^{20}_D$: -4° (c 1.6, $CHCl_3$).

HPLC: SS_WHELK column, 0.7 mL/min, 0.5 % ^{i}PrOH in hexanes, λ = 230, 254 nm. t_R: Major: 17.38 min, Minor: 12.65 min, 99% ee.



4.20f

2,2,2-trichloroethyl (1R,2S)-1-(2-chloropyrimidin-5-yl)-2-phenylcyclopropane-1-carboxylate (**4.20f**)

Prepared according to **general procedure C** using 2,2,2-trichloroethyl 2-(2-chloropyrimidin-5-yl)-2-diazoacetate (**4.6v**) (165 mg, 0.5 mmol, 1.0 equiv), styrene (0.12 mL, 1 mmol, 2 equiv) and Rh_2(*S*-*p*-PhTPCP)$_4$ (8.8 mg, 1 mol %); purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (4: 1) to give the product as a colorless white solid (163 mg, 88%); m.p. 151 - 154 °C; R_f = 0.30 (hexanes: ethyl acetate = 4: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 8.29 (s, 2H), 7.20 – 7.15 (m, 3H), 6.87 (dd, *J* = 7.3, 2.0 Hz, 2H), 4.85 (d, *J* = 11.9 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 3.35 (dd, *J* = 9.4, 7.6 Hz, 1H), 2.41 (dd, *J* = 9.4, 5.6 Hz, 1H), 2.08 (dd, *J* = 7.6, 5.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 162.3, 160.2, 133.5, 128.9, 128.2, 128.1, 127.3, 94.7, 74.8, 34.0, 31.7, 19.0.

IR (neat): 2923, 1734, 1583, 1541, 1405, 1379, 1242, 1211, 1176, 1146, 1109, 1058, 971, 814, 793, 781, 767, 696 cm^{-1}.

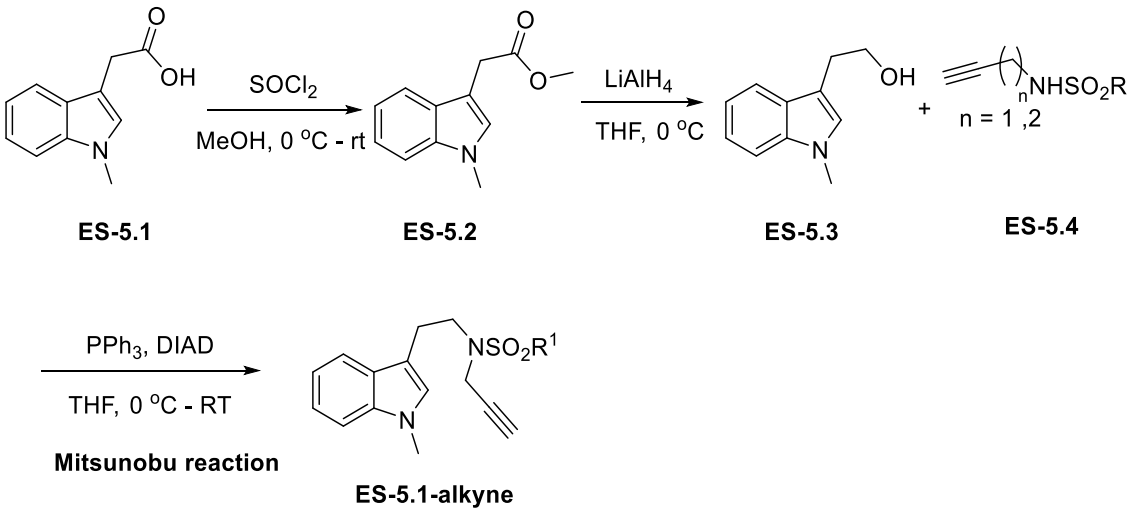
HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{13}O_2N_2Cl_4$ 404.97256; found 404.97278.

$[\alpha]^{20}_D$: +4.1° (c 1.0, $CHCl_3$).

HPLC: AS-H column, 1.0 mL/min, 3 % ^{i}PrOH in hexanes, λ = 254 nm. t_R: Major: 11.66 min, Minor: 9.05 min, 88% ee.

Experimental section for chapter 5: Divergent reactions of indolyl- and pyrrolyl-tethered *N*-sulfonyl-1,2,3-triazoles: efficient synthesis of polycyclic spiroindolines and tetrahydrocarbolines by rhodium(II)-catalyzed intramolecular annulations

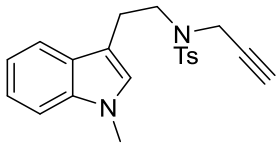
General procedure A:



A solution of 2-(1-methyl-1*H*-indol-3-yl)acetic acid (**ES-5.1**) (0.59 g, 3.07 mmol, 1.0 equiv) in dry MeOH (15 mL) at 0 °C was added thionyl chloride (0.56 mL, 7.67 mmol, 2.5 equiv) slowly. The reaction was warmed to room temperature while stirred over night. The crude residue was concentrated, diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure to give crude methyl ester **ES-5.2**. This crude material was used directly in the next step without purification.

A solution of the crude methyl ester **ES-5.2** in Et_2O (5 mL) was added dropwise to a suspension of $LiAlH_4$ (341 mg, 9.21 mmol, 3.0 equiv) in Et_2O (15 mL) at 0 ℃. After being stirred for 2 h at 0 ℃, the reaction was quenched with 1N HCl (10 mL) carefully at 0 ℃. The layers were separated and the aqueous layer was extracted with ether (50 mL). The combined organics were washed with brine (30 mL), and dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (4: 1 to 2: 1) to afford the alcohol intermediate **2-(1-methyl-1*H*-indol-3-yl)ethan-1-ol** (**ES-5.3**). From this compound, the Mitsunobu reaction with different *N*-sulfonyl propargylamide (**ES-5.4**) afforded different alkynes that were used in the preparation of *N*-sulfonyl-1,2,3-triazoles.

To a stirred solution of *N*-sulfonyl propargylamide (**ES-5.4**) (1.0 equiv) in dry tetrahydrofuran (0.25 M) were added triphenylphosphine (1.5 equiv) and DIAD (1.5 equiv) sequentially at 0 °C. Then a solution of alcohol **ES-5.3** (1.0 equiv) in dry tetrahydrofuran (1.0 M) was added dropwise. The reaction mixture was then stirred at room temperature over night until completion of conversion as judged by TLC analysis. The reaction mixture was concentrated and purified by silica gel chromatography (eluting hexanes: ethyl acetate = 5: 1) to afford the alkyne product **ES-5.1-alkyne**.



ES-5.1a-alkyne

4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (ES-5.1a-alkyne):

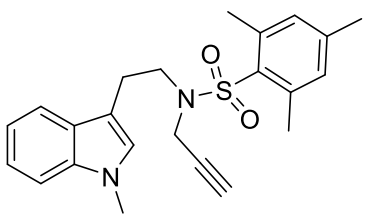
Prepared according to **general procedure A** using 2-(1-methyl-1*H*-indol-3-yl)ethan-1-ol (0.86 g, 4.9 mmol, 1.0 equiv) and 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (1.02 g, 4.9 mmol, 1.0 equiv) in the Mitsunobu reaction. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 10: 1 to 5: 1) to afford a light yellow solid (1.58 g, 88% yield); m.p. 88-90 °C, R_f = 0.50 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.59 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.28 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.29-7.20 (m, 3H), 7.12-7.08 (m, 1H), 6.93 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 3.73 (s, 3H), 3.50-3.46 (m, 2H), 3.08-3.04 (m, 2H), 2.39 (s, 3H), 2.06 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 136.9, 135.8, 129.4, 127.7, 127.6, 126.9, 121.6, 118.9, 118.7, 110.6, 109.3, 76.8, 73.8, 47.1, 36.7, 32.6, 24.2, 21.5.

IR (neat): 3273, 2920, 2119, 1732, 1597, 1473, 1326, 1249, 1185, 1155, 1092, 991, 907, 813, 737, 657 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{22}O_2N_2NaS$ 389.1294 found 389.1298.



ES-5.1e-alkyne

2,4,6-trimethyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**ES-5.1e-alkyne**):

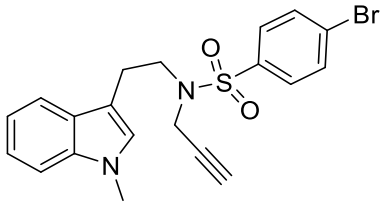
Prepared according to **general procedure A** using 2-(1-methyl-1*H*-indol-3-yl)ethan-1-ol (296 mg, 1.69 mmol, 1.0 equiv) and 2,4,6-trimethyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (401 mg, 1.69 mmol, 1.0 equiv) in the Mitsunobu reaction. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 6: 1) to afford a light yellow solid (586 mg, 88% yield); m.p. 93-95 °C, R_f = 0.42 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.85 (s, 2H), 6.75 (s, 1H), 4.18 (d, *J* = 2.4 Hz, 2H), 3.69 (s, 3H), 3.56-3.53 (m, 2H), 3.01-2.98 (m, 2H), 2.55 (s, 6H), 2.34 (t, *J* = 2.4 Hz, 1H), 2.28 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 142.6, 140.3, 136.9, 132.0, 131.9, 127.5, 126.7, 121.6, 118.8, 118.5, 110.7, 109.2, 77.9, 73.4, 46.3, 34.7, 32.6, 23.2, 22.7, 21.0.

IR (neat): 3278, 2936, 1603, 1472, 1379, 1315, 1150, 1082, 1057, 990, 905, 855, 737 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{27}O_2N_2S$ 395.1788 found 395.1784.



ES-5.1f-alkyne

4-bromo-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**ES-5.1f-alkyne**):

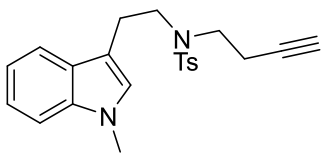
Prepared according to **general procedure A** using 2-(1-methyl-1*H*-indol-3-yl)ethan-1-ol (350 mg, 2.0 mmol, 1.0 equiv) and 4-bromo-*N*-(prop-2-yn-1-yl)benzenesulfonamide (548 mg, 2.0 mmol, 1.0 equiv) in the Mitsunobu reaction. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 10: 1 to 5: 1) to afford an off-white solid (795 mg, 92% yield); m.p. 92-93 °C, R_f = 0.29 (hexanes: ethyl acetate = 4: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.59-7.55 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.23 (td, *J* = 8.4, 1.2 Hz, 1H), 7.11 (td, *J* = 8.4, 1.2 Hz, 1H), 6.92 (s, 1H), 4.18 (d, *J* = 2.8 Hz, 2H), 3.73 (s, 3H), 3.51-3.48 (m, 2H), 3.08-3.04 (m, 2H), 2.09 (t, *J* = 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.9, 132.0, 129.1, 127.6, 127.6, 127.0, 121.7, 119.0, 118.7, 110.4, 109.3, 76.4, 74.1, 47.1, 36.6, 32.7, 24.1.

IR (neat): 3277, 3055, 2932, 1615, 1574, 1472, 1389, 1348, 1328, 1276, 1251, 1161, 1092, 1068, 1010, 910, 821, 757, 744 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{20}O_2N_2BrS$ 431.0423 found 431.0425.



ES-5.1p-alkyne

***N*-(but-3-yn-1-yl)-4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide (ES-5.1p-alkyne)**:

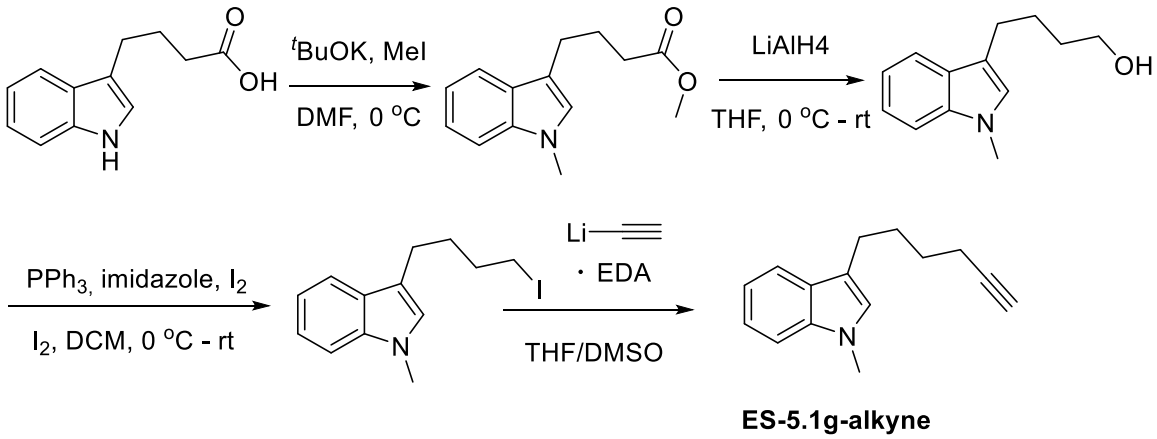
Prepared according to **general procedure A** using 2-(1-methyl-1*H*-indol-3-yl)ethan-1-ol (263 mg, 1.5 mmol, 1.0 equiv) and *N*-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (335 mg, 1.5 mmol, 1.0 equiv) in the Mitsunobu reaction. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 10: 1 to 5: 1) to afford a yellow oil (274 mg, 48% yield); R_f = 0.35 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.32-7.31 (m, 4H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 3.74 (s, 3H), 3.48-3.36 (m, 4H), 3.08-3.03 (m, 2H), 2.50 (td, *J* = 7.5, 2.4 Hz, 2H), 2.41 (s, 3H), 2.01 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (750 MHz, $CDCl_3$): δ 143.3, 136.9, 136.7, 129.7, 127.6, 127.1, 126.9, 121.7, 119.0, 118.7, 109.3, 81.1, 70.4, 49.9, 47.5, 32.6, 25.3, 21.5, 19.8.

IR (neat): 3285, 2924, 1598, 1425, 1327, 1155, 1093, 958, 815, 742, 662 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}O_2N_2S$ 381.1631 found 381.1628.



3-(hex-5-yn-1-yl)-1-methyl-1*H*-indole (**ES-5.1g-alkyne**):

The first step followed a literature precedence[18]: To a suspension of potassium *tert*-butoxide (6.05 g, 54.0 mmol, 3.0 equiv) was added portionwise to a solution was added dropwise a solution of 4-(1*H*-indol-3-yl)butanoic acid (3.65 g, 18.0 mmol, 1.0 equiv) in (36 mL) of dimethylformamide (DMF) over 5 minutes. After cooling to 0 °C, methyl iodide (8.95 mL, 144.0 mmol, 8.0 equiv) was added dropwise over 10 minutes. The reaction mixture was stirred for 16 hours while warmed to room temperature. The reaction was quenched by the careful addition of water (100 mL) at 0 °C and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine (60 mL), dried over $MgSO_4$, and concentrated to afford the crude ester which was used directly in the next step.

A solution of the crude ester in THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (2.0 g, 54.0 mmol, 3.0 equiv) in THF (50 mL) at 0 °C. After being stirred for 2 h at room temperature, the reaction was quenched by careful addition of H_2O at 0 °C until no gas evolution. The mixture was dried over $MgSO_4$, filtered, and concentrated under

[18] Judd, K. E.; Mahon, M. F.; Caggiano, L. *Synthesis* **2009**, 2809.

reduced pressure to give the crude alcohol as a yellow oil (3.65 g). The crude alcohol was used directly in the next step without further purification.

To a solution of the crude alcohol (2.03 g, *c.a.* 10.0 mmol, 1.0 equiv) in dichloromethane (DCM) (100 mL) at 0 ℃ were added triphenylphosphine (2.88 g, 11.0 mmol, 1.1 equiv) and imidazole (1.50 g, 22.0 mmol, 2.2 equiv). Iodine (2.79 g, 11.0 mmol, 1.1 equiv) was then added and the suspension was warmed to ambient temperature and stirred for 2 h. The reaction was quenched with saturated $NaHSO_3$ solution and the aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined organics washed with brine (60 mL), dried over magnesium sulfate, concentrated in vacuo, and purified by column chromatography (hexanes: EtOAc = 6: 1) to afford the iodide product (2.49 g, 80%) as a yellow oil.

This next step follows a literature precedence[19]: The iodide obtained above (1.64 g, 5.24 mmol, 1.0 equiv) was dissolved in THF (8 mL) and DMSO (16 mL) before it was cooled to 0 ℃. Lithium acetylide ethylenediamine complex (0.73 g, 7.85 mmol, 1.5 equiv) was then added. The reaction was warmed to ambient temperature and stirred for 4 hours before it was quenched by the addition of 2N HCl (30 mL). The mixture was extracted with EtOAc (3 x 60 mL) and the combined organics were washed with brine (80 mL), dried over magnesium sulfate, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 30: 1 to 15: 1) to afford **3-(hex-5-yn-1-yl)-1-methyl-1*H*-indole** (**ES-5.1g-alkyne**) as a yellow oil (940 mg, 85% yield). R_f = 0.55 (hexanes: ethyl acetate = 5: 1).

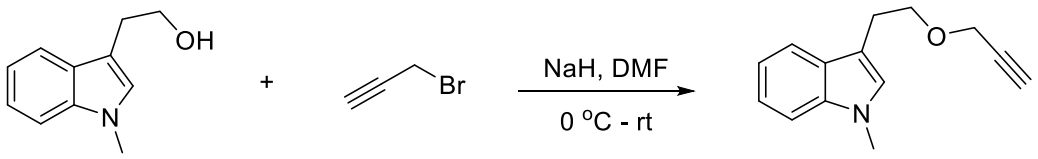
[19] Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.26-7.22 (m, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 3.75 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.25 (td, *J* = 7.2, 2.4 Hz, 2H), 1.97 (t, *J* = 2.4 Hz, 1H), 1.88-1.80 (m, 2H), 1.69-1.62 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 127.9, 126.1, 121.4, 119.0, 118.5, 114.9, 109.1, 84.7, 68.3, 32.6, 29.4, 28.3, 24.5, 18.3.

IR (neat): 3292, 3053, 2933, 2858, 2115, 1614, 1553, 1483, 1472, 1424, 1377, 1323, 1241, 1205, 1131, 1073, 1012, 738.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{18}N$ 212.1434 found 212.1432.



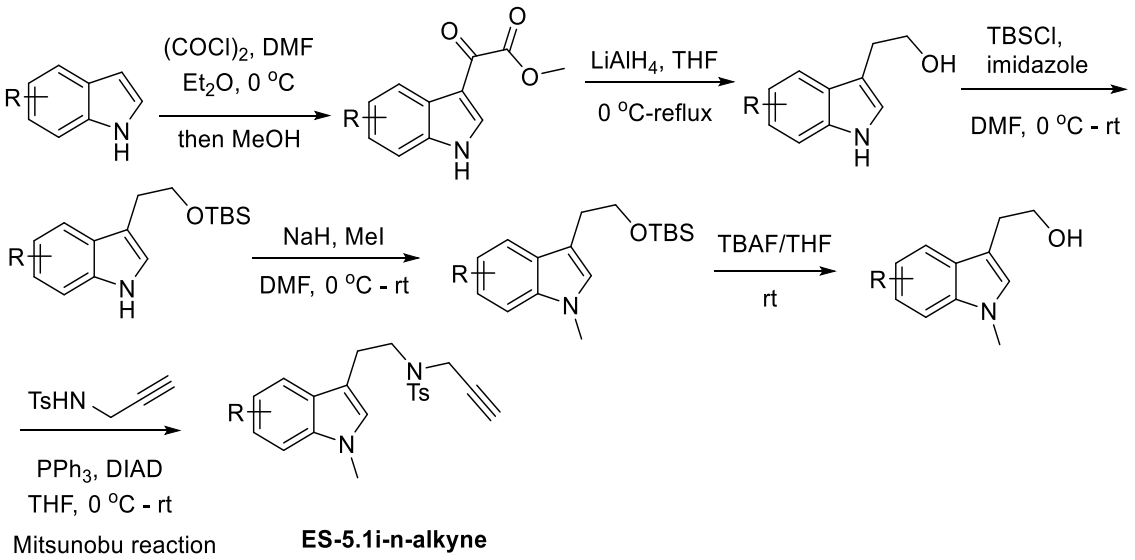
ES-5.1h-alkyne

1-methyl-3-(2-(prop-2-yn-1-yloxy)ethyl)-1*H*-indole (**ES-5.1h-alkyne**):

A solution of 2-(1-methyl-1*H*-indol-3-yl)ethan-1-ol (280 mg, 1.6 mmol, 1.0 equiv) in DMF (5 mL) was added to a suspension of NaH (60% in mineral oil, 130 mg, 3.2 mmol, 2.0 equiv) in DMF (5 mL) dropwise at 0 °C. The reaction mixture was stirred for 0 30 minutes at 0 °C, then propargyl bromide (80% wt. in toluene, 0.36 mL, 3.2 mmol, 2.0 equiv) was added. The reaction was stirred for 2 hours at room temperature before it was diluted with water (100 mL), and extracted with ethyl acetate (100 mL + 50 mL). The combined

organics were washed with brine (100 mL), dried over anhydrous magnesium sulfate, concentrated, and purified by silica gel chromatography (eluting hexanes: ethyl acetate = 10: 1) to give the alkyne **1-methyl-3-(2-(prop-2-yn-1-yloxy)ethyl)-1*H*-indole** (**ES-5.1h-alkyne**) as a yellow oil (120 mg, 36%); R_f = 0.39 (hexanes: ethyl acetate = 3 : 1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 4.19 (d, *J* = 2.4 Hz, 2H), 3.82 (t, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.43 (t, *J* = 2.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.9, 127.9, 126.8, 121.5, 118.9, 118.7, 111.1, 109.2, 79.9, 74.3, 70.4, 58.1, 32.6, 25.5; Data matches that from literature.[20]

General procedure B:[21]



[20] Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358.
[21] Han, L.; Liu, C.; Zhang, W.; Shi, X.-X.; You, S.-L. *Chem. Commun.* 2014, *50*, 1231.

Oxalyl chloride (3.0 qeuiv) was added dropwise to a solution of substituted indoles (1.0 equiv) in ether (0.2 M) at 0 °C. The resulting slurry was stirred at room temperature for 6 h before it was cooled to 0 °C again and quenched with MeOH (5.0 equiv). The resulting suspension was filtered and the solids were washed thoroughly with cold ether, dried, and used directly in the next step.

A solution of the above solid in THF was added dropwise to a suspension of $LiAlH_4$ (3.0 equiv) in THF at 0 °C. The solution was stirred for 4 h at reflux and quenched by H_2O, 10% aqueous NaOH, and H_2O slowly at 0 °C. The solution was then filtered and dried over $MgSO_4$. The crude mixture was purified by column chromatography to afford the corresponding alcohol intermediates.

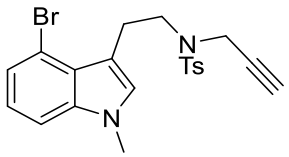
tert-Butyldimethylsilylchloride (1.2 equiv) was added to a solution of the alcohol intermediates obtained in the previous step (1.0 equiv) and imidazole (2.0 equiv) in DMF (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h before it was quenched with water and extracted with EtOAc (3 ×), then the combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the products. The products were used directly for the next step without further purification.

To a suspension of NaH (60% dispersion in mineral oil, 1.2 equiv,) in DMF was added a solution of the above intermediate in DMF (5 mL) was added NaH (400.0 mg, 10.0 mmol, 1.0 equiv, 60% dispersion in mineral oil) at 0 °C. After stirring at rt for 0.5 h, the reaction mixture was cooled to 0 °C, treated with MeI (0.31 mL, 4.8 mmol, 1.2 equiv), and then allowed to stir at room temperature for 8 h. The reaction was quenched by water and

extracted with EtOAc (3 ×). The combined organic layers were washed with brine (50 mL), separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product which was used directly in the next step without further purification.

The crude product from the previous step was treated with *tetra*-*n*-butylammonium fluoride (1.5 equiv) at room temperature for 24 h, and was quenched by saturated ammonium chloride. The organics were extracted with EtOAc (3 ×), washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (2: 1 to 1: 1) to afford the *N*-methyl alcohol intermediates that were used in the following Mitsunobu reaction.

The Mitsunobu reaction: To a stirred solution of *N*-tosyl propargyl amide (1.0 equiv) in dry tetrahydrofuran (0.25 M) were added triphenylphosphine (1.5 equiv) and DIAD (1.3 equiv) sequentially at 0 °C. Then a solution of alcohol (1.0 equiv) in dry tetrahydrofuran (1.0 M) was added dropwise. The reaction mixture was then stirred at room temperature over night until completion of conversion as judged by TLC analysis. The reaction mixture was concentrated and purified by silica gel chromatography (eluting hexanes: ethyl acetate) to afford the alkyne products.



ES-5.1i-alkyne

***N*-(2-(4-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**ES-5.1i-alkyne**):

Prepared according to **general procedure B**:

Oxalyl chloride (2.57 mL, 30.0 mmol, 3.0 qeuiv) was added dropwise to a solution of 4-bromo-1*H*-indole (1.96 g, 10.0 mmo, 1.0 equiv) in ether (50 mL) at 0 °C. The resulting slurry was stirred at room temperature for 6 h before it was cooled to 0 °C again and quenched with MeOH (2.0 mL). The resulting suspension was filtered and the solids were washed thoroughly with cold ether, dried, and used directly in the next step.

A solution of the above solids in THF (25 mL) was added dropwise to a suspension of $LiAlH_4$ (1.14 g, 30.0 mmol, 3.0 equiv) in THF (30 mL) at 0 °C. The solution was stirred for 4 h at reflux and quenched by H_2O (1.5 mL), 10% aqueous NaOH (2.0 mL), H_2O (4.5 mL) slowly at 0 °C. The solution was then filtered and dried over $MgSO_4$. The crude mixture was purified by column chromatography hexanes: ethyl acetate (3: 1 to 3: 2) to afford the alcohol intermediate (1.15 g, 48% for two steps).

tert-Butyldimethylsilylchloride (866 mg, 5.75 mmol, 1.2 equiv) was added to a solution of the alcohol obtained in the previous step (1.15, 4.8 mmol, 1.0 equiv) and imidazole (653 mg, 9.6 mmol, 2.0 equiv) in DMF (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h before it was quenched with water (30 mL) and extracted with EtOAc (3 × 30 mL), then the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the products. The products were used directly for the next step without further purification.

To a suspension of NaH (230 mg, 60% dispersion in mineral oil, 5.76 mmol, 1.2 equiv,) in DMF (8 mL) was added a solution of the above intermediate in DMF (8 mL) at 0 °C. After stirring at rt for 0.5 h, the reaction mixture was cooled to 0 °C, treated with MeI (0.38 mL, 5.76 mmol, 1.2 equiv), and then allowed to stir at room temperature for 8 h. The reaction was quenched by water (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was treated with *tetra-n*-butylammonium fluoride (1 M in THF, 7.2 mL, 7.2 mmol, 1.5 equiv) at room temperature for 24 h, and was quenched by saturated ammonium chloride (30 mL). The organics were extracted with EtOAc (2 × 50 mL), washed with brine (60 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (3: 1 to 1: 1) to afford 2-(4-bromo-1-methyl-1*H*-indol-3-yl)ethan-1-ol (1.06 g, 87% for three steps).

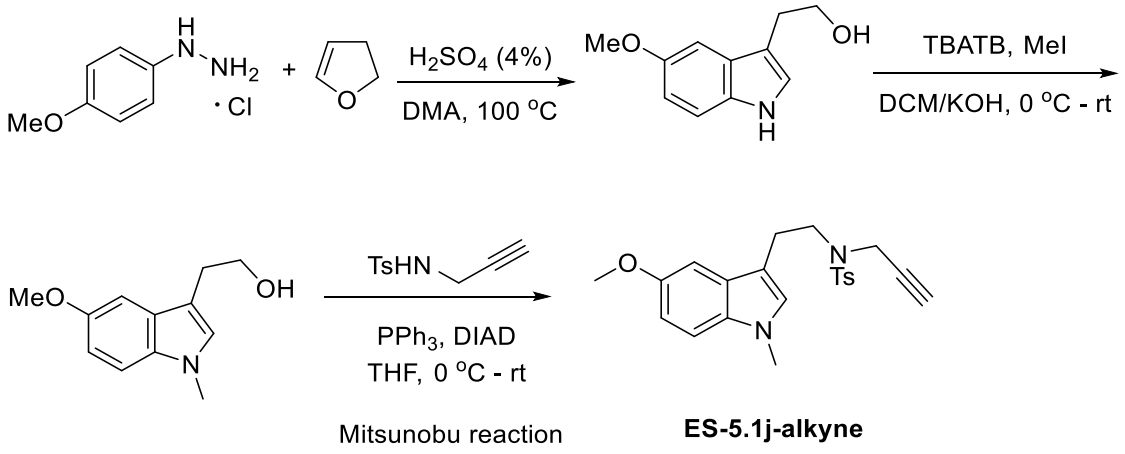
To a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (418 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) were added triphenylphosphine (786 mg, 3.0 mmol, 1.5 equiv) and DIAD (0.52 mL, 2.6 mmol, 1.3 equiv) sequentially at 0 °C. Then a solution of 2-(4-bromo-1-methyl-1*H*-indol-3-yl)ethan-1-ol from the previous step (508 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night, concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 4: 1) to afford a sand-like colorless solid (765 mg, 86% yield); m.p. 109-111 °C, R_f = 0.24 (hexanes: ethyl acetate = 4: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.23-7.19 (m, 4H), 7.02-6.98 (m, 2H), 4.16 (d, *J* = 2.4 Hz, 2H), 3.71 (s, 3H), 3.55-3.51 (m, 2H), 3.30-3.26 (m, 2H), 2.38 (s, 3H), 2.01 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 138.2, 136.0, 129.3, 129.3, 127.7, 125.6, 123.3, 122.3, 114.2, 111.5, 108.6, 77.2, 73.6, 48.4, 36.8, 32.9, 24.9, 21.5.

IR (neat): 3287, 2920, 1597, 1549, 1477, 1454, 1417, 1318, 1155, 1092, 992, 908, 771, 733, 658 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd. for $C_{21}H_{21}O_2N_2BrS$ 444.0502 found 444.0499.



***N*-(2-(5-methoxy-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**ES-5.1j-alkyne**):

(4-Methoxyphenyl)hydrazine hydrochloride (2.62 g, 15.0 mmol, 1.0 equiv.) was charged into a 3-neck round bottom flask, equipped with a reflux condenser. The hydrazine salt was dissolved into a 1:1 mixture of dimethylacetamide (0.692 M) and sulfuric acid (4%

aqueous solution). The solution was heated to 100 °C and then 2,3-dihydrofuran (1.05 g, 15.0 mmol, 1.0 equiv.) was added dropwise over 10 min. The reaction was heated at this temperature for 2 hours and cooled to ambient temperature. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organics were then washed once with water (60 mL), dried with magnesium sulfate and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography (hexanes: EtOAc = 2: 1 to 1: 1) to provide the 2-(5-methoxy-1*H*-indol-3-yl)ethan-1-ol as a yellow oil (2.46 g, 86%).[22]

50% KOH (20 mL) was added to a solution of the 2-(5-methoxy-1*H*-indol-3-yl)ethan-1-ol (573 mg, 3.0 mmol, 1.0 equiv) and tetrabutylammonium tribromide (TBATB) (289 mg, 0.6 mmol, 0.2 equiv) in dichloromethane (30 mL) at 0 °C. Then MeI (0.21 mL, 3.3 mmol, 1.1 equiv) was added. The reaction mixture was stirred at room temperature for 6 h before it was quenched with water (30 mL) and extracted with Et_2O (100 mL + 60 mL), then the combined organic layers were washed with brine, dried over $MgSO_4$, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (3: 1 to 3: 2) to afford 2-(5-methoxy-1-methyl-1*H*-indol-3-yl)ethan-1-ol (0.27 g, 44%).

To a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (276 mg, 1.32 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) were added triphenylphosphine (518 mg, 2.00 mmol, 1.5 equiv) and DIAD (0.34 mL, 1.72 mmol, 1.3 equiv) sequentially at 0 °C. Then a solution of 2-(5-methoxy-1-methyl-1*H*-indol-3-yl)ethan-1-ol from the previous step (270 mg, 1.32 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night, concentrated and

[22] Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 12910.

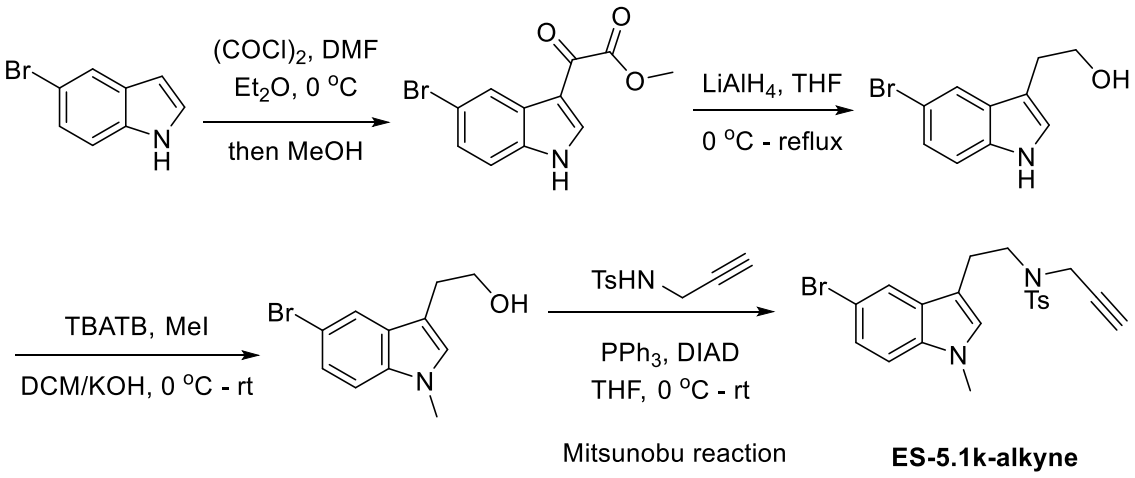
purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 10: 1 to 5: 1) to afford a light yellow solid (450 mg, 86% yield); m.p. 137-139 °C, R_f = 0.37 (hexanes: ethyl acetate = 5: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.89 (s, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.17 (d, *J* = 2.4 Hz, 2H), 3.85 (s, 3H), 3.70 (s, 3H), 3.49-3.45 (m, 2H), 3.04-3.01 (m, 2H), 2.39 (s, 3H), 2.05 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 143.4, 135.8, 132.3, 129.4, 127.9, 127.6, 127.5, 111.9, 110.1, 110.1, 100.5, 76.9, 73.7, 55.9, 47.0, 36.7, 32.8, 24.3, 21.5.

IR (neat): 3273, 2923, 1621, 1597, 1579, 1491, 1454, 1424, 1344, 1305, 1255, 1229, 1157, 1121, 1092, 1035 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}O_3N_2S$ 397.1580 found 397.1569.



***N*-(2-(5-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**ES-5.1k-alkyne**):

Prepared according to **general procedure B**:

Oxalyl chloride (4.05 mL, 45.0 mmol, 3.0 qeuiv) was added dropwise to a solution of 5-bromo-1*H*-indole (2.94 g, 15.0 mmo, 1.0 equiv) in ether (75 mL) at 0 °C. The resulting slurry was stirred at room temperature for 6 h before it was cooled to 0 °C again and quenched with MeOH (3.0 mL). The resulting suspension was filtered and the solids were washed thoroughly with cold ether, dried, and used directly in the next step.

A solution of the above solids in THF (40 mL) was added dropwise to a suspension of $LiAlH_4$ (2.28 g, 60.0 mmol, 3.0 equiv) in THF (60 mL) at 0 °C. The solution was stirred for 4 h at reflux and quenched by H_2O (2.25 mL), 10% aqueous NaOH (3.0 mL), H_2O (6.75 mL) slowly at 0 °C. The solution was then filtered and dried under vacuum to afford 2-(5-bromo-1*H*-indol-3-yl)ethan-1-ol (3.24 g, 90% for two steps).

50% KOH (20 mL) was added to a solution of the 2-(5-bromo-1*H*-indol-3-yl)ethan-1-ol (720 mg, 3.0 mmol, 1.0 equiv) and tetrabutylammonium tribromide (TBATB) (289 mg, 0.6 mmol, 0.2 equiv) in dichloromethane (30 mL) at 0 °C. Then MeI (0.21 mL, 3.3 mmol, 1.1 equiv) was added. The reaction mixture was stirred at room temperature for 6 h before it was quenched with water (30 mL) and extracted with Et_2O (100 mL + 60 mL), then the combined organic layers were washed with brine, dried over $MgSO_4$, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (3: 1 to 3: 2) to afford 2-(5-bromo-1-methyl-1H-indol-3-yl)ethan-1-ol (0.46 g, 60%).

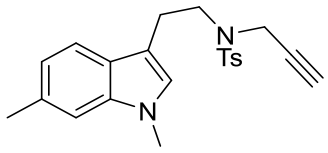
To a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (379 mg, 1.81 mmol, 1.0 equiv) in dry tetrahydrofuran (12 mL) were added triphenylphosphine (712 mg, 2.72 mmol, 1.5 equiv) and DIAD (0.47 mL, 2.35 mmol, 1.3 equiv) sequentially at 0 °C. Then a solution of 2-(5-bromo-1-methyl-1H-indol-3-yl)ethan-1-ol from the previous step (460 mg, 1.81 mmol, 1.0 equiv) in dry tetrahydrofuran (6 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night, concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 10: 1 to 5: 1) to afford a white solid (730 mg, 91% yield); m.p. 118-120 °C, R_f = 0.32 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.27-7.24 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.93 (s, 1H), 4.16 (d, *J* = 2.4 Hz, 2H), 3.69 (s, 3H), 3.45 (t, *J* = 7.6 Hz, 2H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 2.12 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 135.7, 135.6, 129.5, 129.3, 128.2, 127.6, 124.4, 121.3, 112.3, 110.8, 110.3, 76.8, 74.0, 46.9, 36.7, 32.8, 23.8, 21.6.

IR (neat): 3287, 2921, 1597, 1476, 1422, 1330, 1290, 1156, 1092, 1046, 992, 907, 813, 791, 733, 656 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{22}O_2N_2BrS$ 445.0580 found 445.0577.



ES-5.1l-alkyne

***N*-(2-(1,6-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**ES-5.1l-alkyne**):

Prepared according to **general procedure B**:

Oxalyl chloride (2.1 mL, 23.0 mmol, 3.0 qeuiv) was added dropwise to a solution of 6-methyl-1*H*-indole (1.0 g, 7.62 mmo, 1.0 equiv) in ether (40 mL) at 0 °C. The resulting slurry was stirred at room temperature for 6 h before it was cooled to 0 °C again and quenched with MeOH (1.6 mL). The resulting suspension was filtered and the solids were washed thoroughly with cold ether, dried, and used directly in the next step.

A solution of the above solid in THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.87 g, 23.0 mmol, 3.0 equiv) in THF (30 mL) at 0 °C. The solution was stirred for 4 h at reflux and quenched by H_2O (1.2 mL), 10% aqueous NaOH (1.6 mL), H_2O (3.6 mL) slowly at 0 °C. The solution was then filtered and dried over $MgSO_4$. The crude mixture was purified by column chromatography (hexanes: ethyl acetate = 3: 1 to 3: 2) to afford the alcohol intermediate (1.12 g, 84% for two steps).

tert-Butyldimethylsilylchloride (723 mg, 4.8 mmol, 1.2 equiv) was added to a solution of the alcohol obtained in the previous step (700 mg, 4.0 mmol, 1.0 equiv) and imidazole (544 mg, 8.0 mmol, 2.0 equiv) in DMF (11 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h before it was quenched with water (30 mL) and extracted with EtOAc (3 × 30 mL), then the combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the product, which was used directly for the next step without further purification.

To a suspension of NaH (192 mg, 60% dispersion in mineral oil, 4.8 mmol, 1.2 equiv,) in DMF (5 mL) was added a solution of the above intermediate in DMF (5 mL) at 0 °C. After stirring at rt for 0.5 h, the reaction mixture was cooled to 0 °C, treated with MeI (0.31 mL, 4.8 mmol, 1.2 equiv), and then allowed to stir at room temperature for 8 h. The reaction was quenched by water (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was treated with *tetra*-*n*-butylammonium fluoride (1 M in THF, 6 mL, 6 mmol, 1.5 equiv) at room temperature for 24 h, and was quenched by saturated ammonium chloride. The organics were extracted with EtOAc (2 × 60 mL), washed with brine (60 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (2: 1 to 1: 1) to afford 2-(1,6-dimethyl-1*H*-indol-3-yl)ethan-1-ol (653 mg, 86% for three steps).

To a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (418 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) were added triphenylphosphine (786 mg, 3.0 mmol, 1.5 equiv) and DIAD (0.52 mL, 2.6 mmol, 1.3 equiv) sequentially at 0 °C. Then a solution of 2-(1,6-dimethyl-1*H*-indol-3-yl)ethan-1-ol from the previous step (378 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night, concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 10: 1 to 5: 1) to afford a light yellow solid (690 mg, 91% yield); m.p. 98-100 °C, R_f = 0.35 (hexanes: ethyl acetate = 3: 1).

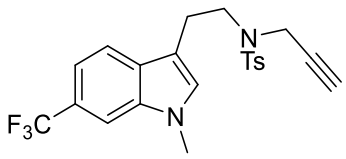
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 0.8 Hz, 1H), 6.96 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.86 (s, 1H), 4.19

(d, *J* = 2.4 Hz, 2H), 3.70 (s, 3H), 3.51-3.47 (m, 2H), 3.07-3.03 (m, 2H), 2.51 (s, 3H), 2.40 (s, 3H), 2.08 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 137.3, 135.9, 131.5, 129.4, 127.7, 126.4, 125.5, 120.7, 118.5, 110.5, 109.3, 76.9, 73.8, 47.2, 36.7, 32.6, 24.3, 21.9, 21.5.

IR (neat): 3273, 2918, 2119, 1476, 1453, 1344, 1327, 1156, 1119, 1092, 992, 908, 800, 735, 657 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{24}O_2N_2NaS$ 403.1451 found 403.1445.



ES-5.1m-alkyne

4-methyl-*N*-(2-(1-methyl-6-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**ES-5.1m-alkyne**):

Prepared according to **general procedure B**:

Oxalyl chloride (1.4 mL, 16.2 mmol, 3.0 qeuiv) was added dropwise to a solution of 6-(trifluoromethyl)-1*H*-indole (1.0 g, 5.4 mmo, 1.0 equiv) in ether (30 mL) at 0 °C. The resulting slurry was stirred at room temperature for 6 h before it was cooled to 0 °C again and quenched with MeOH (1.1 mL). The resulting suspension was filtered and the solids were washed thoroughly with cold ether, dried, and used directly in the next step.

A solution of the above solid in THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (616 mg, 16.2 mmol, 3.0 equiv) in THF (10 mL) at 0 °C. The solution was stirred for 4 h at reflux and quenched by H_2O (1.0 mL), 10% aqueous NaOH (1.5 mL), H_2O (3.0 mL) slowly at 0 °C. The solution was then filtered and dried unver cacuum to afford 2-(6-(trifluoromethyl)-1H-indol-3-yl)ethan-1-ol that was used directly in the next step in quantitative yield.

tert-Butyldimethylsilylchloride (980 mg, 6.5 mmol, 1.2 equiv) was added to a solution of 2-(6-(trifluoromethyl)-1H-indol-3-yl)ethan-1-ol obtained in the previous step (700 mg, 4.0 mmol, 1.0 equiv) and imidazole (735 mg, 10.8 mmol, 2.0 equiv) in DMF (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h before it was quenched with water (20 mL) and extracted with EtOAc (2 × 30 mL), then the combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the product, which was used directly for the next step without further purification.

To a suspension of NaH (260 mg, 60% dispersion in mineral oil, 6.5 mmol, 1.2 equiv,) in DMF (5 mL) was added a solution of the above intermediate in DMF (10 mL) at 0 °C. After stirring at rt for 0.5 h, the reaction mixture was cooled to 0 °C, treated with MeI (0.43 mL, 6.5 mmol, 1.2 equiv), and then allowed to stir at room temperature for 8 h. The reaction was quenched by water (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was treated with *tetra*-*n*-butylammonium fluoride (1 M in THF, 8.1 mL, 8.1 mmol, 1.5 equiv) at room temperature for 24 h, and was quenched by saturated ammonium chloride (20 mL). The organics were extracted with EtOAc (2 ×

30 mL), washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (2: 1 to 3: 2) to afford 2-(1-methyl-6-(trifluoromethyl)-1*H*-indol-3-yl)ethan-1-ol (1.04 g, 79% for five steps).

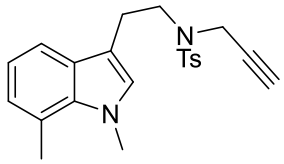
To a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (418 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) were added triphenylphosphine (786 mg, 3.0 mmol, 1.5 equiv) and DIAD (0.52 mL, 2.6 mmol, 1.3 equiv) sequentially at 0 °C. Then a solution of 2-(1-methyl-6-(trifluoromethyl)-1*H*-indol-3-yl)ethan-1-ol from the previous step (486 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night, concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 5: 1) to afford a sand-like colorless solid (752 mg, 87% yield); m.p. 108-110 °C, R_f = 0.31 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.09 (s, 1H), 4.14 (d, *J* = 2.8 Hz, 2H), 3.78 (s, 3H), 3.48-3.44 (m, 2H), 3.08-3.04 (m, 2H), 2.38 (s, 3H), 2.07 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 135.8, 135.7, 130.0, 129.8, 129.5, 127.6, 125.5 (q, *J* = 270 Hz), 123.5 (q, *J* = 32 Hz), 119.2, 115.5 (q, *J* = 4 Hz), 111.1, 106.9 (q, *J* = 4 Hz), 76.8, 74.0, 47.1, 36.8, 32.7, 24.0, 21.4.

IR (neat): 3289, 2925, 1598, 1479, 1367, 1328, 1297, 1249, 1156, 1106, 1093, 1056, 993, 908, 865, 812, 729, 661 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{22}O_2N_2F_3S$ 435.1349 found 435.1345.



ES-5.1n-alkyne

***N*-(2-(1,7-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**ES-5.1n-alkyne**):

Prepared according to **general procedure B**:

Oxalyl chloride (2.57 mL, 30.0 mmol, 3.0 qeuiv) was added dropwise to a solution of 7-methyl-1*H*-indole (1.31 g, 10.0 mmo, 1.0 equiv) in ether (50 mL) at 0 °C. The resulting slurry was stirred at room temperature for 6 h before it was cooled to 0 °C again and quenched with MeOH (2.0 mL). The resulting suspension was filtered and the solids were washed thoroughly with cold ether, dried, and used directly in the next step.

A solution of the above solids in THF (25 mL) was added dropwise to a suspension of $LiAlH_4$ (1.14 g, 30.0 mmol, 3.0 equiv) in THF (30 mL) at 0 °C. The solution was stirred for 4 h at reflux and quenched by H_2O (1.5 mL), 10% aqueous NaOH (2.0 mL), H_2O (4.5 mL) slowly at 0 °C. The solution was then filtered, dried over $MgSO_4$, and concentrated to afford 2-(7-methyl-1H-indol-3-yl)ethan-1-ol (*c.a.* 1.52 g) that was used directly in the next step.

tert-Butyldimethylsilylchloride (1.57 g, 10.5 mmol, 1.2 equiv) was added to a solution of 2-(7-methyl-1H-indol-3-yl)ethan-1-ol obtained in the previous step (1.52 g, *c.a.* 8.7 mmol, 1.0 equiv) and imidazole (1.18 g, 17.4 mmol, 2.0 equiv) in DMF (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h before it was quenched with

water (30 mL) and extracted with EtOAc (2 × 50 mL), then the combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the product, which was used directly for the next step without further purification.

To a suspension of NaH (418 mg, 60% dispersion in mineral oil, 10.4 mmol, 1.2 equiv,) in DMF (10 mL) was added a solution of the above intermediate in DMF (10 mL) at 0 °C. After stirring at rt for 0.5 h, the reaction mixture was cooled to 0 °C, treated with MeI (0.68 mL, 10.4 mmol, 1.2 equiv), and then allowed to stir at room temperature for 8 h. The reaction was quenched by water (30 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was treated with *tetra-n*-butylammonium fluoride (1 M in THF, 13.1 mL, 13.1 mmol, 1.5 equiv) at room temperature for 24 h, and was quenched by saturated ammonium chloride (30 mL). The organics were extracted with EtOAc (2 × 50 mL), washed with brine, dried over $MgSO_4$, concentrated, and purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (3: 1 to 3: 2) to afford 2-(1,7-dimethyl-1H-indol-3-yl)ethan-1-ol (1.36 g, 72% for five steps).

To a stirred solution of 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (418 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) were added triphenylphosphine (786 mg, 3.0 mmol, 1.5 equiv) and DIAD (0.52 mL, 2.6 mmol, 1.3 equiv) sequentially at 0 °C. Then a solution of 2-(1,7-dimethyl-1H-indol-3-yl)ethan-1-ol from the previous step (378 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night, concentrated and purified by flash column

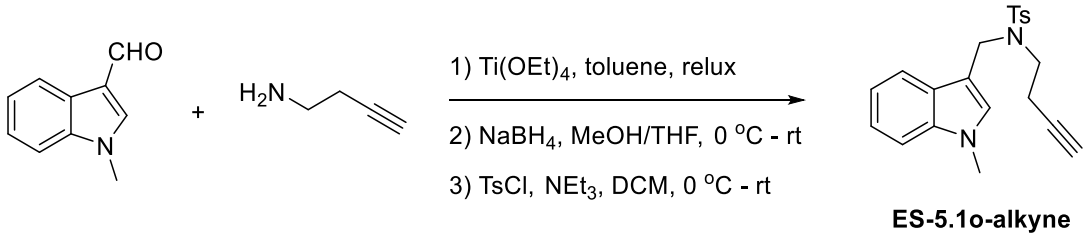
chromatography (silica gel, hexanes: ethyl acetate = 6: 1) to afford a light white solid (660 mg, 87% yield); m.p. 97-99 °C, R_f = 0.33 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.81 (s, 1H), 4.17 (d, *J* = 2.4 Hz, 2H), 3.99 (s, 3H), 3.47-3.43 (m, 2H), 3.03-2.99 (m, 2H), 2.74 (s, 3H), 2.39 (s, 3H), 2.05 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 135.9, 135.7, 129.5, 128.8, 128.7, 127.7, 124.3, 121.4, 119.3, 116.9, 110.3, 76.9, 74.0, 47.1, 36.7, 36.6, 24.1, 21.6, 19.8.

IR (neat): 3273, 2926, 1597, 1494, 1458, 1407, 1343, 1156, 1092, 908, 814, 744, 658 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}O_2N_2S$ 381.1631 found 381.1626.



ES-5.1o-alkyne

***N*-(but-3-yn-1-yl)-4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)benzenesulfonamide** (**ES-5.1o-alkyne**):

To a solution of 1-methyl-1*H*-indole-3-carbaldehyde (636 mg, 4.0 mmol, 1 equiv) and but-3-yn-1-amine (276 mg, 4.0 mmol, 1 equiv) in dichloromethane (20 mL) was added anhydrous $MgSO_4$ (240 mg, 2.0 mmol, 0.5 equiv). The reaction mixture was heated to

reflux over night before it was cooled to room temperature. The residue was dissolved in MeOH (20 mL), and $NaBH_4$ (326 mg, 8.8 mmol, 2.2 equiv) was slowly added at 0 °C. After 4 h stirring at room temperature, the reaction was quenched by slow addition of water at 0 ℃. The mixture was dried over $MgSO_4$, and concentrated under reduced pressure to give crude amide product. This crude material was used directly in the next step without purification.

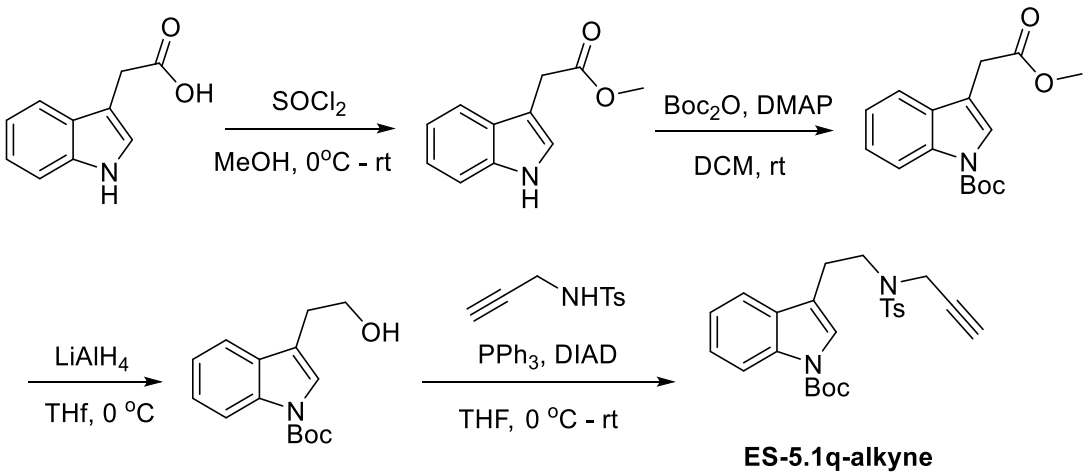
The crude product obtained from previous step (*c.a.* 4.0 mmol, 1.0 equiv) and triethylamine (506 mg, 5.0 mmol, 1.25 equiv) were dissolved in DCM (20 mL), followed by addition of TsCl (953 mg, 5.0 mmol, 1.25 equiv) at 0 ℃. The reaction mixture was stirred overnight at room temperature. Then the reaction was quenched by water (20 mL). The layers were separated and the aqueous later was extracted again with DCM (50 mL). The combined organics were dried over Mg_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1) to afford **ES-5.1o-alkyne** as a light yellow solid (526 mg, 43% yield for three steps). m.p. 125-128 °C, R_f = 0.20 (hexanes: ethyl acetate = 4: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.32-7.21 (m, 4H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 4.52 (s, 2H), 3.72 (s, 3H), 3.26 (t, *J* = 7.6 Hz, 2H), 2.43 (s, 3H), 2.21 (td, *J* = 7.6, 2.8 Hz, 2H), 1.85 (t, *J* = 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 137.1, 136.7, 129.7, 128.7, 127.3, 127.2, 122.1, 119.6, 119.3, 109.3, 108.6, 81.3, 69.9, 46.0, 44.1, 32.8, 21.5, 19.3.

IR (neat): 3284, 3051, 2921, 1597, 1474, 1449, 1330, 1305, 1249, 1155, 1118, 1193, 1063, 983, 919, 815, 741, 677 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{22}O_2N_2NaS$ 389.1294 found 389.1290.



***tert*-butyl 3-(2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)ethyl)-1*H*-indole-1-carboxylate** (**ES-5.1q-alkyne**):

A solution of indole-3-yl acetic acid (1.75 g, 10.0 mmol, 1.0 equiv) in dry MeOH (30 mL) at 0 °C was added thionyl chloride (1.8 mL, 25 mmol, 2.5 equiv) slowly. The reaction was warmed to room temperature while stirred over night. The crude residue was concentrated, diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure to give crude methyl ester. This crude material was used directly in the next step without purification.

To a solution of methyl 2-(1*H*-indol-3-yl)acetate in dichloromethane (50 mL) was added DMAP (122 mg, 1.0 mmol) and di-*tert*-butyl dicarbonate (3.27 g, 15 mmol) under an inert atmosphere at ambient temperature. The resulting reaction mixture was stirred for over night before it was quenched with water (50 mL) was added to the reaction mixture. The organic layer was separated; the aqueous layer was extracted with DCM (50 mL). The

combined extracts were washed with brine (30 mL), and dried over $MgSO_4$. The organics were concentrated under reduced pressure to give the crude product as a brown oil that was used directly in the next step.

A solution of the crude Boc-protected ester in THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (555 mg, 15.0 mmol) in THF (30 mL) at 0 ℃. After being stirred the mixture for 1 hour at 0 ℃, it was quenched with 1N HCl (10 mL) carefully at 0 ℃. The reaction mixture was extracted with ether (100 + 50 mL), washed with brine (50 mL), and dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel eluting with hexanes: ethyl acetate (4: 1 to 2: 1) to afford the alcohol intermediate.

To a stirred solution of *N*-tosyl propargyl amide (209 mg, 1.0 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) were added triphenylphosphine (341 mg, 1.3 mmol) and DIAD (263 mg, 1.3 mmol) at 0 °C sequentially. Then a solution of alcohol obtained above (261 mg, 1.0 mmol) in dry tetrahydrofuran (3 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night until completion of conversion as judged by TLC analysis. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 10: 1 to 5: 1) to afford **ES-5.1q-alkyne** as a white solid (430 mg, 95% yield); m.p. 85-86 °C, R_f = 0.39 (hexanes: ethyl acetate = 3: 1).

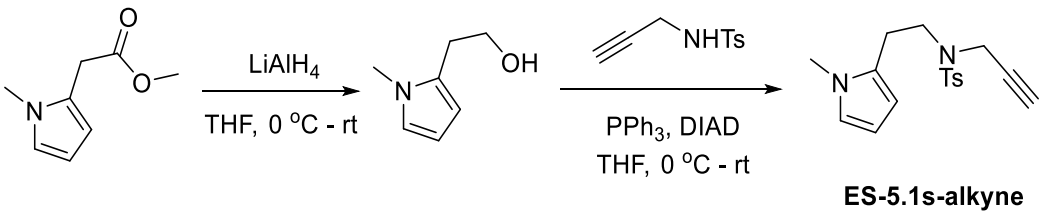
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (br d, *J* = 6.40 Hz, 1H), 7.69 (d, *J* = 8.0, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.44 (s, 1H), 7.32-7.28 (m, 1H), 7.24-7.20 (m, 3H), 4.18 (d, *J* = 2.4 Hz,

2H), 3.50-3.47 (m, 2H), 3.02-2.98 (m, 2H), 2.38 (s, 3H), 2.09 (t, *J* = 2.4 Hz, 1H), 1.66 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 143.5, 135.7, 135.4, 130.2, 129.5, 127.6, 124.4, 123.4, 122.5, 118.8, 116.8, 115.3, 83.6, 76.7, 73.9, 46.4, 36.8, 28.2, 24.3, 21.5.

IR (neat): 3277, 2978, 1729, 1599, 1453, 1381, 1347, 1308, 1256, 1218, 1158, 1098, 1018, 910, 814, 747, 661 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{25}H_{28}N_2O_4NaS$ 475.1662 found 475.1654.



ES-5.1s-alkyne

4-methyl-*N*-(2-(1-methyl-1*H*-pyrrol-2-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**ES-5.1s-alkyne**):

A solution of methyl 2-(1-methyl-1*H*-pyrrol-2-yl)acetate (919 mg, 6.0 mmol, 1 equiv) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (666 mg, 18.0 mmol) in THF (20 mL) at 0 ℃. After being stirred the mixture for 1 hour at 0 ℃, it was quenched with 1N HCl (10 mL) carefully at 0 ℃. The reaction mixture was extracted with ether (100 + 50 mL), washed with brine (50 mL), and dried over $MgSO_4$ and concentrated under reduced pressure to give the crude alcohol intermediate in quantitative yield.

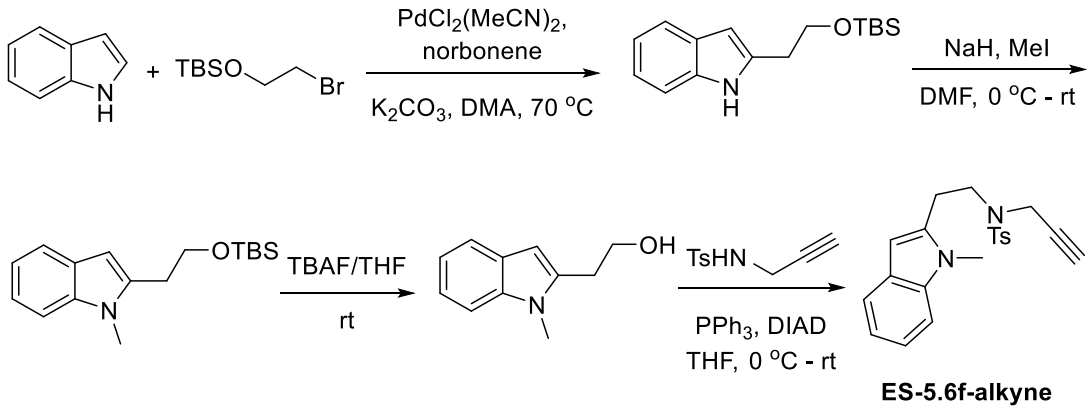
To a stirred solution of *N*-Ts propargyl amide (314 mg, 1.5 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) were added triphenylphosphine (590 mg, 2.25 mmol, 1.5 equiv) and DIAD (0.39 mL, 1.95 mmol, 1.3 equiv) at 0 °C sequentially. Then a solution of alcohol obtained above (188 mg, 1.5 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night until completion of conversion as judged by TLC analysis. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 8: 1 to 4: 1) to afford **ES-5.1s-alkyne** as a colorless oil (403 mg, 85% yield). R_f = 0.15 (hexanes: ethyl acetate = 5: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 2.8, 1.6 Hz, 1H), 6.03 (dd, *J* = 3.6, 2.8 Hz, 1H), 5.91 (dd, *J* = 3.6, 1.6 Hz, 1H), 4.07 (d, *J* = 2.8 Hz, 2H), 3.57 (s, 3H), 3.40-3.36 (m, 2H), 2.91-2.87 (m, 2H), 2.40 (s, 3H), 2.04 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 135.8, 129.6, 129.0, 127.6, 121.9, 106.9, 106.8, 76.8, 74.0, 46.4, 37.1, 33.7, 25.8, 21.6.

IR (neat): 3270, 1923, 2118, 1597, 1493, 1453, 1331, 1305, 1215, 1156, 1090, 985, 908, 871, 813, 707, 654 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{21}O_2N_2S$ 317.1318 found 317.1314.



4-methyl-*N*-(2-(1-methyl-1*H*-indol-2-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**ES-5.6f-alkyne**):

To a mixture of indole (2.68 g, 22.94 mmol, 2.07 equiv), norbornene (2.08 g, 22.16 mmol, 2.0 equiv), K_2CO_3 (3.06 g, 22.16 mmol, 2.0 equiv), and $PdCl_2(MeCN)_2$ (288 mg, 1.11 mmol, 10 mol %) was added a solution of water (450 mg, 0.45 mL) in DMA (50 mL) was added via syringe as the solvent. The resulting solution was briefly evacuated and then backfilled with argon (3 times), and then (2-bromoethoxy)(*tert*-butyl)dimethylsilane (2.65 g, 11.08 mmol, 1.0 equiv) was added *via* syringe. The reaction mixture was then placed in a preheated oil bath at 70 °C and stirred under a balloon pressure of argon. The reaction was monitored by TLC. Upon completion of reaction (14 hours), the reaction mixture was cooled to room temperature, diluted with ether (150 mL), and filtered. The filtrate was concentrated in a water bath (60 °C, 8-10 mbar) to remove ether and most of DMA. The residue was purified by flash column chromatography (eluting hexanes: diethyl ether = 10: 1 to 5: 1) to afford 2.75 g of the crude 2-alkylindole product as an oil, which was used directly in the next step.

To a suspension of NaH (60 % in mineral oil, 480 mg, 12.0 mmol, 1.2 equiv) was added a solution of the 2-alkylindole (2.75 g, *ca*. 10.0 mmol, 1.0 equiv) dropwise at 0 °C. The reaction was allowed to stir at room temperature for 30 minutes before MeI (0.75 mL, 12.0 mmol, 1.2 equiv) was added. The mixture was stirred at room temperature for 8 hours before it was quenched by addition of H_2O (60 mL) and extracted with ethyl acetate (100 mL × 2). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give to give crude **2-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-methyl-1*H*-indole**, which was used in the next step directly.

The **2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-methyl-1*H*-indole** obtained from previous step was treated with TBAF (1 M in THF, 15 mL, 15 mmol, 1.5 equiv) at room temperature for 24 h. The reaction was quenched with saturated aqueous ammonium chloride (60 mL), extracted with ethyl acetate (100 mL × 2). The combined organics were washed with brine (100 mL), dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by silica gel chromatography (eluting hexanes: ethyl acetate = 2: 1 to 1: 1) to give **2-(1-methyl-1*H*-indol-2-yl)ethan-1-ol** as a pink solid (0.98 g, 51% for three steps).

To a stirred solution of *N*-tosyl propargyl amide (418 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (10 mL) were added triphenylphosphine (786 mg, 3.0 mmol, 1.5 equiv) and DIAD (0.52 mL, 2.6 mmol, 1.3 equiv) sequentially at 0 °C. Then a solution of **2-(1-methyl-1*H*-indol-2-yl)ethan-1-ol** (350 mg, 2.0 mmol, 1.0 equiv) in dry tetrahydrofuran (5 mL) was added dropwise. The reaction mixture was then stirred at room temperature over night until completion of conversion as judged by TLC analysis. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl

acetate = 5: 1) to afford the alkyne product **ES-5.6f-alkyne** as a white solid (658 mg, 90% yield); m.p. 126-128 °C, R_f = 0.33 (hexanes: ethyl acetate = 3: 1).

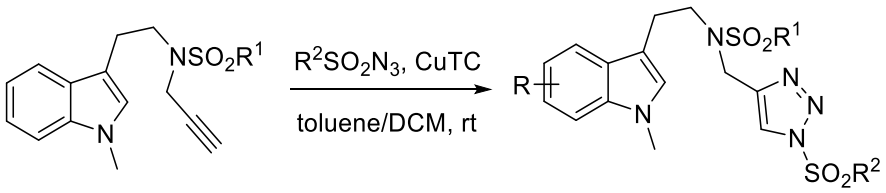
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.27-7.24 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.29 (s, 1H), 4.11 (d, *J* = 2.4 Hz, 2H), 3.70 (s, 3H), 3.51-3.47 (m, 2H), 3.13-3.09 (m, 2H), 2.40 (s, 3H), 2.07 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 137.4, 136.8, 135.6, 129.6, 127.7, 127.6, 121.1, 120.0, 119.5, 109.1, 100.0, 76.8, 74.1, 46.2, 37.2, 29.6, 26.4, 21.6.

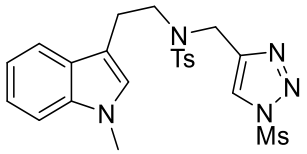
IR (neat): 2918, 1682, 1597, 1493, 1338, 1185, 1158, 1089, 790, 733, 662 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{23}O_2N_2S$ 367.1475 found 367.1473.

General Procedure C:



To a solution of the alkyne was dissolved in toluene (0.2 M) and dichloromethane (0.2 M) at room temperature. Then CuTC (10 mol %) was added. Following this, a solution of sulfonyl azide (1.0 equiv) was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by silica gel chromatography (eluting hexanes: ethyl acetate = 2: 1 to 1: 1) to give the desired triazole products.



5.1a

4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.1a**):

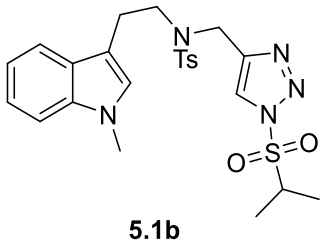
Prepared according to **general procedure C** using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (651 mg, 1.78 mmol, 1.0 equiv) and MsN_3 (216 mg, 1.78 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white foam (720 mg, 83% yield); m.p. 49-51 °C, R_f = 0.14 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.26-7.24 (m, 3H), 7.19-7.17 (m, 1H), 7.06-7.04 (m, 1H), 6.88 (s, 1H), 4.51 (s, 2H), 3.70 (s, 3H), 3.51 (t, *J* = 7.8 Hz, 2H), 3.26(s, 3H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.3, 143.8, 136.9, 136.2, 129.8, 127.5, 127.1, 127.0, 123.0, 121.6, 118.9, 118.6, 110.4, 109.3, 49.2, 43.0, 42.4, 32.6, 24.6, 21.5.

IR (neat): 2926, 1597, 1473, 1377, 1326, 1182, 1154, 1091, 1012, 984, 952, 908, 814, 769, 727, 668 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}O_4N_5S_2$ 488.1421 found 488.1415.



5.1b

***N*-((1-(isopropylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-methyl-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)benzenesulfonamide** (**5.1b**):

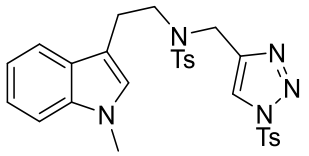
Prepared according to **general procedure C** using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (220 mg, 0.60 mmol, 1.0 equiv) and propane-2-sulfonyl azide (89 mg, 0.60 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white solid (296 mg, 95% yield); m.p. 116-118 °C, R_f = 0.15 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.27-7.24 (m, 3H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 4.55 (s, 2H), 3.70 (s, 3H), 3.64 (sep, *J* = 6.8 Hz, 1H), 3.52-3.48 (m, 2H), 3.00-2.96 (m, 2H), 2.40 (s, 3H), 1.31 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 143.8, 136.9, 136.3, 129.8, 127.5, 127.1, 127.0, 124.5, 121.7, 119.0, 118.7, 110.4, 109.3, 57.3, 49.3, 42.9, 32.6, 24.8, 21.5, 15.9.

IR (neat): 2936, 1597, 1466, 1380, 1367, 1327, 1305, 1178, 1154, 1091, 1059, 1011, 970, 909, 874, 814, 734, 697, 668 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{30}O_4N_5S_2$ 516.1734 found 516.1742.



5.1c

4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.1c**):

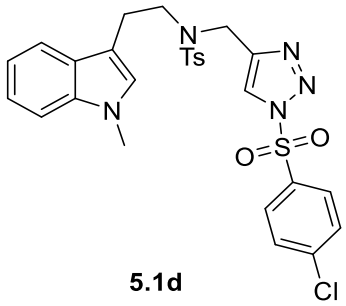
Prepared according to general procedure A using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (220 mg, 0.60 mmol, 1.0 equiv) and TsN_3 (118 mg, 0.60 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white foam (303 mg, 90% yield); m.p. 55-57 °C, R_f = 0.28 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.26-7.18 (m, 4H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 4.49 (s, 2H), 3.69 (s, 3H), 3.46-3.42 (m, 2H), 2.92-2.88 (m, 2H), 2.40 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 144.1, 143.7, 136.9, 136.4, 132.8, 130.5, 129.7, 128.6, 127.5, 127.1, 126.9, 123.0, 121.6, 118.9, 118.7, 110.5, 109.2, 49.2, 42.9, 32.6, 24.8, 21.8, 21.5.

IR (neat): 3054, 2922, 1594, 1473, 1454, 1393, 1327, 1305, 1216, 1194, 1179, 1155, 1090, 1010, 973, 911, 735, 701, 666 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{30}O_4N_5S_2$ 564.1734 found 564.1737.



5.1d

***N*-((1-((4-chlorophenyl)sulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide** (**5.1d**):

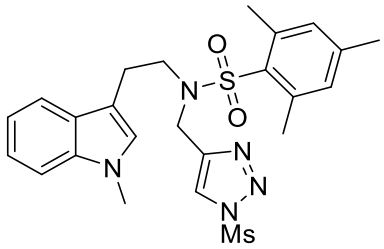
Prepared according to **general procedure C** using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (220 mg, 0.60 mmol, 1.0 equiv) and 4-chlorobenzenesulfonyl azide (131 mg, 0.60 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a light yellow solid (293 mg, 83% yield); m.p. 81-83 °C, R_f = 0.20 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.88 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.21-7.18 (m, 4H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 4.48 (s, 2H), 3.70 (s, 3H), 3.46-3.43 (m, 2H), 2.93-2,89 (m, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 143.8, 142.8, 136.9, 136.3, 134.2, 130.2, 130.0, 129.8, 127.4, 127.1, 126.9, 123.2, 121.7, 119.0, 118.7, 110.4, 109.3, 49.3, 43.0, 32.6, 24.8, 21.5.

IR (neat): 3090, 2929, 1584, 1475, 1402, 1328, 1305, 1193, 1176, 1157, 1092, 1010, 973, 816, 760, 739 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{27}H_{27}O_4N_5ClS_2$ 584.1188 found 584.1195.



5.1e

2,4,6-trimethyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.1e**):

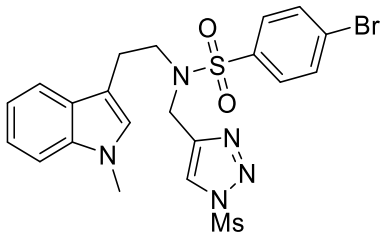
Prepared according to **general procedure C** using **2,4,6-trimethyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (394 mg, 1.0 mmol, 1.0 equiv) and MsN_3 (121 mg, 1.0 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a white foam (398 mg, 77% yield); m.p. 65-67 °C, R_f = 0.15 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.16-7.14 (m, 2H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.83 (s, 2H), 6.71 (s, 1H), 4.70 (s, 2H), 3.67 (s, 3H), 3.44 (s, 3H), 3.38 (t, *J* = 7.8 Hz, 2H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.49 (s, 6H), 2.27 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.7, 142.9, 140.2, 136.9, 132.3, 131.9, 127.3, 126.8, 123.2, 121.5, 118.8, 118.3, 110.3, 109.1, 46.6, 42.6, 40.1, 32.5, 23.3, 22.7, 21.0.

IR (neat): 2928, 1603, 1472. 1376, 1312, 1184, 1148, 1078, 1056, 1013, 952, 909, 857, 769, 733, 682 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{24}H_{29}O_4N_5NaS_2$ 538.1553 found 538.1552.



5.1f

4-bromo-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.1f**):

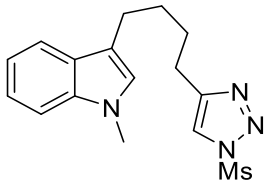
Prepared according to **general procedure C** using **4-bromo-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (431 mg, 1.0 mmol, 1.0 equiv) and MsN_3 (121 mg, 1.0 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a white foam (470 mg, 85% yield); m.p. 45-48°C, R_f = 0.19 (hexanes: ethyl acetate = 3: 2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (s, 1H), 7.57-7.51 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.20 (td, *J* = 8.0, 0.8 Hz, 1H), 7.06 (td, *J* = 8.0, 0.8 Hz, 1H), 6.83 (s, 1H), 4.53 (s, 2H), 3.70 (s, 3H), 3.54 (t, *J* = 7.6 Hz, 2H), 3.32 (s, 3H), 2.98 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 138.3, 136.9, 132.3, 128.5, 127.7, 127.4, 127.0, 123.1, 121.8, 119.0, 118.5, 110.1, 109.4, 49.0, 42.7, 42.5, 32.7, 24.4.

IR (neat): 3024, 2928, 1615, 1574, 1471, 1378, 1327, 1275, 1253, 1221, 1184, 1157, 1090, 1068, 1011, 987, 953, 910, 821, 768, 742 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{23}O_4N_5BrS_2$ 552.0369 found 552.0375.



5.1g

1-methyl-3-(4-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)butyl)-1*H*-indole (**5.1g**):

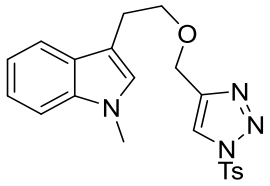
Prepared according to **general procedure C** using **3-(hex-5-yn-1-yl)-1-methyl-1*H*-indole** (253 mg, 1.2 mmol, 1.0 equiv) and MsN_3 (145 mg, 1.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a colorless oil (370 mg, 93% yield); R_f = 0.33 (hexanes: ethyl acetate = 3: 2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.84 (s, 1H), 3.73 (s, 3H), 3.41 (s, 3H), 2.82-2.79 (m, 4H), 1.82-1.78 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 137.0, 127.8, 126.2, 121.4, 120.3, 118.9, 118.5, 114.7, 109.2, 42.5, 32.6, 29.8, 28.7, 25.3, 24.7.

IR (neat): 3142, 3023, 2926, 2856, 1614, 1553, 1483, 1471, 1372, 1325, 1243, 1178, 1131, 1011, 949, 804, 769, 739 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{21}O_2N_4S$ 333.1380 found 333.1377.



5.1h

1-methyl-3-(2-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)-1*H*-indole (**5.1h**):

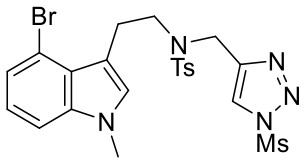
Prepared according to **general procedure C**: To a solution of **1-methyl-3-(2-(prop-2-yn-1-yloxy)ethyl)-1*H*-indole** (213 mg, 1.0 mmol, 1.0 equiv) in toluene (6 mL) and dichloromethane (6 mL) at room temperature was added CuTC (19 mg, 10 mol %). Following this, a solution of TsN_3 (197 mg, 1.0 mmol, 1.0 equiv) in 4 mL toluene was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford the product as a colorless oil (360 mg, 88% yield); R_f = 0.36 (hexanes: ethyl acetate = 3: 2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.23 (t, *J* = 7.6, 1H), 7.11 (t, *J* = 7.6, 1H), 6.90 (s, 1H), 4.65 (s, 2H), 3.79 (t, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 145.4, 136.9, 132.9, 130.4, 128.7, 127.9, 126.9, 122.1, 121.5, 118.9, 111.1, 109.3, 71.6, 64.0, 32.6, 25.6, 21.8.

IR (neat): 3053, 1862, 1732, 1593, 1473, 1390, 1327, 1306, 1247, 1216, 1194, 1174, 1090, 1048, 1010, 963, 812, 739, 701, 667 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{23}O_3N_4S$ 411.1485 found 411.1482.



5.1i

***N*-(2-(4-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1i**):

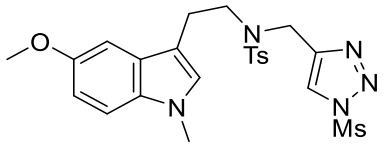
Prepared according to **general procedure C** using ***N*-(2-(4-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (744 mg, 1.67 mmol, 1.0 equiv) and MsN_3 (202 mg, 1.67 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white foam (500 mg, 53% yield); m.p. 49-51 °C, R_f = 0.24 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.19-7.15 (m, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 4.54 (s, 2H), 3.69 (s, 3H), 3.54 (t, *J* = 7.6 Hz, 2H), 3.35 (s, 3H), 3.20 (t, *J* = 7.6 Hz, 2H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 143.8, 138.1, 136.1, 129.7, 129.4, 127.1, 125.4, 123.3, 122.9, 122.3, 113.9, 111.1, 108.8, 50.6, 43.3, 42.5, 32.9, 25.3, 21.5.

IR (neat): 2927, 1597, 1549, 1455, 1417, 1376, 1332, 1182, 1154, 1091, 1013, 952, 814, 769, 653 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{24}O_4N_5BrNaS_2$ 588.0345 found 588.1350.



5.1j

***N*-(2-(5-methoxy-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1j**):

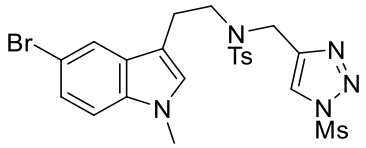
Prepared according to **general procedure C** using ***N*-(2-(5-methoxy-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (396 mg, 1.0 mmol, 1.0 equiv) and MsN_3 (121 mg, 1.0 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 1: 1) to afford a white foam (415 mg, 80% yield); m.p. 48-50 °C, R_f = 0.30 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.84 (s, 1H), 4.52 (s, 2H), 3.85 (s, 3H), 3.68 (s, 3H), 3.50 (t, *J* = 8.0 Hz, 2H), 3.31 (s, 3H), 2.95 (t, *J* = 8.0 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 144.1, 143.9, 136.3, 132.2, 129.8, 127.8, 127.6, 127.1, 123.0, 112.0, 110.2, 109.9, 100.3, 55.9, 49.0, 42.9, 42.4, 32.8, 24.7, 21.5.

IR (neat): 2926, 1621, 1597, 1578, 1492, 1454, 1425, 1378, 1334, 1305, 1225, 1183, 1156, 1092, 1014, 954, 771, 736, 661 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{23}H_{27}O_5N_5NaS_2$ 540.1346 found 540.1342.



5.1k

***N*-(2-(5-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1k**):

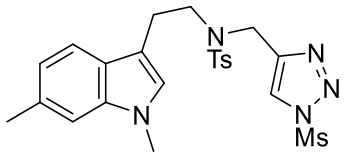
Prepared according to **general procedure C** using ***N*-(2-(5-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (534 mg, 1.2 mmol, 1.0 equiv) and MsN_3 (145 mg, 1.2 mmol, 1.0 equiv) in **step 2**. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 3: 2) to afford a white foam (480 mg, 71% yield); m.p. 52-54 °C, R_f = 0.20 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 1.6 Hz, 1H), 7.26-7.21 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 4.52 (s, 2H), 3.67 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 2H), 3.35 (s, 3H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 144.0, 136.1, 135.5, 129.9, 129.2, 128.3, 127.1, 124.4, 123.0, 121.1, 112.3, 110.9, 110.0, 48.9, 42.9, 42.5, 32.8, 24.2, 21.6.

IR (neat): 2927, 1597, 1549, 1477, 1377, 1333, 1305, 1291, 1183, 1155, 1091, 1013, 953, 815, 770, 734, 673 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{24}O_4N_5BrNaS_2$ 588.0345 found 588.1343.



5.1l

***N*-(2-(1,6-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1l**):

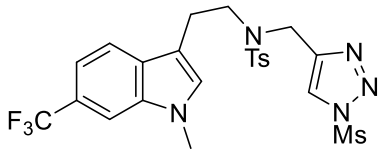
Prepared according to **general procedure C** using ***N*-(2-(1,6-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (456 mg, 1.2 mmol, 1.0 equiv) and MsN_3 (145 mg, 1.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a white foam (540 mg, 93% yield); m.p. 49-51 °C, R_f = 0.20 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H), 4.52 (s, 2H), 3.67 (s, 3H), 3.51 (t, *J* = 8.0 Hz, 2H), 3.28 (s, 3H), 2.96 (t, *J* = 8.0 Hz, 2H), 2.47 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 143.8, 137.3, 136.2, 131.5, 129.8, 127.1, 126.5, 125.4, 123.1, 120.7, 118.4, 110.2, 109.4, 49.2, 43.0, 42.4, 32.6, 24.7, 21.9, 21.5.

IR (neat): 2924, 1597, 1477, 1377, 1327, 1182, 1154, 1090, 1013, 952, 801, 769, 732, 701 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{23}H_{27}O_4N_5NaS_2$ 524.1397 found 524.1394.



5.1m

4-methyl-*N*-(2-(1-methyl-6-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.1m**):

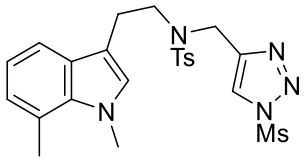
Prepared according to **general procedure C** using **4-methyl-*N*-(2-(1-methyl-6-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (751 mg, 1.73 mmol, 1.0 equiv) and MsN_3 (210 mg, 1.73 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white foam (850 mg, 90% yield); m.p. 50-52 °C, R_f = 0.13 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.55-7.53 (m, 2H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.03 (s, 1H), 4.51 (s, 2H), 3.76 (s, 3H), 3.51 (t, *J* = 7.6 Hz, 2H), 3.31 (s, 3H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 144.0, 136.1, 135.7, 129.9, 129.8, 127.0, 127.0, 125.4 (q, *J* = 270 Hz), 123.4 (q, *J* = 32 Hz), 123.1, 119.1, 115.4 (q, *J* = 4 Hz), 110.9, 106.9 (q, *J* = 32 Hz), 49.0, 42.8, 42.4, 32.8, 24.3, 21.4.

IR (neat): 2931, 1598, 1480, 1380, 1329, 1297, 1184, 1155, 1108, 1092, 1057, 1013, 953, 909, 865, 813, 769, 729 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{23}H_{24}O_4N_5F_3NaS_2$ 578.1114 found 578.1112.



5.1n

***N*-(2-(1,7-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1n**):

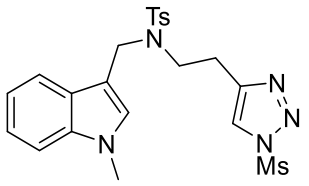
Prepared according to **general procedure C** using ***N*-(2-(1,7-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (570 mg, 1.5 mmol, 1.0 equiv) and MsN_3 (182 mg, 1.5 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 3: 2) to afford a white foam (650 mg, 87% yield); m.p. 49-51 °C, R_f = 0.19 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.78 (s, 1H), 4.52 (s, 2H), 3.97 (s, 3H), 3.50 (t, *J* = 8.0 Hz, 2H), 3.26 (s, 3H), 2.94 (t, *J* = 8.0 Hz, 2H), 2.73 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 143.9, 136.2, 135.6, 129.9, 128.8, 128.6, 127.2, 124.3, 123.0, 121.5, 119.2, 116.7, 110.0, 49.2, 43.1, 42.4, 36.6, 24.5, 21.5, 19.7.

IR (neat): 2927, 1732, 1598, 1459, 1376, 1336, 1184, 1157, 1091, 1014, 954, 816, 771, 746, 656 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{23}H_{27}O_4N_5NaS_2$ 524.1397 found 524.1397.



5.1o

4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)-*N*-(2-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)ethyl)benzenesulfonamide (**5.1o**):

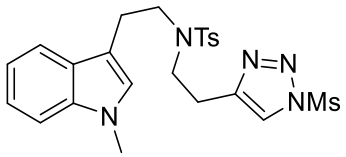
Prepared according to **general procedure C**: To a solution of ***N*-(but-3-yn-1-yl)-4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)benzenesulfonamide** (308 mg, 0.84 mmol, 1.0 equiv) in toluene (4 mL) and dichloromethane (2 mL) at room temperature was added CuTC (16 mg, 0.084 mmol, 10 mol %). Following this, a solution of MsN_3 (102 mg, 0.84 mmol, 1.0 equiv) in 2 mL toluene was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 1: 1) to afford **4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)-*N*-(2-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)ethyl)benzenesulfonamide** as a light yellow foam (310 mg, 76% yield); m.p. 52-54 °C, R_f = 0.25 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.50 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 8.4 Hz, 1H), 6.89 (s, 1H), 4.43 (s, 2H), 3.71 (s, 3H), 3.39 (t, *J* = 7.2 Hz, 2H), 3.31(s, 3H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.6, 143.5, 137.1, 136.1, 129.8, 128.8, 127.2, 127.2, 122.2, 121.7, 119.7, 119.2, 109.5, 108.6, 47.1, 44.7, 42.6, 32.8, 25.5, 21.5.

IR (neat): 3027, 2927, 1597, 1556, 1474, 1451, 1378, 1330, 1249, 1181, 1155, 1090, 1014, 953, 915, 815, 769, 729, 676 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{25}O_4N_5NaS_2$ 510.1240 found 510.1242.



5.1p

4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(2-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)ethyl)benzenesulfonamide (**5.1p**):

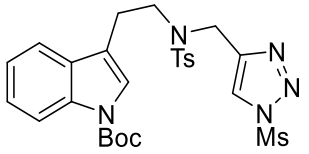
Prepared according to **general procedure C** using ***N*-(but-3-yn-1-yl)-4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide** (274 mg, 0.72 mmol, 1.0 equiv) and MsN_3 (88 mg, 0.72 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a colorless foam (298 mg, 82 yield); m.p. 39-41°C, R_f = 0.22 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.28-7.24 (m, 3H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 3.71 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 2H), 3.41-3.38 (m, 5H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.94-2.90 (m, 2H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 143.5, 136.9, 136.1, 129.8, 127.5, 127.1, 127.0, 121.8, 121.7, 119.0, 118.6, 110.6, 109.4, 50.0, 48.2, 42.6, 32.6, 25.7, 25.2, 21.5.

IR (neat): 2927, 1597, 1473, 1378, 1326, 1247, 1181, 1153, 1091, 1058, 1013, 951, 908, 814, 769, 729, 668 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{28}O_4N_5S_2$ 502.1583 found 502.1590.



5.1q

***tert*-butyl 3-(2-((4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)phenyl)sulfonamido)ethyl)-1*H*-indole-1-carboxylate** (**5.11**):

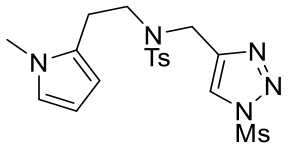
Prepared according to **general procedure C**: To a solution of ***tert*-butyl 3-(2-((4-methyl-*N*-(prop-2-yn-1-yl)phenyl)sulfonamido)ethyl)-1*H*-indole-1-carboxylate** (226 mg, 0.50 mmol, 1.0 equiv) in toluene (3 mL) and dichloromethane (3 mL) at room temperature was added CuTC (10 mg, 10 mol %). Following this, a solution of MsN_3 (61 mg, 0.50 mmol, 1.0 equiv) in 2 mL toluene was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford the produc as a white powder (286 mg, 80% yield); m.p. 150-152 °C, R_f = 0.10 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (br s, 1H), 7.88 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.23-7.19 (m, 3H), 4.56 (s, 2H), 3.54 (t, *J* = 7.8 Hz, 2H), 3.40 (s, 3H), 2.94 (t, *J* = 7.8 Hz, 2H), 2.39 (s, 3H), 1.67 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 149.6, 144.0, 143.9, 136.3, 135.4, 130.0, 129.8, 127.0, 124.4, 123.5, 123.1, 122.6, 118.8, 116.6, 115.3, 83.6, 48.2, 42.7, 42.5, 28.2, 24.5, 21.5.

IR (neat): 2979, 2930, 1725, 1598, 1452, 1371, 1337, 1308, 1256, 1218, 1183, 1153, 1094, 1013, 985, 953, 909, 855, 814, 767, 729, 703, 687, 656 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{26}H_{32}O_6N_5S_2$ 574.1789 found 574.1792.



5.1s

4-methyl-*N*-(2-(1-methyl-1*H*-pyrrol-2-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.1s**):

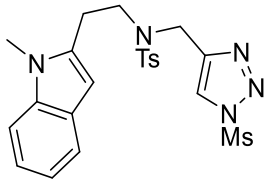
Prepared according to **general procedure C** using **4-methyl-*N*-(2-(1-methyl-1*H*-pyrrol-2-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**ES-5.1s-alkyne**) (316 mg, 1.0 mmol, 1.0 equiv) and MsN_3 (121 mg, 1.0 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a colorless oil (383 mg, 88% yield); R_f = 0.17 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.50 (dd, *J* = 2.4, 1.8 Hz, 1H), 5.99 (dd, *J* = 3.0, 3.0 Hz, 1H), 5.84 (dd, *J* = 3.0, 1.8 Hz, 1H), 4.46 (s, 2H), 3.49 (s, 3H), 3.45 (s, 3H), 3.42 (t, *J* = 7.8 Hz, 2H), 2.82 (t, *J* = 7.8 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.0, 143.8, 136.3, 129.9, 128.7, 127.1, 123.0, 121.8, 107.0, 106.9, 48.2, 42.9, 42.6, 33.6, 26.0, 21.5.

IR (neat): 2926, 1597, 1493, 1377, 1335, 1305, 1226, 1183, 1155, 1090, 1014, 953, 912, 815, 770, 726, 654 $cm^{-1.}$

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{18}H_{23}O_4N_5NaS_2$ 460.1084 found 460.1082.



5.6f

4-methyl-*N*-(2-(1-methyl-1*H*-indol-2-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.6f**):

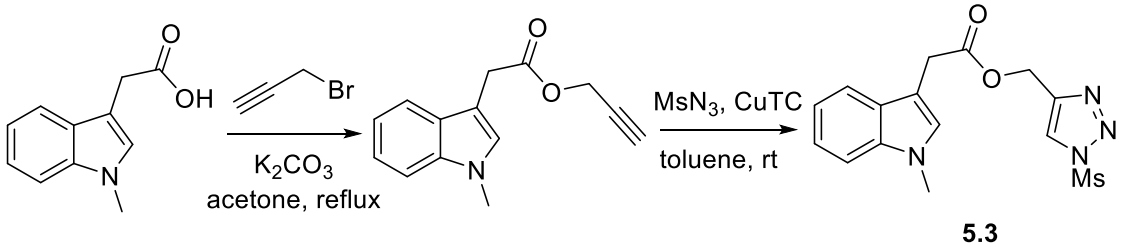
Prepared according to **general procedure C** using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-2-yl)ethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (476 mg, 1.3 mmol, 1.0 equiv) and MsN_3 (157 mg, 1.3 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white foam (589 mg, 93% yield); m.p. 49-51 °C, R_f = 0.11 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.22-7.21 (m, 3H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.23 (s, 1H), 4.48 (s, 2H), 3.60 (s, 3H), 3.56 (t, *J* = 7.8 Hz, 2H), 3.24 (s, 3H), 3.04 (t, *J* = 7.8 Hz, 2H), 2.39 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.0, 143.7, 137.4, 136.6, 136.4, 129.8, 127.7, 127.1, 123.0, 121.0, 120.0, 119.4, 109.0, 100.1, 47.7, 42.7, 42.3, 29.4, 26.4, 21.4.

IR (neat): 3026, 2927, 1597, 1545, 1468, 1378, 1336, 1230, 1184, 1156, 1091, 1014, 954, 771, 751, 735, 684, 654 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{25}O_4N_5NaS_2$ 510.1240 found 510.1241.



5.3

(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl 2-(1-methyl-1*H*-indol-3-yl)acetate (**5.3**):

A mixture of the 2-(1-methyl-1*H*-indol-3-yl)acetic acid (284 mg, 1.5 mmol, 1.0 equiv), propargyl bromide (80% wt. in toluene, 0.20 mL, 1.8 mmol, 1.2 equiv) and K_2CO_3 (414 mg, 3.0 mmol, 2.0 equiv) in 6 mL acetone was refluxed overnight until completion of conversion as judged by TLC analysis. The reaction was then cooled to room temperature, filtered through celite, and concentrated to give 294 mg of the crude alkyne intermediate that was used directly in the next step.

The alkyne intermediate (294 mg, 1.3 mmol) was dissolved in toluene (6 mL) at room temperature. Then CuTC (25 mg, 10 mol %) was added. Following this, a solution of sulfonyl azide (158 mg, 1.3 mmol, 1.0 equiv) in 3 mL toluene was added dropwise. The

reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford **5.3** as a colorless oil (350 mg, 67% yield for two steps); R_f = 0.11 (hexanes: ethyl acetate = 2: 1).

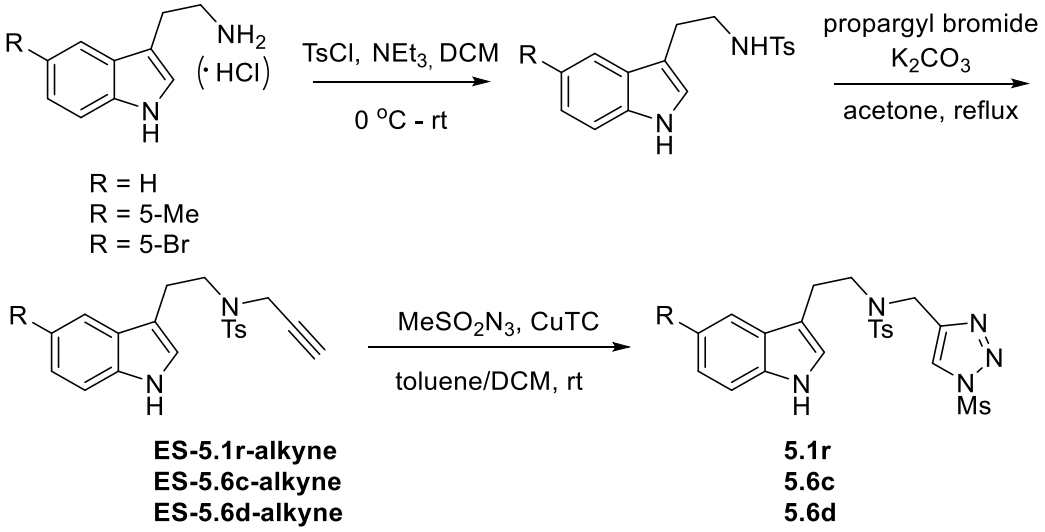
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 7.02 (s, 1H), 5.26 (s, 2H), 3.81 (s, 2H), 3.72 (s, 3H), 3.34(s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 142.9, 136.9, 128.0, 127.5, 123.6, 121.8, 119.2, 118.9, 109.5, 106.1, 57.2, 42.5, 32.7, 31.0.

IR (neat): 3023, 2926, 1737, 1474, 1374, 1331, 1306, 1243, 1182, 1146, 1062, 1016, 993, 953, 770, 743 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{15}H_{16}O_4N_4NaS$ 371.0785 found 371.0786.

General procedure D:



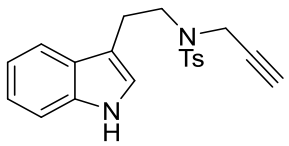
Tryptamine or tryptamine salt (10.5 mmol, 1.05 equiv) was suspended in DCM (25 mL), followed by addition of triethylamine (25.0 or 35.0 mmol, 2.5 or 3.5 equiv). The suspension was cooled to 0 °C, and then TsCl (10.0 mmol, 1.0 equiv) was added in portions. The reaction mixture was stirred overnight at room temperature. Then the reaction mixture was diluted with diethyl ether (100 mL), washed with 1N HCl (3 X 50 mL), and brine (60 mL). The organics were dried over Mg_2SO_4, filtered and concentrated in vacuo to give the crude *N*-Ts-tryptamine product that was used in the next step directly without further purification.

The above obtained *N*-Ts-tryptamine (1.0 mmol or 10.0 mmol, 1 equiv) was dissolved in acetone (3 mL or 30 mL). To the solution were added K_2CO_3 (2.0 equiv) and propargyl bromide (1.2 equiv) at room temperature. The reaction mixture was reflux over night before it was cooled to room temperature. The precipitate was filtered off and the filtrates were concentrated to give the crude product, which was used to the next steps without further purification or purified by column before performing the next step.

CuTc (0.2 mmol, 0.04 equiv) was added into a solution of the obtained alkyne (5.0 mmol, 1.0 equiv) in toluene (10 mL). The reaction mixture was stirred for 3 min at room temperature, followed by addition of MsN3 (6 mmol, 1.2 equiv). The reaction mixture was stirred for 5 h at room temperature and the resulting mixture was directly subjected to a flash column chromatography to afford the desired product as a white solid.

To a solution of the obtained alkyne (1.0 mmol or 2.1 mmol, 1.0 equiv) in toluene and dichloromethane at room temperature was added CuTC (10 mol %). Following this, a solution of MsN_3 (1.0 equiv) in toluene was added dropwise. The reaction was stirred at

room temperature over night, concentrated, and purified by flash column chromatography to afford the corresponding triazoles.



ES-5.1r-alkyne

***N*-(2-(1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (ES-5.1r-alkyne)**:

Prepared according to **general procedure D**. Tryptamine (1.68 g, 10.5 mmol, 1.05 equiv) was suspended in DCM (25 mL), followed by addition of triethylamine (3.5 mL, 25.0 mmol, 2.5 equiv). The suspension was cooled to 0 °C, and then TsCl (1.90 g, 10.0 mmol, 1.0 equiv) was added in portions. The reaction mixture was stirred overnight at room temperature. After general work-up, the crude *N*-Ts-tryptamine product was obtain and used in the next step directly without further purification.

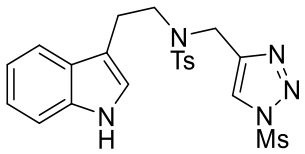
The above obtained *N*-Ts-tryptamine (314 mg, 1.0 mmol, 1 equiv) was dissolved in acetone (3 mL). To this solution were added K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv) and propargyl bromide (80% wt. in toluene, 0.133 mL, 1.2 mmol, 1.2 equiv) at room temperature. The reaction mixture was reflux over night before it was cooled to room temperature. The precipitate was filtered off. The filtrates solution was concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1) to afford a sticky oil (303 mg, 87% yield for two steps); R_f = 0.28 (hexanes: ethyl acetate = 5: 2).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (br s, 1H), 7.75 (d, *J* = 8.4, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 4.21 (d, *J* = 2.4 Hz, 2H), 3.55-3.54 (m, 2H), 3.12-3.09 (m, 2H), 2.41 (s, 3H), 2.13 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.6, 136.3, 135.8, 129.6, 127.7, 127.3, 122.4, 122.0, 119.4, 118.6, 111.9, 111.4, 76.9, 74.0, 47.1, 36.8, 24.3, 21.6.

IR (neat): 3506, 3288, 2921, 1597, 1491, 1423, 1327, 1305, 1185, 1154, 1093, 1010, 990, 907, 813, 727, 657 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{20}N_2O_2NaS$ 375.1134 found 375.1136.



5.1r

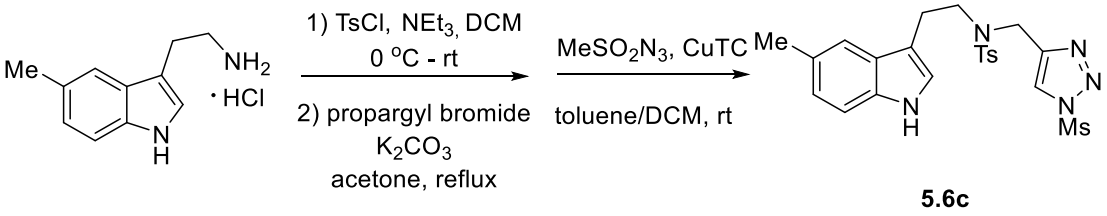
***N*-(2-(1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1r**): Prepared according to general procedure D using ***N*-(2-(1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (352 mg, 1.0 mmol, 1.0 equiv) and MsN_3 (121 mg, 1.0 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a white solid (372 mg, 79% yield); m.p. 122-124 °C, R_f = 0.25 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (br s, 1H), 7.71 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.07-7.04 (m, 2H), 4.49 (s, 2H), 3.55 (t, *J* = 7.8 Hz, 2H), 3.23 (s, 3H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.4, 143.9, 136.1, 136.1, 129.9, 127.1, 127.1, 123.0, 122.3, 122.1, 119.4, 118.5, 111.9, 111.3, 49.1, 43.2, 42.4, 24.7, 21.5.

IR (neat): 3410, 2925, 1597, 1457, 1379, 1335, 1184, 1093, 1014, 955, 912, 816, 771, 744, 656 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{24}O_4N_5S_2$ 474.1264 found 474.1261.



5.6c

4-methyl-*N*-(2-(5-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.6c**):

Prepared according to **general procedure D**. 2-(5-methyl-1*H*-indol-3-yl)ethan-1-amine hydrochloride (2.21 g, 10.5 mmol, 1.05 equiv) was suspended in DCM (25 mL), followed by addition of triethylamine (4.9 mL, 35.0 mmol, 3.5 equiv). The suspension was cooled to 0 °C, and then TsCl (1.90 g, 10.0 mmol, 1.0 equiv) was added in portions. The

reaction mixture was stirred overnight at room temperature. General work-up gave the crude *N*-Ts-tryptamine product that was directly used in the next step.

The above obtained *N*-Ts-tryptamine (*c.a.* 10.0 mmol, 1 equiv) was dissolved in acetone (30 mL). To this solution were added K_2CO_3 (2.76 g, 20.0 mmol, 2.0 equiv) and propargyl bromide (80% wt. in toluene, 1.33 mL, 12.0 mmol, 1.2 equiv) at room temperature. The reaction mixture was reflux over night. The another portion of propargyl bromide (80% wt. in toluene, 0.89 mL) was added. The reaction was stirred at reflux for 6 h before it was cooled to room temperature. The precipitate was filtered off. The filtrates solution was concentrated to give a crude alkyne intermediate that was used directly in the next step.

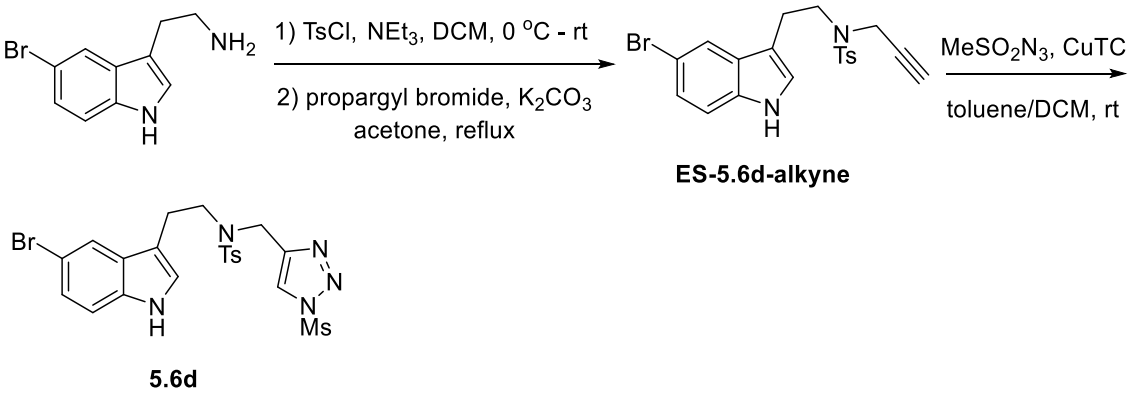
The triazole was prepared according to **general procedure D** using the alkyne obtained from the previous step (770 mg, 2.1 mmol, 1.0 equiv) and MsN_3 (255 mg, 2.1 mmol, 1.0 equiv), and CuTC (40 mg, 0.21 mmol, 10 mol %). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a light yellow foam (660 mg, 59% yield for three steps); m.p. 58-60 °C, R_f = 0.25 (hexanes: ethyl acetate = 3: 2).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 7.72 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.21 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.50 (s, 2H), 3.52 (t, *J* = 7.2 Hz, 2H), 3.24(s, 3H), 2.95 (t, *J* = 7.2 Hz, 2H), 2.40 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 144.4, 143.9, 136.1, 134.4, 129.8, 128.7, 127.3, 127.2, 123.7, 123.0, 122.4, 118.1, 111.4, 110.9, 49.0, 43.1, 42.3, 24.6, 21.5, 21.4.

IR (neat): 3405, 2925, 1731, 1597, 1376, 1333, 1305, 1232, 1184, 1156, 1092, 1046, 955, 800, 771, 655 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}O_4N_5S_2$ 488.1421 found 488.1426.



***N*-(2-(5-bromo-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (**ES-5.6d-alkyne**):

Prepared according to **general procedure D**. 2-(5-bromo-1*H*-indol-3-yl)ethan-1-amine (1.00 g, 4.18 mmol, 1.05 equiv) was suspended in DCM (25 mL), followed by addition of triethylamine (1.4 mL, 10.0 mmol, 2.5 equiv). The suspension was cooled to 0 °C, and then TsCl (0.76 g, 3.98 mmol, 1.0 equiv) was added in portions. The reaction mixture was stirred overnight at room temperature. After general work-up, the crude *N*-Ts-tryptamine product was obtain and used in the next step directly without further purification.

The above obtained *N*-Ts-tryptamine (*c.a.* 3.98 mmol, 1 equiv) was dissolved in acetone (20 mL). To this solution were added K_2CO_3 (1.10 g, 7.96 mmol, 2.0 equiv) and propargyl bromide (80% wt. in toluene, 0.89 mL, 7.96 mmol, 2.0 equiv) at room

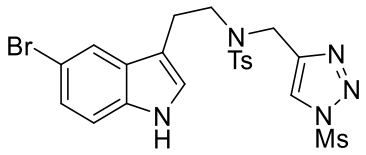
temperature. The reaction mixture was reflux over night before it was cooled to room temperature. The precipitate was filtered off. The filtrates solution was concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 5: 1 to 5: 2) to afford a sticky yellow solid (1.09 g, 64% yield for two steps); R_f = 0.12 (hexanes: ethyl acetate = 4: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (br s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.67-7.67 (m, 1H), 7.26-7.18 (m, 4H), 7.06 (d, *J* = 2.4 Hz, 1H), 4.15 (d, *J* = 2.4 Hz, 2H), 3.49-3.45 (m, 2H), 3.00-2.96 (m, 2H), 2.39 (s, 3H), 2.11 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 135.5, 134.8, 129.6, 129.0, 127.6, 124.8, 123.6, 121.1, 112.8, 112.6, 111.7, 76.7, 74.1, 46.7, 36.7, 23.9, 21.6.

IR (neat): 3409, 3291, 2922, 1597, 1459, 1327, 1230, 1156, 1096, 1062, 909, 883, 813, 797, 734, 663 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{20}H_{19}O_2N_2BrNaS$ 453.0243 found 453.0242.



5.6d

***N*-(2-(5-bromo-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.6d**):

Prepared according to **general procedure D** using ***N*-(2-(5-bromo-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (862 mg, 2.0 mmol, 1.0

equiv) and MsN_3 (242 mg, 2.0 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white foam (661 mg, 60% yield); m.p. 73-75 °C, R_f = 0.20 (hexanes: ethyl acetate = 2: 1).

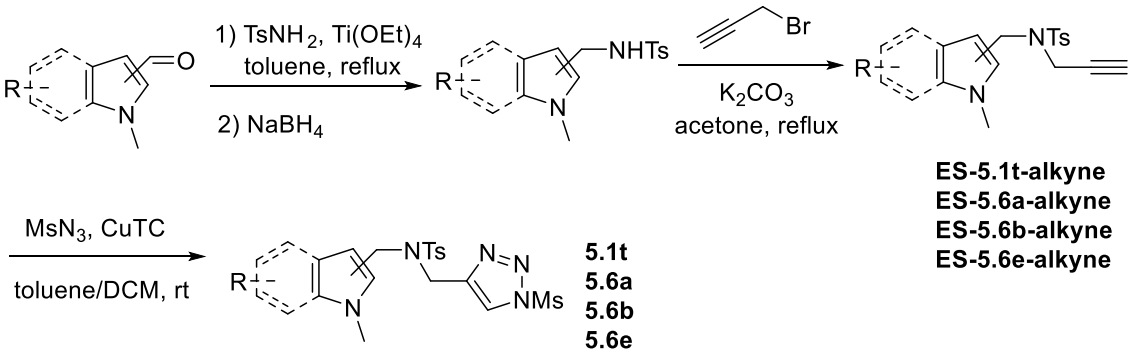
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (br s, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.51 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.19-7.19 (m, 2H), 7.03 (d, *J* = 2.4 Hz, 1H), 4.50 (s, 2H), 3.50 (t, *J* = 7.2 Hz, 2H), 3.32(s, 3H), 2.92 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 144.1, 135.8, 134.7, 129.9, 128.9, 127.1, 124.8, 123.7, 123.0, 121.0, 112.9, 112.6, 111.5, 48.8, 42.9, 42.5, 24.3, 21.6.

IR (neat): 3411, 3144, 2926, 1728, 1597, 1456, 1376, 1329, 1305, 1249, 1229, 1182, 1154, 1091, 1014, 984, 953, 912, 882, 798, 769, 731, 658 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{23}O_4N_5BrS_2$ 552.0375 found 552.0376.

General procedure E:

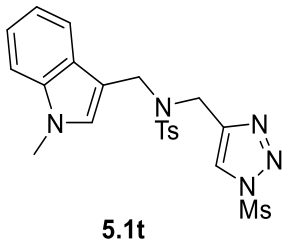


The first two steps were adapted from a known procedure.[23] To a solution of the aldehyde (1.0 equiv) in toluene (0.25 M) were added tosyl amide (1.5 equiv) and $Ti(OEt)_4$ (2.0 equiv). The mixture was refluxed for 4 h before it was cooled to room temperature. After removal of the solvent, the residue was dissolved in MeOH/THF (1/1 v/v, 0.2 M). Then $NaBH_4$ (4.0 equiv) was slowly added at 0 ℃. After 4 h stirring at room temperature, water was slowly added at 0 ℃. The mixture was dried over $MgSO_4$, and concentrated under reduced pressure to give crude product. This crude sulfonamide was used directly in the next step without purification.

A mixture of the sulfonamide obtained from previous step (1.0 equiv), propargyl bromide (2.0 equiv) and K_2CO_3 (2.0 equiv) in acetone (0.2 M) was refluxed overnight until completion of conversion as judged by TLC analysis. The reaction was then cooled to room temperature, filtered through Celite®, and concentrated to give the crude alkylation product that was purified by column chromatography (hexanes: ethyl acetate).

The material obtained from the previous step (1.0 equiv) was dissolved in toluene (0.25 M) and dichloromethane (0.25 M) at room temperature. Then CuTC (10 mol %) was added. Following this, a solution of sulfonyl azide (1.00-1.05 equiv) was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate) to afford the triazole products.

[23] Bandini, M.; Gualandi, A.; Monari, M.; Romaniello, A.; Savoia, D.; Tragni, M. *J. Organomet. Chem.* **2011**, *696*, 338.



5.1t

4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.1t**):

Prepared according to **general procedure E**: To a solution of 1-methyl-1*H*-indole-3-carbaldehyde (3.18 g, 20.0 mmol, 1.0 equiv) in toluene (40 mL) were added tosyl amide (5.13 g, 30.0 mmol, 1.5 equiv) and $Ti(OEt)_4$ (9.12 g, 40.0 mmol, 2.0 equiv). The mixture was refluxed for 4 h before it was cooled to room temperature. After removal of the solvent, the residue was dissolved in MeOH/THF (25mL/25mL). Then $NaBH_4$ (3.04, 80 mmol, 4.0 equiv) was slowly added at 0 ℃. After 4 h stirring at room temperature followd by general work up, the residue was purified by column chromatography (hexanes: ethyl acetate = 2: 1 to 1: 1) to give a crude sulfonamide that was contaminated by tosyl amide (6.45 g). This material was used in the next step without further attempts of purification.

A mixture of the sulfonamide obtained from previous step (1.57 g), propargyl bromide (80% wt. in toluene, 1.1 mL) and K_2CO_3 (1.38 g) in acetone (20 mL) was refluxed overnight before it was cooled to room temperature, filtered through Celite®, and concentrated. The residue was purified by column chromatography (hexanes: ethyl acetate = 15: 2 to 15: 3), followed by recrystallization from hexanes/dichloromethane (20/1 (v/v)) to afford 4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (800 mg).

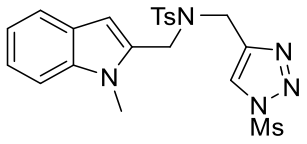
The alkyne obtained from the previous step (0.80 g, 2.3 mmol) was dissolved in toluene (9 mL) and dichloromethane (9 mL) at room temperature. Then CuTC (43 mg, 10 mol %) was added. Following this, a solution of MsN_3 (289 mg, 2.4 mmol, 1.05 equiv) in toluene (5 mL) was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white solid (1.01 g, 92% yield); m.p. 127-129 °C, R_f = 0.12 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.23-7.15 (m, 2H), 7.09-7.05 (m, 1H), 6.99 (s, 1H), 4.57 (s, 2H), 4.40 (s, 2H), 3.69 (s, 3H), 3.13 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 143.8, 137.1, 136.3, 129.9, 129.7, 127.2, 127.1, 122.7, 122.0, 119.6, 119.4, 109.3, 107.9, 44.1, 42.4, 41.7, 32.8, 21.5.

IR (neat): 2926, 1474, 1377, 1330, 1305, 1220, 1183, 1156, 1091, 1060, 1012, 953, 903, 816, 770, 738, 676 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{24}O_4N_5S_2$ 474.1264 found 474.1278.



5.6e

4-methyl-*N*-((1-methyl-1*H*-indol-2-yl)methyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.6e**):

Prepared according to **general procedure E**: To a solution of 1-methyl-1*H*-indole-2-carbaldehyde (397 mg, 2.50 mmol, 1.0 equiv) in toluene (10 mL) were added tosyl amide (641 mg, 3.75 mmol, 1.5 equiv) and $Ti(OEt)_4$ (1.14 g, 5.0 mmol, 2.0 equiv). The mixture was refluxed for 4 h before it was cooled to room temperature. After removal of the solvent, the residue was dissolved in MeOH/THF (25mL/25mL). Then $NaBH_4$ (380 mg, 10.0 mmol, 4.0 equiv) was slowly added at 0 ℃. After 4 h stirring at room temperature followed by general work up, the residue was purified by column chromatography (hexanes: ethyl acetate = 2: 1 to 1: 1) to give **4-methyl-*N*-((1-methyl-1*H*-indol-2-yl)methyl)benzenesulfonamide** (471 mg, 60%).

A mixture of the sulfonamide obtained from previous step (471 mg, 1.5 mmol, 1.0 equiv), propargyl bromide (80% wt. in toluene, 0.33 mL, 2.0 equiv) and K_2CO_3 (414 mg, 3.0 mmol, 2.0 equiv) in acetone (10 mL) was refluxed overnight before it was cooled to room temperature, filtered through Celite®, and concentrated. The residue (c.a. 528 mg, 1.5 mmol, 1.0 equiv) was dissolved in toluene (5 mL) and dichloromethane (5 mL) at room temperature. Then CuTC (28.5 mg, 10 mol %) was added. Following this, a solution of MsN_3 (182 mg, 1.5 mmol, 1.0 equiv) in toluene (3 mL) was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white solid (500 mg, 71% yield for two steps); m.p. 160-162°C (decomposed), R_f = 0.25 (hexanes: ethyl acetate = 2: 1).

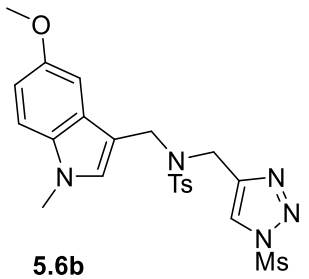
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.01 (t, *J*

= 8.0 Hz, 1H), 6.34 (s, 1H), 4.60 (s, 2H), 4.40 (s, 2H), 3.80 (s, 3H), 2.80 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 143.3, 138.0, 135.0, 132.3, 130.0, 127.3, 126.8, 122.2, 121.6, 120.7, 119.7, 109.3, 104.3, 45.8, 42.7, 41.8, 30.0, 21.6.

IR (neat): 2927, 1732, 1597, 1469, 1469, 1374, 1335, 1307, 1244, 1183, 1158, 1090, 1046, 1011, 952, 910, 894, 815, 770, 749, 710, 695, 656 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{24}O_4N_5S_2$ 474.1264 found 474.1265.



5.6b

***N*-((5-methoxy-1-methyl-1*H*-indol-3-yl)methyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.6b**):

Prepared according to **general procedure E**: To a solution of 5-methoxy-1-methyl-1*H*-indole-3-carbaldehyde (1.00 g, 5.29 mmol, 1.0 equiv) in toluene (20 mL) were added tosyl amide (1.35 g, 7.93 mmol, 1.5 equiv) and $Ti(OEt)_4$ (2.40 g, 10.57 mmol, 2.0 equiv). The mixture refluxed for 4 h before it was cooled to room temperature. After removal of the solvent, the residue was dissolved in MeOH (15 mL) and THF (15 mL), and $NaBH_4$ (0.81 g, 21.16 mmol, 4.0 equiv) was slowly added at 0 °C. After 4 h stirring at room temperature, general work-up afforded a crude material. This crude material was dissolved

in acetone (30 mL), and then propargyl bromide (80% wt. in toluene, 1.18 mL, 10.58 mmol, 2.0 equiv) and K_2CO_3 (2.19 g, 15.87 mmol, 3.0 equiv) were added. The reaction was refluxed overnight before it was cooled to room temperature, filtered through Celite®, and concentrated. The residue was purified by column chromatography (hexanes: ethyl acetate = 3: 1) to afford ***N*-((5-methoxy-1-methyl-1*H*-indol-3-yl)methyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide** (927 mg, 46% for two steps).

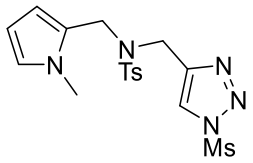
The alkyne obtained from the previous step (458 mg, 1.2 mmol, 1.0 equiv) was dissolved in toluene (5 mL) and dichloromethane (5 mL) at room temperature. Then CuTC (23 mg, 10 mol %) was added. Following this, a solution of MsN_3 (145 mg, 1.2 mmol, 1.0 equiv) in toluene (3 mL) was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white solid (530 mg, 88% yield); m.p. 149-151 °C (decomposed), R_f = 0.25 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.60 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.10-7.08 (m, 2H), 6.93 (s, 1H), 6.81 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.53 (s, 2H), 4.02 (s, 2H), 3.81 (s, 3H), 3.65(s, 3H), 3.20 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 154.1, 144.3, 143.8, 136.5, 132.3, 130.1, 129.8, 127.5, 127.2, 122.8, 112.6, 110.1, 107.3, 100.6, 55.8, 44.1, 42.3, 41.6, 32.9, 21.5.

IR (neat): 3008, 2927, 1622, 1597, 1579, 1550, 1492, 1455, 1426, 1376, 1330, 1305, 1265, 1225, 1182, 1155, 1090, 1059, 1012, 953, 894, 802, 769, 737, 667cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{25}O_5N_5NaS_2$ 526.1189 found 526.1192.



5.6a

4-methyl-*N*-((1-methyl-1*H*-pyrrol-2-yl)methyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (**5.6a**):

Prepared according to **general procedure E**:

To a solution of 1-methyl-1*H*-pyrrole-2-carbaldehyde (872 mg, 8.0 mmol, 1.0 equiv) in toluene (16 mL) were added tosyl amide (2.05 g, 12.0 mmol, 1.5 equiv) and $Ti(OEt)_4$ (3.65 g, 16.0 mmol, 2.0 equiv). The mixture refluxed for 6 h before it was cooled to room temperature. After removal of the solvent, the residue was dissolved in MeOH (10 mL) and THF (10 mL), and $NaBH_4$ (1.22 g, 32.0 mmol, 4.0 equiv) was slowly added at 0 ℃. After stirred at room temperature over night, general work-up followed by purified by flash column chromatography (silica gel, hexanes: ethyl acetate: dichloromethane = 3: 1: 0 to 3: 1: 1) afforded 4-methyl-N-((1-methyl-1*H*-pyrrol-2-yl)methyl)benzenesulfonamide (1.8 g, 85%). This material (792 mg, 3.0 mmol, 1.0 equiv) was dissolved in acetone (15 mL), and then propargyl bromide (80% wt. in toluene, 0.66 mL, 6.0 mmol, 2.0 equiv) and K_2CO_3 (828 mg, 6.0 mmol, 2.0 equiv) were added. The reaction was refluxed overnight before it was then cooled to room temperature, filtered through Celite®, and concentrated. The residue (*c.a.* 453 mg, 1.5 mmol) was dissolved in toluene (6 mL) and dichloromethane (6 mL) at room temperature. Then CuTC (29 mg, 10 mol %) was added. Following this, a solution of MsN_3 (182 mg, 1.5 mmol, 1.0 equiv) in toluene (3 mL) was added dropwise. The reaction was stirred at room temperature over night, concentrated, and purified by flash

column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a white solid (551 mg, 87% yield for two steps); m.p. 137-139 °C, R_f = 0.15 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.31 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.55 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.01 (dd, *J* = 3.6, 1.8 Hz, 1H), 5.93 (dd, *J* = 3.6, 2.4 Hz, 1H), 4.39 (s, 2H), 4.33 (s, 2H), 3.59 (s, 3H), 3.40 (s, 3H), 2.42 (s, 3H).

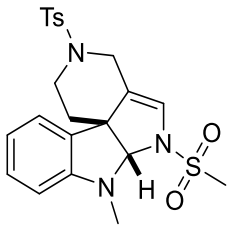
^{13}C NMR (150 MHz, $CDCl_3$): δ 144.1, 143.7, 135.5, 129.9, 127.2, 124.7, 123.9, 121.9, 111.6, 107.1, 44.9, 42.5, 41.5, 33.9, 21.5.

IR (neat): 2928, 1597, 1495, 1376, 1332, 1302, 1267, 1231, 1182, 1156, 1090, 1054, 1011, 951, 891, 814, 769, 726, 679, 653 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{17}H_{21}O_4N_5NaS_2$ 446.0927 found 446.0933.

General Procedure F for formal [3+2] cyclization of triazole (Table 5.2 and 5.3)

To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, triazole (0.10 mmol) and the Rh_2(*S*-PTTL)$_4$ (0.001 mmol) were added together under ambient atmosphere followed by 2.0 mL of ethyl acetate. The homogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was stirred at 80 °C for 4-8 hours until the triazole was completely consumed as judged by TLC analysis. The reaction mixture was then cooled to room temperature, concentrated for ^{1}H NMR analysis of crude mixture, and purified by flash silica chromatography (hexanes: ethyl acetate) to afford the cyclization products as white solids or foams.



5.2a

7-methyl-6-(methylsulfonyl)-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2a**):

Prepared according to **General Procedure F** using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1a**) (49 mg, 0.1 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white solid (40 mg, 87% yield); m.p. 195-197 °C, R_f = 0.28 (hexanes: ethyl acetate = 2: 1).

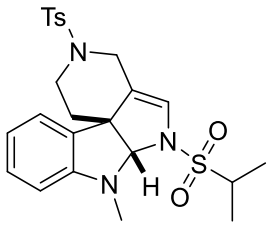
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.53 (t, *J* = 7.6 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.23 (d, *J* = 1.6 Hz, 1H), 5.38 (s, 1H), 4.37 (d, *J* = 13.2 Hz, 1H), 3.89-3.84 (m, 1H), 3.51 (dd, *J* = 13.2, 1.6 Hz, 1H), 3.25 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1H), 3.03 (s, 3H), 2.92 (s, 3H), 2.48 (s, 3H), 2.03 (ddd, *J* = 12.8, 3.2, 3.2 Hz, 1H), 1.94 (ddd, *J* = 12.8, 12.8, 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 144.1, 133.6, 130.1, 130.0, 129.1, 127.7, 125.1, 122.9, 120.1, 117.8, 107.4, 92.9, 57.3, 42.6, 42.6, 38.8, 36.9, 33.4, 21.6.

IR (neat): 2925, 1601, 1492, 1342, 1304, 1155, 1099, 999, 953, 906, 816, 725, 675 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}O_4N_3S_2$ 460.1359 found 460.1352.

HPLC: OD-R column, 1 mL/min, 15 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 49.62 min, Minor: 38.66 min, 31% ee.



5.2b

6-(isopropylsulfonyl)-7-methyl-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2b**):

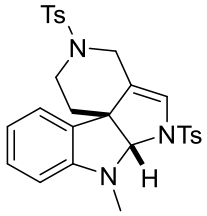
Prepared according to **General Procedure F** using ***N*-((1-(isopropylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-methyl-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)benzenesulfonamide** (**5.1b**) (103 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 4: 1) to afford a yellow foam (83 mg, 85% yield); m.p. 130-132 °C, R_f = 0.39 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.56 (t, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 6.19 (s, 1H), 5.53 (s, 1H), 4.36 (d, *J* = 13.2 Hz, 1H), 3.81 (ddd, *J* = 13.2, 4.0, 4.0 Hz, 1H), 3.53 (d, *J* = 13.2 Hz, 1H), 3.27-3.19 (m, 2H), 3.04 (s, 3H), 2.47 (s, 3H), 1.93-1.90 (m, 2H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 144.0, 133.8, 131.1, 129.9, 128.9, 127.7, 126.0, 122.9, 118.2, 116.2, 108.0, 93.6, 56.9, 55.5, 42.9, 42.4, 36.5, 34.9, 21.6, 16.6, 16.3.

IR (neat): 2924, 1720, 1678, 1600, 1491, 1466, 1336, 1305, 1268, 1162, 1143, 1100, 1003, 909, 817, 737, 696, 674 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{30}O_4N_3S_2$ 488.1672 found 488.1673.



5.2c

7-methyl-3,6-ditosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2c**):

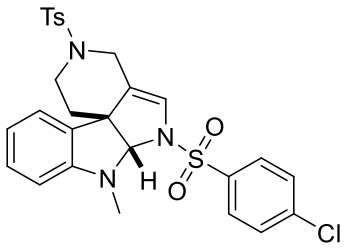
Prepared according to **General Procedure F** using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1c**) (113 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white solid (88 mg, 82% yield); m.p. 137-139 °C, R_f = 0.41 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 4H), 7.06 (td, *J* = 8.0, 0.8 Hz, 1H), 6.63 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.41-6.38 (m, 2H), 6.34 (s, 1H), 5.07 (s, 1H), 4.25 (d, *J* = 12.8 Hz, 1H), 3.46 (ddd, *J* = 12.8, 4.0, 4.0 Hz, 1H), 3.32 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.02 (s, 3H), 3.00 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1H), 2.48 (s, 3H), 2.47 (s, 3H), 1.74 (ddd, *J* = 12.8, 3.2, 3.2 Hz, 1H), 0.88 (ddd, *J* = 12.4, 12.4, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 144.6, 143.9, 133.5, 133.2, 130.0, 129.9, 129.4, 128.9, 127.6, 127.5, 126.0, 122.8, 122.5, 117.0, 106.2, 92.1, 57.1, 42.4, 42.4, 36.5, 31.9, 21.7, 21.6.

IR (neat): 2921, 1600, 1492, 1432, 1349, 1305, 1185, 1162, 1120, 1088, 1006, 947, 909, 815, 732, 707, 670, 654 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{30}O_4N_3S_2$ 536.1672 found 536.1669.



5.2d

6-((4-chlorophenyl)sulfonyl)-7-methyl-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2d**):

Prepared according to **General Procedure F** using ***N*-((1-((4-chlorophenyl)sulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)-4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide** (**5.1d**) (117 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 4: 1) to afford a white foam (89 mg, 80% yield); m.p. 104-106 °C, R_f = 0.48 (hexanes: ethyl acetate = 2: 1).

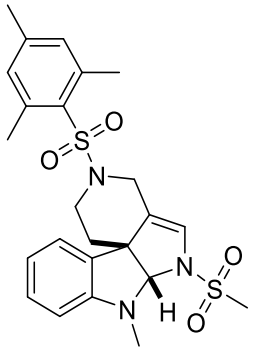
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.44 (t, *J* = 7.6 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 6.34 (s, 1H), 5.09 (s, 1H), 4.28 (d, *J* =

12.8 Hz, 1H), 3.52 (ddd, *J* = 12.8, 4.0, 4.0 Hz, 1H), 3.38 (dd, *J* = 12.8, 1.2 Hz, 1H), 3.06 (ddd, *J* = 12.8, 12.4, 3.2 Hz, 1H), 3.01 (s, 3H), 2.48 (s, 3H), 1.79 (ddd, *J* = 12.8, 3.2, 3.2 Hz, 1H), 1.00 (ddd, *J* = 12.8, 12.4, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 144.0, 140.1, 135.4, 133.4, 129.9, 129.7, 129.4, 129.0, 128.9, 127.5, 125.5, 122.9, 122.7, 117.3, 106.5, 92.3, 57.3, 42.4, 42.4, 36.7, 32.3, 21.6.

IR (neat): 3092, 2922, 1676, 1602, 1492, 1477, 1394, 1350, 1304, 1267, 1163, 1090, 1042, 1007, 947, 908, 817, 753, 734, 677 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{27}H_{27}O_4N_3ClS_2$ 556.1126 found 556.1128.



5.2e

3-(mesitylsulfonyl)-7-methyl-6-(methylsulfonyl)-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2e**):

Prepared according to **General Procedure F** using **2,4,6-trimethyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-**

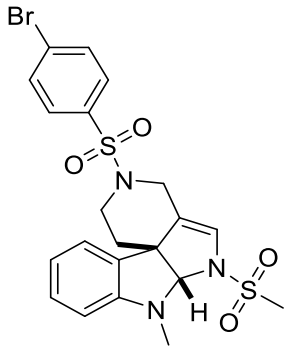
yl)methyl)benzenesulfonamide (**5.1e**) (103 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 4: 1) to afford a light yellow oil (84 mg, 86% yield); R_f = 0.41 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.96 (s, 2H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 6.23 (s, 1H), 5.42 (s, 1H), 4.22 (d, *J* = 14.0 Hz, 1H), 3.84 (dd, *J* = 14.0, 1.6 Hz, 1H), 3.74–3.60 (m, 2H), 3.04 (s, 3H), 2.98 (s, 3H), 2.61 (s, 6H), 2.31 (s, 3H), 2.06-2.03 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 143.0, 140.4, 132.1, 131.4, 130.2, 129.1, 124.7, 123.1, 121.5, 117.9, 107.2, 92.9, 58.0, 41.5, 41.0, 38.7, 37.283, 33.0, 22.8, 21.0.

IR (neat): 2936, 1676, 1603, 1493, 1343, 1318, 1215, 1150, 1099, 1055, 981, 904, 855, 728, 711, 684 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{30}O_4N_3S_2$ 488.1672 found 488.1671.



5.2f

3-((4-bromophenyl)sulfonyl)-7-methyl-6-(methylsulfonyl)-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2f**):

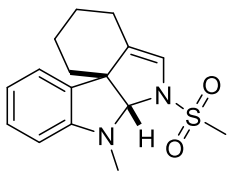
Prepared according to **General Procedure F** using **4-bromo-*N*-(2-(1-methyl-1H-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1f**) (110.4 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 5: 2) to afford a white solid (98 mg, 93% yield); m.p. 198-201 °C (decomposition), R_f = 0.25 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.14 (td, *J* = 7.8, 1.2 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.58 (t, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 6.26 (d, *J* = 1.6 Hz, 1H), 5.41 (s, 1H), 4.39 (d, *J* = 13.2 Hz, 1H), 3.90-3.84 (m, 1H), 3.55 (dd, *J* = 13.2, 1.6 Hz, 1H), 3.29 (ddd, *J* = 13.2, 12.8, 3.2 Hz, 1H), 3.04 (s, 3H), 2.94 (s, 3H), 2.05 (ddd, *J* = 13.2, 3.2, 2.8 Hz, 1H), 1.95 (ddd, *J* = 12.8, 12.8, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 136.0, 132.7, 130.0, 129.2, 129.1, 128.3, 125.3, 122.8, 119.6, 117.9, 107.5, 92.9, 57.3, 42.7, 42.6, 39.0, 36.9, 33.5.

IR (neat): 2928, 1603, 1574, 1492, 1346, 1304, 1222, 1159, 1100, 954, 909, 825, 748 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{23}O_4N_3BrS_2$ 524.0308 found 524.0313.



5.2g

7-methyl-6-(methylsulfonyl)-2,3,4,6,6a,7-hexahydro-1*H*-isoindolo[1,7a-*b*]indole (**5.2g**):

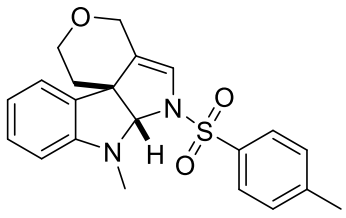
Prepared according to **General Procedure F** using **1-methyl-3-(4-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)butyl)-1*H*-indole** (**5.1g**) (66.4 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl ether = 2: 1 to 1: 1) to afford a white solid (46 mg, 76% yield); m.p. 162-164 °C, R_f = 0.36 (hexanes: ethyl ether = 1: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.15 (td, *J* = 7.6, 1.2 Hz, 1H), 6.67 (td, *J* = 7.6, 1.2 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 5.98 (d, *J* = 1.6 Hz, 1H), 5.34 (s, 1H), 3.04 (s, 3H), 2.92 (s, 3H), 2.43–2.30 (m, 2H), 2.19 – 2.06 (m, 3H), 1.85-1.78 (m, 1H), 1.59 (td, *J* = 13.2, 4.4 Hz, 1H), 1.53 – 1.45 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 131.7, 129.8, 128.5, 123.7, 120.5, 117.4, 106.6, 92.9, 59.8, 38.6, 37.6, 33.0, 28.0, 23.5, 22.1.

IR (neat): 2932, 1602, 1493, 1445, 1431, 1342, 1303, 1236, 1159, 1069, 986, 950, 884, 831, 747 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{21}O_2N_2S$ 305.1318 found 305.1314.



5.2h

7-methyl-6-tosyl-1,2,4,6,6a,7-hexahydropyrano[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2h**):

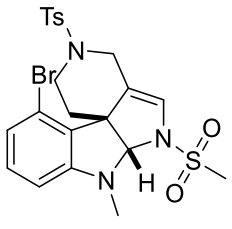
Prepared according to **General Procedure F** using **1-methyl-3-(2-((1-tosyl-1*H*-1,2,3-triazol-4-yl)methoxy)ethyl)-1*H*-indole** (**5.1h**) (205 mg, 0.5 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1) to afford a white solid (59 mg, 31% yield); m.p. 189-190°C, R_f = 0.38 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.13 (td, *J* = 7.6, 0.8 Hz, 1H), 6.63 (td, *J* = 7.6, 0.8 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 6.31 (s, 1H), 5.13 (s, 1H), 4.32–4.23 (m, 2H), 4.06 (ddd, *J* = 12.4, 12.4, 2.8 Hz, 1H), 3.68 (ddd, *J* = 12.4, 5.2, 2.4 Hz, 1H), 3.06 (s, 3H), 2.44 (s, 3H), 1.73 (ddd, *J* = 12.8, 2.8, 2.4 Hz, 1H), 1.08 (ddd, *J* = 12.4, 12.4, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 144.2, 134.0, 130.5, 129.8, 128.8, 127.6, 125.4, 124.7, 123.3, 117.3, 106.2, 92.6, 63.9, 62.4, 57.4, 39.2, 32.1, 21.6.

IR (neat): 2927, 1675, 1601, 1493, 1386, 1351, 1304, 1210, 1164, 1088, 1062, 1010, 937, 815, 738, 667 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd. for $C_{21}H_{22}O_3N_2S$ 382.1346 found 382.1341.



5.2i

11-bromo-7-methyl-6-(methylsulfonyl)-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2i**):

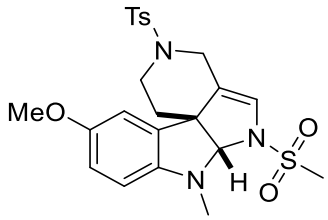
Prepared according to **General Procedure F** using ***N*-(2-(4-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1i**) (113 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white foam (79 mg, 73% yield); R_f = 0.40 (hexanes: ethyl acetate = 1: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 5.40 (s, 1H), 4.58 (dd, *J* = 12.8, 2.0 Hz, 1H), 4.18 (d, *J* = 12.8 Hz, 1H), 3.77 (ddd, *J* = 12.4, 8.0, 4.0 Hz, 1H), 3.35 (ddd, *J* = 12.4, 8.0, 4.0 Hz, 1H), 3.06 (s, 3H), 2.86 (s, 3H), 2.43 (s, 3H), 2.28 (ddd, *J* = 14.4, 8.0, 4.0 Hz, 1H), 1.86 (ddd, *J* = 14.4, 8.0, 4.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 143.8, 134.2, 130.6, 130.5, 130.2, 129.8, 127.6, 124.2, 117.4, 115.4, 106.7, 97.4, 58.7, 44.6, 41.9, 40.5, 35.6, 34.8, 21.6.

IR (neat): 2925, 1596, 1570, 1467, 1427, 1341, 1291, 1233, 1157, 1089, 1040, 958, 911, 817, 769, 733, 671 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}O_4N_3BrS_2$ 538.0464 found 538.0460.



5.2j

10-methoxy-7-methyl-6-(methylsulfonyl)-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2j**):

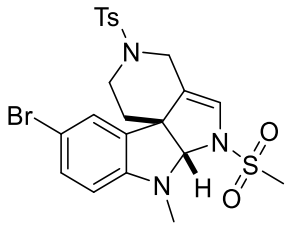
Prepared according to **General Procedure F** using ***N*-(2-(5-methoxy-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (5.1j)** (103 mg, 0.2 mmol, 1.0 equiv). The solids that crushed out was filtered, washed with hexanes, and dried to afford a white solid (90 mg, 92% yield); m.p. 190-192 °C, R_f = 0.20 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.68 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.44 (s, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.24 (s, 1H), 5.34 (s, 1H), 4.36 (d, *J* = 13.2 Hz, 1H), 3.85 (d, *J* = 13.2 Hz, 1H), 3.55 (s, 3H), 3.47 (d, *J* = 13.2 Hz, 1H), 3.18 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 2.99 (s, 3H), 2.93 (s, 3H), 2.46 (s, 3H), 2.03 (d, *J* = 13.2 Hz, 1H), 1.95 (ddd, *J* = 12.8, 12.8, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 144.1, 144.0, 133.3, 131.6, 129.9, 127.7, 125.2, 118.8, 113.3, 110.6, 108.5, 94.0, 57.3, 55.7, 42.7, 42.6, 39.4, 36.8, 35.2, 21.6.

IR (neat): 2923, 1595, 1494, 1430, 1346, 1288, 1215, 1158, 1093, 993, 978, 949, 823, 749, 677, 656 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd. for $C_{23}H_{27}O_5N_3S_2$ 489.1387 found 489.1372.



5.2k

10-bromo-7-methyl-6-(methylsulfonyl)-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2k**):

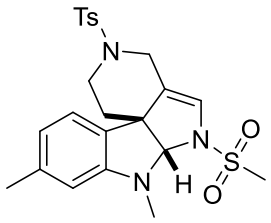
Prepared according to **General Procedure F** using ***N*-(2-(5-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1k**) (113 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white solid (96 mg, 89% yield); m.p. 207-209 °C (decomposition), R_f = 0.23 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.18 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.72 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 8.4 Hz, 1H), 6.25 (d, *J* = 1.6 Hz, 1H), 5.36 (s, 1H), 4.36 (d, *J* = 13.2 Hz, 1H), 3.88-3.83 (m, 1H), 3.38 (dd, *J* = 13.2, 2.0 Hz, 1H), 3.11 (ddd, *J* = 13.2, 3.6 Hz, 1H), 2.98 (s, 3H), 2.93 (s, 3H), 2.47 (s, 3H), 2.02 (ddd, *J* = 12.8, 3.2, 3.2 Hz, 1H), 1.95 (ddd, *J* = 12.8, 12.8, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 144.5, 132.5, 131.8, 131.6, 130.0, 127.7, 126.0, 125.4, 119.8, 108.9, 108.3, 92.4, 57.1, 42.4, 42.4, 38.5, 36.4, 33.0, 21.7.

IR (neat): 2925, 1678, 1597, 1492, 1344, 1277, 1157, 1098, 998, 980, 956, 907, 816, 789, 766, 735, 681, 655 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd. for $C_{22}H_{24}O_4N_3BrS_2$ 537.0386 found 537.0391.



5.2l

7,9-dimethyl-6-(methylsulfonyl)-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2l**):

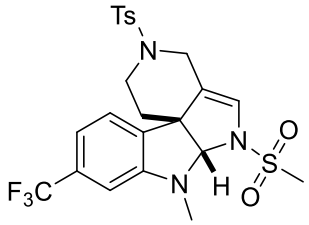
Prepared according to **General Procedure F** using ***N*-(2-(1,6-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1l**) (100 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white foam (85 mg, 90% yield); m.p. 93-95°C, R_f = 0.25 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 6.31 (s, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 5.37 (s, 1H), 4.36 (d, *J* = 13.2 Hz, 1H), 3.86 (ddd, *J* = 13.2, 3.6, 3.6 Hz, 1H), 3.48 (dd, *J* = 13.2, 2.0 Hz, 1H), 3.23 (ddd, *J* = 12.8, 12.8, 3.6 Hz, 1H), 3.01 (s, 3H), 2.91 (s, 3H), 2.47 (s, 3H), 2.24 (s, 3H), 2.00 (ddd, *J* = 12.8, 3.2, 3.2 Hz, 1H), 1.92 (ddd, *J* = 12.8, 12.4, 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 144.1, 139.3, 133.6, 129.9, 127.7, 127.4, 124.8, 122.6, 120.3, 118.4, 108.3, 93.1, 57.1, 42.6, 42.6, 38.7, 36.9, 33.3, 21.6, 21.6.

IR (neat): 2922, 1612, 1497, 1342, 1217, 1156, 1095, 999, 956, 914, 865, 816, 800, 751, 734, 666 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd. for $C_{23}H_{27}O_4N_3S_2$ 473.1438 found 473.1423.



5.2m

7-methyl-6-(methylsulfonyl)-3-tosyl-9-(trifluoromethyl)-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2m**):

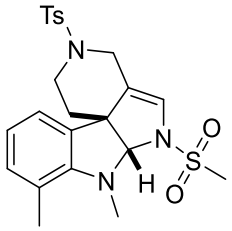
Prepared according to **General Procedure F** using **4-methyl-*N*-(2-(1-methyl-6-(trifluoromethyl)-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1m**) (111mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 4: 1 to 2: 1) to afford a white powder (81 mg, 77% yield); m.p. 212-214°C (decomposition), R_f = 0.25 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.77 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.62 (d, *J* = 1.6 Hz, 1H), 6.27 (d, *J* = 1.6 Hz, 1H), 5.45 (s, 1H), 4.39 (d, *J* = 13.6 Hz, 1H), 3.88 (ddd, *J* = 13.6, 3.2, 3.2 Hz, 1H), 3.47 (dd, *J* = 13.2, 2.0 Hz, 1H), 3.22 (ddd, *J* = 13.2, 12.0, 3.6 Hz, 1H), 3.06 (s, 3H), 2.95 (s, 3H), 2.48 (s, 3H), 2.05 (ddd, *J* = 13.2, 3.2, 3.2 Hz, 1H), 1.98 (td, *J* = 12.8, 12.4, 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 144.3, 133.6, 133.4, 131.5 (q, *J* = 32 Hz), 130.0, 127.7, 125.7, 124.1 (q, *J* = 271 Hz), 122.9, 119.6, 114.6 (q, *J* = 4 Hz), 103.1 (q, *J* = 4 Hz), 92.5, 57.2, 42.5, 42.4, 38.6, 36.6, 32.7, 21.6.

IR (neat): 2928, 1615, 1596, 1423, 1345, 1317, 1244, 1158, 1120, 1006, 955, 911, 817, 733, 658 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{25}O_4N_3F_3S_2$ 528.1233 found 528.1236.



5.2n

7,8-dimethyl-6-(methylsulfonyl)-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.2n**):

Prepared according to **General Procedure F** using ***N*-(2-(1,7-dimethyl-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1n**) (100 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 4: 1 to 2: 1) to afford a white solid (77 mg, 81% yield); m.p. 198-200 °C, R_f = 0.33 (hexanes: ethyl acetate = 2: 1).

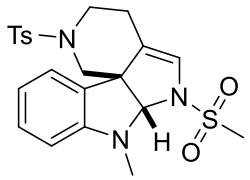
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.69 (t, *J* = 7.5 Hz, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 5.23 (s, 1H), 4.34 (d, *J* = 13.2 Hz, 1H), 3.83 (ddd, *J* = 13.2, 4.0, 4.0 Hz, 1H), 3.51 (dd, *J* =

13.2, 1.8 Hz, 1H), 3.24 (ddd, *J* = 13.2, 9.6, 6.0 Hz, 1H), 3.06 (s, 3H), 2.97 (s, 3H), 2.47 (s, 3H), 2.28 (s, 3H), 2.08–1.90 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 144.1, 134.3, 133.9, 131.5, 129.9, 127.7, 124.7, 124.2, 122.0, 120.7, 116.0, 96.5, 56.9, 43.0, 42.3, 41.9, 41.4, 37.1, 21.6, 18.9.

IR (neat): 2925, 1672, 1596, 1471, 1341, 1268, 1155, 1003, 958, 908, 817, 730, 664 cm^{-1}.

HRMS (NSI) *m/z*: $[M]^+$ calcd. for $C_{23}H_{27}O_4N_3S_2$ 473.1438 found 473.1435.



5.2o

7-methyl-6-(methylsulfonyl)-2-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[3',4':3,4]pyrrolo[2,3-*b*]indole (**5.2o**):

Prepared according to **General Procedure F** using **4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)-*N*-(2-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)ethyl)benzenesulfonamide** (**5.1o**) (97.4 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white solid (77 mg, 84% yield); m.p. 205-207 °C, R_f = 0.23 (hexanes: ethyl acetate = 2: 1).

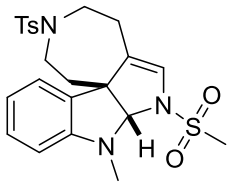
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.03 (d, *J* = 1.8 Hz, 1H), 5.44 (s, 1H), 4.15 (dd, *J* = 10.8, 5.4 Hz, 1H), 4.00 (d, *J* = 10.4 Hz,

1H), 3.06 (s, 3H), 2.91 (s, 3H), 2.69-2.64 (m, 1H), 2.42 (s, 3H), 2.39–2.35 (m, 2H), 2.28 (ddd, *J* = 12.0, 12.0, 3.6 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 150.0, 144.0, 132.8, 129.9, 129.5, 129.1, 127.5, 124.5, 122.3, 122.1, 119.2, 107.8, 89.9, 59.3, 55.4, 48.3, 40.3, 35.5, 23.2, 21.5.

IR (neat): 2923, 1717, 1601, 1492, 1341, 1231, 1160, 1097, 1005, 971, 942, 866, 768, 743, 723 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}O_4N_3S_2$ 460.1359 found 460.1368.



5.2p

8-methyl-7-(methylsulfonyl)-3-tosyl-1,2,3,4,5,7,7a,8-octahydroazepino[4',5':3,4]pyrrolo[2,3-*b*]indole (**5.2p**):

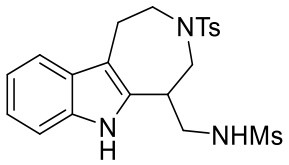
Prepared according to **General Procedure F** using **4-methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-(2-(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)ethyl)benzenesulfonamide** (**5.1p**) (100 mg, 0.2 mmol, 1.0 equiv). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1) to afford a white solid (33 mg, 35% yield); m.p. 189-191 °C (decomposition), R_f = 0.26 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 1H), 5.36 (s, 1H), 3.77 (ddd, *J* = 12.8, 4.4, 4.4 Hz, 1H), 3.69 (ddd, *J* = 14.8, 8.0, 2.8 Hz, 1H), 3.08–2.96 (m, 8H), 2.52 (ddd, *J* = 14.8, 4.4, 4.4 Hz, 1H), 2.46-2.38 (m, 4H), 2.30 (ddd, *J* = 14.8, 8.0, 2.8 Hz, 1H), 2.04 (ddd, *J* = 14.8, 8.0, 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 143.5, 136.0, 130.8, 129.9, 128.7, 127.0, 126.9, 125.7, 123., 118.5, 106.7, 94.7, 61.6, 49.3, 46.5, 40.9, 39.2, 33.2, 26.3, 21.5.

IR (neat): 2919, 1602, 1494, 1341, 1327, 1307, 1156, 1094, 1012, 997, 954, 899, 868, 757, 750, 716, 701, 671 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{28}O_4N_3S_2$ 474.1516 found 474.1516.



5.2r

***N*-((3-tosyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indol-5-yl)methyl)methanesulfonamide** (**5.2r**):

Prepared according to **general procedure F** using ***N*-(2-(1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1r**) (95 mg, 0.20 mmol, 1.0 equiv). After the reaction was complete, the solvent was evaporated. The residue was dissolved in dichloromethane (4 mL) and treated with

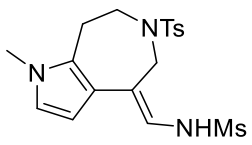
$NaBH_3CN$ (25 mg, 0.40 mmol, 2.0 equiv) at room temperature. The reaction was stirred over night, concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 2: 1) to afford a white solid (49 mg, 53% yield); m.p. 103-105 °C, R_f = 0.18 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.8, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 5.65 (dd, *J* = 8.4, 5.4 Hz, 1H), 4.23-4.19 (m, 2H), 3.49 (ddd, *J* = 14.4, 10.2, 4.8 Hz, 1H), 3.37 (ddd, *J* = 14.4, 8.4, 4.8 Hz, 1H), 3.27-3.24 (m, 1H), 3.09 (dt, *J* = 16.2, 3.0 Hz, 1H), 3.02-2.97 (m, 1H), 2.95 (s, 3H), 2.87 (d, *J* = 13.8 Hz, 1H), 2.66 (td, *J* = 13.2, 2.4 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 135.6, 134.8, 134.1, 130.0, 128.4, 126.8, 122.1, 119.5, 117.9, 111.6, 110.8, 50.7, 49.6, 43.6, 42.5, 40.4, 26.4, 21.5.

IR (neat): 3364, 2925, 1493, 1462, 1321, 1153, 1109, 1088, 1011, 961, 815, 745, 719, 689, 655 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{25}O_4N_3NaS_2$ 470.1179 found 470.1186.



5.2s

(*Z*)-*N*-((1-methyl-6-tosyl-5,6,7,8-tetrahydropyrrolo[2,3-*d*]azepin-4(1*H*)-ylidene)methyl)methanesulfonamide (**5.2s**):

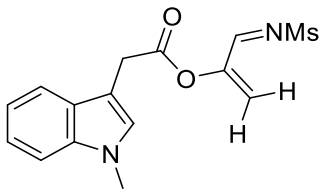
Prepared according to **general procedure F** using **4-methyl-*N*-(2-(1-methyl-1*H*-pyrrol-2-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1s**) (87.4 mg, 0.2 mmol). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a light yellow foam (46 mg, 56% yield); m.p. 81-83°C, R_f = 0.21 (hexanes: ethyl acetate = 2: 1). The *Z*-configuration was assigned based on HMQC and NOE (see Appendix 5).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.67 (d, *J* = 11.2 Hz, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 6.16 (d, *J* = 11.2 Hz, 1H), 5.98 (d, *J* = 2.8 Hz, 1H), 3.97 (s, 2H), 3.56 (t, *J* = 5.6 Hz, 2H), 3.45 (s, 3H), 2.98 (s, 3H), 2.80 (t, *J* = 5.6 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 136.6, 129.7, 129.1, 126.9, 121.8, 120.5, 115.3, 113.0, 105.3, 55.1, 45.2, 41.1, 34.1, 27.9, 21.5.

IR (neat): 3288, 2930, 1661, 1597, 1501, 1327, 1240, 1153, 1093, 967, 897, 816, 759, 726, 687, 656 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{18}H_{23}O_4N_3NaS_2$ 432.1022 found 432.1017.



5.5

3-((methylsulfonyl)imino)prop-1-en-2-yl 2-(1-methyl-1*H*-indol-3-yl)acetate (**5.5**):

Prepared according to **General Procedure F** using **(1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl 2-(1-methyl-1*H*-indol-3-yl)acetate** (**5.3**) (70 mg, 0.2 mmol, 1.0 equiv). The product was afforded in nearly quantitative yield without further purification as a colorless oil. R_f = 0.19 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 5.98 (d, *J* = 2.4 Hz, 1H), 5.94 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 2H), 3.76 (s, 3H), 2.83 (s, 3H).

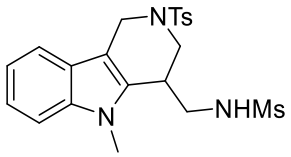
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 165.4, 149.6, 136.9, 128.2, 127.5, 124.9, 121.9, 119.3, 118.9, 109.4, 105.5, 39.9, 32.8, 30.8.

IR (neat): 3025, 2931, 1758, 1602, 1320, 1291, 1147, 1129, 964, 930, 815, 737 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{15}H_{16}O_4N_2NaS_2$ 343.0723 found 343.0728.

General procedure G: for the Friedel-Crafts-type annuation reaction (Table 5.5)

To a 35 mL high pressure screw-cap tube equipped with a magnetic stir bar, triazole (0.10 mmol) and the $Rh_2(OOct)_4$ (0.001 mmol) were added together under ambient atmosphere followed by 2.0 mL of ethyl acetate. The homogeneous reaction mixture was flushed with argon and sealed. The reaction mixture was stirred at 80 °C for 4-8 hours until the triazole was completely consumed as judged by TLC analysis. The reaction mixture was then cooled to room temperature, and treated with $NaBH_3CN$ (2 equiv) at room temperature. The reaction was stirred over night, concentrated and purified by flash column chromatography (silica gel, hexanes: ethyl acetate)



5.2t

***N*-((5-methyl-2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-4-yl)methyl)methanesulfonamide**: (**5.2t**)

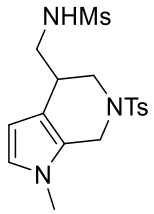
Prepared according to **general procedure G** using **4-methyl-*N*-((1-methyl-1*H*-indol-3-yl)methyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.1t**) (47.3 mg, 0.1 mmol). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white solid (36 mg, 81%); m.p. 102-104 °C, R_f = 0.19 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.38-7.35 (m, 3H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 5.23 (t, *J* = 7.2 Hz, 1H), 4.89 (d, *J* = 13.2 Hz, 1H), 4.23 (d, *J* = 12.6 Hz, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.70 (s, 3H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.27-3.24 (m, 1H), 3.00 (s, 3H), 2.77 (d, *J* = 12.6 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.9, 137.3, 134.0, 132.8, 129.9, 127.2, 124.4, 122.0, 119.6, 117.8, 109.3, 105.7, 45.1, 44.0, 43.2, 40.6, 35.3, 29.4, 21.5.

IR (neat): 89, 2930, 1597, 1471, 1325, 1245, 1162, 1120, 1089, 1011, 960, 908, 817, 729, 708, 669 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{25}O_4N_3NaS_2$ 470.1179 found 470.1181.



5.7a

***N*-((1-methyl-6-tosyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)methyl)methanesulfonamide** (**5.7a**):

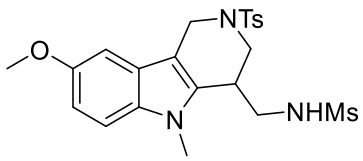
Prepared according to **general procedure G** using **4-methyl-*N*-((1-methyl-1H-pyrrol-2-yl)methyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.6a**) (85 mg, 0.2 mmol). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a light yellow foam (64 mg, 81%); R_f = 0.18 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 6.47 (d, *J* = 2.4 Hz, 1H), 5.94 (d, *J* = 2.4 Hz, 1H), 4.81 (t, *J* = 6.6 Hz, 1H), 4.40 (d, *J* = 13.2 Hz, 1H), 3.79 (d, *J* = 13.8 Hz, 1H), 3.66 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.43 (s, 3H), 3.33-3.29 (m, 1H), 3.26–3.21 (m, 1H), 2.99-2.96 (m, 1H), 2.94 (s, 3H), 2.89 (dd, *J* = 12.6, 3.6 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.9, 133.6, 129.9, 127.4, 123.2, 121.7, 115.7, 105.5, 46.0, 45.9, 42.9, 40.1, 34.7, 33.2, 21.5.

IR (neat): 3292, 2930, 1597, 1502, 1408, 1317, 1266, 1185, 1151, 1089, 1028, 966, 935, 816, 732, 660 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{17}H_{23}O_4N_3NaS_2$ 420.1022 found 420.1020.



5.7b

***N*-((8-methoxy-5-methyl-2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-4-yl)methyl)methanesulfonamide** (**5.7b**):

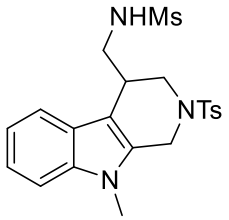
Prepared according to **general procedure G** using ***N*-((5-methoxy-1-methyl-1*H*-indol-3-yl)methyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.6b**) (101 mg, 0.2 mmol). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2) to afford a white solid (69 mg, 72%); m.p. 203-205 °C (decomposition), R_f = 0.25 (hexanes: ethyl acetate = 3: 2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 5.21 (t, *J* = 6.4 Hz, 1H), 4.86 (d, *J* = 13.6 Hz, 1H), 4.22 (d, *J* = 12.4, 1.6 Hz, 1H), 3.85-3.82 (m, 4H), 3.67 (s, 3H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.23 (t, *J* = 7.2 Hz, 1H), 3.00 (s, 3H), 2.76 (dd, *J* = 12.4, 2.8 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 143.9, 134.0, 133.3, 132.5, 129.9, 127.3, 124.6, 112.0, 110.1, 105.2, 99.7, 55.9, 45.1, 44.0, 43.2, 40.5, 35.3, 29.6, 21.6.

IR (neat): 3292, 2930, 1623, 1596, 1488, 1463, 1324, 1226, 1158, 1119, 1089, 962, 815, 732, 661 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{28}O_5N_3S_2$ 478.1465 found 478.1472.



5.7e

***N*-((9-methyl-2-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-4-yl)methyl)methanesulfonamide** (**5.7e**)

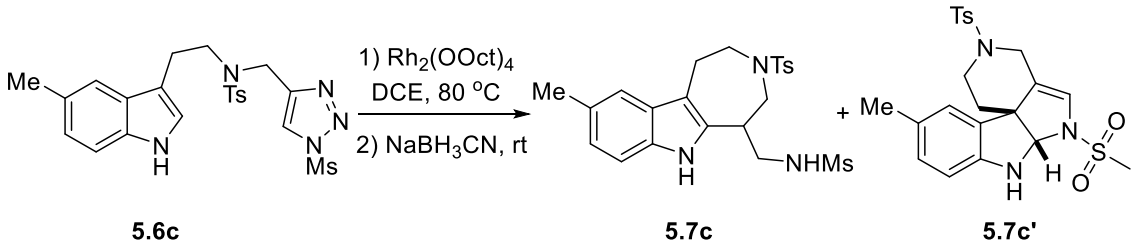
Prepared according to **general procedure G** using **4-methyl-*N*-((1-methyl-1*H*-indol-2-yl)methyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.6e**) (95 mg, 0.2 mmol). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white solid (71 mg, 80%); m.p. 198-200 °C (decomposition), R_f = 0.25 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.20 (td, *J* = 8.0, 1.2 Hz, 1H), 7.11 (td, *J* = 8.0, 1.2 Hz, 1H), 4.93–4.89 (m, 1H), 4.77 (d, *J* = 14.4 Hz, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.87 (d, *J* = 14.4 Hz, 1H), 3.59 (s, 3H), 3.55–3.50 (m, 1H), 3.38–3.30 (m, 2H), 2.96 (s, 3H), 2.80 (dd, *J* = 12.4, 2.8 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 137.1, 133.6, 130.7, 130.0, 127.3, 125.5, 121.9, 119.9, 118.3, 109.0, 107.8, 45.7, 45.1, 43.0, 40.2, 34.5, 29.6, 21.6.

IR (neat): 3295, 2927, 1597, 1471, 1456, 1390, 1322, 1272, 1243, 1146, 1089, 1015, 970, 945, 912, 816, 734, 708, 676, 660 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{25}O_4N_3NaS_2$ 470.1179 found 470.1176.



5.6c **5.7c** **5.7c'**

Prepared according to **general procedure G** using **4-methyl-*N*-(2-(5-methyl-1*H*-indol-3-yl)ethyl)-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.6c**) (97.4 mg, 0.2 mmol). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 3: 1 to 3: 2).

***N*-((9-methyl-3-tosyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indol-5-yl)methyl)methanesulfonamide** (**5.7c**): Isolated as a white solid (28 mg, 30%); m.p. 188-190 °C (decomposition), R_f = 0.20 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (br s, 1H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.21 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.61 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.24-4.19 (m, 2H), 3.48 (ddd, *J* = 14.4, 10.2, 4.8 Hz, 1H), 3.38–3.33 (m, 1H), 3.24-3.21 (m, 1H), 3.06 (dt, *J* = 16.2, 3.0 Hz, 1H), 2.99-2.94 (m, 4H), 2.88 (d, *J* = 14.4 Hz, 1H), 2.66 (t, *J* = 12.0 Hz, 1H), 2.42 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.8, 135.6, 134.2, 133.1, 130.0, 128.8, 128.6, 126.8, 123.6, 117.6, 111.1, 110.4, 50.8, 49.7, 43.6, 42.6, 40.3, 26.4, 21.5, 21.5.

IR (neat): 3365, 2920, 1597, 1452, 1324, 1186, 1151, 1109, 1014, 909, 814, 800, 734, 677 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{28}O_4N_3S_2$ 462.1516 found 462.1523.

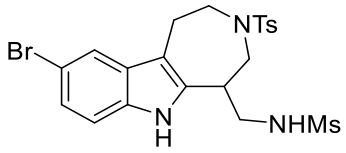
10-Methyl-6-(methylsulfonyl)-3-tosyl-2,3,4,6,6a,7-hexahydro-1*H*-pyrido[4',3':3,4]pyrrolo[2,3-*b*]indole (**5.7c'**): Isolated as a white solid (23 mg, 25%); m.p. 187-189 °C (decomposition), R_f = 0.24 (hexanes: ethyl acetate = 3: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 1.8 Hz, 1H), 6.18 (d, *J* = 1.8 Hz, 1H), 5.40 (d, *J* = 1.8 Hz, 1H), 4.74 (d, *J* = 1.8 Hz, 1H), 4.39 (d, *J* = 13.8 Hz, 1H), 3.87 (ddd, *J* = 12.6, 3.6 Hz, 1H), 3.48 (dd, *J* = 13.8, 1.8 Hz, 1H), 3.12 (ddd, *J* = 13.2, 10.8, 5.4 Hz, 1H), 2.92 (s, 3H), 2.47 (s, 3H), 2.07 (s, 3H), 2.00–1.94 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 145.4, 144.1, 133.1, 130.5, 129.8, 129.4, 128.8, 127.9, 124.1, 124.1, 118.3, 110.5, 87.2, 57.3, 43.0, 42.5, 38.6, 36.0, 21.6, 20.8.

IR (neat): 3393, 2925, 1597, 1493, 1339, 1160, 1009, 965, 816, 734, 662 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}O_4N_3S_2$ 460.1359 found 460.1364.



5.7d

***N*-((9-bromo-3-tosyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indol-5-yl)methyl)methanesulfonamide** (**5.7d**):

Prepared according to **general procedure G** using ***N*-(2-(5-bromo-1*H*-indol-3-yl)ethyl)-4-methyl-*N*-((1-(methylsulfonyl)-1*H*-1,2,3-triazol-4-**

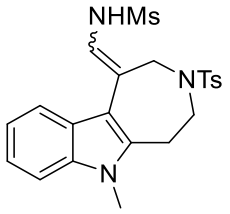
yl)methyl)benzenesulfonamide (**5.6d**) (110 mg, 0.2 mmol). Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford a white solid (61 mg, 58%); m.p. 221-223 °C, R_f = 0.21 (hexanes: ethyl acetate = 2: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (br s, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.54 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 5.64-5.61 (m, 1H), 4.21 (d, *J* = 13.8 Hz, 2H), 3.52-3.47 (m, 1H), 3.39-3.34 (m, 1H), 3.24 (d, *J* = 10.2 Hz, 1H), 3.01–2.93 (m, 5H), 2.87 (d, *J* = 14.4 Hz, 1H), 2.64 (t, *J* = 10.2 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 143.9, 135.5, 135.4, 133.4, 130.2, 130.0, 126.8, 124.9, 120.7, 112.8, 112.1, 111.4, 50.5, 49.5, 43.5, 42.6, 40.5, 26.3, 21.5.

IR (neat): 3362, 2926, 1732, 1597, 1450, 1373, 1324, 1244, 1154, 1111, 1089, 1047, 970, 912, 814, 799, 660 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{25}O_4N_3BrS_2$ 526.0464 found 526.0476.



5.7f

***N*-((6-methyl-3-tosyl-3,4,5,6-tetrahydroazepino[4,5-*b*]indol-1(2*H*)-ylidene)methyl)methanesulfonamide** (**5.7f**):

Prepared according to **general procedure G** using **4-methyl-N-(2-(1-methyl-1H-indol-2-yl)ethyl)-N-((1-(methylsulfonyl)-1H-1,2,3-triazol-4-yl)methyl)benzenesulfonamide** (**5.6f**) (97.4 mg, 0.2 mmol) except that the products of the first step were not treated with $NaBH_3CN$. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 2: 1 to 1: 1) to afford 43 mg of the *Z*-isomer and 40 mg of a mixture of *Z*- and *E*-isomers (90% combined yield). *Z* isomer was assigned by analogy to compound **5.2s**. The *Z*/*E* ratio was determined by ^{1}H NMR to be 2.4/1.0. ***E*-5.7f** was not completely separated from ***Z*-5.7f** and only proton data was provided: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.23–7.10 (m, 4H), 6.59 (d, *J* = 9.6 Hz, 1H), 4.12 (s, 2H), 3.64-3.60 (m, 5H), 3.09 (s, 3H), 3.08 (d, *J* = 5.4 Hz, 2H), 2.39 (s, 3H).

***Z*-5.7f** was isolated as a yellow foam; m.p. 87-89 °C, R_f = 0.30 (hexanes: ethyl acetate = 1: 1).

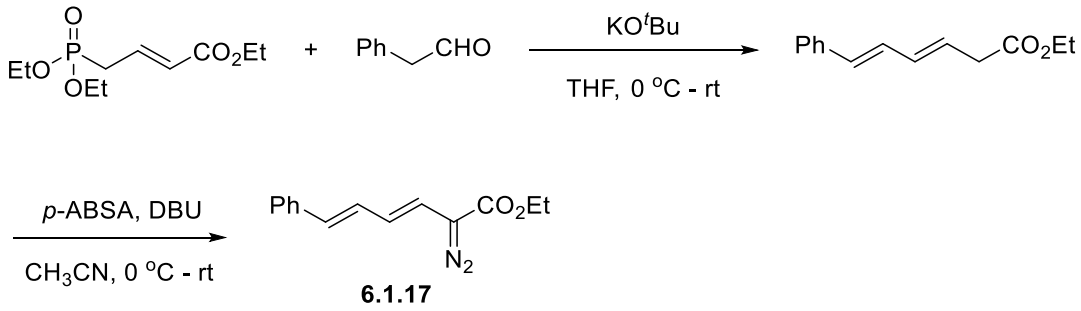
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.28–7.18 (m, 5H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.38 (d, *J* = 11.2 Hz, 1H), 6.20 (d, *J* = 11.2 Hz, 1H), 4.14-4.11 (s, 2H), 3.72 (t, *J* = 5.6 Hz, 2H), 3.58 (s, 3H), 3.05-3.03 (m, 2H), 2.98 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 136.2, 136.7, 136.4, 129.0, 126.8, 124.0, 122.1, 121.7, 120.4, 118.3, 110.0, 109.6, 106.0, 55.4, 43.1, 41.5, 29.7, 29.1, 21.5.

IR (neat): 3272, 3053, 2929, 1662, 1597, 1545, 1471, 1324, 1289, 1152, 1092, 983, 953, 908, 860, 815, 734, 675 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{25}O_4N_3NaS_2$ 482.1179 found 482.1177.

Experimental section for chapter 6.1: Vinylogous reactivity of ethyl (3*E*,5*E*)-2-diazo-6-phenylhexa-3,5-dienoate



6.1.17

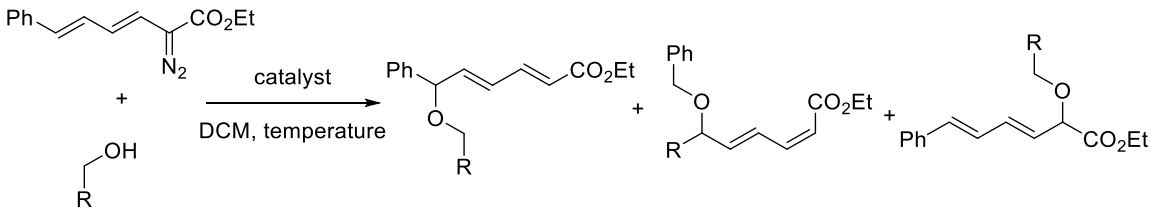
ethyl (3*E*,5*E*)-2-diazo-6-phenylhexa-3,5-dienoate (**6.1.17**):

To a solution of ethyl (E)-4-(diethoxyphosphoryl)but-2-enoate (0.30 g, 1.2 mmol, 1.2 equiv) in THF (5 mL) was added a solution of KO^{t}Bu (0.14 g, 1.2 mmol, 1.2 equiv) in THF (5 mL) dropwise at 0 °C. This solution was stirred for 10 min at 0 °C before 2-phenylacetaldehyde (0.12 g, 1.0 mmol, 1.0 equiv) was added. The reaction was stirred for 2 h before it was purified by column chromatography to afford ethyl (3*E*,5*E*)-6-phenylhexa-3,5-dienoate (180 mg) as an oil. This material was taken into the next step directly.

The ester obtained in the previous step (180mg, 0.83 mmol, 1.0 equiv) was treated with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (0.26 g, 1.08 mmol, 1.3 equiv) in acetonitrile, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.16 mL, 1.25 mmo, 1.5 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature gradually and stirred overnight before it was concentrated. The residue was diluted with dichloromethane (20 mL), washed with of saturated aqueous ammonium chloride (15 mL). The layers were separated and the aqueous layer was with dichloromethane (20 mL). The

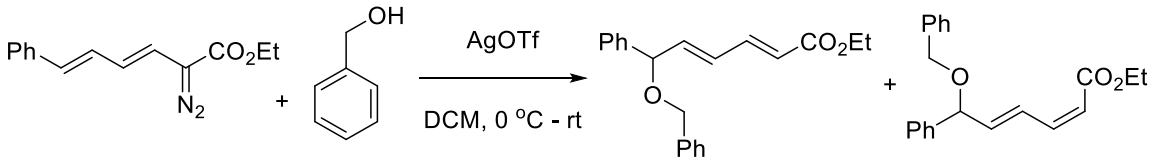
combined organics were dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chromatography on silica gel eluting with hexanes: diethyl ether (30: 1) to give **6.1.17** as a red solid (145 mg, 60% for two steps); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 15.6, 9.2 Hz, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 6.12–6.01 (m, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H). Data matched that of literature.[24]

General Procedure A:



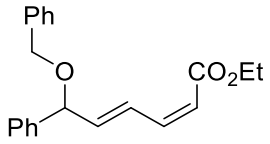
A solution of alcohol substrate (0.4 mmol, 2.0 equiv) and the catalyst (1 mol % $Rh_2(OOct)_4$ or 5 mol % AgOTf, or 8 mol % AgOTf/10 mol % gold catalyst) in dichloromethane (2 mL) was degassed for 10 mins. This solution was stirred at the indicated temperature. Then a solution of diazo compound (**6.1.17**) (0.2 mmol, 1.0 equiv) in solvent (2 mL) was added *via* 2hrs. The reaction was further stirred over night. The reaction was concentrated and analyzed by ^{1}H NMR. Purification of the residue by column chromatography provided the products.

[24] Davies, H. M. L.; Clark, T. J.; Smith, H. D. *J. Org. Chem.* **1991**, *56*, 3817.



6.1.17 **6.1.18** ***E,E*-6.1.19** ***E,Z*-6.1.19**

Following general procedure A using benzyl alcohol (86 mg, 0.8 mmol, 2.0 equiv), AgOTf (4.4 mg, 5.0 mol %) and (3*E*,5*E*)-ethyl 2-diazo-6-phenylhexa-3,5-dienoate (97 mg, 0.4 mmol, 1.0 equiv). The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ ethyl acetate = 35/1).



***E,Z*-6.1.19**

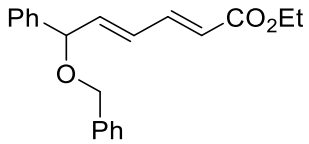
(2*Z*,4*E*)-ethyl 6-(benzyloxy)-6-phenylhexa-2,4-dienoate (*E,Z*-6.1.19): Isolated as a colorless oil (9 mg, 7% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (dd, *J* = 15.6, 11.2 Hz, 1H), 7.37-7.32 (m, 8H), 7.30-7.25 (m, 2H), 6.54 (t, *J* = 11.6 Hz, 1H), 6.11 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.66 (d, *J* = 11.2 Hz, 1H), 4.97 (d, *J* = 7.2 Hz, 1H), 4.50 (s, 2H), 4.17 (q, *J* = 6.8 Hz, 2H), 1.26 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165. 5, 143.9, 143.3, 140.6, 138.3, 128.9, 128.6, 128.2, 128.0, 127.8, 127.6, 127.2, 118.7, 81.3, 70.5, 60.3, 14.5.

IR (neat): 3029, 2925, 2855, 1712, 1639, 1602, 1453, 1273, 1181, 1093, 1028, 965, 737, 698 cm^{-1}.

HRMS: (FTMS + *p* ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{22}O_3Na$ 345.1461 found 345.1458.



***E,E*-6.1.19**

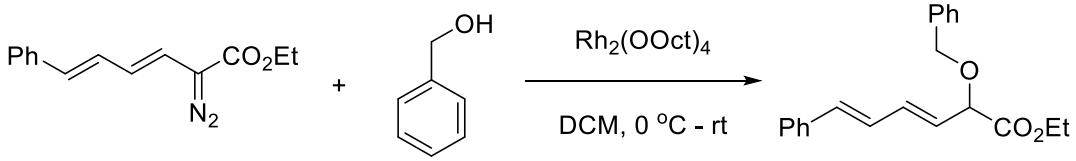
(2*E*,4*E*)-ethyl 6-(benzyloxy)-6-phenylhexa-2,4-dienoate (*E,E*-6.1.19): Isolated as a colorless oil (94 mg, 74% yield); R_f = 0.63 (hexanes: ethyl acetate = 9: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.25 (m, 11H), 6.43 (dd, *J* = 15.2, 11.6 Hz, 1H), 6.22 (dd, *J* = 15.2, 6.0 Hz, 1H), 5.91 (d, *J* = 15.2 Hz, 1H), 4.96 (d, *J* = 6.0 Hz, 1H), 4.51 (AB, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 143.9, 142.7, 140.2, 138.3, 129.0, 128.7, 128.6, 128.4, 128.0, 127.4, 122.2, 80.8, 70.5, 60.6, 14.5.

IR (neat): 2981, 2980, 2865, 1711, 1643, 1617, 1453, 1302, 1263, 1228, 1175, 136, 1000, 741, 699 cm^{-1}.

HRMS: (FTMS + *p* ESI) *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{23}O_3$ 323.1642 found 323.1644.



6.1.17 **6.1.18** **6.1.20**

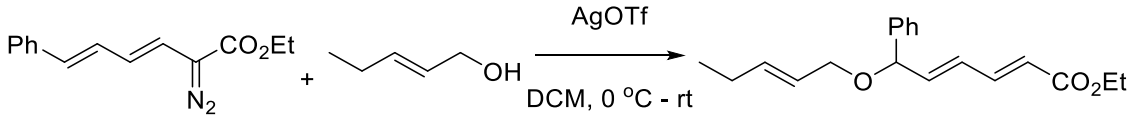
(3*E*,5*E*)-ethyl 2-(benzyloxy)-6-phenylhexa-3,5-dienoate (6.1.20): following typical procedure A using benzyl alcohol (108 mg, 1.0 mmol, 2.0 equiv), $Rh_2(OOct)_4$ (3.9 mg, 1.0 mol %) and (3*E*,5*E*)-ethyl 2-diazo-6-phenylhexa-3,5-dienoate (**6.1.17**) (121 mg, 0.5 mmol, 1.0 equiv). The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ ethyl acetate = 30/1) to afford a colorless oil (123 mg, 76% yield); R_f = 0.60 (hexanes: ethyl acetate = 8: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40-7.34 (m, 6H), 7.32-7.29 (m, 3H), 7.24-7.22 (m, 1H), 6.77 (dd, *J* = 16.2, 11.2 Hz, 1H), 6.61-6.54 (m, 2H), 5.85 (dd, *J* = 15.6, 7.2 Hz, 1H), 4.63 (AB, 2H), 4.51 (d, *J* = 7.2 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 137.3, 136.8, 134.5, 134.2, 128.6, 128.5, 128.0, 127.9, 127.6, 127.5, 126.5, 78.4, 71.3, 61.3, 14.2.

IR (neat): 3027, 2981, 2869, 1745, 1496, 1448, 1367, 1266, 1184, 1115, 1027, 990, 741, 692 cm^{-1};

HRMS: (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{21}H_{22}O_3Na$ 345.1461 found 345.1459.



6.1.17 **6.1.20a** **6.1.21a**

(2*E*,4*E*)-ethyl 6-((E)-pent-2-en-1-yloxy)-6-phenylhexa-2,4-dienoate (6.1.21a): following typical procedure A using alcohol **6.1.20a** (17 mg, 0.2 mmol, 2.0 equiv), AgOTf (1.1 mg, 5.0 mol %) and (3*E*,5*E*)-ethyl 2-diazo-6-phenylhexa-3,5-dienoate (**6.1.17**) (24 mg,

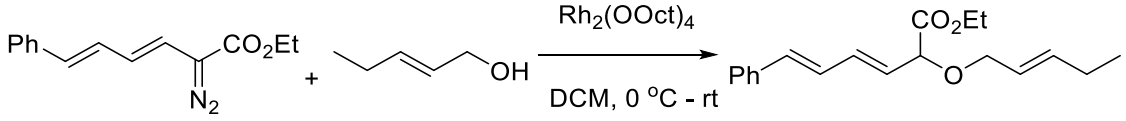
0.1 mmol, 1.0 equiv). The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ ethyl acetate = 30/1) to afford **6.1.20a** as a colorless oil (21 mg, 70% yield); R_f = 0.45 (hexanes: ethyl acetate = 9: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.20 (m, 6H), 6.36 (dd, *J* = 15.2, 11.6 Hz, 1H), 6.16 (dd, *J* = 15.2, 6.0 Hz, 1H), 5.86 (d, *J* = 15.2 Hz, 1H), 5.72-5.67 (m, 1H), 5.57-5.52 (m, 1H), 4.89 (d, *J* = 6.4 Hz, 1H), 4.17 (q, *J* = 6.8 Hz, 2H), 3.89 (d, *J* = 6.4 Hz, 2H), 2.08-2.01 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 3.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 144.0, 142.8, 140.4, 136.9, 128.9, 128.5, 128.2, 127.3, 125.1, 122.1, 80.7, 69.6, 60.6, 25.5, 14.5, 13.5.

IR (neat): 2963, 2932, 2851, 1712, 1644, 1617, 1453, 1367, 1301, 1261, 1226, 1174, 1134, 1101, 1029, 999, 968, 762, 699 cm^{-1}.

HRMS: (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{25}O_3$ 301.1798 found 301.1798.



6.1.17 **6.1.20a** **6.1.22a**

(3*E*,5*E*)-ethyl 2-((E)-pent-2-en-1-yloxy)-6-phenylhexa-3,5-dienoate (6.1.22a): following typical procedure A using alcohol **6.1.20a** (86 mg, 1.0 mmol, 2.0 equiv), $Rh_2(OOct)_4$ (3.9 mg, 1.0 mol %) and (3*E*,5*E*)-ethyl 2-diazo-6-phenylhexa-3,5-dienoate (**6.1.17**) (121 mg, 0.5 mmol, 1.0 equiv). The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ ethyl acetate = 30/1) to

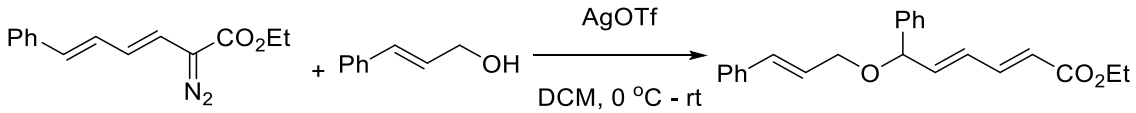
afford **6.1.22a** as a colorless oil (113 mg, 75% yield); R_f = 0.55 (hexanes: ethyl acetate = 6: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.4 Hz, 2H), 7.26-7.21 (m, 1H), 6.77 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.62-6.52 (m, 2H), 5.84-5.74 (m, 2H), 5.62-5.54 (m, 1H), 4.49 (d, *J* = 6.8 Hz, 1H), 4.23 (q, *J* = 6.8 Hz, 2H), 4.08-3.99 (m, 2H), 2.18-2.04 (m, 2H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 137.8, 134.6, 134.3, 128.9, 128.1, 127.9, 127.8, 126.7, 124.6, 78.4, 70.6, 61.5, 25.5, 14.4, 13.4.

IR (neat): 3025, 2963, 2933, 2872, 1747, 1448, 1368, 1266, 1181, 1112, 1028, 990, 970, 745, 692 cm^{-1}.

HRMS: (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{19}H_{24}O_3Na$ 323.1618 found 323.1614.



6.1.17 **6.1.20b** **6.1.21b**

(2*E*,4*E*)-ethyl 6-(cinnamyloxy)-6-phenylhexa-2,4-dienoate (6.1.21b): following typical procedure A using alcohol **6.1.20b** (purified by column chromatography before use) (53.6 mg, 0.4 mmol, 2.0 equiv), AgOTf (2.2 mg, 5.0 mol %) and (3*E*,5*E*)-ethyl 2-diazo-6-phenylhexa-3,5-dienoate (**6.1.17**) (48.4 mg, 0.2 mmol, 1.0 equiv). The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/

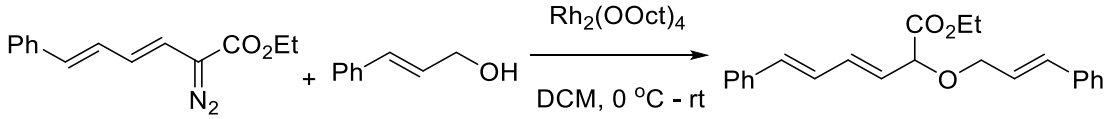
ethyl acetate = 35/1) to afford **6.1.21b** as a colorless oil (52 mg, 75% yield); R_f = 0.60 (hexanes: ethyl acetate = 8: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38-7.23 (m, 11H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.41 (dd, *J* = 15.6, 11.4 Hz, 1H), 6.29 (dt, *J* = 10.2, 6.0 Hz, 1H), 6.20 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 4. 98 (d, *J* = 6.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.14-4.12 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 143.9, 142.6, 140.2, 136.8, 132.9, 129.0, 128.8, 128.6, 128.3, 128.0, 127.3, 126.7, 126.0, 122.2, 80.9, 69.3, 60.6, 14.5.

IR (neat): 3027, 2927, 2853, 1712, 1644, 1616, 1450, 1302, 1263, 1228, 1175, 1136, 1030, 1001, 967, 747, 699 cm^{-1}.

HRMS: (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{23}H_{24}O_3Na$ 371.1618 found 371.1619.



6.1.17 **6.1.20b** **6.1.22b**

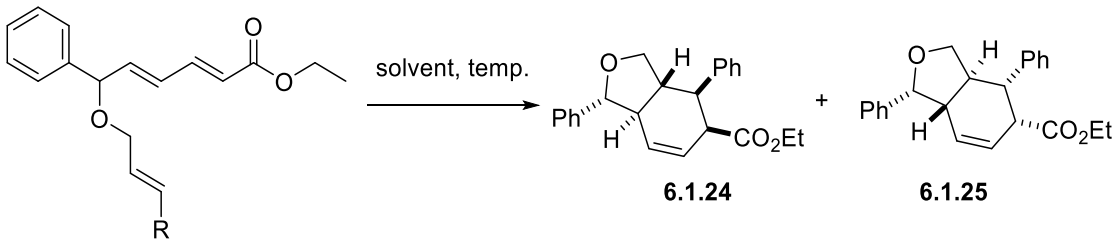
(3*E*,5*E*)-ethyl 2-(cinnamyloxy)-6-phenylhexa-3,5-dienoate (6.1.22b): following typical procedure A using alcohol **6.1.20b** (134 mg, 1.0 mmol, 2.0 equiv), $Rh_2(OOct)_4$ (3.9 mg, 1.0 mol %) and (3*E*,5*E*)-ethyl 2-diazo-6-phenylhexa-3,5-dienoate (**6.1.17**) (121 mg, 0.5 mmol, 1.0 equiv). The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ ethyl acetate = 35/1) to afford **6.1.22b** as a colorless oil (91 mg, 52% yield); R_f = 0.50 (hexanes: ethyl acetate = 8: 1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41-7.39 (m, 4H), 7.32 (t, *J* = 7.2 Hz, 4H), 7.26-7.23 (m, 3H), 6.79 (dd, *J* = 16.2, 11.4 Hz, 1H), 6.64-6.57 (m, 3H), 6.32 (dt, *J* = 16.2, 6.6 Hz, 1H), 5.85 (dd, *J* = 15.0, 6.6 Hz, 1H), 4. 56 (d, *J* = 7.2 Hz, 1H), 4.30-4.22 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 136.8, 136.4, 134.6, 134.3, 133.5, 128.6, 128.6, 127.9, 127.9, 127.5, 127.4, 126.6, 126.5, 125.1, 78.4, 70.2, 61.4, 14.2.

IR (neat): 3025, 2980, 2927, 1745, 1597, 1578, 1495, 1448, 1368, 1266, 1183, 1122, 1073, 1028, 991, 968, 745, 692 cm^{-1}.

HRMS: (NSI) *m/z*: $[M+Na]^+$ calcd. for $C_{23}H_{24}O_3Na$ 371.1618 found 371.1614.



6.1.21a-b **6.1.24** **6.1.25**

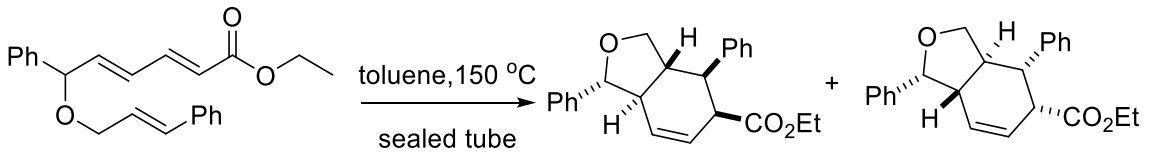
General Procedure B: A solution of starting material **6.1.21a-b** (1.0 equiv) in dichloromethane (0.05M) was stirred with Lewis acid (10-20 mol %) at 0 ℃ or room temperature. Then the reaction mixture was monitored by TLC and analyzed by ^{1}H NMR.

General Procedure C: A solution of starting material **6.1.21a-b** (1.0 equiv) in toluene (0.05M) was stirred under microwave at 150 ℃ or 200 ℃ for 30 min. Then the reaction mixture was cooled to room temperature and analyzed ^{1}H NMR.

General Procedure D: A solution of starting material **6.1.21a-b** (1.0 equiv) in toluene (0.05M) was stirred in a sealed tube at the indicated temperature for 10 hrs. Then the reaction mixture was cooled to room temperature and analyzed ^{1}H NMR. Purification of the residue provided the products.

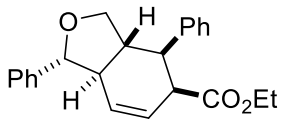
General Procedure E: A solution of alcohol substrate (0.4 mmol, 2.0 equiv) and AgOTf (5 mol %) in dichloromethane (2 mL) was degassed for 10 mins. This solution was stirred at 0 ℃. Then a solution of diazo compound (**6.1.17**) (0.2 mmol, 1.0 equiv) in dichloromethane (2 mL) was added *via* 2hrs. The reaction was further stirred while warmed to room temperature. Then the reaction was filtered through SiO_2 or Celite® and the filtrate was concentrated. The residue was dissolved in toluene (4 mL) and was heated to 150 ℃ in a sealed tube. The reaction was stirred at 150 ℃ for 10 h before it was cooled to room temperature and purified by column chromatography.

General Procedure F: A solution of alcohol substrate (0.4 mmol, 2.0 equiv) and AgOTf (5 mol %) in the solvent (2 mL) was degassed for 10 mins. This solution was stirred at 0 ℃. Then a solution of diazo compound (**6.1.17**) (0.2 mmol, 1.0 equiv) in solvent (2 mL) was added *via* 2hrs. The reaction was further stirred while warmed to room temperature. Then the reaction was filtered through SiO_2 and the filtrate was concentrated. The residue was dissolved in the same solvent (4 mL) and was heated to 150 ℃ in a sealed tube. The reaction was stirred at 150 ℃ for 10 h before it was cooled to room temperature and purified by column chromatography.



6.1.21b **6.1.24** **6.1.25**

Following **general procedure D** using (2*E*,4*E*)-ethyl 6-(cinnamyloxy)-6-phenylhexa-2,4-dienoate (37 mg, 106 μmol, 1.0 equiv) and toluene (2.0 mL) as the solvent at 150 °C. The crude residue was analyzed by ^{1}H NMR and purified by flash column chromatography (silica gel, hexanes/ ethyl acetate = 30/1 to 20/1 to 10/1) to afford the products **6.1.24** (27 mg) and **6.1.25** (7 mg) (92% combined yield).



6.1.24

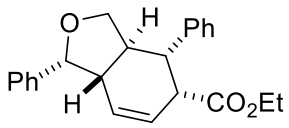
***rac*-(1*R*,3*aR*,4*R*,5*S*,7*aR*)-ethyl 1,4-diphenyl-1,3,3a,4,5,7a-hexahydroisobenzofuran-5-carboxylate (6.1.24)**: Isolated as a colorless solid (27 mg); m.p. 104-106 °C. R_f = 0.52 (hexanes: ethyl acetate = 8: 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.34 (m, 4H), 7.31-7.28 (m, 3H), 7.24-7.21 (m, 3H), 6.04 (d, *J* = 10.0 Hz, 1H), 5.71 (dt, *J* = 10.0, 2.8 Hz, 1H), 4.72 (d, *J* = 10.8 Hz, 1H), 4.25 (d, *J* = 6.8 Hz, 1H), 3.80-3.72 (m, 1H), 3.67-3.60 (m, 2H), 3.55-3.52 (m, 1H), 3.35-3.23 (m, 2H), 2.42 (t, *J* = 10.0 Hz, 1H), 0.84 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 141.5, 140.3, 128.8, 128.6, 128.2, 128.1, 127.7, 127.3, 126.9, 126.4, 83.7, 71.3, 60.7, 53.8, 50.4, 45.9, 42.4, 13.9.

IR (neat): 3028, 2929, 2855, 1727, 1494, 1454, 1333, 1222, 1177, 1160, 1038, 1021, 981, 748, 699 cm^{-1}.

HRMS: (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{25}O_3$ 349.1798 found 349.1800.



6.1.25

***rac*-ethyl (1*R*,3a*S*,4*S*,5*R*,7a*S*)-1,4-diphenyl-1,3,3a,4,5,7a-hexahydroisobenzofuran-5-carboxylate** (**6.1.25**): minor diastereomer; isolated from the same reaction as a colorless oil (**6.1.25**) (7 mg). R_f = 0.48 (hexanes: ethyl acetate = 8: 1).

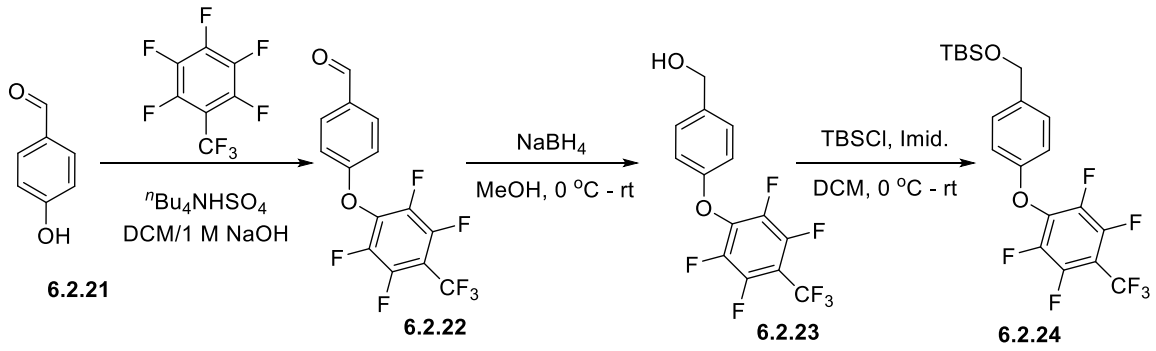
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 4H), 7.28-7.25 (m, 3H), 7.23-7.20 (m, 3H), 5.95 (d, *J* = 10.0 Hz, 1H), 5.50 (dt, *J* = 10.0, 3.6 Hz, 1H), 5.31 (d, *J* = 8.4 Hz, 1H), 4.34 (t, *J* = 6.8 Hz, 1H), 3.66-3.55 (m, 2H), 3.48-3.43 (m, 2H), 3.29-3.21 (m, 2H), 2.94-2.90 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 141.4, 140.6, 128.6, 128.3, 128.2, 128.2, 127.6, 127.3, 126.4, 126.1, 81.5, 71.5, 60.5, 50.3, 49.2, 46.0, 38.2, 13.8.

IR (neat): 3064, 2924, 2855, 1720, 1650, 1600, 1494, 1451, 1370, 1269, 1222, 1177, 1096, 1025, 735, 700 cm^{-1}.

HRMS: (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{25}O_3$ 349.1798 found 349.1803.

Experimental section for chapter 6.2: Efforts towards the formal total synthesis of ephedradine *via* sequential C−H functionalization strategy



tert-butyldimethyl((4-(2,3,6-trifluoro-4-(trifluoromethyl)phenoxy)benzyl)oxy)silane (6.2.24)

To a solution of 4-hydroxybenzaldehyde **6.2.21** (0.84 g, 6.9 mmol, 1.0 equiv) in a mixture of dichloromethane (20 mL) and 1 M NaOH (20 mL, freshly prepared dissolving NaOH (0.80 g) in H_2O (20 mL)) was added $^{n}Bu_4NHSO_4$ (1.23 g, 3.6 mmol, 0.52 equiv) at room temperature, followed by the addition of 1,2,3,4,5-pentafluoro-6-(trifluoromethyl)benzene (1.0 mL, 7.05 mmol, 1.02 equiv). The reaction mixture was stirred at room temperature and monitored by TLC. After 4 h of stirring, another portion of heated ^{n}Bu4HSO4^{-} (1.23 g, 3.6 mmol, 0.52 equiv) was added. The reaction was further stirred over night until a total of 12h at which point the layers were separated and the aqueous layer was extracted with dichloromethane (30 mL). The combined organics were washed with brine (30mL), dried over $MgSO_4$, concentrated. The residue obtained was used directly in the next step.

The residue obtained from the previous step was dissolved in MeOH (25 mL), and $NaBH_4$ (400 mg, 10.35 mmol, 1.5 equiv) was slowly added at 0 °C. After 4 h stirring at

room temperature, the reaction was quenched by slow addition of water at 0 ℃. The mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (2 × 30 mL), then the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated to give crude alcohol product. This crude material was used directly in the next step without purification.

tert-Butyldimethylsilylchloride (1.25 g, 8.30 mmol, 1.2 equiv) was added to a solution of the alcohol intermediate obtained in the previous step (*c.a.* 6.90 mmol, 1.0 equiv) and imidazole (0.94 g, 13.80 mmol, 2.0 equiv) in dicholomethane (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h before it was quenched with water and extracted with EtOAc (2 × 30 mL), then the combined organic layers were washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated. The residue was Purified by flash column chromatography (silica gel, hexanes: diethyl ether = 40: 1 to 20: 1) to afford **6.2.24** as a colorless oil (2.08 g, 66% for three steps); R_f = 0.50 (hexanes: diethyl ether = 20: 1).

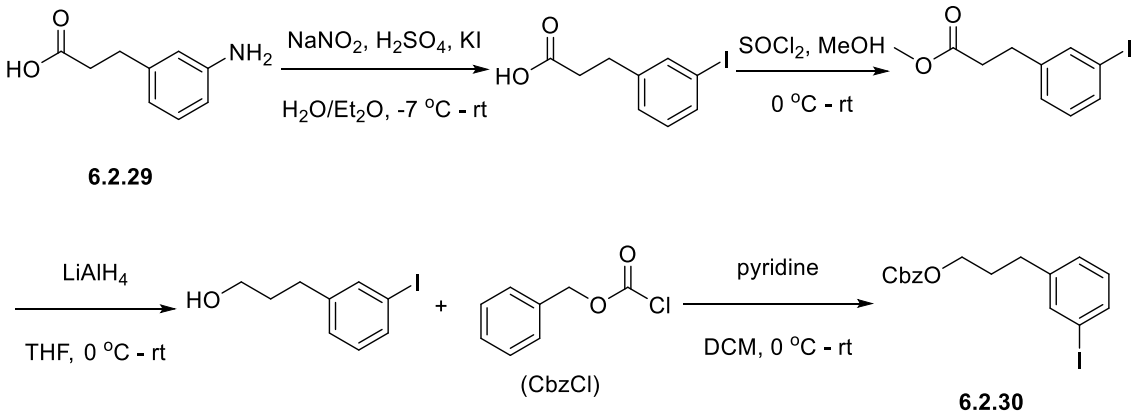
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 4.76 (s, 2H), 0.97 (s, 9H), 0.14 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 137.9, 127.6, 115.8, 64.2, 25. 9, 18.4, -5.3, the carbon signals for the C_7F_7 protecting group were not resolved.

^{19}F NMR (470 MHz, $CDCl_3$): δ -55.9 (t, *J* = 21.6 Hz, 3F), -140.5 (m, 2F), -152.0 (m, 2F).

IR (neat): 2956, 2931, 2859, 1655, 1502, 1428, 1343, 1231, 1150, 1091, 997, 883, 837, 778, 717 cm^{-1}.

HRMS: (NSI) *m/z*: $[M-H]^-$ calcd. for $C_{20}H_{20}O_2F_7Si$ 453.1115 found 453.1121.



Benzyl (3-(3-iodophenyl)propyl) carbonate (6.2.30):

3-(3-aminophenyl)propanoic acid **6.2.29** (5.0 g, 30.3 mmol, 1.0 equiv) was suspended in H_2O (50 mL), then H_2SO_4 (4.0 mL) was added. The mixture was cooled in an ice-salt bath. Then a solution of $NaNO_2$ (2.51 g, 36.4 mmol, 1.2 equiv) in minimal amount of H_2O (*c.a.* 9 mL) was added. The reaction was stirred for 15 mins, then Et_2O (50 mL) was added, followed by addition of a solution of KI (15.09 g, 50.9 mmol, 3.0 equiv) in minimal amount of H_2O (*c.a.* 9 mL). The reaction was warmed to rt while stirred for 3 h. The organics were extracted with EtOAc (3 × 50 mL). The combined organics were washed with 5% $NaHSO_3$ (2 × 50 mL), brine (60mL), dried over $MgSO_4$ and concentrated. The residue obtained was used directly in the next step.

A solution of the crude acid obtained from the previous step was dissolved in MeOH (100 mL), cooled to Et_2O (5 mL) was 0 °C, then $SOCl_2$ (9.02 g, 75.8 mmol, 2.5 equiv) was added dropwise. Then reaction was warmed to rt while stirred over night at which point it

was quenched carefully by adding saturated aqueous $NaHCO_3$ solution at 0 ℃. Then the bulk of solvents were removed and the organics were extracted with EtOAc (2 × 60 mL). The combined organics were washed with brine (60mL), dried over $MgSO_4$ and concentrated. The crude ester was used directly in the next step.

The crude ester obtained from the previous step was dissolved in dichloromethane (60 mL) and cooled to -78 ℃. Then a solution of DIBAl-H in dichloromethane (1 M, 67.3 mL, 2.2 equiv) was added dropwise under argon. The reaction was warmed to rt and stirred for 3 h. Then the reaction was quenched with MeOH carefully at 0 ℃. The solids were filtered off and the filtrates were concentrated to give the crude alcohol that was used directly in the next step.

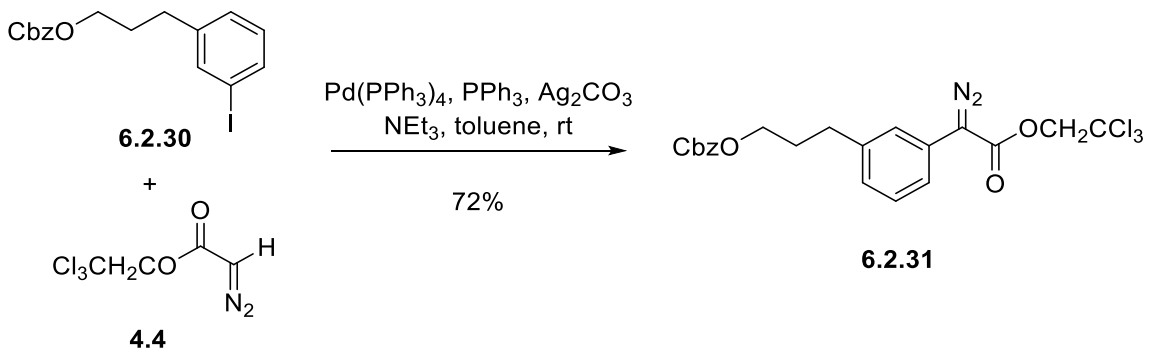
The crude alcohol obtained from the previous step was dissolved in dichloromethane (90 mL) and cooled to 0 ℃. Then pyridine (4.9 mL, 61.2 mmol, 2.0 equiv) was added, followed by dropwise addition of CbzCl (5.3 mL, 36.7 mmol, 1.2 equiv). The reaction mixture was stirred over night at room temperature before it was concentrated and purified by flash column chromatography (silica gel, hexanes: diethyl ether = 8: 1) to afford **6.2.30** as a colorless oil (7.2 g, 49% for four steps); R_f = 0.45 (hexanes: diethyl ether = 4: 1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58-7.55 (m, 2H), 7.45-7.38 (m, 5H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 5.20 (s, 2H), 4.19 (t, *J* = 6.5 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.03-1.97 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 143.5, 137.5, 135.3, 135.2, 130.3, 128.7, 128.6, 128.4, 127.8, 94.6, 69.7, 67.2, 31.5, 30.1.

IR (neat): 2956, 1741, 1562, 1455, 1396, 1246, 1065, 995, 949, 905, 778, 752, 694, 657 cm^{-1}.

HRMS: (NSI) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{18}O_3I$ 397.0295 found 397.0295.



2,2,2-trichloroethyl 2-(3-(3-(((benzyloxy)carbonyl)oxy)propyl)phenyl)-2-diazoacetate (**6.2.31**)

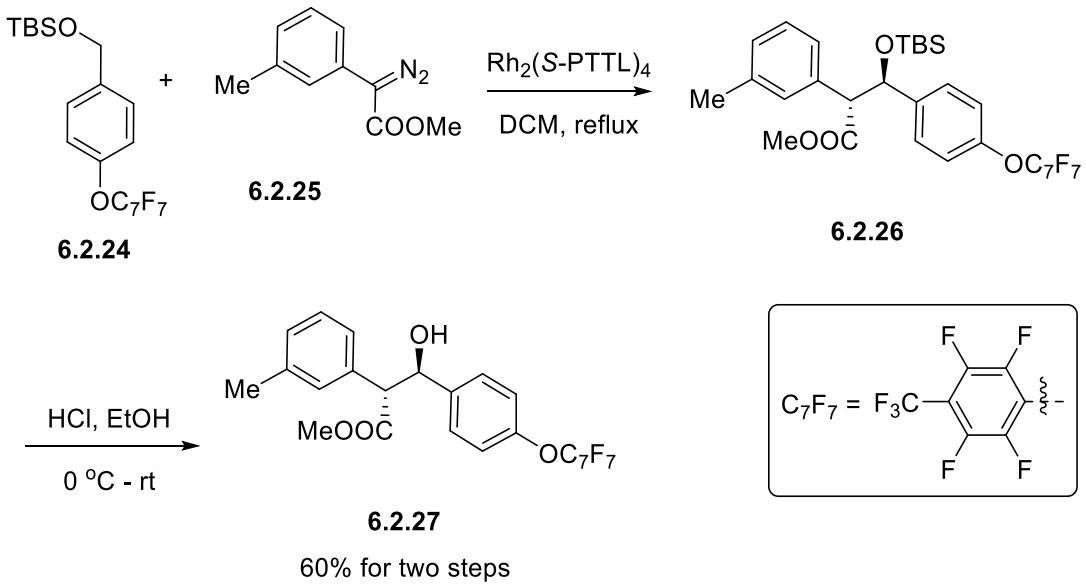
$Pd(PPh_3)_4$ (231 mg, 0.2 mmol, 5 mol%), PPh_3 (106 mg, 0.4 mmol, 10 mol %), benzyl (3-(3-iodophenyl)propyl) carbonate (**6.2.30**) (1.584 g, 4.0 mmol, 1.0 equiv), Ag_2CO_3 (550 mg, 2.0 mmol, 0.5 equiv) were suspended in toluene (16 mL) under argon, followed by addition of NEt_3 (0.73 mL, 5.2 mmol, 1.3 equiv) and 2,2,2-trichloroethyl diazoacetate **4.4** (1.13 g, 5.2 mmol, 1.3 equiv). The resulting reaction was stirred at room temperature for 4 h and then filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in *vacuo* and the residue was purified by column chromatography on silica gel eluting with hexanes: diethyl ether (8: 1) to give the product **6.2.31** as an orange oil (1.40 g, 72%); R_f = 0.30 (hexanes: diethyl ether = 6: 1).

^{1}H NMR (500 MHz; $CDCl_3$) δ 7.44-7.33 (m, 8H), 7.04 (dt, *J* = 6.5, 2.0 Hz, 1H), 5.19 (s, 2H), 4.93 (s, 2H), 4.20 (t, *J* = 6.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.06-2.01 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 155.2, 142.0, 135.3, 129.2, 128.6, 128.6, 128.4, 126.5, 124.8, 124.2, 121.8, 95.1, 73.8, 69.6, 67.3, 32.0, 30.2 (the resonance resulting from the diazo carbon was not detected).

IR (neat): 2956, 2090, 1742, 1710, 1602, 1582, 1454, 1374, 1240, 1134, 904, 788, 695 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{20}O_5N_2Cl_3$ 485.0432 found 485.0437.



Methyl (2*R*,3*R*)-3-hydroxy-3-(4-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy)phenyl)-2-(*m*-tolyl)propanoate (**6.2.27**)

An oven dried 10 ml round bottom flask was charged with *tert*-butyldimethyl((4-(2,3,6-trifluoro-4-(trifluoromethyl)phenoxy)benzyl)oxy)silane (**6.2.24**) (127 mg, 0.28 mmol, 1.0 equiv) and Rh_2(*S*-PTTL)$_4$ (7.0 mg, 0.0056 mmol, 0.02 equiv) in dichloromethane (2 mL). To this solution at reflux (oil bath temperature 50 °C) was added a solution of diazo compound methyl 2-diazo-2-(m-tolyl)acetate (**6.2.25**) (106 mg, 0.56 mmol, 2.0 eq) in

dichloromethane (3 mL) over 2 h under argon. The reaction was then stirred for an additional 1 h. After cooling down to room temperature, the solvent was removed under vacuum and the crude mixture was analyzed by ^{1}H NMR to determine the diastereoselectivity. This crude material was used directly in the next step for desilylation.

To the crude product obtained in the previous step (*c.a.* 320 mg) in ethanol (5 ml) at 0^{o}C added conc HCl (1 mL) dropwise. The resulting mixture was warmed to rt and stirred for 24 h by when TLC indicated completion of reaction. The reaction was diluted with dichloromethane (10 mL), and quenched with saturated aqueous $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layer was washed with saturated brine (10 mL), dried over $MgSO_4$, concentrated, and Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 6: 1 to 3: 1) to afford **6.2.27** as a white solid (84 mg, 60% yield for two steps); m.p. 94-96 °C; R_f = 0.36 (hexanes: ethyl acetate = 3: 1). The stereochemistry of the produce was assigned by analogy to similar products from the same transformation.[25]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 2H), 7.28–7.24 (m, 1H), 7.17-7.15 (m, 3H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.29 (d, *J* = 7.6 Hz, 1H), 3.81 (d, *J* = 7.6 Hz, 1H), 3.57 (s, 3H), 2.76 (brs, 1H), 2.37 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 156.1, 138.5, 137.4, 134.2, 129.8, 128.9, 128.6, 128.4, 126.1, 115.8, 74.3, 59.6, 52.1, 21.4, the carbon signals for the C_7F_7 protecting group were not resolved.

[25] Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6774.

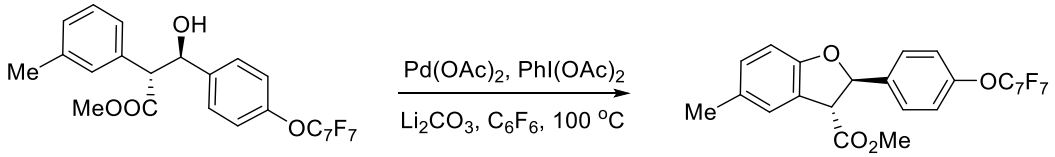
^{19}F NMR (470 MHz, $CDCl_3$): δ -55.9 (t, *J* = 21.6 Hz, 3F), -140.4 (m, 2F), -152.0 (m, 2F).

IR (neat): 3504, 2954, 1732, 1655, 1606, 1502, 1429, 1342, 1230, 1200, 1147, 996, 882, 716 cm^{-1}.

HRMS (NSI) *m/z*: $[M\text{-}OH+H]^+$ calcd for $C_{24}H_{16}O_3F_7$ 485.0982 found 485.0985.

General procedure for Pd-catalyzed *O*-arylation:

A pressure tube (35 mL) was charged with an alcohol substrate (1 equiv), palladium catalyst, lithium carbonate or sodium phosphate dibasic (1.5 equiv) and oxidant (1.5 equiv) in hexafluorobenzene (0.033 M). The tube was capped with Teflon cap and placed in a 100 ºC oil bath. After stirring at this temperature for 24-30 hours, the reaction was cooled down to room temperature and filtered through a plug of silica gel. After the removal of solvent, crude ^{1}H NMR was taken to determine the regioselectivity. The crude residue was purified by flash chromatography.



6.2.27 **6.2.28**

Methyl (2*R*,3*R*)-5-methyl-2-(4-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy)phenyl)-2,3-dihydrobenzofuran-3-carboxylate (6.2.28):

A pressure tube (35 mL) was charged with an alcohol substrate **6.2.27** (25 mg, 0.05 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 0.1 equiv), lithium carbonate (6 mg, 0.075 mmol, 1.5 equiv) and $PhI(OAc)_2$ (24 mg, 0.075 mmol, 1.5 equiv) in hexafluorobenzene (1.5 mL). The tube was capped with Teflon cap and placed in a 100ºC oil bath. After stirring at this temperature for 36 h, the reaction was cooled down to room temperature and filtered through a plug of silica gel. After the removal of solvent, the reaction was analyzed by ^{1}H NMR. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 12: 1) to afford **6.2.28** as a colorless oil (9 mg, 36% yield); R_f = 0.60 (hexanes: ethyl acetate = 4: 1). The stereochemistry of the produce was assigned by analogy to similar products from the same transformation.[25]

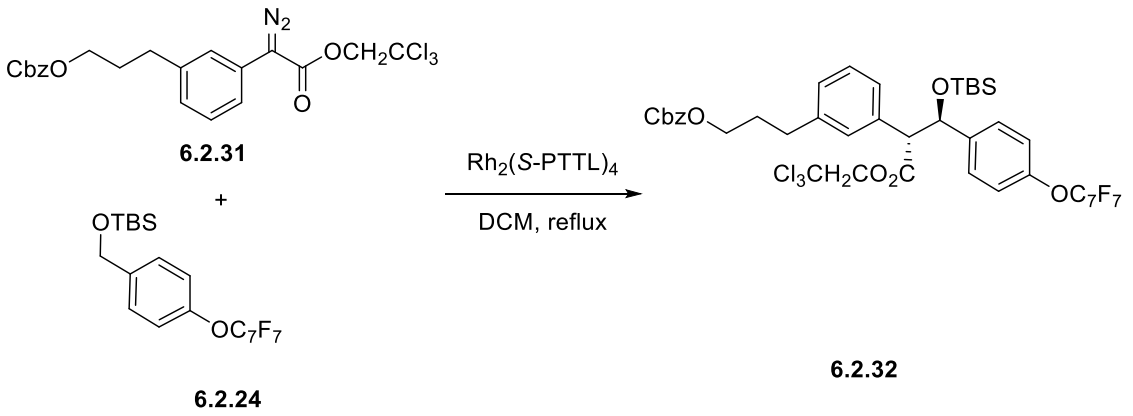
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 9.0, 0.5 Hz, 2H), 7.19-7.18 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.09 (d, *J* = 7.5 Hz, 1H), 4.24 (d, *J* = 7.5 Hz, 1H), 3.86 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 157.1, 156.4, 137.1, 130.6, 130.2, 127.6, 125.6, 123.5, 116.2, 109.5, 84.9, 55.8, 52.8, 20.8, the carbon signals for the C_7F_7 protecting group were not resolved.

^{19}F NMR (470 MHz, $CDCl_3$): δ -55.9 (t, *J* = 21.6 Hz, 3F), -140.1 (m, 2F), -151.7 (m, 2F).

IR (neat): 2927, 1740, 1655, 1607, 1503, 1429, 1342, 1229, 1148, 1093, 996, 882, 716 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{16}O_4F_7$ 501.0931 found 501.0930.



2,2,2-trichloroethyl (2*R*,3*R*)-2-(3-(3-(((benzyloxy)carbonyl)oxy)propyl)phenyl)-3-((tert-butyldimethylsilyl)oxy)-3-(4-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy)phenyl)propanoate (**6.2.32**):

An oven dried 10 ml round bottom flask was charged with *tert*-butyldimethyl((4-(2,3,6-trifluoro-4-(trifluoromethyl)phenoxy)benzyl)oxy)silane (**6.2.24**) (45 mg, 0.10 mmol, 1.0 equiv) and Rh_2(*S*-PTTL)$_4$ (1.3 mg, 0.001 mmol, 0.01 equiv) in dichloromethane (1.0 mL). To this solution at reflux (oil bath temperature 50 ℃) was added a solution of diazo compound 2,2,2-trichloroethyl 2-(3-(3-(((benzyloxy)carbonyl)oxy)propyl)phenyl)-2-diazoacetate (**6.2.31**) (97 mg, 0.20 mmol, 2.0 equiv) in dichloromethane (1.8 mL) over 2 h under argon. The reaction was then stirred for an additional 1 h. After cooling down to room temperature, the solvent was removed under vacuum and the crude mixture was analyzed by ^{1}H NMR to determine the diastereoselectivity. Purified by flash column chromatography (silica gel, hexanes: diethyl ether = 20: 1 to 8: 1) to afford **6.2.32** as a colorless oil (71 mg, 77% yield); R_f = 0.25 (hexanes: diethyl ether = 6: 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.22 (m, 10H), 7.10 (dt, *J* = 7.2, 1.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.16 (s, 2H), 5.09 (d, *J* = 9.2 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.36 (d,

J = 12.0 Hz, 1H), 4.17 (t, *J* = 6.4 Hz, 2H), 3.89 (d, *J* = 9.2 Hz, 1H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.01–1.94 (m, 2H), 0.58 (s, 9H), -0.40 (s, 3H), -0.41 (s, 3H).

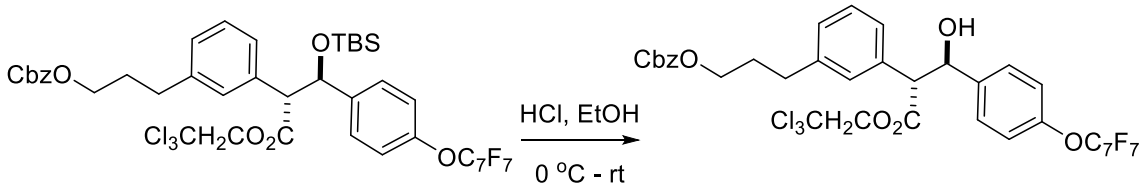
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 156.0, 155.2, 141.1, 138.8, 135.6, 135.2, 129.3, 128.9, 128.6, 128.5, 128.5, 128.4, 127.9, 127.1, 115.6, 94.4, 76.4, 73.8, 69.6, 67.4, 61.2, 31.9, 30.3, 25.4, 17.8, -5.0, -5.8, the carbon signals for the C_7F_7 protecting group were not resolved.

^{19}F NMR (282 MHz, $CDCl_3$): δ -55.8 (t, *J* = 21.7 Hz, 3F), -140.2 (m, 2F), -151.9 (m, 2F).

IR (neat): 2955, 2857, 1746, 1655, 1605, 1502, 1342, 1258, 1230, 1203, 1146, 1086, 997, 882, 863, 778, 716, 697 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{40}O_7Cl_3F_7NaSi$ 933.1389 found 933.1398.

Chiral HPLC: OD-H column, 1 mL/min, 1 % ^{i}PrOH in hexanes, λ = 230 nm. t_R: Major: 9.83 min, Minor: 7.04 min, 97% ee; **[α]$^{20}_D$**: +30.4° (c 2.1, $CHCl_3$).



6.2.32 **6.2.33**

***rac*-2,2,2-trichloroethyl (2*R*,3*R*)-2-(3-(3-(((benzyloxy)carbonyl)oxy)propyl)phenyl)-3-hydroxy-3-(4-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy)phenyl)propanoate (6.2.33)**

To a solution of **6.2.32** (640 mg, 0.70 mmol, 1.0 equiv) in ethanol (4.5 ml) and THF (4.5 mL) at 0^{o}C added conc HCl (3.0 mL) dropwise. The resulting mixture was warmed to rt and stirred for 6 h, then another 2.0 mL of HCl was added dropwise. The reaction was further stirred for 30 h before it was diluted with water (30 ml). The organics were then extracted with AcOEt (3 x 30 ml). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, concentrated, and purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 15: 1 to 5:1) to afford **6.2.33** as a colorless oil (339 mg, 61% yield, 90% based on recovery of staring material) with recovery of starting material **6.2.32** (210 mg); R_f = 0.25 (hexanes: ethyl acetate = 4: 1).

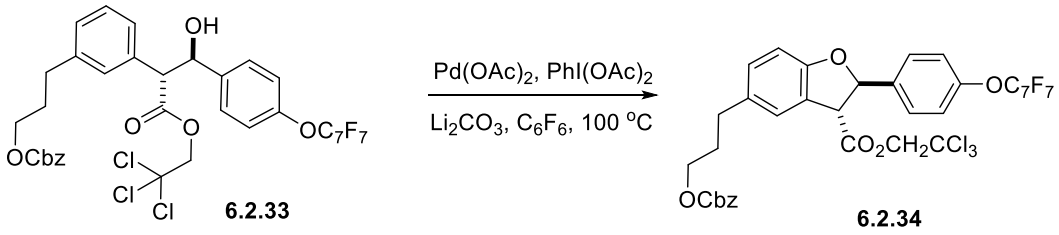
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.37 (m, 7H), 7.34-7.30 (m, 2H), 7.28-7.27 (m, 1H), 7.20–7.18 (m, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 5.33 (d, *J* = 8.5 Hz, 1H), 5.18 (s, 2H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.99 (d, *J* = 8.5 Hz, 1H), 2.74 (t, *J* = 7.5 Hz, 2H), 2.57 (brs, 1H), 2.04–1.98 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 156.3, 155.2, 141.7, 137.1, 135.3, 134.1, 129.3, 129.0, 128.7, 128.6, 128.6, 128.6, 128.4, 126.9, 115.8, 94.4, 74.4, 74.0, 69.6, 67.3, 59.8, 31.8, 30.1, the carbon signals for the C_7F_7 protecting group were not resolved.

^{19}F NMR (470 MHz, $CDCl_3$): δ -55.8 (t, *J* = 21.7 Hz, 3F), -140.2 (m, 2F), -151.8 (m, 2F).

IR (neat): 2957, 1743, 1655, 1502, 1342, 1262, 1229, 1201, 1142, 996, 882, 715, 698 cm^{-1}.

HRMS (NSI) *m/z*: $[M+Cl]^-$ calcd for $C_{35}H_{26}O_7Cl_4F_7$ 831.0326 found 831.0331.



***rac*-2,2,2-trichloroethyl (2*R*,3*R*)-5-(3-(((benzyloxy)carbonyl)oxy)propyl)-2-(4-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy)phenyl)-2,3-dihydrobenzofuran-3-carboxylate (6.2.34)**:

A pressure tube (35 mL) was charged with an alcohol substrate **6.2.33** (151 mg, 0.19 mmol, 1.0 equiv), $Pd(OAc)_2$ (6.4 mg, 0.0285 mmol, 0.15 equiv), lithium carbonate (21 mg, 0.285 mmol, 1.5 equiv) and $PhI(OAc)_2$ (92 mg, 0.285 mmol, 1.5 equiv) in hexafluorobenzene (5.0 mL). The tube was capped with Teflon cap and placed in a 100 ºC oil bath. The reaction was monitord by TLC. After stirring at 100ºC for 80 h, the reaction was cooled down to room temperature and filtered through a plug of silica gel. After the removal of solvent, the reaction was analyzed by ^{1}H NMR. Purified by flash column chromatography (silica gel, hexanes: ethyl acetate = 12: 1) to afford **6.2.34** as a colorless oil (60 mg, 40% yield); R_f = 0.62 (hexanes: ethyl acetate = 4: 1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.34 (m, 8H), 7.09 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.03 (d, *J* = 8.5, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.15 (d, *J* = 7.0 Hz, 1H), 5.19 (s, 2H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 7.0 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 2.69 (dd, *J* = 8.5, 6.5 Hz, 2H), 2.02-1.96 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 157.6, 156.5, 155.2, 136.7, 135.3, 134.1, 130.1, 128.6, 128.6, 128.4, 127.6, 125.6, 122.6, 116.3, 109.8, 94.5, 84.6, 74.6, 69.6, 67.3, 55.6, 31.3, 30.5, the carbon signals for the C_7F_7 protecting group were not resolved.

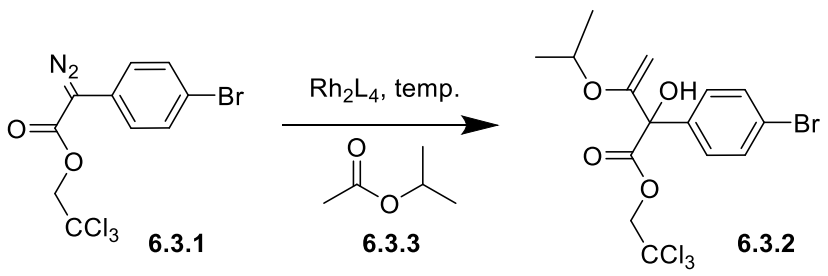
^{19}F NMR (470 MHz, $CDCl_3$): δ -55.8 (t, *J* = 21.6 Hz, 3F), -140.0 (m, 2F), -151.7 (m, 2F).

IR (neat): 2930, 1747, 1655, 1608, 1429, 1505, 1342, 1261, 1230, 1148, 997, 882, 716 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{25}O_7Cl_3F_7$ 795.0549 found 795.0551.

Experimental section for chapter 6.3: Exploration of the formation of a tertiary carbinol *via* a rhodium(II)-catalyzed reaction with isopropyl acetate

General procedure: In a 4 mL screw-cap vial equipped with a magnetic stirring bar, desired dirhodium complex (0.003 mol, 1 mol %) was dissolved in the solvent. Diazo compound 2,2,2-trichloroethyl (*p*-bromophenyl)diazoacetate (0.3 mmol, 112 mg, 1.o equiv) was added in one portion or in a solution of the solvent with a syringe pump. The vial was flushed with argon and capped. Evolution of nitrogen was immediately observed in all cases. The resulting solution was stirred at the indicated temperature until complete conversion of the diazo compound (checked by TLC). The solvent was evaporated and the reaction was analyzed by ^{1}H NMR. The mixture was purified by column chromatography over silica gel (hexanes: diethyl ether = 10: 1).



2,2,2-trichloroethyl 2-(4-bromophenyl)-2-hydroxy-3-isopropoxybut-3-enoate (**6.3.2**):

Prepared according to general procedure. In a 4 mL screw-cap vial equipped with a magnetic stirring bar, $Rh_2(OOct)_4$ (2.3 mg, 0.003 mol, 1 mol %) was dissolved in mixed solvent of isopropyl acetate/dichloromethane (0.5 mL/0.5 mL) under argon. The mixture was heated to 40 ºC. Then diazo compound 2,2,2-trichloroethyl (*p*-bromophenyl)diazoacetate (**6.3.1**) (0.3 mmol, 112 mg, 1.0 equiv) was added in one portion as solids. The resulting solution was stirred at 40 ºC for 0.5 h before the solvent was evaporated. The reaction was analyzed by ^{1}H NMR and the mixture was purified by column chromatography over silica gel (hexanes: diethyl ether = 10: 1) to afford the product **6.3.2** as a sticky colorless solid (91 mg, 68%). R_f = 0.31 (hexanes: diethyl ether = 8: 1). m.p. 31-32 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.9 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.32 (dt, *J* = 12.1, 6.0 Hz, 1H), 4.25 (d, *J* = 3.3 Hz, 1H), 4.17 (d, *J* = 3.3 Hz, 1H), 3.92 (s, 1H), 1.26 (d, *J* = 6.0 Hz, 6H)**.**

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 160.3, 136.2, 131.0, 129.4, 122.9, 94.2, 86.2, 80.6, 75.7, 70.4, 21.5, 21.5.

IR (neat): 3513, 2978, 1752, 1631, 1487, 1265, 1174, 1117, 1075, 1008, 824, 785, 720 cm^{-1}.

HRMS (NSI) *m/z*: $[M+H_2O+H]^+$ calcd. for $C_{15}H_{19}O_5BrCl_3$ 462.9476 found 462.9485.

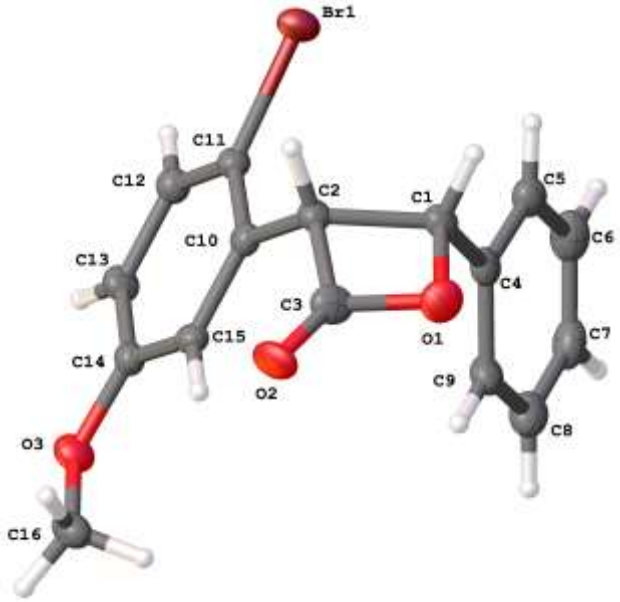
APPENDIX

1. X-ray crystallographic structure of product *cis*-2.39a

Crystal submitted by: **Fu, L.**

Structure solved by: **Bacsa, J.**

Crystal Data and Experimental



Experimental. Colourless prism-shaped crystals of (***cis*-2.39a**) were recrystallised from hexane. A suitable crystal (0.67 × 0.22 × 0.13 mm^3) was selected and mounted on a loop with paratone oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at $T = 110(2)$ K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXS-97** (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with the **ShelXL-97** (Sheldrick, 2008) refinement package using Least Squares minimisation.

Crystal Data. $C_{16}H_{13}BrO_3$,$M_r = 333.17$,monoclinic,$P2_1$ (No. 4),$a = 7.952(2)$ Å,$b = 12.184(4)$ Å,$c = 14.721(4)$ Å,$\beta = 92.596(4)^\circ$, $\alpha = \gamma = 90^\circ$,$V = 1424.8(7)$ $Å^3$,$T = 110(2)$ K,$Z = 4$,$Z' = 2.000$,μ (MoK_α) = 2.889),10404 reflections measured,5160 unique ($R_{int} = 0.0398$) which were used in all calculations.The final wR_2 was 0.1092 (all data) and R_1 was 0.0471 (I > 2(I)).

Compound	***cis*-2.39a**
CCDC	
Formula	$C_{16}H_{13}BrO_3$
$D_{calc.}$/ g cm^{-3}	1.553
μ/mm^{-1}	2.889
Formula Weight	333.17
Colour	colourless
Shape	prism
Max Size/mm	0.67
Mid Size/mm	0.22
Min Size/mm	0.13
T/K	110(2)
Crystal System	monoclinic
Space Group	$P2_1$
a/Å	7.952(2)
b/Å	12.184(4)
c/Å	14.721(4)
α/°	90
β/°	92.596(4)
γ/°	90
V/Å^3	1424.8(7)
Z	4
Z'	2.000
Θ_{min}/°	1.385
Θ_{max}/°	27.484
Measured Refl.	10404
Independent Refl.	5160
Reflections Used	3987
R_{int}	0.0398
Parameters	374
Restraints	148
Largest Peak	1.157
Deepest Hole	-0.376
GooF	1.000
wR_2 (all data)	0.1092
wR_2	0.1002
R_1 (all data)	0.0672
R_1	0.0471

Experimental Extended. A colourless prism-shaped crystal with dimensions 0.67 × 0.22 × 0.13 mm^3 was on a loop with paratone oil on a Data were collected using a Bruker APEX-II CCD diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at T = 110(2) K.

Data were measured using ϕ and ω scans with a narrow frame width scans of 1.00° per frame using MoK_α radiation (fine-focus sealed tube, 45 kV, 30 mA). The total number of runs and images

was based on the strategy calculation from the program **APEX2** (Bruker, 2013). The resulting resolution was $\Theta = 27.484$.

Cell parameters were retrieved using the SAINT v8.34A (Bruker, 2013) software and refined using SAINT v8.34A (Bruker, 2013) on 2781 reflections, 27% of the observed reflections.

Data reduction was performed using the SAINT v8.34A (Bruker, 2013) software which corrects for Lorentz polarisation. The final completeness is 100.00% out to 27.484 in Θ. The absorption coefficient (MU) of this material is 2.889 and the minimum and maximum transmissions are 0.4785 and 0.7457.

The structure was solved by Direct Methods using the **ShelXS-97** (Sheldrick, 2008) structure solution program and refined by Least Squares using **ShelXL-97** (Sheldrick, 2008).

The structure was solved in the space group $P2_1$ (# 4). All non-hydrogen atoms were refined anisotropically. Hydrogens postions were calculated geometrically and refined using the riding model.

The Flack parameter was refined to 0.045(10), confirming the absolute stereochemistry. Determination of absolute structure using Bayesian statistics on Bijvoet differences using the program within **PLATON** (Spek, 2003) also report that we have the correct enantiomer based on this comparison. Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 mans that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

Table 1: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for ***cis*-2.39a**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
Br1'	1780.2(8)	4099.2(5)	-731.6(5)	42.1(3)
O2'	8263(5)	3984(6)	868(3)	40.6(13)
O3'	7588(6)	7034(4)	-1583(3)	35.8(11)
O1'	6028(5)	4306(4)	1778(3)	35.2(11)
C11'	3633(7)	5036(5)	-940(4)	27.1(13)
C3'	6810(7)	4145(6)	989(4)	29.0(13)
C15'	6458(7)	5630(5)	-607(4)	25.7(13)
C2'	5209(7)	4177(5)	386(4)	25.5(13)
C7'	2386(10)	7705(6)	1453(4)	45.3(17)
C13'	4831(8)	6439(6)	-1843(4)	33.7(14)
C8'	4105(10)	7542(6)	1581(5)	43.2(17)
C10'	5098(7)	4960(4)	-401(4)	21.8(12)
C16'	9166(8)	6894(6)	-1150(5)	44.3(18)
C12'	3482(7)	5775(5)	-1664(4)	32.4(14)
C14'	6309(7)	6362(5)	-1328(4)	27.1(13)
C1'	4368(7)	4463(5)	1293(4)	29.4(13)
C4'	3713(8)	5615(5)	1385(4)	28.0(13)

Atom	x	y	z	U_{eq}
C9'	4761(8)	6480(6)	1540(4)	35.6(13)
C6'	1324(10)	6817(6)	1323(4)	44.6(16)
C5'	1968(8)	5779(6)	1287(4)	33.2(14)
Br1	6875.5(7)	1510.7(5)	4360.8(4)	39.0(3)
O3	12644(5)	4436(4)	3424(3)	39.6(12)
O1	11168(5)	1812(4)	6832(3)	40.7(12)
O2	13386(5)	1553(6)	5918(3)	43.7(13)
C6	6393(9)	4268(7)	6380(4)	46.8(17)
C2	10351(6)	1609(6)	5445(3)	27.5(14)
C13	9878(8)	3842(5)	3191(4)	31.5(15)
C15	11554(7)	3056(5)	4425(4)	26.0(12)
C10	10209(7)	2379(5)	4652(4)	25.3(12)
C3	11960(8)	1629(6)	6048(4)	36.5(16)
C16	14241(7)	4341(6)	3854(4)	40.0(17)
C11	8713(7)	2440(5)	4125(4)	26.2(12)
C12	8535(7)	3185(5)	3405(4)	30.3(13)
C14	11377(7)	3758(5)	3693(4)	27.2(13)
C1	9506(7)	1927(5)	6354(4)	28.1(13)
C9	9825(8)	3960(6)	6583(4)	35.1(14)
C4	8814(8)	3063(5)	6423(4)	31.1(14)
C5	7085(9)	3215(6)	6339(4)	35.4(15)
C8	9136(10)	5000(6)	6640(5)	44.3(17)
C7	7413(9)	5141(6)	6532(4)	44.5(17)

Table 2: Anisotropic Displacement Parameters ($\times 10^4$) ***cis*-2.39a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[a^{*2} \times U_{11} + ... 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1'	32.1(4)	44.1(7)	49.3(5)	4.0(4)	-5.6(3)	-10.4(3)
O2'	22(2)	53(4)	46(3)	27(3)	-1.5(18)	14(2)
O3'	40(3)	28(3)	40(3)	8(2)	4.0(19)	-5(2)
O1'	38(2)	39(3)	29(2)	5(2)	-4.8(16)	10(2)
C11'	26(3)	25(3)	30(3)	0(3)	3(2)	-1(2)
C3'	35(3)	20(3)	31(3)	8(3)	-3(2)	4(3)
C15'	26(3)	23(3)	28(3)	-3(3)	0(2)	4(2)
C2'	31(3)	18(3)	27(3)	-1(3)	-1(2)	1(2)
C7'	69(4)	37(4)	30(4)	6(3)	11(3)	17(3)
C13'	44(3)	35(4)	22(3)	3(3)	4(2)	6(3)
C8'	67(4)	33(3)	31(4)	1(3)	14(3)	3(3)
C10'	28(3)	17(3)	20(3)	-5(2)	1(2)	2(2)
C16'	32(4)	35(4)	66(5)	9(4)	9(3)	-5(3)
C12'	31(3)	39(4)	26(3)	-4(3)	-4(2)	6(3)
C14'	30(3)	26(4)	26(3)	-2(3)	7(2)	6(3)
C1'	34(3)	27(3)	27(3)	6(2)	1(2)	-1(2)
C4'	36(3)	31(3)	17(3)	7(2)	5(2)	0(2)
C9'	41(3)	34(3)	33(3)	-1(3)	10(2)	-2(3)
C6'	57(4)	45(4)	33(4)	4(3)	13(3)	18(3)
C5'	36(3)	39(3)	25(3)	2(3)	5(2)	3(2)
Br1	33.9(4)	44.3(6)	38.3(4)	5.9(4)	-3.2(3)	-12.4(3)
O3	42(3)	40(3)	38(3)	9(2)	5(2)	-9(2)
O1	42(3)	46(3)	32(2)	7(2)	-8.8(19)	5(2)
O2	19(2)	50(4)	63(3)	-6(4)	7.8(19)	0(2)
C6	47(3)	56(4)	37(4)	3(3)	3(3)	14(3)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C2	31(3)	24(4)	28(3)	1(3)	4(2)	-3(3)
C13	36(3)	29(4)	29(3)	9(3)	4(2)	-3(2)
C15	27(3)	23(3)	28(3)	-2(2)	1(2)	-2(2)
C10	28(3)	25(3)	24(3)	-2(2)	3(2)	3(2)
C3	40(4)	36(5)	32(3)	13(3)	-8(3)	-1(3)
C16	37(3)	34(4)	51(4)	-2(3)	13(3)	-5(3)
C11	29(3)	23(3)	26(3)	0(2)	2(2)	-3(2)
C12	32(3)	31(3)	28(3)	1(2)	3(2)	0(2)
C14	30(3)	27(3)	25(3)	0(2)	5(2)	-1(2)
C1	27(3)	30(4)	27(3)	6(3)	1(2)	-2(2)
C9	40(3)	34(3)	32(3)	3(3)	11(2)	-2(2)
C4	37(3)	35(3)	22(3)	5(3)	5(2)	0(2)
C5	37(3)	43(4)	26(3)	2(3)	1(2)	0(3)
C8	59(4)	36(4)	38(4)	4(3)	10(3)	0(3)
C7	59(4)	43(4)	32(4)	0(3)	12(3)	13(3)

Table 3: Bond Lengths in Å for ***cis*-2.39a**.

Atom	Atom	Length/Å
Br1'	C11'	1.900(6)
O2'	C3'	1.193(7)
O3'	C16'	1.393(7)
O3'	C14'	1.371(7)
O1'	C3'	1.356(7)
O1'	C1'	1.485(7)
C11'	C10'	1.384(7)
C11'	C12'	1.395(8)
C3'	C2'	1.519(7)
C15'	C10'	1.399(7)
C15'	C14'	1.387(8)
C2'	C10'	1.501(8)
C2'	C1'	1.559(8)
C7'	C8'	1.385(10)
C7'	C6'	1.381(10)
C13'	C12'	1.379(9)
C13'	C14'	1.372(8)
C8'	C9'	1.397(10)
C1'	C4'	1.505(8)
C4'	C9'	1.357(9)
C4'	C5'	1.402(8)
C6'	C5'	1.366(9)
Br1	C11	1.894(6)
O3	C16	1.398(7)
O3	C14	1.375(7)
O1	C3	1.358(8)
O1	C1	1.475(7)
O2	C3	1.163(7)
C6	C5	1.399(10)
C6	C7	1.350(11)
C2	C10	1.497(8)
C2	C3	1.523(7)
C2	C1	1.572(7)
C13	C12	1.383(8)

Atom	Atom	Length/Å
C13	C14	1.378(8)
C15	C10	1.403(8)
C15	C14	1.377(8)
C10	C11	1.392(8)
C11	C12	1.397(8)
C1	C4	1.494(9)
C9	C4	1.371(9)
C9	C8	1.385(10)
C4	C5	1.387(9)
C8	C7	1.383(10)

Table 4: Bond Angles in ° for ***cis*-2.39a**.

Atom	Atom	Atom	Angle/°
C14'	O3'	C16'	117.7(5)
C3'	O1'	C1'	92.2(4)
C10'	C11'	Br1'	120.4(4)
C10'	C11'	C12'	121.5(5)
C12'	C11'	Br1'	118.1(4)
O2'	C3'	O1'	129.5(5)
O2'	C3'	C2'	135.1(6)
O1'	C3'	C2'	95.3(5)
C14'	C15'	C10'	120.1(5)
C3'	C2'	C1'	83.5(4)
C10'	C2'	C3'	119.1(5)
C10'	C2'	C1'	120.4(5)
C6'	C7'	C8'	120.0(7)
C14'	C13'	C12'	120.6(6)
C7'	C8'	C9'	119.7(7)
C11'	C10'	C15'	118.4(5)
C11'	C10'	C2'	120.3(5)
C15'	C10'	C2'	121.3(5)
C13'	C12'	C11'	119.0(6)
O3'	C14'	C15'	123.7(5)
O3'	C14'	C13'	115.8(5)
C13'	C14'	C15'	120.5(6)
O1'	C1'	C2'	88.6(4)
O1'	C1'	C4'	112.3(5)
C4'	C1'	C2'	116.7(5)
C9'	C4'	C1'	121.8(6)
C9'	C4'	C5'	120.2(6)
C5'	C4'	C1'	117.9(6)
C4'	C9'	C8'	119.9(6)
C5'	C6'	C7'	120.2(7)
C6'	C5'	C4'	119.9(7)
C14	O3	C16	118.8(5)
C3	O1	C1	92.9(4)
C7	C6	C5	119.7(7)
C10	C2	C3	118.4(5)
C10	C2	C1	119.3(5)
C3	C2	C1	83.1(4)
C14	C13	C12	119.6(6)

Atom	Atom	Atom	Angle/°
C14	C15	C10	120.0(5)
C15	C10	C2	121.5(5)
C11	C10	C2	120.1(5)
C11	C10	C15	118.5(5)
O1	C3	C2	95.1(5)
O2	C3	O1	130.3(6)
O2	C3	C2	134.7(6)
C10	C11	Br1	120.8(4)
C10	C11	C12	120.9(5)
C12	C11	Br1	118.3(4)
C13	C12	C11	119.7(6)
O3	C14	C13	115.3(5)
O3	C14	C15	123.3(5)
C15	C14	C13	121.4(5)
O1	C1	C2	88.5(4)
O1	C1	C4	112.4(5)
C4	C1	C2	117.3(5)
C4	C9	C8	120.6(7)
C9	C4	C1	122.3(6)
C9	C4	C5	118.7(6)
C5	C4	C1	119.0(6)
C4	C5	C6	120.6(7)
C7	C8	C9	120.0(7)
C6	C7	C8	120.4(7)

Table 5: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for ***cis*-2.39a**. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H15'	7464	5584	-261	31
H7'	1948	8413	1455	54
H13'	4739	6943	-2317	40
H8'	4818	8136	1694	52
H16A	9973	7347	-1438	67
H16B	9497	6139	-1190	67
H16C	9116	7100	-522	67
H12'	2487	5819	-2019	39
H9'	5915	6367	1618	43
H6'	167	6925	1260	54
H5'	1251	5182	1198	40
H6	5236	4367	6303	56
H2	10057	858	5261	33
H13	9770	4338	2712	38
H15	12564	3031	4768	31
H16D	15020	4802	3553	60
H16E	14610	3592	3827	60
H16F	14190	4562	4478	60
H12	7517	3238	3071	36
H9	10984	3869	6655	42
H5	6380	2612	6254	42
H8	9832	5603	6750	53
H7	6955	5841	6565	53
H1	8800(50)	1310(30)	6560(30)	13(13)
H1'	3630(50)	3840(30)	1450(30)	19(10)
H2'	4940(70)	3436(19)	140(30)	19(10)

Table 6: Hydrogen Bond information for ***cis*-2.39a**.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
C15	H15	O2	0.93	2.54	3.165(8)	125.2
C12	H12	O1'	0.93	2.55	3.338(7)	142.5

Citations

, Bruker axs, Madison, WI (2013).

A.L. Spek, *J. Appl. Cryst.*, (2003), **36**, 7-13.

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

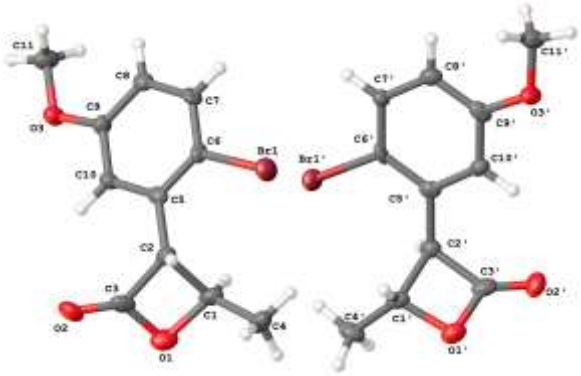
Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

2. X-ray crystallographic structure of product *trans*-2.39b

Crystal submitted by: **Fu, L.**

Structure solved by: **Bacsa, J**

Crystal Data and Experimental



Experimental. Single colourless prism-shaped crystals of (***trans-2.39b***) were recrystallised from hexane by slow evaporation. A suitable crystal (0.73 × 0.73 × 0.15 mm^3) was selected and mounted on a loop with paratone oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at T = 110(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXS-97** (Sheldrick, 2008) structure solution program, using the Direct Methods solution method. The model was refined with the **ShelXL-97** (Sheldrick, 2008) refinement package using Least Squares minimisation.

Crystal Data. $C_{11}H_{11}BrO_3$,M_r = 271.11,orthorhombic,$P2_12_12_1$ (No. 19),a = 12.060(2) Å,b = 12.066(2) Å,c = 14.641(3) Å,α = β = γ = 90 °,V = 2130.5(6) $Å^3$,T = 110(2) K,Z = 8,Z' = 2.000,μ (MoK_α) = 3.842),26029 reflections measured,5736 unique (R_{int} = 0.0858) which were used in all calculations.The final wR_2 was 0.0875 (all data) and R_1 was 0.0424 (I > 2(I)).

Compound	***trans*-2.39b**
CCDC	n/a
Formula	$C_{11}H_{11}BrO_3$
$D_{calc.}$/ g cm^{-3}	1.690
μ/mm^{-1}	3.842
Formula Weight	271.11
Colour	colourless
Shape	prism
Max Size/mm	0.73
Mid Size/mm	0.73
Min Size/mm	0.15
T/K	110(2)
Crystal System	orthorhombic
Space Group	$P2_12_12_1$
a/Å	12.060(2)
b/Å	12.066(2)
c/Å	14.641(3)
α/°	90
β/°	90
γ/°	90
V/$Å^3$	2130.5(6)
Z	8
Z'	2.000
Θ_{min}/°	1.689
Θ_{max}/°	29.130
Measured Refl.	26029
Independent Refl.	5736
Reflections Used	5086
R_{int}	0.0858
Parameters	279
Restraints	64
Largest Peak	1.019
Deepest Hole	-0.686
GooF	1.016
wR_2 (all data)	0.0875
wR_2	0.0832
R_1 (all data)	0.0528
R_1	0.0424

Experimental Extended. A colourless prism-shaped crystal with dimensions 0.73 × 0.73 × 0.15 mm^3 was mounted on on a loop with paratone oil. Data were collected using a Bruker APEX-II CCD diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at $T = 110(2)$ K.

Data were measured using ϕ and ω scans scans of 1.00° per frame for 10 s using MoK_α radiation (fine-focus sealed tube, 45 kV, 30 mA). The total number of runs and images was based on the strategy calculation from the program **APEX2** (Bruker, 2013). The actually achieve resoltion was $\Theta = 29.130$.

Cell parameters were retrieved using the SAINT v8.34A (Bruker, 2013) software and refined using SAINT v8.34A (Bruker, 2013) on 8641 reflections, 33% of the observed reflections.

Data reduction was performed using the SAINT v8.34A (Bruker, 2013) software which corrects for Lorentz polarisation. The final completeness is 100.00% out to 29.130 in Θ. The absorption coefficient (MU) of this material is 3.842 and the minimum and maximum transmissions are 0.3793 and 0.7462.

The structure was solved by Direct Methods using the **ShelXS-97** (Sheldrick, 2008) structure solution program and refined by Least Squares using **ShelXL-97** (Sheldrick, 2008).

The structure was solved in the space group $P2_12_12_1$ (# 19). The crystal was a pseudo-merohedral twin. The unit cell appeared to be tetragonal with a=b. The correct system is orthorhombic with a~b and the twin law is 010 100 00-1. The BASF parameter refined to 0.46. All non-hydrogen atoms were refined anisotropically. Hydrogens postions were calculated geometrically and refined using the riding model.

The Flack parameter was refined to 0.029(7), confirming the absolute stereochemistry. Determination of absolute structure using Bayesian statistics on Bijvoet differences using the program within **PLATON** (Spek, 2003) also report that we have the correct enantiomer based on this comparison. Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 mans that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

Refined as a 2-component twin.

Table 1: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for ***trans-2.39b***. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
Br1'	1941.5(6)	847.9(6)	-4932.1(6)	28.86(17)
O3'	-373(4)	-3561(4)	-5124(4)	30.4(13)
O1'	-2088(4)	1104(4)	-5255(3)	30.1(13)
O2'	-2281(5)	-227(5)	-6345(4)	34.5(13)
C4'	-600(7)	2450(6)	-4942(7)	28.7(16)
C8'	1294(6)	-2511(6)	-4793(4)	22.7(15)

Atom	x	y	z	U_{eq}
C7'	1791(6)	-1481(5)	-4744(4)	19.7(14)
C2'	-505(6)	416(6)	-5589(4)	21.7(14)
C6'	1205(6)	-537(5)	-5000(5)	19.5(13)
C9'	205(6)	-2590(5)	-5081(6)	24.2(15)
C11'	184(6)	-4549(6)	-4853(6)	30.1(17)
C5'	113(6)	-590(6)	-5300(4)	18.9(14)
C1'	-955(6)	1264(6)	-4880(5)	24.0(16)
C3'	-1727(6)	307(6)	-5846(5)	25.3(15)
C10'	-376(6)	-1635(6)	-5330(5)	21.5(14)
Br1	1636.0(7)	-32.5(7)	-2360.6(5)	32.07(18)
O3	5843(4)	2599(4)	-2730(4)	28.7(13)
C8	4913(6)	827(6)	-2851(4)	20.9(13)
O1	1098(5)	3951(4)	-2343(4)	34.9(13)
C2	1935(6)	2485(6)	-1924(5)	22.9(13)
O2	2469(5)	4380(4)	-1319(4)	36.3(14)
C11	6841(6)	2108(6)	-3089(5)	30.6(17)
C10	3971(6)	2486(6)	-2341(5)	18.9(14)
C4	-126(7)	2335(8)	-2513(7)	33.1(18)
C7	3910(6)	249(5)	-2749(5)	23.3(15)
C6	2957(6)	795(5)	-2453(4)	19.9(12)
C3	1951(6)	3739(6)	-1763(5)	26.7(15)
C9	4928(6)	1954(5)	-2647(5)	20.7(14)
C5	2972(6)	1911(6)	-2241(4)	20.0(13)
C1	1032(6)	2784(6)	-2636(6)	25.8(16)

Table 2: Anisotropic Displacement Parameters ($\times 10^4$) ***trans-2.39b***. The anisotropic displacement factor exponent takes the form: $-2\pi^2[a^{*2} \times U_{11} + ... 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1'	22.6(3)	21.8(3)	42.1(4)	3.0(4)	-0.9(4)	-5.4(3)
O3'	23(3)	18(2)	51(4)	0(3)	-4(3)	0(2)
O1'	22(3)	33(3)	35(3)	5(2)	2(2)	3(2)
O2'	30(3)	35(4)	39(3)	0(3)	-12(2)	-2(3)
C4'	40(4)	20(3)	26(4)	3(3)	2(4)	7(3)
C8'	23(3)	24(3)	21(4)	2(3)	4(3)	5(3)
C7'	19(3)	16(3)	24(3)	-2(2)	-1(3)	0(3)
C2'	24(4)	23(3)	18(3)	1(3)	1(3)	3(3)
C6'	22(3)	15(3)	21(3)	-5(3)	6(3)	-9(2)
C9'	32(4)	17(3)	23(3)	0(3)	10(3)	-2(3)
C11'	25(4)	22(3)	43(5)	1(3)	6(4)	2(3)
C5'	21(3)	21(4)	14(3)	3(2)	6(3)	4(3)
C1'	25(4)	27(3)	20(4)	3(3)	1(3)	8(3)
C3'	24(4)	28(4)	25(3)	10(3)	3(3)	7(3)
C10'	17(3)	27(4)	20(3)	-1(3)	0(3)	4(3)
Br1	28.8(4)	22.6(4)	44.8(4)	0.7(4)	2.2(3)	-6.8(3)
O3	23(3)	20(3)	43(3)	-4(3)	3(3)	-1(2)
C8	23(3)	21(3)	19(3)	4(3)	-1(2)	2(3)
O1	30(3)	28(3)	46(3)	10(2)	3(3)	4(2)
C2	20(3)	26(3)	23(3)	0(3)	-2(3)	2(3)
O2	37(4)	24(3)	48(4)	-12(3)	4(3)	5(2)
C11	22(4)	27(4)	42(4)	6(3)	8(4)	1(3)
C10	23(3)	14(3)	20(3)	0(3)	3(3)	1(2)
C4	21(4)	46(5)	32(4)	-7(4)	-3(3)	4(3)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C7	27(3)	11(3)	32(4)	2(3)	-1(3)	1(2)
C6	20(3)	16(3)	24(3)	6(2)	-3(3)	-7(2)
C3	24(3)	24(3)	32(4)	1(3)	12(3)	5(3)
C9	18(3)	22(3)	22(3)	0(3)	2(3)	-3(2)
C5	27(3)	19(3)	14(3)	2(2)	-2(3)	4(2)
C1	23(4)	29(3)	25(3)	1(3)	3(3)	8(3)

Table 3: Bond Lengths in Å for ***trans-2.39b***.

Atom	Atom	Length/Å
Br1'	C6'	1.895(6)
O3'	C9'	1.365(8)
O3'	C11'	1.425(9)
O1'	C1'	1.485(9)
O1'	C3'	1.366(9)
O2'	C3'	1.181(9)
C4'	C1'	1.497(11)
C8'	C7'	1.381(10)
C8'	C9'	1.382(10)
C7'	C6'	1.392(10)
C2'	C5'	1.486(9)
C2'	C1'	1.556(10)
C2'	C3'	1.527(10)
C6'	C5'	1.390(10)
C9'	C10'	1.397(11)
C5'	C10'	1.393(10)
Br1	C6	1.885(6)
O3	C11	1.440(9)
O3	C9	1.356(8)
C8	C7	1.404(10)
C8	C9	1.393(10)
O1	C3	1.359(9)
O1	C1	1.474(9)
C2	C3	1.532(10)
C2	C5	1.503(11)
C2	C1	1.550(11)
O2	C3	1.188(9)
C10	C9	1.394(10)
C10	C5	1.398(10)
C4	C1	1.509(11)
C7	C6	1.394(10)
C6	C5	1.382(9)

Table 4: Bond Angles in ° for ***trans-2.39b***.

Atom	Atom	Atom	Angle/°
C9'	O3'	C11'	117.7(6)
C3'	O1'	C1'	91.9(5)
C7'	C8'	C9'	119.3(6)
C8'	C7'	C6'	120.2(6)
C5'	C2'	C1'	121.4(6)
C5'	C2'	C3'	118.9(6)
C3'	C2'	C1'	83.4(5)
C7'	C6'	Br1'	118.0(5)
C5'	C6'	Br1'	120.1(5)
C5'	C6'	C7'	121.9(6)
O3'	C9'	C8'	124.0(6)
O3'	C9'	C10'	116.0(7)
C8'	C9'	C10'	120.0(6)
C6'	C5'	C2'	121.9(6)
C6'	C5'	C10'	116.9(6)
C10'	C5'	C2'	121.2(6)
O1'	C1'	C4'	111.4(6)
O1'	C1'	C2'	89.4(5)
C4'	C1'	C2'	119.2(7)
O1'	C3'	C2'	95.2(5)
O2'	C3'	O1'	126.5(7)
O2'	C3'	C2'	138.2(7)
C5'	C10'	C9'	121.7(7)
C9	O3	C11	118.4(6)
C9	C8	C7	118.2(7)
C3	O1	C1	92.5(6)
C3	C2	C1	83.2(5)
C5	C2	C3	119.5(6)
C5	C2	C1	119.0(6)
C9	C10	C5	121.2(6)
C6	C7	C8	120.6(6)
C7	C6	Br1	118.0(5)
C5	C6	Br1	120.8(6)
C5	C6	C7	121.3(7)
O1	C3	C2	94.6(6)
O2	C3	O1	128.2(7)
O2	C3	C2	137.2(7)
O3	C9	C8	123.5(6)
O3	C9	C10	116.0(6)
C8	C9	C10	120.5(6)
C10	C5	C2	121.4(6)
C6	C5	C2	120.4(7)
C6	C5	C10	118.2(7)
O1	C1	C2	89.4(6)
O1	C1	C4	111.0(6)
C4	C1	C2	119.1(7)

Table 5: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for ***trans-2.39b***. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H4'A	-748	2725	-5545	43
H4'B	180	2503	-4818	43
H4'C	-1003	2882	-4503	43
H8'	1688	-3145	-4634	27
H7'	2518	-1418	-4539	24
H2'	-99	803	-6074	26
H11A	834	-4649	-5223	45
H11B	-303	-5171	-4931	45
H11C	397	-4491	-4223	45
H1'	-894	981	-4254	29
H10'	-1109	-1699	-5521	26
H8	5550	466	-3050	25
H11D	7085	1528	-2687	46
H11E	7408	2663	-3135	46
H11F	6694	1805	-3683	46
H10	3998	3238	-2202	23
H4A	-333	2384	-1881	50
H4B	-148	1575	-2705	50
H4C	-635	2762	-2875	50
H7	3882	-504	-2881	28
H1	1298	2685	-3263	31
H2	1560(60)	2170(60)	-1400(30)	31

Citations

, Bruker axs, Madison, WI (2013).

A.L. Spek, *J. Appl. Cryst.*, (2003), **36**, 7-13.

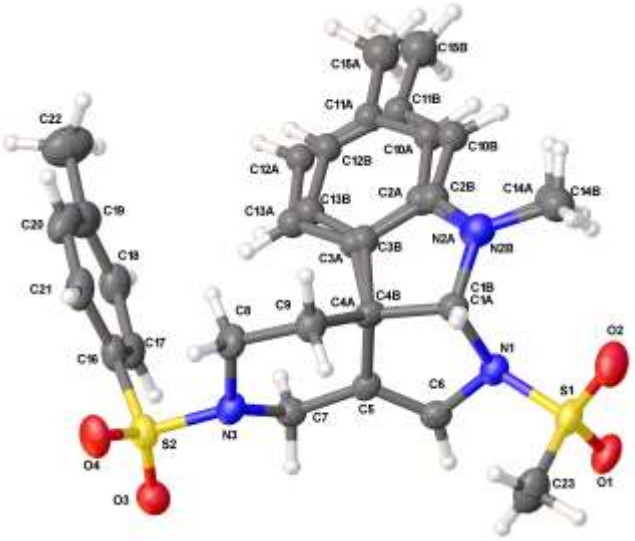
O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

3. X-ray crystallographic structure of product 5.2l

Submitted by: **Liangbing Fu**
Emory University
Solved by: **John Bacsa**
Sample ID: **5.2L**

Crystal Data and Experimental



Experimental. Single colourless prism-shaped crystals of (**5.2L**) were recrystallised from a mixture of hexane and diethyl ether by slow evaporation. A suitable crystal (0.75×0.35×0.14) was selected and mounted on a loop with paratone oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at T = 173(2) K during data collection. The structure was solved with the **XT** (Sheldrick, 2008) structure solution program, using direct and dual-space solution methods and by using **Olex2** (Dolomanov et al., 2009), as the graphical interface. The model was refined with version of **ShelXL-97** (Sheldrick, 2008) using Least Squares minimisation.

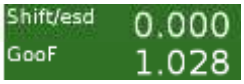
Crystal Data. $C_{23}H_{27}N_3O_4S_2$, M_r = 473.59, monoclinic, $P2_1$ (No. 4), a = 8.4373(3) Å, b = 6.1045(2) Å, c = 22.2510(8) Å, β = 92.183(2)°, $\alpha = \gamma = 90°$, V = 1145.22(7) Å^3, T = 173(2) K, Z = 2, Z' = 1, μ(CuK_α) = 2.403, 7552 reflections measured, 3229 unique (R_{int} = 0.0367) which were used in all calculations. The final wR_2 was 0.1004 (all data) and R_1 was 0.0382 (I > 2(I)).

Compound	**5.2L**
Formula	$C_{23}H_{27}N_3O_4S_2$
$D_{calc.}$/ g cm^{-3}	1.373
μ/mm^{-1}	2.403
Formula Weight	473.59
Colour	colourless
Shape	prism
Max Size/mm	0.75
Mid Size/mm	0.35
Min Size/mm	0.14
T/K	173(2)
Crystal System	monoclinic
Flack Parameter	0.048(10)
Hooft Parameter	0.048(11)
Space Group	$P2_1$
a/Å	8.4373(3)
b/Å	6.1045(2)
c/Å	22.2510(8)
α/°	90
β/°	92.183(2)
γ/°	90
V/Å^3	1145.22(7)
Z	2
Z'	1
Θ_{min}/°	1.987
Θ_{max}/°	67.117
Measured Refl.	7552
Independent Refl.	3229
Reflections Used	3150
R_{int}	0.0367
Parameters	322
Restraints	64
Largest Peak	0.362
Deepest Hole	-0.263
GooF	1.028
wR_2 (all data)	0.1004
wR_2	0.0998
R_1 (all data)	0.0389
R_1	0.0382

Structure Quality Indicators

Reflections:

Refinement:



A colorless prism-shaped crystal with dimensions 0.75×0.35×0.14 was mounted on a loop with paratone oil. Data were collected using a Bruker APEX-II CCD diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at T = 173(2) K.

Data were measured using ϕ and ω scans of 1° per frame with variable scan rates using CuK$_\alpha$ radiation (sealed tube, 40 kV, 35 mA). The total number of runs and images was based on the strategy calculation from the program **APEX2** (Bruker, 2014). The actually achieved resolution was Θ = 67.117°.

Cell parameters were retrieved using the **APEX2** (Bruker, 2014) software and refined using **SAINT** (Bruker, V8.34A, 2013) on 7231 reflections, 96% of the observed reflections. Data reduction was performed using the **SAINT** (Bruker, V8.34A, 2013) software which corrects for Lorentz polarisation. The final completeness is 90% out to 67.117 in Θ. The absorption coefficient (μ) of this material is 2.403 mm^{-1} and the minimum and maximum transmissions are 0.4533 and 0.7529.

The structure was solved in the space group P2$_1$ (# 4) by direct and dual-space solution methods using the **XT** (Sheldrick, 2008) structure solution program and refined by Least Squares using version of **ShelXL-97** (Sheldrick, 2008). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were located or calculated geometrically and refined using restraints and constraints.

The Flack parameter was refined to 0.048(10). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.048(11). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

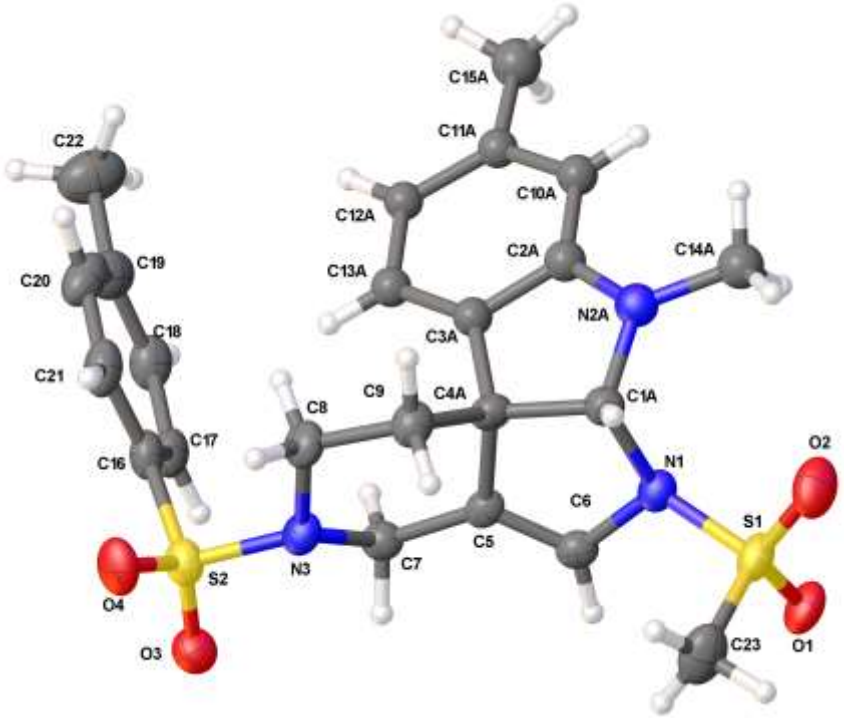


Figure 1: View of the asymmetric unit of **5.2L** with one of the two disorder components.

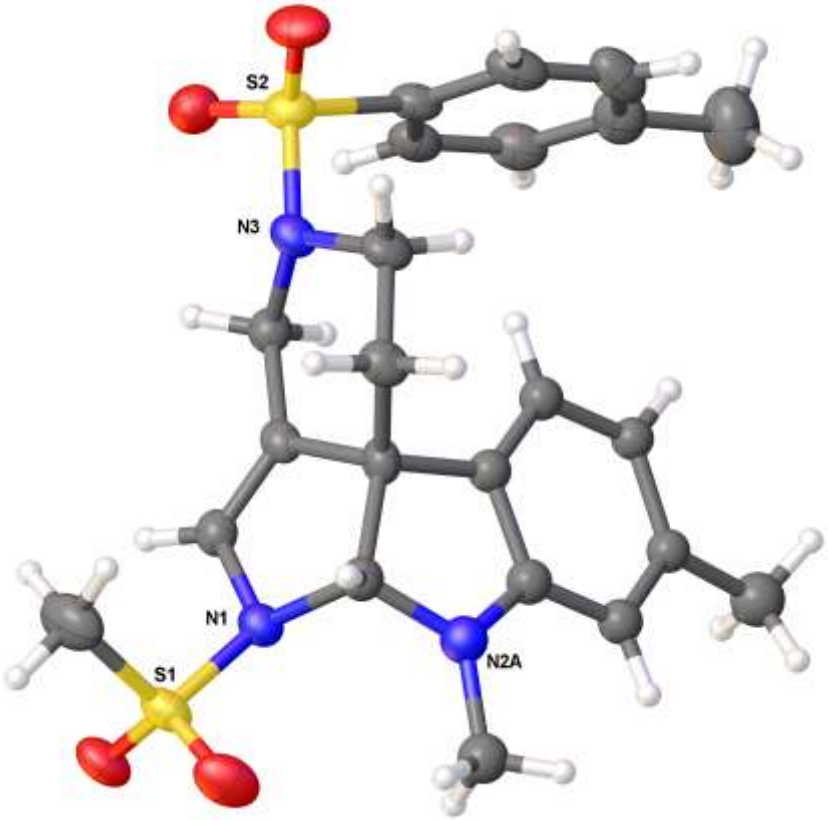


Figure 2: View of the asymmetric unit of **5.2L** with one of the two disorder components.

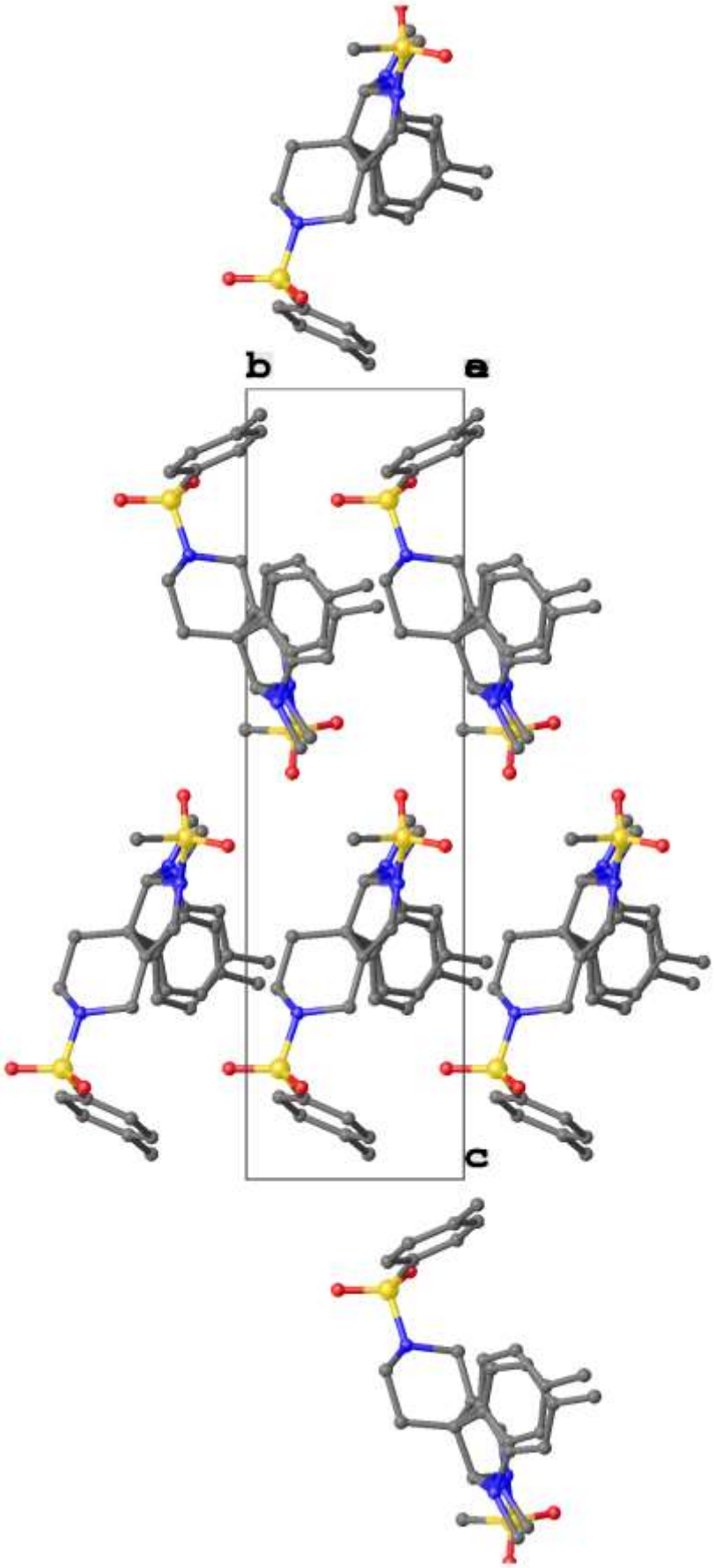
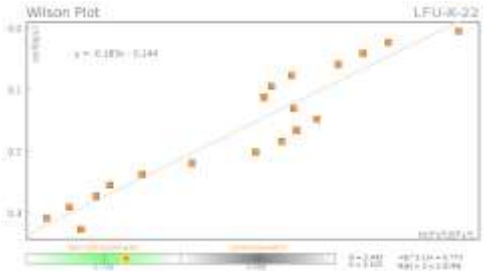
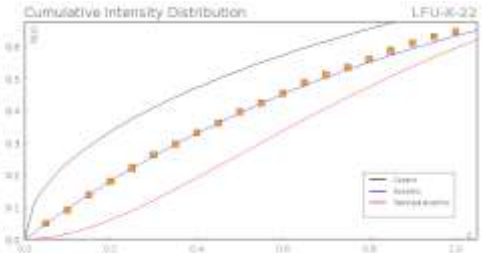
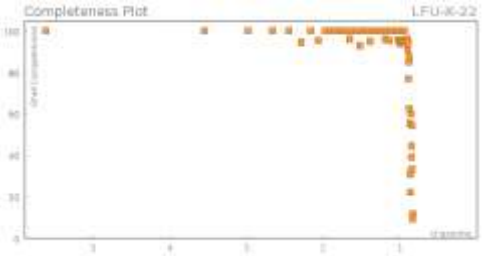

b
a
c

Figure 3: Packing diagram of **5.2L**.

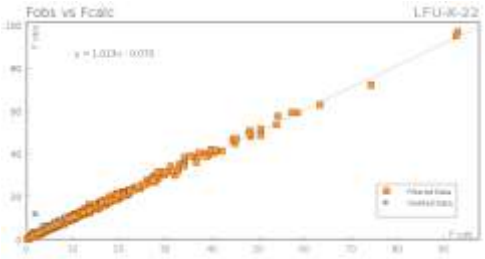
Data Plots: Diffraction Data

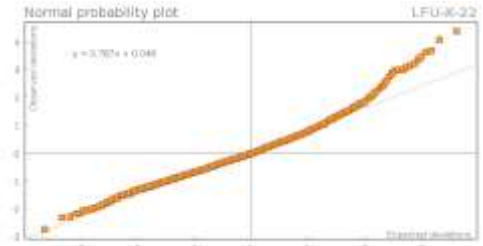






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	7566	Unique reflections	3229
Completeness	0.789	Mean I/σ	17.47
hklsub>max</sub> collected	(9, 6, 23)	hklsub>min</sub> collected	(-9, -6, -26)
hkl_{max} used	(9, 6, 26)	hkl_{min} used	(-9, -6, 0)
Lim d_{max} collected	100.0	Lim d_{min} collected	0.77
d_{max} used	22.23	d_{min} used	0.84
Friedel pairs	1478	Friedel pairs merged	0
Inconsistent equivalents	0	R_{int}	0.0367
R_{sigma}	0.046	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	12
Multiplicity	(2786, 1150, 584, 182)	Maximum mulitplicity	6
Removed systematic absences	2	Filtered off (Shel/OMIT)	0

Images of the Crystal on the Diffractometer



Table 1: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **5.2L**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
C14A	3781(10)	2074(16)	5597(3)	38.7(14)
N2A	4191(6)	3310(13)	6132(2)	32.9(9)
C2A	3448(9)	2921(15)	6677(3)	31.2(10)
C3A	4118(10)	4219(19)	7135(3)	27.5(9)
C4A	5534(4)	5393(7)	6867.4(14)	26.9(9)
C1A	5627(4)	4544(7)	6222.9(14)	27.8(8)
C10A	2234(8)	1459(13)	6796(4)	29.8(12)
C11A	1740(8)	1238(13)	7382(4)	28.5(12)
C15A	561(9)	-539(16)	7520(5)	44.7(17)
C12A	2359(7)	2604(15)	7834(3)	27.2(11)
C13A	3574(9)	4087(14)	7714(3)	29.1(11)
C14B	3864(12)	2520(20)	5464(4)	38.7(14)
N2B	4145(7)	3589(17)	6034(3)	32.9(9)
C2B	3443(11)	2906(19)	6560(3)	31.2(10)
C3B	4075(13)	4080(20)	7055(3)	27.5(9)
C4B	5534(4)	5393(7)	6867.4(14)	26.9(9)
C1B	5627(4)	4544(7)	6222.9(14)	27.8(8)
C10B	2306(10)	1282(15)	6602(4)	29.8(12)
C11B	1700(9)	883(15)	7161(5)	28.5(12)
C15B	585(12)	-1012(17)	7250(6)	44.7(17)
C12B	2226(10)	2120(16)	7656(4)	27.2(11)
C13B	3400(11)	3727(18)	7606(3)	29.1(11)
N1	7072(3)	3038(6)	6251.6(13)	28.5(7)
S2	7286.4(12)	8468.3(18)	8600.6(4)	33.4(3)
S1	8226.4(11)	2777.9(19)	5672.8(4)	33.3(3)
O1	9165(4)	853(6)	5777.1(14)	41.2(8)
O4	7138(4)	10788(5)	8599.3(13)	43.1(8)
O3	8707(3)	7473(6)	8834.4(12)	40.5(7)
O2	7223(4)	2890(7)	5145.5(12)	50.0(8)
N3	7037(4)	7640(6)	7897.1(13)	29.4(7)
C16	5657(5)	7361(7)	8978.3(16)	30.5(9)
C5	7044(4)	4627(7)	7180.4(16)	24.0(8)
C6	7860(4)	3358(7)	6826.9(15)	27.2(8)
C8	5622(5)	8584(8)	7581.7(18)	33.5(9)
C18	4424(6)	4374(8)	9466.4(18)	38.2(10)

C9	5482(5)	7887(8)	6926.7(16)	32.1(9)
C17	5774(5)	5319(8)	9230.5(17)	34.3(10)
C21	4215(5)	8496(9)	8958.0(17)	38.9(10)
C7	7381(5)	5265(7)	7819.6(17)	28.5(9)
C19	2973(5)	5429(9)	9439.6(18)	42.1(11)
C20	2890(5)	7535(9)	9188.7(18)	43.1(11)
C22	1506(6)	4376(12)	9679(3)	63.1(16)
C23	9515(7)	5042(9)	5693(2)	49.4(13)

Table 2: Anisotropic Displacement Parameters ($\times 10^4$) **5.2L**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C4A	23.9(18)	27(2)	29.9(19)	5.0(16)	4.4(14)	-0.2(16)
C1A	27.6(19)	26(2)	30.2(19)	1.7(17)	0.4(14)	1.2(17)
C4B	23.9(18)	27(2)	29.9(19)	5.0(16)	4.4(14)	-0.2(16)
C1B	27.6(19)	26(2)	30.2(19)	1.7(17)	0.4(14)	1.2(17)
N1	31.1(15)	25(2)	29.3(14)	0.8(14)	3.6(11)	3.1(15)
S2	42.7(5)	26.7(6)	30.9(5)	-3.0(4)	2.2(4)	-2.0(4)
S1	40.6(5)	32.6(6)	27.3(4)	-0.2(4)	8.1(3)	9.1(4)
O1	46.3(18)	39(2)	39.0(16)	-3.4(14)	10.1(13)	15.5(15)
O4	64(2)	23.9(19)	41.8(17)	-5.2(13)	6.0(14)	-6.5(14)
O3	40.0(16)	45(2)	36.2(14)	-3.8(14)	-1.3(11)	-0.9(15)
O2	64.5(19)	56(2)	29.8(13)	0.4(16)	3.6(12)	15.0(18)
N3	33.8(16)	23.8(19)	30.9(15)	0.6(14)	4.8(12)	4.3(15)
C16	44(2)	24(2)	23.4(17)	-2.0(16)	2.7(14)	3.0(18)
C5	27.0(18)	17(2)	28.0(18)	5.7(16)	6.0(14)	0.9(16)
C6	27.5(18)	25(2)	29.6(17)	5.8(18)	2.0(13)	-1.0(17)
C8	41(2)	24(2)	36(2)	-1.0(19)	2.9(15)	7.7(19)
C18	55(3)	31(3)	28(2)	4.1(19)	4.4(17)	2(2)
C9	39(2)	27(3)	29.7(18)	4.5(18)	2.6(14)	5.2(19)
C17	45(2)	34(3)	24.5(18)	-3.3(17)	1.7(16)	5(2)
C21	57(3)	30(3)	29.7(19)	-0.1(19)	3.8(17)	10(2)
C7	29.1(19)	25(2)	31.2(19)	2.8(16)	1.2(14)	0.2(17)
C19	45(3)	53(3)	29(2)	5(2)	5.0(17)	-1(2)
C20	47(2)	51(3)	32.3(19)	6(2)	6.8(16)	18(2)
C22	54(3)	75(4)	61(3)	23(3)	11(2)	2(3)
C23	62(3)	41(3)	47(3)	5(2)	23(2)	-2(2)

Table 3: Bond Lengths in Å for **5.2L**.

Atom	**Atom**	**Length/Å**
C14A	N2A	1.439(7)
N2A	C2A	1.406(6)
N2A	C1A	1.435(5)
C2A	C3A	1.392(7)
C2A	C10A	1.392(7)
C3A	C4A	1.532(5)
C3A	C13A	1.387(6)
C4A	C1A	1.530(3)
C4A	C5	1.504(5)
C4A	C9	1.529(6)
C1A	N1	1.526(5)
C10A	C11A	1.391(8)
C11A	C15A	1.511(9)
C11A	C12A	1.394(9)

Atom	Atom	Length/Å
C12A	C13A	1.401(8)
C14B	N2B	1.438(7)
N2B	C2B	1.395(7)
N2B	C1B	1.428(6)
C2B	C3B	1.402(7)
C2B	C10B	1.385(8)
C3B	C4B	1.539(5)
C3B	C13B	1.388(7)
C4B	C1B	1.530(3)
C4B	C5	1.504(5)
C4B	C9	1.529(6)
C1B	N1	1.526(5)
C10B	C11B	1.385(9)
C11B	C15B	1.509(9)
C11B	C12B	1.394(10)
C12B	C13B	1.401(8)
N1	S1	1.652(3)
N1	C6	1.433(5)
S2	O4	1.422(4)
S2	O3	1.424(3)
S2	N3	1.651(3)
S2	C16	1.772(4)
S1	O1	1.431(3)
S1	O2	1.422(3)
S1	C23	1.758(6)
N3	C8	1.478(5)
N3	C7	1.490(6)
C16	C17	1.369(6)
C16	C21	1.399(6)
C5	C6	1.316(6)
C5	C7	1.491(5)
C8	C9	1.519(6)
C18	C17	1.396(7)
C18	C19	1.383(7)
C21	C20	1.379(7)
C19	C20	1.402(8)
C19	C22	1.509(7)

Table 4: Bond Angles in ° for **5.2L**.

Atom	Atom	Atom	Angle/°
C2A	N2A	C14A	121.6(5)
C2A	N2A	C1A	111.6(4)
C1A	N2A	C14A	124.5(5)
C3A	C2A	N2A	110.7(4)
C10A	C2A	N2A	128.8(5)
C10A	C2A	C3A	120.5(5)
C2A	C3A	C4A	106.4(4)
C13A	C3A	C2A	120.5(5)
C13A	C3A	C4A	132.7(5)
C1A	C4A	C3A	105.9(3)
C5	C4A	C3A	109.5(5)

Atom	Atom	Atom	Angle/°
C5	C4A	C1A	104.8(3)
C5	C4A	C9	107.2(3)
C9	C4A	C3A	114.0(5)
C9	C4A	C1A	114.9(3)
N2A	C1A	C4A	103.7(3)
N2A	C1A	N1	111.0(5)
N1	C1A	C4A	103.6(3)
C11A	C10A	C2A	119.3(6)
C10A	C11A	C15A	119.0(7)
C10A	C11A	C12A	120.1(5)
C12A	C11A	C15A	120.9(6)
C11A	C12A	C13A	120.4(5)
C3A	C13A	C12A	119.0(5)
C2B	N2B	C14B	122.9(6)
C2B	N2B	C1B	105.7(4)
C1B	N2B	C14B	123.9(6)
N2B	C2B	C3B	110.2(5)
C10B	C2B	N2B	126.0(6)
C10B	C2B	C3B	123.8(5)
C2B	C3B	C4B	109.7(4)
C13B	C3B	C2B	117.2(5)
C13B	C3B	C4B	132.8(5)
C1B	C4B	C3B	98.5(3)
C5	C4B	C3B	112.6(6)
C5	C4B	C1B	104.8(3)
C5	C4B	C9	107.2(3)
C9	C4B	C3B	118.0(6)
C9	C4B	C1B	114.9(3)
N2B	C1B	C4B	109.8(3)
N2B	C1B	N1	117.1(5)
N1	C1B	C4B	103.6(3)
C11B	C10B	C2B	117.8(6)
C10B	C11B	C15B	120.4(8)
C10B	C11B	C12B	119.8(6)
C12B	C11B	C15B	119.6(7)
C11B	C12B	C13B	121.3(6)
C3B	C13B	C12B	119.7(6)
C1A	N1	S1	121.3(2)
C1B	N1	S1	121.3(2)
C6	N1	C1A	107.3(3)
C6	N1	C1B	107.3(3)
C6	N1	S1	116.2(2)
O4	S2	O3	119.9(2)
O4	S2	N3	107.18(19)
O4	S2	C16	108.1(2)
O3	S2	N3	106.90(18)
O3	S2	C16	108.7(2)
N3	S2	C16	105.04(18)
N1	S1	C23	106.7(2)
O1	S1	N1	106.96(18)
O1	S1	C23	107.7(2)
O2	S1	N1	106.77(17)
O2	S1	O1	118.8(2)
O2	S1	C23	109.3(3)

Atom	Atom	Atom	Angle/°
C8	N3	S2	113.7(3)
C8	N3	C7	118.8(3)
C7	N3	S2	112.9(3)
C17	C16	S2	119.8(3)
C17	C16	C21	120.9(4)
C21	C16	S2	119.0(3)
C6	C5	C4A	111.0(3)
C6	C5	C4B	111.0(3)
C6	C5	C7	129.7(3)
C7	C5	C4A	119.2(3)
C7	C5	C4B	119.2(3)
C5	C6	N1	112.3(3)
N3	C8	C9	112.2(3)
C19	C18	C17	121.7(5)
C8	C9	C4A	111.1(3)
C8	C9	C4B	111.1(3)
C16	C17	C18	118.9(4)
C20	C21	C16	119.6(5)
N3	C7	C5	109.5(3)
C18	C19	C20	118.3(4)
C18	C19	C22	121.5(5)
C20	C19	C22	120.2(5)
C21	C20	C19	120.7(4)

Table 5: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **5.2L**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H14A	4228	631	5632	58
H14B	4194	2799	5254	58
H14C	2648	1968	5550	58
H1A	5724	5728	5929	33
H10A	1758	639	6486	36
H15A	-92	-842	7167	67
H15B	-94	-61	7839	67
H15C	1120	-1844	7643	67
H12A	1963	2532	8218	33
H13A	4010	4970	8018	35
H14D	4468	1191	5454	58
H14E	4182	3475	5147	58
H14F	2756	2190	5410	58
H1B	5846	5782	5958	33
H10B	1961	486	6266	36
H15D	-82	-1200	6894	67
H15E	-61	-717	7586	67
H15F	1187	-2324	7325	67
H12B	1790	1873	8028	33
H13B	3724	4552	7939	35
H22A	1688	2783	9730	95
H22B	598	4620	9392	95
H22C	1272	5034	10073	95
H8A	4650(30)	8150(90)	7771(17)	40(5)
H7A	8500(30)	5120(90)	7940(20)	40(5)
H7B	6690(40)	4340(70)	8051(18)	40(5)
H9A	4440(30)	8410(80)	6782(18)	40(5)
H8B	5670(50)	10180(30)	7620(20)	40(5)
H9B	6380(40)	8560(80)	6733(18)	40(5)
H6	8850(30)	2820(80)	6901(19)	39(6)
H18	4400(50)	2990(50)	9616(19)	39(6)
H17	6740(40)	4670(80)	9220(20)	39(6)
H21	4250(50)	9860(50)	8792(19)	39(6)
H20	1890(30)	8100(80)	9148(19)	39(6)
H23A	10170(50)	4700(100)	5358(16)	56(9)
H23B	10200(50)	5010(110)	6050(16)	56(9)
H23C	8990(60)	6450(60)	5710(20)	56(9)

Citations

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Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

4. X-ray crystallographic structure of product 6.1.24

Crystal submitted by: **Liangbing Fu**
Structure solved by: **John Bacsa**

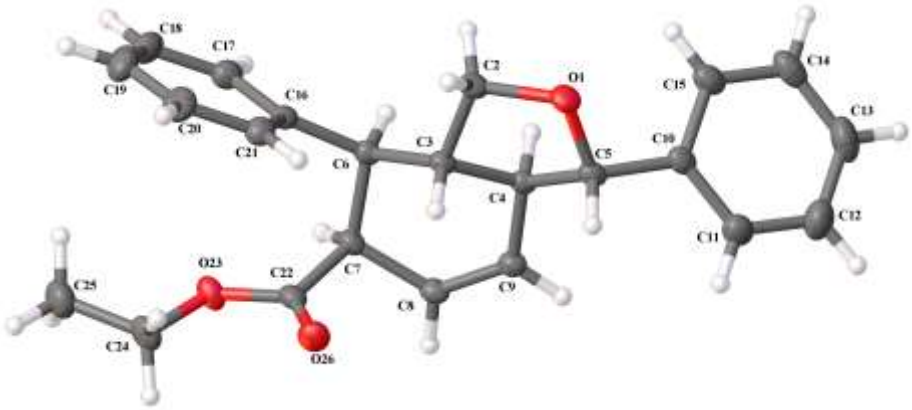

Table 1 Crystal data and structure refinement for 6.1.24

Identification code	**6.1.24**
Empirical formula	$C_{23}H_{24}O_3$
Formula weight	348.42
Temperature/K	110(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.7460(8)
b/Å	16.3891(16)
c/Å	29.458(3)
α/°	90
β/°	91.1052(16)
γ/°	90
Volume/Å^3	3739.0(7)
Z	8
ρ_{calc}mg/mm^3	1.238
m/mm^{-1}	0.081
F(000)	1488.0
Crystal size/mm^3	0.978 × 0.392 × 0.10
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection	5.16 to 56.564°
Index ranges	$-10 \leq h \leq 10$, $-21 \leq k \leq 21$, $-39 \leq l \leq 39$
Reflections collected	51845
Independent reflections	9266[R(int) = 0.0448]

Data/restraints/parameters	9266/84/586
Goodness-of-fit on F^2	1.031
Final R indexes [I>=2σ (I)]	R_1 = 0.0561, wR_2 = 0.1354
Final R indexes [all data]	R_1 = 0.0726, wR_2 = 0.1461
Largest diff. peak/hole / e $Å^{-3}$	0.38/-0.22

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$×10^3) for 6.1.24. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
C13	11333(3)	5227.2(13)	4157.9(7)	40.8(5)
C17	8189(2)	3407.8(11)	1136.1(6)	27.5(4)
C12	10150(3)	5816.6(14)	4023.5(7)	41.8(5)
C25	3685(3)	4425.0(13)	429.0(7)	36.9(4)
C24	4027(2)	5047.8(12)	796.0(6)	30.8(4)
C11	9781(2)	5936.3(11)	3564.9(6)	32.3(4)
C19	8763(2)	3912.9(13)	389.6(6)	36.5(4)
C20	9047(2)	4684.8(12)	568.2(6)	32.5(4)
C14	12151(2)	4757.7(12)	3835.3(7)	35.0(4)
C21	8890(2)	4823.8(11)	1030.9(6)	24.8(3)
C18	8350(2)	3272.6(12)	674.9(6)	33.7(4)
C2	11041(2)	5056.5(11)	2038.7(6)	23.8(3)
C10	10583(2)	5466.2(9)	3237.7(5)	22.4(3)
C16	8442.5(19)	4187.4(10)	1319.8(5)	20.9(3)
C22	5376.5(19)	5027.8(10)	1526.5(5)	20.9(3)
C15	11782(2)	4877.1(10)	3377.2(6)	27.6(4)
C4	8796.3(19)	4949.4(9)	2561.7(5)	18.3(3)
C5	10093.2(19)	5575.0(9)	2743.5(5)	20.6(3)
C3	9074.8(19)	5021.6(9)	2052.0(5)	18.4(3)
C9	6924(2)	5019.4(9)	2666.5(5)	20.3(3)
C6	8096.1(19)	4326.0(9)	1817.3(5)	19.5(3)
C7	6114.4(19)	4466.3(9)	1895.1(5)	19.6(3)
C8	5725(2)	4803(1)	2361.1(5)	21.0(3)
O23	4586.0(15)	4593.5(7)	1196.7(4)	26.6(3)
O1	11577.5(14)	5441.3(7)	2463.4(4)	25.0(3)
O26	5519.3(16)	5758.4(7)	1519.3(4)	28.9(3)
C20B	6552(3)	4199.3(15)	4600.8(7)	45.2(5)
C18B	5866(3)	2789.1(15)	4684.0(6)	41.5(5)
C19B	6088(3)	3554.0(17)	4872.8(7)	47.7(6)

C25B	11206(3)	2902.7(17)	4827.9(7)	51.9(6)
C21B	6825(2)	4078.7(12)	4139.6(6)	33.3(4)
C13B	3743(2)	2323.2(13)	1094.2(6)	35.8(4)
C12B	4913(2)	1742.3(13)	1246.9(6)	35.6(4)
C17B	6113(2)	2664.7(12)	4222.9(6)	30.9(4)
C14B	2847(2)	2789.1(11)	1403.2(6)	32.0(4)
C24B	11050(3)	2328.9(14)	4433.5(6)	42.5(5)
C11B	5206(2)	1632.0(11)	1709.5(6)	27.0(3)
C15B	3131(2)	2679.8(10)	1866.5(6)	24.4(3)
C5B	4784.8(19)	2012.1(9)	2518.9(5)	20.0(3)
C7B	8917(2)	2998.1(10)	3359.0(5)	21.1(3)
C10B	4334.5(19)	2104.1(9)	2023.3(5)	21.1(3)
C16B	6608(2)	3310.4(11)	3945.3(5)	24.3(3)
C4B	6162.7(19)	2604.1(9)	2693.3(5)	18.0(3)
C6B	6960.1(19)	3192.2(9)	3444.2(5)	19.9(3)
C9B	8019.7(19)	2479.9(9)	2585.7(5)	20.1(3)
C22B	9601(2)	2406.3(10)	3716.6(5)	23.7(3)
C3B	5878.3(19)	2545.7(9)	3203.2(5)	18.6(3)
C2B	3915(2)	2577.9(11)	3216.7(5)	24.6(3)
C8B	9247(2)	2661.9(10)	2888.8(5)	22.6(3)
O23B	10484.0(15)	2805.9(8)	4043.0(4)	30.2(3)
O1B	3317.7(14)	2208.9(8)	2794.3(4)	26.7(3)
O26B	9359.8(17)	1679.5(8)	3717.6(5)	35.4(3)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 6.1.24. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C13	47.5(12)	43.9(11)	30.5(9)	0.8(8)	−15.6(8)	−8.0(9)
C17	24.2(8)	24.6(8)	33.5(9)	−3.2(7)	−1.5(7)	0.8(7)
C12	49.0(12)	42.9(12)	33.2(10)	−11.5(8)	−5.3(9)	2.0(9)
C25	37.1(10)	44.4(11)	28.9(9)	2.0(8)	−8.3(8)	0.7(9)
C24	31.4(9)	35.3(10)	25.5(8)	7.0(7)	−6.2(7)	2.2(7)
C11	32.2(9)	29.0(9)	35.5(9)	−5.5(7)	−7.2(7)	5.1(7)
C19	31.5(9)	49.8(12)	28.2(9)	−11.8(8)	5.9(7)	−1.3(8)
C20	27.6(9)	39.3(10)	30.9(9)	0.1(8)	7.6(7)	−4.0(8)

C14	30.7(9)	30.7(9)	42.8(10)	5.7(8)	−15.4(8)	−3.0(7)
C21	20.4(8)	26.0(8)	28.1(8)	−1.3(6)	1.7(6)	−1.7(6)
C18	29.9(9)	33(1)	38.1(10)	−13.5(8)	0.5(7)	1.4(8)
C2	16.0(7)	26.8(8)	28.5(8)	−0.3(7)	−0.9(6)	0.7(6)
C10	19.5(7)	18.2(7)	29.2(8)	−1.0(6)	−5.3(6)	−3.7(6)
C16	15.4(7)	22.0(8)	25.2(7)	−2.3(6)	−1.2(6)	2.0(6)
C22	14.4(7)	24.4(8)	24.0(7)	0.6(6)	0.8(5)	1.5(6)
C15	23.4(8)	22.6(8)	36.4(9)	−0.5(7)	−6.0(7)	−1.1(6)
C4	16.6(7)	15.4(7)	22.9(7)	0.5(5)	−2.0(5)	1.8(5)
C5	16.5(7)	17.1(7)	28.1(8)	0.1(6)	−2.2(6)	−0.1(6)
C3	14.7(7)	16.4(7)	23.9(7)	1.3(5)	−1.0(5)	0.4(5)
C9	19.5(7)	18.6(7)	22.9(7)	2.0(6)	1.1(6)	0.3(6)
C6	17.4(7)	17.0(7)	24.0(7)	1.0(6)	−1.1(6)	1.0(6)
C7	15.5(7)	19.5(7)	23.7(7)	1.7(6)	−2.2(5)	−1.8(6)
C8	16.3(7)	21.1(7)	25.7(8)	3.6(6)	1.7(6)	−0.3(6)
O23	25.7(6)	27.6(6)	26.1(6)	4.6(5)	−7.1(5)	−3.0(5)
O1	15.5(5)	29.0(6)	30.5(6)	−2.5(5)	−1.0(4)	−2.0(4)
O26	33.6(7)	22.0(6)	31.0(6)	0.6(5)	−4.2(5)	4.8(5)
C20B	41.7(11)	59.2(14)	34.4(10)	−18.6(9)	−5.6(8)	3.7(10)
C18B	30(1)	68.1(14)	26.3(9)	8.9(9)	−0.2(7)	−5.7(9)
C19B	34.9(11)	84.9(17)	23.3(9)	−9.5(10)	−0.3(8)	−0.1(11)
C25B	39.2(12)	88.1(18)	28.1(10)	8.6(10)	−9.4(8)	−2.8(12)
C21B	32.5(9)	37.1(10)	30.2(9)	−6.1(7)	−5.4(7)	2.2(8)
C13B	35.7(10)	45.3(11)	26.2(9)	7.5(8)	−6.4(7)	−14.6(8)
C12B	34.5(10)	43.3(11)	29.3(9)	−6.0(8)	5.2(7)	−7.1(8)
C17B	24.7(8)	41.1(10)	26.9(8)	3.4(7)	−1.2(6)	−0.6(7)
C14B	26.5(9)	31.0(9)	37.9(10)	10.3(7)	−12.3(7)	−8.4(7)
C24B	39.1(11)	58.5(13)	29.6(9)	17.7(9)	−11.1(8)	−7.2(9)
C11B	22.4(8)	27.3(8)	31.2(8)	−0.3(7)	−0.5(6)	−1.9(7)
C15B	20.5(7)	21.2(8)	31.3(8)	1.2(6)	−6.0(6)	−2.9(6)
C5B	15.6(7)	19.1(7)	25.3(7)	1.1(6)	−2.3(6)	0.5(6)
C7B	18.6(7)	21.2(8)	23.3(7)	2.3(6)	−2.8(6)	−2.1(6)
C10B	16.7(7)	20.2(7)	26.2(8)	1.0(6)	−3.0(6)	−3.7(6)
C16B	17.6(7)	32.6(9)	22.5(7)	−1.1(6)	−3.0(6)	3.5(6)

C4B	16.4(7)	15.0(7)	22.5(7)	0.4(5)	-2.0(5)	0.6(5)
C6B	19.0(7)	19.0(7)	21.5(7)	1.8(6)	-2.2(5)	1.8(6)
C9B	18.0(7)	19.2(7)	23.1(7)	2.5(6)	0.9(6)	0.5(6)
C22B	14.6(7)	30.3(9)	26.1(8)	3.3(6)	-1.6(6)	1.3(6)
C3B	14.8(7)	18.1(7)	23.0(7)	1.8(6)	-0.8(5)	2.1(5)
C2B	17.4(7)	29.9(9)	26.5(8)	-1.4(6)	-1.0(6)	2.3(6)
C8B	17.0(7)	25.3(8)	25.5(8)	2.8(6)	1.4(6)	-0.6(6)
O23B	26.7(6)	39.4(7)	24.2(6)	8.1(5)	-8.0(5)	-6.8(5)
O1B	14.5(5)	38.7(7)	26.9(6)	-1.8(5)	-0.9(4)	-1.0(5)
O26B	36.0(7)	26.0(7)	43.9(7)	7.1(5)	-9.7(6)	4.1(5)

Table 4 Bond Lengths for 6.1.24.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C13	C12	1.384(3)	C20B	C19B	1.379(3)
C13	C14	1.386(3)	C20B	C21B	1.393(3)
C17	C18	1.385(3)	C18B	C19B	1.381(3)
C17	C16	1.400(2)	C18B	C17B	1.390(3)
C12	C11	1.389(3)	C25B	C24B	1.498(3)
C25	C24	1.507(3)	C21B	C16B	1.392(3)
C24	O23	1.454(2)	C13B	C12B	1.384(3)
C11	C10	1.390(2)	C13B	C14B	1.385(3)
C19	C20	1.386(3)	C12B	C11B	1.389(2)
C19	C18	1.386(3)	C17B	C16B	1.396(2)
C20	C21	1.389(2)	C14B	C15B	1.390(2)
C14	C15	1.388(3)	C24B	O23B	1.452(2)
C21	C16	1.394(2)	C11B	C10B	1.390(2)
C2	C3	1.525(2)	C15B	C10B	1.399(2)
C2	O1	1.454(2)	C5B	C10B	1.502(2)
C10	C15	1.396(2)	C5B	C4B	1.524(2)
C10	C5	1.508(2)	C5B	O1B	1.4453(19)
C16	C6	1.512(2)	C7B	C6B	1.573(2)
C22	C7	1.526(2)	C7B	C22B	1.520(2)
C22	O23	1.3426(19)	C7B	C8B	1.517(2)
C22	O26	1.203(2)	C16B	C6B	1.519(2)
C4	C5	1.525(2)	C4B	C9B	1.493(2)
C4	C3	1.526(2)	C4B	C3B	1.525(2)
C4	C9	1.493(2)	C6B	C3B	1.519(2)
C5	O1	1.4448(19)	C9B	C8B	1.326(2)

C3	C6	1.527(2)	C22B	O23B	1.340(2)
C9	C8	1.329(2)	C22B	O26B	1.206(2)
C6	C7	1.573(2)	C3B	C2B	1.523(2)
C7	C8	1.515(2)	C2B	O1B	1.4514(19)

Table 5 Bond Angles for 6.1.24.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C12	C13	C14	120.02(18)	C19B	C20B	C21B	120.3(2)
C18	C17	C16	120.73(17)	C19B	C18B	C17B	120.6(2)
C13	C12	C11	119.95(19)	C20B	C19B	C18B	119.60(18)
O23	C24	C25	106.32(15)	C16B	C21B	C20B	120.65(19)
C12	C11	C10	120.66(17)	C12B	C13B	C14B	119.94(17)
C18	C19	C20	119.85(17)	C13B	C12B	C11B	120.14(18)
C19	C20	C21	120.39(17)	C18B	C17B	C16B	120.39(19)
C13	C14	C15	120.02(18)	C13B	C14B	C15B	120.17(17)
C20	C21	C16	120.24(16)	O23B	C24B	C25B	107.17(18)
C17	C18	C19	120.00(17)	C12B	C11B	C10B	120.51(17)
O1	C2	C3	105.25(12)	C14B	C15B	C10B	120.21(16)
C11	C10	C15	118.87(16)	C10B	C5B	C4B	114.31(13)
C11	C10	C5	119.76(15)	O1B	C5B	C10B	110.65(12)
C15	C10	C5	121.31(15)	O1B	C5B	C4B	102.82(12)
C17	C16	C6	119.05(14)	C22B	C7B	C6B	110.04(12)
C21	C16	C17	118.77(15)	C8B	C7B	C6B	113.52(12)
C21	C16	C6	122.02(14)	C8B	C7B	C22B	109.77(13)
O23	C22	C7	110.76(13)	C11B	C10B	C15B	119.02(15)
O26	C22	C7	125.42(14)	C11B	C10B	C5B	118.93(14)
O26	C22	O23	123.78(15)	C15B	C10B	C5B	121.96(14)
C14	C15	C10	120.48(17)	C21B	C16B	C17B	118.51(16)
C5	C4	C3	100.89(12)	C21B	C16B	C6B	119.50(15)
C9	C4	C5	120.76(13)	C17B	C16B	C6B	121.96(15)
C9	C4	C3	110.73(12)	C5B	C4B	C3B	100.28(12)
C10	C5	C4	114.30(13)	C9B	C4B	C5B	120.86(13)
O1	C5	C10	110.19(12)	C9B	C4B	C3B	111.02(12)
O1	C5	C4	102.91(12)	C16B	C6B	C7B	111.85(12)
C2	C3	C4	100.85(12)	C3B	C6B	C7B	107.99(12)
C2	C3	C6	120.24(13)	C3B	C6B	C16B	115.83(13)

C4	C3	C6	108.01(12)	C8B	C9B	C4B	120.50(14)
C8	C9	C4	120.57(14)	O23B	C22B	C7B	110.59(14)
C16	C6	C3	117.06(13)	O26B	C22B	C7B	125.47(15)
C16	C6	C7	110.79(12)	O26B	C22B	O23B	123.91(15)
C3	C6	C7	107.59(12)	C6B	C3B	C4B	109.13(12)
C22	C7	C6	109.74(12)	C6B	C3B	C2B	120.40(13)
C8	C7	C22	110.28(13)	C2B	C3B	C4B	100.76(12)
C8	C7	C6	113.39(12)	O1B	C2B	C3B	105.39(12)
C9	C8	C7	124.17(14)	C9B	C8B	C7B	124.44(15)
C22	O23	C24	116.12(13)	C22B	O23B	C24B	116.58(14)
C5	O1	C2	109.87(11)	C5B	O1B	C2B	109.45(11)

Table 6 Torsion Angles for 6.1.24.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C13	C12	C11	C10	0.3(3)	C20B	C21B	C16B	C17B	0.0(3)
C13	C14	C15	C10	-0.3(3)	C20B	C21B	C16B	C6B	-178.42(16)
C17	C16	C6	C3	154.07(14)	C18B	C17B	C16B	C21B	-0.8(3)
C17	C16	C6	C7	-82.09(17)	C18B	C17B	C16B	C6B	177.53(15)
C12	C13	C14	C15	-0.1(3)	C19B	C20B	C21B	C16B	1.0(3)
C12	C11	C10	C15	-0.7(3)	C19B	C18B	C17B	C16B	0.7(3)
C12	C11	C10	C5	176.69(17)	C25B	C24B	O23B	C22B	-153.36(16)
C25	C24	O23	C22	163.52(15)	C21B	C20B	C19B	C18B	-1.1(3)
C11	C10	C15	C14	0.7(3)	C21B	C16B	C6B	C7B	86.90(18)
C11	C10	C5	C4	-98.12(18)	C21B	C16B	C6B	C3B	-148.78(15)
C11	C10	C5	O1	146.58(15)	C13B	C12B	C11B	C10B	-0.2(3)
C19	C20	C21	C16	-0.1(3)	C13B	C14B	C15B	C10B	0.6(2)
C20	C19	C18	C17	1.3(3)	C12B	C13B	C14B	C15B	0.6(3)
C20	C21	C16	C17	1.2(2)	C12B	C11B	C10B	C15B	1.4(2)
C20	C21	C16	C6	-174.21(15)	C12B	C11B	C10B	C5B	-175.34(15)
C14	C13	C12	C11	0.1(3)	C17B	C18B	C19B	C20B	0.2(3)
C21	C16	C6	C3	-30.5(2)	C17B	C16B	C6B	C7B	-91.42(18)
C21	C16	C6	C7	93.35(17)	C17B	C16B	C6B	C3B	32.9(2)
C18	C17	C16	C21	-1.1(2)	C14B	C13B	C12B	C11B	-0.8(3)

C18	C17	C16	C6	174.47(15)	C14B	C15B	C10B	C11B	-1.5(2)
C18	C19	C20	C21	-1.1(3)	C14B	C15B	C10B	C5B	175.06(14)
C2	C3	C6	C16	-54.73(19)	C5B	C4B	C9B	C8B	-143.98(16)
C2	C3	C6	C7	179.81(13)	C5B	C4B	C3B	C6B	-171.65(12)
C10	C5	O1	C2	145.14(13)	C5B	C4B	C3B	C2B	-43.98(14)
C16	C17	C18	C19	-0.1(3)	C7B	C6B	C3B	C4B	-63.32(15)
C16	C6	C7	C22	-42.59(16)	C7B	C6B	C3B	C2B	-178.95(13)
C16	C6	C7	C8	-166.40(13)	C7B	C22B	O23B	C24B	173.35(15)
C22	C7	C8	C9	-118.75(17)	C10B	C5B	C4B	C9B	-75.39(18)
C15	C10	C5	C4	79.24(19)	C10B	C5B	C4B	C3B	162.40(13)
C15	C10	C5	O1	-36.1(2)	C10B	C5B	O1B	C2B	-146.81(13)
C4	C5	O1	C2	22.85(15)	C16B	C6B	C3B	C4B	170.38(12)
C4	C3	C6	C16	-169.48(12)	C16B	C6B	C3B	C2B	54.75(19)
C4	C3	C6	C7	65.06(14)	C4B	C5B	C10B	C11B	92.39(17)
C4	C9	C8	C7	0.7(2)	C4B	C5B	C10B	C15B	-84.20(18)
C5	C10	C15	C14	-176.68(15)	C4B	C5B	O1B	C2B	-24.33(15)
C5	C4	C3	C2	43.21(14)	C4B	C9B	C8B	C7B	0.3(2)
C5	C4	C3	C6	170.19(12)	C4B	C3B	C2B	O1B	30.27(15)
C5	C4	C9	C8	144.75(15)	C6B	C7B	C22B	O23B	-99.56(15)
C3	C2	O1	C5	4.77(16)	C6B	C7B	C22B	O26B	78.8(2)
C3	C4	C5	C10	-160.54(13)	C6B	C7B	C8B	C9B	-5.3(2)
C3	C4	C5	O1	-41.06(13)	C6B	C3B	C2B	O1B	150.16(13)
C3	C4	C9	C8	27.3(2)	C9B	C4B	C3B	C6B	59.44(16)
C3	C6	C7	C22	86.52(15)	C9B	C4B	C3B	C2B	-172.89(13)
C3	C6	C7	C8	-37.29(17)	C22B	C7B	C6B	C16B	41.49(18)
C9	C4	C5	C10	77.20(18)	C22B	C7B	C6B	C3B	-87.10(15)
C9	C4	C5	O1	-163.33(13)	C22B	C7B	C8B	C9B	118.31(17)
C9	C4	C3	C2	172.24(13)	C3B	C4B	C9B	C8B	-27.1(2)
C9	C4	C3	C6	-60.79(15)	C3B	C2B	O1B	C5B	-3.88(16)
C6	C7	C8	C9	4.8(2)	C8B	C7B	C6B	C16B	164.96(13)

C7	C22	O23	C24	-172.13(13)	C8B	C7B	C6B	C3B	36.36(17)
O23	C22	C7	C6	98.50(14)	C8B	C7B	C22B	O23B	134.82(14)
O23	C22	C7	C8	-135.89(13)	C8B	C7B	C22B	O26B	-46.9(2)
O1	C2	C3	C4	-30.20(15)	O1B	C5B	C10B	C11B	-152.11(14)
O1	C2	C3	C6	-148.63(13)	O1B	C5B	C10B	C15B	31.3(2)
O26	C22	C7	C6	-79.25(19)	O1B	C5B	C4B	C9B	164.62(13)
O26	C22	C7	C8	46.4(2)	O1B	C5B	C4B	C3B	42.42(13)
O26	C22	O23	C24	5.7(2)	O26B	C22B	O23B	C24B	-5.0(2)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 6.1.24.

Atom	*x*	*y*	*z*	U(eq)
H20B	6684	4717	4726	54
H18B	5549	2353	4867	50
H19B	5924	3633	5182	57
H25D	12044	3316	4763	78
H25E	11566	2606	5094	78
H25F	10107	3154	4879	78
H21B	7155	4516	3960	40
H13B	3559	2401	784	43
H12B	5505	1425	1039	43
H17B	5948	2148	4099	37
H14B	2053	3176	1300	38
H24C	12155	2075	4376	51
H24D	10217	1904	4496	51
H11B	5991	1239	1810	32
H15B	2519	2990	2073	29
H2BA	3495	2275	3475	30
H2BB	3518	3138	3238	30
H7B	9550(20)	3508(12)	3397(6)	26(5)
H4B	5800(20)	3139(12)	2605(6)	21(4)
H5B	5160(20)	1442(5)	2583(6)	25
H3B	6280(20)	1992(5)	3297(6)	25
H8B	10470(30)	2564(13)	2818(7)	34(5)
H9B	8310(30)	2269(13)	2291(7)	34(5)

H6B	6740(20)	3731(6)	3297(5)	18(4)
H3	8630(20)	5554(9)	1965(6)	17(4)
H6	8410(20)	3831(9)	1978(6)	23(5)
H9	6610(20)	5209(11)	2960(5)	21(4)
H8	4537(18)	4871(11)	2434(6)	24(5)
H7	5530(20)	3939(11)	1858(6)	19(4)
H4	9240(20)	4399(11)	2658(6)	19(4)
H2A	11470(20)	5387(11)	1793(6)	20(4)
H2B	11570(20)	4502(12)	2042(6)	26(5)
H5	9650(20)	6141(5)	2694(5)	16(4)
H15	12340(30)	4554(11)	3160(6)	38(3)
H13	11580(30)	5136(13)	4468(4)	38(3)
H12	9620(30)	6133(11)	4248(6)	38(3)
H14	12930(20)	4340(10)	3917(7)	38(3)
H11	8980(20)	6340(10)	3473(7)	38(3)
H21	9090(20)	5367(7)	1146(6)	25(5)
H18	8150(30)	2730(7)	559(6)	34(5)
H20	9330(30)	5136(9)	373(6)	32(5)
H17	7880(20)	2966(9)	1336(6)	30(5)
H19	8840(30)	3815(13)	68(4)	38(6)
H24A	4940(20)	5433(11)	711(6)	31(5)
H24B	2990(20)	5367(12)	869(6)	31(5)
H25A	3290(30)	4702(14)	151(6)	55(4)
H25B	4740(20)	4116(14)	373(8)	55(4)
H25C	2750(30)	4062(13)	524(8)	55(4)

5. X-ray crystallographic structure of product 6.3.2

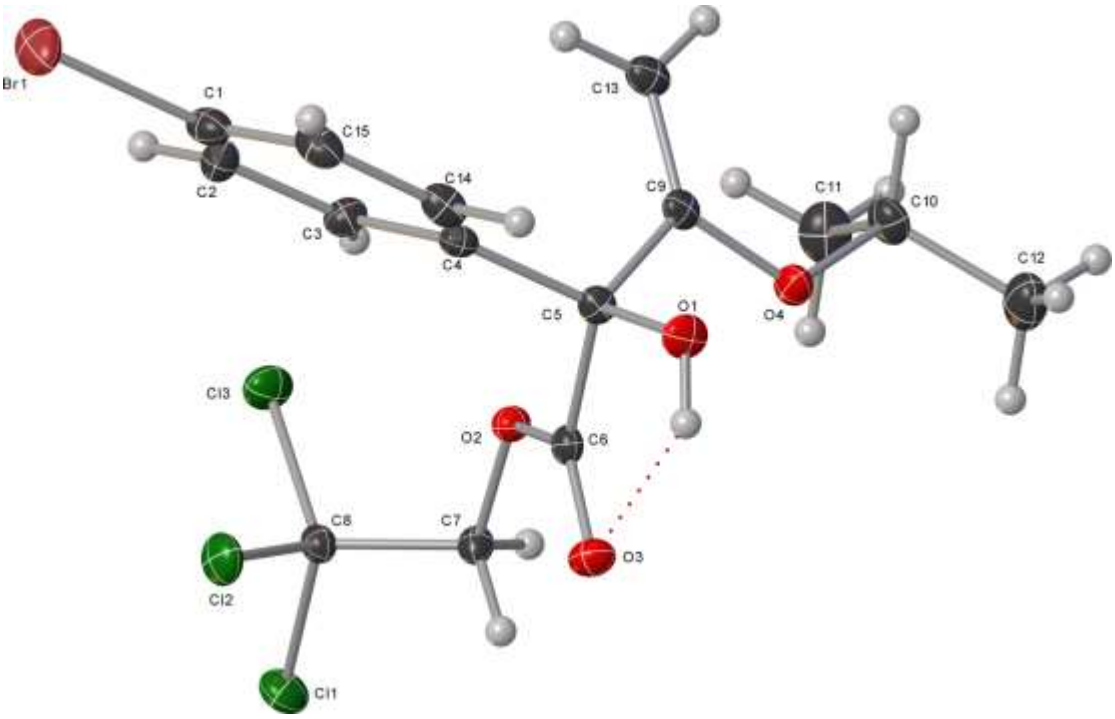

Table 1 Crystal data and structure refinement for 6.3.2.

Identification code	**6.3.2**
Empirical formula	$C_{15}H_{16}BrCl_3O_4$
Formula weight	446.53
Temperature/K	100(2)
Crystal system	triclinic
Space group	P1
a/Å	8.8431(2)
b/Å	9.5550(3)
c/Å	12.1445(5)
α/°	111.821(3)
β/°	96.360(3)
γ/°	102.190(2)
Volume/Å^3	910.68(6)
Z	2
ρ_{calc}g/cm^3	1.628
μ/mm^{-1}	2.711
F(000)	448.0
Crystal size/mm^3	0.824 × 0.723 × 0.228
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.694 to 59.15
Index ranges	$-12 \leq h \leq 12$, $-13 \leq k \leq 13$, $-16 \leq l \leq 16$

Reflections collected	18423
Independent reflections	9988 [R_{int} = 0.0240, R_{sigma} = 0.0294]
Data/restraints/parameters	9988/7/435
Goodness-of-fit on F^2	1.025
Final R indexes [I>=2σ (I)]	R_1 = 0.0382, wR_2 = 0.0937
Final R indexes [all data]	R_1 = 0.0403, wR_2 = 0.0949
Largest diff. peak/hole / e $Å^{-3}$	1.46/-0.38
Flack parameter	0.476(6)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$×10^3) for 6.3.2. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Br1'	937.3(4)	7655.1(4)	11606.0(3)	21.33(10)
Cl2'	4282.5(12)	1557.1(12)	7407.3(9)	21.7(2)
Cl3'	1473.9(11)	2294.7(13)	6574.4(10)	23.7(2)
Cl1'	2587.8(12)	-153.7(12)	4895.7(10)	25.4(2)
O2'	4754(3)	4374(3)	6757(2)	13.8(5)
O3'	3473(3)	5481(4)	5714(3)	17.5(5)
O1'	5044(4)	8377(3)	7298(3)	17.8(6)
O4'	7501(3)	6876(4)	7158(3)	17.7(6)
C4'	4089(4)	7251(4)	8689(3)	12.5(6)
C6'	4350(4)	5583(5)	6601(3)	12.9(7)
C9'	6851(4)	7368(4)	8151(3)	14.0(7)
C14'	3432(4)	8517(4)	9113(4)	13.6(7)
C15'	2504(5)	8643(5)	9987(4)	15.3(7)
C13'	7570(5)	8015(5)	9325(4)	17.9(8)
C2'	2888(5)	6215(5)	10033(4)	16.2(7)
C5'	5085(4)	7157(4)	7711(3)	13.0(6)
C7'	4191(4)	2859(5)	5752(3)	15.2(7)
C1'	2236(4)	7478(5)	10431(3)	14.3(7)
C10'	9215(5)	7161(5)	7327(4)	19.0(8)
C8'	3177(4)	1709(4)	6159(3)	13.8(6)
C3'	3805(5)	6101(5)	9160(3)	15.4(7)
C11'	9512(5)	5920(7)	6224(4)	29.8(10)
C12'	9945(5)	8831(6)	7465(5)	28.8(10)
Br1	8881.6(5)	3527.8(5)	-1604.0(4)	28.44(12)
Cl3	5674.1(12)	8680.4(12)	2836.1(9)	21.9(2)
Cl2	8366.1(11)	7770.5(13)	3682.3(10)	21.9(2)

Cl1	7202.9(12)	10154.4(12)	5395.1(9)	21.25(19)
O3	6087(3)	4371(4)	4214(3)	18.6(6)
O4	2231(3)	2804(4)	2638(3)	17.1(5)
O1	4807(4)	1622(3)	2338(3)	18.1(6)
O2	4996(3)	5705(3)	3281(2)	14.2(5)
C13	2270(5)	2634(5)	588(4)	17.4(8)
C6	5353(4)	4420(4)	3336(3)	13.1(6)
C1	7611(5)	3353(5)	-466(4)	18.0(8)
C7	5550(4)	7146(4)	4348(3)	14.0(7)
C15	7330(5)	2010(5)	-239(4)	19.0(8)
C2	6970(5)	4577(5)	101(4)	17.4(7)
C14	6400(5)	1911(5)	608(4)	16.9(7)
C5	4706(4)	2968(4)	2109(3)	13.1(7)
C10	540(5)	2733(5)	2508(4)	18.9(8)
C3	6017(5)	4451(5)	923(3)	15.4(7)
C4	5730(4)	3120(4)	1192(3)	12.8(6)
C9	2942(4)	2793(4)	1694(3)	13.9(7)
C12	-25(6)	2143(6)	3436(5)	28.8(10)
C8	6650(4)	8372(4)	4058(3)	14.1(7)
C11	341(6)	4357(6)	2737(5)	27.5(10)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 6.3.2. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Br1'	23.2(2)	27.2(2)	16.77(18)	9.24(16)	10.09(14)	9.69(16)
Cl2'	24.7(5)	19.6(4)	22.9(4)	12.7(4)	1.2(4)	5.0(4)
Cl3'	13.8(4)	26.2(5)	32.1(5)	10.0(4)	11.5(4)	7.6(4)
Cl1'	20.9(4)	14.1(4)	27.9(5)	-2.7(4)	0.6(4)	1.1(4)
O2'	15.4(12)	11.2(12)	14.2(12)	5.1(10)	2.1(9)	3.5(10)
O3'	16.1(12)	23.3(14)	15.4(13)	9.2(11)	3.1(10)	7.6(11)
O1'	22.3(14)	16.8(14)	21.7(14)	14.0(12)	6.2(11)	8.1(11)
O4'	9.7(11)	25.4(15)	15.7(13)	7.3(11)	2.4(10)	2.2(11)
C4'	11.3(15)	11.8(16)	13.9(15)	5.4(13)	1.1(12)	2.6(13)
C6'	11.3(16)	16.5(18)	15.0(16)	8.4(14)	7.9(13)	5.6(14)
C9'	11.8(15)	13.9(17)	17.6(17)	8.4(14)	3.1(13)	2.2(13)
C14'	12.4(15)	9.2(16)	19.7(17)	6.9(14)	2.0(13)	2.6(13)
C15'	14.5(16)	10.1(16)	18.1(17)	1.8(14)	2.9(13)	4.5(13)
C13'	16.1(17)	17.8(19)	19.0(18)	7.4(15)	2.9(14)	3.5(15)
C2'	20.1(18)	17.4(18)	15.0(16)	9.3(14)	5.4(14)	7.1(15)

C5'	13.9(15)	11.7(16)	16.4(16)	8.3(13)	3.8(12)	4.6(13)
C7'	14.5(17)	15.3(17)	14.0(16)	3.9(14)	5.8(13)	3.1(14)
C1'	11.4(16)	16.5(18)	12.1(15)	3.9(14)	3.4(12)	1.0(14)
C10'	10.9(16)	25(2)	23.4(19)	12.7(17)	3.5(14)	4.7(15)
C8'	12.5(15)	11.7(16)	15.6(16)	3.8(13)	3.0(12)	3.4(13)
C3'	19.0(17)	11.9(16)	17.1(17)	6.2(14)	4.0(14)	7.2(14)
C11'	18.4(19)	45(3)	25(2)	9(2)	8.1(16)	14.9(19)
C12'	15.9(19)	36(3)	40(3)	26(2)	2.5(18)	0.7(18)
Br1	24.3(2)	30.9(3)	24.8(2)	4.19(19)	15.65(17)	4.81(18)
Cl3	27.1(5)	19.8(5)	20.8(4)	11.3(4)	1.0(4)	6.6(4)
Cl2	14.6(4)	27.0(5)	26.4(5)	11.1(4)	10.0(3)	7.2(4)
Cl1	21.3(4)	14.4(4)	20.9(4)	1.9(3)	1.0(3)	2.2(3)
O3	18.9(13)	22.1(14)	14.9(12)	7.6(11)	1.6(10)	6.8(11)
O4	12.1(12)	22.4(14)	18.1(13)	10.2(11)	2.8(10)	4(1)
O1	23.2(14)	13.9(13)	20.8(14)	10.5(11)	2.1(11)	7.0(11)
O2	16.1(13)	13.3(13)	12.6(12)	5.1(10)	2.2(10)	3.4(10)
C13	17.9(18)	13.1(18)	19.1(18)	6.2(15)	-0.6(14)	3.4(15)
C6	10.9(15)	13.9(17)	15.3(16)	6.5(13)	4.9(12)	3.3(13)
C1	14.6(17)	22(2)	13.2(16)	1.8(15)	3.3(13)	4.7(15)
C7	15.9(16)	12.1(16)	12.7(15)	3.2(13)	5.6(12)	3.3(13)
C15	15.4(17)	15.9(19)	19.5(18)	-0.3(15)	3.9(14)	5.7(14)
C2	18.4(18)	18.0(18)	16.8(17)	8.5(15)	4.8(14)	4.0(15)
C14	15.8(17)	11.9(17)	21.4(18)	4.6(15)	1.5(14)	5.8(14)
C5	13.4(16)	11.9(16)	15.4(16)	6.4(13)	2.4(13)	5.3(13)
C10	11.3(17)	21(2)	24.5(19)	9.6(16)	3.6(14)	5.0(15)
C3	18.8(17)	15.4(18)	13.2(16)	5.0(14)	4.8(13)	7.7(15)
C4	13.8(16)	11.0(16)	11.7(15)	3.3(13)	0.1(12)	3.1(13)
C9	15.6(16)	8.8(15)	17.1(17)	5.8(13)	2.0(13)	2.9(12)
C12	21(2)	37(3)	33(2)	19(2)	9.2(18)	6.3(19)
C8	12.9(16)	13.6(16)	14.4(16)	4.3(13)	4.0(13)	2.7(13)
C11	26(2)	25(2)	38(3)	16(2)	10.5(19)	13.8(19)

Table 4 Bond Lengths for 6.3.2.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Br1'	C1'	1.910(4)	Br1	C1	1.907(4)
Cl2'	C8'	1.780(4)	Cl3	C8	1.784(4)
Cl3'	C8'	1.775(4)	Cl2	C8	1.780(4)

Cl1'	C8'	1.788(4)	Cl1	C8	1.787(4)
O2'	C6'	1.349(5)	O3	C6	1.207(5)
O2'	C7'	1.442(5)	O4	C10	1.470(5)
O3'	C6'	1.215(5)	O4	C9	1.365(5)
O1'	C5'	1.435(4)	O1	C5	1.431(4)
O4'	C9'	1.361(5)	O2	C6	1.353(5)
O4'	C10'	1.460(5)	O2	C7	1.437(5)
C4'	C14'	1.402(5)	C13	C9	1.347(5)
C4'	C5'	1.543(5)	C6	C5	1.552(5)
C4'	C3'	1.407(5)	C1	C15	1.389(7)
C6'	C5'	1.545(5)	C1	C2	1.390(6)
C9'	C13'	1.340(5)	C7	C8	1.531(5)
C9'	C5'	1.538(5)	C15	C14	1.404(6)
C14'	C15'	1.399(6)	C2	C3	1.398(6)
C15'	C1'	1.396(6)	C14	C4	1.400(5)
C2'	C1'	1.394(6)	C5	C4	1.540(5)
C2'	C3'	1.391(6)	C5	C9	1.539(5)
C7'	C8'	1.530(5)	C10	C12	1.521(6)
C10'	C11'	1.516(7)	C10	C11	1.524(6)
C10'	C12'	1.527(7)	C3	C4	1.408(5)

Table 5 Bond Angles for 6.3.2.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6'	O2'	C7'	117.2(3)	C9	O4	C10	118.7(3)
C9'	O4'	C10'	118.9(3)	C6	O2	C7	117.8(3)
C14'	C4'	C5'	118.8(3)	O3	C6	O2	125.6(4)
C14'	C4'	C3'	118.9(4)	O3	C6	C5	122.7(3)
C3'	C4'	C5'	122.2(3)	O2	C6	C5	111.7(3)
O2'	C6'	C5'	112.6(3)	C15	C1	Br1	119.6(3)
O3'	C6'	O2'	125.3(4)	C15	C1	C2	121.8(4)
O3'	C6'	C5'	122.1(3)	C2	C1	Br1	118.5(3)
O4'	C9'	C5'	108.0(3)	O2	C7	C8	109.2(3)
C13'	C9'	O4'	128.5(4)	C1	C15	C14	118.7(4)
C13'	C9'	C5'	123.4(4)	C1	C2	C3	119.0(4)
C15'	C14'	C4'	120.9(4)	C4	C14	C15	121.0(4)
C1'	C15'	C14'	118.7(4)	O1	C5	C6	107.1(3)
C3'	C2'	C1'	119.2(4)	O1	C5	C4	109.5(3)
O1'	C5'	C4'	110.7(3)	O1	C5	C9	107.3(3)

O1'	C5'	C6'	106.9(3)	C4	C5	C6	109.7(3)
O1'	C5'	C9'	105.2(3)	C9	C5	C6	108.5(3)
C4'	C5'	C6'	108.8(3)	C9	C5	C4	114.4(3)
C9'	C5'	C4'	114.2(3)	O4	C10	C12	105.5(3)
C9'	C5'	C6'	110.8(3)	O4	C10	C11	109.3(3)
O2'	C7'	C8'	109.0(3)	C12	C10	C11	112.5(4)
C15'	C1'	Br1'	118.0(3)	C2	C3	C4	120.8(4)
C2'	C1'	Br1'	120.5(3)	C14	C4	C5	119.7(3)
C2'	C1'	C15'	121.5(4)	C14	C4	C3	118.7(4)
O4'	C10'	C11'	106.0(3)	C3	C4	C5	121.6(3)
O4'	C10'	C12'	108.8(3)	O4	C9	C5	107.1(3)
C11'	C10'	C12'	113.3(4)	C13	C9	O4	128.1(4)
Cl2'	C8'	Cl1'	109.3(2)	C13	C9	C5	124.8(4)
Cl3'	C8'	Cl2'	109.2(2)	Cl3	C8	Cl1	109.3(2)
Cl3'	C8'	Cl1'	109.6(2)	Cl2	C8	Cl3	109.5(2)
C7'	C8'	Cl2'	110.9(3)	Cl2	C8	Cl1	109.77(19)
C7'	C8'	Cl3'	111.1(3)	C7	C8	Cl3	111.3(3)
C7'	C8'	Cl1'	106.6(3)	C7	C8	Cl2	110.1(3)
C2'	C3'	C4'	120.7(4)	C7	C8	Cl1	106.7(3)

Table 6 Hydrogen Bonds for 6.3.2.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O1'	H1'	O3'	0.84	2.26	2.667(4)	110.4
O1	H1	O3	0.84	2.16	2.664(4)	118.6

Table 7 Torsion Angles for 6.3.2.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O2'	C6'	C5'	O1'	160.4(3)	Br1	C1	C15	C14	179.6(3)
O2'	C6'	C5'	C4'	-80.0(4)	Br1	C1	C2	C3	179.0(3)
O2'	C6'	C5'	C9'	46.4(4)	O3	C6	C5	O1	13.7(5)
O2'	C7'	C8'	Cl2'	-58.8(3)	O3	C6	C5	C4	-105.1(4)
O2'	C7'	C8'	Cl3'	62.9(3)	O3	C6	C5	C9	129.2(4)
O2'	C7'	C8'	Cl1'	-177.7(2)	O1	C5	C4	C14	8.4(4)
O3'	C6'	C5'	O1'	-21.4(5)	O1	C5	C4	C3	-171.5(3)
O3'	C6'	C5'	C4'	98.1(4)	O1	C5	C9	O4	63.2(4)
O3'	C6'	C5'	C9'	-135.5(4)	O1	C5	C9	C13	-115.7(4)
O4'	C9'	C5'	O1'	-73.5(4)	O2	C6	C5	O1	-166.5(3)

O4'	C9'	C5'	C4'	164.9(3)	O2	C6	C5	C4	74.7(4)
O4'	C9'	C5'	C6'	41.7(4)	O2	C6	C5	C9	-51.0(4)
C4'	C14'	C15'	C1'	-0.2(6)	O2	C7	C8	Cl3	57.7(3)
C6'	O2'	C7'	C8'	-120.7(3)	O2	C7	C8	Cl2	-64.0(3)
C9'	O4'	C10'	C11'	155.1(4)	O2	C7	C8	Cl1	176.9(2)
C9'	O4'	C10'	C12'	-82.8(4)	C6	O2	C7	C8	119.3(3)
C14'	C4'	C5'	O1'	-5.7(5)	C6	C5	C4	C14	125.7(3)
C14'	C4'	C5'	C6'	-122.8(4)	C6	C5	C4	C3	-54.2(4)
C14'	C4'	C5'	C9'	112.8(4)	C6	C5	C9	O4	-52.2(4)
C14'	C4'	C3'	C2'	0.0(5)	C6	C5	C9	C13	128.9(4)
C14'	C15'	C1'	Br1'	-179.0(3)	C1	C15	C14	C4	1.7(6)
C14'	C15'	C1'	C2'	0.9(6)	C1	C2	C3	C4	1.1(6)
C13'	C9'	C5'	O1'	103.2(4)	C7	O2	C6	O3	1.0(6)
C13'	C9'	C5'	C4'	-18.4(5)	C7	O2	C6	C5	-178.8(3)
C13'	C9'	C5'	C6'	-141.7(4)	C15	C1	C2	C3	0.1(6)
C5'	C4'	C14'	C15'	179.2(3)	C15	C14	C4	C5	179.5(3)
C5'	C4'	C3'	C2'	-179.4(3)	C15	C14	C4	C3	-0.6(6)
C7'	O2'	C6'	O3'	4.7(5)	C2	C1	C15	C14	-1.5(6)
C7'	O2'	C6'	C5'	-177.2(3)	C2	C3	C4	C14	-0.8(5)
C1'	C2'	C3'	C4'	0.6(6)	C2	C3	C4	C5	179.0(3)
C10'	O4'	C9'	C13'	-5.2(6)	C10	O4	C9	C13	-4.1(6)
C10'	O4'	C9'	C5'	171.3(3)	C10	O4	C9	C5	177.0(3)
C3'	C4'	C14'	C15'	-0.2(5)	C4	C5	C9	O4	-175.1(3)
C3'	C4'	C5'	O1'	173.7(3)	C4	C5	C9	C13	6.0(5)
C3'	C4'	C5'	C6'	56.5(4)	C9	O4	C10	C12	158.8(4)
C3'	C4'	C5'	C9'	-67.8(5)	C9	O4	C10	C11	-80.0(4)
C3'	C2'	C1'	Br1'	178.8(3)	C9	C5	C4	C14	-112.1(4)
C3'	C2'	C1'	C15'	-1.1(6)	C9	C5	C4	C3	68.0(4)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 6.3.2.

Atom	*x*	*y*	*z*	U(eq)
H1'	4209	8103	6776	27
H14'	3620	9301	8802	16
H15'	2065	9505	10274	18
H2'	2708	5442	10355	19
H7'A	5100	2479	5478	18
H7'B	3555	2940	5066	18
H10'	9634	7035	8073	23
H3'	4244	5238	8879	18

H11A	8951	4879	6149	45
H11B	10649	6017	6314	45
H11C	9129	6064	5495	45
H12A	9456	8985	6770	43
H12B	11085	9002	7500	43
H12C	9764	9578	8214	43
H1	5377	1911	3026	27
H7A	6126	6971	5011	17
H7B	4640	7524	4620	17
H15	7758	1174	-649	23
H2	7175	5486	-68	21
H14	6223	1011	788	20
H10	-43	1975	1673	23
H3	5558	5273	1304	19
H12D	204	1137	3292	43
H12E	-1168	2004	3359	43
H12F	524	2907	4254	43
H11D	917	5096	3556	41
H11E	-784	4315	2661	41
H11F	762	4705	2140	41
H13C	1145(19)	2530(80)	370(60)	33
H13D	2940(50)	2610(80)	0(40)	33
H13A	8706(14)	8190(70)	9570(60)	29(11)
H13B	6940(50)	8240(70)	9950(30)	29(11)