ACTIVATION OF CARBODICARBENE CATALYSTS FOR DIENE HYDROFUNCTIONALIZATION AND EXPLORATION OF CHEMICAL REACTIVITY USING COMMODITY CHEMICALS

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

Chapel Hill
2018

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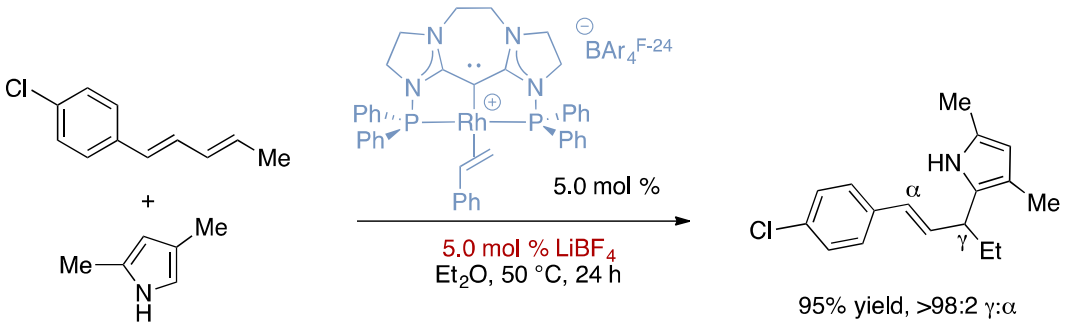
ABSTRACT

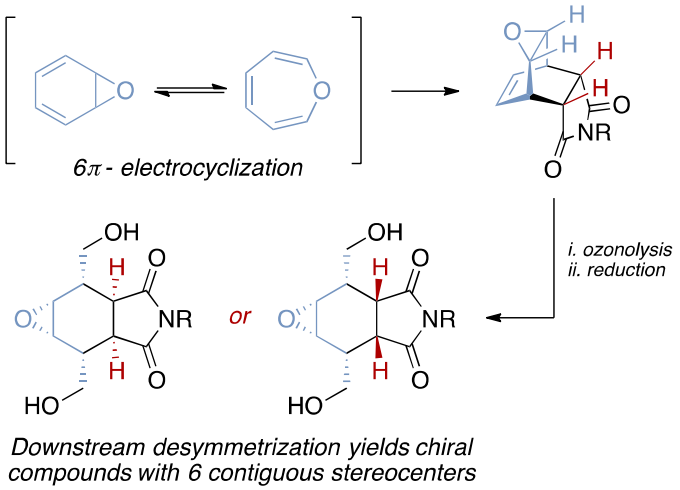
Desirée Marie Matías: Activation of Carbodicarbene Catalysts for Diene Hydrofunctionalization Chemistry AND Exploration of Chemical Reactivity Using Commodity Chemicals
(Under the direction of Simon J. Meek and Jeffrey S. Johnson)

I. Lewis Acid Activation of Carbodicarbene Catalysts for Rh-Catalyzed Hydroarylation of Dienes



The activation of carbodicarbene (CDC)−Rh(I) pincer complexes by secondary binding of metal salts is reported for the catalytic site-selective hydroarylation of 1,3-dienes. The reactions are promoted by 5 mol % of a readily available tridentate (CDC)−Rh complex in the presence of an inexpensive lithium salt. A variety of terminal and internal dienes were tolerated under the reaction conditions, as well as ester, alkyl halide, and boronate ester functional groups. X-ray crystallographic data and mechanistic experiments provide support for the role of the metal salts on catalyst activation and shed light on the reaction mechanism. The increased efficiency (120 to 22 °C) made available by catalytic amounts of metal salts to catalysts containing C(0) donors is a significant aspect of the disclosed studies.

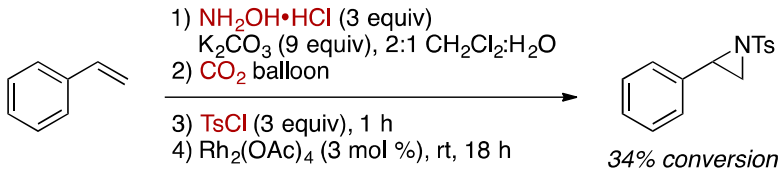
II. Synthesis and Desymmetrization of Fully Substituted, *Meso*-Fused Systems Derived from Benzene Oxide



Ozonolysis of the Diels–Alder adducts derived from benzene oxides and *N*-alkylmaleimides resulted in fully-substituted, *meso*-bicyclic systems bearing six contiguous stereocenters, isolated as diols upon reductive workup with $NaBH_4$. Variation in the workup allowed for isolation of two different diastereomers, through double epimerization of the imide stereocenters. Detailed study of each component of the workup revealed that the unexpected diastereomer arose from epimerization of the product through the action of *in situ*-generated base, rather than a retro-Diels–Alder/recombination sequence during the ozonolysis. These *meso*-diols were transformed in high yields to enantioenriched desymmetrized products via asymmetric nucleophilic epoxide opening and acylation reactions, providing a strategy for obtaining highly-substituted, enantioenriched fused rings through desymmetrization.

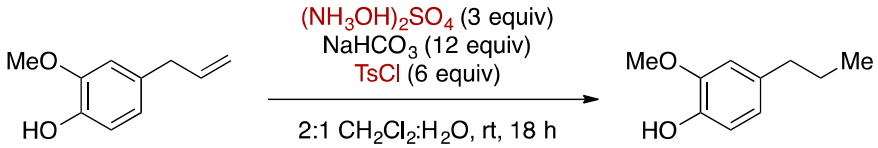
III. Hydroxylamine as a Precursor for Nitrene and Diimide Formation: C−C Bond Aziridination and Reduction

Part I: Aziridination of Alkenes



34% conversion

Part II: Redution with Diimide



94% yield

Hydroxylamine is used as a precursor for metal-nitrenoids and diimide. The first part of this chapter covers the initial discovery that hydroxylamine can be used for the aziridination of alkenes in the presence of CO_2, a protecting group, and a rhodium catalyst. The reactivity remains unoptimized, despite significant efforts. During these studies, the reduction of alkenes under similar conditions was observed. The second part of this chapter discusses the *in situ* formation of diimide with the use of hydroxylamine and a protecting group. An initial substrate scope is presented, although some challenges remain. Terminal olefins are reduced in high yields, whereas internal olefins are less reactive. The reduction of terminal alkynes is also possible, albeit in lower yields. Further studies should reveal the mechanism of the reaction and should provide optimize conditions for the less reactive substrates.

ACKNOWLEDGEMENTS

I would like to start by thanking Professor Jeffrey S. Johnson for taking a chance and allowing me to work in his lab. These three years have taught me how to be a better chemist, coworker, leader, and friend, and I am incredibly grateful for that opportunity. Jeff, the environment that you work so hard to create in the lab has allowed me to grow both professionally and personally. Thank you for recognizing that diversity makes us stronger and that inclusion is key for a resilient group. Thank you for teaching us that collaboration leads to better and brighter ideas. Your guidance and patience is greatly appreciated, not only by me, but also by every lab member.

I would also like to thank Professors David Nicewicz, Alexander Miller, Marcey Waters, and Michel Gagné for serving on my final defense committee. Thank you to Professor Maurice Brookhart for serving on my preliminary oral exam committee. Finally, thank you to Professor Simon Meek for his guidance during the first two years of my graduate studies and for his support during the rest of the time.

My graduate career would not have been the same without the lab members that shared most of their waking hours with me. The members of the Johnson lab are incredible people that I consider friends. Thanks to Jessica Griswold for collaborating with me in the hydroxylamine work; this project would not be where it is if it wasn't for your hard work and dedication. I have to thank my "bay" (Steffen Good, Sam Bartlett, Kendrick Smith, Michael McLaughlin, Will Mackay, and Pedro de Jesús) for the great daily conversations and for their chemical knowledge.

Blane Zavesky, Jennifer Fulton, Jacob Robins, and Cody Padgett, thank you for being incredible lab members. Jenn and Jess, thank you for all the Starbucks runs and for your amazing friendship. A special thanks to Will Mackay, for helping me in my transition to the Johnson lab and for assisting during the job search.

This journey would have been incredibly boring if it wasn't for my amazing friends, Cortney Cavanaugh, Jake Green, Tony Carestia, and Cole Cruz. You guys have made these five years a hundred times better and I hope that our friendship continues forever and ever. Cortney, thank you for being the friend I didn't know I needed. Thank you for your support during the difficult times. Thank you for the coffee runs, the mid-afternoon walks, the pottery paintings, and the shopping sessions. And thank you for the love you have shown Carlos throughout the years. We love you.

I would most definitely not have completed my graduate studies if it weren't for my family. Their incredible support has fueled me and will continue to fuel me in the future. Thank you to my dad, Reinaldo, for raising three amazing daughters and for teaching us that we can achieve whatever we set our minds to. Thank you to my sisters, Alanis and Ashley, for making me unbelievably proud to be an older sister and for being the incredible people that you both are. I have to thank my dad's wife, Elsa, for raising these wonderful girls and for her support throughout graduate school. Thanks to my mom's husband, Jorge, for loving my mom the way you do and for loving me like a daughter. Finally, I have to thank my mom, Grace. Mami, thank you for all the love, encouragement, patience, and guidance you have given me. Thank you for showing me the value of perseverance and hard work. I am extremely appreciative of all the sacrifices you have made so that I can have the opportunities that I've had and will continue to have. Thank you for being the person you are, because that is the person I want to be.

Lastly, I have to thank my amazing husband, Carlos Julio. I never thought I would meet someone that loved me and supported me as much as you do. Thank you for coming on this journey with me and for basically being a graduate student yourself. Thank you for being so understanding when I had to work long days (specially those 12 hour days) and when we couldn't take long weekends off because I had to work on holidays. Thank you for cooking when I got home late, for cleaning when I was working Saturdays, for jumping up and down when I got the NSF, for every moment we spent together. But most of all, thank you for working as hard as you did so that we could be together. I have never met a person that has worked as hard as you have to get where you are right now and I'm grateful that I'm standing next to you. Por todos los bellos momentos que hemos pasado y por los que vendran, gracias.

To my mom, for showing me that anything is possible if you work hard enough for it.
And to my husband, for making me smile every day since the day we met.

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LIST OF ABBREVIATIONS AND SYMBOLS

[M]	metal center
[O]	oxidation
$[Rh(cod)Cl]_2$	chloro(1,5-cyclooctadiene)rhodium(I) dimer
$[RhCl(CO)_2]_2$	di-μ-chloro-tetracarbonyldirhodium(I)
°C	degree celcius
Å	Armstrong
Ac_2O	acetic anhydride
$AgBF_4$	silver tetrafluoroborate
AgCl	silver chloride
Aq.	aqueous
Au	gold
AuCl	gold chloride
BAr_4^{F-24}	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BF_4	tetrafluoroborate
bm	broad multiplet
Bn	benzyl
Boc	di-tert-butyl dicarbonate
Br_2	bromine
bs	broad singlet
C-C	carbon-carbon
C-H	carbon-hydrogen
C(0)	carbon(0)

C_6H_5Cl	chlorobenzene
C_6H_6	benzene
CaH_2	calcium hydride
cat.	catalyst
CD_2Cl_2	deuterated dichloromethae
CD_3CN	deuterated acetonitrile
CDC	carbodicarbene
$CDCl_3$	deuterated chloroform
CDP	carbodiphosphorane
CF_3CH_2OH	2,2,2-trifluoroethanol
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
Cl	chloride
cm^{-1}	$centimeters^{-1}$
CO	carbon monoxide
Co	cobalt
CO_2	carbon dioxide
Conc.	concentrated
Cr	chromium
Cu	copper
$Cu(acac)_2$	
$Cu(OTf)_2$	copper triflate
CuBr	copper bromide

CuCl	copper chloride
d	doublet
D	Debye
d	days
D_2O	deuterated water
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DIEA	diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPH	*O*-(2,4-dinitrophenyl)hydroxylamine
dr	diastereoselective ratio
dt	doublet of triplets
Equiv	equivalents
er	enantiomeric ratio
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
EWG	electron-withdrawing group

h	hour
H_2O	water
HBF_4	tetrafluoroboric acid
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
*i*PrOH	isopropanol
IR	infrared spectroscopy
K_2CO_3	potassium carbonate
K_3PO_4	potassium phosphate
$KB(C_6H_5)_4$	potassium tetraphenylborate
kcal	kilocalories
KHMDS	potassium bis(trimethylsilyl)amide
$KMnO_4$	potassium permanganate
KOAc	potassium acetate
$LiBF_4$	lithium tetrafluoroborate
LTMP	lithium tetramethylpiperidide
m	multiplet
M	molar
*m*CPBA	meta-chloroperoxybenzoic acid
Me_2S	dimethylsulfate
Me_2Zn	dimethylzinc

MeCN	acetonitrile
MeO	methoxy
MeOH	methanol
Mes	mesityl
MgO	magnesium oxide
MHz	mega hertz
Min	minutes
MsCl	mesyl chloride
N-Me	N-methyl
N_2	nitrogen
$NaBAr_4^{F-24}$	sodium-tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
$NaBH_4$	sodium borohydride
NaCl	sodium chloride
$NaHCO_3$	sodium bicarbonate
$NaIO_4$	sodium periodate
NaN_3	sodium azide
NaOAc	sodium acetate
NaOH	sodium hydroxide
NaOMe	sodium methoxide
NH_2NHOH	hydroxyhydrazine
$NH_2OH•H_2SO_4$	hydroxylamine sulfate
$NH_2OH•HCl$	hydroxylamine hydrochloride
NH_4OAc	ammonium acetate

NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NO_2	nitro
nOe	nuclear Overhauser effect
NsCl	nosyl chloride
Nu	nucleophile
O_3	ozone
P. ribis	pseudomonas ribis
P_2O_5	phosphorus pentoxide
PA	proton affinity
Ph	phenyl
Ph_2PCl	chlorodiphenylphosphine
$PhCF_3$	trifluoromethyltoluene
PhCl	chlorobenzene
PhCOOH	benzoic acid
PhH	benzene
$PhI(OAc)_2$	(diacetoxyiodo)benzene
PhMe	toluene
$PhNH_2$	phenylamine
PPL	porcine pancreas lipase
ppm	parts per million
psi	pounds per square inch
Pt	platinum

Rh	rhodium
Rh-H	rhodium hydride
$Rh_2(esp)_2$	bis[rhodium(α,α,α',α'-tetramethyl-1,3,-benzenedipropionic acid)]
$Rh_2(OAc)_4$	rhodium acetate dimer
$Rh_2(OPiv)_4$	rhodium pivolate
$Rh_2(pfb)_4$	dirhodium tetracaprolactamate
$Rh_2(TFA)_4$	rhodium(II) trifluoroacetate dimer
$Rh_2(tfacam)_4$	rhodium(II) trifluoroacetamide dimer
$Rh_2[(S)\text{-Br-nttl}]_4$	dirhodium(ii) tetrakis[N-bromo-1,8-naphthoyl-(S)-tert-leucinate]
rt	room temperature
Ru	ruthenium
s	singlet
Sat.	saturated
SbF_6	antimony pentafluoride
SiO_2	silicon dioxide
t	triplet
t-Bu	tert-butyl
td	triplet of doublets
TEBAC	benzyltriethylammonium chloride
TFA	trifluoroacetic anhydride
TfO	triflate
THF	tetrahydrofuran

TIPS	triisopropylsilane
TLC	thin layer chromatography
$TMSN_3$	trimethylsilyl azide
TsCl	tosyl chloride
TsNHOH	N-tosyl hydroxylamine
υ_{CO}	CO frequency

CHAPTER ONE

LEWIS ACID ACTIVATION OF CARBODICARBENE CATALYSTS FOR RH-CATALYZED HYDROARYLATION OF DIENES [*]

1.1 Introduction

Catalysis constitutes one of the most important areas in organic synthesis. Whether the catalyst is organic in nature or contains a metal, the improvement in the reaction rate of a reaction under catalytic control cannot be ignored. The activity of a given catalyst is strongly dependent on its structure, with both ligand and backbone being highly influential. Consequently, significant efforts go towards the development of new ligands and alternative backbones. In this chapter, we report the activation of a carbodicarbene Rh(I) catalyst with the use of a metal salt. The addition of catalytic amounts of a Lewis acid enables the hydroarylation of indoles across 1,3-dienes at 50 °C, a significant improvement from 120 °C in the absence of the metal salt. A number of substitutions and functional groups are tolerated under this reaction, making it amenable for the synthesis of organic compounds. Mechanistic studies reveal the role of the Lewis acid in the reaction and shed light into the nature of (CDC)-Rh(I) complexes.

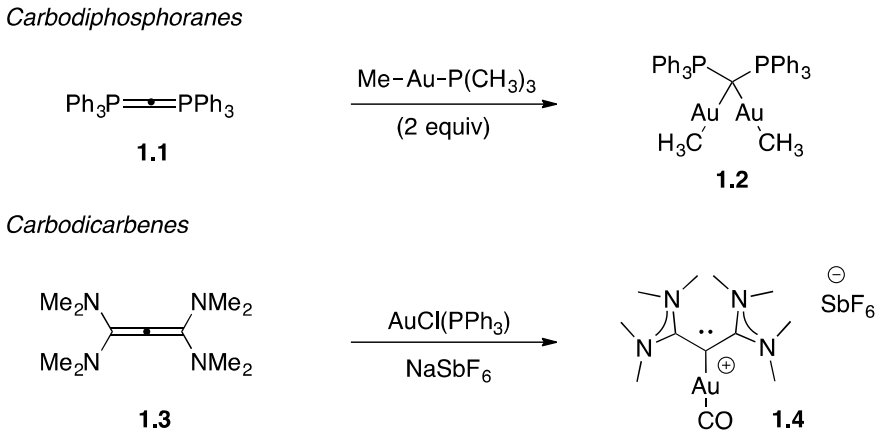
[*]Reprinted in part with permission from Roberts, C. R.; Matías, D. M.; Goldfogel, M. J.; Meek, S. J. *J. Am. Chem. Soc.* **2015,** *137,* 6488.

1.2 Background

1.2.1 Introduction and History of Divalent Carbon(0) Compounds

Divalent carbon(0) compounds, such as carbodiphosphoranes (CDPs; **1.1**) and carbodicarbenes (CDCs; **1.3**), represent an emerging area in ligand development for transition-metal catalysis and provide strategies to access new modes of reactivity.[1] Principal to their reactivity is a divalent carbon(0) supported by two L-type donor groups.[2] Phosphanes and NHCs make good ligands for the stabilization of carbon(0) due to their strong σ donation and weak to moderate π acceptance. These qualities allow the formation of the divalent carbon(0) and prevent the bonding situation that is found in allenes.

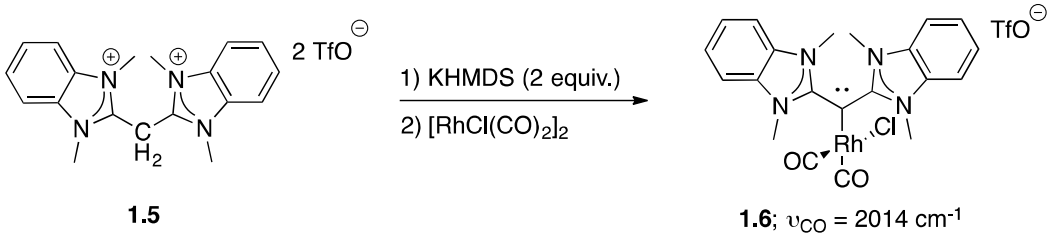
Scheme 1-1. Stabilized Divalent Carbon(0) Compounds



Unlike their carbon(II) analogs, carbenes, the reactivity profile of carbon(0) ligands is centered around two lone-pairs of electrons that are available for protonation, or binding to Lewis acids. Frenking and coworkers studied the second proton affinities (PA) of carbon bases and showed that the second PA of NHCs were in the range of 40-100 kcal/mol, whereas divalent carbon(0) displayed values between 110 and 200 kcal/mol.[3] Furthermore, a CDC-Rh(I)-CO complex developed by Bertrand revealed lower CO frequency (υ_{CO} = 2014 cm^{-1}) than analogous

NHC-Rh(I)-CO complexes (υ_{CO} = 2058-2036 cm^{-1}).[4] This data is indicative of a strong donation from the CDC ligand (Scheme 1-2).

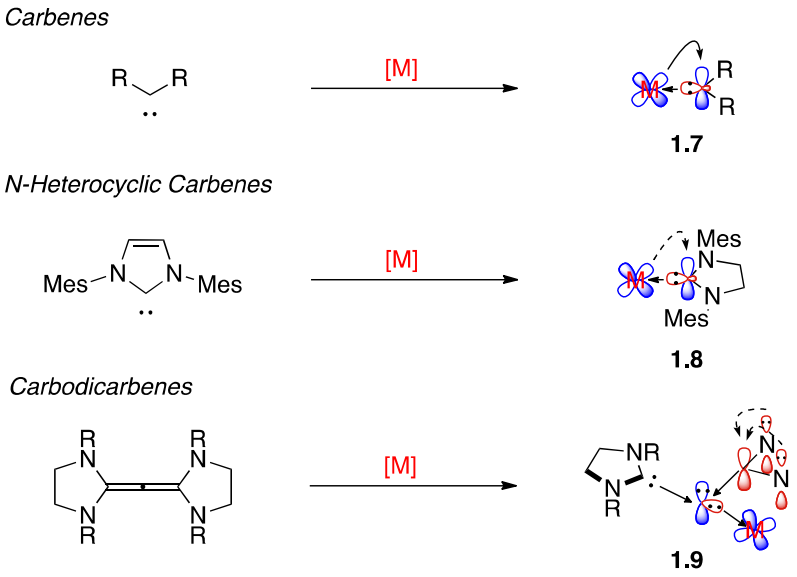
Scheme 1-2. Bertrand's Synthesis of a Carbodicarbene Rhodium Complex



1.5 **1.6**; υ_{CO} = 2014 cm^{-1}

This behavior can be explained by comparing the manner in which carbenes, NHCs, and CDCs bind to metals (Scheme 1-3).[5] In the case of carbenes, there is σ donation to the metal from the carbene carbon and significant back-donation into the empty p orbital. NHCs contain similar bonds, but the stability afforded by the adjacent nitrogens significantly decreases the backdonation. CDCs contain a second pair of electrons and no empty p orbital, thus the backdonation is not present. Compared to singlet carbenes, CDC complexes are stronger σ donors and weaker π acceptors.

Scheme 1-3. Orbital Donation of Carbenes, NHCs, and CDCs to a Metal



Homo- and hetero-bimetallic transition-metal complexes of carbon(0) have been reported and primarily employ CDP ligand frameworks and coinage metals (I–IV Figure 1-1).[6] Strong electron-donor properties paired with the ability to form dinuclear species provides a framework to electronically and sterically modify catalyst reactivity profiles through binding of a second Lewis acid to the carbon(0) either temporarily or permanently. The use of carbon(0) bimetallic complexes as catalysts, or the application of Lewis acids to alter catalyst reactivity by secondary binding to carbon(0) ligands in catalysts has not been reported.[7-8]

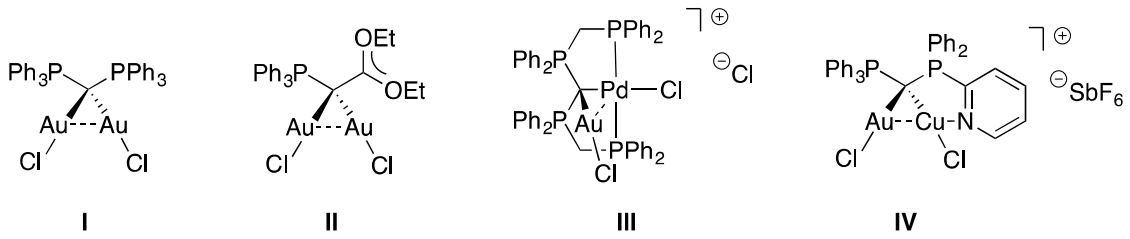
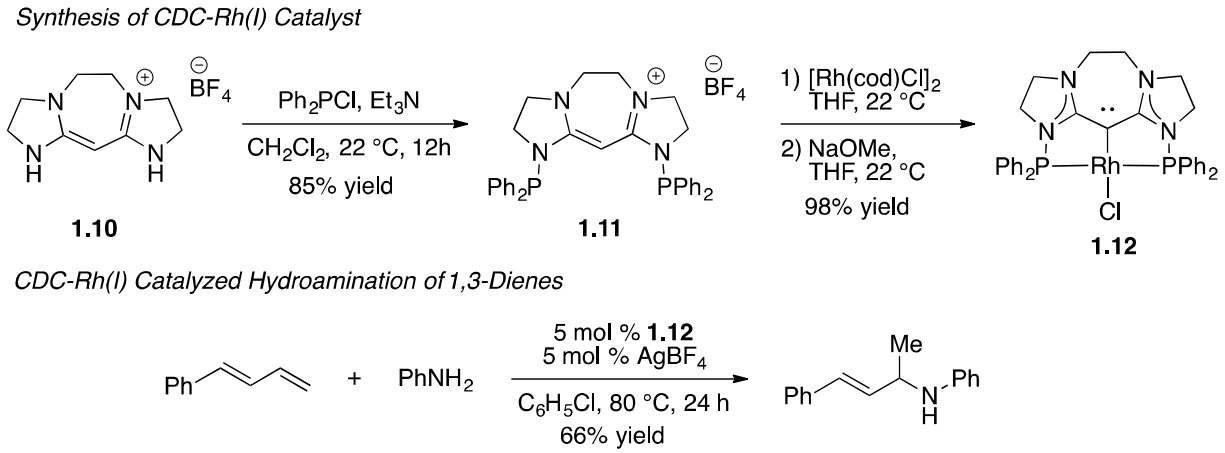


Figure 1-1. Bimetallic Carbodiphosphorane Complexes

1.2.2 First Examples of CDCs in Catalysis

Even though CDCs were ubiquitous across the synthetic organic and inorganic community, the development of a CDC catalyst remained a challenge. Our group reported the first example of a CDC employed in catalysis.[9] The use of a CDC-Rh(I) complex **1.12** allowed for the hydroamination of terminal 1,3-dienes (Scheme 1-4). The CDC-Rh(I) complex **1.12** was characterized as having a tethered scaffold that allowed for better orbital alignment and thus better stabilization of the divalent carbon(0). Furthermore, bidentate phosphines were incorporated in order to have a tunable catalyst and to prevent side reactivity. These characteristics provided for strong donation from the ligand, which allowed the use of nucleophilic amines in the hydroamination reaction. Electron-withdrawing amines could also be employed, allowing for the expansion of the scope of the catalyst. This strategy overcame a great challenge in hydroamination, since a general catalyst tolerant of both electron-donating and electron-withdrawing amines is quite uncommon.

Scheme 1-4. Synthesis and Reactivity of Meek's CDC-Rh(I) Catalyst



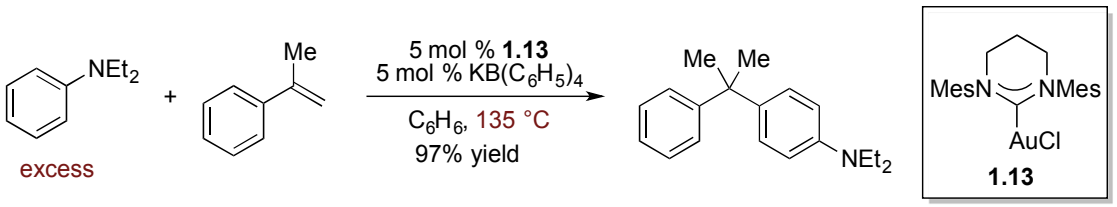
Shortly after this initial publication, an array of catalytic transformations using CDC-metal complexes were reported by multiple groups. Hsu and Ong presented the synthesis of a

tridentate Bis(pyridine)carbodicarbene-PdCl complex and its activity in the Mizoroki-Heck reaction.[10] Later, the same group reported the organo-catalyzed methylation of amines using CO_2 and a CDC catalyst.[11] More recently, Grubbs developed a CDC-Ru complex for Ru-catalyzed olefin metathesis, showing the first case of a CDC-metal complex being used for olefin metathesis.[12] In this last report, Grubbs mentions the lability of the CDC ligand, which is easily displaced by 2-isopropoxy-β-methylstyrene. Recently, our group disclosed the use of chiral pincer carbodicarbene ligands for enantioselective catalysis.[13] Beyond these reports, the use of CDCs in catalysis remains limited.

1.2.3 Introduction to Hydroarylation Chemistry

Throughout the years, organic chemists have developed a "toolbox" of transformations that are useful for the synthesis of complex molecules. This "toolbox" continues to grow, with the development of new transformations or the improvement of known ones. Among those reactions regularly used in organic synthesis is the hydrofunctionalization of unsaturated C−C bonds.[14] Hydroarylation reactions are amongst these, characterized by a C−C bond forming transformation with a net C−H addition across a C−C double bond (Scheme 1-5). While common, there are multiple disadvantages to this chemistry, including the use of precious metals as catalysts and the employment of harsh conditions (strong acids and high temperatures). Thus, significant efforts have been made to develop a hydroarylation method that is both efficient and practical. [15-18]

Scheme 1-5. Gold Catalyzed Hydroarylation of Anilines



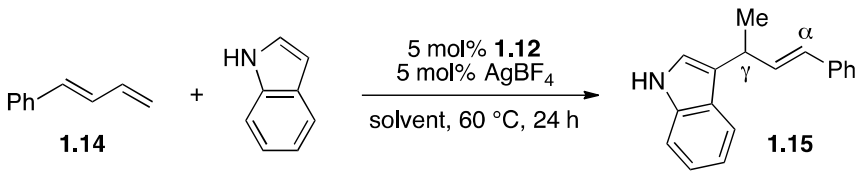
Prior examples of hydroarylation typically proceed at elevated temperatures (70−135 °C) in the presence of a cationic Pt,[18d-f] or Au[18e-i] catalyst with electron-rich alkenes, and are generally inhibited by Lewis-basic functionality,[18i] a problem also common to catalytic hydroamination.[19] To address some of these limitations, we initiated a program to develop new catalysts and catalytic methods which would enable the addition of nucleophiles to C−C double bonds.

1.3 Results and Discussion

1.3.1 Initial Results and Optimization

We began our investigations with CDC−Rh(I) complex **1.12** (Table 1-1). Treatment of indole and diene **1.14** with 5 mol % **1.12** and 5 mol % $AgBF_4$ in C_6H_5Cl at 60 °C resulted in >98% conversion (83:17 γ:α, entry 1).[20] In order to determine if the selectivity could be improved, a solvent screen was performed. Changing the solvent to toluene led to an increase in selectivity (93:7 γ:α), but a decrease in conversion was observed; however, when a second trial was performed using the same conditions, >98% conversion was obtained with decreased selectivity (85:15 γ:α). Using other solvents led to similar discrepancies between trials. Notably, the use of CH_2Cl_2 afforded completely different results (Table 1-1, entry 5). We noticed that most of these reactions afforded a heterogeneous mixture and concluded that the inconsistencies observed were the result of this heterogeneity.

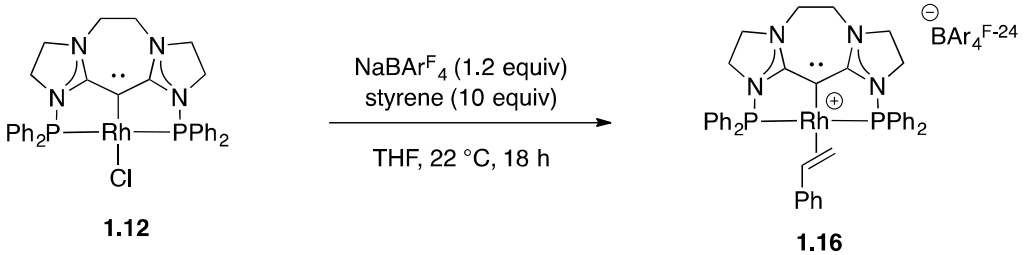
Table 1-1. Solvent Screen of Hydroarylation Reaction



entry	solvent	conversion (1st trial)	γ : α	conversion (2nd trial)	γ : α
1	PhCl	> 98%	87:13	95%	94:6
2	PhMe	70%	93:7	> 98%	85:15
3	PhH	62%	87:13	92%	80:20
4	MeCN	< 2%	---	< 2%	---
5	CH_2Cl_2	< 2%	---	56%	86:14
6	THF	96%	78:22	54%	83:17

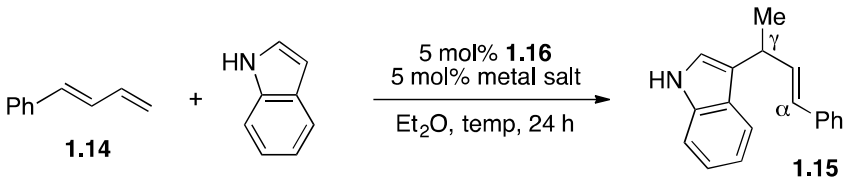
In order to increase the solubility of the catalyst, cationic Rh(I)− styrene complex **1.16** was synthesized (Scheme 1-6).[21] Attempted hydroarylation in the presence of 5 mol % styrene complex **1.16** in dioxane at 80 °C for 24 h led to < 5% conversion (Table 1-2, entry 1). Increasing the temperature to 120 °C afforded only 6% conversion after 24 h (entry 2). While trying to understand why the cationic catalyst had such a detrimental effect on the reactivity, we envisioned a scenario where the silver salt acted as a catalyst activator. To determine if Ag(I) was responsible for the catalyst reactivity, 5 mol % AgCl was added in dioxane at 80 °C and >98% conversion was obtained (>98:2 γ:α, entry 3).

Scheme 1-6. Synthesis of Cationic Styrene (CDC)-Rh(I) Complex **1.16**



These initial observations demonstrate the ability of AgCl as an additive to increase the activity of the (CDC)−Rh complexes for hydroarylation. We next examined the effect of other Lewis acid additives on catalyst activity (Table 1-2). As illustrated in entries 4−6, reaction of 5 mol % **1.16** with an equimolar amount of Cu-, Ag-, or Au chloride in Et_2O at 50 °C for 24 h affords indole **1.15** in high yield (up to 96%) and selectivity (up to 95:5 γ:α). Lithium salts were also found to promote catalytic hydroarylation with similar efficiency (entries 7−8) as 5 mol % $LiBAr^F{}_4$-OEt_2 and $LiBF_4$ deliver **1.15** in 76% and 94% yield and >98:2 and 97:3 γ:α, respectively.[1b,22] Notably, sodium salts proved ineffective at increasing catalyst reactivity, likely due to the decreased Lewis acidity of sodium compared to lithium (entry 9, Table 1-2). Decreasing the reaction temperature to 22 °C results in 98% yield, 85:15 γ:α, (entry 13). To achieve both high conversion and site-selectivity in further studies, cost-effective $LiBF_4$ at 50 °C was chosen as the optimal reaction conditions. Notably, catalytic hydroarylation in the presence of 10 mol % 2,6-di-*t*-Bu-pyridine as a Brønsted acid scavenger does not inhibit the reaction, indicating that the reaction is not catalyzed by *in situ* generated Brønsted acid (entry 14, Table 1-2).[23]

Table 1-2. Additive Effect in (CDC)-Rh-Catalyzed Addition of Indole to Phenyl-1,3-Butadiene



entry	metal salt	temp (°C)	conv (%);[a] γ:α	yield (%)[b]
1[c]	---	80	>2%; ---	---
2[c]	---	120	6; ---	---
3[c]	AgCl	80	>98; >98:2	---
4	CuCl	50	> 98; 90:10	91
5	AgCl	50	92; 95:5	89
6	AuCl	50	> 98; 85:15	96
7	$LiBAr^F_4 \bullet OEt_2$	50	87; > 98:2	76
8	$LiBAr^F_4$	50	> 98; 97:3	94
9	$NaBAr^F_4$	50	< 2; ---	---
10	CuCl	22	< 2; ---	---
11	AgCl	22	< 2; ---	---
12	AuCl	22	60; 81:19	53
13	$LiBF_4$	22	> 98; 85:15	98
14[d]	$LiBF_4$, 2,6-di-*t*-Bu-pyridine	50	>98; 94:6	74

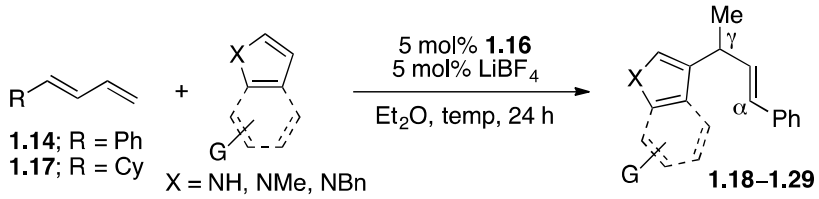
[a]Conversion to product. [b]Yields of purified products are an average of two runs. [c]Dioxane as solvent. [d]10 mol % 2,6-di-*t*-Bu-pyridine.

1.3.2 Scope of Hydroarylation Reaction

With $LiBF_4$ identified as the optimal additive, the scope of the reaction was investigated using a range of *N*-heterocycles and phenyl or cyclohexyl 1,3-dienes **1.14** and **1.17**. As shown in Table 1-3, phenyl-substituted 1,3-diene **1.14** undergoes site selective hydroarylation with N-Me and 7-Cl indole at 50 °C (entries 1−2) to afford **1.18** (63%, >98:2 γ:α) and **1.19** (71%, 96:4 γ:α). More nucleophilic 2,4-dimethylpyrrole reacts at 22 °C in the presence of 5 mol % Rh(I) **1.16** and $LiBF_4$ to deliver **1.20** in 88% yield, >98:2 γ:α, and 91:9 C2:C3 site-selectivity on the pyrrole ring. Indoles bearing electron-withdrawing groups require a slightly higher temperature (60 °C) to achieve good conversion; treatment of 6-NO_2 indole with **1.20** in the presence of **1.16** and $LiBF_4$ reacts to generate **1.21** in 57% yield and 91:9 γ:α (entry 4). 3-Methylindole directs the diene

addition to the 2-position of indole (entry 5) to afford **1.22** in 33% yield and 92:8 selectivity. Similarly, increasing the steric demand and decreasing the nucleophilicity of the N-hetereoarene results in a less efficient reaction; TIPS-pyrrole undergoes catalytic hydroarylation at 70 °C to yield **1.23** in 38% yield and >98:2 γ:α (entry 6, Table 1-3). The reaction does not improve if >5.0 mol % $LiBF_4$ is used. Alkyl dienes are equally effective reaction partners for Rh-catalyzed hydroarylation as illustrated by the reactions of cyclohexyl-1,3-diene **1.17** with a variety of substituted indoles (entries 7−10, Table 1-3); reactions proceed efficiently with catalytic $LiBF_4$ (5 mol %) at 50 °C and deliver the alkylated indoles (**1.24**−**1.27**) in good yields (66−91%) and excellent site-selectivity (>98:2 γ:α). 2,4-Dimethyl pyrrole affords 2-substituted pyrrole **1.28** in 53% yield and >98:2 diene γ:α selectivity (entry 11) at 22 °C in 24 h. Again, alkyl 1,3-dienes react more sluggishly with indoles bearing larger groups on nitrogen and require longer reaction times and higher temperatures; 60 °C for 48 h is required to generate substituted N-benzyl indole **1.29** in 85% yield and 87:13 γ:α site-selectivity.

Table 1-3. (CDC)-Rh-Catalyzed Addition of *N*-Heteroarenes to 1,3-Dienes

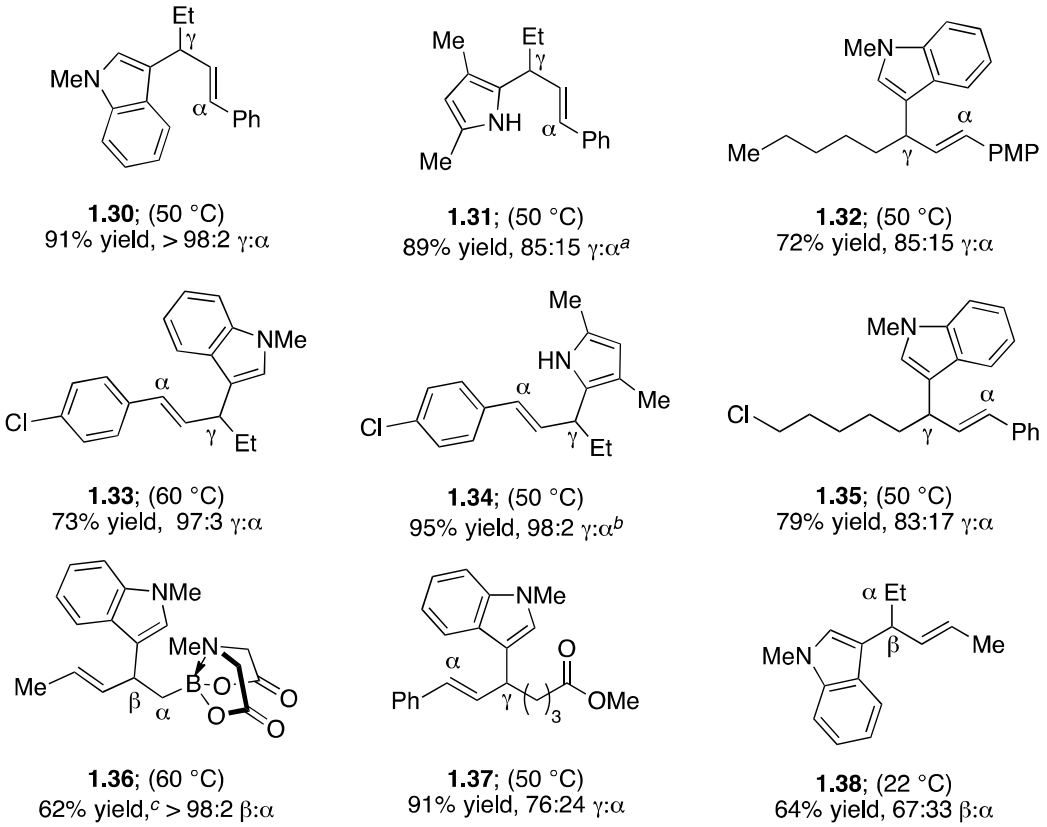


entry	heterocycle; product	diene	temp (°C)	yield (%);[a] γ:α
1	N-Me-indole; **1.18**	**1.14**	40	63; > 98:2
2	7-Cl-indole; **1.19**	**1.14**	50	71; 96:4
3[b]	2,4-Me_2-pyrrole; **1.20**	**1.14**	22	88; > 98:2
4	6-NO_2-indole; **1.21**	**1.14**	60	57; 91:9
5	3-Me-indole; **1.22**	**1.14**	60	33; 92:8
6	N-TIPS-pyrrole; **1.23**	**1.14**	70	38; > 98:2[c]
7	indole; **1.24**	**1.17**	50	85; > 98:2
8	6-MeO-indole; **1.25**	**1.17**	50	91; 98:2
9	N-Me-indole; **1.26**	**1.17**	50	66; > 98:2
10	2-Me-indole; **1.27**	**1.17**	50	66; > 98:2
11[d]	2,4-Me_2-pyrrole; **1.28**	**1.17**	22	53; > 98:2
12[e]	N-Bn-indole; **1.29**	**1.17**	60	85; 87:13

[a]Yields of purified products are an average of two runs. [b]91:9 C2:C3 site selectivity on pyrrole. [c]^{1}H NMR yield; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with DMF as an internal standard. [d]85:15 C2:C3 site-selectivity on pyrrole. [e]48 h reaction.

We next extended the utility of the Rh(I)-catalyzed protocol to the more challenging site-selective addition to internal dienes.[24-25] Products delivered through these catalytic reactions afford differentially functionalized allyl-substituted heterocycles (Scheme 1-7). 1,4-Aryl-alkyl-substituted dienes undergo catalytic hydro-heteroarylation with indole and 2,4-dimethyl pyrrole to deliver functionalized heterocycles (**1.30**− **1.32**) in good yield but with a slight diminution in diene site-selectivity (>98:2−85:15 γ:α). The Rh-catalyzed synthesis of *p*-chlorostyrene derivatives **1.33** and **1.34** is notable, as such electron-deficient dienes are not compatible with Au-catalyzed methods;[18] 5 mol % **1.16** and 5 mol % $LiBF_4$ at 60 °C delivers **1.33** and **1.34** in 73% and 95% yield. The reaction demonstrates good functional group tolerance to alkyl halides (**1.35**), boronate esters (**1.36**), and esters (**1.37**). Addition of indole to symmetrical hexa-2,4-diene at 22 °C affords **1.38** in 64% yield in 67:33 β:α selectivity.

Scheme 1-7. (CDC)-Rh-Catalyzed Hydroheteroarylation of 1,4-Disubstituted Dienes



1.30; (50 °C)
91% yield, > 98:2 γ:α

1.31; (50 °C)
89% yield, 85:15 γ:α[a]

1.32; (50 °C)
72% yield, 85:15 γ:α

1.33; (60 °C)
73% yield, 97:3 γ:α

1.34; (50 °C)
95% yield, 98:2 γ:α[b]

1.35; (50 °C)
79% yield, 83:17 γ:α

1.36; (60 °C)
62% yield,[c] > 98:2 β:α

1.37; (50 °C)
91% yield, 76:24 γ:α

1.38; (22 °C)
64% yield, 67:33 β:α

[a]85:15 C2:C3 site-selectivity on pyrrole. [b]98:2 C2:C3 site selectivity on pyrrole. [c]^{1}H NMR yield; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with DMF as an internal standard.

1.3.3 Catalyst Structure and Mechanistic Studies

To gain insight into the catalyst structure and the effect of the metal salt additive, we obtained an X-ray structure of cationic (CDC)−Rh−styrene complex **1.16** (Figure 1-1). Complex **1.16** has a square-planar structure, with an sp^2 hybridized C(0)-donor and a C(0)−Rh bond length of 2.07 Å. The styrene ligand exhibits significant metal−alkene π-back-donation demonstrated by an elongated styrene C−C bond (1.395 Å).[26]

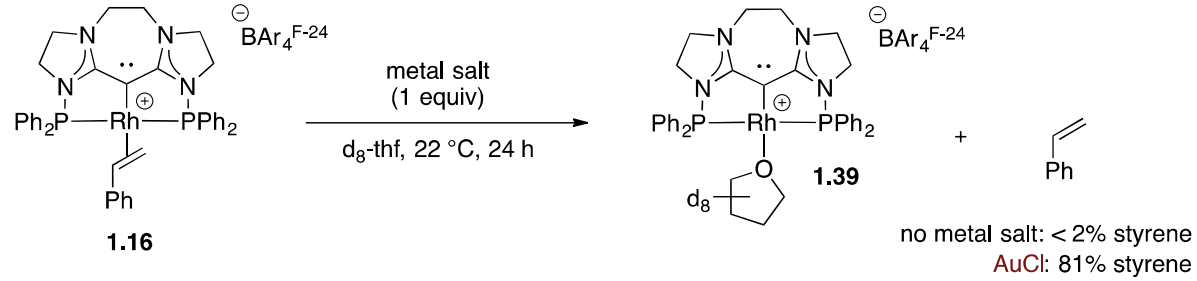
Figure 1-2. X-Ray Structure of Cationic (CDC)-Rh(I) Complex **1.16**

To investigate the electronic changes that occur to the Rh−alkene bond upon binding a second species to the carbon(0) donor, we attempted to analyze the ^{13}C NMR spectrum of the coordinated styrene in complex **1.16** in the presence of a Lewis acid additive (Scheme 1-8a). However, when complex **1.16** is treated with a metal salt, loss of styrene is observed; treatment of (CDC)−Rh(I)−styrene complex **1.16** with $LiBAr^F_4$ or AuCl in d_8-THF at 22 °C for 24 h leads to THF bound **1.39** and free styrene (AuCl: 81% styrene and $LiBAr^F_4$: 6% styrene (17% in 72 h)). No loss of styrene (<2%) is observed when no additive is present. These results indicate olefin substitution is facilitated by binding of a metal salt to the CDC, which destabilizes the olefin complex by decreasing π-back-donation, leading to styrene substitution by a weakly donating THF molecule. In addition, rapid substitution of styrene occurs when complex **1.16** is reacted with 1 equivalent of indole and $LiBF_4$ at 40 °C. No Rh−H signals are observed in the ^1H NMR spectrum, indicating an alkene activation pathway, as opposed to a C−H activation mechanism. To quantify the electronic changes that occur at Rh(I) upon binding to the carbon(0) donor, pincer (CDC)-Rh(I)-CO complex **1.40**[9] was treated with HBF_4-OEt_2 to cleanly yield **1.41** in >98% conversion (Scheme 1-8b). Protonation at C(0) leads to shortening of the CO bond length, indicated by an increase in the IR stretching frequency (υ_{CO} = 2016 cm^{-1}), representing a

significant decrease in π-back-donation and decrease in electron density at Rh. Tetrafluoroboric acid is a less effective activator, compared to $LiBF_4$, for diene hydroarylation.[27] This is likely due to ligand protonation being less reversible than binding $LiBF_4$, which would indicate the importance of a reversible interaction provided by Lewis acid additives such as AgCl and $LiBF_4$. Coinage metal salts also present the possibility of a bimetallic interaction,[6] although this is unlikely with lithium. Together, the enhanced ligand substitution and reactivity suggest that the metal additives bind to the C(0) of the olefin complex promoting ligand substitution (styrene by THF) and also addition of a nucleophile to the bound C−C bond.[28] Further analysis of the catalytic reaction mechanism with $LiBF_4$ through deuterium labeling studies with C-3 deuterium labeled N-Me-indole results in formation of d_1-**1.15** with >95% deuterium transfer (Scheme 1-8c).

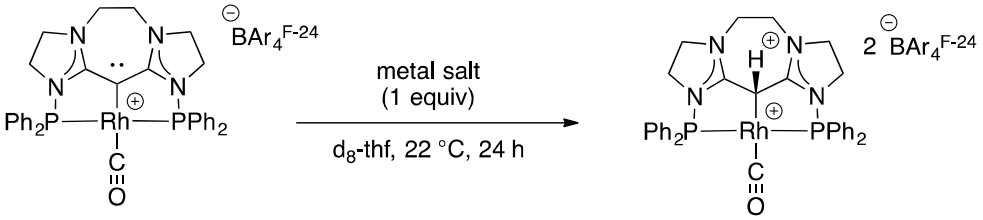
Scheme 1-8. Additive Effect on (CDC)-Rh(I) Complexes **1.16** and **1.40**

(a) *Styrene substitution in (CDC)-Rh(I) complex **1.16***



no metal salt: < 2% styrene
AuCl: 81% styrene
$LiBAr^F_4$: 6% styrene

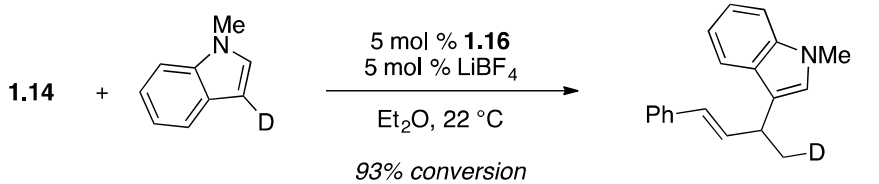
(b) *Addition of HBF_4 to CDC-Rh(I) carbonyl complex **1.40***



1.40; υ_{CO} = 1986 cm^1

1.41; υ_{CO} = 2016 cm^1

(c) *deuterium d_1-N-Me indole*



d_1-**1.15**
(>95% D incorporation)

1.4 Conclusions

In summary, these studies describe a key attribute of carbon(0)-donor ligands that expands their limited use in catalysis.[29] We show the potential for tuning ligand donation in CDCs through secondary binding of Lewis acids, which enables the use of cationic (CDC)−Rh-based complexes as catalysts for diene hydroarylation. Notably, simple lithium salts emerged as effective catalytic Lewis acids that promote reactions under mild conditions for a range of heteroarenes with terminal and internal dienes.

1.5 Experimental Details

Methods

All reactions were carried out in flame or oven (140 ºC) dried glassware that had been cooled under vacuum. Unless otherwise stated, all reactions were carried out under an inert N_2 atmosphere. All reagents were purged or sparged with N_2 for 20 min prior to distillation or use. All solid reagents were dried by azeotropic distillation with benzene three times prior to use. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer or a ASI ReactIR 1000, Model: 001-1002 for air sensitive rhodium carbonyl complexes. Mass spectra were obtained using a Thermo LTqFT mass spectrometer with electrospray ionization and external calibration. All samples were prepared in MeOH, MeCN or $CHCl_3$ for metal complexes. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400 or a Bruker AVANCE III 600 CryoProbe (^{1}H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 100 or 151 MHz, ^{31}P NMR at 160 or 243 MHz and ^{19}F NMR at 376 or 564 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: Chloroform-d at 7.26 ppm, CD_2Cl_2 at 5.32 ppm, CD_3CN at 1.94 ppm; ^{13}C NMR: Chloroform-d at 77.16 ppm, CD_2Cl_2 at 53.84 ppm, CD_3CN at 1.32 ppm). NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet, bs = broad singlet, bm = broad multiplet, etc.), and coupling constants (Hz). X-ray diffraction studies were conducted on a Bruker-AXS SMART APEXII diffractometer. Crystals were selected and mounted using Paratone oil on a MiteGen Mylar tip.

Materials

Solvents were purged with argon and purified under a positive pressure of dry argon by a SG Waters purification system: dichloromethane (EMD Millipore), diethyl ether (EMD Millipore, hexanes (EMD Millipore), benzene (EMD Millipore), and THF (EMD Millipore) were passed through activated alumina columns. Chloroform – d_1 and Dichloromethane – d_2 were purchased from Cambridge Isotope Labs, distilled over CaH_2 and stored in a dry box over activated 4 Å molecular sieves.

(E)-phenyl-1,3-butadiene,[30] (1E,3Z/E)-penta-1,3-dien-1-ylbenzene,[31] 1-methoxy-4-((1E,3Z/E)-penta-1,3-dien-1-yl)benzene,[32] *(E)/(Z)*-1-buta-1,3-dien-1-ylcylohexane,[33] *(E)*-dodeca-1,3-diene,[34] 6-methyl-2-((1E,3E)-penta-1,3-dien-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione,[35-38] (4E,6E)-methyl 7-phenylhepta-4,6-dienoate and ((1E,3E)-8-chloroocta-1,3-dien-1-yl)benzene,[39] 1-methoxy-4-((1E,3E)-octa-1,3-dien-1-yl)benzene,[40,41] 1-chloro-4-((1E,3E)-penta-1,3-dien-1-yl)benzene,[42,43] TIPS pyrrole,[44] 1-Benzylindole,[45] sodium tetrakis[3,5-*bis*(trifluoromethyl)phenyl]borate,[9] and complexes **1.12** and **1.40**[46] were synthesized according to a literature method or a modified literature method and matched reported spectra.

7-Chloroindole was purchased from Acros, recrystallized from hexanes, and stored in a dry box.

Chloro(1,5-cyclooctadiene)rhodium(I) dimer was purchased from Pressure Chemicals, stored in a dry box and used as received.

Copper(I) Chloride was purchased from Strem, stored in a dry box and used without further purification.

Copper(II) Chloride was purchased from Sigma Aldrich, stored in a dry box after overnight heating under vacuum and used without further purification.

Copper(I) hexafluorophosphate *tetrakis*(acetonitrile) was purchased from Sigma Aldrich, stored in the dry box, and used without further purification.

2,4-Dimethylpyrrole was purchased from Alfa Aesar, distilled from molecular sieves, and stored at – 20 ^{o}C in the dark.

2,6-di-*tert*-butylpyridine was purchased from Alfa Aesar, dried by azeotropic distillation with benzene directly after purchase, and stored in a dry box.

Lithium tetrafluoroborate was purchased from Sigma Aldrich, stored in the dry box after overnight heating over P_2O_5 under vacuum and used without further purification.

Lithium *tetrakis*(pentafluorophenyl)borate - ethyl ether complex was purchased from Boulder Scientific, stored in a dry box, and used as received.

Indole was purchased from Alfa Aesar, purified by recrystallization from aqueous ethanol, dried by azeotropic distillation with benzene and stored in a dry box.

5-Methoxyindole was purchased from Matrix Scientific, recrystallized from hexanes/ether, and stored in a dry box.

1-Methylindole was purchased from Alfa Aesar, dried by azeotropic distillation with benzene directly after purchase, and stored at – 20 ^{o}C in a dry box.

2-Methylindole was purchased from Alfa Aesar, purified by recrystallization from benzene, and stored in a dry box.

3-Methylindole was purchased from Alfa Aesar, purified by recrystallization from benzene, and stored in a dry box.

5-Nitroindole was purchased from ChemImpex, purified by recrystallization from aqueous ethanol and stored in a dry box.

Silver tetrafluoroborate was purchased from Strem, stored in a dry box, and used without further purification.

Silver chloride was purchased from Strem, stored in a dry box, and used without further purification.

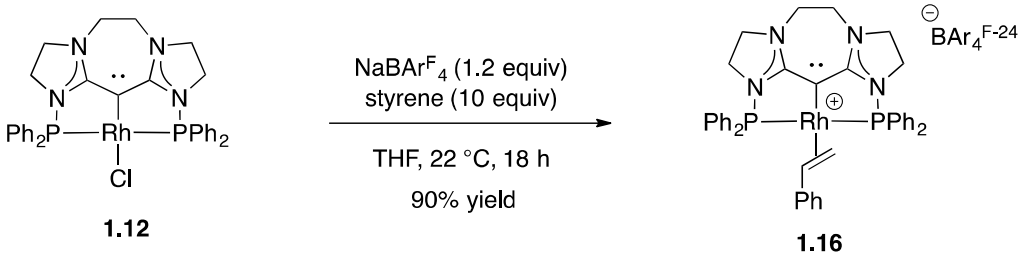
Sodium methoxide was purchased from Strem, stored in a dry box, and used without further purification.

Styrene was purchased from Alfa Aesar, distilled over CaH_2, and stored at – 20 ºC in a dry box.

Tetrafluoroboric acid etherate was purchased from Alfa Aesar, stored at -20 ºC and used as received.

Trityl tetra(pentafluorophenyl)borate was purchased from Strem, stored in a dry box, and used as received.

Procedure for the preparation of (CDC)-Rh(I)styrene $BAr_4^{f\text{-}24}$ complex 1.16:



1.12 **1.16**

In an N_2 filled dry box, a 20-mL scintillation vial with a stir bar was charged with (CDC)-RhCl complex **1.12** (540 mg, 0.788 mmol, 1.0 equiv) and $NaBAr_4^{f\text{-}24}$ (733 mg, 0.827 mmol, 1.05 equiv) Tetrahydrofuran (16 mL, [ ] = 0.049 M) was added followed by the addition of styrene (0.451 mL, 3.94 mmol, 5.0 equiv) via syringe. The vial was capped and the resulting dark orange mixture was allowed to stir for 18 h at 22 °C. After the reaction was complete, the NaCl precipitate was allowed to settle and the solution was filtered through a Celite® pad followed by washing with 5 mL of THF. The orange solution was concentrated and more THF (2.0 mL) was added to remove excess styrene. The solvent was removed *in vacuo* and two more aliquots of

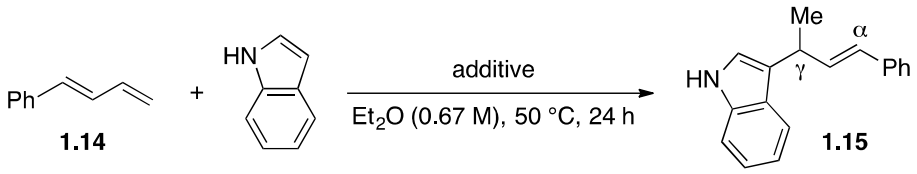
THF (2.0 mL) and 1 aliquot (2.0 mL) of ether were added to repeat this process. The tacky dark orange solid on the side of the vial was crushed into a powder via spatula and left to dry *in vacuo* for 6 h. The dark orange powder was isolated in 90% yield (1.15 g, 0.709 mmol). ^{1}H NMR (600 MHz, Methylene Chloride-d_2) δ 7.81-7.73 (m, 12H), 7.69 – 7.55 (m, 16H), 7.49 (t, J = 7.5 Hz, 4H), 6.79 (t, J = 7.4 Hz, 1H), 6.58 (t, J = 7.6 Hz, 2H), 5.90 (d, J = 7.7 Hz, 2H), 4.90 (td, J = 8.1, 4.1 Hz, 1H), 4.06 – 3.94 (m, 4H), 3.44 (m, 5H), 3.27 (m, 4H), 2.99 (d, J = 8.2 Hz, 1H). ^{13}C NMR (151 MHz, Methylene Chloride-d_2) δ 172.8 (t, J = 21.3 Hz), 162.1 (m), 140.8, 135.2, 133.3 (dt, J = 60.1, 7.5 Hz), 131.9 (d, J = 47.2 Hz), 130.7 (td, J = 22.3, 13.1 Hz), 129.4 (dt, J = 19.8, 9.9 Hz), 129.1 (m), 128.4, 127.7, 126.3, 125.9, 125.5, 124.1, 122.3, 117.9 (q, J = 4.2 Hz), 83.7 (dt, J = 34.3, 11.4 Hz), 75.6 (d, J = 6.7 Hz), 58.7, 53.3 (d, J = 8.1 Hz), 46.8, 41.38 ^{31}P NMR (243 MHz, Methylene Chloride-d_2) δ 86.47 (d, J = 164.3 Hz). HRMS (ES+) $[M]^+$ calcd for $C_{41}H_{40}N_4P_2Rh^+$ 753.18 , found: 753.09.

General procedure for the (CDC)-Rh-catalyzed hydroarylations of 1,3-dienes in Tables 1-1, 1-2, and SI-1.

In an N_2 filled dry box, an 8-mL vial equipped with a stir bar was charged with the appropriate (CDC)-Rh complex and additive. The appropriate solvent was added via syringe, the vial was capped and the mixture was allowed to stir for 1 h at 22 °C. If the additive was a silver salt, the mixture was allowed to stir in the dark. The nucleophile was added either as a solid or via syringe followed by addition of the 1,3-diene. The vial was capped with a Teflon® lined lid or septum cap, taped with electrical tape and brought outside the dry box. Any highly volatile or acidic compounds (HBF_4.OEt_2) were added outside the dry box via syringe through the Teflon® septa under an atmosphere of N_2. The reaction was allowed to warm to the appropriate temperature and stir for 24 h. Then the reaction was allowed to cool to room temperature and an

aliquot was taken to determine the conversion by ^{1}H NMR using DMF (5.0 μL) as an internal standard. The remaining solvent was removed *in vacuo*. The products were purified by SiO_2 column chromatography.

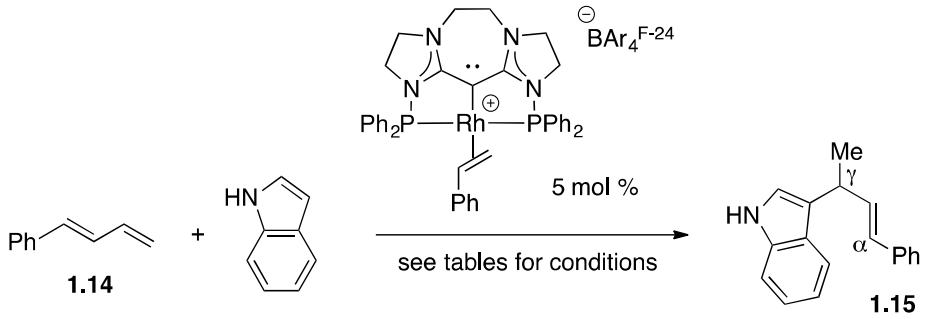
Control Reactions



entry	additives (mol %)	conversion (%)	γ : α
1	**1.16** (5), $LiBF_4$ (5), t-Bu lutidine (10)	>98	92:8
2[a,b]	trityl BArf (5)	48	73:27
3	trityl BArf (5), t-Bu lutidine	< 2	---
4[c]	HBF_4 (10)	< 2%	---
5[d]	trityl BArf (5)	22	44:56

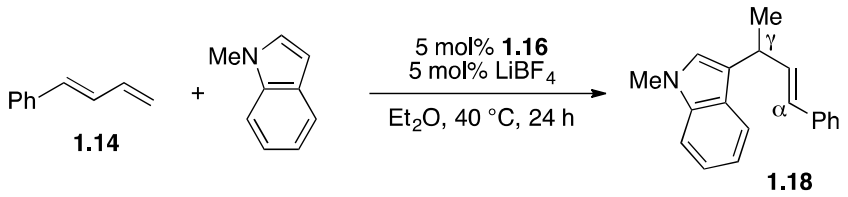
a. Unknown byproduct obtained in 13% conversion.
b. < 2% conversion at 22 °C.
c. Diene decomposed.
d. 1-Me indole used.

Procedure and characterization for the (CDC)-Rh-catalyzed hydroarylations of 1,3-dienes in Tables 1-1, 1-2.



Synthesis of (*E*)-3-(4-phenylbut-3-en-2-yl)-1H-indole (Table 1-1, entries 1-6; Table 1-2, entries 1-14).

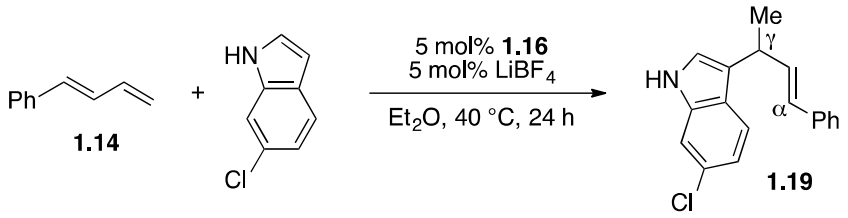
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, indole (12.9 mg, 0.110 mmol) and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.12** or **1.16** (0.0050 mmol) and additive (0.0050 mmol) in diethyl ether or dioxane (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 22 or 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.15** as a colorless oil (see Table 1-1, and Table 1-2, for conversions, yields, and selectivity.) ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.33 – 7.27 (m, 3H), 7.23 – 7.15 (m, 2H), 7.10 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.03 (dd, *J* = 2.5, 0.9 Hz, 1H), 3.95 (p, *J* = 6.9 Hz, 1H), 1.58 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform – d_1) δ 137.9, 136.7, 135.5, 128.5, 128.3, 127.0, 126.9, 126.29, 122.1, 120.6, 120.5, 119.7, 119.4, 111.2, 34.4, 20.8. IR (ν/cm^{-1}): 3025 (s), 2962 (s), 1492 (s), 1456 (s), 1417 (s), 1337 (s), 1221 (w), 1095 (w) MS (ES$^+$) [M+H]$^+$ calcd for $C_{18}H_{18}N^+$ 248.14, found: 248.18.



Synthesis of (*E*)-1-methyl-3-(4-phenylbut-3-en-2-yl)-1H-indole (Table 1-2, entry 1).

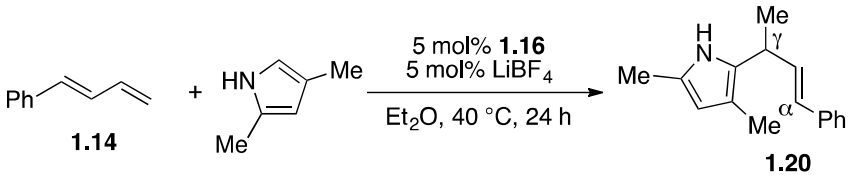
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 40 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.18** (16.4 mg, 0.064 mmol, 63% yeld) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.39 – 7.34

(m, 2H), 7.33 – 7.26 (m, 4H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.09 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1H), 6.88 (d, *J* = 0.8 Hz, 1H), 6.56 – 6.43 (m, 2H), 3.94 (m, 1H), 3.77 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 4H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 137.9, 137.3, 135.7, 128.5, 128.1, 127.3, 126.9, 126.2, 125.4, 121.6, 119.8, 119.0, 118.8, 109.3, 34.3, 32.7, 20.9. IR (ν/cm^{-1}): 2925 (m), 2870 (s), 1472 (m), 1374 (w), 1328 (w), 1134 (s). MS (ES$^+$) [M+H]$^+$ calcd for $C_{19}H_{20}N^+$ 262.16, found: 262.00.



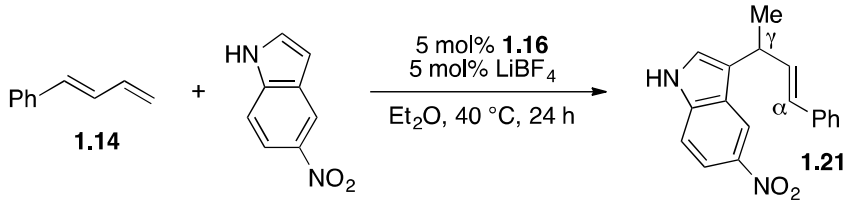
Synthesis of (*E*)-7-chloro-3-(4-phenylbut-3-en-2-yl)-1H-indole (Table 1-2, entry 2).

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 7-chloroindole (16.7 mg, 0.110 mmol) and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (15:1 Pentane/EtOAc) to afford **1.19** (19.9 mg, 0.071 mmol, 71% yield, 96:4) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.29 (td, *J* = 7.8, 1.9 Hz, 2H), 7.20 (td, *J* = 7.4, 1.1 Hz, 2H), 7.09 (dd, *J* = 2.4, 0.8 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 16.1 Hz, 1H), 6.44 (dd, *J* = 15.8, 6.6 Hz, 1H), 3.92 (m, 1H), 1.57 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 137.7, 135.1, 133.9, 128.6, 128.4, 127.1, 126.2, 121.7, 121.4, 121.2, 120.2, 118.4, 116.7, 34.4, 20.8. IR (ν/cm^{-1}): 2964 (s), 2856 (m), 1566 (w), 1491 (m), 1436 (m), 1335 (w), 1197 (s), 1144 (w), 1088 (w). MS (ES$^+$) [M+H]$^+$ calcd for $C_{18}H_{17}ClN^+$ 282.10, found: 282.18.



Synthesis of (E)-3,5-dimethyl-2-(4-phenylbut-3-en-2-yl)-1H-pyrrole (Table 1-2, entry 3).

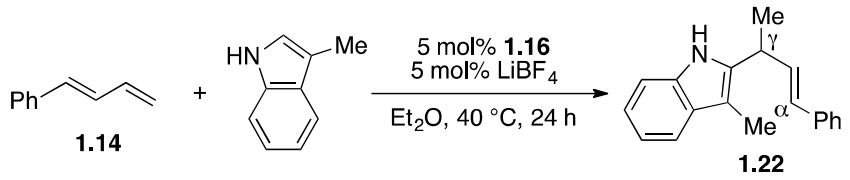
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 2,4-dimethylpyrrole (10.5 mg, 0.11 mmol) and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 22 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.20** (19.9 mg, 0.088 mmol, 88% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.81 – 7.73 (m, 2H), 7.70 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 1H), 6.86 – 6.71 (m, 2H), 6.09 (d, *J* = 2.8 Hz, 1H), 4.20 – 4.11 (m, 1H), 2.61 (d, *J* = 0.8 Hz, 3H), 2.44 (s, 3H), 1.83 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 137.5, 133.6, 128.6, 128.5, 127.2, 126.3, 125.3, 113.9, 108.3, 33.6, 19.7, 13.0, 11.0. IR (ν/cm^{-1}): 3275 (br, m), 2968 (w), 2925 (m), 2866 (w), 1698 (m), 1653 (m), 1541 (m), 1507 (m), 1457 (m), 1268 (m), 968 (br, m). MS (ES$^+$) $[M+H]^+$ calcd for $C_{16}H_{20}N^+$ 226.16, found:. 226.27.



Synthesis of (*E*)-5-nitro-3-(4-phenylbut-3-en-2-yl)-1H-indole (Table 1-2, entry 4).

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 5-nitroindole (17.8 mg, 0.110 mmol) and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M),

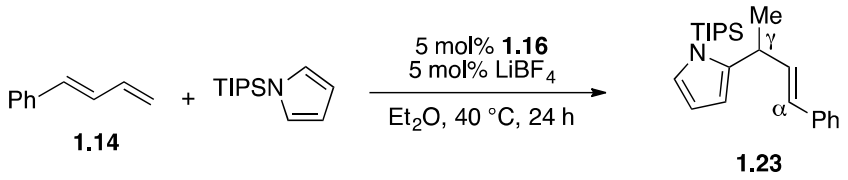
and the reaction allowed to stir at 60 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (100% Chloroform) to afford **1.21** (21.0 mg, 0.057 mmol, 57% yield) as a yellow solid. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 2.1 Hz, 1H), 8.38 (d, *J* = 15.6 Hz, 1H), 8.11 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.22 – 7.18 (m, 2H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.42 (dd, *J* = 15.8, 7.0 Hz, 1H), 3.98 (m, 1H), 1.59 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 141.6, 139.6, 137.4, 134.4, 129.1, 128.6, 127.3, 126.3, 126.3, 123.6, 123.3, 117.9, 117.0, 111.2, 34.1, 20.9. IR (ν/cm^{-1}): 2967 (w), 1621 (m), 1517 (m), 1470 (m), 1329 (s), 1094 (w). MS (ES$^+$) $[M+H]^+$ calcd for $C_{18}H_{17}N_2O_2^+$ 293.13, found: 293.27.



Synthesis of (*E*)-3-methyl-2-(4-phenylbut-3-en-2-yl)-1H-indole (Table 1-2, entry 5).

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 3-methylindole (14.4 mg, 0.110 mmol) and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 60 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.22** (8.6 mg, 0.033 mmol, 33% yield) as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.54 (d, 1H, *J* = 6.0 Hz), 7.40 – 7.33 (m, 2H), 7.34 – 7.27 (m, 3H), 7.25 – 7.19 (m, 1H), 7.12 (m, *J* = 7.1, 1.4 Hz, 2H), 6.44 (m, 2H), 4.02 (m, 1H), 2.31 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 137.2, 136.9, 135.2, 132.4, 129.5, 129.5, 128.7, 127.5, 126.3, 121.3, 119.2, 118.3, 110.5,

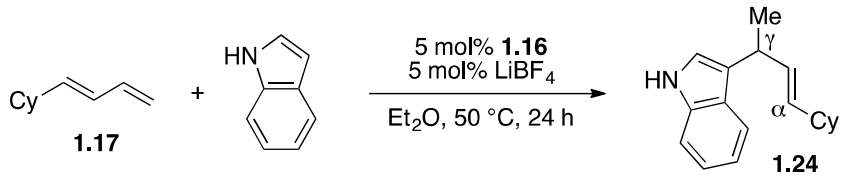
106.8, 33.8, 19.5, 8.6. IR (ν/cm^{-1}): 2920 (s), 2851 (s), 1461 (s). MS (ES$^+$) [M+H]$^+$ calcd for $C_{19}H_{20}N^+$ 262.16, found: 262.09.



1.14 1.23

Synthesis of (E)-2-(4-phenylbut-3-en-2-yl)-1-(triisopropylsilyl)-1H-pyrrole (Table 1-2, entry 6).

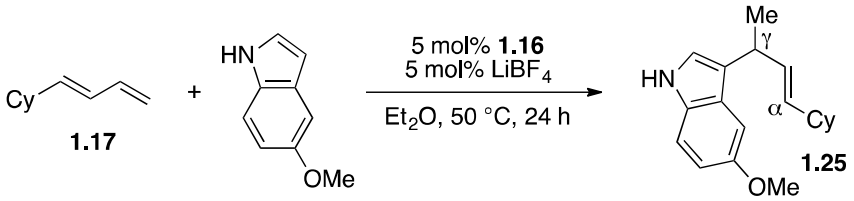
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, TIPS pyrrole (44.7 mg, 0.200 mmol) and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 70 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (100% Pentane) to afford **1.23** as a colorless oil which could not be separated from starting material for a yield. NMR yield is based on addition of 5.0 μL of DMF as an internal standard. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 8.2 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 6.55 (s, 1H), 6.36 (m, 2H), 6.20 (t, *J* = 1.9 Hz, 1H), 3.58 (m, 1H), 1.42 (m, 6H), 1.09 (d, *J* = 7.6 Hz, 18H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 138.2, 137.0, 130.0, 128.5, 127.5, 126.8, 126.2, 124.2, 120.5, 109.8, 35.6, 21.4, 18.0, 11.8. IR (ν/cm^{-1}): 2946 (s), 2867 (s), 1464 (m), 1263 (w), 1099 (s) MS (ES$^+$). [M+H]$^+$ calcd for $C_{23}H_{36}NSi^+$ 354.26, found: 354.27.



1.17 1.24

Synthesis of (*E*)-3-(4-cyclohexylbut-3-en-2-yl)-1H-indole (Table 1-2, entry 7).

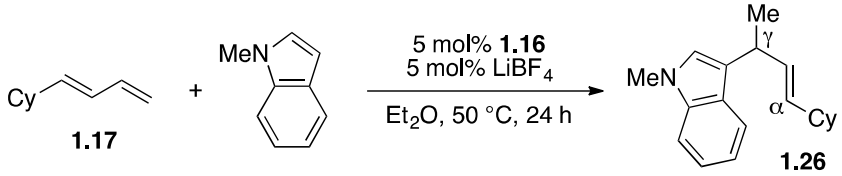
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, indole (12.9 mg, 0.110 mmol) and (*E/Z*)-1-cyclohexylbuta-1,3-diene (13.6 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (15:1 Pentane/EtOAc) to afford **1.24** (21.0 mg, 0.083 mmol, 85% yield) as a white solid. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.89 (s, 1H), 7.64 (m, 1H), 7.35 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.18 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.93 (m, 1H), 5.57 (m, 1H), 5.49 (m, 1H), 3.70 (m, 1H), 1.94 (tdt, *J* = 10.9, 6.8, 3.5 Hz, 1H), 1.71 (qd, *J* = 8.4, 6.9, 4.1 Hz, 4H), 1.63 (dtt, *J* = 12.4, 3.3, 1.6 Hz, 2H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.20 (m, 2H), 1.04 (m, 3H). ^{13}C NMR (150 MHz, Chloroform-d): δ 136.7, 135.0, 132.4, 127.0, 121.9, 121.5, 120.2, 119.9, 119.1, 111.1, 40.7, 34.1, 33.4, 33.3, 26.3, 26.2, 21.1. IR (ν/cm^{-1}): 2922 (s), 2849 (m), 1455 (m), 1417 (w), 1337 (w), 1222 (w), 1092 (w), 1008 (w). MS (ES$^+$) $[M+H]^+$ calcd for $C_{18}H_{24}N^+$ 254.39, found: 254.27.



Synthesis of (E)-3-(4-cyclohexylbut-3-en-2-yl)-5-methoxy-1H-indole (Table 1-2, entry 8).

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 5-methoxyindole (16.2 mg, 0.110 mmol) and (*E/Z*)-1-cyclohexylbuta-1,3-diene (13.6 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (7:3 Pentane/Ether) to afford **1.25** (25.8 mg, 0.091 mmol, 91%

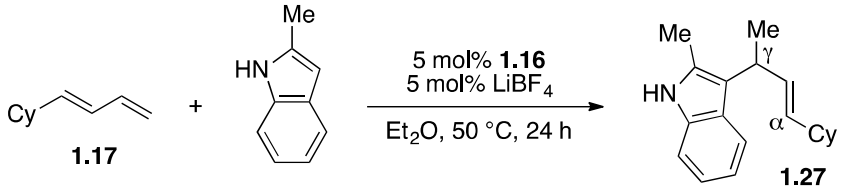
yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.80 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.94 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.49 (m, 2H), 3.85 (s, 3H), 3.64 (m, 1H), 1.94 (dtt, *J* = 11.0, 6.6, 3.3 Hz, 1H), 1.67 (m, 3H), 1.63 (dtt, *J* = 12.2, 3.1, 1.5 Hz, 2H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.25 (dddt, *J* = 15.9, 12.5, 6.2, 3.2 Hz, 2H), 1.03 (m, 3H). ^{13}C NMR (150 MHz, Chloroform-d): δ 153.5, 134.9, 132.2, 131.7, 127.2, 120.9, 120.9, 112.0, 111.6, 101.6, 55.8, 40.6, 34.0, 33.3, 33.2, 26.2, 26.1, 26.0, 20.7. IR (ν/cm^{-1}): 2923 (s), 2849 (m), 1623 (w), 1581 (w), 1483 (s), 1451 (s), 1281 (w), 1212 (s), 1173 (m), 1031 (w). MS (ES^{+}) [M+H]$^{+}$ calcd for $C_{19}H_{26}NO^{+}$ 284.20, found: 284.27.



Synthesis of (*E*)-3-(4-cyclohexylbut-3-en-2-yl)-1-methyl-1H-indole (Table 1-2, entry 9).

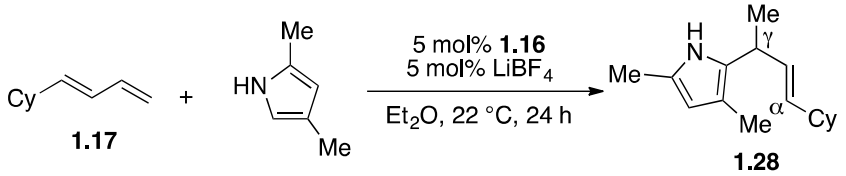
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and (*E/Z*)-1-cyclohexylbuta-1,3-diene (13.6 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (40:1 Pentane/EtOAc) to afford **1.26** (17.6 mg, 0.066 mmol, 66% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-d): 7.66 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.29 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.22 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.09 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.81 (d, *J* = 0.8 Hz, 1H), 5.61 (ddd, *J* = 15.4, 6.9, 1.0 Hz, 1H), 5.53 (ddd, *J* = 15.4, 6.6, 1.0 Hz, 1H), 3.75 (s, 3H), 3.70 (m, 1H), 1.95 (dtt, *J* = 11.0, 6.8, 3.5 Hz, 1H), 1.69 (m, 4H), 1.59 (m, 1H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.21 (m, 2H), 1.07 (m, 3H). ^{13}C NMR (150 MHz, Chloroform-d): δ 137.3, 134.8, 132.5, 127.3, 125.1, 121.4, 119.9, 119.8, 118.5, 109.2, 40.7, 34.1, 33.4, 33.3, 32.7,

26.3, 26.2, 21.3. IR (ν/cm^{-1}): 2923 (s), 2850 (m), 2359 (s), 1448 (m), 1373 (w), 1327 (w), 1236 (w). MS (ES$^+$) [M+H]$^+$ calcd for $C_{19}H2_6N^+$ 268.21, found: 268.36.



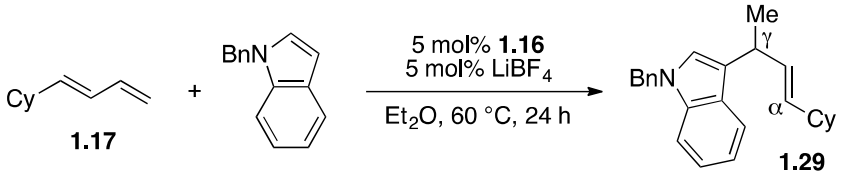
Synthesis of (*E*)-3-(4-cyclohexylbut-3-en-2-yl)-2-methyl-1H-indole (Table 1-2, entry 10).

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 2-methylindole (14.4 mg, 0.110 mmol) and (*E/Z*)-1-cyclohexylbuta-1,3-diene (13.6 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 µL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (20:1 Pentane/EtOAc, 3% Et_3N) to afford **1.27** (17.5 mg, 0.066 mmol, 66% yield) as a yellow oil. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.64 (s, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.07 (dtd, *J* = 22.0, 7.1, 1.2 Hz, 3H), 5.77 (ddd, *J* = 15.5, 5.4, 1.2 Hz, 1H), 5.47 (ddd, *J* = 15.6, 6.8, 1.8 Hz, 1H), 3.65 (m, 1H), 2.37 (d, *J* = 2.6 Hz, 3H), 1.68 (m, 3H), 1.60 (m, 2H), 1.45 (d, *J* = 7.3 Hz, 3H), 1.02 (m, 5H). ^{13}C NMR (150 MHz, Chloroform-d): δ 135.4, 134.4, 131.9, 130.0, 127.8, 120.7, 119.5, 118.8, 115.7, 110.2, 40.8, 33.4, 33.3, 33.2, 26.4, 26.3, 20.5, 12.3. IR (ν/cm^{-1}): 2922 (mb), 1682 (w), 1619 (w), 1458 (w), 1141 (s). MS (ES$^+$) [M+H]$^+$ calcd for $C_{19}H_{26}N^+$ 268.21, found: 268.27.



Synthesis of (E)-2-(4-cyclohexylbut-3-en-2-yl)-3,5-dimethyl-1H-pyrrole (Table 1-2, entry 11).

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 2,4-dimethylpyrrole (10.5 mg, 0.110 mmol) and (*E/Z*)-1-cyclohexylbuta-1,3-diene (13.6 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 µL, [ ] = 0.67 M), and the reaction allowed to stir at 22 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.28** (12.2 mg, 0.053 mmol, 53% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-d): δ 5.66 (d, *J* = 2.8 Hz, 1H), 5.51 (ddd, *J* = 15.5, 5.9, 1.1 Hz, 1H), 5.43 (ddd, *J* = 15.6, 6.6, 1.4 Hz, 1H), 3.53 – 3.47 (m, 1H), 2.21 (s, *J* = 0.9 Hz, 3H), 1.99 (s, 3H), 1.75 – 1.68 (m, 6H), 1.65 (dtd, *J* = 11.9, 3.3, 1.7 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.22 – 1.03 (m, 5H). ^{13}C NMR (150 MHz, Chloroform-d): δ 135.4, 130.5, 108.2, 40.7, 33.4, 33.4, 33.3, 26.3, 26.2, 26.2, 20.0, 13.0, 11.0. IR (ν/cm^{-1}): 3282 (br, s), 2925 (s), 2852 (m), 1697 (s), 1652 (w), 1448 (m), 1374 (m), 1266 (br, m), 971 (m). MS (ES$^+$) $[M+H]^+$ calcd for $C_{16}H_{25}N^+$ 232.21, found: 232.36.

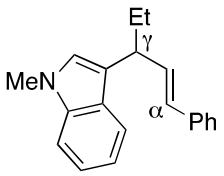


Synthesis of (*E*)-1-benzyl-3-(4-cyclohexylbut-3-en-2-yl)-1H-indole (Table 1-2, entry 12).

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-benzylindole (22.8 mg, 0.110 mmol) and (*E/Z*)-1-cyclohexylbuta-1,3-diene (13.6 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 µL, [ ] = 0.67 M), and the reaction allowed to stir at 60 °C for 48 h. The resulting oil was purified by SiO_2 column chromatography (40:1 Pentane/EtOAc) to afford **1.29** (29.2 mg, 0.085 mmol,

85% yield) as a pale orange oil. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.33 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.17 (m, 1H), 7.12 (m, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.88 (s, 1H), 5.60 (dd, *J* = 15.5, 6.8 Hz, 1H), 5.52 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.28 (s, 2H), 3.70 (m, 1H), 1.94 (dtt, *J* = 11.6, 7.2, 3.8 Hz, 1H), 1.75 (m, 5H), 1.65 (m, 1H), 1.43 (dd, *J* = 7.0, 1.2 Hz, 3H), 1.30 (m, 3H), 1.19 (m, 3H). ^{13}C NMR (150 MHz, Chloroform-d): δ 138.0, 137.0, 134.9, 132.5, 128.8, 127.7, 127.5, 126.8, 124.5, 121.6, 120.6, 120.1, 118.7, 109.7, 50.0, 40.7, 34.1, 33.4, 33.3, 26.3, 26.2, 21.2. IR (ν/cm^{-1}): 2922 (s), 2849 (m), 1613 (w), 1466 (w), 1451 (s), 1354 (m), 1177 (m). MS (ES^{+}) $[M+H]^{+}$ calcd for $C_{25}H_{30}N^{+}$ 344.24, found: 344.27.

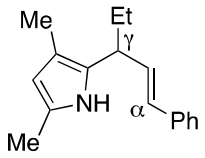
Synthesis of (E)-1-methyl-3-(1-phenylpent-1-en-3-yl)-1H-indole (Scheme 1-2).



1.30

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and (1E,3E)-penta-1,3-dien-1-ylbenzene (14.4 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.30** (25.3 mg, 0.091 mmol, 91% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.67 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.33 – 7.25 (m, 7H), 7.22 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.11 – 7.04 (m, 1H), 6.89 (s, 1H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.40 (dd, *J* = 15.8, 7.8 Hz, 1H), 3.77 (s, 3H), 3.63 (m, 1H), 1.99 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.88 (dt, *J* = 13.3, 7.5 Hz, 1H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 137.3, 134.4, 129.2, 128.5, 127.4, 126.9, 126.2, 125.7, 121.6, 119.8, 118.7, 117.7, 109.3, 42.3, 32.8, 28.4, 12.6. IR (ν/cm^{-1}): 2958 (m), 2871 (m), 1471 (m), 1374 (m), 1326 (s), 1333 (m). MS (ES^{+}) $[M+H]^{+}$ calcd for $C_{20}H_{22}N^{+}$ 276.17, found: 276.09.

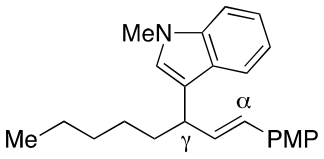
Synthesis of (E)-3,5-dimethyl-2-(1-phenylpent-1-en-3-yl)-1H-pyrrole (Scheme 1-2).



1.31

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 2,4-dimethylpyrrole (10.5 mg, 0.110 mmol) and (1E,3E)-penta-1,3-dien-1-ylbenzene (14.4 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.31** (19.9 mg, 0.11 mmol, 89% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.39 – 7.36 (m, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.23 – 7.19 (m, 1H), 6.43 – 6.38 (m, 1H), 6.31 (dd, *J* = 15.9, 6.7 Hz, 1H), 5.69 (d, *J* = 2.8 Hz, 1H), 3.45 (q, *J* = 7.8, 7.3 Hz, 1H), 2.22 (s, 3H), 2.04 (s, 3H), 1.86 – 1.80 (m, 1H), 1.75 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 137.6, 132.5, 129.3, 128.6, 127.3, 127.2, 126.2, 125.4, 114.7, 108.1, 41.5, 27.6, 13.1, 12.4, 11.2. IR (ν/cm^{-1}): 2921 (s), 2854 (m), 1682 (m), 1652 (m), 1558 (m), 1540 (m), 1488 (m), 1455 (s), 966 (m). MS (ES$^+$) $[M+H]^+$ calcd for $C_{17}H_{22}N^+$ 276.17, found: 276.09.

Synthesis of (E)-3-(1-(4-methoxyphenyl)pent-1-en-3-yl)-1-methyl-1H-indole (Scheme 1-2).

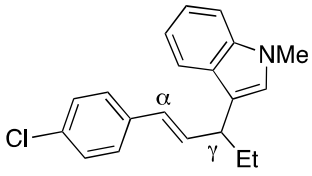


1.32

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and 1-methoxy-4-((1E,3E)-penta-1,3-dien-1-yl)benzene (17.4 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (15:1 Pentane/EtOAc) to afford **1.32** (25.0 mg, 0.072 mmol, 72% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.68 (dt, *J* = 8.0, 0.9 Hz, 1H),

7.30 (d, *J* = 3.2 Hz, 1H), 7.29 (d, *J* = 3.8 Hz, 1H), 7.22 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.88 (s, 1H), 6.84-6.81 (m, 2H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.26 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.70 (m, 1H), 2.06 (s, 1H), 1.95 (dddd, *J* = 13.1, 10.1, 6.5, 5.4 Hz, 1H), 1.84 (dddd, *J* = 13.3, 9.9, 8.0, 5.2 Hz, 1H), 1.36 (m, 1H), 1.32 (ddt, *J* = 8.7, 3.7, 1.8 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.7, 137.3, 132.6, 130.8, 129.3, 128.3, 127.3, 125.6, 121.5, 119.8, 118.7, 118.2, 113.9, 109.3, 40.5, 35.6, 32.8, 32.1, 27.6, 22.8, 14.3. IR (ν/cm^{-1}): 3059 (m), 3029 (m), 2918 (m), 2862 (m), 1612 (w), 1463 (m), 1356 (m), 1317 (m), 1255 (m), 1181 (m), 1139 (w), 1077 (w), 1011 (w). MS (ES$^+$) $[M+H]^+$ calcd for $C_{24}H_{30}NO^+$ 348.23, found: 348.36.

Synthesis of (E)-3-(1-(4-chlorophenyl)pent-1-en-3-yl)-1-methyl-1H-indole (Scheme 1-2).

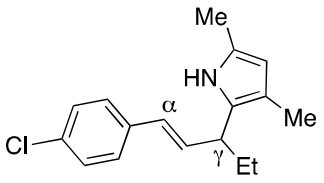


1.33

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and 1-chloro-4-((1E,3E)-penta-1,3-dien-1-yl)benzene (17.9 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 60 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (15:1 Pentane/Et_2O) to afford **1.33** (22.6 mg, 0.073 mmol, 73% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.68 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.30 (d, *J* = 3.2 Hz, 1H), 7.29 (d, *J* = 3.8 Hz, 1H), 7.22 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.88 (s, 1H), 6.81 (m, 2H), 6.44 (d, *J* = 15.7 Hz, 1H), 6.26 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.70 (m, 1H), 2.06 (s, 1H), 1.95 (dddd, *J* = 13.1, 10.1, 6.5, 5.4 Hz, 1H), 1.84 (dddd, *J* = 13.3, 9.9, 8.0, 5.2 Hz, 1H), 1.36 (m, 1H), 1.32 (ddt, *J* = 8.7, 3.7, 1.8 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 158.7, 137.3, 132.6, 130.8, 129.3, 128.3, 127.3, 125.6, 121.5, 119.8,

118.7, 118.2, 113.9, 109.3, 40.5, 35.6, 32.8, 32.1, 27.6, 22.8, 14.3. IR (ν/cm^{-1}): 3048 (w), 3029 (w), 2959 (m), 2928 (m), 2871 (m), 1698 (m), 1653 (m), 1541 (m), 1507 (m), 1457 (m) 1418 (w), 1374 (w), 1338 (w), 1234 (w), 1091 (m), 1011 (m), 966 (m). MS (ES$^+$) [M+H]$^+$ calcd for $C_{20}H_{21}ClN^+$ 310.14, found: 310.27.

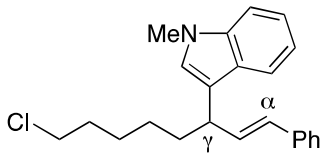
Synthesis of (E)-2-(1-(4-chlorophenyl)pent-1-en-3-yl)-3,5-dimethyl-1H-pyrrole (Scheme 1-2).



1.34

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 2,4-dimethylpyrrole (10.5 mg, 0.110 mmol) and 1-chloro-4-((1E,3E)-penta-1,3-dien-1-yl)benzene (17.9 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 18 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/Et_2O) to afford **1.34** (25.8 mg, 0.095 mmol, 95% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.28 – 7.23 (m, 4H), 6.37 – 6.23 (m, 2H), 5.67 (d, *J* = 2.7 Hz, 1H), 3.45 – 3.37 (m, 1H), 2.21 (d, *J* = 0.9 Hz, 3H), 2.02 (s, 3H), 1.86 – 1.76 (m, 1H), 1.72 (dt, *J* = 13.4, 7.6 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 136.1, 133.3, 132.7, 128.7, 128.1, 127.4, 127.0, 125.5, 114.96, 108.1, 41.6, 27.5, 13.1, 12.4, 11.2. IR (ν/cm^{-1}): 3452 (w), 2962 (s), 2928 (s), 3871 (m), 1691 (m), 1597 (w), 1490 (s), 1451 (m), 1402 (m), 1100 (s), 1013 (s), 968 (s) MS (ES$^+$) [M+H]$^+$ calcd for $C_{21}H_{30}NO^+$ 274.14, found: 274.36.

Synthesis of (E)-3-(8-chloro-1-phenyloct-1-en-3-yl)-1-methyl-1H-indole (Scheme 1-2).

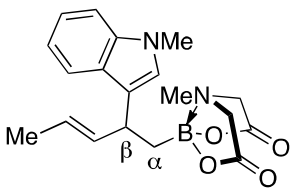


1.35

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and ((1E,3E)-8-chloroocta-1,3-dien-1-yl)benzene (22.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl

ether (150 µL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.35** (27.7 mg, 0.079 mmol, 79% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 11.9, 7.9 Hz, 3H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.89 (s, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.39 (dd, *J* = 15.7, 7.9 Hz, 1H), 3.77 (s, 3H), 3.72 (m, 1H), 3.52 (t, *J* = 6.7 Hz, 2H), 1.97 (m, 1H), 1.91 – 1.83 (m, 1H), 1.77 (p, *J* = 6.9 Hz, 2H), 1.53 – 1.35 (m, 4H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 137.8, 137.3, 134.4, 129.1, 128.5, 127.3, 127.0, 126.2, 125.6, 121.6, 119.7, 118.8, 117.6, 109.3, 45.3, 40.5, 35.3, 32.8, 32.7, 27.2, 27.0. IR (ν/cm^{-1}): 3024 (w), 2932 (s), 2856 (m), 1598 (w), 1447 (s), 1327 (w). MS (ES$^+$) $[M+H]^+$ calcd for $C_{23}H_{27}ClN^+$ 352.18, found: 352.09.

Synthesis of (E)-6-methyl-2-(2-(1-methyl-1H-indol-3-yl)pent-3-en-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (Scheme 1-2).

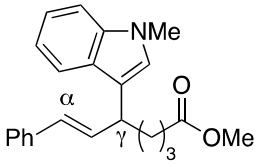


1.36

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and 6-methyl-2-((1E,3E)-penta-1,3-dien-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione (22.3 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 µL, [ ] = 0.67 M), and the reaction allowed to stir at 60 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (20:1 DCM:MeOH) to afford **1.36** as a colorless oil which could not be separated from starting material for a yield. NMR yield is based on addition of 5.0 µL of DMF as an internal standard. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.55 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.28 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.86 – 6.81 (m, 1H), 5.72

– 5.63 (m, 1H), 5.54 – 5.44 (m, 1H), 3.74 (s, 3H), 3.73 – 3.69 (m, 1H), 3.52 – 3.39 (m, 2H), 3.23 (dd, *J* = 45.8, 16.3 Hz, 2H), 2.65 (s, 3H), 1.66 (dd, *J* = 15.2, 7.2 Hz, 1H), 1.60 (dd, *J* = 15.2, 8.0 Hz, 1H), 1.43 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 166.8, 166.8, 137.6, 137.3, 126.8, 125.1, 124.4, 121.8, 119.7, 119.3, 118.7, 109.6, 62.3, 62.2, 45.1, 34.0, 32.8, 20.7. IR (ν/cm^{-1}): 3054 (w), 3011 (m), 2959 (m), 2926 (m), 2871 (w), 1770 (s), 1541 (m), 1457 (m), 1337 (m), 1300 (m), 1240 (w), 1074 (w), 1024 (m), 993 (m), 896 (m). MS (ES$^+$) [M+H]$^+$ calcd for $C_{19}H_{24}BN_2O_4^+$ 355.19, found: 355.36.

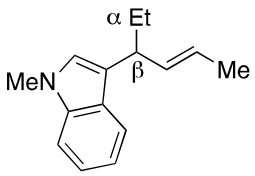
Synthesis of (E)-methyl 5-(1-methyl-1H-indol-3-yl)-7-phenylhept-6-enoate (Scheme 1-2).



1.37

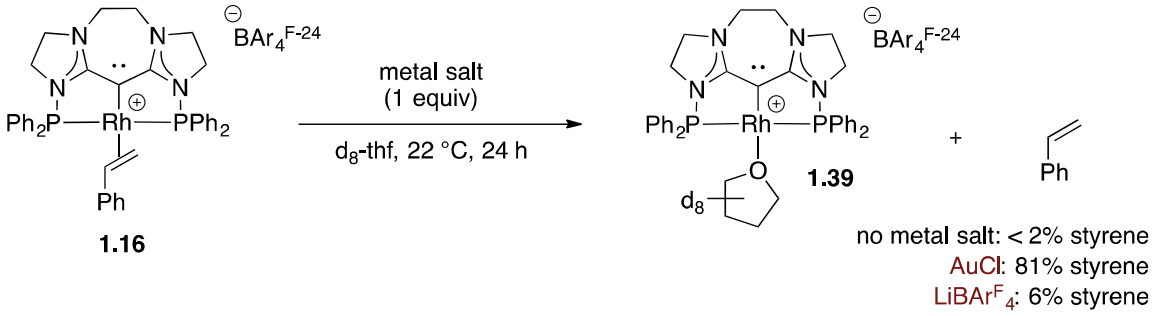
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and (4E,6E)-methyl 7-phenylhepta-4,6-dienoate (21.6 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 µL, [ ] = 0.67 M), and the reaction allowed to stir at 50 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (25:1 Pentane/EtOAc) to afford **1.37** (22.5 mg, 0.091 mmol, 91% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.65 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.36 – 7.32 (m, 2H), 7.31 – 7.24 (m, 4H), 7.21 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.19 – 7.16 (m, 1H), 7.08 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.90 (s, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 6.38 (dd, *J* = 15.8, 7.8 Hz, 1H), 3.75 (m, 5H), 3.65 (d, *J* = 1.9 Hz, 3H), 2.36 (t, *J* = 7.5 Hz, 2H), 1.99 (m, 1H), 1.89 (m, 1H), 1.82 – 1.68 (m, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 174.2, 134.0, 129.3, 128.5, 128.4, 127.2, 127.0, 126.3, 125.7, 121.6, 119.7, 118.8, 117.2, 109.3, 51.6, 40.3, 34.8, 34.2, 32.8, 23.3. IR (ν/cm^{-1}): 3024 (wb), 2919 (s), 2849 (m), 1736 (s), 1543 (w), 1450 (m), 1372 (w), 1328 (w), 1154 (m), 1012 (w). MS (ES$^+$) [M+H]$^+$ calcd for $C_{23}H_{26}NO_2^+$ 348.20, found: 348.09.

Synthesis of (E)-3-(hex-4-en-3-yl)-1-methyl-1H-indole (Scheme 1-2).



1.38

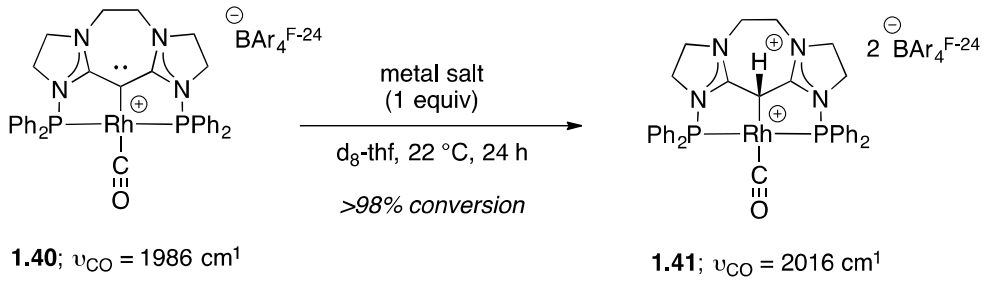
Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, 1-methylindole (14.4 mg, 0.110 mmol) and (2E,4E)-hexa-2,4-diene (8.2 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 µL, [ ] = 0.67 M), and the reaction allowed to stir at 22 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (40:1 Pentane/EtOAc) to afford **1.38** (13.7 mg, 0.064 mmol, 64% yield) as a colorless oil. ^{1}H NMR (600 MHz, Chloroform-d): δ 7.65 – 7.63 (m, 1H), 7.28 (ddt, *J* = 8.1, 2.2, 0.9 Hz, 1H), 7.21 (tdd, *J* = 8.2, 3.2, 1.2 Hz, 1H), 7.08 (dddd, *J* = 8.0, 6.9, 3.0, 1.0 Hz, 1H), 6.81 (d, *J* = 0.8 Hz, 1H), 5.65 – 5.60 (m, 2H), 3.75 (s, 3H), 3.73 – 3.68 (m, 1H), 2.07 – 2.01 (m, 2H), 1.43 (d, *J* = 7.0 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (150 MHz, Chloroform-d): δ 134.1, 130.4, 125.1, 121.5, 119.9, 119.9, 118.5, 109.2, 34.0, 32.7, 25.6, 21.29, 14.1. IR (ν/cm^{-1}): 2960 (b), 1540 (w), 1507 (w), 1473 (m), 1374 (w), 1326 (w). MS (ES$^+$) $[M+H]^+$ calcd for $C_{15}H_{20}N^+$ 214.16, found: 214.18.



Procedure for styrene substitution in 1.16 (Scheme 1-3a)

In a dry box, an 8 mL vial was charged with **1.16** (10.0 mg, 6.18 µmol) and appropriate metal salt (6.18 µmol). THF-d_8 (0.5 mL, [ ] = 0.012) was added and the reaction was allowed to stir for the

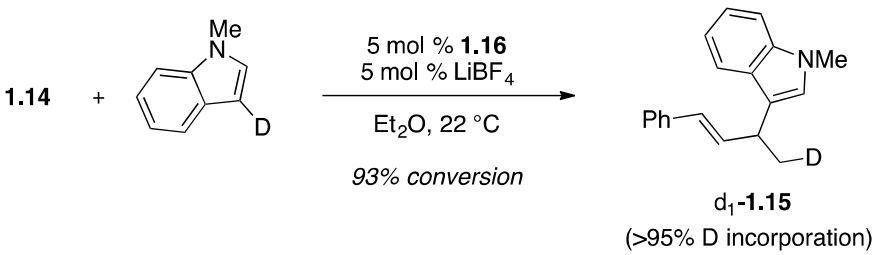
specified time. Analysis of loss of styrene conducted on a 600 MHz NMR spectrometer. See Scheme 1-3 for conditions.



1.40; υ_{CO} = 1986 cm^{1} **1.41**; υ_{CO} = 2016 cm^{1}

Procedure for protonation of 1.40 (Scheme 1-3b)

In a dry box, an 8 mL vial was charged with **1.40**[9] (10.0 mg, 0.013 mmol) and CH_2Cl_2 (0.5 mL, [ ] = 0.012). The vial was fitted with a Teflon lined septum cap and brought outside the glovebox. Tetrafluoroboric acid (50% solution in diethyl ether, 4.0 μL, 0.014 mmol) was added via syringe and immediately the solution turned from dark to light yellow. A solution phase IR was taken after 20 minutes using air free techniques. ^{1}H NMR (600 MHz, Methylene Chloride-d_2) δ 7.88 (q, J = 6.9 Hz, 4H), 7.76 – 7.58 (m, 16H), 4.51 (q, J = 11.0 Hz, 2H), 4.39 (s, 1H), 4.23 (td, J = 11.4, 5.6 Hz, 2H), 3.96 (s, 4H), 3.79 (q, J = 10.7 Hz, 2H), 3.50 (td, J = 10.9, 5.6 Hz, 2H). ^{13}C NMR (151 MHz, Methylene Chloride-d_2) δ 177.3 (t, J = 18.8 Hz), 134.4 (t, J = 8.2 Hz), 133.7, 133.0, 132.4 (t, J = 8.3 Hz), 130.0 (dt, J = 14.5, 5.5 Hz), 128.3 (dt, J = 116.5, 26.6 Hz), 59.0, 46.0, 42.5, 29.0 (m). IR (ν/cm^{-1}): 2016 (s), 2000 (m), 1614 (s), 1481 (m), 1437 (m), 1285 (w), 1012 (s).

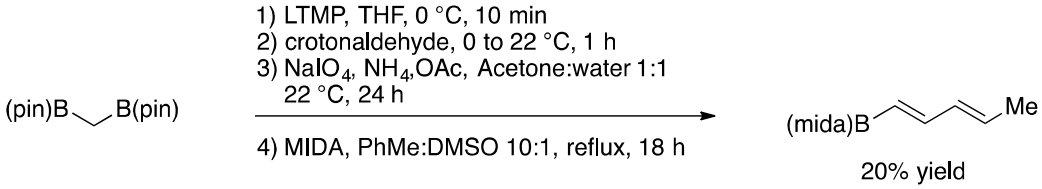


Procedure for deuterium incorporation experiments (Scheme 1-3c)

Synthesis of (*E*)-3-(4-phenylbut-3-en-2-yl)-d$_1$-N-methyl-indole

Following the general procedure for (CDC)-Rh-catalyzed hydroarylation, d$_1$-N-methyl indole (13.2 mg, 0.100 mmol, 98% C3-D), and phenyl 1,3-butadiene (13.0 mg, 0.100 mmol) were added to a solution of **1.16** (8.1 mg, 0.0050 mmol) and $LiBF_4$ (0.5 mg, 0.0050 mmol) in diethyl ether (150 μL, [ ] = 0.67 M), and the reaction allowed to stir at 22 °C for 24 h. The resulting oil was purified by SiO_2 column chromatography (20:1 Pentane/EtOAc) to afford d$_1$-**1.15** as a colorless oil (93% NMR yield, >95% D-incorporation).

Preparation of new dienes



Procedure for the synthesis of 6-methyl-2-((1E,3E)-penta-1,3-dien-1-yl)-1,3,6,2-dioxazaborocane-4,8-dione.[35-38]

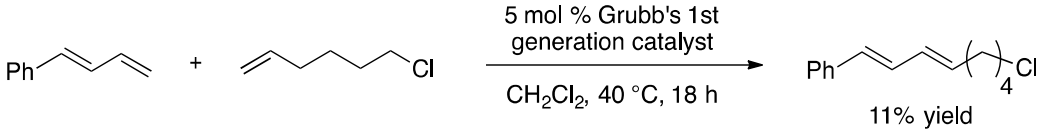
At 0 °C under anhydrous, oxygen-free conditions, a THF solution of LTMP (165 mg, 1.12 mmol, [ ] = 0.31) was added via cannula to an 8 mL vial containing a THF solution of $Me(Bpin)_2$ (300 mg, 1.12 mmol, [ ] = 0.52). The reaction was allowed to stir at 0 °C for 10 min. *Trans*-crotonaldehyde (60.2 mg, 0.0.86 mmol) was added via syringe and the reaction was allowed to warm to room temperature while stirring. After 1 h, the reaction was slowly quenched by the

addition of 2 mL of ether and 2 mL of water. The reaction mixture was diluted with 10 mL more of ether and extracted 3 times (10 mL ether). The combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, filtered through a plug of cotton, and concentrated. The diene was purified by column chromatography (20:1 hexanes:EtOAc) to yield a clear oil (123 mg, 74% yield). In a 25 mL round bottom flask, to this oil was added $NaIO_4$ (488.2 mg, 2.28 mmol) and NH_4OAc (175.7 mg, 2.28 mmol). Acetone and water (0.5 mL each, [ ] = 0.63 total) were added to the flask which was capped with a septum and allowed to stir for 24 h at 22 °C. This solution was filtered using acetone (5 mL) through a plug of Celite. The acetone was removed *in vacuo* and the remaining solution was diluted with water (2 mL) and ether (10 mL). The organic layer was separated and the water layer was extracted an additional 2 times (10 mL ether). The combined organic layers were washed with brine, dried over sodium sulfate, filtered through cotton, concentrated and used immediately. The boronic acid and methyl amino diacetic acid (98 mg, 067 mmol) were added to a 50 mL round bottom flask equipped with a stir bar. The flask was fitted with a Dean Stark trap and purged with N_2. Anhydrous DMSO (3.2 mL) and toluene (32 mL) were added to the flask and the flask was purged. The reaction was allowed to heat to reflux with stirring for 18 h. After 18 h, the flask was cooled to room temperature and concentrated using a rotary evaporator with a water bath at 60 °C. The crude mixture was immediately purified by column chromatography (100% ether to 10:1 ether:MeCN) to yield a white solid (50.4 mg, 20% overall yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.63 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.13 (ddt, *J* = 14.1, 10.3, 2.0 Hz, 1H), 5.89 – 5.74 (m, 1H), 5.40 (d, *J* = 17.4 Hz, 1H), 3.86 – 3.64 (m, 4H), 2.83 (s, 3H), 1.77 (dd, *J* = 6.7, 1.8 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.1, 145.2, 133.5, 132.6, 61.4, 46.7, 30.4, 18.2. IR: 3501 (br, m), 3012 (m), 2960 (m), 2854 (w), 1768

(s), 1650 (m), 1604 (m), 1456 (m), 1338 (m), 1301 (s), 1249 (w), 1154 (m), 1126 (m), 1007 (s), 956 (m). MS (ES^+) $[M+H]^+$ calcd for $C_{10}H_{15}BNO_4^+$ 224.11, found: 224.18.

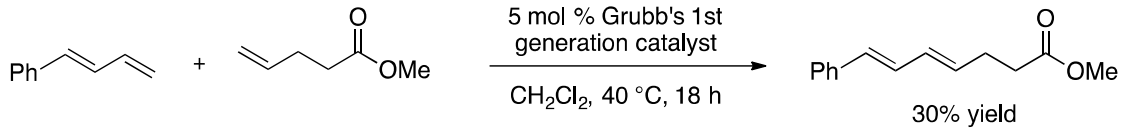
General procedure for substrates prepared through metathesis.[41]

Grubb's 1st generation catalyst (5 mol%) was weighed into an oven dried 8 mL vial or 50 mL flask equipped with a stir bar which was then capped using a Teflon lined lid. The vial was purged with N_2 for 10 min then charged with dichloromethane ([ ] = 0.20). Alkene followed by diene were added via syringe. The reaction was allowed to warm to 40 °C and stir for 18 h. The reaction was plugged through a plug of silica gel using hexanes then concentrated. The residue was purified by column chromatography using 100% hexanes to 25:1 hexanes:ether.



((1E,3E)-8-chloroocta-1,3-dien-1-yl)benzene

Following the general procedure, Grubb's 1st generation catalyst (168 mg, 0.205 mmol) was solvated with dichloromethane (20 mL, [ ] = 0.20). 6-Chloro-1-hexene (1.0 mL, 8.17 mmol) and phenylbutadiene (532 mg, 4.09 mmol) were added, the reaction was allowed to warm to 40 °C and stir for 18 h. The colorless liquid was obtained in an 11% yield (122 mg, 0.50 mmol). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.75 (dd, *J* = 15.7, 10.4 Hz, 1H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.26 – 6.18 (m, 1H), 5.81 (dt, *J* = 14.6, 7.0 Hz, 1H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.19 (qd, *J* = 7.2, 1.3 Hz, 2H), 1.82 (dt, *J* = 15.0, 6.8 Hz, 2H), 1.59 (m, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 137.6, 134.8, 131.2, 130.6, 129.2, 128.7, 127.3, 126.2, 45.0, 32.1, 32.1, 26.6. IR: 3059 (w), 3022 (s), 2936 (s), 2860 (m), 1643 (w), 1596 (m), 1494 (m), 1447 (s), 1304 (m), 1071 (w).



(4E,6E)-methyl 7-phenylhepta-4,6-dienoate

Following the general procedure, Grubb's 1st generation catalyst (62.5 mg, 0.076 mmol) was solvated with dichloromethane (6 mL, [ ] = 0.25). Methyl pent-4-enoate (348 mg, 3.05 mmol) and phenyl-1,3-butadiene (200 mg, 1.52 mmol) were added, the reaction was allowed to warm to 40 ^{o}C and stir for 18 h. The colorless liquid was obtained in an 30% yield (100 mg, 0.46 mmol). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 10.8 Hz, 2H), 7.31 (t, *J* = 11.4 Hz, 2H), 7.21 (t, *J* = 10.8 Hz, 1H), 6.74 (dd, *J* = 15.7, 10.4 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.25 (dd, *J* = 14.9, 10.4 Hz, 1H), 5.81 (ddd, *J* = 15.6, 7.8, 5.1 Hz, 1H), 3.69 (s, 3H), 2.46 (td, *J* = 3.8, 3.3, 1.9 Hz, 4H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 173.5, 137.5, 132.9, 131.7, 131.1, 129.0, 128.7, 127.4, 126.3, 51.7, 33.8, 28.2. IR (ν/cm^{-1}): 3023 (m), 2951 (m), 2360 (w), 1734 (s), 1540 (b), 1196 (m). MS (ES^{+}) $[M+H]^{+}$ calcd for $C_{14}H_{17}O_2^{+}$ 217.1223, found: 217.27.

Crystallographic data for complex 1.16

Figure S1. ORTEP drawing of **1.16**

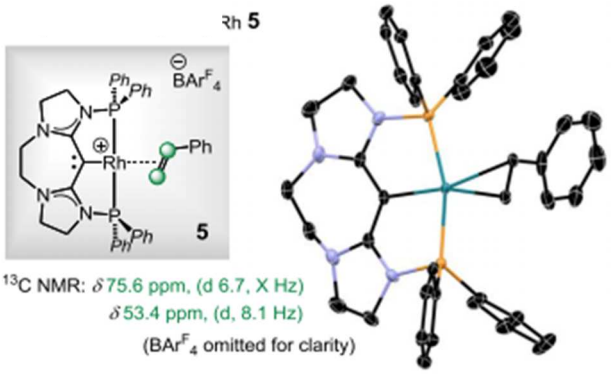


Table S2. Crystal structure data for **1.16**

Identification code	x1411004
Empirical formula	C75 H52 B F24 N4 P2 Rh
Formula weight	1640.87
Temperature	100K
Wavelength	0.71073
Crystal system	triclinic
Space group	P-1
Unit cell dimensions	a = 14.5732(5) Å α= 72.9946(16) b = 16.2543(6) Å β= 69.1536(17) c = 16.4636(6) Å γ = 78.1710(16)

Volume	3462.92
Z	2
Density (calculated)	1.548 g/cm-1
Absorption coefficient	0.406 (mm-1)
F(000)	1624.5
Crystal size	0.193 x 0.238 x 0.283
Theta max	70.15
	Hmax = 17, kmax = 19, lmax =
Index ranges	20
Reflections collected	13181
Independent reflections	12784
Completeness to theta	97
Max. and min. transmission	0.663, 0.753
Refinement method	XS least squares
Goodness-of-fit on F2 0	1.019
R indices	R1 = 0.0336, wR2 = 0.1139

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[27] Rh-catalyzed hydroarylation of **1.14** with of 5 mol % HBF_4-OEt_2 as an additive (Et_2O, 50 °C, 24 h) results in 82% conversion to **1.15**, (>98:2 γ:α). Hydroarylation of diene **1.14** with 5 mol % HBF_4-OEt2 in the absence (CDC)-Rh **1.16** (50 °C, Et_2O 24 h) results in < 2% conversion to **1.15** and decomposition of diene **1.14**.

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CHAPTER TWO

SYNTHESIS AND DESYMMETRIZATION OF FULLY SUBSTITUTED, *MESO*-FUSED SYSTEMS DERIVED FROM BENZENE OXIDE *

2.1 Introduction

The synthesis of highly substituted, enantioenriched molecules is an area of interest in organic synthesis. Natural products with biological activity often posses multiple contiguous stereocenters and a number of functionalities that are still challenging to access through common organic transformations. As part of a long-term goal of utilizing aromatic feedstocks for the creation of complex, chiral compounds, we sought to explore the reactivity of the 1,2-disubstituted cyclohexadiene, benzene oxide. Herein, we present the synthesis of new, chiral, fully substituted cyclohexanes using benzene oxide as the starting building block. The ozonolysis of benzene oxide Diels-Alder cycloadducts provides access to *meso* diols containing six contiguous stereocenters. The reductive ozonolysis workup gives access to two different diastereoisomers, through a double epimerization at the imide centers. Desymmetrization of these *meso* compounds yields fully substituted, enantioenriched cyclohexanes. This work constitutes one of the few cases where benzene oxide is utilized for the synthesis of complex molecules.

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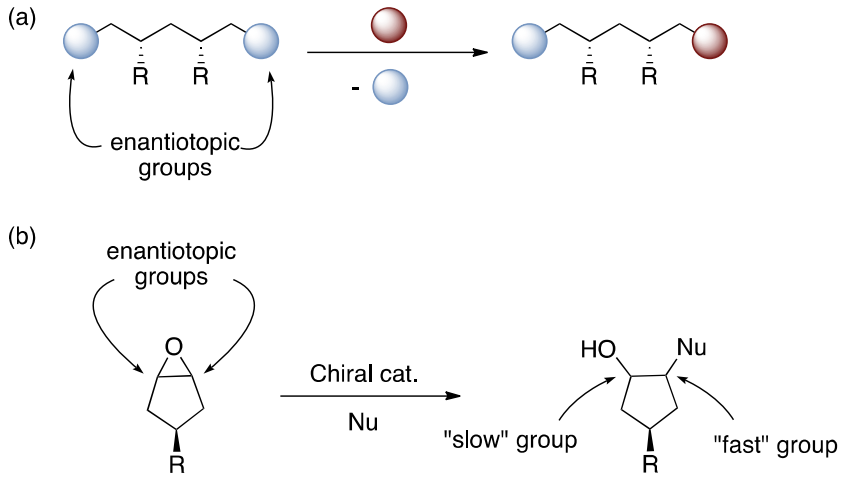
2.2 Background

2.2.1 Importance of Desymmetrization in Organic Synthesis

The desymmetrization of *meso*-compounds has proven to be a powerful approach for the synthesis of chiral scaffolds bearing multiple stereocenters.[1] This strategy rapidly builds complexity by differentiating enantiotopic groups through the use of a chiral catalyst. An enantiotopic group is a functionality within a molecule that when replaced with a different group renders the molecule chiral (Scheme 2-1a). In the case of *meso*-compounds, two enantiotopic groups are present, with one reacting faster or more efficiently when in the presence of a chiral catalyst (Scheme 2-1b).[2] A variety of transformations have been deployed in enantioselective desymmetrizations, including epoxide openings,[3] alcohol functionalizations,[4] and C□C bond formation[5] of prochiral or *meso*-compounds.

Scheme 2-1. Enantiotopic Groups and Desymmetrization

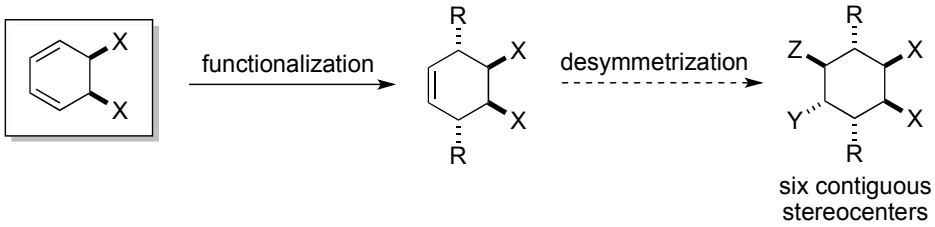


The synthesis of highly substituted, enantioenriched cyclohexanes is an ongoing challenge in organic synthesis.[6] Cyclohexadienes serve as versatile building blocks for the efficient synthesis of these molecules, and complex natural products and pharmaceuticals have benefited

from their manipulation.[7] Specifically, functionalization of 1,2-disubstituted cyclohexadienes has allowed access to complex molecules with multiple stereocenters (Scheme 2-2).[8]

1,2-Disubstituted cyclohexa-3,5-dienes are useful precursors for the synthesis of chiral, functionalized cyclohexanes.[9] Efforts to efficiently synthetize these type of molecules often include dearomatization chemistry, due to the fast complexity building and the use of feedstock aromatic materials. The resulting diene functionality can be easily functionalized through a number of transformations to access complex molecules. A number of natural products have been accessed by taking advantage of this fact.

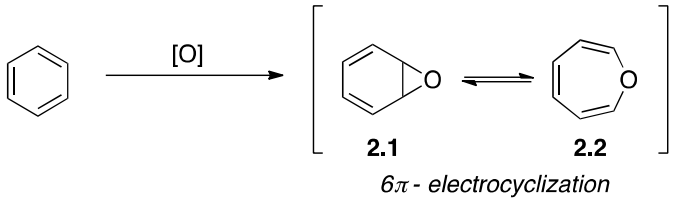
Scheme 2-2. Desymmetrization of 1,2-Disubstituted Cyclohexadiene Derived Molecules



2.2.2 Introduction to Benzene Oxide

One type of 1,2-disubstituted cyclohexa-3,5-diene, benzene oxide, offers the potential of both diene and epoxide functionalization, rendering it an attractive building block. The metabolic pathway for the oxidation of arenes begins with an epoxidation step, which in the case of benzene leads to benzene oxide.[10] Particular to benzene epoxidation is the fact that benzene oxide is in equilibrium with its valence tautomer, oxepin, by via a 6-π electrocyclization event (**2.1** to **2.2**, Scheme 2-3). This equilibrium is fast at room temperature and can be shifted either way with the change of solvents, temperature, and substituents around the ring.

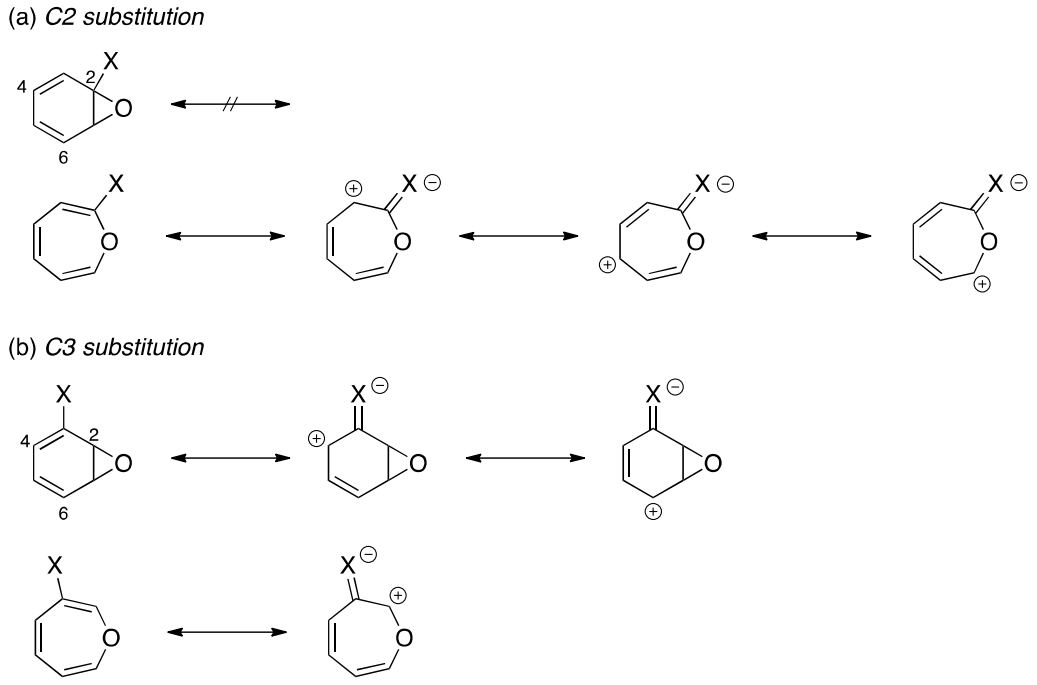
Scheme 2-3. Oxidation of Benzene to Benzene Oxide and 6π-Electrocyclization to Oxepin



Solvent and temperature effects have been studied for the benzene oxide-oxepin equilibrium.[11] Non-polar solvents favor the formation of oxepin, whereas polar solvents provide better stabilization for benzene oxide. This is because the oxide has a higher dipole moment than oxepin (1.5-2.0 D for benzene oxide versus 0.8-1.4 D for oxepin), and thus a higher percentage of the oxide is observed in polar solvents.[11a] Likewise, the temperature of the solution has an effect on the equilibrium. Although higher temperatures lead to decomposition of the oxide, NMR studies have shown that benzene oxide is favored at low temperatures.[11b]

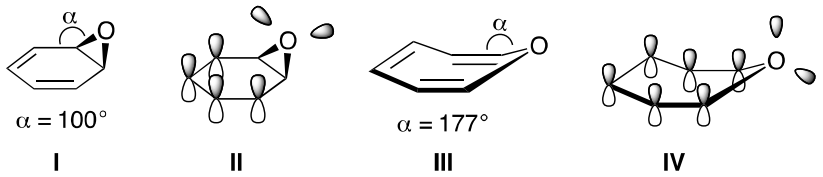
Perhaps the most notable effect on the equilibrium shift is the substitutions around the ring of benzene oxide.[12] These substitutions can completely shift the equilibrium to either the oxide or oxepin, depending on stability. For example, substitutions on C2 lead to formation of oxepin almost exclusively due to the better resonance stabilization which is not present with the oxide (Scheme 2-4a). On the other hand, substitution on C3 favors formation of the oxide, as better resonance stabilization is achieved than with oxepin. Electron-withdrawing groups have also been generally shown to favor the oxide over oxepin.[12b]

Scheme 2-4. Substitution Effect on Benzene Oxide – Oxepin Equilibrium



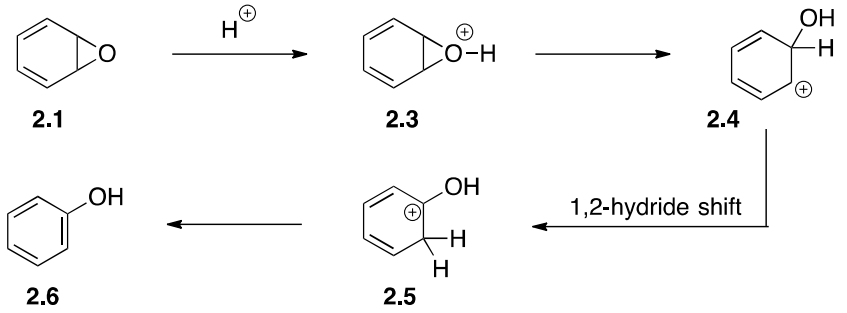
The conformational structures of both benzene oxide and oxepin have been predicted by multiple computational studies. The cyclohexane ring of benzene oxide has a largely planar conformation, whereas the epoxide is significantly angled, with α ~ 100° (Scheme 2-5).[11a] The magnitude of this angle is most likely due to orbital interactions between the oxygen of the epoxide and the π-orbitals of the diene. In cases where such an interaction is not possible (i.e. norcaradienes), this angle is smaller (62° for norcardienes).[12a] On the other hand, oxepin has a largely non-planar conformation. Oxepin has been predicted to sit in a boat-like conformation; a similar orbital interaction could be at play here.

Scheme 2-5. Conformation of Benzene Oxide and Oxepin



In terms of stability, benzene oxide has been shown to undergo rapid decomposition to phenol in the presence of acid or heat.[11b] The accepted mechanism for this transformation is outlined in Scheme 2-6. Protonation of the epoxide yields oxonium **2.3**, which has been calculated to be at an energy minimum.[13] Then, rate determining epoxide opening through C−O cleavage affords carbocation **2.4**. A 1,2-hydride shift (NIH shift) followed by rearomatization results in the formation of phenol. This decomposition pathway is perhaps the most limiting aspect of benzene oxide as a synthetic building block. Nevertheless, benzene oxide is stable in neutral and basic solutions at room temperature and we recognized its potential for functionalization and desymmetrization in order to obtain highly complex molecules.

Scheme 2-6. Pathway of Decomposition of Benzene Oxide to Phenol

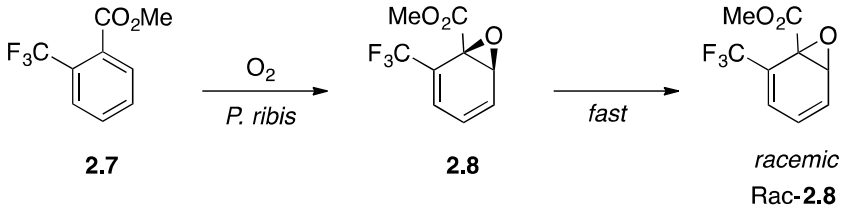


2.2.3 Synthesis and Reactivity of Benzene Oxide and Derivatives

The direct oxidative dearomatization of aromatic feedstock to arene oxide derivatives has primarily been accomplished *via* enzymatic pathways, with the isolation of phenol as the final product in most cases.[14] The isolation of a stable benzene oxide derivative was accomplished using *P. ribis* under oxygen.[15] Here, the stabilization of electron-withdrawing groups was necessary for the isolation of the oxide. The stereodefined oxide was observed, but rapid racemization occurred, presumably through the formation of the corresponding oxepin (Scheme

2-7). Non-enzymatic pathways have been limited by low yields and operational practicality.[16] To date, an efficient, dearomative, non-enzymatic synthesis of benzene oxide has not been reported.

Scheme 2-7. Synthesis and Isolation of Stable Benzene Oxide Derivative



2.7 **2.8** *racemic* Rac-**2.8**

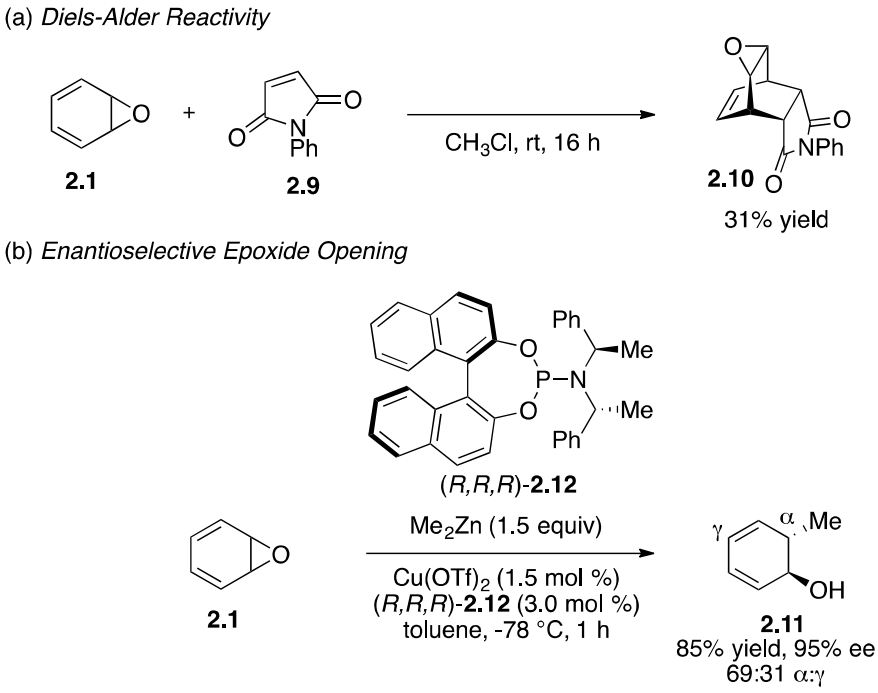
Benzene oxide can be accessed in a stepwise fashion, starting from commercially available 1,4-cyclohexadiene. This method, developed initially by Günther, has allowed access to benzene oxide for mechanistic and kinetic studies.[11b] We modified this procedure in order to obtain an operationally simple route that does not require heat or column chromatography (see Experimental Details).

Günther's synthesis of benzene oxide has allowed some exploration of benzene oxide's reactivity; however, the utility of these molecules as building blocks in organic synthesis has not been extensively researched. The Diels-Alder reaction of benzene oxide and selected dienophiles has been studied as a mode of trapping benzene oxide (Scheme 2-8a).[17] Maleic anhydride, *N*-phenyl maleimide, 4-phenyl-1,2,4-triazole-3,5-dione (PTAD), and dimethyl acetylenedicarboxylate (DMAD) have all been used as trapping agents for benzene oxide. All of these examples provide *endo* selectivity and *anti* selectivity in respect to the epoxide. Other dieneophiles remain underexplored.

Epoxide opening has been achieved under certain conditions.[18] Most remarkably is the enantioselctive epoxide opening of benzene oxide utilizing a chiral phosphoramidite catalyst and

dialkyl zinc (Scheme 2-8b).[18b] Although with a limited scope, this transformation serves as a noteworthy example of the potential of benzene oxide as a building block in organic synthesis.

Scheme 2-8. Reactivity of Benzene Oxide



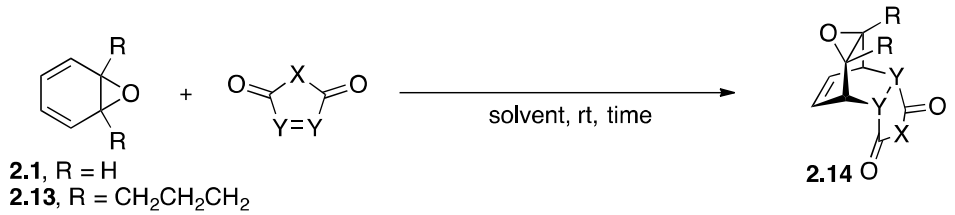
2.3 Results and Discussion

2.3.1 Synthesis of *Meso* Tricycles Derived from Benzene Oxide

The synthesis of new, chiral, fully substituted cyclohexanes derived from benzene oxide commenced with the synthesis of *meso*-tricycles **2.14a-f**. These were accessed from the Diels-Alder reaction of benzene oxide and a number of dienophiles (Table 2-1). These *meso*-compounds bearing six contiguous stereocenters have not been employed in organic synthesis prior to this study; only conformational studies have been performed with **2.14c**.[17b] The tricyclic products **2.14a-c** exhibit poor solubility in a number of organic solvents, limiting their use in downstream transformations. In order to increase their solubilities, the *N*-octyl maleimide adduct

2.14d (entry 4) and indane-derived adduct **2.14f** (entry 6) were synthetized in 61% and 57% yield, respectively.

Table 2-1. Synthesis of *Meso*-Tricyclic Compounds from Benzene Oxides **2.1** and **2.13**



2.1, R = H
2.13, R = $CH_2CH_2CH_2$

2.14

entry	product	R	X	Y	solvent	time	yield
1	**2.14a**	H	O	CH	Et_2O	72 h	71%
2	**2.14b**	H	NBn	CH	Et_2O	24 h	50%
3	**2.14c**	H	NPh	CH	Et_2O	24 h	53%
4	**2.14d**	H	NC_8H_{17}	CH	Et_2O	72 h	61%
5	**2.14e**	H	NPh	N	acetone	1 h	65%
6	**2.14f**	$CH_2CH_2CH_2$	NBn	CH	Et_2O	24 h	57%

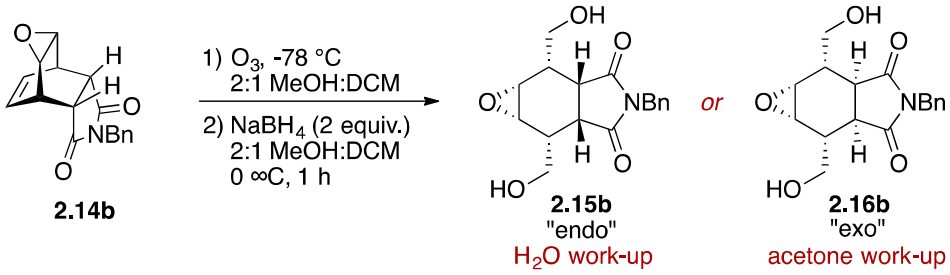
Other dienophiles were studied, but no reactivity was observed in most cases. The use of DMAD did not yield the desired Diels-Alder adduct, even though this adduct has been previously reported.[11b,17b] Furthermore, any attempts to obtain a chiral adduct proved unsuccessful. Employing asymmetric iminium catalysis only led to benzene oxide decomposition to phenol. The use of asymmetric dienophiles also led to formation of phenol (*vide infra*).

The use of aqueous NaCl solutions has been shown to improve the rate of Diels-Alder reactions *via* the hydrophobic effect.[19] In an attempt to improve the yields and reaction times for the formation of Diels-Alder adduct **2.14a-f**, the reactions were performed using a saturated aqueous NaCl solution as solvent. Using maleic anhydride, full decomposition to phenol was observed after 20 min. More than 40% conversion to **2.14d** was observed after stirring for 16 h, but 48% conversion to phenol was also detected.

2.3.2 Ozonolysis of *Meso* Tricyclic Compounds

An oxidative cleavage reaction was employed to access substituted *meso*-fused cyclohexanes with six contiguous stereocenters. Ozonolysis of anhydride **2.14a** resulted in a mixture of starting material and decomposition as the compound was highly insoluble under the reaction conditions. Fortunately, Diels-Alder adduct **2.14b** was soluble and tolerant of the reaction conditions, providing diol **2.15b** in 98% yield after a $NaBH_4$ workup (Scheme 2-9). Using Me_2S for the workup conditions rendered a labile putative dialdehyde that decomposed readily. Unexpectedly, the conditions by which the $NaBH_4$ was quenched had an effect in the stereoselectivity of the reaction. Addition of water to quench the remaining $NaBH_4$ resulted in the expected *endo* product **2.15b**; however, if acetone was added instead and the solution was concentrated and allowed to stir overnight, the thermodynamically favored *exo* product **2.16b** was obtained in a 9:1 dr.

Scheme 2-9. Ozonolysis Reaction of *Meso*-Compound **2.14b** and Effect of Quenching Conditions on the Diastereoselectivity



To elucidate the identity of the diastereoisomers, an X-ray crystallography study of the related diol **2.16d** was performed, revealing a *syn*-relationship between the epoxide and the α-protons, characteristic of having arisen from the *exo* Diels-Alder adduct.[20]

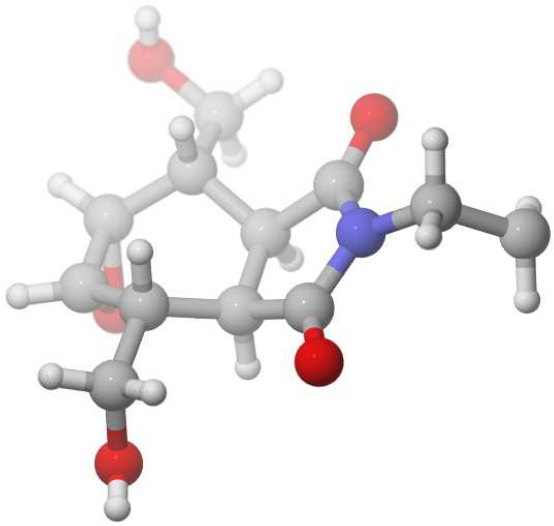


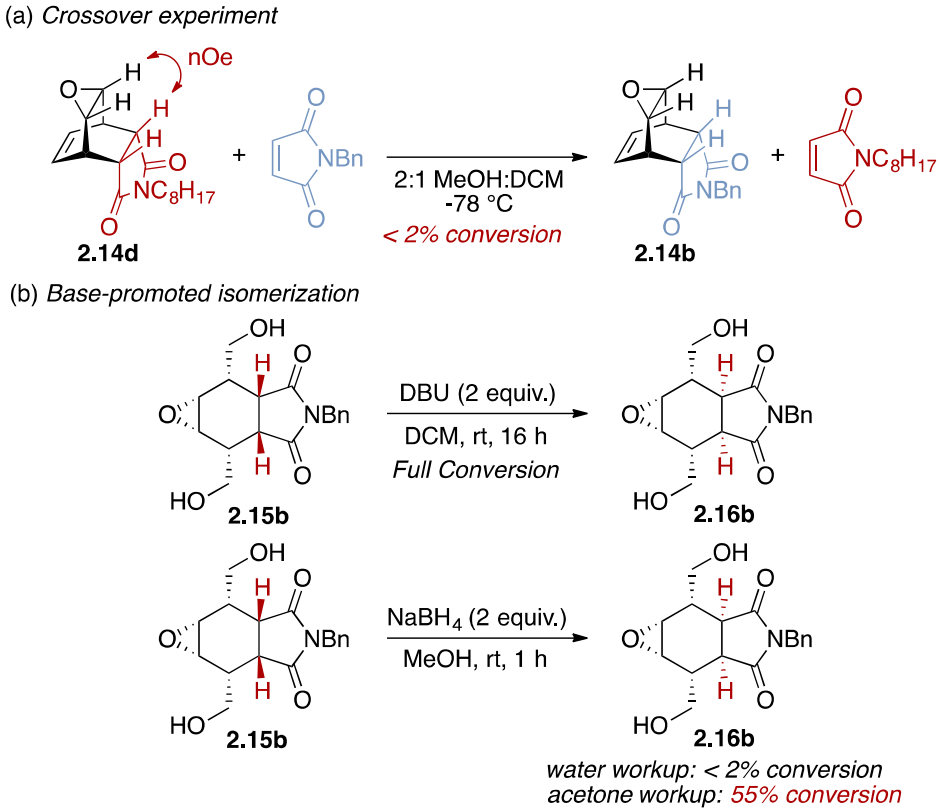
Figure 2-1. X-ray structure of succinimide **2.16d**. The *n*-octyl chain was truncated for better visualization.

In contrast, an nOe correlation was observed between the epoxide C-H methine and the proximal succinimide C-H methine in cycloadduct **2.14d**, thus showing that the initial Diels-Alder adduct is *endo*-selective. In order to rule out an unlikely retro-Diels-Alder/Diels-Alder pathway where the *exo*-Diels-Alder adduct would be trapped at the lower temperatures required by the ozonolysis reaction, we performed a crossover experiment using *N*-octyl adduct **2.14d** and *N*-benzyl maleimide; however, as expected, only *N*-octyl maleimide adduct **2.14d** was observed, ruling out the retro-Diels-Alder pathway (Scheme 2-10a).

Alternatively, we considered the possibility that the *exo* product **2.16b** could form directly from *endo* diol **2.15b** through a double epimerization pathway. Addition of DBU to **2.15b** resulted in complete conversion to **2.16b** after 16 h (Scheme 2-10b). Double epimerization reactions of *N*-substituted maleimides are unusual;[21] it is possible that the presence of the diol increases the acidity of the α-protons *via* formation of a hydrogen bond with the carbonyl oxygen. To ensure that a double epimerization was occurring under our ozonolysis conditions with the

acetone workup, we subjected the *endo* diol **2.15b** to the reductive conditions and aqueous or acetone workups. Using the aqueous workup, only the *endo* diol **2.15b** was observed, whereas the acetone workup provided the *exo* diol **2.16b** with 55% conversion after only 1 h. Thus, addition of acetone in the presence of $NaBH_4$ results in the formation of a base sufficiently potent to promote the double epimerization reaction.

Scheme 2-10. Experiments Probing the Mechanism of Diastereomerization



2.3.3 Scope of Ozonolysis Reactions

We next sought to expand the scope of the oxidative cleavage. Ozonolysis of the *N*-phenyl adduct **2.14c** using the aqueous workup resulted in 46% yield of the *endo* product **2.15c**; however, application of the acetone workup proved difficult and resulted mainly in an inseparable mixture of products. Pleasingly, when utilizing the *N*-octyl adduct **2.14d**, both the *endo* and *exo*

products could be obtained. While *endo* product **2.15d** was obtained selectively, the corresponding *exo* diol **2.16d** was obtained in a 1.4:1 dr; the diastereoselectivity could be improved to >20:1 if the diol was stirred in the presence of DBU overnight. Using the adduct derived from the indane benzene oxide **2.14f**, both diols were obtained selectively; the *exo* diol **2.16f** was obtained directly from the acetone workup and did not require further manipulation. Finally, ozonolysis of the tetracyclic dihydrotriazolopyridazinedione **2.14e** resulted in the derived diol **2.15e** in 65% yield. These products are sensitive to silica gel: a reduction in diastereoselectivity was observed in various cases after column chromatography (see Experimental Details).

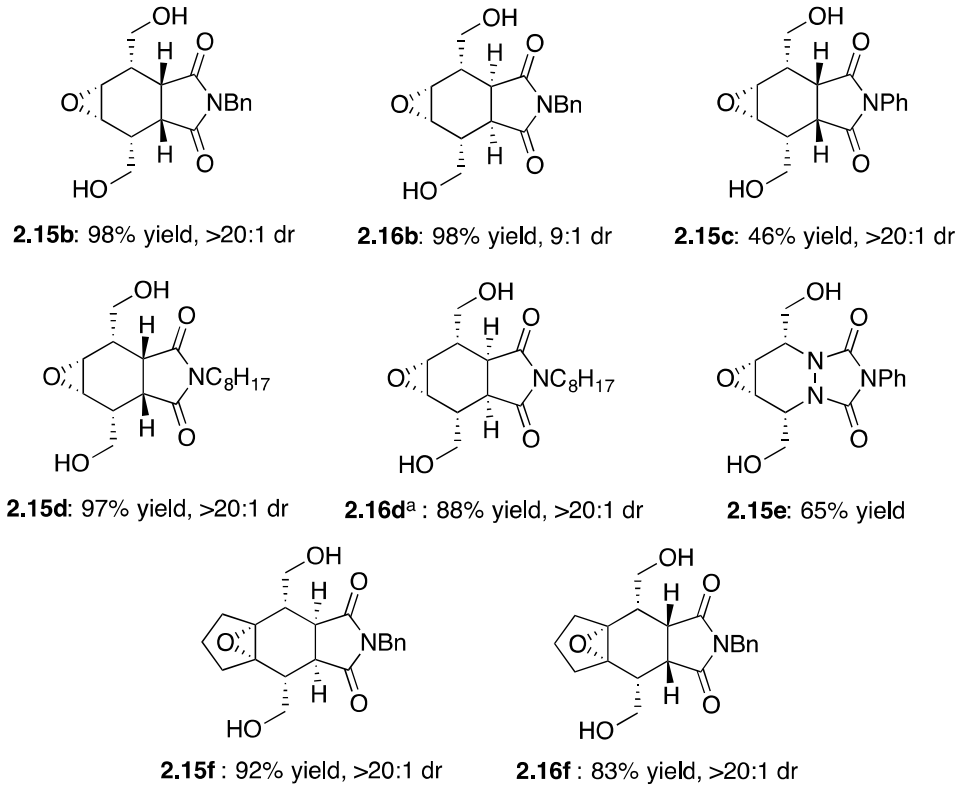
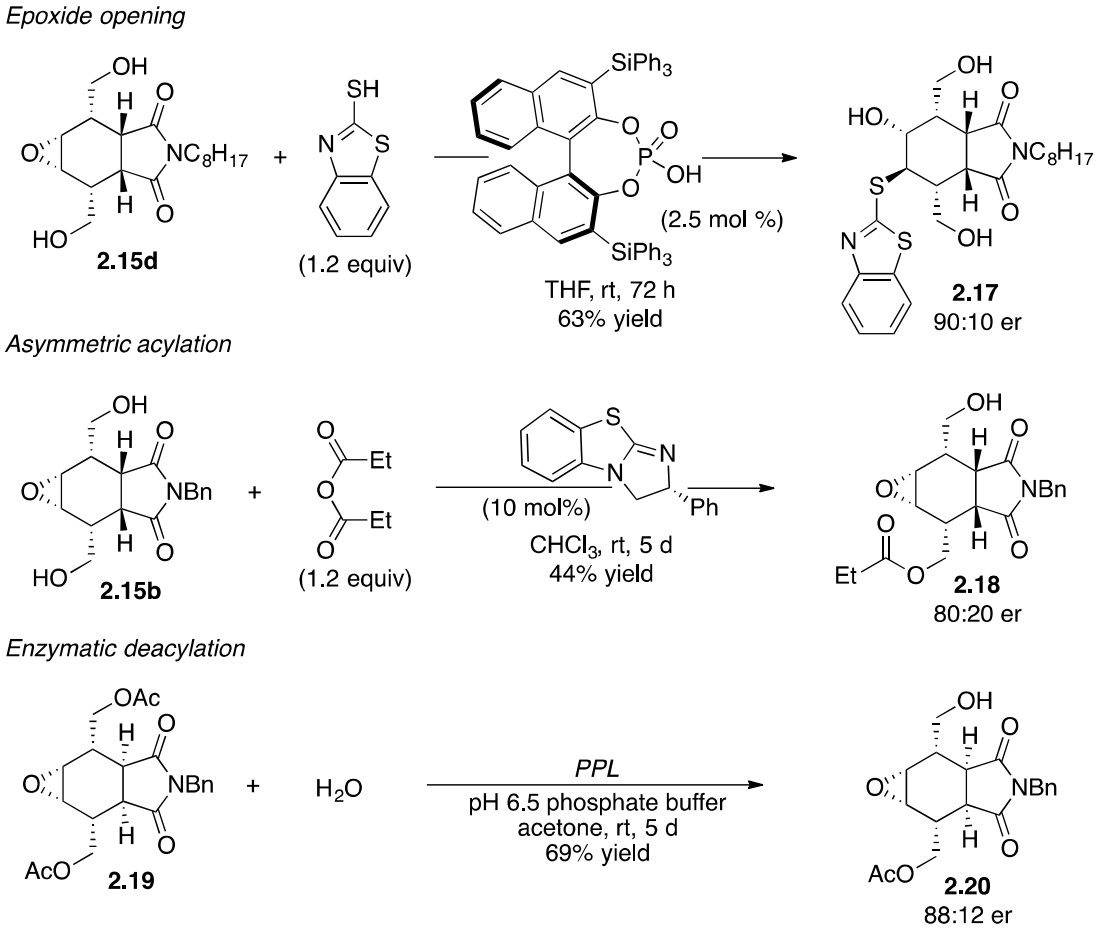


Figure 2-2. Scope of the ozonolysis reaction of *meso*-tricyclic compounds. [a]After DBU stir.

2.3.4 Desymmetrization of *Meso* Compounds

With these *meso*-diols in hand, we sought to carry out initial explorations of desymmetrizing transformations that would provide access to fully substituted, chiral cyclohexanes with six contiguous stereocenters. The use of a chiral phosphoric acid catalyst and 2-mercaptothiazole resulted in the opening of the epoxide **2.15d**, providing alcohol **2.17** in 63% yield and 90:10 er (Scheme 2-11a).[22] Employing the opposite imide diastereoisomer (**2.16d**) or changing the *N*-substituent resulted in lower enantiomeric ratios. Enantioselective diol mono-functionalization could be achieved using Birman's acylation catalyst and propionic anhydride.[23] The *endo* diol **2.15b** was mono-acylated to obtain propionate **2.18** in 44% yield and 80:20 er. Finally, subjecting the *meso* diacetate **2.19** to enzymatic deacylating conditions using porcine pancreatic lipase yielded mono-acetate **2.20** in 69% yield and 88:12 er.[24,25]

Scheme 2-11. Enantioselective Desymmetrization of *Meso* Products

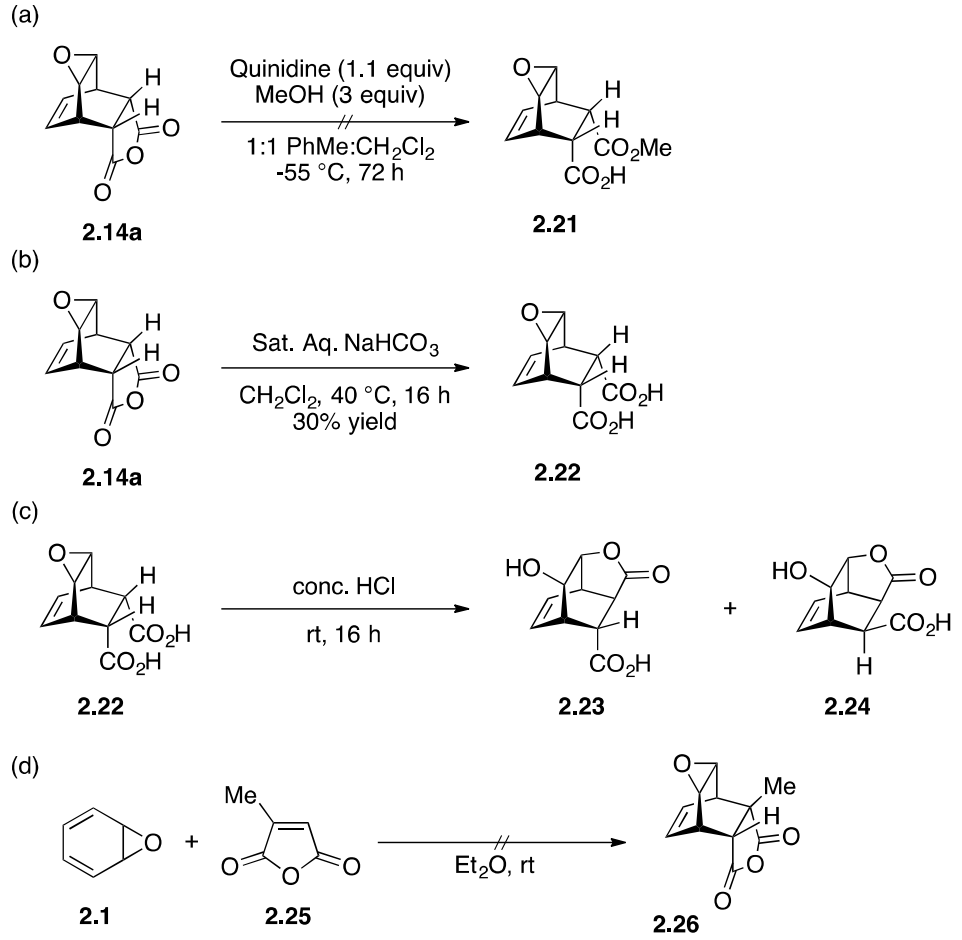


During the course of these studies, multiple efforts were made to achieve desymmetrizing transformations of *meso* tricycles **2.14a-f**. Our studies commenced with the attempted desymmetrization of *meso* anhydride **2.14a**. Subjection of **2.14a** to anhydride opening conditions with stoichiometric amounts of quinine and methanol in PhMe:DCM led to no product formation (Scheme 2-12a).[26] Thorough investigation of the reaction conditions revealed that compound **2.14a** was not soluble in the PhMe:DCM mixture. This observation prompted a solvent screen of **2.14a** in order to gauge the solubility of the anhydride. This compound was found to be only

partially soluble in methanol at room temperature; heating the mixture led to a suspension of anhydride and monoester product.

While investigating the solubility of this compound, we found that stirring with a saturated aqueous solution of $NaHCO_3$ led to 30% yield of *meso* diacid **2.22** (Scheme 2-12b). Furthermore, reaction of this diacid with concentrated HCl leads to a mixture of products resulting in epimerization and epoxide opening to form lactone **2.23**, which was detected by ^1H NMR and could not be isolated (Scheme 2-12c). In an attempt to better control the reaction, citraconic anhydride was employed as dienophile. Unfortunately, phenol was obtained as the major product of the reaction and the desired Diels-Alder adduct **2.26** was not detected (Scheme 2-12d).

Scheme 2-12. Attempted Desymmetrazation Reactions on Anhydride **2.14a** and Derivatives

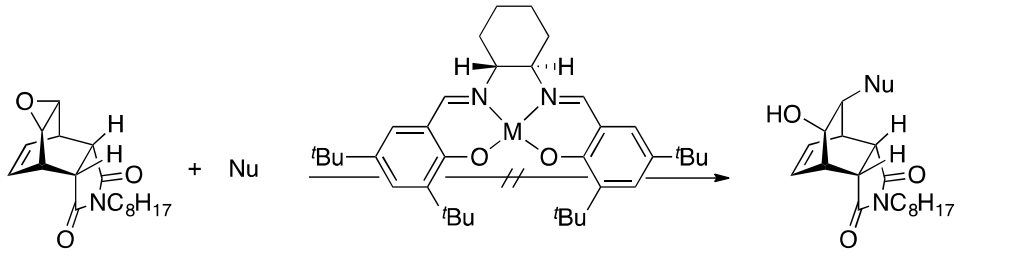


Motivated by the epoxide opening of **2.22**, we wished to investigate additional epoxide opening conditions with other *meso* tricycles **2.14b-e**. Unfortunately, similar solubility issues were faced using **2.14b** and **2.14c**. Although more soluble than **2.14a**, the solvents were limited to polar aprotic or the compounds had to be extremely diluted; both of these aspect hampered the epoxide opening transformations. The long alkyl chain in **2.14d** provided for an increase in solubility. This compound was selected for the epoxide opening trials.

First, desymmetrization using salen metal complexes were attempted. Employing salen-Co complex in the presence of benzoic acid as nucleophile led to no product formation.[27]

Likewise, utilizing a salen-Cr complex and $TMSN_3$ did not yield the epoxide opening product **2.28** (Scheme 2-13).[28] An increase in temperature to 50 °C did not have an effect on the reactivity.

Scheme 2-13. Attempted Epoxide Opening of **2.14d** Using a Salen Metal Complex



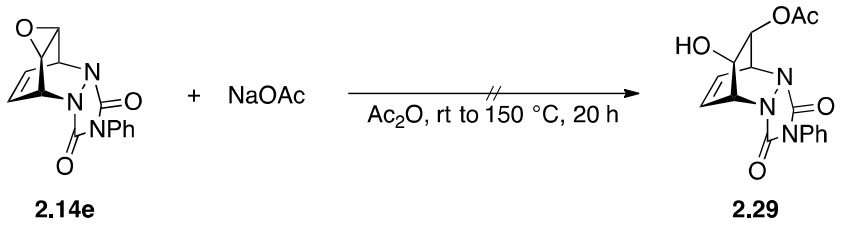
2.14d

2.27: M = Co; Nu = PhCOOH
2.28: M = Cr; Nu = $TMSN_3$

Use of catalytic amounts of copper enabled the addition of benzylmagnesium chloride across the epoxide at 50 °C. The use of a chiral ligand allowed for a temperature drop to 0 °C. Unfortunately, after screening a number of chiral pybox ligands, no enantioselectivity was observed for the reaction.

In order to get a better sense of the lability of the epoxide, a series of nucleophiles were screened under acidic or basic conditions. NaN_3, NaOAc, and KOAc were all screened at different temperatures and with a number of solvent systems but no reactivity was observed. Furthermore, thiol nucleophiles were employed with no success. In an effort to understand why this epoxide was so reluctant to open under well known epoxide opening conditions, we hypothesized that the succinimide hydrogens could be blocking the reactive site. To test this hypothesis, *meso* tricycle **2.14e** was subjected to NaOAc in acetic anhydride. Unfortunately, **2.29** was not observed, even when the reaction was heated to 150 °C.

Scheme 2-14. Attempted Epoxide Opening of **2.14e**



2.14e **2.29**

2.4 Conclusions

In conclusion, we have disclosed the synthesis of novel, *meso*-diols derived from the benzene oxide/oxepin equilibrium. These compounds have not been previously accessed through other synthetic methods and similar compounds are still challenging to obtain. Our efforts to realize desymmetrizing transformations on the initial *meso* tricycles were not successful. However, fully substituted chiral compounds were acquired through desymmetrizing epoxide opening and acylation reactions. This work provides further support to the notion that the synthesis of complex, chiral molecules can be achieved using benzene oxide as a building block.

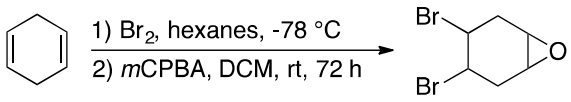
2.5 Experimental Details

Methods: Proton and carbon magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded on either a Bruker model DRX 400 or 600 spectrometer (^{1}H-NMR at 400 or 600 MHz and ^{13}C-NMR at 100 or 150 MHz) with solvent resonance as the internal standard (^{1}H-NMR: $CDCl_3$ at 7.26 ppm and ^{13}C-NMR: $CDCl_3$ at 77.0 ppm). ^{1}H-NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, qt = quintet, and m = multiplet), coupling constant (Hz) and integration. Melting points (mp) were determined using a Thomas Hoover Capillary Melting Point Apparatus. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier Transform Infrared Spectrometer. High-resolution mass spectrometry (HRMS) was performed using a Thermo Scientific LTQ FT Ultra mass spectrometer S2 with direct infusion in the positive ion mode. Samples were prepared in HPLC grade methanol. High performance liquid chromatography (HPLC) was performed on a Perkin Elmer Flexar® HPLC system equipped with Daicel Chiralpak IA and IC columns. Samples were prepared using 90/10 HPLC grade *i*PrOH/hexanes and eluted with HPLC grade hexanes with the indicated percentage of *i*PrOH with an oven temperature of 40 °C. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. Ozonolysis reactions were performed using an Ozotech OZ4BTU Ozone Generator. Thin layer chromatography (TLC) was performed on Sorbtech plastic-backed 0.20 mm silica gel 60 plates. Visualization was accomplished with UV light and potassium permanganate ($KMnO_4$) solution, followed by heating. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Yields and diastereomeric ratios (dr's) are reported herein for a specific experiment and as a result may differ slightly from those found in the schemes, which are

averages of at least two experiments.

Materials: Nitrogen was dried by passage through anhydrous calcium sulfate with 3% cobalt chloride as indicator (commercial Drierite). *N*-benzylmaleimide,[29] *N*-octylmaleimide,[30] *N*-phenylmaleimide,[31] and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[32] were prepared according to known literature procedures. Birman's catalyst[23] and the phosphoric acid catalyst (TiPSY)[33] were prepared according to known literature procedures. The benzene oxides were prepared by a modified literature procedure.[17b] All other reagents and solvents were purchased from commercial sources and used as received.

Modified Procedure for the Synthesis of 3,4-dibromo-7-oxabicyclo[4.1.0]heptane

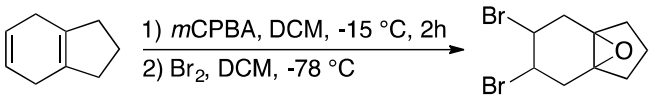


4,5-dibromo-1-cyclohexene: A solution of Br_2 (2.05 ml, 40 mmol) in hexanes (20 ml) was added dropwise to a solution of 1,4-cyclohexadiene (3.78 ml, 40 mmol) in hexanes (45 ml) that had been cooled to -45 °C using a dry ice/acetonitrile bath. (Note: the reaction turns yellow upon addition of bromine and should not be allowed to turn completely orange since lower yields resulted when this occurred). After addition was complete, the yellow solution was allowed to reach room temperature and then filtered. The solution was concentrated under reduced pressure. The resulting oil solidified upon cooling and was used in the next step without further purification.

3,4-dibromo-7-oxabicyclo[4.1.0]heptane: A solution of the crude 4,5-dibromo-1-cyclohexene in dichloromethane (20 mL) was added to a solution of *m*CPBA (13.4 g, 58 mmol) in dichloromethane (330 ml) at room temperature. The reaction was allowed to stir at that temperature for 72 hours. A 20% aq. solution of $Na_2S_2O_5$ (100 ml) was added and the solution

was allowed to stir for 20 min. The layers were then separated and the organic layer was washed with a sat. aq. $NaHCO_3$ solution (2 x 100 ml) and brine (100 ml × 1). The organic layer was dried with sodium sulfate, filtered, and concentrated under vacuum to yield the clean product as an off white crystalline solid (6.85 g, 26.8 mmol, 68% yield over two steps). The product was carried on to the next step without further purification. Spectroscopic data was identical to those previously reported: **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.30 (td, *J* = 7.1, 4.6 Hz, 1H), 4.19 (q, *J* = 6.7 Hz, 1H), 3.17 (m, 2H), 3.00 (dd, *J* = 16.0, 4.6 Hz, 1H), 2.90 (ddd, *J* = 16.5, 6.4, 3.6 Hz, 1H), 2.65 (dd, *J* = 16.6, 6.3 Hz, 1H), 2.46 (ddd, *J* = 16.1, 6.7, 3.4 Hz, 1H).

Synthesis of 5,6-dibromohexahydro-1*H*-3a,7a-epoxyindene

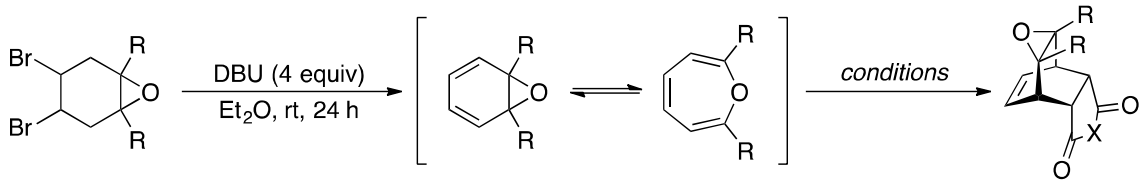


2,3,4,7-tetrahydro-1*H*-3a,7a-epoxyindene: The title compound was prepared according to a literature procedure[37] and used directly in the next step. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 5.49 (d, *J* = 2.4 Hz, 2H), 2.62 (d, *J* = 18.4 Hz, 2H), 2.38 (d, *J* = 16.0 Hz, 2H), 2.05 (dd, *J* = 12.8, 7.4 Hz, 2H), 1.54 (m, 4H).

5,6-dibromohexahydro-1*H*-3a,7a-epoxyindene: A solution of bromine (0.19 ml, 3.67 mmol) in dichloromethane (6 mL) was added over a period of 30 min to a solution of 2,3,4,7-tetrahydro-1*H*-3a,7a-epoxyindene (1.0 g, 3.67 mmol) in dichloromethane (30 mL) cooled to -78 °C. Addition was stopped when the orange color persisted (Note: the bromine solution was not added completely). The reaction was allowed to reach room temperature and the solution was concentrated under reduced pressure to yield a yellow oil. The oil was crystallized from pentanes at -20 °C to obtain the product as clear crystals (722 mg, 2.44 mmol, 66% yield). Spectroscopic

data was identical to those previously reported:[7] **^{1}H-NMR** (400 MHz, $CDCl_3$): 4.41 (q, *J* = 5.4 Hz, 1H), 4.29 (q, *J* = 5.9 Hz, 1H), 3.01 (dd, *J* = 15.9, 4.4 Hz, 1H), 2.82 (dd, *J* = 16.4, 6.3 Hz, 1H), 2.68 (dd, *J* = 16.4, 4.9 Hz, 1H), 2.42 (dd, *J* = 15.9, 5.4 Hz, 1H), 2.05 (dt, *J* = 12.4, 8.9 Hz, 2H), 1.55 (m, 4H).

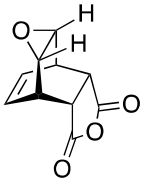
General procedure A for the preparation of Diels-Alder adducts (3a-3d)



Benzene oxide/oxepin: DBU (4 equiv) was added to a solution of 3,4-dibromo-7-oxabicyclo[4.1.0]heptane (1 equiv) in Et_2O (10 mL) at room temperature. The reaction was allowed to stir for 24 h at that temperature and then a sat. aq. solution of $NaHCO_3$ was added until all the precipitate was dissolved. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The organic layers were combined and washed with brine (Note: if the organics are not washed with brine, lower yields result in Diels-Alder reactions). The organic extracts were dried with sodium sulfate, filtered, and concentrated under a stream of air. The yellow liquid was used immediately to avoid decomposition. The same procedure was used for the substituted benzene oxide, where R = $CH_2CH_2CH_2$.

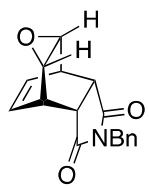
The crude benzene oxide/oxepin was re-dissolved in approximately 10 mL of ether and the dienophile (1 equiv) was added as a solid. The reaction was allowed to stir at room temperature for the required time. The resulting precipitate was collected and washed with cold ether. Only products **3d** and **3f** required further purification.

1a,2,2a,5a,6,6a-hexahydro-2,6-ethenooxireno[2,3-*f*]isobenzofuran-3,5-dione (2.14a): The title compound was prepared according to general procedure A using benzene oxide (7.8 mmol), maleic anhydride (766 mg, 7.8 mmol), and Et_2O (20 mL) and stirred for 72 h. The product was obtained as a white powder (1.06 g, 7.81 mmol, 71% yield). Spectroscopic data was identical to those previously reported:[11b] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.97 (dd, *J* = 4.7, 3.5 Hz, 2H), 3.73-3.66 (m, 2H), 3.40 (dd, *J* = 4.0, 2.2 Hz, 2H), 3.27 (t, 1.8 Hz, 2H).



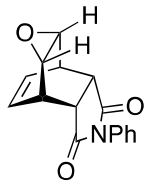
2.14a

4-benzyl-1a,2,2a,5a,6,6a-hexahydro-3*H*-2,6-ethenooxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.14b): The title compound was prepared according to general procedure A using benzene oxide (4.12 mmol), benzyl maleimide (771 mg, 4.12 mmol), and Et_2O (10 mL) and stirred for 24 h. The product was obtained as a white powder (263 mg, 0.935 mmol, 48% yield). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.24 (m, 5H), 5.71 (dd, *J* = 4.8, 3.4 Hz, 2H), 4.57 (s, 2H), 3.65-3.57 (m, 2H), 3.40-3.35 (m, 2H), 2.97 (t, *J* = 1.8 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.7, 137.1, 123.3, 48.6, 31.1. **IR** (thin film, cm^{-1}): 3433, 1769, 1698, 1396, 1266, 1173, 1054. **HRMS** (ESI^+) Calcd for $C_{17}H_{15}NO_3$ ([M+1]): 304.0944, Found: 304.0947. **mp**: 180-185 °C.



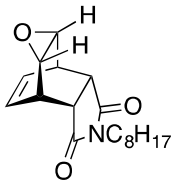
2.14b

4-phenyl-1a,2,2a,5a,6,6a-hexahydro-3*H*-2,6-ethenooxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.14c): The title compound was prepared according to general procedure A using benzene oxide (4.12 mmol), phenyl maleimide (771 mg, 4.12 mmol), and Et_2O (10 mL) and stirred for 24 h. The product was obtained as a white powder (277 mg, 1.04 mmol, 53% yield). Spectroscopic data was identical to those previously reported:[17b] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48-7.35 (m, 3H), 7.19-7.11 (m, 2H), 5.95 (dd, *J* = 4.7, 3.4 Hz, 2H), 3.76-3.66 (m, 2H), 3.47-3.39 (m, 2H), 3.13 (t, *J* = 1.8 Hz, 2H).



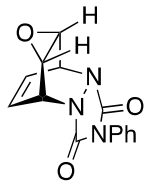
2.14c

4-octyl-1a,2,2a,5a,6,6a-hexahydro-3*H*-2,6-ethenooxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.14d): The title compound was prepared according to general procedure A using benzene oxide (4.12 mmol), octyl maleimide (771 mg, 4.12 mmol), and Et_2O (10 mL) and stirred for 72 h. The solution was concentrated and the crude was purified using column chromatography with hexanes/ethyl acetate 5/1 to 1/1 to yield the clean product as a white solid (380 mg, 1.25 mmol, 64% yield). Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.80 (dd, *J* = 4.7, 3.4 Hz, 2H), 3.66-3.55 (m, 2H), 3.43-3.32 (m, 4H), 2.93 (t, *J* = 1.8 Hz, 2H), 1.50-1.39 (m, 2H), 1.32-1.15 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHZ, $CDCl_3$): δ 177.1, 126.6, 47.4, 42.0, 38.8, 35.5, 31.7, 29.1, 27.6, 26.7, 22.6, 14.1. **IR** (thin film, cm^{-1}): 2928, 2855, 1772, 1698, 1402, 1266, 1171. **HRMS** (ESI^+) Calcd. for $C_{18}H_{25}NO_3$ ([M+1]): 304.1907, Found: 304.1912. **mp**: 110-114 °C. **TLC** (1:1 hexanes: ethyl acetate): R_f = 0.4.



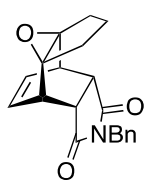
2.14d

5-phenyl-1a,2,8,8a-tetrahydro-4*H*-2,8-ethenooxireno[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-4,6(5*H*)-dione (2.14e): The title compound was made according to a literature procedure[35] using benzene oxide (1.95 mmol) and 4-phenyl-1,2,4-triazole-3,5-dione (171 mg, 0.977 mmol). The product was purified using column chromatography with 1/1 hexanes/ethyl acetate to obtain **3e** as a white solid (171 mg, 0.635 mmol, 65% yield). Spectroscopic data was identical to those previously reported:[35] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54-7.29 (m, 5H), 6.17 (t, *J* = 3.8 Hz, 2 H), 5.31 (d, *J* = 3.9 Hz, 2 H), 3.79-3.61 (m, 2H).



2.14e

2-benzyl-3a,4,6,7,8,8a-hexahydro-1*H*,5*H*-4a,7a-epoxy-4,8-ethenocyclopenta[*f*]isoindole-1,3(2*H*)-dione (2.14f): The title compound was prepared according to general procedure A using



2.14f

2,3-dihydro-1*H*-3a,7a-epoxyindene (1.69 mmol), benzyl maleimide (316 mg, 1.69 mmol), and Et_2O (8.5 mL) and stirred for 24 h. The solution was concentrated and the crude was purified using column chromatography with hexanes/ethyl acetate 5/1 to 1/1 to yield the clean product as a white solid (331 mg, 1.03 mmol, 61% yield). Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 5.76 (dd, *J* = 4.7, 3.2 Hz, 2H), 4.56 (s, 2H), 3.58-3.44 (m, 2H), 3.08-3.01 (m, 2H), 2.02-1.95 (m, 2H), 1.86-1.78 (m, 1H), 1.75-1.67 (m, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 177.1, 135.5, 128.6, 128.5, 127.8, 64.3, 42.4, 42.3, 37.2, 25.4, 25.1. **IR** (thin film, cm^{-1}): 2953, 1699, 1396, 1340, 1174, 916. **HRMS** (ESI^+) Calcd. for $C_{20}H_{19}NO_3$ ([M+Na]): 344.1257, Found: 344.1265. **mp**: 179-181 °C. **TLC** (1/1 hexanes/ethyl acetate): R_f = 0.4.

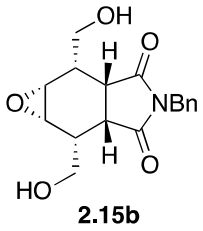
General procedure B for the preparation of diols (2.15a-2.15f)

The Diels-Alder adduct (1 equiv) was dissolved in a 2:1 mixture of DCM:MeOH (0.11 M) and cooled to -78 °C in a dry ice/acetone bath. Ozone was bubbled through the solution until the reaction turned light blue, at which point the ozone bubbling was stopped and the solution was sparged with nitrogen to purge excess ozone. Solid $NaBH_4$ (2 equiv) was added and the reaction was moved to an ice bath. The reaction was allowed to stir for 1 h, then 1 mL of water was added. The layers were separated and the aqueous layer was extracted with DCM (2 ml x 3). The organic extracts were combined and dried with sodium sulfate, filtered, and concentrated to obtain the desired diol.

General Procedure C for the preparation of diols (2.16a-2.16f)

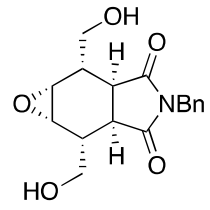
The Diels-Alder adduct (1 equiv) was dissolved in a 2:1 mixture of DCM:MeOH (0.11 M) and cooled to -78 °C in a dry ice/acetone bath. Ozone was bubbled through the solution until the reaction turned light blue at which point the ozone bubbling was stopped and the solution was purged with nitrogen to get rid of excess ozone. Solid $NaBH_4$ (2 equiv) was added and the reaction was moved to an ice bath. After stirring for 1 h, 1 mL of acetone was added and the reaction was stirred for 5 min. The solvent was removed in vacuo and the residue was stirred overnight. Then, 1 mL of water and 1 mL of EtOAc are then added and the layers are separated. The aqueous layer is extracted with EtOAc (3 x 2 mL) and the organics are combined, dried with sodium sulfate, and concentrated to yield the crude diol.

(1*R*, 2*S*, 5*R*, 6*R*, 6*S*)-4-benzyl-2,6-bis(hydroxymethyl)hexahydro-3*H*-oxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.15b): The title compound was prepared according to general procedure B using **2.14b** (50 mg, 0.18 mmol), $NaBH_4$ (13.4 mg, 0.36 mmol), and 2:1 DCM:MeOH (1.5 mL), and was obtained as a clear amorphous solid (56 mg, 0.18 mmol, >98% yield, >20:1 d.r.). Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.1 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.29-7.25 (m, 1H), 4.66 (s, 2H), 4.07 (dd, *J* = 11.9, 9.3 Hz, 2H), 3.97 (dd, *J* = 11.9, 5.5 Hz, 2H), 3.12 (s, 2H), 3.11-3.07 (m, 2H), 2.66-2.59 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 179.2, 138.6, 121.6, 64.1, 32.9. **IR** (thin film, cm^{-1}): 3417, 2939, 2885, 1769, 1683, 1405, 1186, 1029. **HRMS** (ESI^+) Calcd for $C_{17}H_{19}NO_5$ ([M+1]): 318.1336, Found: 318.1333.



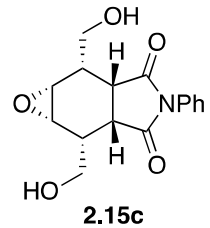
2.15b

(1a*R*,2*S*,2a*R*,5a*S*,6*R*,6a*S*)-4-benzyl-2,6-bis(hydroxymethyl)hexahydro-3*H*-oxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.16b): The title compound was prepared according to general procedure C using **2.14b** (50 mg, 0.18 mmol), $NaBH_4$ (13.4 mg, 0.36 mmol), and 2:1 DCM:MeOH (1.5 mL), and was obtained as a white solid (55 mg, 0.17 mmol, 98% yield, 9:1 d.r.). Analytical data: **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 4.65 (s, 2H), 4.15-4.05 (m, 2H), 4.04-3.95 (m, 2H), 3.29 (s, 2H), 2.94-2.85 (m, 2H), 2.85-2.78 (m, 2H), 2.30-2.20 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 179.6, 135.2, 128.8, 128.6, 128.2, 65.2, 51.6, 42.6, 38.6, 37.1. **IR** (thin film, cm^{-1}): 3420, 1697, 1558, 1402, 1340, 1175, 1030. **HRMS** (ESI^+) Calcd. for $C_{17}H_{19}NO_5$ ([M+1]): 318.1336, Found: 318.1334. **mp**: 96-98 °C.



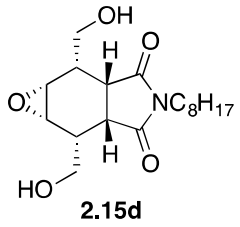
2.16b

(1a*R*,2*S*,2a*S*,5a*R*,6*R*,6a*S*)-2,6-bis(hydroxymethyl)-4-phenylhexahydro-3*H*-oxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.15c): The title compound was prepared according to general procedure B using **2.14c** (50.0 mg, 0.19 mmol), $NaBH_4$ (14.2 mg, 0.37 mmol) and 2:1 DCM:MeOH (1.5 mL), and was obtained as a white amorphous solid (42 mg, 0.14 mmol, 74% yield, >20:1 d.r.). Analytical data: **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.52-7.47 (m, 2H), 7.45-7.41 (m, 1H), 7.30-7.27 (m, 2H), 4.15 (dd, *J* = 11.9, 9.4 Hz, 2H), 4.03 (dd, *J* = 11.9, 5.6 Hz, 2H), 3.31-3.26 (m, 2H), 3.22 (s, 2H), 2.76-2.70 (m, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 178.7, 129.3, 129.0, 126.7, 62.7, 52.4, 39.2, 37.7. **IR** (thin film, cm^{-1}): 3446, 1698, 1497, 1396, 1201, 1042. **HRMS** (ESI^+) Calcd. for $C_{16}H_{17}NO_5$ ([M+Na]): 326.0999, Found: 326.0990.



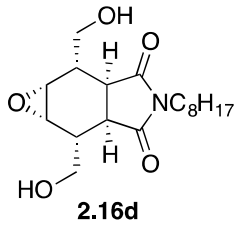
2.15c

(1*R*, 2*S*, 5*R*, 6*R*, 6*S*)-2,6-bis(hydroxymethyl)-4-octylhexahydro-3*H*-oxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.15d): The title compound was prepared according to general procedure B using **2.14d** (50 mg, 0.17 mmol), $NaBH_4$ (12.5 mg, 0.33 mmol), and 2:1 DCM:MeOH (1.5 mL), and was obtained as a white solid (53 mg, 0.16 mmol, 95% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.13-4.02 (m, 2H), 4.02-3.92 (m, 2H), 3.60-3.50 (m, 2H), 3.47 (t, *J* = 7.4 Hz, 2H), 3.12 (s, 2H), 3.09-3.00 (m, 2H), 2.67-2.54 (m, 2H), 1.62-1.47 (m, 2H), 1.35-1.16 (m, 10H), 0.85 (t, *J* = 6.7 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 179.6, 62.7, 52.2, 39.0, 37.3, 31.7, 29.1, 29.0, 27.1, 26.7, 22.5, 14.1. **IR** (thin film, cm^{-1}): 3420 (b), 2927, 2856, 1684, 1439, 1353, 1034. **HRMS** (ESI^+) Calcd. for $C_{18}H_{29}NO_5$ ([M+Na]): 362.1938, Found: 362.1938. **mp**: 65-69 °C.



2.15d

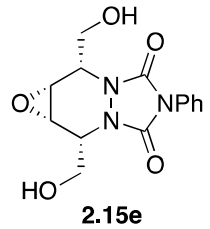
(1a*R*,2*S*,2a*R*,5a*S*,6*R*,6a*S*)-2,6-bis(hydroxymethyl)-4-octylhexahydro-3*H*-oxireno[2,3-*f*]isoindole-3,5(4*H*)-dione (2.16d): The title compound was prepared according to general procedure C using **2.14d** (50 mg, 0.17 mmol), $NaBH_4$ (12.5 mg, 0.33 mmol), and 2:1 DCM:MeOH (1.5 mL), and was obtained with a 1.4:1 d.r. To obtain the product in >20:1 d.r., a DCM (0.7 mL) solution of the diastereomeric mixture was stirred with DBU (44 μL, 0.29 mmol) at room temperature for 16 h. A sat. aq. $NaHCO_3$ solution (2 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 2 mL), the organics were combined, dried with sodium sulfate and concentrated to afford the product as a white solid (47 mg, 0.14 mmol, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.15-4.06 (m, 2H), 4.06-3.94 (m, 2H), 3.49 (t, *J* = 11.3 Hz, 2H), 3.30 (s, 2H), 2.99-2.81 (m, 4H), 2.32-2.19 (m, 2H), 1.71-1.47 (m, 3H), 1.34-1.16 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 180.0, 65.4, 65.4, 51.6, 39.1, 38.7, 38.7, 37.2, 31.7, 29.1, 29.0, 27.5, 26.7, 22.6, 14.1. **IR** (thin film, cm^{-1}): 3420 (b), 2926,



2.16d

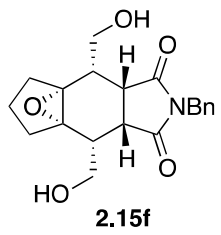
2856, 1769, 1694, 1406, 1065. **HRMS** (ESI^+) Calcd. for $C_{18}H_{29}NO_5$ ([M+1]): 340.2118, Found: 340.2111. **mp**: 78-81 °C.

(1a*R*,2*S*,8*R*,8a*S*)-2,8-bis(hydroxymethyl)-5-phenyltetrahydro-4*H*-oxireno[2,3-*d*][1,2,4]triazolo[1,2-*a*]pyridazine-4,6(5*H*)-dione (2.15e): The title compound was prepared according to general procedure B using **2.14e** (50 mg, 0.19 mmol), $NaBH_4$ (14.1 mg, 0.37 mmol), and 2:1 DCM:MeOH (1.5 mL). The product was purified using silica gel column chromatography with DCM/MeOH 20/1 and was obtained as a white solid (34.0 mg, 0.11 mmol, 60% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.51-7.44 (m, 4H), 7.43-7.39 (m, 1H), 4.32-4.26 (m, 2H), 4.20-4.08 (m, 4H), 3.64 (dd, *J* = 2.3, 1.0 Hz, 2H), 3.49 (dd, *J* = 9.4, 4.2 Hz, 2H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 153.4, 130.4, 129.3, 128.8, 125.7, 61.5, 55.9, 51.4. **IR** (thin film, cm^{-1}): 3419, 2894, 1769, 1698, 1430, 1292, 1077, 768. **HRMS** (ESI^+) Calcd. for $C_{14}H_{15}N_3O_5$ ([M+Na]): 328.0904, Found: 328.0893. **mp**: 119-122 °C. **TLC** (20/1 DCM/MeOH): R_f = 0.2.



2.15e

(3*R*, 4*R*, 4*S*, 7*R*, 8*S*, 8*S*)-2-benzyl-4,8-bis(hydroxymethyl)hexahydro-1*H*,5*H*-4a,7a-epoxycyclopenta[*f*]isoindole-1,3(2*H*)-dione (2.15f): The title compound was prepared according to general procedure B using **2.14f** (50 mg, 0.16 mmol), $NaBH_4$ (11.8 mg, 0.31 mmol), and 2:1 DCM:MeOH (1.5 mL). The crude was purified using column chromatography with DCM/MeOH 20/1 and was obtained as a white amorphous solid (53 mg, 0.15 mmol, 95 % yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 7.33-7.29 (m, 2H), 7.29-7.27 (m, 1H), 4.67 (s, 2H), 4.09 (ddd, *J* = 12.0, 9.8, 6.8 Hz, 2H), 3.98 (ddd, *J* = 12.3, 7.9, 4.8 Hz, 2H), 3.58 (dd, *J* = 7.9, 6.9 Hz, 2H), 3.20-3.14 (m, 2H), 2.66-2.59 (m, 2H), 2.11-2.02 (m, 2H), 1.63-1.53 (m, 4H), 1.36-1.27 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): 179.6, 135.3, 128.6, 128.4, 127.9, 66.6, 61.6, 42.7,



2.15f

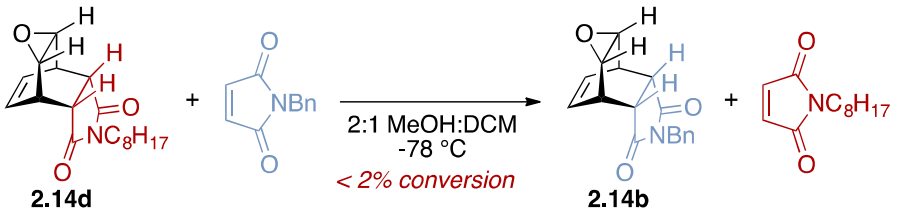
40.2, 39.3, 28.2, 19.5. **IR** (thin film, cm^{-1}): 3446, 2952, 1685, 1431, 1350, 1169, 1054. **HRMS** (ESI^+) Calcd. for $C_{20}H_{23}NO_5$ ([M+Na]): 380.1468, Found: 380.1467. **TLC** (20/1 DCM/MeOH): R_f = 0.3.

(3a*R*,4*S*,4a*R*,7a*S*,8*R*,8a*S*)-2-benzyl-4,8-bis(hydroxymethyl)hexahydro-1*H*,5*H*-4a,7a-epoxycyclopenta[*f*]isoindole-1,3(2*H*)-dione (2.16f): The title compound was prepared according to general procedure C using **2.14f** (50 mg, 0.16 mmol), $NaBH_4$ (11.8 mg, 0.31 mmol), and 2:1 DCM:MeOH (1.5 mL), and was obtained as a light pink solid (51.6 mg, 0.14 mmol, 93% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 5H), 4.65 (s, 2H), 4.16 – 4.07 (m, 2H), 3.96 (dd, *J* = 11.1, 5.9 Hz, 2H), 3.14 – 3.07 (m, 2H), 2.91-2.83 (m, 2H), 2.29-2.23 (m, 2H), 2.18-2.11 (m, 2H), 1.67-1.55 (m, 5H), 1.46-1.36 (m, 1H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 180.0, 135.3, 128.8, 128.7, 128.2, 66.2, 63.9, 42.6, 40.3, 39.0, 29.1, 19.5. **IR** (thin film, cm^{-1}): 3445, 2953, 1696, 1430, 1174, 1071, 733. **HRMS** (ESI^+) Calcd. for $C_{20}H_{23}NO_5$ ([M+Na]): 380.1468, Found: 380.1488. **mp**: 151-155 °C.

2.16f

Mechanistic Experiments

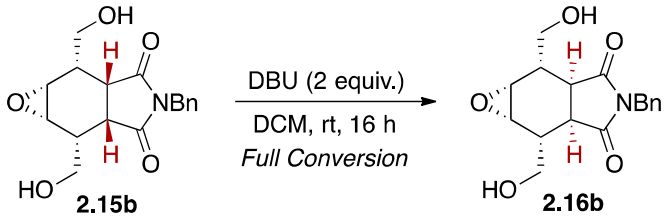
Crossover experiment



A solution of **2.14d** (25.0 mg, 0.08 mmol) in dichloromethane (0.5 mL) was cooled to -78 °C. *N*-benzyl maleimide (15.4 mg, 0.08 mmol) was added and the reaction was stirred for 20 min. The reaction was moved to an ice bath and stirred for 1 h. The solvent was evaporated under reduced

pressure and the crude oil analyzed. Only returned starting materials were observed, indicating that no retro Diels-Alder reaction had taken place.

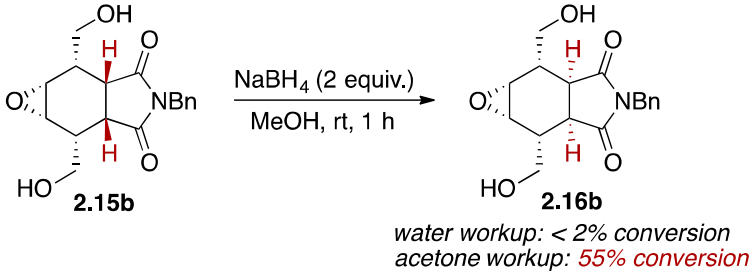
Double epimerization experiments



In a flame-dried 1 dram vial, DBU (8 µL, 0.05 mmol) was added to a solution of **2.15b** (10 mg, 0.06 mmol) in dichloromethane (0.1 mL) and the reaction was allowed to stir at room temperature for 16 h. A sat. aq. $NaHCO_3$ solution (1 mL) was added and the solution was extracted with EtOAc (3 x 1 mL). The organics were combined, dried with sodium sulfate and concentrated. Full conversion to the opposite diastereoisomer was observed by ^1H NMR.

Effect of base:

Entry	Base	Conversion to **5b**
1	Et_3N	< 2%
2	$NaHCO_3$	< 2%
3	K_2CO_3	21%

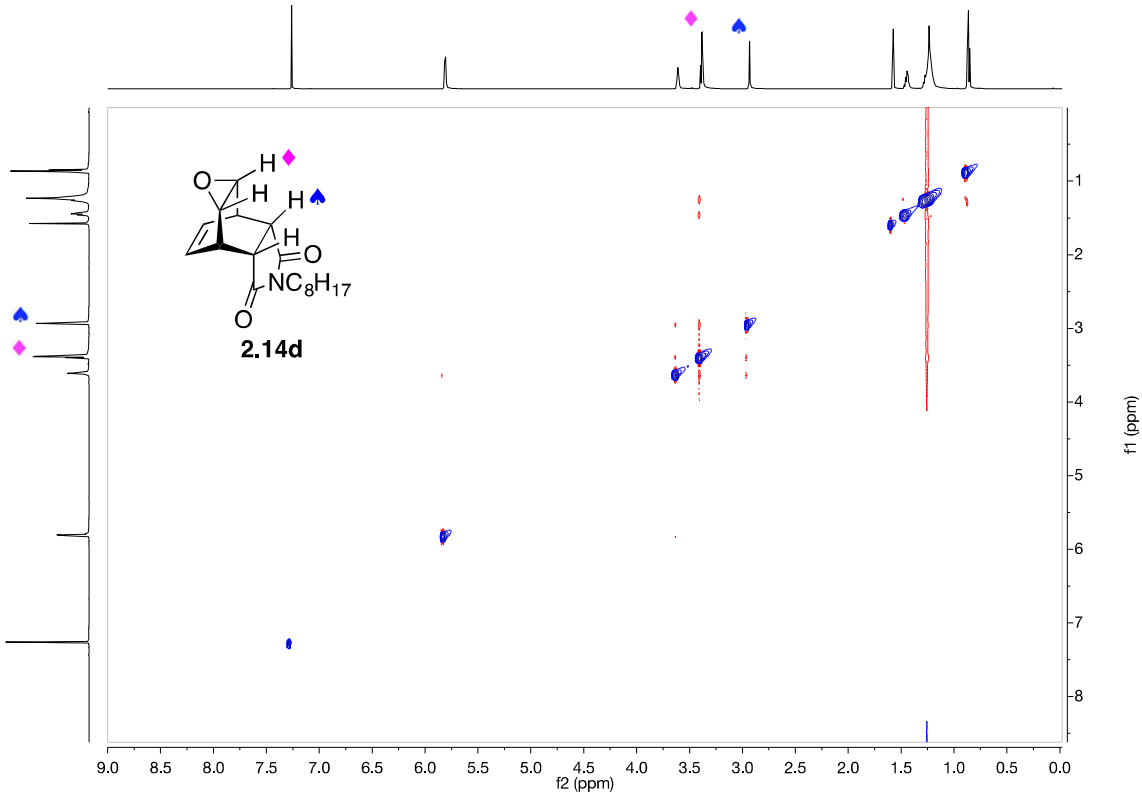


To a solution of **2.15b** (30.0 mg, 0.09 mmol) in methanol (0.7 mL) was added $NaBH_4$ (7.15 mg, 0.19 mmol) at room temperature and the reaction was allowed to stir for 1 h.

Water workup: 1 mL of water and 1 mL of ethyl acetate were added and the layers were separated. The aqueous layer was extracted using ethyl acetate (3 x 2 mL) and the organics were combined, dried with sodium sulfate and concentrated. Only **2.15b** was observed by ^{1}H NMR.

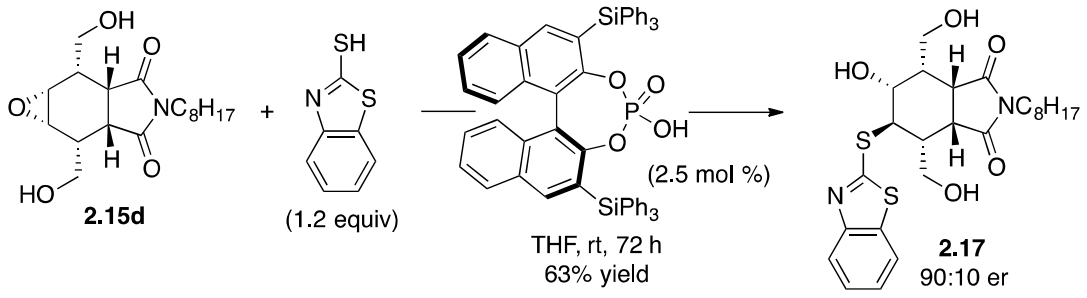
Acetone workup: 1 mL of acetone was added and the solvent was removed under reduced pressure. The residue was passed through a silica gel plug using ethyl acetate and the solvent was removed to obtain a 1:1.2 mixture of diastereoisomers, favoring **2.16b**.

nOe experiment for 2.14d



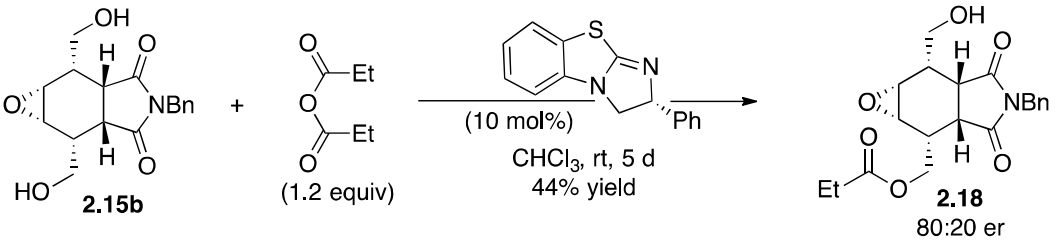
Desymmetrization Reactions

Epoxide opening



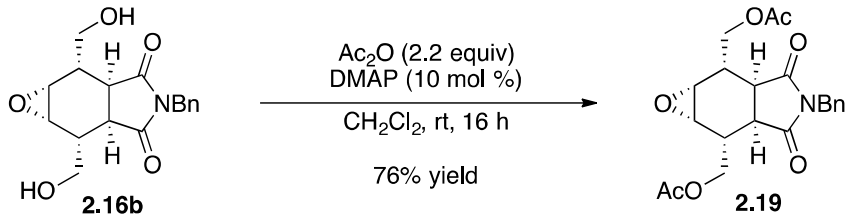
Under inert atmosphere, **2.15d** (17.0 mg, 0.05 mmol), the phosphoric acid (1.1 mg, 0.0012 mmol), and 2-mercaptobenzothiazole (10.0 mg, 0.06 mmol) were dissolved in anhydrous tetrahydrofuran (0.1 mL) and stirred at room temperature for 72 h. The reaction was stopped by removal of the solvent under reduced pressure. Purification with column chromatography using 40/1 to 20/1 DCM/MeOH yielded **2.17** as a clear oil (16.0 mg, 0.032 mmol, 63% yield, 90:10 er). The (*S*) enantiomer was chosen arbitrarily for display. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.78-7.70 (m, 2H), 7.43-7.36 (m, 1H), 7.34-7.27 (m, 1H), 4.24 (d, *J* = 2.7 Hz, 1H), 4.17-4.01 (m, 3H), 3.99-3.81 (m, 4H), 3.52 (td, *J* = 7.2, 2.2 Hz, 2H), 3.39 (dd, *J* = 9.8, 5.1 Hz, 1H), 3.31 (dd, *J* = 9.8, 7.1 Hz, 1H), 2.99-2.88 (m, 1H), 2.53-2.43 (m, 1H), 2.21-2.11 (m, 1H), 1.78-1.68 (m, 1H), 1.64-1.53 (m, 2H), 1.38-1.17 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 179.6, 179.4, 166.2, 152.5, 134.9, 126.2, 124.7, 121.2, 121.1, 74.6, 74.5, 62.5, 61.7, 50.2, 42.6, 39.4, 39.3, 37.9, 36.9, 31.8, 29.2, 27.09, 27.06, 22.6, 14.1. **IR** (thin film, cm^{-1}): 3392, 2926, 2855, 1681, 1426, 1353, 999, 756, 728. **HRMS** (ESI^{+}) Calcd. for $C_{25}H_{34}N_2O_5S_2$ ([M+Na]): 529.1801, Found: 529.1798. **HPLC** (45/55 Hexane/^{i}PrOH, Daicel CHIRALPAK IA): 91:9 er, t_R (minor): 4.416 min, t_R (major): 6.583 min. **$[\alpha]_D$** = -65.2 (c = 0.007, $CHCl_3$). **TLC** (20/1 DCM/MeOH): R_f = 0.5.

Asymmetric monoacylation

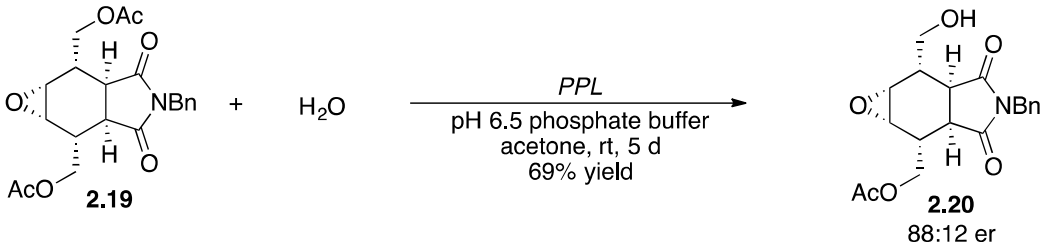


To a $CHCl_3$ (0.7 mL) solution of **2.15b** (50.0 mg, 0.16 mmol), the catalyst (3.9 mg, 0.02 mmol), and Na_2SO_4 (78.3 mg, 0.55 mmol) was added propionic anhydride (22 μL, 0.17 mmol) at room temperature. The reaction was allowed to stir for 5 days and stopped by removal of the solvent under reduced pressure. Purification via column chromatography using a gradient from 1/1 to 1/2 hexanes: ethyl acetate afforded **2.18** as a clear oil (26.0 mg, 0.07 mmol, 44% yield, 14:1 dr, 80:20 er). The (*S*) enantiomer was chosen arbitrarily for display. Note: some epimerization was observed after column chromatography, resulting in the 14:1 dr. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.39-7.35 (m, 2H), 7.33-7.29 (m, 2H), 7.29-7.25 (m, 1H), 4.81 (dd, *J* = 11.4, 6.2 Hz, 1H), 4.65 (s, 2H), 4.58 (dd, *J* = 11.4, 8.8 Hz, 1H), 4.05-3.99 (m, 1H), 3.96-3.89 (m, 1H), 3.48-3.41 (m, 1H), 3.28 (d, *J* = 4.8 Hz, 1H), 3.14-3.08 (m, 2H), 3.00 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.67-2.60 (m, 2H), 2.35 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (150 Mhz, $CDCl_3$): δ 178.9, 177.1, 174.1, 135.3, 128.5, 128.4, 127.8, 63.7, 62.8, 52.4, 51.9, 42.5, 38.9, 38.3, 37.0, 35.1, 27.5, 9.0. **IR** (thin film, cm^{-1}): 3444, 2943, 1694, 1353, 1187, 1082, 1018, 881. **HRMS** (ESI^+) Calcd. for $C_{20}H_{23}NO_6$ ([M+Na]): 396.1418, Found: 396.1418. **HPLC** (65:35 Hexane:^{i}PrOH, Daicel CHIRALPAK IC): 82:18 er, $t_{R\ (major)}$: 16.533 min, $t_{R\ (minor)}$: 29.609 min. **[α]$_D$** = -5.08 (c = 0.01, $CHCl_3$). **TLC** (1:2 hexanes: ethyl acetate): R_f = 0.1.

Enzymatic deacylation



Acetic anhydride (34 µL, 0.36 mmol) was added to a dichloromethane (0.8 mL) solution of **2.16b** (52.0 mg, 0.16 mmol) and DMAP (2.0 mg, 0.02 mmol) at room temperature and the reaction was allowed to stir overnight. The solvent was subsequently removed under reduced pressure and the crude material was purified using column chromatography (1/1 hexanes/ethyl acetate) to obtain **2.19** as a clear oil (50.0 mg, 0.13 mmol, 76% yield). Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 4.70 (ddd, *J* = 11.1, 3.9, 1.2 Hz, 2H), 4.62 (s, 2H), 4.37 (ddd, *J* = 11.1, 6.8, 1.1 Hz, 2H), 3.28 (s, 2H), 2.84-2.77 (m, 2H), 2.40-2.33 (m, 2H), 2.10 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 177.8, 170.7, 135.4, 128.7, 128.1, 64.6, 51.2, 42.4, 36.8, 34.7, 20.8. **IR** (thin film, cm^{-1}): 3648, 3456, 2951, 2359, 1698, 1401, 1235, 1040. **HRMS** (ESI^+) Calcd. for $C_{21}H_{23}NO_7$ ([M+Na]): 424.1367, Found: 424.1349. **TLC** (1:1 hexanes: ethyl acetate): R_f = 0.4.

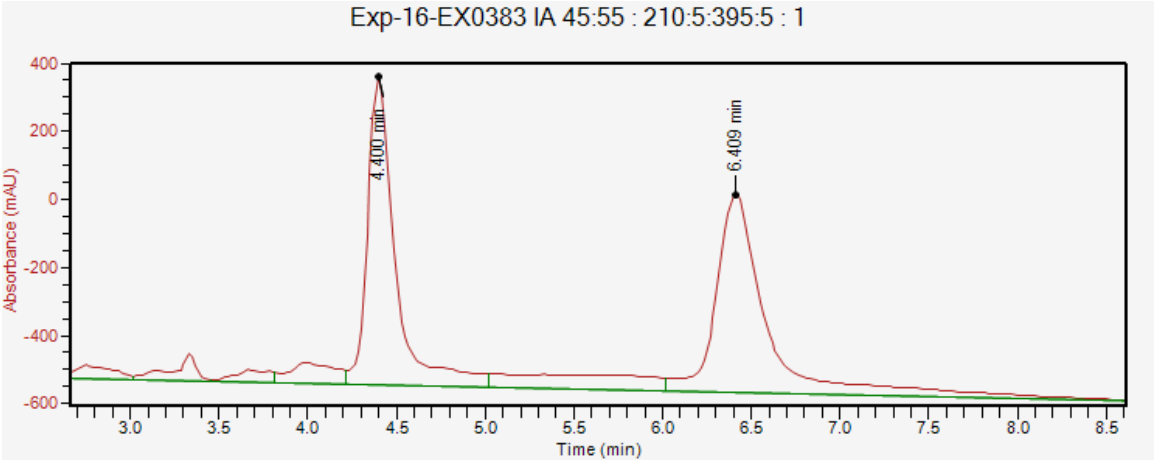


A mixture of **2.19** (50 mg, 0.13 mmol), porcine pancreatic lipase (100 mg), acetone (2.5 mL) and pH 6.5 phosphate buffer (5 mL) was stirred for 5 days at room temperature. Ethyl acetate (5 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The organics were combined, dried with sodium sulfate and concentrated under reduced

pressure. Purification via column chromatography using hexanes/ethyl acetate 1/1 to 1/2 afforded **2.20** as a clear oil (31.0 mg, 0.09 mmol, 69% yield, 88:12 er). The (*S*) enantiomer was chosen arbitrarily for display. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 4.72 (ddd, *J* = 11.1, 3.9, 1.9 Hz, 1H), 4.63 (d, *J* = 1.9 Hz, 2H), 4.42-4.34 (m, 1H), 4.11-4.03 (m, 1H), 4.03-3.94 (m, 1H), 3.29 (q, *J* = 4.6 Hz, 2H), 2.92-2.77 (m, 3H), 2.40-2.33 (m, 1H), 2.28-2.21 (m, 1H), 2.10 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 179.4, 178.0, 170.8, 135.3, 128.8, 128.1, 65.2, 64.6, 51.7, 51.2, 42.5, 38.4, 37.1, 36.9, 36.6, 34.8, 20.8. **IR** (thin film, cm^{-1}): 3502, 2926, 1697, 1400, 1241, 1176, 1037. **HRMS** (ESI^+) Calcd. for $C_{19}H_{21}NO_6$ ([M+Na]): 382.1261, Found: 382.1251. **HPLC** (65:35 Hexane:^{i}PrOH, Daicel CHIRALPAK IC): 88:12 er, $t_{R\,(major)}$: 23.117 min, $t_{R\,(minor)}$: 34.612 min. **$[\alpha]_D$** = +20.9 (c = 0.01, $CHCl_3$). **TLC** (1:1 hexanes: ethyl acetate): R_f = 0.2.

HPLC Traces of Racemic and Optically Active Desymmetrization Products

Compound 2.17



Channel	Ret. Time	Area	Height
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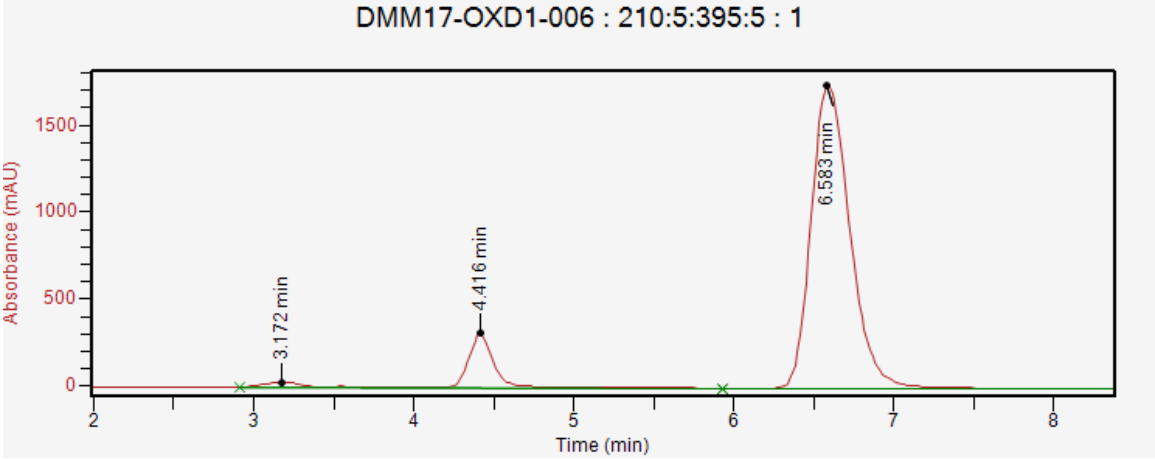
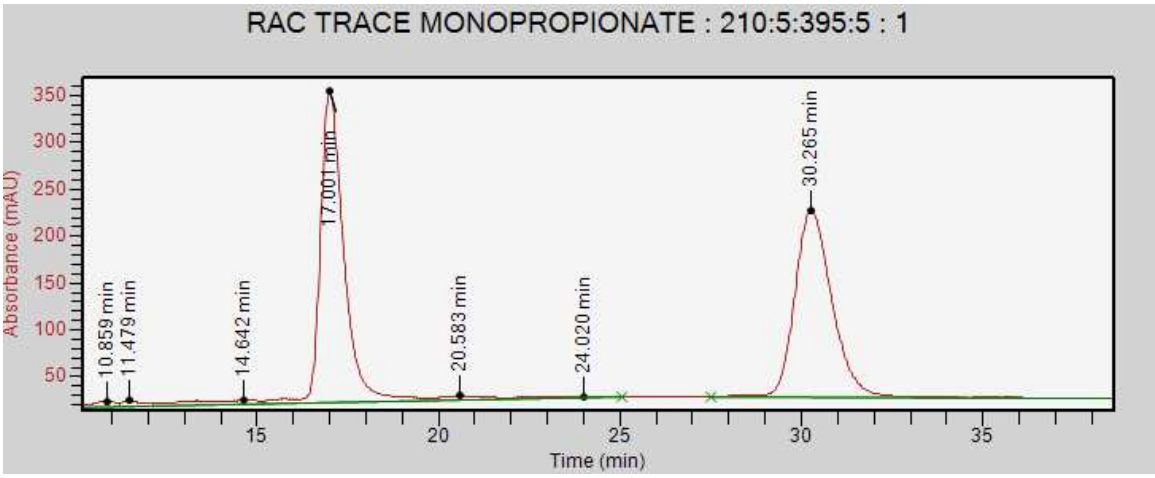
210:5:395:5	6.409 min	11956289.52	584583.69

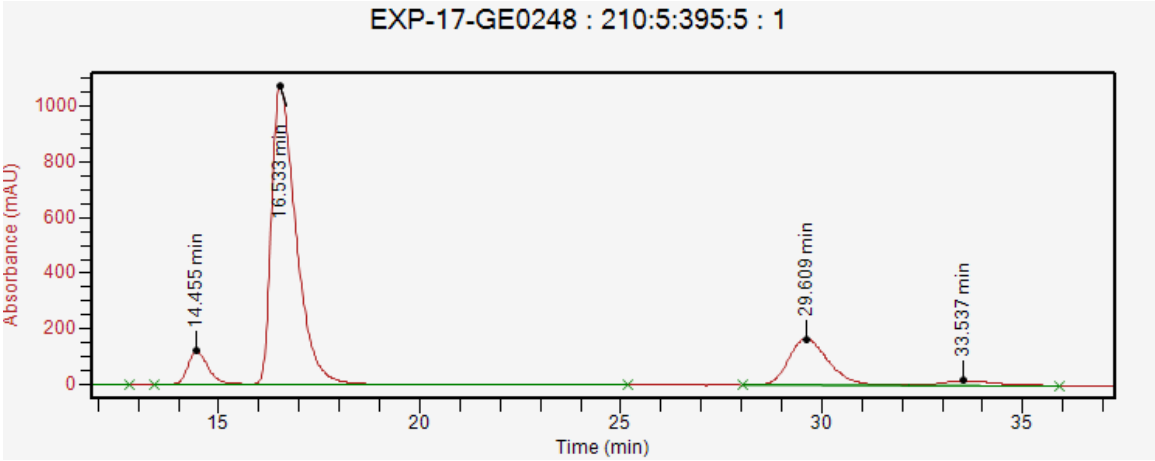


Channel	Ret. Time	Area	Height
210:5:395:5	4.416 min	3342624.28	313171.62
210:5:395:5	6.583 min	29164163.62	1738356.90

Compound 2.18

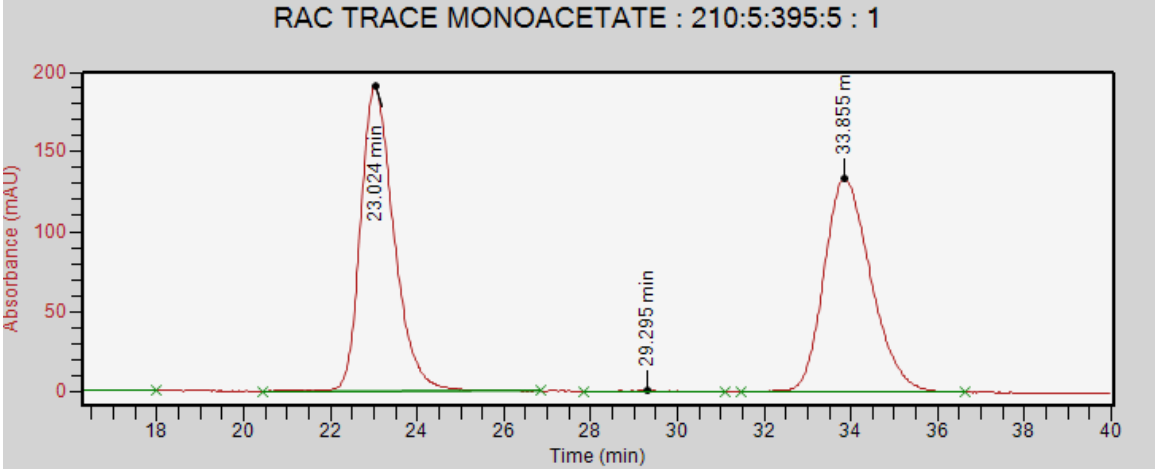


Channel	Ret. Time	Area	Height
210:5:395:5	17.001 min	14950419.41	333050.22
210:5:395:5	30.265 min	14339241.57	198885.42

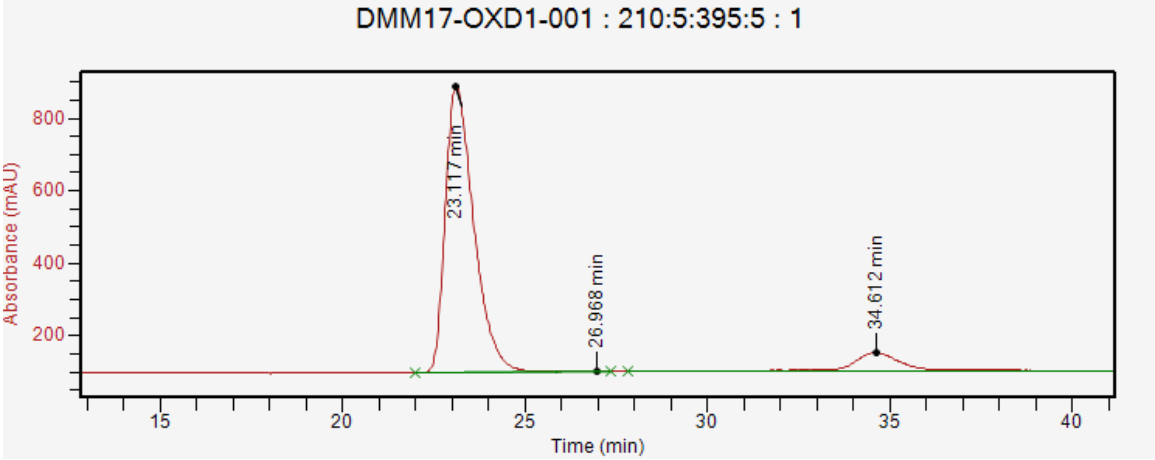


Channel	Ret. Time	Area	Height
210:5:395:5	16.533 min	45878443.13	1074573.49
210:5:395:5	29.609 min	11510821.50	167790.40

Compound 2.20



Channel	Ret. Time	Area	Height
210:5:395:5	23.024 min	10248305.99	191246.18
210:5:395:5	33.855 min	10075514.22	133769.43



Channel	Ret. Time	Area	Height
210:5:395:5	23.117 min	43053094.08	792074.24
210:5:395:5	34.612 min	6096713.01	52065.35

Crystallographic data for compound 2.16d

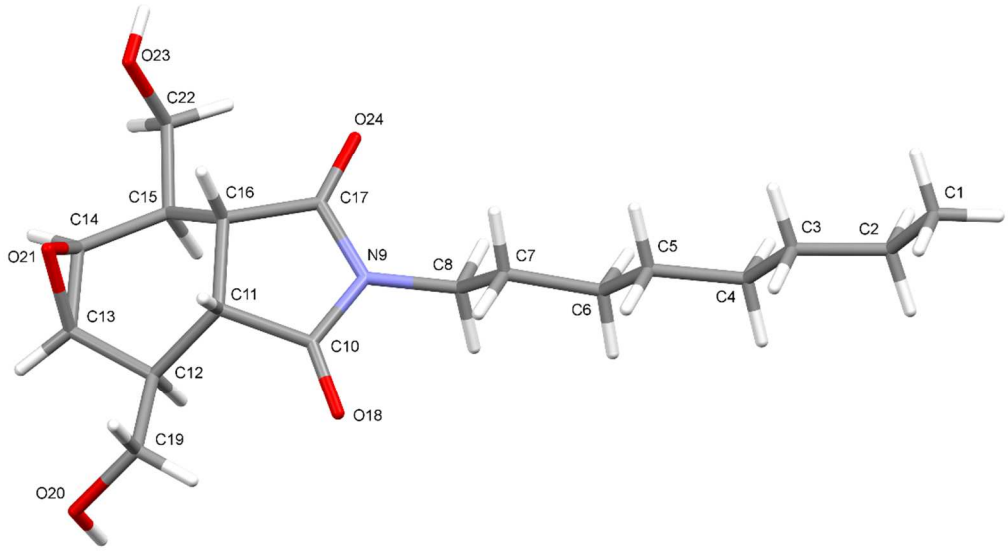


Table 1 Crystal data and structure refinement for 2.16d.

Identification code	x1602003
Empirical formula	$C_{18}H_{29}NO_5$
Formula weight	339.42
Temperature/K	100
Crystal system	orthorhombic
Space group	Pbca
a/Å	5.79580(6)

b/Å	14.35143(15)
c/Å	43.7743(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3641.06(7)
Z	8
ρ_{calc}g/cm^3	1.238
μ/mm^{-1}	0.732
F(000)	1472.0
Crystal size/mm^3	0.262 × 0.189 × 0.036
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	4.036 to 133.198
Index ranges	$-6 \leq h \leq 6$, $-15 \leq k \leq 17$, $-51 \leq l \leq 52$
Reflections collected	40425
Independent reflections	3201 [R_{int} = 0.0298, R_{sigma} = 0.0173]
Data/restraints/parameters	3201/0/226

Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0491, wR_2 = 0.1242
Final R indexes [all data]	R_1 = 0.0638, wR_2 = 0.1336
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.16

Crystal structure determination of [x1602003]

Crystal Data for $C_{18}H_{29}NO_5$ (*M* =339.42 g/mol): orthorhombic, space group Pbca (no. 61), *a* = 5.79580(6) Å, *b* = 14.35143(15) Å, *c* = 43.7743(5) Å, *V* = 3641.06(7) $Å^3$, *Z* = 8, *T* = 100 K, μ(CuKα) = 0.732 mm^{-1}, *Dcalc* = 1.238 g/cm^3, 40425 reflections measured (4.036° ≤ 2Θ ≤ 133.198°), 3201 unique (R_{int} = 0.0298, R_{sigma} = 0.0173) which were used in all calculations. The final R_1 was 0.0491 (I > 2σ(I)) and wR_2 was 0.1336 (all data).

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CHAPTER THREE

HYDROXYLAMINE AS A PRECURSOR FOR NITRENE AND DIIMIDE FORMATION: C−C DOUBLE BOND AZIRIDINATION AND REDUCTION

3.1 Introduction

The reduction of C−C double bonds is an important transformation in organic synthesis. Double bonds are commonly used to build complexity through asymmetric oxidations and alkene functionalization. In this chapter, hydroxylamine is used as a precursor for metal-nitrenoids and diimide. The first part of this chapter covers the initial discovery that hydroxylamine can be used for the aziridination of alkenes in the presence of CO_2, a protecting group, and a rhodium catalyst. The reactivity remains unoptimized, despite significant efforts. During these studies, the reduction of alkenes under similar conditions was observed. The second part of this chapter discusses the *in situ* formation of diimide with the use of hydroxylamine and a protecting group. An initial substrate scope is presented, although some challenges remain. Terminal olefins are reduced in high yields, whereas internal olefins are less reactive. The reduction of terminal alkynes is also possible, albeit at lower yields. Further studies should reveal the mechanism of the reaction and should provide optimize conditions for the less reactive substrates.

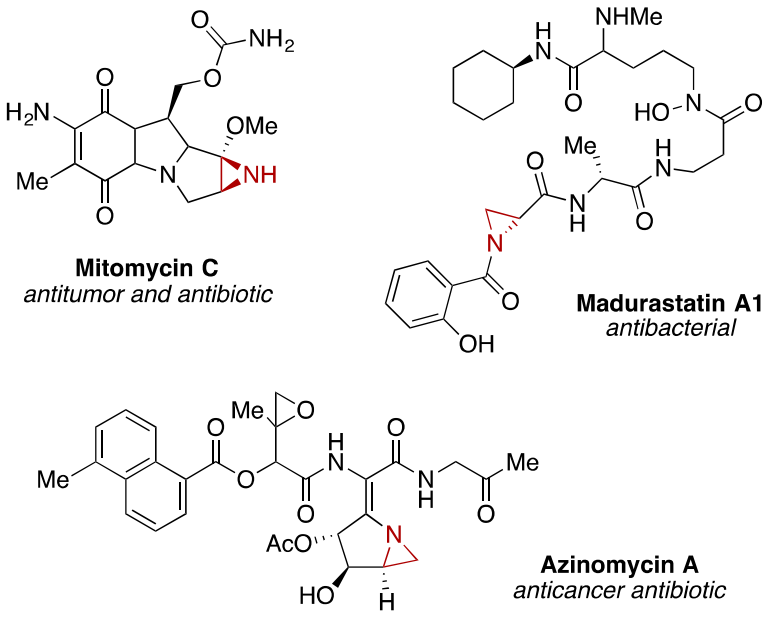
Part I: Aziridination of C−C Double Bonds Using Hydroxylamine as Nitrene Precursor

3.2 Background

3.2.1 Importance of Aziridines

Aziridines constitute the smallest nitrogen containing heterocycle and their existence has synthetic and pharmacological value. A number of aziridine containing natural products hold interesting biological activity.[1] More importantly, medicinal chemists have recognized the utility of this functional group and have incorporated it in many synthetic and semi-synthetic targets.[2] These molecules have been related to antitumor, antibacterial, and antibiotic activities (Scheme 3-1). Thus, the synthesis of aziridines is a topic of interest in the synthetic community.

Scheme 3-1. Aziridine Containing Compounds with Biological Activity



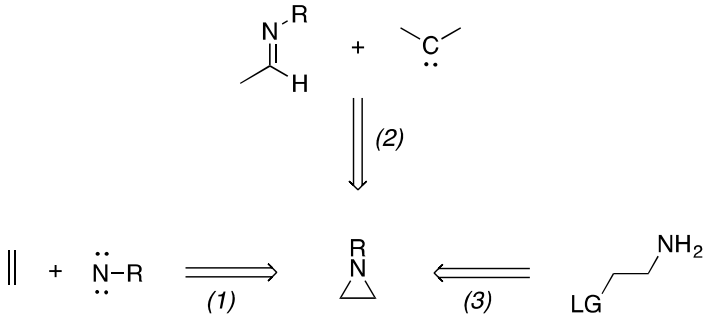
Apart from their biological importance, aziridines are also useful synthetic building blocks due to the reactivity of the strained 3-membered heterocycle. Multiple functionalities can be accessed through aziridine reactivity including amines, amino alcohols, amino acids, etc.[3] Thus,

efficient methods for the generation of aziridines are needed to access different functionalities that are challenging to obtain through other methods.

3.2.2 Synthetic Methods for the Generation of Aziridines

An array of reactions have been developed for the synthesis of aziridines.[4] In general, three current methods exist: (1) the addition of nitrogen to a C−C double bond; (2) the addition of carbon to imines; and (3) the intramolecular cyclization of amines (Scheme 3-2). Of these methods, the addition of nitrogen across a C−C double bond is the only one that does not require the presence of an amine in the starting molecule. This liberty allows for the use of diverse starting materials and thus is more attractive for synthetic chemists.

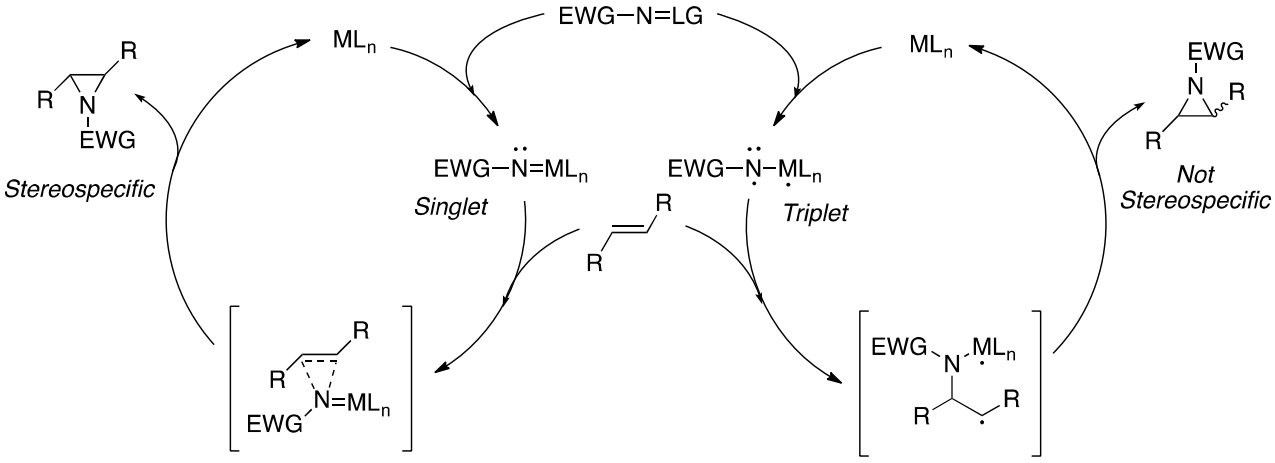
Scheme 3-2. General Transformations for the Synthesis of Aziridines



In this case, two possible nitrogen sources have been utilized. The first and most commonly employed involves the generation of metal nitrenes or nitrenoids. The second is an aza-Michael-initiated ring closure and will not be discussed in this chapter.[5] Nitrenes are reactive intermediates that contain an electron-withdrawing group and a nitrogen atom with four valence electrons. These intermediates are stabilized by hypervalent iodines or a group 7-11 metal. Nitrene precursors include aryl azides, sulfonyl azides, imino iodanes, halo amines, and tosyloxy carbamates. The reactivity of metal nitrenes is still debated, but two conceivable reactive intermediates, singlet and triplet nitrenes, have been proposed. Singlet nitrenes are proposed to

react in a concerted manner, and thus lead to stereospecific reactions. On the other hand, triplet nitrenes are thought to have a stepwise mechanism; no stereospecificity is observed with triplet nitrene reactions (Scheme 3-3).

Scheme 3-3. Proposed Mechanism for the Aziridination of Alkenes via Singlet or Triplet Nitrene Intermediates



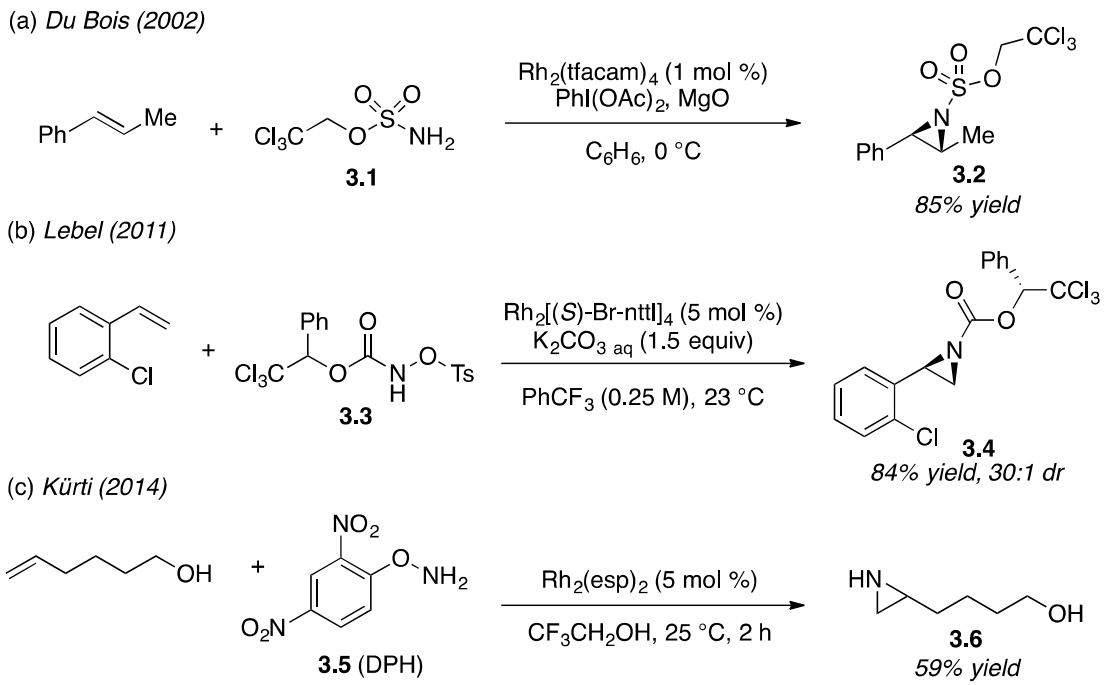
Abramovitch, Yamada, and Breslow studied the use of sulfonamide-derived aryliodanes as nitrene precursors and opened the way for synthetic chemists to utilize this intermediate in aziridination reactions.[6] Later, Du Bois exploited these aryliodanes and utilized it for the synthesis of amines through C−H amination and for the synthesis of protected aziridines through nitrogen transfer to alkenes.[7] In the latter case, sulfamate esters are oxidized in the presence of $PhI(OAc)_2$ and then react with the rhodium catalyst to form the metal-nitrenoid (Scheme 3-4a).[8] This method has been applied extensively for the inter- and intramolecular aziridination of olefins. The sulfonic protecting group can be removed in the presence of zinc.

Lebel and co-workers have developed a different C−H amination/aziridination strategy.[9] In this case, *N*-tosyloxycarbamates are used as nitrene precursors in the presence of a rhodium catalyst (Scheme 3-4b). This method has gained attention since the use of hypervalent iodine

reagents is not required and the only byproduct obtained is potassium tosylate. As is the case with the Du Bois chemistry, protected aziridines are obtained as the final product.

The methods thus far described provide access to protected aziridines and an extra deprotection step is need to obtain the free aziridine moiety that is present in some natural product with biological activity. Although prevalent in nature and pharmaceuticals, the synthesis of free aziridines remains a challenge. Kürti has disclosed the use of *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) for the synthesis of unprotected aziridines (Scheme 3-4 c).[10] Furthermore, the use of hydroxylamine-*O*-sulfonic acids allowed the selective synthesis of free or protected aziridines.[11] Even though these methods are efficient and provide the desired products in high yield, a need for other reactions that deliver free aziridines is still prevalent.

Scheme 3-4. Common Methods for the Synthesis of Aziridines



3.2.3 Challenges and Limitations

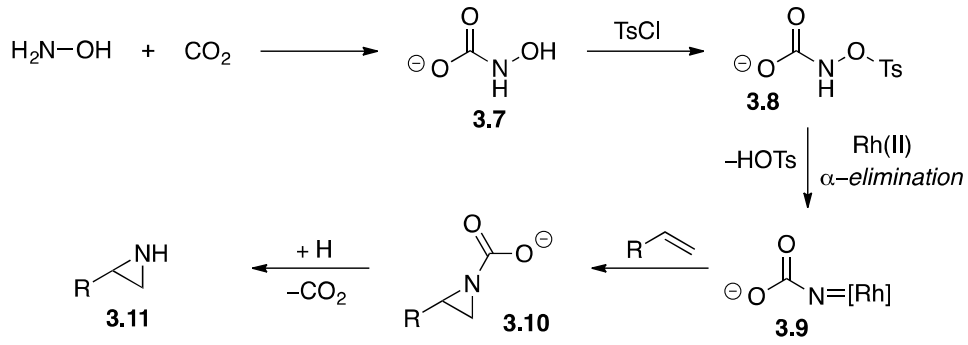
The aziridination of C−C double bonds is still plagued by synthetic challenges and limitations. The most commonly used method utilizes stoichiometric amounts of hypervalent iodine reagents and delivers a full equivalent of iodobenzene as a byproduct. Other methods that do not utilize iodinated reagents require the synthesis and isolation of the nitrene precursor in order to carry out the reaction. Furthermore, the restriction of obtaining protected aziridines requires the deprotection of such molecules with stoichiometric amounts of transition metals. The limited amount of methods for the synthesis of free aziridines impedes the efficient synthesis of complex molecules possessing this functional group.

3.3 Results and Discussion

3.3.1 Proposed Reactivity for the Formation of Free Aziridines

Our efforts towards the synthesis of unprotected aziridines started with the hypothesis outlined in Scheme 3-5. Reaction between free hydroxylamine and carbon dioxide should lead to the *N*-protected hydroxycarbamate **3.7**. Addition of tosyl chloride and an equivalent of base should result in *O*-sulfonyl protected hydroxycarbamate **3.8**. Then, exposure to a rhodium catalyst would lead to formation of the Rh-nitrenoid **3.9** by way of an α-elimination pathway.[12] This species is now available to react with an olefin. Subsequent removal of the CO_2 atmosphere and workup should result in the unprotected aziridine **3.11**.

Scheme 3-5. Proposed Pathway for the Synthesis of Free Aziridines

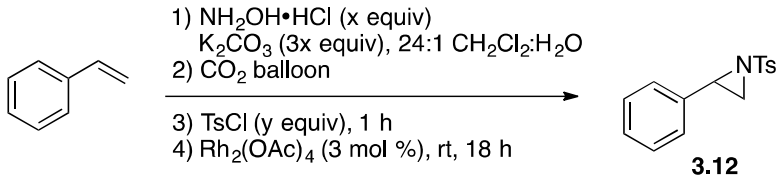


3.3.2 Initial Results and Optimization Experiments

In order to test this hypothesis, we attempted the aziridination of styrene. Using 1 equivalent of hydroxylamine hydrochloride, 1 equivalent of *p*-toluenesulfonyl chloride, and 3 equivalents of potassium carbonate in 20:1 DCM:H_2O under a CO_2 atmosphere, 25% conversion to protected aziridine **3.12** was observed (Table 3-1, entry 1). Although this was a promising result, the expected free aziridine was not observed. In an attempt to learn more about the reaction, a number of control experiments were performed. First, removal of CO_2 or the protecting group (TsCl) completely shut down the reactivity, indicating that both components are

necessary for the formation of the Rh-nitrenoid species (entries 2 and 3). Next, addition of 2 equivalents of TsCl under a nitrogen atmosphere resulted in only 5% conversion to the protected aziridine (entry 4). This result demonstrates that diprotected hydroxylamine (TsNHOTs) is not an active intermediate in the reaction. Finally, addition of previously synthetized *N*-sulfonyl protected hydroxylamine (TsNHOH) with 3 mol % of rhodium acetate dimer under a CO_2 atmosphere led to no product formation (entry 5).

Table 3-1. Initial Result and Control Experiments for the Aziridination of Styrene



3.12

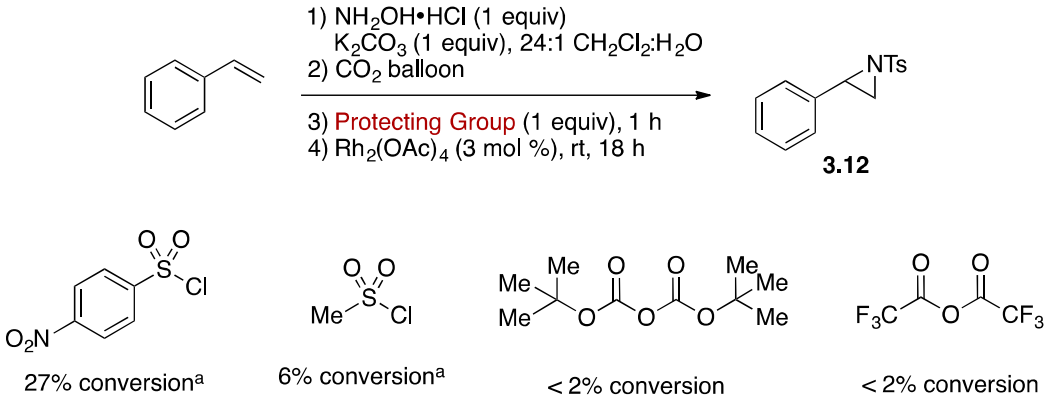
entry	NH_2OH HCl	TsCl	CO_2	conversion (%)[a]
1	1 equiv	1 equiv	balloon	25
2	1 equiv	1 equiv	---	< 2
3	1 equiv	---	balloon	< 2
4	1 equiv	2 equiv	---	5
5[b]	---	---	balloon	< 2

[a]Conversion to product; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures. [b]TsNHOH added directly to the reaction.

With this knowledge, we proceeded to optimize the reaction conditions. First, a protecting group screen was conducted in order to identify if other protecting groups provided better yields than TsCl. Use of the electron-withdrawing *p*-nitrosulfonyl chloride (NsCl) led to 27% conversion to the corresponding protected aziridine (Table 3-2, entry 1). On the other hand, use of methanesulfonyl chloride (MsCl) led to only 6% conversion. The use of anhydrides would be beneficial, since the deprotection of these is more achievable than sulfonyl deprotections. Unfortunately, use of di-tert-butyl dicarbonate (Boc) and trifluoroacetic anhydride (TFA)

completely shut down the reactivity and no product formation could be detected (entries 3 and 4). Moving forward, TsCl was chosen for further optimization.

Scheme 3-6. Protecting Group Screen for the Aziridination of Styrene



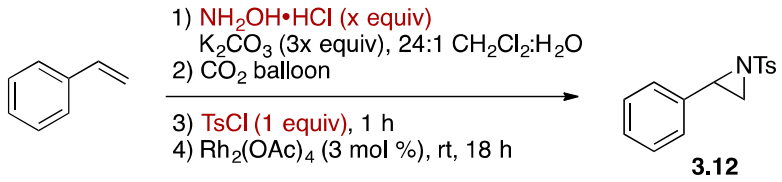
[a]Conversion to product; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures.

Next, we examined the effect of the amount of hydroxylamine and TsCl in the reaction. We started by repeating our optimal conditions of 1 equivalent of hydroxylamine hydrochloride and 1 equivalent of protecting group. A decrease in conversion (15%) was observed, indicating that the first result was not reproducible (Table 3-2, entry 1). Increasing the amount of hydroxylamine hydrochloride to 3 equivalents provided only 9% conversion. Additional amounts of TsCl only afforded an increase to 17% conversion of the aziridination product (entry 3). If the addition of the protecting group was done in two portions, an increase to 27% conversion was observed. Finally, addition of 3 equivalents of hydroxylamine hydrochloride and 4 equivalents of TsCl added in portions led to 59% conversion (entry 5). Unfortunately, when this trial was done again, only 16% conversion was observed (entry 6).

During the execution of these experiments, we noticed that the solutions were highly heterogeneous and we predicted that this heterogeneity was responsible for the inconsistencies in the reaction. In order to improve the solubility, the amount of water was increased. This change

allowed for the use of 3 equivalents of hydroxylamine and 3 equivalents of TsCl leading to 34% conversion to the aziridine (entry 7).

Table 3-2. Effect of the Amount of Reagents in the Aziridination of Styrene



3.12

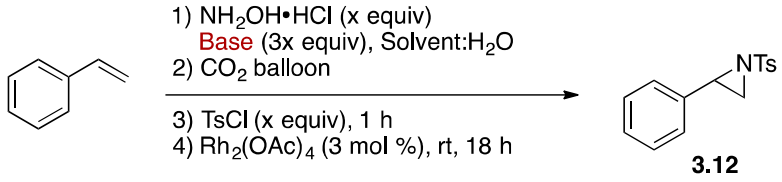
entry	$NH_2OH•HCl$	TsCl	TsCl[a]	conversion (%)[b]
1	1 equiv	1 equiv	---	15
2	3 equiv	1 equiv	---	9
3	3 equiv	3 equiv	---	17
4	3 equiv	1 equiv	1 equiv	27
5	3 equiv	3 equiv	1 equiv	59
6	3 equiv	3 equiv	1 equiv	16
7	3 equiv	3 equiv	---	34

[a]Second addition done 1 hour after first addition. [b]Conversion to product; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures. [c]2:1 CH_2Cl_2:H_2O used as solvent.

Using these optimized conditions, we next examined the effects of base and solvents. We envisioned that a proton source could be needed after the aziridine formation step to obtain the desired unprotected aziridine **3.11**. Thus, Hünigs base was employed instead of sodium bicarbonate, but unfortunately, no product was obtained (Table 3-3, entry 1). The use of tripotassium phosphate as base only afforded 12% conversion to the protected aziridine. Likewise, sodium acetate provided 12% conversion (entry 3). Employing sodium bicarbonate led to 32% conversion under the reaction conditions. Interestingly, if the CO_2 balloon was removed, a similar result was obtained (entry 5). We believe that the CO_2 released from the sodium bicarbonate was enough to carry out the aziridination. However, the results obtained with potassium carbonate were still higher, so the effects of solvent were examined using this base.

A preliminary study of the effect of solvents showed that only chlorinated solvents were effective in the reaction. In order to test if the amount of water was detrimental to the reactivity, we chose polar solvents that could allow a homogeneous solution. Unfortunately, alcoholic solvents could not be employed in this reaction since these resulted in the corresponding sulfonyl protected product. The use of acetonitrile, 1,4-dioxane, acetone, or dimethylformamide provided no product formation (Table 3-4, entries 6-9). However, employing dichloroethane and chloroform, 35% and 30% conversion were obtained, respectively.

Table 3-3. Effects of Base and Solvent in the Aziridination of Styrene



3.12

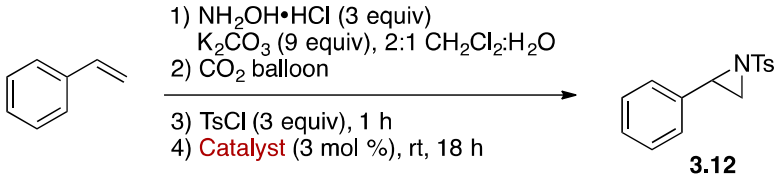
entry	x equiv	base	solvent	solvent:water	conversion (%)[a]
1[b]	1	DIEA	CH_2Cl_2	24:1	< 2
2[b]	1	K_3PO_4	CH_2Cl_2	24:1	12
3	1	NaOAc	CH_2Cl_2	2:1	12
4	3	$NaHCO_3$	CH_2Cl_2	2:1	32
5[c]	3	$NaHCO_3$	CH_2Cl_2	2:1	29
6	1	K_2CO_3	MeCN	2:1	< 2
7	3	K_2CO_3	1,4-dioxane	24:1	< 2
8	3	K_2CO_3	acetone	24:1	< 2
9	3	K_2CO_3	DMF	24:1	< 2
10	3	K_2CO_3	DCE	24:1	35
11	3	K_2CO_3	$CHCl_3$	24:1	30

[a]Conversion to product; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures. [b]2 equivalents of TsCl. [c]No CO_2.

Finally, a catalyst screen was performed to investigate if other metal catalyst could improve the reactivity. A number of rhodium sources were subjected to the reaction conditions, including $Rh_2(esp)_2$, $Rh_2(TFA)_4$, $Rh_2(OPiv)_4$, and $Rh_2(pfb)_4$ (Table 3-4, entries 1-4). Only $Rh_2(OPiv)_4$ afforded any product formation, with 16% conversion to the protected aziridine.

Copper sources, $Cu(acac)_2$ and CuBr, were also tried, since Cu-nitrenoids are precedented,[9a,13] but no aziridine was observed. Furthermore, a silver source was not tolerated under the reaction conditions.[14] Given that the reaction operates under biphasic conditions, a phase transfer catalyst (PTC) was added in addition to the rhodium catalyst (entry 8). Benzyltriethylammonium chloride was subjected to the reaction conditions using a saturated aqueous solution of potassium carbonate. Only 8% NMR yield was obtained, but 27% consumption of styrene was obtained. Based on these results, rhodium acetate dimer, which provided 34% conversion, is the only viable catalyst for the reaction.

Table 3-4. Catalyst Screen for the Aziridination of Styrene



3.12

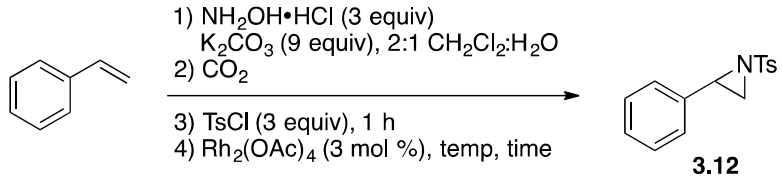
entry	catalyst	conversion (%)[a]
1	$Rh_2(esp)_2$	< 2
2	$Rh_2(TFA)_4$	< 2
3	$Rh_2(OPiv)_4$	16
4	$Rh_2(pfb)_4$	< 2
5[b]	$Cu(acac)_2$	< 2
6[b]	CuBr	< 2
7[b]	AgOTf	< 2
8	TEBAC	8[c]

[a]Conversion to product; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures. [b]1 equiv of NH_2OH HCl was used. [c]^{1}H NMR yield; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with duroquinone as an internal standard.

A number of miscellaneous experiments were also performed to optimize the reaction. Heating the reaction to reflux (40 °C) led to 30% NMR yield (able 3-5, entry 1). Further heating did not seem viable for the solvent mixture, since most of the dichloromethane evaporated under the 40 °C conditions. Furthermore, cooling down the reaction led to significantly lower

conversions. In order to investigate if the performance of the reaction was affected by the addition of reagents, slow additions of the protecting group, the catalyst, or the base were performed, but the yields remained similar or were lowered. Next, 4-dimethylaminepyridine (DMAP) was added to the reaction to facilitate the addition of hydroxylamine to TsCl (entry 2). These conditions completely shut down the reactivity. Finally, the CO_2 pressure was altered to understand the effect on the reactivity (Table 3-5, entry 3). Increasing the pressure to 50 psi for 6 hours and working up the reaction right away provided only returned styrene. However, if 50 psi of CO_2 are applied for only 1 hour and the reaction is then allowed to stir for 18 hours at atmospheric pressure, the reaction afforded 16% of the protected aziridine. This result could be of significance for the elucidation of the mechanism of the reaction. It seems that while CO_2 is needed for the reaction to occur, at some point the CO_2 moiety must leave for the aziridination to take place. Based on the results thus far obtained, CO_2 could be acting as a protecting group for *N*-alkylation to form **3.8** (Scheme 3-5), as initially proposed. However, before aziridine formation can occur, the amine could undergo a second protection with TsCl to incorporate the protecting group observed in the product obtained. Further exploration is necessary to prove this hypothesis and understand the mechanism of the reaction.

Table 3-5. Additive and Pressure Experiments for the Optimization of the Aziridination of Styrene



3.12

entry	temp (°C)	additive	CO_2	time	yield (%)[a]
1	40	---	15 psi (balloon)	18 h	30
2	25	DMAP	15 psi (balloon)	18 h	< 2
3	25	---	50 psi	6 h	< 2
4	25	---	50 psi for 1 h	19 h	16

[a] ^{1}H NMR yield; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with duroquinone as an internal standard.

Throughout the course of these studies, a byproduct could be observed under some reaction conditions. Noticeably, when $Rh_2(pfb)_4$ was employed (Table 3-4, entry 4), 55% NMR yield of this byproduct was observed. Upon further investigation, this product was determined to be ethyl benzene, which would result from the hydrogenation of styrene. The second part of this chapter is focused on the occurrence of this reaction and its optimization.

Part II: Reduction of C−C Unsaturated Bonds Through Diimide Generation from Hydroxylamine

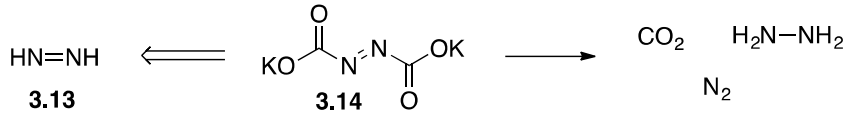
3.4 Background

3.4.1 Structure and Stability of Diimide

The existence of diimide (**3.13**) was first discovered by the decomposition of dipotassium azodicarboxylate salt **3.14**, which produced carbon dioxide, nitrogen, and hydrazine (Scheme 3-7a).[15] The production of hydrazine and nitrogen was later explained through the disproportionation of *cis*- and *trans*-diimide (Scheme 3-7b).[16] The structure of diimide has been studied thoroughly in order to better understand its stability. Three possible structures exist for diimide: *cis*-diimide **3.15**, *trans*-diimide **3.16**, and 1,1-diimide **3.17**; 1,1-diimide is generated and trapped by the thermal decomposition of carbamoyl azide.[17]

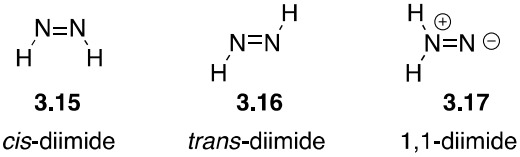
Scheme 3-7. Structure of Diimide

(a) *Diimide and It's Discovery*



(b) *Disproportionation of Diimide*

(b) *Structure of Diimide*



Although three potential structures exist, stereochemical studies have shown that the reduction of C−C unsaturated bonds is performed by *cis*-diimide.[18] *Trans*-diimide is 47-73 kcal/mol more stable than *cis*-diimide,[19] which would indicate that *trans*-diimide should be

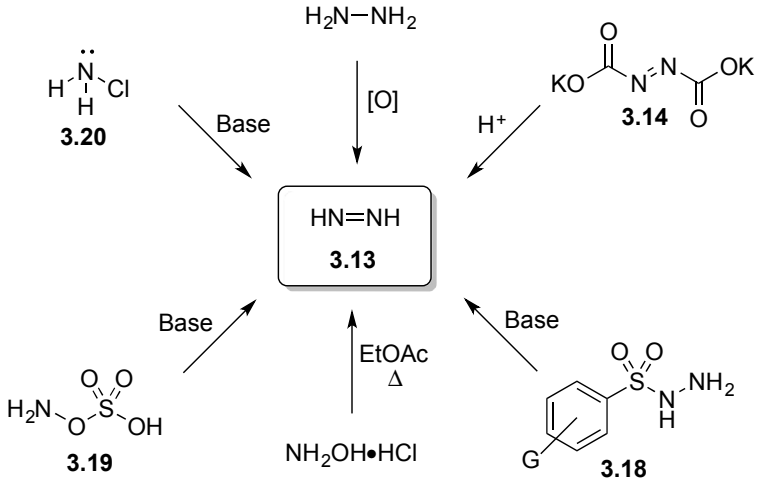
prevalent. The inversion barrier for *trans*- to *cis*-diimide is 46-66 kcal/mol.[20] In solution, *trans*-diimide is proposed to isomerize through a fast deprotonation-protonation event, which would allow for the formation of *cis*-diimide and thus the reduction of C−C double bonds.

3.4.2 Generation and Reactivity of Diimide

Multiple methods have been developed for the efficient generation of diimide.[21] The most common method is the oxidation of hydrazine. This transformation can be performed using oxygen or hydrogen peroxide and a catalyst. Copper[22], iron[23,24], mercury[23], periodates[25], and sulfur[26] have been used in catalytic or stoichiometric amounts to aid in the oxidation of hydrazine (Scheme 3-8). Another common method is the acid promoted decarboxylation of the dipotassium azodicarboxylate salt **3.14**.[27] This salt is prepared from potassium hydroxide and azodicarboxamide,[28] and has been known to detonate when exposed to direct light.[29] The base promoted decomposition of arylsubstituted sulfonylhydrazides **3.18** has also been employed for the generation of diimide. Like in the case of the azodicarboxylate salt, this compound must be synthetized and isolated before use, limiting the practicality of the method.

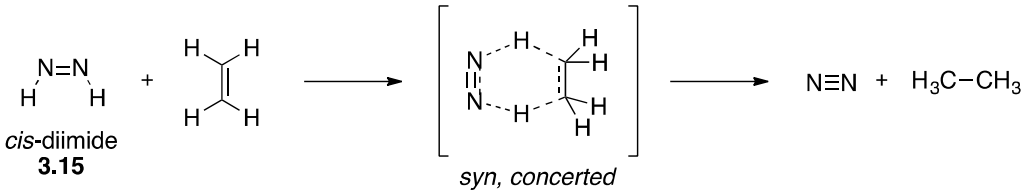
A number of methods utilize hydroxylamine as a diimide precursor. The first is the reaction of hydroxylamine with ethyl acetate in the presence of heat.[30] Furthermore, the hydroxylamine derived hydroxylamine-*O*-sulfonic acid **3.19** reacts with base to form diimide.[31] Finally, chloramine **3.20** can be reacted with base to form diimide.[32] These are some of the most commonly used methods to generate diimide, but others have been shown as well. Heat is necessary in a number of cases.

Scheme 3-8. Methods for the Generation of Diimide



The proposed mechanism for the reduction of C−C unsaturated bonds is outlined in Scheme 3-9. The reduction step is proposed to happen in a cyclic transition state with *syn*, concerted addition in order to obtain the alkane and nitrogen. This step is proposed to be fast, with the formation of diimide being the rate-determining step of the reaction.[21] In some hydrazine oxidation cases, low concentrations of acetic acid accelerate the reaction, presumably by aiding the *trans*-*cis* equilibrium.

Scheme 3-9. Proposed Mechanism for Diimide Reductions



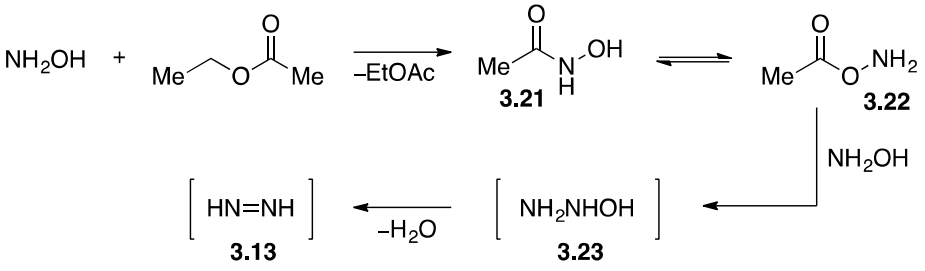
The relative reactivity of diimide has been thoroughly studied.[21] In general, alkynes react faster with diimide than alkenes, but then there is competitive reactivity once the alkene is formed. Strained alkenes are reduced more efficiently than unstrained alkenes. Furthermore, *trans*-olefins react faster than *cis*-olefins, and less substituted alkenes are better substrates than

higher substituted alkenes. This reactivity pattern allows for some selectivity in molecules with mono-and tri substituted alkenes; the mono-substituted olefin reacts with the more substituted alkene remains untouched. Finally, although some examples of aryl aldehydes and imines have been shown to react with diimide, polarized bonds (C=O, C=N, CN, etc.) are slow to react or unreactive under diimide reduction conditions.

3.4.3 Hydroxylamine as a Diimide Precursor

The generation of diimide from hydroxylamine was discovered by Wade, et. al. in 1982.[30] This report disclosed the reaction between hydroxylamine and ethyl acetate to form diimide and carry out the reduction of C−C double bonds. The reaction must be heated to 100 °C for the reduction to occur. The proposed mechanism for this reaction involves the addition of hydroxylamine to ethyl acetate, releasing ethanol (Scheme 3-10). Hydroxyamide **3.21** is proposed to be in equilibrium with the *O*-acylated species **3.22**. **3.22** can then react with a second equivalent of hydroxylamine to form hydroxyhydrazine **3.23**. This intermediate has been shown to lead to diimide through loss of water.[33]

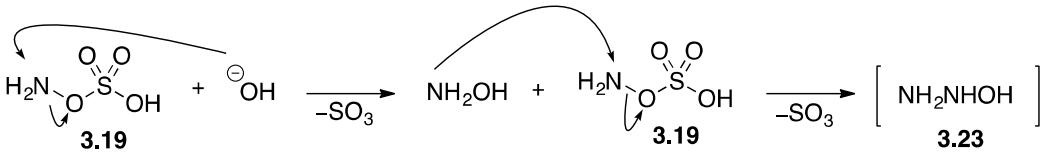
Scheme 3-10. Proposed Mechanism for the Formation of Diimide Through the Reaction of Hydroxylamine and Ethyl Acetate



The use of hydroxylamine-*O*-sulfonic acid **3.19** as diimide precursor has also been reported.[31] In this case, **3.19** needed to be synthetized and isolated before the reaction could take

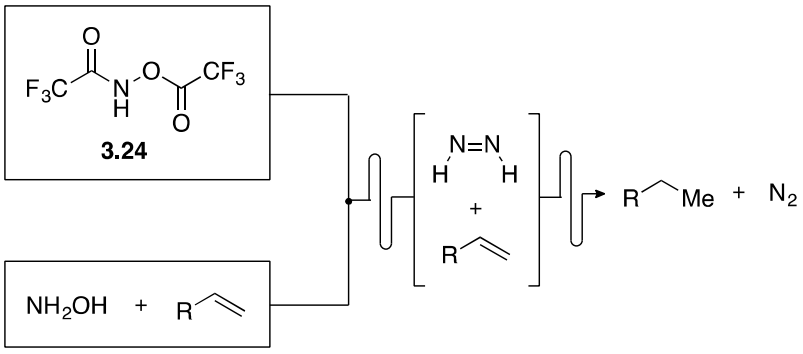
place.[34] A similar mechanism to the ethyl acetate case is proposed for this method. Hydroxylamine generated from the reaction of hydroxide and **3.19**, reacts with another equivalent of **3.19** to generate hydroxyhydrazine **3.23** (Scheme 3-11). Through loss of water, diimide is generated.

Scheme 3-11. Mechanism for the Diimide Generation Using Hydroxylamine-*O*-Sulfonic Acid



More recently, a continuous flow methods for the generation of diimide was disclosed.[35] In this case, hydroxylamine reacts with *N*,*O*-bisfluoroacetylhydroxylamine **324** to generate hydroxyhydrazine. This reaction requires 1.5 equivalents of **3.24** and 5 equivalents of hydroxylamine hydrochloride. Continuous flow at high temperatures and pressures are employed.

Scheme 3-12. Continuous Flow Method for the Generation of Diimide



3.4.4 Advantages and Limitations of Diimide Reductions

The most common reduction method of C−C unsaturated bonds is catalytic hydrogenation. However, diimide reductions are advantageous for a number of reasons. First, the use of hydrogen gas and expensive pressure equipment is not necessary. Catalysts for diimide

reductions are usually copper based, unlike the precious metals used in catalytic hydrogenations.[36] Second, diimide reductions do not reduce certain functionalities and this may provide a level of selectivity that other methods do not. For example, benzoyl groups stay intact under diimide conditions. Likewise, N−O, O−O, and N−N bonds are not reduced by diimide.[21] Finally, under most diimide reduction conditions, ketones, aldehydes, and imines remain untouched. This functional group tolerance is not usually present with other hydrogenation methods.

Although diimide reductions are useful, a number of limitations still exist. For example, a large excess of diimide precursors most be used in most reactions. This is most likely due to the known disproportionation of diimide to nitrogen and hydrazine. Another significant limitation is the use of dangerous starting materials. Hydrazine is a suspected carcinogen, while the dipotassium azodicarboxylate salt has been shown to detonate violently in the presence of sunlight. When these compounds are not employed, the necessity of isolating the diimide precursor or the use of harsh conditions (heat, acid) limits the method.

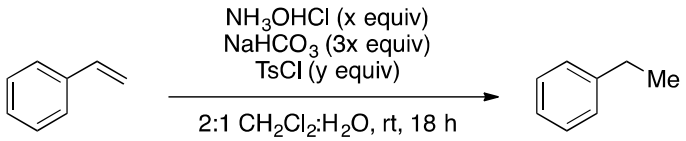
Here, the use of hydroxylamine and a protecting group in order to access diimide reductions at room temperature is presented. This method utilizes cheap, readily accessible starting materials, and a simple set-up. The results presented are preliminary, but show the utility of this method for the reduction of C−C unsaturated bonds through diimide generation.

3.5 Results and Discussion

3.5.1 Initial Studies and Optimization

The investigations for diimide formation began with the observation that ethyl benzene was formed under the aziridination conditions in the presence of $Rh_2(pfb)_4$ (Table 3-6, entry 1). Removal of the rhodium catalyst leads to a decrease in NMR yield (33%, entry 2). However, an increase in the amount of hydroxylamine hydrochloride and protecting group increased the yield to 75%. Unfortunately, remaining styrene made it impossible to isolate the reduced product. In an effort to obtain full consumption of styrene, and with the knowledge of previous use of hydroxylamine for diimide generation, we studied the effects of excess hydroxylamine (entry 4) and excess TsCl (entry 5). While excess hydroxylamine led to a decrease in yield, excess TsCl was completely detrimental to the reaction. If TsCl is removed from the reaction, no reduction is observed.

Table 3-6. Initial results for the Diimide Reduction of Styrene



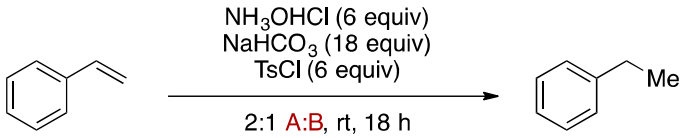
entry	catalyst	$NH_2OH•HCl$	TsCl	yield (%)[a]
1	$Rh_2(pfb)_4$	3 equiv	3 equiv	55
2	---	3 equiv	3 equiv	33
3	---	6 equiv	6 equiv	75
4	---	6 equiv	3 equiv	43
5	---	3 equiv	6 equiv	5
6	---	3 equiv	---	< 2

[a] ^{1}H NMR yield; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with duroquinone as an internal standard.

Next, the effect of solvent on the conversion of the reaction was explored. As it was the case in the aziridination reaction, alcoholic solvents were not viable since only alcohol protection

is observed. The use of polar aprotic solvents (THF, MeCN, and 1,4-dioxane) completely shut down the reaction. The use of non-polar solvents led to similar results, only toluene afforded trace amounts of product. Water has been shown to have adverse effects in some diimide reduction methods,[27] so an exploration of other polar solvents in place of water was performed. The use of 2:1 DCM:DMF led to only trace amounts of reduced product. Using 2:1 DCM:THF, howerver, yielded 20% ethyl benzene. Motivated by this result, 1,4-dioxane was employed as the second solvent. Unfortunately, only trace amounts of product were observed. These results show that water may be the most viable solvent to solubilize hydroxylamine and the base.

Table 3-7. Solvent Screen for the Diimide Reduction of Styrene



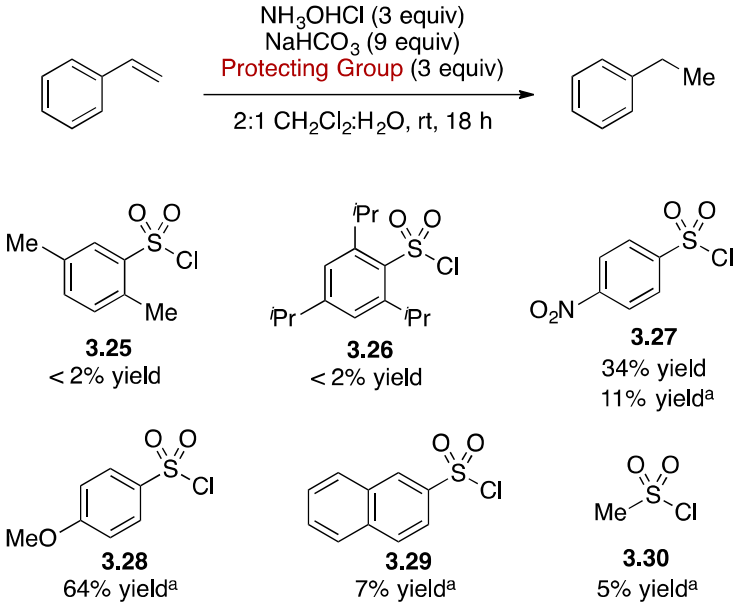
entry	solvent A	solvent B	NMR yield (%)[a]
1	EtOH	H_2O	< 2
2	THF	H_2O	< 2
3	MeCN	H_2O	< 2
4	1,4-dioxane	H_2O	< 2
5	Et_2O	H_2O	< 2
6	PhCl	H_2O	5
7	PhMe	H_2O	< 2
8	hexanes	H_2O	< 2
9	CH_2Cl_2	DMF	5
10[b]	CH_2Cl_2	THF	20
11	CH_2Cl_2	1,4-dioxane	5

[a] ^{1}H NMR yield; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with duroquinone as an internal standard. [b]Conversion related to styrene.

In order to further optimize the reaction, a protecting group screen was performed. We noticed that in the reactions with TsCl a significant amount of insoluble white solid crashed out of the reaction. Upon further inspection, the white solid was identified as the sodium salt of tosic

acid. This hydrolysis reaction could be a result of the highly basic conditions employed in the reaction. The generation of this salt could also be the reason why full consumption of styrene is not observed. In an attempt to prevent this reactivity, sterically hindered sulfonyl chloride derivatives were employed (Scheme 3-13). No reaction was observed with 2,5-dimethylsulfonyl chloride and 2,4,6-triisopropylsulfonyl chloride as protecting groups. The napthylsulfonyl chloride **3.29** led to only 7% yield of ethyl benzene. Next, the electronics of the protecting groups were explored. Using 4-methoxysulfonyl chloride, 64% yield was obtained. Furthermore, the use of 4-nitrosulfonyl chloride afforded 34% yield using 3 equivalents of hydroxylamine and 11% yield using 6 equivalents of hydroxylamine. The decrease in yield is consistent with increased hydrolysis or addition of hydroxylamine to the more reactive protecting group. Finally, employing methanesulfonyl chloride led to only trace amounts of product.

Scheme 3-13. Protecting Group Scheme for the Diimide Reduction of Styrene



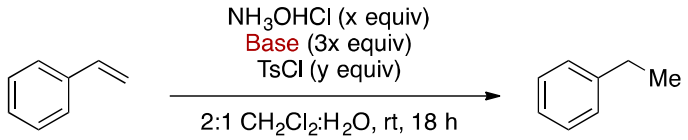
[1]H NMR yield; determined by analysis of 400 or 600 MHz [1]H NMR spectra of unpurified mixtures with duroquinone as an internal standard.[a]6 equiv $NH_2OH \bullet HCl$ and protecting group, 18 equiv $NaHCO_3$.

The effects of base were examined next. First, a 10 M solution of sodium bicarbonate was used instead of solid sodium bicarbonate. This seemingly insignificant change was detrimental to the reaction, possibly because of the hydrolysis obtained under the more basic conditions. Likewise, significant decrease in yield was obtained with NaOH, probably for the same reason. Interestingly, switching the counter ion of the bicarbonate salt (potassium bicarbonate) afforded only 20% yield. Since some of these reactions afforded only hydrolysis product, we decided to use an amine base in place of the water. Thus, a 2:1 DCM:pyridine mixture was employed as the solvent syntem, but no reaction was obtained. Furthermore, using 18 equivalents of pyridine in 2:1 DCM:MeCN also led to no product formation. In an effort to control the hydrolysis of TsCl, a screen of buffers was performed. Using a range of pH 5.6 to 12 buffers, no reduction product was obtained. This is an unexpected result and further investigation is required in order to provide and explanation. Nevertheless, employing 12 equivalents of sodium bicarbonate provided 75% yield of ethyl benzene and only trace amounts of styrene.

At this point, we decided to try changing the counter ion of the hydroxylamine salt to see if it had an effect in the reactivity. Using the sulfate salt with 12 equivalents of sodium bicarbonate led to 75% yield of ethyl benzene and full consumption of styrene. The use of this salt results in the generation of sodium sulfate as byproduct, which is a drying agent. The detrimental effects of water could be improved in this case, with sodium sulfate trapping some of the water and restricting the hydrolysis of tosyl chloride. For the exploration of the substrate scope, the sulfate salt was employed.

Table 3-8. Base Screen and Use of Hydroxylamine Sulfate

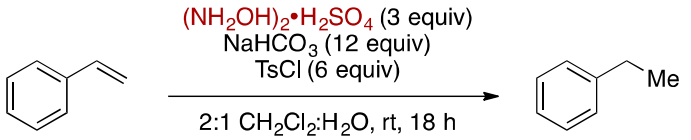
(a) *Base Screen*



entry	NH_2OH•HCl	base	NMR yield (%)[a]
1[b]	3 equiv	10M $NaHCO_3$	< 2
2	6 equiv	NaOH	25
3	6 equiv	$KHCO_3$	19
4[c]	6 equiv	pyridine	< 2
5[d]	6 equiv	pyridine	< 2
6[c]	6 equiv	pH 8 buffer	< 2
7[c]	6 equiv	pH 10 buffer	< 2
8[c]	6 equiv	pH 12 buffer	< 2
9	6 equiv	$NaHCO_3$ (12 equiv)	75

[a] ^{1}H NMR yield; determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of unpurified mixtures with duroquinone as an internal standard. [b] 5 equiv of TsCl. [c] 2:1 CH_2Cl_2:base. [d] 2:1 CH_2Cl_2:MeCN.

(b) *Hydroxylamine Sulfate Salt*



75% NMR yield

3.5.2 Reaction Scope

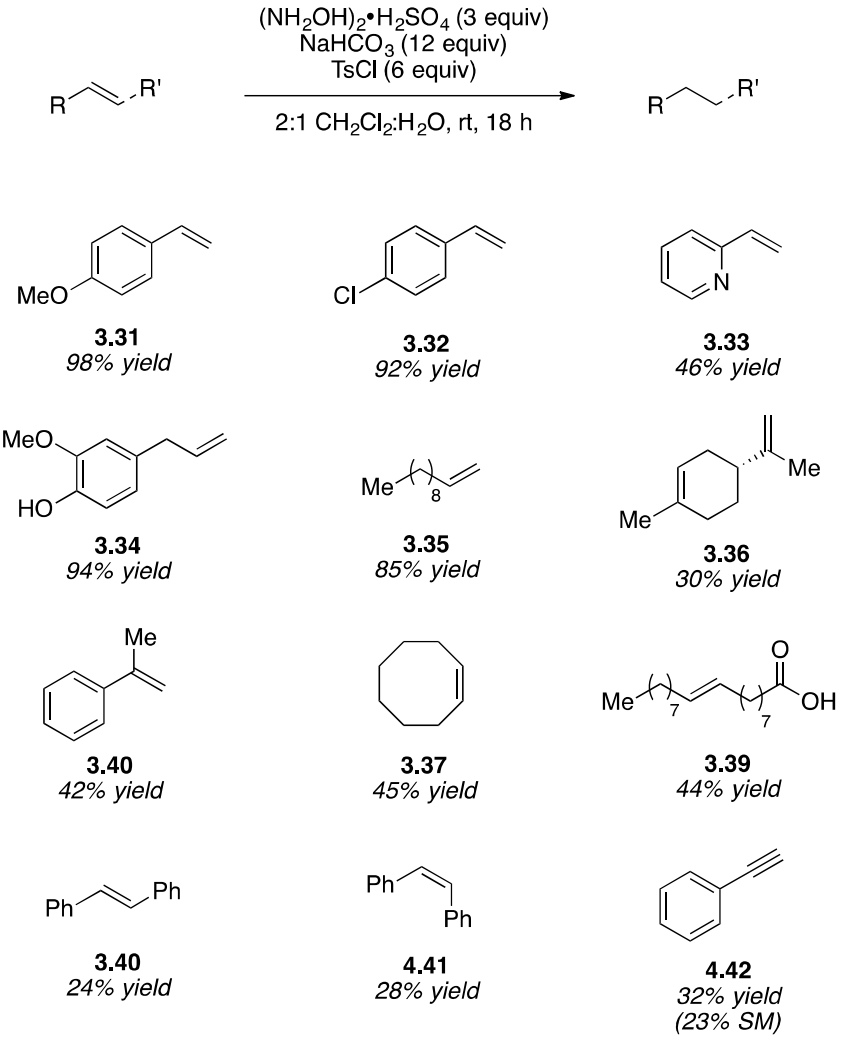
With these optimized conditions a preliminary substrate scope was explored (Scheme 3-14). We started by exploring the reactivity of other styrene derivatives. The more electron-rich 4-methoxy styrene **3.31** provided 98% yield of the reduced product. Halogen substituents were also tolerated and reacted in high yields. Furthermore, 2-vinyl pyridine **3.33** resulted in 46% yield of the reduction product with full consumption of the starting material. We believe the starting material could be polymerizing under the reaction conditions. Aliphatic terminal olefins were also

tolerated. Phenol **3.34** was reduced in 94% yield. Likewise, 1-undecane was obtained in 85% yield from the reduction of 1-undecene **3.35**. Looking at more complex substrates, the terminal olefin of (*S*)-(−)-Limonene was reduced with a 30% yield, whereas the internal, tertiary olefin remained untouched. Finally, the reduction product α-methyl styrene **3.37** was obtained in 42% yield.

We next examined the reactivity of internal olefins. Octane was obtained in 45% yield from octane **3.37** and no remaining starting materials were observed. Likewise, oleic acid was reduced with 44% yield and only trace amounts of oleic acid were detected. Exploring the more stabilized *trans*- and *cis*-stilbene, only 24 and 28% yields were obtained of the reduced products, respectively. Finally, the reaction conditions allowed for the reduction of phenylacetylene **4.43** to obtain ethyl benzene in 32% yield. In this case, 6 equivalents of hydroxylamine and 12 equivalents of tosyl chloride were necessary. While no styrene was observed, 23% of phenylacetylene remained at the end of the reaction.

It should be noted that with the exception of *trans*- and *cis*-stilbene, and phenylacetylene, the starting materials were consumed under the reaction conditions, even in the cases where the yields were low. Switching to hydroxylamine hydrochloride did not change this result and afforded similar or worse yields. Further investigation is necessary to draw any conclusions about the decomposition of these substrates.

Scheme 3-14. Preliminary Substrate Scope for the Diimide Reductions

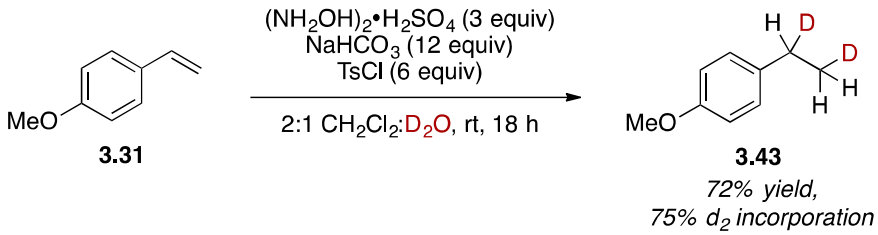


[1]H NMR yield; determined by analysis of 400 or 600 MHz [1]H NMR spectra of unpurified mixtures with duroquinone as an internal standard.

Previous work involving hydroxylamine in the reductions with diimide has provided some mechanistic explanation for the reactivity observed. While major mechanistic investigations still need to be conducted, a deuterium incorporation experiment was explored (Scheme 3-15). Using 4-methoxy styrene under the optimized reaction conditions and employing deuterated water as the second solvent, 72% NMR yield of ethyl benzene with 75% d_2 incorporation was observed.

Hydrogen-deuterium exchange in hydroxylamine explains the result observed, indicating that the diimide protons come directly from hydroxylamine.

Scheme 3-15. Deuterium Incorporation Experiment



3.6 Conclusions

The access of metal-nitrenoids and diimide through the use of hydroxylamine is a useful discovery for the aziridination and reduction of alkenes, respectively. The use of readily accessible reagents is beneficial to the isolation of commonly used precursors for the generation of these molecules. The ease of reaction set up elevates the importance for these methods in organic transformations.

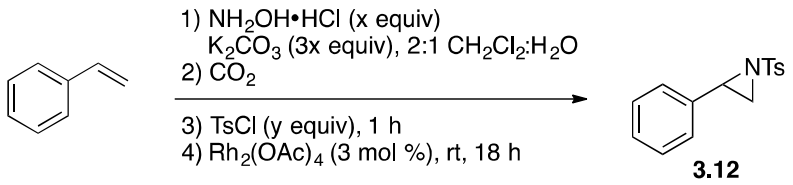
Using a CO_2 balloon and a Rh(II) catalyst, aziridination of styrene was optimized to 34% NMR yield. A screen of base, protecting group, catalyst, and CO_2 pressures could not provide increased yields of the aziridinated product. Further exploration is required to effectively optimize this reaction that has the potential to be a useful method for the access of protected aziridines.

Finally, the reduction of C−C unsaturated bonds was achieved using hydroxylamine sulfate, sodium bicarbonate, and tosyl chloride. This method provides for a simple, safe, and efficient generation of diimide starting from hydroxylamine. Further studies will expand the scope and provide insight into the mechanism of the reaction.

3.7 Experimental Details

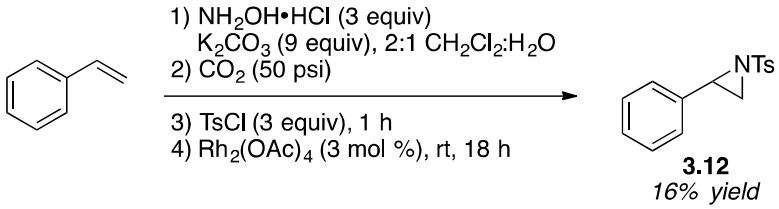
Methods: All reactions were carried out in glassware that had been purged with nitrogen. Proton and carbon magnetic resonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded on either a Bruker model DRX 400 or 600 spectrometer (^{1}H-NMR at 400 or 600 MHz and ^{13}C-NMR at 100 or 150 MHz) with solvent resonance as the internal standard (^{1}H-NMR: $CDCl_3$ at 7.26 ppm and ^{13}C-NMR: $CDCl_3$ at 77.0 ppm). ^{1}H-NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, qt = quintet, and m = multiplet), coupling constant (Hz) and integration. 0.1 equiv of duroquinone or 2,4,6-trimethoxybenzene were used as internal standards for ^{1}H NMR yields. The yields reported are of unpurified materials. Thin layer chromatography (TLC) was performed on Sorbtech plastic-backed 0.20 mm silica gel 60 plates. Visualization was accomplished with UV light and potassium permanganate (KMnO4) solution, followed by heating. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Yields are reported herein for a specific experiment and as a result may differ slightly from those found in the schemes, which are averages of at least two experiments.

Materials: Nitrogen was dried by passage through anhydrous calcium sulfate with 3% cobalt chloride as indicator (commercial Drierite). Solvents were purged with nitrogen and purified under a positive pressure of dry nitrogen by a SG Waters purification system: dichloromethane (EMD Millipore), diethyl ether (EMD Millipore), THF (EMD Millipore), and toluene (EMD Millipore) were passed through activated alumina columns. All other reagents and solvents were purchased from commercial sources and used as received.



General Procedure for the Aziridination of Styrene (Tables 3-1 to 3-5)

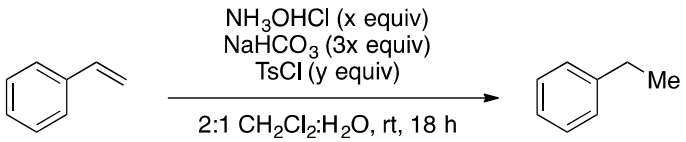
See tables for specific reagent amounts and conversions. Hydroxylamine hydrochloride (1-6 equiv) and base (3-18 equiv) were dissolved in 2:1 solvent A: solvent B (3.6 ml) and stirred for 10 min under positive pressure of nitrogen. The flask was then equipped with a CO_2 ballooon and the solution was purged for 5-10 min. The needle was left in the headspace and the protecting group (1-6 equiv) was added. The reaction was allowed to stir for 1 h. The catalyst (3 mol %) was then added, followed by addition of styrene (1 equiv). The reaction was allowed to stir at room temperature (40 °C for table 3-6, entry 1) for 18 h with the CO_2 balloon still attached to the flask. After this time, the balloon was removed and water and DCM were added. The layers were separated and the aqueous layer was extracted with DCM (2 x 2ml). The organics were combined, dried with sodium sulfate, filtered and concentrated. See tables for conversion details. The spectral data was identical to that previously reported for **3.12**:[37] ^{1}H NMR (400 or 600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.33-7.30 (m, 2H), 7.30-7.24 (m, 2H), 7.23-7.18 (m, 2H), 3.78 (dd, *J* = 7.2, 4.5 Hz, 1H), 2.98 (d, *J* = 7.2 Hz, 1H), 2.43 (s, 3H), 2.39 (d, *J* = 4.5 Hz, 1H).



3.12
16% yield

Procedure for the Aziridination of Styrene under CO_2 Pressure (Table 3-6, entry 4)

NH_2OH•HCl (33.4 mg, 0.48 mmol) and K_2CO_3 (199 mg, 1.44 mmol) were added to a test tube equipped with a stir bar and dissolved in 2:1 DCM:H_2O (2.4 ml). The test tube was introduced into a Fischer Porter Tube and sealed. The chamber was pressurized to 50 psi using a CO_2 tank and the reaction was allowed to stir for 30 min. The pressure was released and TsCl was added (91.5 mg, 0.48 mmol). The tube was sealed and pressurized to 50 psi. The reaction was allowed to stir for 1 hour. Then, the pressure was released and the solution was stirred for 20 minutes. After this time, TsCl (91.5 mg, 0.48 mmol) was added, followed by addition of $Rh_2(OAc)_4$ (6.37 mg, 0.01 mmol) and styrene (55 μL, 0.48 mmol). The test tube was removed from the Fischer Porter tube and sealed with a septa. The reaction was allowed to stir at room temperature for 18 h. DCM and water were added and the layers separated. The aqueous layer was extracted with DCM (2 x 2 mL) and the organics were combined, dried with sodium sulfate, filtered, and concentrated to afford **3.12** in a green oil mixture (16% ^{1}H NMR yield).



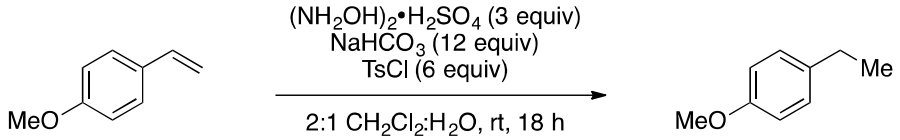
General Procedure A for the Diimide Reduction of Styrene (Tables 3-6 to 3-8)

The hydroxylamine salt (3-6 equiv) and base (9-18 equiv) were dissolved in 2:1 solvent A: solvent B (3.6 ml) and stirred for 10 min (a vent needle was used to avoid pressure build-up). Styrene was then added followed by immediate addition of the protecting group (3-6 equiv). The

reaction was allowed to stir for 18 h, in which time a white precipitate formed. The solid was filtered off using Celite® and the filtrate was dried with sodium sulfate and concentrated to afford ethyl benzene in a crude mixture (see tables for yield details). The spectral data was in agreement with literature values.[38] **^{1}H NMR** (400 or 600 MHz, $CDCl_3$): δ 7.33-7.24 (m, 2H), 7.23-7.14 (m, 3H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H).

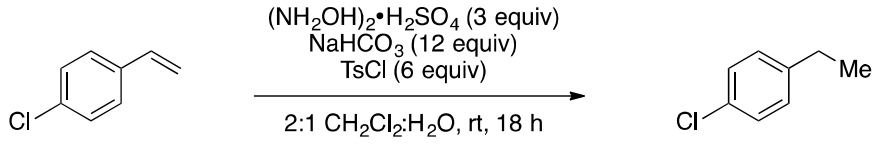
General Procedure B for the Diimide Reduction

$(NH_2OH)_2H_2SO_4$ (355 mg, 2.16 mmol) and $NaHCO_3$ (723 mg, 8.64 mmol) were dissolved in 2:1 DCM:H_2O (3.6 ml) and stirred for 10 min (a vent needle was used to avoid pressure build-up). The substrate (0.72 mmol) was then added followed by immediate addition of TsCl (823 mg, 4.32 mmol). The reaction was allowed to stir for 18 h, in which time a white precipitate formed. The internal standard (0.072 mmol) was added. The solid was filtered off using Celite® and the filtrate was dried with sodium sulfate and concentrated to afford the product in a crude mixture.



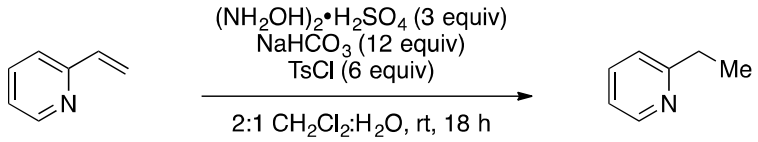
3.31 *98% yield*

1-ethyl-4-methoxybenzene: The title compound was synthetized following general procedure B with the use of 4-methoxystyrene **3.31** (97 μL, 0.72 mmol) and was obtained in 98% yield. The spectral data was in agreement with literature values.[39] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.2 Hz, 2H), 6.84 – 6.79 (m, 2H), 3.77 (s, 3H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H).



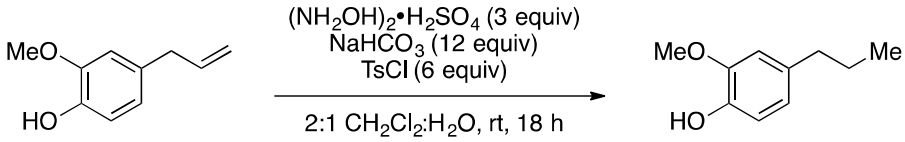
3.32 *92% yield*

1-ethyl-4-chlorobenzene: The title compound was synthetized following general procedure B with the use of 4-chlorostyrene **3.32** (100 mg, 0.72 mmol) and was obtained in 92% yield. The spectral data was in agreement with literature values.[40] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.14 – 7.09 (m, 2H), 2.61 (d, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 2.0 Hz, 3H).



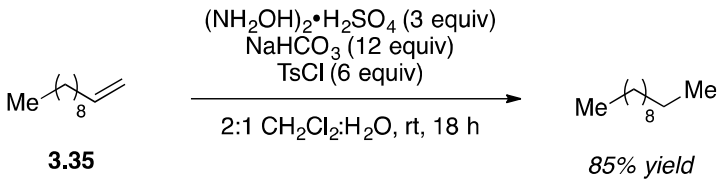
3.33 *46% yield*

2-ethylpyridine: The title compound was synthetized following general procedure B with the use of 2-vinylpyridine **3.33** (78 μL, 0.72 mmol) and was obtained in 46% yield. The spectral data was in agreement with literature values.[41] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (t, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.31 (dd, *J* = 11.6, 8.0 Hz, 2H), 3.19 (q, *J* = 7.6 Hz, 2H), 1.43 (t, *J* = 2.0 Hz, 3H).



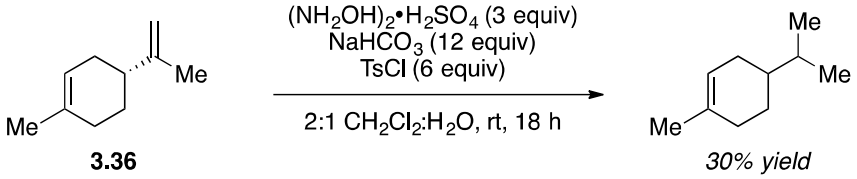
3.34 *94% yield*

2-methoxy-4-propylphenol: The title compound was synthetized following general procedure B with the use of eugenol **3.34** (110 μL, 0.72 mmol) and was obtained in 94% yield. The spectral data was in agreement with literature values.[41] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 7.8 Hz, 1H), 6.73 – 6.62 (m, 2H), 3.87 (s, 3H), 2.56-2.49 (m, 2H), 1.67-1.54 (m, 2H), 0.93 (t, *J* = 2.0 Hz, 2H).



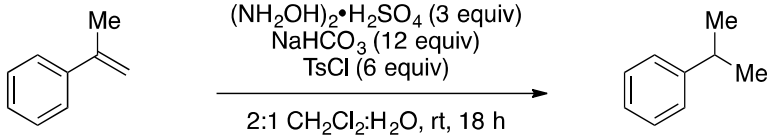
3.35 *85% yield*

Undecane: The title compound was synthetized following general procedure B with the use of 1-undecene **3.35** (0.15 mL, 0.72 mmol) and was obtained in 85% yield. The spectral data was in agreement with literature values.[42] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.25 (s, 16H), 0.87 (t, *J* = 6.9 Hz, 6H).



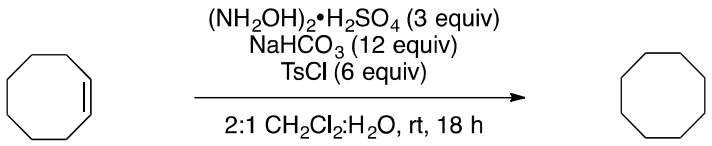
3.36 *30% yield*

(*R*)-4-isopropyl-1-methylcyclohex-1-ene: The title compound was synthetized following general procedure B with the use of (*R*)-limonene **3.36** (0.12 mL, 0.72 mmol) and was obtained in 30% yield. The spectral data was in agreement with literature values.[41] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.69 (t, *J* = 1.6 Hz, 1H), 2.43 (d, *J* = 10.9 Hz, 4H), 2.13-1.85 (m, 4H), 1.64 (s, 3H), 0.87 (t, *J* = 7.0Hz, 6H).



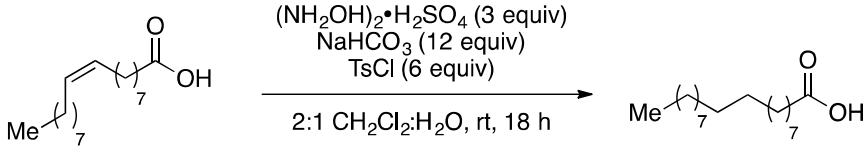
3.37 *42% yield*

Isopropylbenzene: The title compound was synthetized following general procedure B with the use of α-methylstyrene **3.37** (94 μL, 0.72 mmol) and was obtained in 42% yield. The spectral data was in agreement with literature values.[43] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51-7.12 (m, 5H), 2.95-2.81 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 6H).



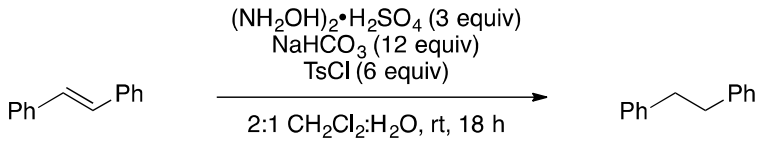
3.38 *45% yield*

Cycloctane: The title compound was synthetized following general procedure B with the use of octane **3.38** (94 μL, 0.72 mmol) and was obtained in 45% yield. The spectral data was in agreement with literature values.[41] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.51 (s, 16H).



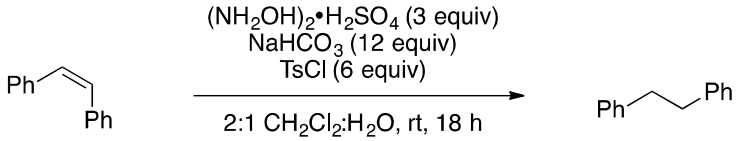
3.39 *44% yield*

Dotriacontanoic acid: The title compound was synthetized following general procedure B with the use of oleic acid **3.39** (0.23 mL, 0.72 mmol) and was obtained in 94% yield. The spectral data was in agreement with literature values.[41] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.66-1.57 (m, 2H), 1.41 – 1.14 (m, 25H), 0.87 (t, J = 6.8 Hz, 3H).



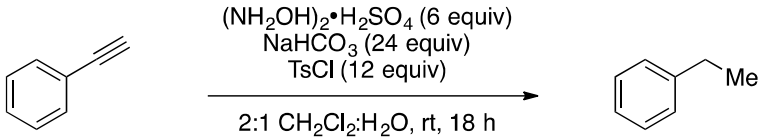
3.40 *24% yield*

1,2-diphenylethane: The title compound was synthetized following general procedure B with the use of *trans*-stilbene **3.40** (130 mg, 0.72 mmol) and was obtained in 24% yield. The spectral data was in agreement with literature values.[44] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 10H), 2.92 (s, 4H).



3.41 *28% yield*

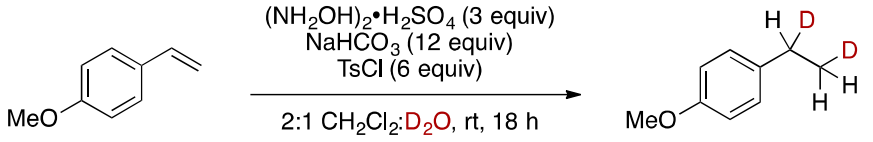
1,2-diphenylethane: The title compound was synthetized following general procedure B with the use of *cis*-stilbene **3.41** (130 mg µL, 0.72 mmol) and was obtained in 28% yield. The spectral data was in agreement with literature values.[44] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 10H), 2.92 (s, 4H).



3.42 *32% yield*

Ethylbenzene: The title compound was synthetized following general procedure B with the use of phenylacetylene **3.42** (79 µL, 0.72 mmol), $(NH_2OH)_2•H_2SO_4$ (709 mg, 4.32 mmol), $NaHCO_3$ (1.45 g, 17.3 mmol), TsCl (1.65 g, 8.64 mmol), and 2:1 DCM:H_2O (7.2) and was obtained in 32% yield. The spectral data was in agreement with literature values.[38] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.24 (m, 2H), 7.23-7.14 (m, 3H), 2.66 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H).

Deuterium Incorporation Experiment



3.31 **3.43**
72% yield,
75% d_2 incorporation

3.43 was synthetized following general procedure B with the use of 4-methoxystyrene **3.31** (97 µL, 0.72 mmol), $(NH_2OH)_2•H_2SO_4$ (355 mg, 2.16 mmol), $NaHCO_3$ (723 mg, 8.64 mmol), TsCl (823 mg, 4.32 mmol), and 2:1 DCM:D_2O (7.2) and was obtained in 72% yield, 75% d_2

incorporation . **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.2 Hz, 2H), 6.84 – 6.79 (m, 2H), 3.77 (s, 3H), 2.58 (q, *J* = 7.6 Hz, 1.23H), 1.20 (t, *J* = 7.6 Hz, 2.25H).

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