

**NOVEL APPLICATIONS OF DONOR–ACCEPTOR CYCLOPROPANES AND DEAROMATIZATION
TOWARDS THE EXPEDIENT SYNTHESIS OF HIGHLY SUBSTITUTED CARBOCYCLES**

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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
2017

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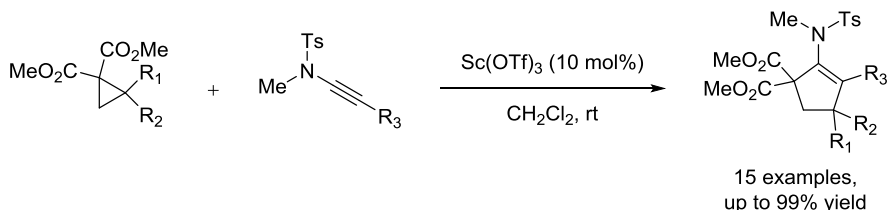
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ABSTRACT

William Daniel Mackay: Novel Applications of Donor–Acceptor Cyclopropanes and Dearomatization towards the Expedient Synthesis of Highly Substituted Carbocycles
(Under the direction of Jeffrey S. Johnson)

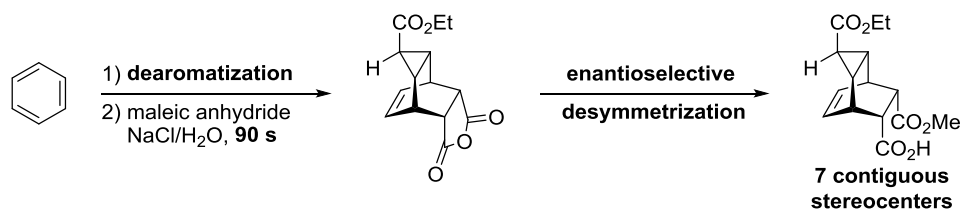
I. Lewis Acid Catalyzed (3+2)-Annulations of Donor–Acceptor Cyclopropanes and Ynamides.

The $\text{Sc}(\text{OTf})_3$ -catalyzed (3+2)-annulation of donor–acceptor cyclopropanes and ynamides is described, providing the corresponding cyclopentene sulfonamides in good to excellent yield. Deprotection and hydrolysis of the resulting cyclopentenenesulfonamides delivers 2,3-substituted cyclopentanones with high diastereoselectivity.



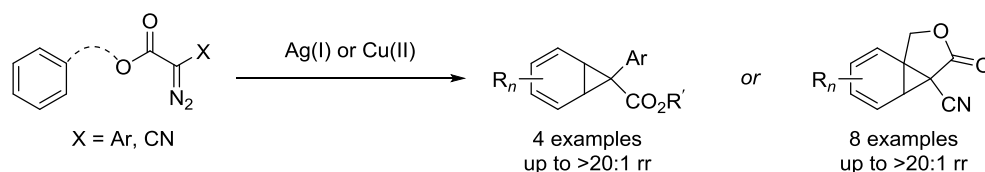
II. Kinetic Separation and Asymmetric Reactions of Norcaradiene Cycloadducts: Facilitated Access via H_2O -Accelerated Cycloaddition.

We exploit the Buchner reaction to access 1,2-disubstituted cyclohexadiene synthons (norcaradienes), which participate in H_2O -accelerated cycloaddition with dienophiles to provide cyclopropyl-fused [2.2.2]-bicyclooctene derivatives in good yields. Regioisomeric mixtures can be kinetically separated exploiting different reaction rates in Diels–Alder reactions. *meso*-Diels–Alder products may be enantioselectively desymmetrized, providing highly substituted cyclohexanes with up to seven contiguous stereocenters.



III. The Development of Regioisomerically Enriched Buchner Products for Use as Cyclohexadienyl Synthetic Intermediates.

We have investigated two conceptual methods to generate highly regioisomerically enriched norcaradienyl intermediates through arene cyclopropanation. Intermolecular Buchner reaction of aryl diazoacetates under either thermolysis or silver(I) catalysis provide expedient routes to single regioisomeric norcaradienes, in some cases favoring the least sterically encumbered site of cyclopropanation. Intramolecular Buchner reaction of benzyl cyanodiazooacetates allow for the site-selective cyclopropanation of the tethered arene, and the installation of an activated cyclopropane for downstream functionalization. Both methods generate norcaradienes that are amenable to further transformations to generate highly stereochemically complex carbocyclic products.



ACKNOWLEDGEMENTS

First of all, I would like to thank my family who has helped me develop as an individual over the years. I could not have completed this program without the love and support of all my family members.

I would especially like to thank my wife, Kelsey, whose sacrifices for me have allowed me to develop professionally and individually. For all of the days that we only spent just one or two waking hours together, for all of the vacations that were only taken in our minds, for all of the time you have spent without a dog: these moments will not be forgotten. My love for you increases each day, and despite the hardships that you were put through these past four years, know that when I saw you each night, all of my stress from the day subsided, and your smile made everything better. I could not have been as successful in my time here without you.

I would also like to thank all of the Johnson group members—past and present—who have assisted in my training, through assistance with revising manuscripts and presentations, through helping me prepare for my preliminary candidacy exam, and through sharing knowledge, catalysts, and reagents. I would like to provide special mention to the following former members for their contributions to my development: Dung Do: for his patience and mentorship as I began my graduate studies, and for telling me why all of my ideas during my first year were terrible, and teaching me better ways to think about solving problems. Robert Sharpe: for healthy discussions about chemistry, Disney, and college football, and who provided an excellent role model for what kind of chemist that I should strive to become. Guy Goodman: for always being willing to discuss anything, and for being the group historian, and also for allowing me to share the Clemson football

experience at Death Valley with you. Lexi Akeyson: for being a hard-working undergraduate mentee who helped me develop as a teacher and a mentor, and allowing me the proud moment of listening to you effectively talk about the silver Buchner project for the presentation to your class.

Last, I would like to express my sincere gratitude to my PI, Jeff Johnson. Thank you for affording me the opportunity to learn and develop under your tutelage. Throughout the synthetic community, your name garners respect for your work, and through my time in your group I have found that that respect is well-deserved for your creativity, industriousness, and continuation to support your students to become the best that they can. Your leadership has allowed me to see the world in new and unique ways. You have given me the freedom explore non-conventional reactivity and the opportunity to address challenging and significant problems in organic chemistry, and for that I am forever grateful. I could not have chosen a better advisor for my time in graduate school.

Dear Kelsey:

For all the sacrifices that have been made.

For all the time that has been shared.

For all the compassionate love that is had.

For the promising future yet to unfold.

For all the good times and bad.

Forever, for you.

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LIST OF ABBREVIATIONS AND SYMBOLS

°C	degrees Centigrade
(TsNH) ₂	bis-toluenesulfonylhydrazine
[α] _D	specific rotation
¹³ C NMR	carbon nuclear magnetic resonance
¹ H NMR	proton nuclear magnetic resonance
2,3-(CH ₂ O ₂)Ph	piperonyl
2-OMePh	2-methoxyphenyl
3,5-CF ₃ -C ₆ H ₃	3,5-bis-(1,1,1-trifluoromethyl)phenyl
4-ClPh	4-chlorophenyl
4-MePh	4-methylphenyl
4-NMe ₂ Ph	4- <i>N,N</i> -dimethylaminophenyl
4-OMePh	4-methoxyphenyl
Å	Angstrom
A _{1,3} strain	allylic 1,3-strain
Ac	acetyl
Ac ₂ O	acetic anhydride
acc	acceptor
Ad	adamantyl
Ag	silver
AgPF ₆	silver(I) hexafluorophosphate
AgSbF ₆	silver(I) hexafluoroantimonate
AgSTRIP	silver(I)((1 <i>r</i> ,5 <i>aS</i> ,10 <i>r</i>)-1,10-bis(2,4,6-triisopropylphenyl)-4,5,6,7-tetrahydrodiindeno[7,1- <i>de</i> :1',7'- <i>fg</i>][1,3,2]dioxaphosphocin-12-olate 12-oxide)
AIBN	azobisisobutyronitrile

Al	aluminum
Al(O ^{<i>i</i>} Pr) ₃	aluminium isopropoxide
AlCl ₃	aluminum trichloride
Ar	aryl
B	boron
B(OMe) ₃	trimethyl borate
BBr ₃	boron tribromide
BF ₄ ⁻	tetrafluoroborate
Bn	benzyl
Br	bromine
br s	broad singlet
Bu	butyl
Bu ₃ SnH	tributyltin hydride
C	carbon
c	concentration
C ₁₀ H ₈	naphthalene
C ₅ H ₁₁	<i>n</i> -pentyl
C ₆ H ₁₃	<i>n</i> -hexyl
C ₆ H ₆	benzene
C ₈ H ₁₇	<i>n</i> -octyl
Ca	calcium
CaH ₂	calcium hydride
calcd	calculated
CAM	ceric ammonium molybdate
CCl ₃	1,1,1-trichloromethyl

CCl ₄	carbon tetrachloride
CD ₃ OD	methanol-D ₄
CDCl ₃	chloroform-D
Celite	diatomaceous earth
CF ₃	1,1,1-trifluoromethyl
CH ₂ (OMe) ₂	dimethoxymethane
CH ₂ Cl ₂	methylene chloride
CHCl ₃	chloroform
CHT	cycloheptatriene
Cl	chlorine
Cl ₃ CCOCCl ₃	hexachloroacetone
cm ⁻¹	wavenumbers
CN	nitrile
Co	cobalt
CO ₂	carbon dioxide
CO ₂ Ad	adamantyl ester
CO ₂ Bn	benzyl ester
CO ₂ C ₈ H ₁₇	<i>n</i> -octyl ester
CO ₂ Et	ethyl ester
CO ₂ Me	methyl ester
CoCp ₂	cobaltocene
CONHTs	<i>N</i> -(toluenesulfonyl) amide
Cp	cyclopentadienyl
Cu	copper
Cu(hfacac) ₂	cuprous hexafluoroacetoacetate

CuCl ₂	cuprous chloride
CuSO ₄	cuprous sulfate
CuSO ₄ •5H ₂ O	cuprous sulfate pentahydrate
δ	chemical shift
Δ	heat
d	days
d	doublet
D	deuterium
D–A	donor-acceptor
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
decomp	decomposition
DKR	dynamic kinetic resolution
dm	decimeter
DMAD	dimethylacetylene dicarboxylate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMSO	dimethylsulfoxide
don	donor
dq	doublet of quartets
dr	diastereomeric ratio

dt	doublet of triplets
DyKAT	dynamic kinetic asymmetric transformation
EDA	ethyl diazoacetate
EDG	electron donating group
equiv	equivalents
er	enantiomeric ratio
ESI ⁺	electrospray ionization
Et	ethyl
Et ₂ O	diethyl ether
Et ₃ N	triethylamine
EtAlCl ₂	ethyl dichloroaluminate
etc.	et cetera
EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron withdrawing group
F	fluorine
Fe	iron
Fe(TPP)Cl	5,10,15,20-tetraphenyl-21H,23H-porphine iron(III) chloride
FeCl ₂	ferrous chloride
FeCl ₃	ferric chloride
FeI ₂	ferrous iodide
FeSO ₄ •7H ₂ O	ferrous sulfate heptahydrate
FT	Fourier transform
gem	geminal
h	hours

H	hydrogen
H ⁺	proton or generic acid source
H ₂	dihydrogen
H ₂ O	water
H ₂ SO ₄	sulfuric acid
H ₃ N _(l)	liquid ammonia
HCl	hydrochloric acid
HF	hydrogen fluoride
Hf	hafnium
Hf(OTf) ₄	hafnium(IV) trifluoromethanesulfonate
Hg	mercury
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
hν	electromagnetic irradiation
Hz	Hertz
I	iodine
I ₂	diiodide
ⁱ Pr	isopropyl
IR	infrared
<i>J</i>	coupling constant
K	potassium
K ₂ CO ₃	potassium carbonate
K _a	dissociation constant
kcal	kilocalories

KMnO ₄	potassium permanganate
KOH	potassium hydroxide
L	ligand
LA	Lewis acid
LiAlH ₄	lithium aluminum hydride
LiBH ₄	lithium borohydride
LiEt ₃ BH	lithium triethylborohydride (Super Hydride)
LiSPh	lithium thiophenolate
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet
<i>m</i>	<i>meta</i>
M+H	protonated molecular ion
mAU	milli-absorbance units
Me	methyl
Me ₂ AlCl	dimethyl chloroaluminate
Me ₃ NO	trimethylamine <i>N</i> -oxide
MeCN	acetonitrile
MeMgBr	methyl magnesium bromide
MeMgI	methyl magnesium iodide
MeNH ₂	methylamine
MeOH	methanol
Mg	magnesium
mg	milligram

MgI ₂	magnesium iodide
μL	microliter
μm	micrometers
μwave	microwave
MgSO ₄	magnesium sulfate
M–H	deprotonated molecular ion
MHz	megahertz
min	minute
mL	milliliters
mm	millimeters
mmol	millimoles
Mn	manganese
mol	mole
mp	melting point
N	nitrogen
N ₂	diazo
N ₂	dinitrogen
N ₃	azide
Na	sodium
Na ₂ CO ₃	sodium carbonate
Na ₂ S ₂ O ₃	sodium thiosulfate
Na ₂ SO ₄	sodium sulfate
NaCl	sodium chloride
NaHCO ₃	sodium bicarbonate
NaIO ₄	sodium periodate

NBS	<i>N</i> -bromosuccinimide
NCD	norcaradiene
NH ₄ Cl	ammonium chloride
NMO	morpholine <i>N</i> -oxide
NMR	nuclear magnetic resonance
NO ₂	nitro
nOe	nuclear Overhauser effect
nOesy	nuclear Overhauser effect spectroscopy
O	oxygen
<i>o</i>	<i>ortho</i>
O ₂	dioxygen
<i>o</i> -C ₆ H ₄	1,2-disubstituted benzene
OPiv	pivalate
Os	osmium
OsO ₄	osmium(VIII) tetraoxide
OTf	trifluoromethane sulfonate
Oxone®	potassium peroxymonosulfate
P	phosphorus
<i>p</i>	<i>para</i>
<i>P. putida</i>	<i>Pseudomonas putida</i>
Pb	lead
Pb(OAc) ₄	lead tetraacetate
Pd	palladium
Pd ₂ (dba) ₃ •CHCl ₃	bis-palladium-tris-dibenzylideneacetone chloroform adduct
pdt	product

PF ₆ ⁻	hexafluorophosphate
Ph	phenyl
PhMe	toluene
PIDA	diacetoxy iodobenzene
PIFA	di(trifluoroacetoxy)iodobenzene
pK _a	-ln(dissociation constant)
PMP	4-methoxyphenyl
<i>p</i> -NO ₂ -C ₆ H ₄	4-nitro-phenyl
PPh ₃	triphenyl phosphine
ppm	parts per million
PTAD	4-phenyl-1,2,4-triazoline-3,5-dione
pybox	pyridine bis-oxazolidine
qt	quintet
quant.	quantitative
R	radical
R _f	retention factor
Rh	rhodium
Rh ₂ (esp) ₂	bis[rhodium(a,a,a',a'-tetramethyl-1,3-benzenedipropionate)]
Rh ₂ (OAc) ₄	rhodium acetate
Rh ₂ (oct) ₄	rhodium octanoate
Rh ₂ (Opiv) ₄	rhodium pivalate
Rh ₂ (<i>S</i> -PTTL) ₄	rhodium <i>N</i> -phthaloyl-(<i>S</i>)- <i>tert</i> -leucinate
Rh ₂ (TFA) ₄	rhodium trifluoroacetate
rr	regioisomeric ratio
rt	room temperature

RT	retention time
Ru(byp) ₃ Cl ₂	tris(bipyridine)ruthenium(II) chloride
rxn	reaction
s	seconds
S	sulfur
s	singlet
salen	<i>N,N'</i> -Ethylenebis(salicylimine)
Sb	antimony
SbCl ₆ N(4-Br-C ₆ H ₄) ₃	tris(4-bromophenyl)ammoniumyl hexachloroantimonate
Sc	scandium
Sc(OTf) ₃	scandium(III) trifluoromethane sulfonate
SFC	supercritical fluid chromatography
Si	silicon
Sn	tin
SnCl ₄	tin(IV) chloride
SO ₃ •pyridine	sulfur trioxide pyridine complex
t	triplet
TBDPS	<i>tert</i> -butyl diphenylsilyl
TBDPSCl	<i>tert</i> -butyl diphenylsilyl chloride
TBS	<i>tert</i> -butyl dimethylsilyl
^t Bu	<i>tert</i> -butyl
^t BuOH	<i>tert</i> -butanol
^t BuOK	potassium <i>tert</i> -butoxide
td	triplet of doublets
temp	temperature

TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TES	triethylsilyl
TfOH	1,1,1-trifluoromethanesulfonic acid
THF	tetrahydrofuran
Ti	titanium
Ti(O ^{<i>i</i>} Pr) ₄	titanium(IV) isopropoxide
TiCl ₄	titanium(IV) chloride
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	5,10,15,20-tetraphenyl-21H,23H-porphyrin
Ts	toluene sulfonyl (tosyl)
TsCl	toluene sulfonylchloride
TsNCO	toluene sulfonyl isocyanate
tt	triplet of triplets
UV	ultraviolet
W	Watts
w/w	weight per weight
Y	yttrium
Y(O ^{<i>i</i>} Pr) ₃	yttrium(III) isopropoxide
Yb	ytterbium
Yb(OTf) ₃	ytterbium(III) trifluoromethanesulfonate

CHAPTER ONE:
**LEWIS ACID CATALYZED (3+2)-ANNULATIONS OF DONOR–ACCEPTOR CYCLOPROPANES AND
YNAMIDES ***

1.1 Introduction

The rapid generation of substituted carbocyclic compounds continues to be a useful endeavor in organic synthesis. In this chapter, we report the use of donor–acceptor cyclopropanes and ynamides to construct highly-substituted cyclopentene sulfonamides in high yields and excellent regioselectivity. Subsequently, these products were hydrolyzed to reveal 2,3-disubstituted cyclopentenones as single diastereomers. This class of compounds is structurally related to prostaglandins, which possess numerous roles in biological systems.

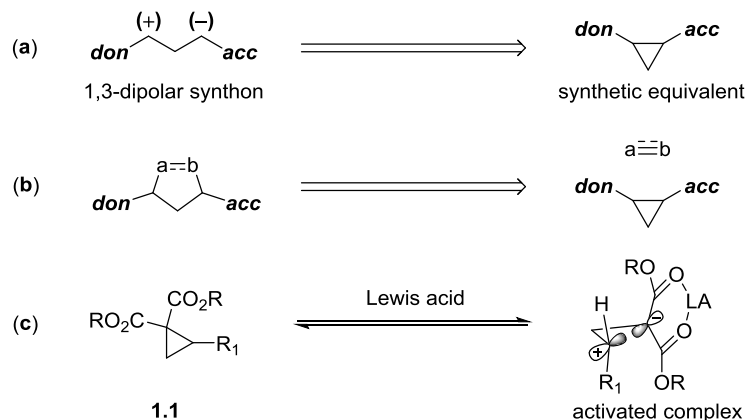
1.2 Background

1.2.1 Introduction and History of Donor–Acceptor Cyclopropanes

Donor–acceptor (D–A) cyclopropanes continue to receive significant attention as useful synthetic building blocks, particularly for their ability to act as synthetic equivalents to 1,3-dipolar synthons in cycloaddition reactions (Scheme 1-1a).¹ The deployment of these carbogenic building blocks has been widespread in the efficient assembly of heterocycles by (3+*n*)-annulation (Scheme 1-1b, a or b ≠ carbon),² but fewer cases have been described for carbocycle assembly (a, b = carbon).³⁻⁵

*Reprinted in part with permission from Mackay, W. D.; Fistikci, M.; Carris, R. M.; Johnson, J. S. *Org. Lett.* **2014**, *16*, 1626–1629.

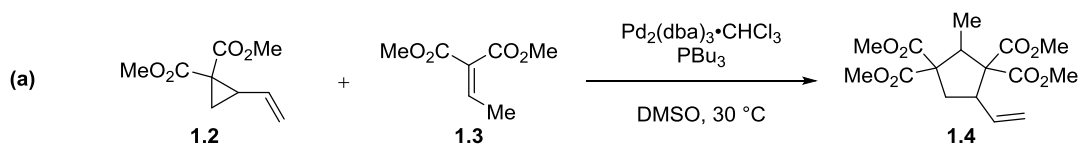
Scheme 1-1. Donor–Acceptor Cyclopropanes as 1,3-Dipole Synthons



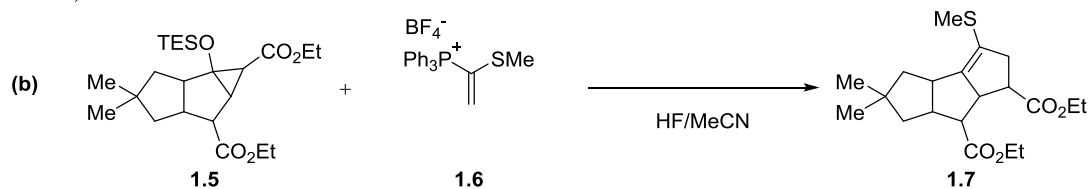
Notable examples of the latter include the annulation between Pd π -allyl activated vinyl D–A cyclopropanes **1.2** and electron-deficient alkenes **1.3** (Scheme 1-2a).^{3a,c,d} Marino and Laborde have achieved silyloxycyclopropane ester activation of **1.5** via fluoride-induced silyl ether cleavage, which enabled annulation with activated alkenes to provide cyclopentenones **1.7** (Scheme 1-2b).^{3b}

Scheme 1-2. Base-Promoted (3+2)-Annulations of Donor–Acceptor Cyclopropanes

Tsuji, 1985



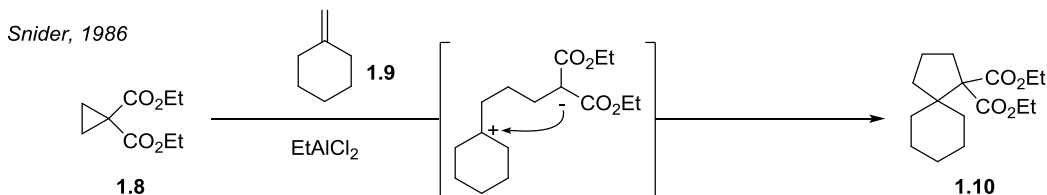
Marino, 1985



A common embodiment of annulations involving D–A cyclopropanes is the use of a 1,1-cyclopropane diester **1.1** in conjunction with a Lewis acid activator to create an activated intimate ion pair (Scheme 1-1c). In the realm of Lewis acid activation of the acceptor group, Snider has

shown EtAlCl_2 to effectively catalyze the annulation between D–A cyclopropanes **1.8** and methylenecyclohexane derivatives **1.9**,^{4b} providing spiro-bicyclic products **1.10** with the regioselectivity controlled by the preferential formation of a tertiary carbocation; however, a mixture of isomers was observed upon annulation with internal alkenes (Scheme 1-3).

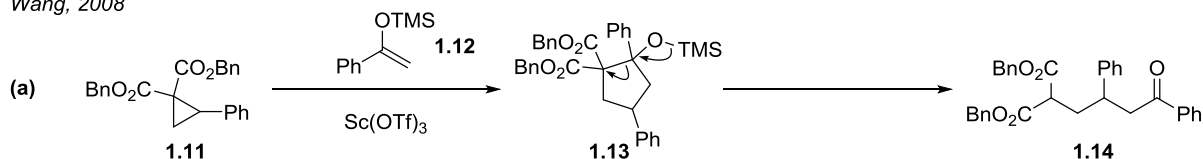
Scheme 1-3. Lewis-Acid Promoted (3+2)-Annulation with Cyclohexene Alkylidenes



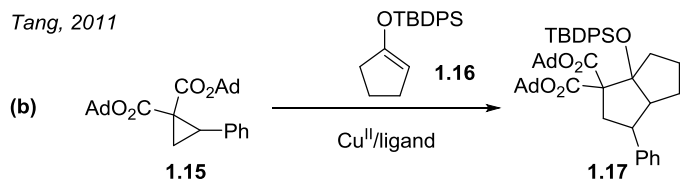
Several groups have reported annulations between D–A cyclopropanes **1.11** and enolsilanes **1.12** providing cyclopentanes **1.13**; the products commonly undergo subsequent ring-opening under the reactions conditions to provide linear products **1.14** (Scheme 1-4a).^{4k,n} Tang suppressed the ring-opening pathway in the annulation between D–A cyclopropanes and enolsilanes through the use of bulky silyl groups (TBDPS) on the enol silane **1.16** and ester groups (adamantyl) on the D–A cyclopropane **1.15** (Scheme 1-4b).^{4s} The use of allenyl silanes eliminates the potential for subsequent ring opening; however, these trials are complicated by 1,2-silyl migrations, providing a mixture of cyclopentane alkylidene and cyclohexene annulation products.^{4f} Ready and Qi have shown ynolsilanes **1.19** to be effective annulation partners for D–A cyclopropanes under Lewis acidic conditions, providing access to highly substituted cyclopentenones **1.20**; however, this union was hindered by numerous challenges, including the instability of ynolsilanes, the requisite of cryogenic temperatures, and the use of a harsh Lewis acid. (Scheme 1-4c).^{4j}

Scheme 1-4. (3+2)-Annulation Reactions using Enol- and Ynolsilanes

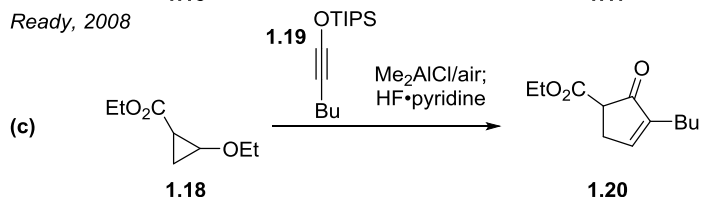
Wang, 2008



Tang, 2011



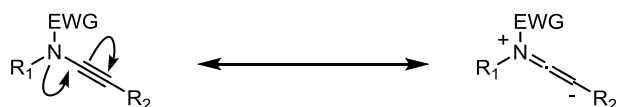
Ready, 2008



1.2.2 Utility of Ynamides in Cycloaddition Reactions

To circumvent the challenges that plague ynolsilanes, ynamides were seen as a viable alternative, since they are easily prepared,⁶ stable upon storage, and can react with a variety of annulation partners at ambient conditions. Ynamides have been shown to be excellent partners for (*n*+2)-annulations⁷ due to the high regioselectivity with which they react. This selectivity is typically attributed to the major zwitterionic resonance structure (Scheme 1-5).

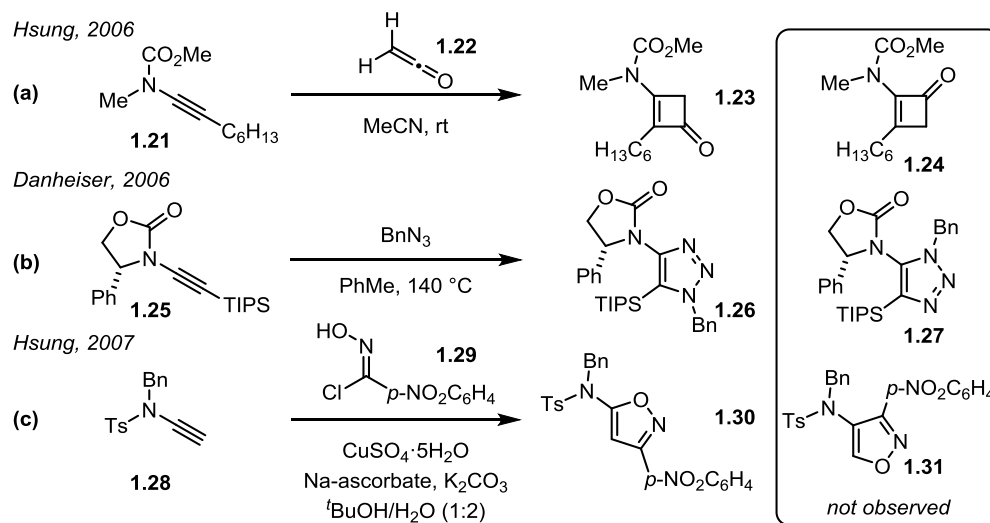
Scheme 1-5. Resonance Structures of Ynamides



Notable examples of such regiospecific reactivity include the stepwise (2+2)-annulation of ynamide **1.21** and ketene **1.22** to provide cyclobutenone **1.23** (Scheme 1-6a).⁸ More represented in this class of ring-forming reactions with ynamides are the formation of five-membered heterocycles, such as the alkyne-azide cycloaddition to provide triazoles **1.26** (Scheme 1-6b).⁹ Nitrile oxides have also been used to produce oxazoles **1.30** using terminal ynamide **1.28** (Scheme

1-6c).¹⁰ In all such examples outlined herein, only a single regioisomer was formed, with no evidence for the production of the other possible regioisomers (**1.24**, **1.27**, **1.31**), suggesting that the strong polarization of the alkyne, as shown in Scheme 1-5, greatly influences the reactivity of ynamides.

Scheme 1-6. Selected Examples of Regioselective (*n*+2)-Annulation Reactions of Ynamides

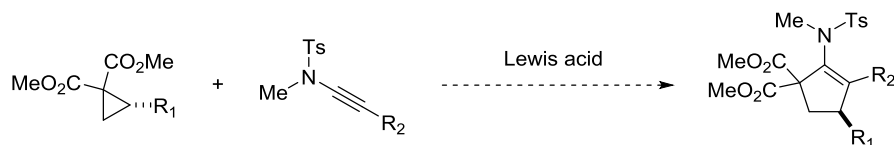


1.3 Results and Discussion

1.3.1 Initial Reaction Design and Optimization

Despite the advantageous reactivity of both D–A cyclopropanes and ynamides, at the onset of this project, their union remained unachieved; therefore, the site-selective capture of the intimate ion pair from Lewis acid activation of the D–A cyclopropane by ynamide “dipolarophiles” is the subject of this chapter (Scheme 1-7). The preparation of useful functionalized cyclopentenesulfonamides by these (3+2)-annulations is demonstrated. Deprotection of the ensulfonamide reveals 2,3-substituted cyclopentanones with high levels of diastereoselectivity. This strategy provides access to an important structural motif resembling products of diastereoselective 1,4-addition to 2-substituted cyclopentenones.

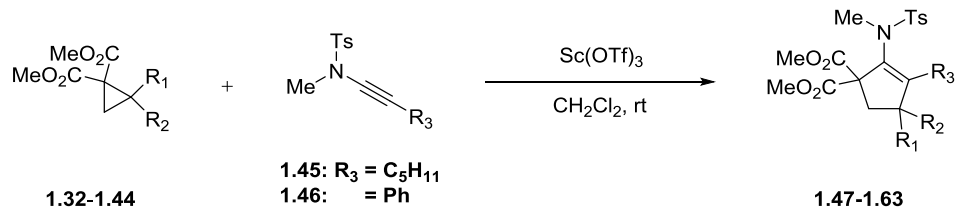
Scheme 1-7. Proposed (3+2)-Annulation of Donor–Acceptor Cyclopropanes and Ynamides



Working first with cyclopropane **1.33** and ynamide **1.45**, a brief Lewis acid screen revealed Sc(OTf)₃ to be a superior promotor for the reaction, providing complete starting material conversion with catalyst loadings as low as 10 mol %. The efficacy of this particular Lewis acid is congruent with our previously demonstrated (3+2)-annulation of D–A cyclopropanes with aldehydes.¹¹ Attempts to lower the catalyst loading further were met with incomplete consumption of **1.33** after 20 h. Two equivalents of the ynamide were required in the annulation to maximize product yields as ynamide hydrolysis was found to be a competitive decomposition pathway; investigations into this hydrolysis will be discussed later in this chapter (Section 1.3.5).

1.3.2 Substrate Scope of the Reaction

With the optimized conditions in hand, we began to examine the scope of the annulation (Table 1-1). The reaction proceeded smoothly for a number of substrates, particularly for cyclopropanes bearing electron-rich aromatic groups (**1.32**, **1.33**, **1.35**). This observation is in agreement with our previous findings that greater stabilization of the carbenium ion in the zwitterionic intermediate provides faster reaction rates.¹¹ However, there is an apparent limit to the electron releasing ability of the donor group towards promotion of the annulation. *N,N*-dimethylaniline substituted cyclopropane **1.41** (entry 14), the most electron rich of the substrates tested, failed to react after 100 h, presumably due to a marked decrease in electrophilicity at the donor site. This trend may also explain the yield discrepancy between the *para*- and *ortho*-methoxyphenyl substituted cyclopropanes (entries 3 and 7).

Table 1-1. Substrate Scope^{a,b}

entry	R ₁	R ₂	R ₃	pdt	yield (%) ^c
1	4-MePh	H (1.32)	C ₅ H ₁₁	1.47	>99
2	4-MePh	H (1.32)	Ph	1.48	>99
3	4-OMePh	H (1.33)	C ₅ H ₁₁	1.49	89(86) ^d
4	4-OMePh	H (1.33)	Ph	1.50	>99
5	4-OMePh	Me (1.34)	C ₅ H ₁₁	1.51	64
6	4-OMePh	Me (1.34)	Ph	1.52	53
7	2-OMePh	H (1.35)	C ₅ H ₁₁	1.53	>99
8	2,3-(CH ₂ O ₂)Ph	H (1.36)	C ₅ H ₁₁	1.54	64
9	2-furyl	H (1.37)	C ₅ H ₁₁	1.55	46
10	2-thienyl	H (1.38)	C ₅ H ₁₁	1.56	84
11	2-thienyl	H (1.38)	Ph	1.57	93
12	(<i>E</i>)-CH=CHPh	H (1.39)	C ₅ H ₁₁	1.58	69
13	4-ClPh	H (1.40)	C ₅ H ₁₁	1.59	NR ^e
14	4-NMe ₂ Ph	H (1.41)	C ₅ H ₁₁	1.60	NR ^e
15	Ph	Me (1.42)	C ₅ H ₁₁	1.61	59(90) ^f
16	Ph	C≡CH (1.43)	C ₅ H ₁₁	1.62	63
17	Ph	H (1.44)	C ₅ H ₁₁	1.63	82

^aReactions performed with 1.0 equiv of D–A cyclopropane and 2.0 equiv of ynamide in dry CH₂Cl₂ (0.1 M) with 0.10 equiv Sc(OTf)₃. ^bReactions were run for 18 h. ^cIsolated yield. ^dRun on 20 mmol scale of **1.33**. ^eNo reaction observed after 100 h. ^fRun with 3.0 equiv **1.45** and 0.15 equiv Sc(OTf)₃.

Decreased yields were also observed for the 2-furyl substituted cyclopropane **1.37** (entry 9). This iteration suffered from significant amounts of unidentified side reactions and starting material decomposition. A plausible degradation pathway for **1.37** might be the competing Piancatelli rearrangement, which has been previously observed for furyl-substituted D–A cyclopropanes.¹² Cyclopropanes bearing a vinyl donor group proceeded in low yields (<30%) upon annulation with **1.45** under Lewis acidic conditions. These annulation products were unable to be isolated cleanly, since no conditions that were tested prevented coelution of the amide resulting

from the hydrolysis of **1.45** from the desired product. Alkyl-substituted cyclopropanes ($R_1 = \text{Bu}$, $R_2 = \text{H}$) failed to react with **1.45** under standard reaction conditions, even upon refluxing in DCE for 24 h.

2,2-Disubstituted cyclopropanes (entries 5,6,15,16) all suffered from diminished yields under the standard reaction conditions, presumably due to a slower rate of annulation. Since *in situ* ynamide hydrolysis is competitive with the annulation, at extended reaction times the availability of the ynamide is compromised. In these cases, the addition of 3 equiv of ynamide (entry 15) resulted in dramatically increased yields of **1.61**. The alkynyl moiety, which has been shown to be an effective donor for (3+2)-annulations between D–A cyclopropanes and aldehydes,¹³ (entry 16) also functions as an effective donor in the annulation with ynamides, providing **1.63** in 63% yield.

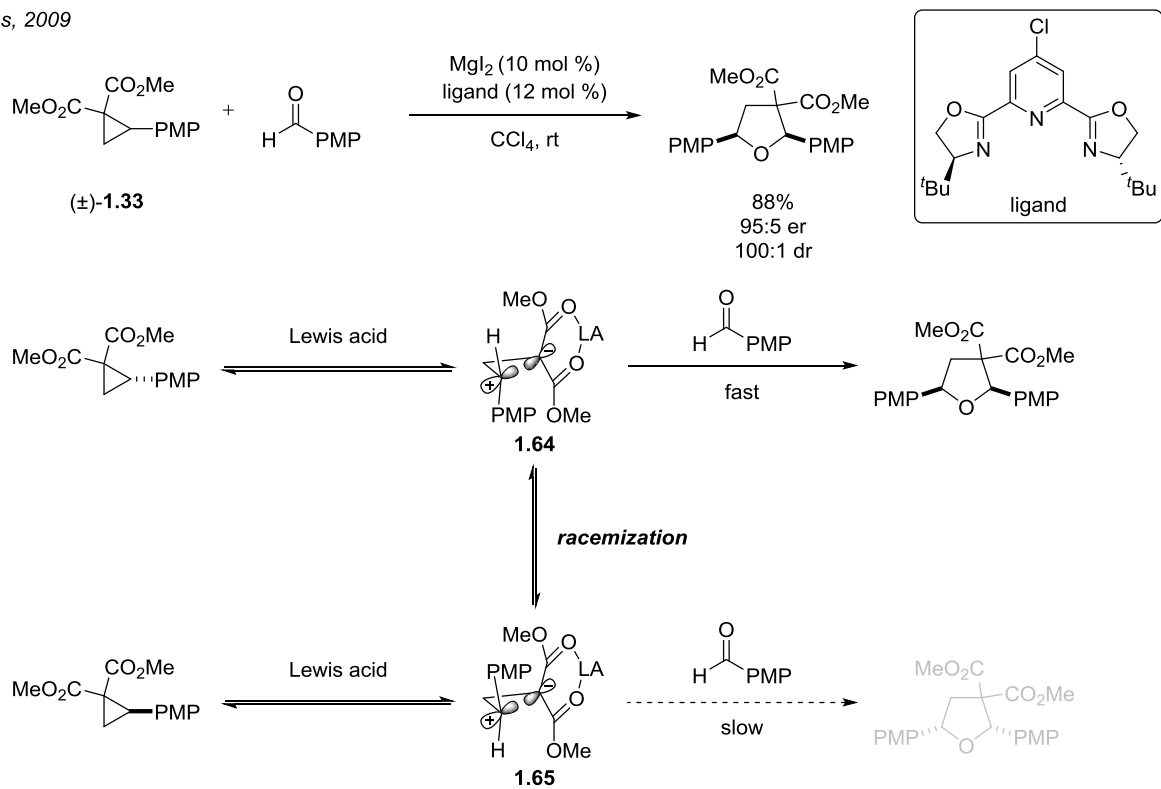
1.3.3 Generation of Enantioenriched Cyclopentenesulfonamides

Having developed robust conditions for the generation of racemic cyclopentenesulfonamides, we then began to examine the feasibility of performing a dynamic kinetic asymmetric transformation (DyKAT)¹⁴ of racemic D–A cyclopropanes and ynamides based on our previous work in the cases of tetrahydrofurans^{2h} and pyrrolidines,²ⁱ in order to access enantioenriched products (Scheme 1-8).

Upon coordination of the Lewis acid, the diastereomeric intimate ion pairs **1.64/1.65** readily racemize, allowing for all of the racemic starting cyclopropane **1.33** to funnel towards a single tetrahydrofuran product. Applying these conditions to our system should allow for analogous enantiomerization of starting cyclopropane, concomitant with ring closure.

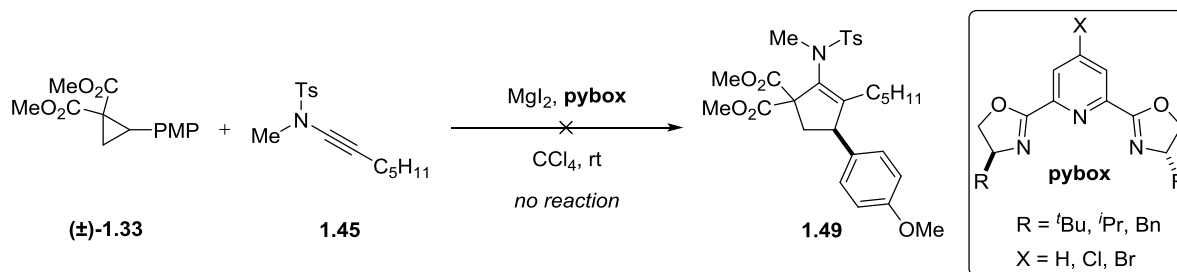
Scheme 1-8. DyKAT of D–A Cyclopropanes and Aldehydes

Parsons, 2009



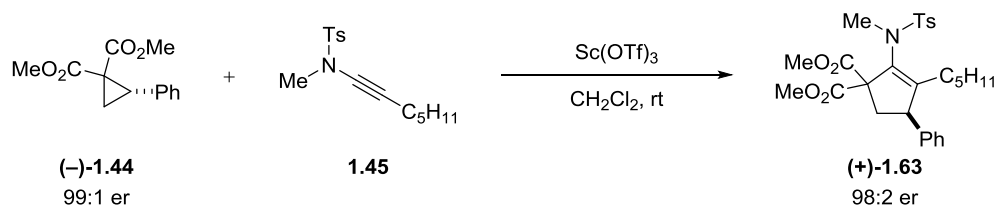
In the event, however, we found this tactic to be ineffective, as the reactivity of **1.33** and **1.45** were significantly hindered by the application of the MgI_2 (pybox) catalyst system (Scheme 1-9). Varying the electronic profile of the pybox ligand by introducing halogens at the 4-position ($\text{X} = \text{Cl}, \text{Br}$) had no effect on the annulation. In addition, variation of the reaction solvent or temperature showed no promise for increasing starting material conversion. For example, treatment of **1.33** with **1.45** in refluxing CCl_4 for 2 d resulted in only trace degradation (<5%) of **1.33**. Notably, no degradation of the ynamide was observed. This lack of reactivity was attributed to unfavorable steric interactions between the chiral ligand ($\text{R} = \textit{t}\text{Bu}$) and the approaching ynamide. In an attempt to minimize this strain, less sterically demanding pybox ligands ($\text{R} = \textit{t}\text{Pr}, \text{Bn}$) were evaluated, neither of which was successful in promoting the annulation.

Scheme 1-9. Attempted DyKAT of D–A Cyclopropanes and Ynamides



Despite the complications with accessing enantioenriched products through a DyKAT mechanism, our group has shown previously^{2d,11} that enantioenriched D–A cyclopropanes transfer chirality to their annulation products with high fidelity, undergoing complete inversion at the donor site stereogenic center. As shown in Scheme 1-10, this mechanistic feature was also observed in the case of annulation with ynamides. Stereospecific back-side capture of the intimate ion pair (eq 3) would account for this finding.¹¹

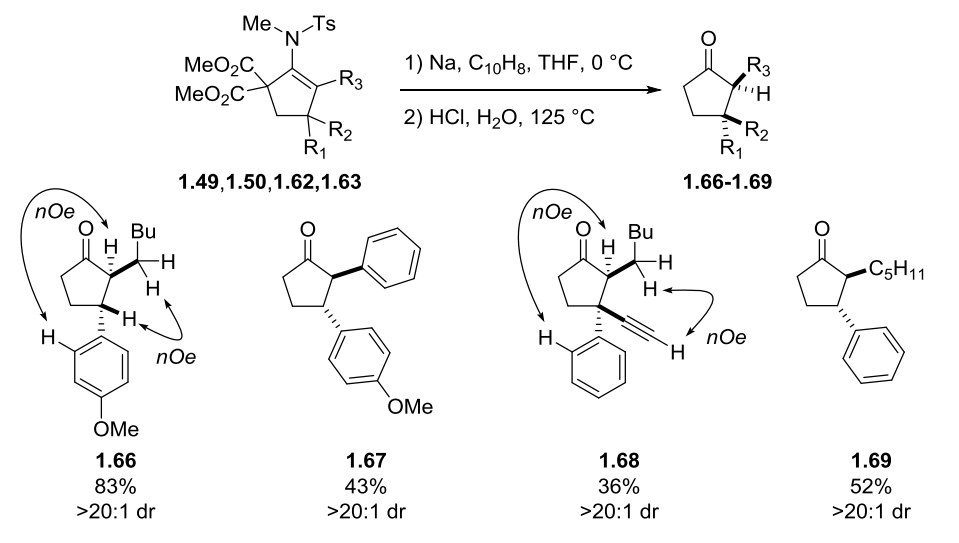
Scheme 1-10. Chirality Transfer of Enantioenriched D–A Cyclopropane



1.3.4 Deprotection and Hydrolysis of the Cyclopentenesulfonamide Intermediates

In an effort to provide synthetically attractive cyclopentanones from the enamide products **1.47-1.63**, the sulfonyl group was first cleaved via single electron reduction using sodium naphthalenide. The resultant enamine was then hydrolyzed under acidic conditions to provide cyclopentanones **1.66-1.69** as single diastereomers (Table 2).

Table 1-2. Tosyl Reduction and Hydrolysis^{a,b}



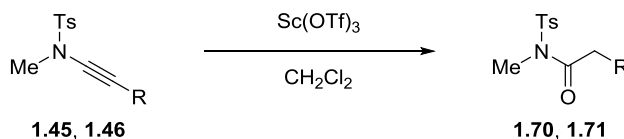
^aIsolated yield of **1.67-1.70** over two steps. ^bDiastereomeric ratio (dr) determined by ¹H NMR of isolated product.

The *gem*-diester moiety was also removed during the hydrolysis. nOesy analysis of the cyclopentanone products **1.66**, **1.68** confirmed an *anti* relationship between R₁ and R₃ substituents. These 3,3-disubstituted cyclopentanones **1.68** are of particular note, as they represent an expedient synthesis of formal conjugate addition products of 2,3-disubstituted cyclopentenones, whose enantioselective synthesis via conjugate addition to enones is non-trivial.¹⁵

Unsubstituted ynamides (R₃ = H) were not tested in the annulation with D–A cyclopropanes, since the resultant cyclopentanones that would be accessed from these substrates are analogous to the products of 1,4-addition to cyclopentenone or the 1,4-reduction of β-substituted cyclopentenones. There are already several excellent reports of enantioselective variants of these reactions.^{16,17}

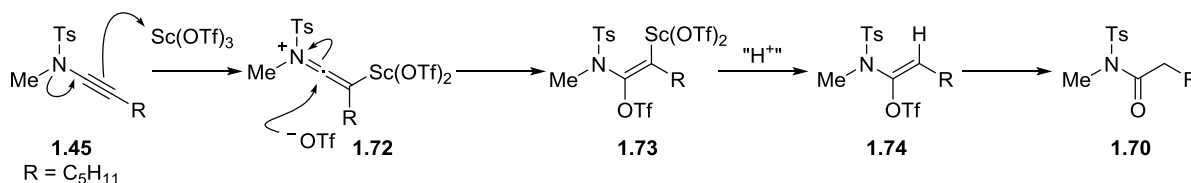
1.3.5 Unexpected Byproduct from Ynamide Hydrolysis

Scheme 1-11. Lewis Acid Promoted Ynamide Hydrolysis



Investigation of this reaction was a result of the first attempt at isolating **1.49**, whereupon the amide side product **1.70** was definitively identified. Since it had been reported that ynamides are readily hydrolyzed in the presence of water,⁷ the CH_2Cl_2 was distilled from CaH_2 and stored over 3 Å molecular sieves under inert atmosphere prior to use, in an attempt to minimize the hydrolysis from trace water in the solvent. In the subsequent trials with the freshly distilled solvent, ynamide hydrolysis was still observed in appreciable quantities. The inclusion of 3 Å molecular sieves in the reaction vessel was also ineffective at suppressing the hydrolysis. It was then proposed that the Lewis acid was responsible for the observed hydrolysis (Scheme 1-12). The ynamide would first coordinate to the Lewis acid, displacing triflate, which subsequently adds back to the ketene iminium intermediate **1.72**, forming a hemiaminal **1.73**. Replacement of the Lewis acid with a proton, potentially from the solvent or during work up, and decomposition of the triflate provides the observed amide **1.70**.

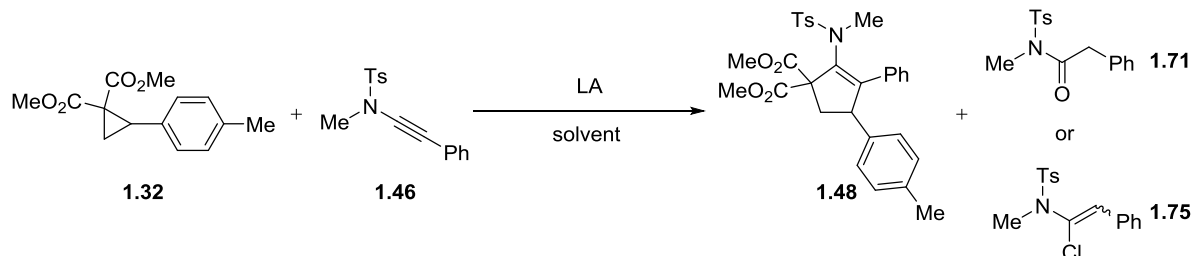
Scheme 1-12. Plausible Mechanism for Hydrolysis of Ynamides using Lewis Acidic Conditions



In order to elucidate the degradation mechanism, Lewis acids with chloride counterions were screened, in hopes of isolating the chloro enamide products **1.75**. Utilizing AlCl_3 , TiCl_4 , and SnCl_4 to promote the annulation resulted in isolation of the chloro enamide **1.75** (Table 1-3, entries

6-12), confirming our suspicions. A variety of conditions and catalysts were then screened in an attempt to suppress the decomposition pathway, albeit with limited success (Table 1-3). All Lewis acids with triflate counterions caused significant accumulation of the amide byproduct **1.71** (entries 1-5). Altering the reaction temperature offered no benefit towards formation of **1.48**. The degradation of the ynamide out-competes the annulation at low temperatures (entry 2). Using toluene as the solvent also resulted in appreciable quantities of the amide **1.71** (entry 3). At lower catalyst loadings (entries 8-12), the annulation attenuates appreciably, leaving a majority of **1.32** unreacted and large amounts of **1.75** relative to **1.48**.

An alternative method for the synthesis of ynamides **1.46** involves the isomerization of *N*-propargylamides with alkoxide bases (i.e., ^tBuOK).^{6c} As expected, those Lewis acids with alkoxide ligands (entries 13-16) did not cause ynamide degradation; unfortunately, however, they were also ineffective at promoting the annulation. Since none of the conditions screened provided complete suppression of the degradation pathway, we decided to carry forward with two equivalents of the ynamide in the annulation to maximize product yields. This was deemed an acceptable compromise, since the ynamide synthesis is trivial—providing good yields and easily purified—starting from inexpensive materials (see Section 1.5 for the experimental details).

Table 1-3. Lewis Acid Screen to Suppress Amide Byproduct

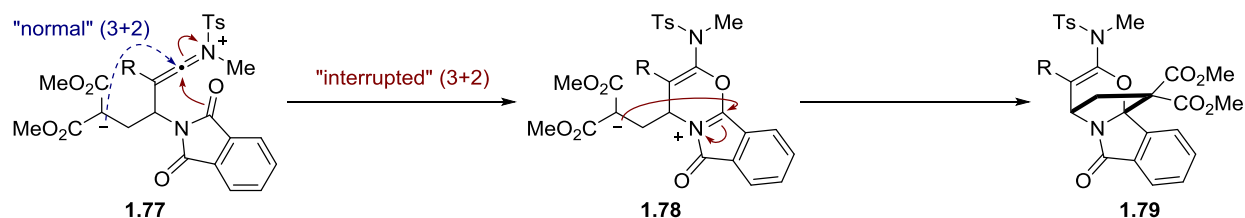
entry	Lewis acid (mol %)	solvent	temp (°C)	1.48 : 1.71 or 1.75 ^a
1	Sc(OTf) ₃ (10)	CH ₂ Cl ₂	23	1 : 0.65 ^b
2	Sc(OTf) ₃ (10)	CH ₂ Cl ₂	0	1 : 1.03 ^b
3	Sc(OTf) ₃ (10)	PhMe	23	1 : 4.04 ^b
4	Sc(OTf) ₃ (10)	CH ₂ Cl ₂	23	1 : 0.32 ^{b,c}
5	Yb(OTf) ₃ (20)	CH ₂ Cl ₂	23	0% 1.48 , 24% 1.71 ^b
6	TiCl ₄ (20)	CH ₂ Cl ₂	23	1 : 1.70 ^d
7	SnCl ₄ (20)	CH ₂ Cl ₂	23	1 : 0.29 ^d
8	AlCl ₃ (50)	CH ₂ Cl ₂	23	1 : 0.69 ^d
9	AlCl ₃ (20)	CH ₂ Cl ₂	23	1 : 0.83 ^d
10	AlCl ₃ (10)	CH ₂ Cl ₂	23	1 : 1.86 ^d
11	AlCl ₃ (5)	CH ₂ Cl ₂	23	1 : 3.95 ^d
12	AlCl ₃ (2)	CH ₂ Cl ₂	23	1 : 4.60 ^d
13	Hf(O ^{<i>i</i>} Bu) ₄ (10)	CH ₂ Cl ₂	23	no rxn, minor decomp ^b
14	Al(O ^{<i>i</i>} Pr) ₃ (10)	CH ₂ Cl ₂	23	no rxn, no decomp ^b
15	Ti(O ^{<i>i</i>} Pr) ₄ (10)	CH ₂ Cl ₂	23	no rxn, minor decomp ^b
16	Y(O ^{<i>i</i>} Pr) ₃ (10)	CH ₂ Cl ₂	23	no rxn, minor decomp ^b

^aDetermined from crude ¹H NMR. ^bByproduct refers to **1.71**. ^cRun with 1.8 mmol of **1.32** (435 mg) and **1.45** (500 mg). ^dByproduct refers to **1.75**.

1.3.6 Investigation of the “Interrupted” (3+2)-Annulation

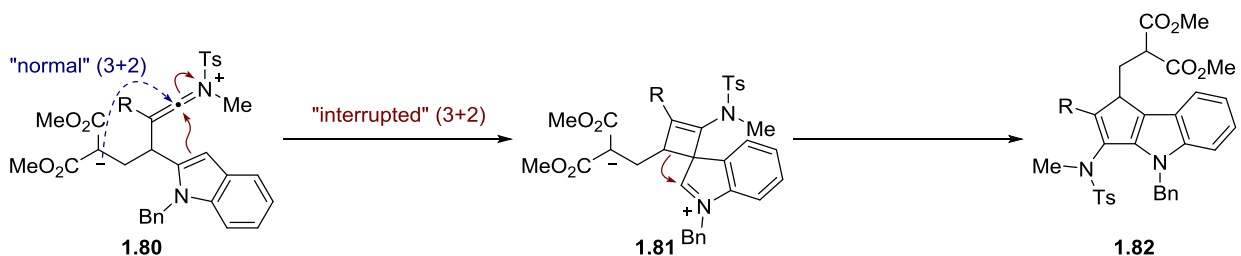
While screening the phthalimido-substituted D–A cyclopropane **1.76**, a new side product arose, which was identified as the “interrupted” (3+2)-annulation product **1.79**, as confirmed by X-ray crystallography (Scheme 1-13).

Scheme 1-13. “Interrupted” (3+2)-Annulation of Phthalimido D–A Cyclopropane and Ynamide



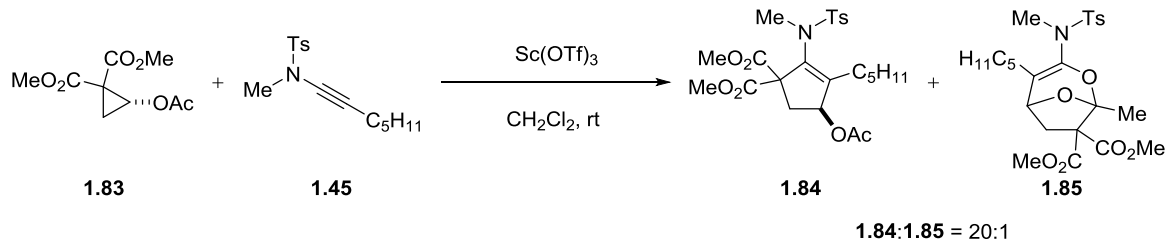
Instead of trapping of the ketene iminium intermediate **1.77** with the malonate to yield the “normal” cyclopentenesulfonamide, the “interrupted” pathway proceeds via trapping with the phthalimide oxygen to provide the oxazine intermediate **1.78**. Quenching of the resulting zwitterionic intermediate yields the bridged byproduct **1.79**. An analogous reaction pathway was observed in the case of indolyl-substituted D–A cyclopropane. Initial indole trapping of intermediate **1.80** would provide the spirocyclic intermediate **1.81**. Ring expansion of **1.81** and subsequent restoration of aromaticity would provide the tricyclic **1.82**.

Scheme 1-14. “Interrupted” (3+2)-Annulation of Indolyl D–A Cyclopropane and Ynamide



Further attempts at exploiting this alternative reactive pathway proved unfruitful. Acetate-substituted cyclopropane **1.83**, provided high yields of the “normal” (3+2)-annulation product **1.84**, with only trace amounts of the “interrupted” product **1.85** (Scheme 1-15). With the limited scope available to this niche observation, further investigations into this transformation were not pursued.

Scheme 1-15. “Interrupted” (3+2)-Annulation Using Acetate Trap



1.4 Conclusions

In conclusion, we have shown ynamides to be suitable partners in (3+2)-annulation reactions with D–A cyclopropanes, providing cyclopentenonesulfonamide products. Though the steric congestion of the system prevents a DyKAT to access enantioenriched products under the conditions screened, the reaction was stereospecific and relayed the stereochemistry of the starting cyclopropane to the product with high fidelity. Subsequent deprotection and hydrolysis provided 2,3-substituted cyclopentanone products with high stereoselectivity. This route represents a practical alternative to enantioselective conjugate addition reactions to cyclopentenones, especially for the generation of α -stereogenic- β -quaternary cyclopentanones.

1.5 Experimental Details

Methods

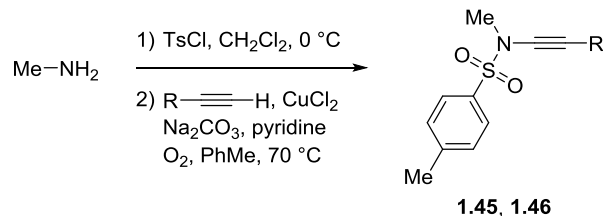
Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on either a Bruker model DRX 400 or 600 Spectrometer (^1H NMR at 400 or 600 MHz and ^{13}C NMR at 100 or 150 MHz) with solvent resonance as the internal standard (^1H NMR: CDCl_3 at 7.28 ppm and ^{13}C NMR: CDCl_3 at 77.0 ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = 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 and are uncorrected. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier Transform Infrared Spectrometer. Low resolution mass spectra (LRMS) were obtained using a Micromass Quattro-II triple quadrupole mass spectrometer in combination with an Advion NanoMate chip-based positive ion electrospray sample introduction system and nozzle. 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 methanol, plus a few drops of acetone if needed to dissolve the compound, and trace aqueous formic acid solution. All reported masses correspond to the protonated molecular ion ($\text{M}+\text{H}$) unless otherwise noted. Supercritical fluid chromatography was performed on a Berger SFC system equipped with Chiracel AD, AS, OD, and WO columns (ϕ 4.6 mm x 250 mm). Samples were eluted with SFC grade CO_2 with 10% methanol with an oven temperature of 40 $^\circ\text{C}$. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring unless stated otherwise. Thin layer chromatography (TLC) was performed on Sorbtech plastic-backed 0.20 mm silica gel 60 plates. Visualization was

accomplished with UV light and an aqueous ceric ammonium molybdate (CAM) solution, followed by heating. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Unless otherwise specified, all crude materials were introduced to the chromatography column after dissolution in the specified eluent (plus a few drops dichloromethane, if required). Purification via high performance liquid chromatography (HPLC) was performed on a Varian Prepstar SD-1 Solvent Delivery System equipped with a Cyano 60 Å 6u column from Berger Instruments, using 15% ethyl acetate/hexanes eluent system at a flow rate of 15.00 mL/min. 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 tables, which are averages of at least two experiments.

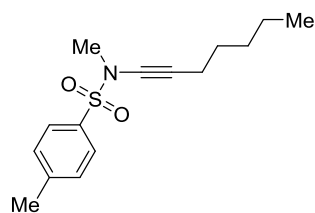
Materials

Nitrogen was dried by passage through anhydrous calcium sulfate with 3% cobalt chloride as indicator (commercial Drierite). Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were passed through a column of neutral alumina under nitrogen prior to use. All cyclopropanes **1.32-1.44**, **1.76**, **1.80** used in this study are known compounds and were prepared according to literature procedures.¹⁸ The enantiomers of cyclopropane **1.44** had been resolved previously in our laboratory.¹¹ Ynamide **1.45** was stored in the freezer as a solution in benzene to retain its integrity. The benzene was removed by rotary evaporation prior to addition into the reaction vessel. All other reagents and solvents were purchased from commercial sources and used as received.

General Procedure A for the Preparation of Ynamides (1.45, 1.46)

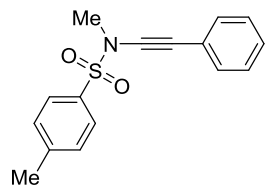


Based on the literature procedure,^{6b} CH₂Cl₂ (40 mL) was added to TsCl (1.0 equiv) in a 125 mL round-bottomed flask and the solution was cooled to 0 °C. MeNH₂ (40% in H₂O, 2.2 equiv) was added slowly, and the reaction was stirred for 1 h. The mixture was then warmed to room temperature and washed with brine (40 mL), water (40 mL), and brine (40 mL), and then dried over Na₂SO₄. The solvent was removed by rotary evaporation, yielding a white solid, which was recrystallized in 95% EtOH/H₂O if impure by ¹H NMR. The product was then transferred to a 300 mL 3-necked flask and combined with CuCl₂ (0.067 equiv) and Na₂CO₃ (0.67 equiv) and the flask was purged with O₂ for 15 min. A solution of pyridine (0.67 equiv) in toluene (75 mL) was added to the flask via syringe and the flask was heated to 70 °C. The alkyne (0.33 equiv as a solution in 18 mL of toluene) was then added to the flask via syringe pump at a rate of 3.5 – 4.0 mL/h. After complete addition of the alkyne, the reaction mixture stirred for 20 h at 70 °C. After cooling to room temperature, the crude mixture was filtered through a pad of Celite, concentrated by rotary evaporation, and purified by flash chromatography (20% EtOAc/hexanes) to provide the desired product, which was stored in the freezer either neat or frozen as a solution in benzene.



***N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide (1.45):** The title compound was prepared according to General Procedure A using *N*,4-dimethylbenzenesulfonamide (2.89 g, 15.6 mmol) and 1-heptyne (0.68 mL, 5.2 mmol). Flash chromatography provided a yellow oil (1.23 g, 85%) that was stored in the freezer, frozen as a solution in benzene. Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 7.80

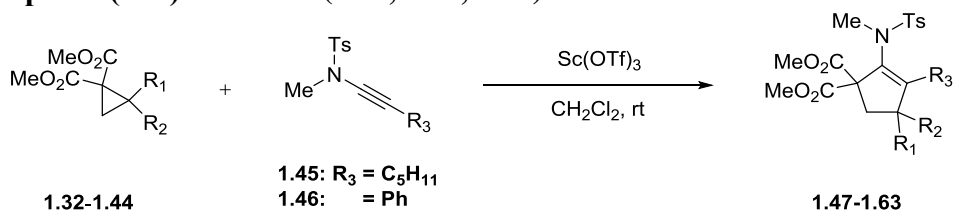
(d, $J = 8.0$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 3.03 (s, 3H), 2.47 (s, 3H), 2.25 (t, $J = 7.0$ Hz, 2H), 1.49 (tt, $J = 7.0, 4.6$ Hz, 2H), 1.33 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.4, 133.2, 129.6, 127.8, 74.8, 68.7, 39.4, 30.9, 28.6, 22.2, 21.6, 18.3, 14.0; **IR** (thin film, cm^{-1}) 3033, 2953, 2932, 2860, 2253, 1597, 1364, 1173, 814, 677; **TLC** (20% EtOAc/hexanes) $R_f = 0.48$; **LRMS** (ESI^+) Calcd. for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$: 280.14, Found: 280.07.



***N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide (1.46):** The title compound was prepared according to General Procedure A using *N*,4-dimethylbenzenesulfonamide (2.79 g, 15.1 mmol) and phenylacetylene

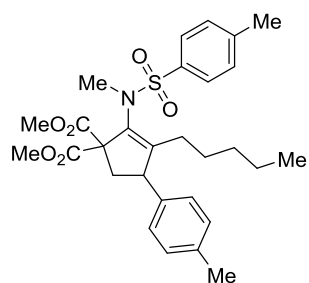
(0.55 mL, 5.1 mmol). Flash chromatography provided a yellow solid (1.12 g, 78%) that was stored neat in the freezer. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 7.87 (m, 2H), 7.40 (m, 4H), 7.31 (m, 3H), 3.17 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 144.8, 133.1, 131.3, 129.8, 128.2, 127.8, 122.6, 83.9, 68.9, 39.3, 21.6 (one peak missing due to peak overlap); **mp** 79-81 $^\circ\text{C}$; **IR** (thin film, cm^{-1}) 3056, 2983, 2934, 2299, 2234, 1598, 1382, 1168, 964, 815; **TLC** (20% EtOAc/hexanes) $R_f = 0.35$; **LRMS** (ESI^+) Calcd. for $\text{C}_{16}\text{H}_{16}\text{NO}_2\text{S}$: 286.09, Found: 286.07.

General Procedure B for the Preparation of (3+2)-Annulation Products (1.47-1.63, 1.84), and the “Interrupted” (3+2)-Products (1.79, 1.82, 1.85)



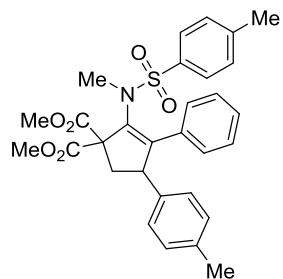
To an oven-dried 1 dram vial in a nitrogen-filled glovebox was added $\text{Sc}(\text{OTf})_3$ (9 mg, 0.018 mmol, 0.1 equiv) and a magnetic stir bar. The vial was then fitted with a septum screw cap and removed from the glovebox, where the cyclopropane (0.18 mmol) and ynamide (0.36 mmol) were combined and added to the vial via syringe as a solution in anhydrous CH_2Cl_2 (1.5 mL). The reaction was allowed to stir for 18 h, after which the crude mixture was concentrated by rotary

evaporation and purified by flash chromatography to provide the desired product. In the cases where multiple impurities coeluted with the desired product, analytically pure samples were obtained using preparatory HPLC after initial subsection of the crude material to flash chromatography.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-3-pentyl-4-(p-methylphenyl)cyclopent-2-ene-1,1-dicarboxylate (1.47):

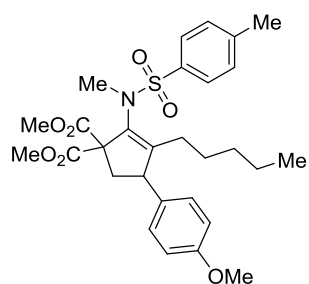
The title compound was prepared according to General Procedure B using dimethyl 2-(p-methylphenyl)cyclopropane-1,1-dicarboxylate **1.32** (44 mg, 0.18 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white crystalline solid (98 mg, quant.). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.76 (br s, 2H), 7.27 (s, 2H), 7.15 (s, 2H), 7.09 (br s, 2H), 3.82 (br s, 3H), 3.77 (s, 3H), 3.62 (br s, 1H), 3.22 (s, 3H), 2.93 (br s, 1H), 2.58 (br s, 1H), 2.39 (s, 3H), 2.36 (s, 3H), 1.25-0.93 (m, 8H), 0.75 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 172.5, 169.1, 152.6, 143.2, 139.4, 137.1, 136.4, 133.3, 129.4, 129.3, 127.9, 127.4, 66.2, 53.4, 52.7, 47.1, 41.4, 37.7, 31.2, 26.9, 25.6, 22.0, 21.4, 21.0, 13.7; **mp** 117-119 °C; **IR** (thin film, cm⁻¹) 2953, 2928, 2861, 1733, 1455, 1348, 1272, 1156; **TLC** (20% EtOAc/hexanes) *R_f* = 0.22; **LRMS** (ESI⁺) Calcd. for C₂₉H₃₈NO₆S: 528.24, Found: 528.26.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-3-phenyl-4-(p-methylphenyl)cyclopent-2-ene-1,1-dicarboxylate (1.48):

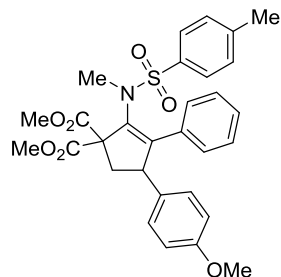
The title compound was prepared according to General Procedure B using dimethyl 2-(p-methylphenyl) cyclopropane-1,1-dicarboxylate **1.32** (44 mg, 0.18 mmol) and *N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide **1.46** (100 mg, 0.35 mmol). Flash chromatography (5% Et₂O/CH₂Cl₂) provided a colorless oil (96 mg, quant.). Analytical data: **¹H**

NMR (400 MHz, CDCl₃) δ 7.28 (m, 2H), 7.05 (m, 5H), 6.95 (m, 6H), 4.32 (dd, J = 8.8, 6.6 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.31 (dd, J = 13.6, 8.8 Hz, 1H), 3.20 (s, 3H), 2.55 (dd, J = 13.6, 6.6 Hz, 1H), 2.33 (s, 3H), 2.25 (s, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.3, 170.6, 150.4, 142.3, 139.2, 136.9, 136.1, 134.5, 133.9, 129.1, 128.9, 128.1, 128.0, 127.8, 127.6, 127.1, 66.6, 53.1, 52.8, 49.8, 41.2, 38.0, 21.3, 21.0; **IR** (thin film, cm⁻¹) 3053, 3024, 2952, 2923, 1732, 1599, 1434, 1343, 1252; **TLC** (5% Et₂O/CH₂Cl₂) R_f = 0.67; **LRMS** (ESI⁺) Calcd. for C₃₀H₃₂NO₆S: 534.20, Found: 534.26.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-3-pentyl-4-(p-methoxyphenyl)cyclopent-2-ene-1,1-dicarboxylate (1.49): The title compound was prepared according to General Procedure B using dimethyl 2-(p-methoxyphenyl)cyclopropane-1,1-dicarboxylate **1.33** (47

mg, 0.18 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white crystalline solid (87 mg, 89%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.74 (br s, 2H), 7.25 (d, J = 7.4 Hz, 2H), 7.08 (br s, 2H), 6.86 (d, J = 7.4 Hz, 2H), 3.80 (s, 6H), 3.75 (s, 3H), 3.60 (br s, 1H), 3.19 (s, 3H), 2.88 (br s, 1H), 2.55 (br s, 1H), 2.37 (s, 3H), 1.25-0.91 (m, 8H), 0.73 (t, J = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 172.4, 169.0, 158.4, 152.6, 143.2, 137.0, 134.4, 133.1, 129.4, 128.9, 127.3, 113.9, 66.1, 55.1, 52.2, 46.7, 41.4, 37.7, 31.2, 26.8, 25.4, 21.9, 21.3, 13.7 (one peak missing due to peak overlap); **mp** 125-127 °C; **IR** (thin film, cm⁻¹) 2953, 2930, 2861, 1732, 1611, 1513, 1456, 1347; **TLC** (20% EtOAc/hexanes) R_f = 0.16; **HRMS** (ESI⁺) Calcd. for C₂₉H₃₈NO₇S: 544.2363, Found: 544.2368.



Dimethyl

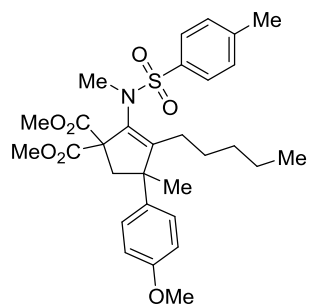
2-((N,4-dimethylphenyl)sulfonamido)-4-(p-

methoxyphenyl)-3-phenylcyclopent-2-ene-1,1-dicarboxylate (1.50):

The title compound was prepared according to General Procedure B using dimethyl 2-(p-methoxyphenyl)cyclopropane-1,1-dicarboxylate **1.33** (46

mg, 0.18 mmol) and N,4-dimethyl-N-(phenylethynyl)benzenesulfonamide **1.46** (100 mg, 0.35 mmol). Flash chromatography (20% EtOAc/hexanes) provided a yellow solid (97 mg, quant.).

Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.22 (m, 2H), 7.04 (m, 2H), 7.02 (m, 1H), 6.89 (m, 6H), 6.72 (m, 2H), 4.27 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.26 (dd, *J* = 14.0, 8.4, 1H), 3.16 (s, 3H), 2.52 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.17 (s, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.3, 170.7, 158.2, 150.5, 142.4, 136.9, 134.5, 134.4, 133.8, 129.2, 128.9, 128.1, 127.8, 127.6, 127.1, 113.8, 66.6, 55.1, 53.1, 52.8, 49.5, 41.2, 38.0, 21.3; **mp** 152-154 °C; **IR** (thin film, cm⁻¹) 3055, 2999, 2952, 2838, 1733, 1611, 1513, 1435, 1342, 1250; **TLC** (20% EtOAc/hexanes) *R_f* = 0.08; **LRMS** (ESI⁺) Calcd. for C₃₀H₃₂NO₇S: 550.19, Found: 550.19.



Dimethyl

2-((N,4-dimethylphenyl)sulfonamido)-4-(p-

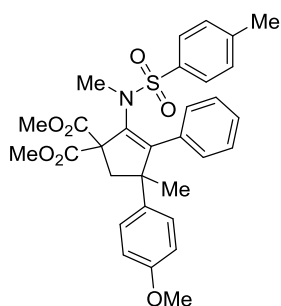
methoxyphenyl)-4-methyl-3-pentylcyclopent-2-ene-1,1-

dicarboxylate (1.51): The title compound was prepared according to General Procedure B using dimethyl 2-(p-methoxyphenyl)-2-methylcyclopropane-1,1-dicarboxylate **1.34** (50 mg, 0.18 mmol) and N-

(hept-1-yn-1-yl)-N,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white amorphous solid (64 mg, 64%).

Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.28 (m, 4H), 6.89 (br s, 2H), 3.82 (s, 3H), 3.77 (s, 6H), 3.27 (s, 3H), 2.39 (s, 3H), 2.23 (br s, 1H), 1.47 (br s, 4H), 1.32-1.14 (m, 2H), 1.01 (s, 1H), 0.93 (m, 3H), 0.77 (m, 2H), 0.69 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150

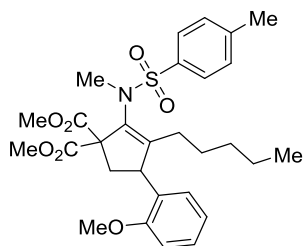
MHz, CDCl₃) δ 173.6, 169.3, 157.9, 156.5, 143.2, 139.4, 137.8, 132.4, 129.4, 127.6, 127.3, 113.5, 65.7, 55.2, 52.9, 52.8, 49.8, 49.7, 38.0, 32.2, 27.5, 27.2, 23.4, 21.8, 21.4, 13.8; **mp** 140-142 °C; **IR** (thin film, cm⁻¹) 2951, 2930, 2871, 1733, 1609, 1512, 1457, 1345, 1252; **TLC** (20% EtOAc/hexanes) R_f = 0.15; **LRMS** (ESI⁺) Calcd. for C₃₀H₄₀NO₇S: 558.26, Found: 558.27.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-4-(p-methoxyphenyl)-4-methyl-3-phenylcyclopent-2-ene-1,1-dicarboxylate

(1.52): The title compound was prepared according to General Procedure B using dimethyl 2-(p-methoxyphenyl)-2-methylcyclopropane-1,1-dicarboxylate **1.34** (48 mg, 0.18 mmol) and N,4-dimethyl-N-

(phenylethynyl) benzenesulfonamide **1.46** (100 mg, 0.35 mmol). Flash chromatography (10% → 20% EtOAc/hexanes) provided a white solid (52 mg, 53%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.37 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.09 (tt, J = 7.5, 1.3 Hz, 1H), 6.92 (m, 6H), 6.58 (d, J = 7.5 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.43 (d, J = 14.4 Hz, 1H), 3.13 (s, 3H), 2.54 (d, J = 14.4 Hz, 1H), 2.29 (s, 3H), 1.40 (s, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 173.1, 170.0, 158.2, 155.3, 142.4, 139.0, 137.0, 134.3, 132.3, 129.0, 128.9, 128.4, 127.6, 127.5, 127.1, 113.6, 65.6, 55.3, 53.2, 53.0, 50.6, 49.3, 37.7, 24.1, 21.4; **mp** 138-140 °C; **IR** (thin film, cm⁻¹) 3066, 2952, 2839, 1732, 1609, 1514, 1457, 1435, 1339; **TLC** (20% EtOAc/hexanes) R_f = 0.13; **LRMS** (ESI⁺) Calcd. for C₃₁H₃₄NO₇S: 564.21, Found: 564.19.

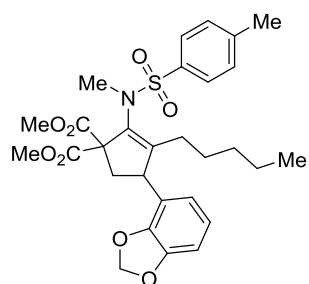


Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-3-pentyl-4-(o-methoxyphenyl)cyclopent-2-ene-1,1-dicarboxylate

(1.53): The title compound was prepared according to General Procedure B using dimethyl 2-(o-methoxyphenyl)cyclopropane-1,1-dicarboxylate **1.35** (47

mg, 0.18 mmol) and N-(hept-1-yn-1-yl)-N,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36

mmol). Flash chromatography (20% EtOAc/hexanes) provided a white crystalline solid (99 mg, quant.). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.79 (br s, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.13 (br s, 1H), 6.97 (br s, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.24 (br s, 1H), 3.82 (s, 3H), 3.77 (s, 6H), 3.21 (s, 3H), 2.93 (br s, 1H), 2.55 (br s, 1H), 2.39 (s, 3H), 1.14-0.90 (m, 8H), 0.76 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 172.6, 169.2, 157.1, 153.1, 143.1, 137.1, 132.6, 130.3, 129.3, 129.2, 127.8, 127.5, 120.8, 110.5, 66.3, 55.2, 52.7, 40.2, 38.8, 37.8, 31.2, 27.2, 25.6, 22.0, 21.4, 13.7 (one peak missing due to peak overlap); **mp** 112-113 °C; **IR** (thin film, cm⁻¹) 2953, 2926, 2861, 1733, 1599, 1457, 1347, 1246; **TLC** (20% EtOAc/hexanes) *R_f* = 0.27; **LRMS** (ESI⁺) Calcd. for C₂₉H₃₈NO₇S: 544.24, Found: 544.26.

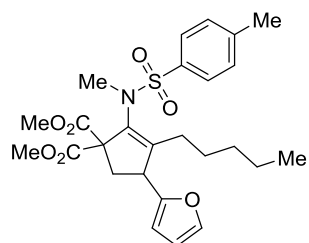


Dimethyl 4-(benzo[*d*][1,3]dioxol-4-yl)-2-((*N*,4-dimethylphenyl)sulfonamido)-3-pentylcyclopent-2-ene-1,1-

dicarboxylate (1.54): The title compound was prepared according to General Procedure B using dimethyl 2-(benzo[*d*][1,3]dioxol-4-yl)

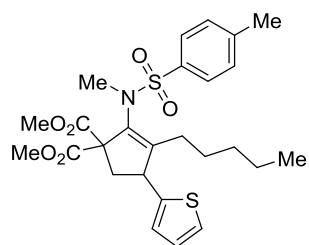
cyclopropane-1,1-dicarboxylate **1.36** (50 mg, 0.18 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36 mmol). Flash chromatography (20% EtOAc/hexanes) provided a brown crystalline solid (64 mg, 64%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.77 (br s, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.66 (br s, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 5.95 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.63 (br s, 1H), 3.19 (s, 3H), 2.83 (br s, 1H), 2.60 (br s, 1H), 2.40 (s, 3H), 1.16-0.94 (m, 8H), 0.76 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 172.4, 169.0, 152.5, 147.9, 146.4, 143.2, 137.0, 136.4, 133.4, 129.4, 127.4, 121.2, 108.2, 108.1, 101.0, 66.1, 52.8, 52.7, 47.3, 41.4, 37.7, 31.3, 26.9, 25.6, 22.0, 21.4, 13.8; **mp** 118-119 °C; **IR** (thin film, cm⁻¹) 2951, 2928, 2871, 1732, 1599, 1488, 1347, 1247;

TLC (20% EtOAc/hexanes) R_f = 0.22; **LRMS** (ESI⁺) Calcd. for C₂₉H₃₆NO₈S: 558.22, Found: 558.27.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-4-(furan-2-yl)-3-pentylcyclopent-2-ene-1,1-dicarboxylate (1.55): The title compound was prepared according to General Procedure B using dimethyl 2-(furan-

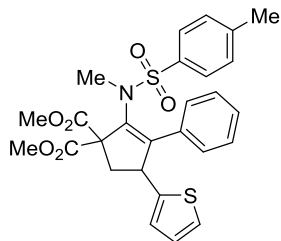
2-yl)cyclopropane-1,1-dicarboxylate **1.37** (87 mg, 0.39 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (216 mg, 0.78 mmol). Flash chromatography (20% EtOAc/hexanes), followed by purification by HPLC (15% EtOAc/hexanes) provided a light brown oil (83 mg, 46%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.78 (br s, 2H), 7.36 (s, 1H), 7.27 (d, J = 7.6 Hz, 2H), 6.32 (s, 1H), 6.12 (br s, 1H), 3.82 (s, 4H), 3.77 (s, 3H), 3.18 (s, 3H), 2.45 (m, 1H), 2.41 (s, 3H), 1.63 (br s, 1H), 1.27 (br s, 2H), 1.09-0.97 (m, 6H), 0.79 (t, J = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.8, 168.9, 154.4, 150.8, 143.2, 141.7, 136.8, 133.3, 129.4, 127.6, 110.2, 106.6, 65.8, 62.4, 58.0, 52.8, 40.9, 37.7, 31.5, 27.4, 26.0, 22.0, 21.4, 13.8; **IR** (thin film, cm⁻¹) 3117, 2954, 2929, 2871, 1733, 1598, 1456, 1349, 1269; **TLC** (20% EtOAc/hexanes) R_f = 0.24; **LRMS** (ESI⁺) Calcd. for C₂₆H₃₄NO₇S: 504.21, Found: 504.27.



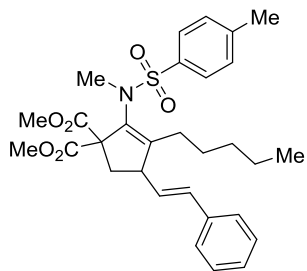
Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-3-pentyl-4-(thiophen-2-yl)cyclopent-2-ene-1,1-dicarboxylate (1.56): The title compound was prepared according to General Procedure B using dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate **1.38** (43 mg,

0.18 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36 mmol). Flash chromatography (20% EtOAc/hexanes), followed by purification by HPLC (15% EtOAc/hexanes) provided a clear oil (78 mg, 84%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.76 (br s, 2H), 7.27 (s, 2H), 7.22 (s, 1H), 6.95 (s, 1H), 6.86 (s, 1H), 4.01 (br s, 1H), 3.81 (br s,

3H), 3.77 (s, 3H), 3.20 (s, 3H), 3.00 (br s, 1H), 2.66 (br s, 1H), 2.40 (s, 3H), 1.21-0.94 (m, 8H), 0.77 (br s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.1, 168.7, 151.8, 145.6, 143.2, 136.8, 133.3, 129.4, 127.5, 126.7, 125.2, 124.3, 66.0, 52.8, 42.6, 41.8, 38.4, 37.9, 31.4, 26.9, 25.9, 21.9, 21.4, 13.7; **IR** (thin film, cm^{-1}) 2953, 2929, 2861, 1733, 1456, 1434, 1349, 1270, 1156; **TLC** (20% EtOAc/hexanes) R_f = 0.19; **LRMS** (ESI^+) Calcd. for $\text{C}_{26}\text{H}_{34}\text{NO}_6\text{S}_2$: 520.19, Found: 520.25.

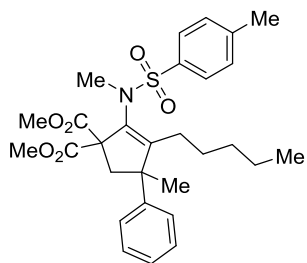


Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-3-phenyl-4-(thiophen-2-yl)cyclopent-2-ene-1,1-dicarboxylate (1.57): The title compound was prepared according to General Procedure B using dimethyl 2-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate **1.38** (42 mg, 0.18 mmol) and *N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide **1.46** (100 mg, 0.35 mmol). Flash chromatography (10% \rightarrow 20% EtOAc/hexanes) provided a yellow oil (85 mg, 93%). Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 7.25 (d, J = 7.8 Hz, 2H), 7.10 (tt, J = 7.4, 1.2 Hz, 1H), 7.05 (d, J = 5.4 Hz, 1H), 7.01 (t, J = 7.4 Hz, 2H), 6.97 (m, 4H), 6.79 (dd, J = 5.4, 3.6 Hz, 1H), 6.72 (d, J = 3.6 Hz, 1H), 4.63 (dd, J = 8.4, 5.4 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.43 (dd, J = 13.6, 8.4 Hz, 1H), 3.41 (s, 3H), 2.66 (dd, J = 13.6, 5.4 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.1, 170.1, 149.6, 145.2, 142.4, 136.9, 134.0, 133.9, 129.0, 128.1, 127.91, 127.88, 127.2, 126.6, 125.4, 124.1, 66.5, 53.2, 52.9, 45.1, 41.2, 38.1, 21.4; **IR** (thin film, cm^{-1}) 3059, 2951, 2859, 1734, 1541, 1435, 1342, 1253, 1152; **TLC** (20% EtOAc/hexanes) R_f = 0.18; **LRMS** (ESI^+) Calcd. for $\text{C}_{27}\text{H}_{28}\text{NO}_6\text{S}_2$: 526.14, Found: 526.18.



Dimethyl (E)-2-((N,4-dimethylphenyl)sulfonamido)-3-pentyl-4-styrylcyclopent-2-ene-1,1-dicarboxylate (1.58): The title compound was prepared according to General Procedure B using dimethyl (*E*)-2-styrylcyclopropane-1,1-dicarboxylate **1.39** (47 mg, 0.18 mmol) and *N*-

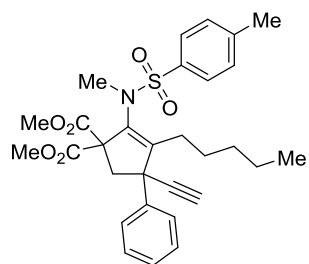
(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36 mmol). Flash chromatography (20% EtOAc/hexanes), followed by purification by HPLC (15% EtOAc/hexanes) provided a yellow oil (66 mg, 69%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.78 (br s, 2H), 7.38-7.33 (m, 4H), 7.31 (d, $J = 7.8$ Hz, 2H), 7.27 (t, $J = 7.2$ Hz, 1H), 6.47 (d, $J = 15.6$ Hz, 1H), 6.02 (br s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.35 (br s, 1H), 3.18 (s, 3H), 2.81 (br s, 1H), 2.43 (s, 3H), 1.76 (br s, 1H), 1.64 (s, 1H), 1.51 (br s, 1H), 1.35 (br s, 1H), 1.14 (br s, 3H), 1.02 (m, 2H), 0.81 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 172.3, 169.2, 152.6, 143.2, 137.0, 136.8, 132.9, 132.0, 130.4, 129.4, 128.6, 127.6, 127.5, 126.2, 66.1, 52.82, 52.76, 45.5, 38.5, 38.1, 31.7, 27.4, 25.8, 22.1, 21.4, 13.9; **IR** (thin film, cm^{-1}) 3029, 2953, 2926, 2866, 1733, 1653, 1457, 1348, 1270, 1155; **TLC** (20% EtOAc/hexanes) $R_f = 0.29$; **LRMS** (ESI^+) Calcd. for $\text{C}_{30}\text{H}_{38}\text{NO}_6\text{S}$: 540.24, Found: 540.31.



Dimethyl 2-((*N*,4-dimethylphenyl)sulfonamido)-4-methyl-3-pentyl-4-phenylcyclopent-2-ene-1,1-dicarboxylate (1.61): The title compound was prepared according to General Procedure B using dimethyl 2-methyl-2-phenylcyclopropane-1,1-dicarboxylate **1.42** (44

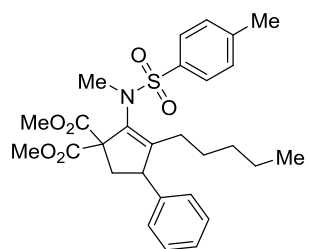
mg, 0.18 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (100 mg, 0.36 mmol). Flash chromatography (20% EtOAc/hexanes), followed by purification by HPLC (15% EtOAc/hexanes) provided a yellow oil (55 mg, 59%). Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.79 (d, $J = 7.8$ Hz, 2H), 7.34 (m, 4H), 7.27 (m, 3H), 3.78 (s, 6H), 3.28 (s, 3H), 2.40 (s, 3H), 1.61 (s, 1H), 1.52 (br s, 4H), 1.28 (br s, 1H), 1.05-0.89 (m, 5H), 0.80-0.73 (m, 2H), 0.68 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 173.6, 169.4, 156.4, 147.3, 143.2, 137.8, 132.8, 129.5, 128.3, 127.4, 126.6, 126.3, 65.9, 52.9, 52.8, 50.3, 49.8, 38.1, 32.2, 27.6, 27.3, 23.3, 21.8,

21.4, 13.8; **IR** (thin film, cm^{-1}) 2953, 2926, 2871, 1734, 1599, 1457, 1435, 1346, 1270; **TLC** (20% EtOAc/hexanes) $R_f = 0.24$; **LRMS** (ESI^+) Calcd. for $\text{C}_{29}\text{H}_{38}\text{NO}_6\text{S}$: 528.24, Found: 528.34.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-4-ethynyl-3-pentyl-4-phenylcyclopent-2-ene-1,1-dicarboxylate (1.62): The title compound was prepared according to General Procedure B using

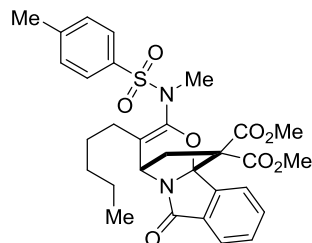
dimethyl 2-ethynyl-2-phenylcyclopropane-1,1-dicarboxylate **1.43** (62 mg, 0.24 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (134 mg, 0.48 mmol). Flash chromatography (20% EtOAc/hexanes) provided a tan solid (72 mg, 56%). Analytical data: **^1H NMR** (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.0$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 2H), 7.41 (t, $J = 8.0$ Hz, 2H), 7.29 (m, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.33 (s, 3H), 2.54 (s, 1H), 2.46 (t, $J = 7.2$ Hz, 1H), 2.40 (s, 3H), 1.42 (br s, 1H), 1.23 (m, 4H), 0.91 (m, 4H), 0.68 (t, $J = 7.2$ Hz, 3H); **^{13}C NMR** (150 MHz, CDCl_3) δ 171.8, 168.5, 151.1, 143.5, 141.6, 136.9, 135.7, 129.5, 128.4, 127.4, 127.3, 126.9, 84.2, 74.8, 66.0, 53.1, 52.7, 50.8, 49.5, 38.0, 31.8, 27.6, 26.1, 21.7, 21.4, 13.7; **mp** 117-118 $^\circ\text{C}$; **IR** (thin film, cm^{-1}) 3276, 3062, 3028, 2954, 2871, 1739, 1599, 1456, 1348; **TLC** (20% EtOAc/hexanes) $R_f = 0.22$; **LRMS** (ESI^+) Calcd. for $\text{C}_{30}\text{H}_{36}\text{NO}_6\text{S}$: 538.23, Found: 538.27.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-3-pentyl-4-phenylcyclopent-2-ene-1,1-dicarboxylate (1.63): The title compound was prepared according to General Procedure B using dimethyl 2-

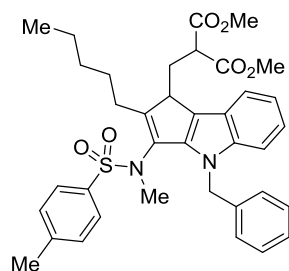
phenylcyclopropane-1,1-dicarboxylate **1.44** (1.86 g, 7.9 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (4.44 g, 15.9 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white solid (3.91 g, 96%). Analytical data: **^1H NMR** (600 MHz, CDCl_3) δ 7.74 (br s, 2H), 7.33 (s, 2H), 7.25 (s, 3H), 7.17 (s, 2H), 3.79 (br s, 3H), 3.76 (s, 3H), 3.64 (br s, 1H), 3.20 (s, 3H), 2.92 (br s, 1H), 2.58 (br s, 1H), 2.16 (s, 3H), 1.25-0.87

(m, 8H), 0.72 (t, $J = 7.2$, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.3, 168.9, 152.3, 143.1, 142.4, 136.9, 133.4, 129.3, 128.5, 127.9, 127.3, 126.8, 66.1, 53.3, 52.6, 47.4, 41.2, 37.6, 31.1, 26.8, 25.4, 21.8, 21.2, 13.6; **mp** 93-94 °C; **IR** (thin film, cm^{-1}) 2953, 1733, 1433, 1384, 1271, 1155, 1087, 667; **TLC** (20% EtOAc/hexanes) $R_f = 0.20$; **LRMS** (ESI^+) Calcd. for $\text{C}_{28}\text{H}_{36}\text{NO}_6\text{S}$: 514.23, Found: 514.27.



Dimethyl 2-((N,4-dimethylphenyl)sulfonamido)-6-oxo-3-pentyl-4H,6H-4,10b-ethano[1,3]oxazino[2,3-a]isoindole-11,11-dicarboxylate (1.79): The title compound was prepared according to General Procedure B using dimethyl 2-phenylcyclopropane-1,1-

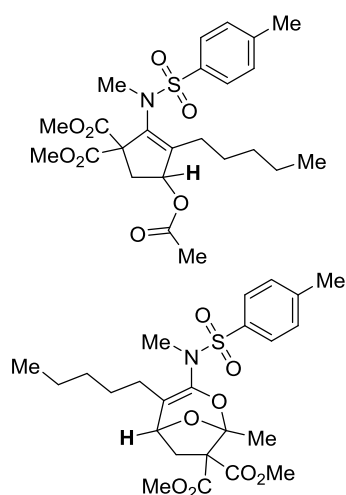
dicarboxylate **S1** (121 mg, 0.4 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (224 mg, 0.8 mmol). Flash chromatography (20% to 40% EtOAc/hexanes) provided a white solid (156 mg, 67%). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, $J = 7.2$ Hz, 1H), 7.56 (dt, $J = 7.2, 1.2$ Hz, 1H), 7.45 (t, $J = 7.4$ Hz, 1H), 7.38 (br s, 2H), 6.76 (br s, 2H), 4.65 (d, $J = 6.4$ Hz, 1H), 3.83 (s, 3H), 3.36 (d, $J = 12.8$ Hz, 1H), 3.22 (s, 3H), 2.88–2.76 (m, 4H), 2.40 (m, 1H), 2.24 (m, 1H), 2.16 (br s, 3H), 1.64–1.28 (m, 6H), 0.92 (m, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 168.1, 167.4, 161.1, 143.1, 141.0, 138.8, 134.5, 131.6, 130.2, 128.7, 127.5, 123.3, 123.1, 118.5, 96.7, 67.2, 53.0, 52.6, 49.5, 47.9, 35.6, 31.5, 29.2, 27.1, 22.3, 21.4, 13.9



Dimethyl 2-((4-benzyl-3-((N,4-dimethylphenyl)sulfonamido)-2-pentyl-1,4-dihydrocyclopenta[b]indol-1-yl)methyl)malonate (1.82):

The title compound was prepared according to General Procedure B using dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **S2** (133 mg, 0.36 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (204 mg, 0.73 mmol). Flash chromatography (10% EtOAc/hexanes) provided a white solid (71 mg, 30%). Analytical data: ^1H

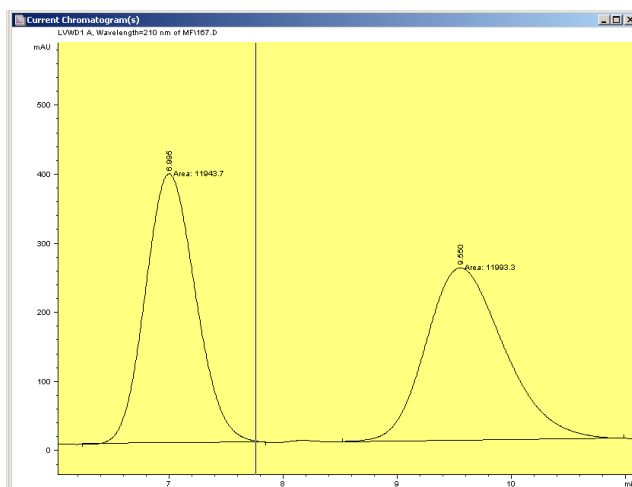
NMR (600 MHz, CDCl₃) δ 7.79 (d, J = 7.8 Hz, 2H), 7.27 (m, 2H), 7.18 (m, 3H), 7.07 (m, 2H), 7.00 (m, 1H), 6.68 (m, 1H), 5.94 (d, J = 7.8 Hz, 1H), 5.43 (d, J = 16.5 Hz, 1H), 5.33 (d, J = 16.5 Hz, 1H), 3.72 (s, 3H), 3.26 (m, 2H), 3.22 (s, 3H), 2.94 (m, 5H), 2.64 (m, 1H), 2.42 (s, 3H), 2.25 (m, 1H), 1.58-1.28 (m, 7H), .878 (t, J = 6.6 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 170.03, 169.96, 146.2, 143.2, 141.9, 139.9, 136.8, 135.8, 134.2, 129.7, 128.7, 128.1, 127.6, 126.7, 120.7, 119.7, 119.5, 119.1, 118.9, 109.7, 52.9, 51.8, 48.2, 46.0, 40.5, 36.7, 31.6, 29.3, 27.1, 26.0, 22.4, 21.5, 14.0.



Dimethyl 4-acetoxy-2-((N,4-dimethylphenyl)sulfonamido)-3-pentylcyclopent-2-ene-1,1-dicarboxylate; dimethyl 3-((N,4-dimethylphenyl)sulfonamido)-1-methyl-4-pentyl-2,8-dioxabicyclo[3.2.1]oct-3-ene-7,7-dicarboxylate (1.84/1.85): The title compound was prepared according to General Procedure B using dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1.83** (50 mg, 0.23 mmol) and *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide

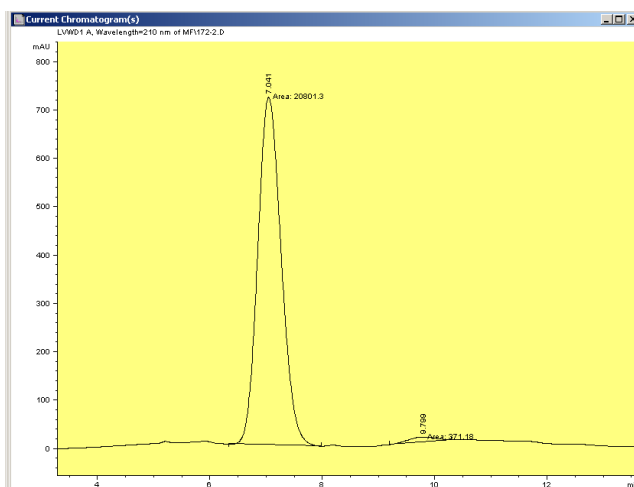
1.45 (129 mg, 0.46 mmol). The ratio of isomers (~20:1 **1.84/1.85**) was determined by the resonances of the α -hydroxy methine protons (shown and bolded) in the crude ¹H NMR, which appear at 5.43 (major) and 4.87 ppm (minor). Analytical data: **¹H NMR** (400 MHz, CDCl₃, **1.84**) δ 7.84 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 5.43 (t, J = 7.4 Hz, 1H), 3.71 (s, 3H), 3.32 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H), 1.58–0.74 (m, 11 H).

SFC analysis of (±)-1.63



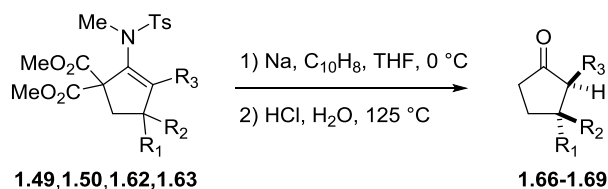
peak #	RT (min)	area (mAU×s)	height (mAU)	area %
1	6.995	11943.74	390.04	49.9
2	9.550	11993.30	249.93	50.1

SFC analysis of (+)-1.63

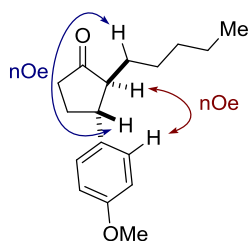


peak #	RT (min)	area (mAU×s)	height (mAU)	area %
1	7.041	20801.28	719.69	98.2
2	9.799	371.18	10.73	1.8

General Procedure C for the Preparation of Cyclopentanones (1.66-1.69)



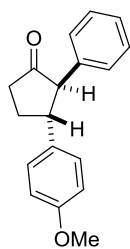
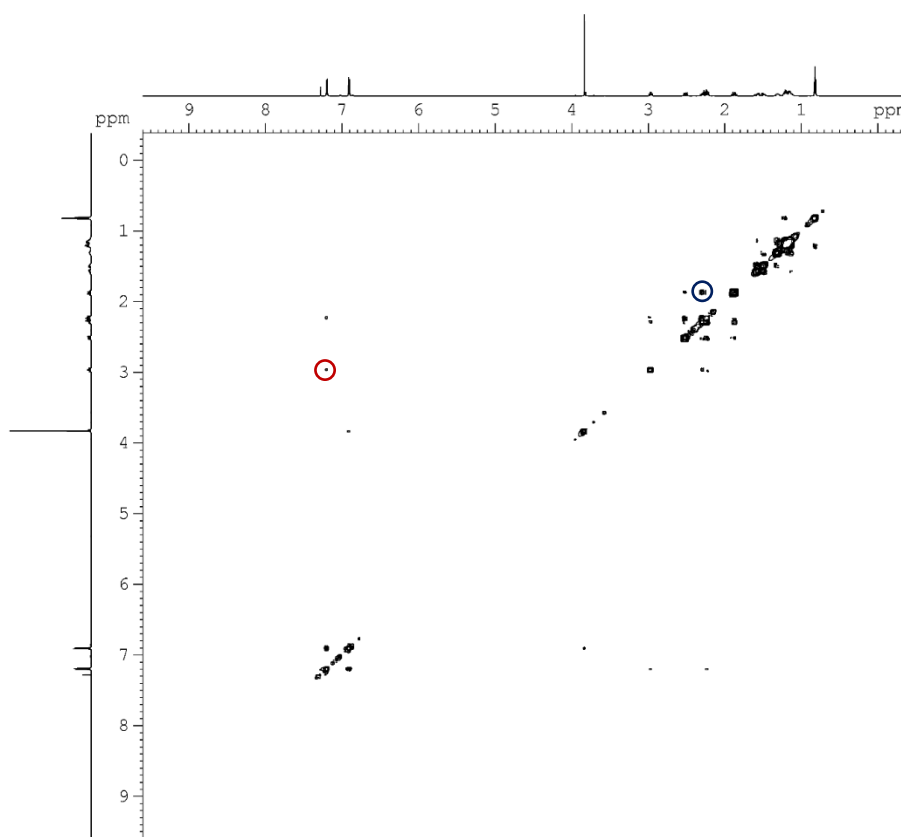
To a flame-dried 10 mL round-bottomed flask, charged with a magnetic stir bar, was added sodium metal (10.0 equiv) and naphthalene (4.0 equiv) under N₂ atmosphere. Anhydrous THF (2 mL) was added to the flask, which was then cooled to 0 °C and rapidly stirred for 1 h. To the resultant dark green solution was added the cyclopentene sulfonamide (1.0 equiv) as a solution in anhydrous THF (0.5 M) via syringe. After complete consumption of the starting material determined by TLC (4 – 18 h), the reaction was quenched with saturated aqueous NH₄Cl solution (3 mL), and the mixture was stirred for 30 min, forming an off white precipitate. The precipitate was removed by filtration, and the aqueous layer was then extracted with EtOAc (2 × 15 mL). The combined organic layer was concentrated by rotary evaporation. To the brown residue was added 3 M HCl (10 mL) and the mixture was heated to reflux (125 °C) for 36 – 72 h, when a white solid appeared in the reflux condenser. The reaction was then cooled to room temperature and the aqueous layer was first extracted with EtOAc (20 mL), then basified with saturated Na₂CO₃ solution and further extracted with EtOAc (20 mL). The combined organic layer was washed with brine (30 mL), dried over Na₂SO₄, and concentrated by rotary evaporation. The brown oil was then purified by column chromatography, yielding the desired product.



3-(*p*-methoxyphenyl)-2-pentylcyclopentan-1-one (1.66): The title compound was prepared according to General Procedure C using dimethyl 2-((*N*,4-dimethylphenyl)sulfonamido)-3-pentyl-4-(*p*-methoxyphenyl) cyclopent-2-ene-1,1-dicarboxylate **1.49** (2.00 g, 3.7 mmol), naphthalene

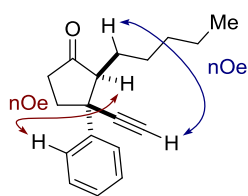
(1.88 g, 14.7 mmol), and sodium (0.85 g, 36.8 mmol), and 3 M HCl (50 mL). Flash

chromatography (20% EtOAc/hexanes) provided a dark yellow oil (0.79 g, 83%) as a single diastereomer. Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.20 (d, *J* = 6.8 Hz, 2H), 6.91 (d, *J* = 6.8 Hz, 2H), 3.82 (s, 3H), 2.97 (dt, *J* = 12.0, 6.0 Hz, 1H), 2.51 (m, 1H), 2.26 (m, 3H), 1.88 (m, 1H), 1.55 (m, 2H), 1.38-1.10 (m, 6H), 0.83 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 219.2, 158.2, 134.8, 127.8, 113.8, 55.7, 54.9, 47.6, 38.1, 31.7, 30.1, 27.6, 26.1, 22.1, 13.7; **IR** (thin film, cm⁻¹) 3434, 1735, 1646, 1514, 1246, 828; **TLC** (20% EtOAc/hexanes) *R_f* = 0.39; **LRMS** (ESI⁺) Calcd. for C₁₇H₂₅O₂: 261.19, Found: 261.19. **NOESY data shown below:**



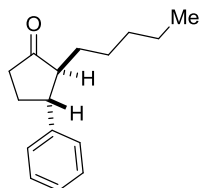
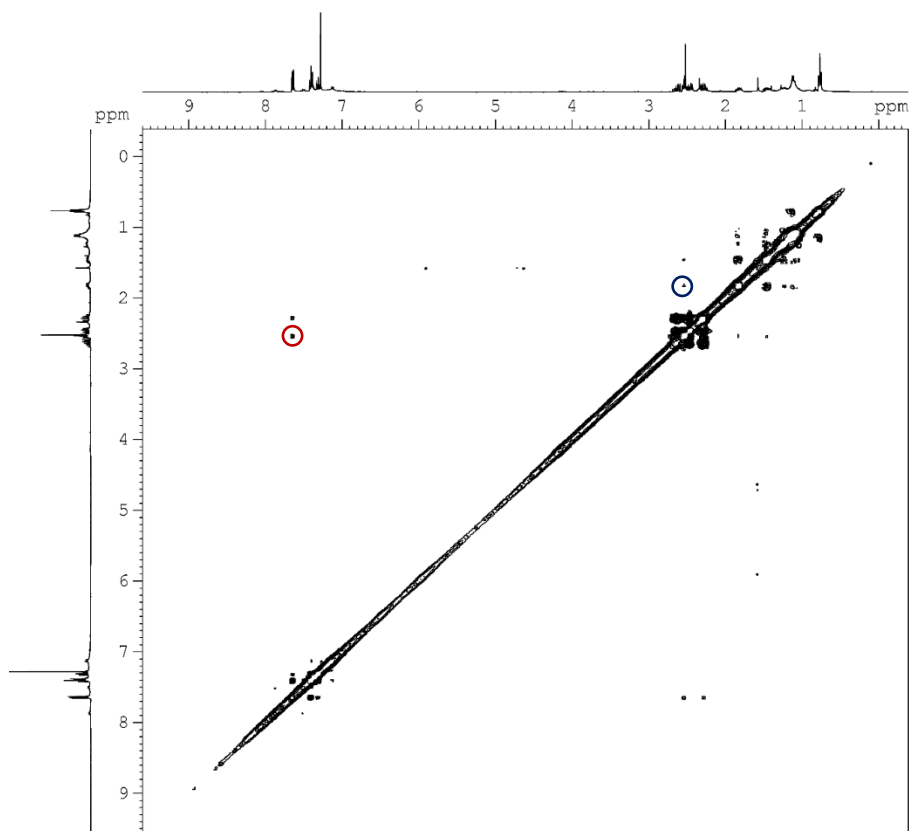
3-(*p*-methoxyphenyl)-2-phenylcyclopentan-1-one (1.67): The title compound was prepared according to General Procedure C using dimethyl 2-((*N*,4-dimethylphenyl)sulfonamido) -4- (*p*-methoxyphenyl) -3- phenylcyclopent-2-ene-1,1-dicarboxylate **1.50** (77 mg, 0.14 mmol), naphthalene (72 mg, 0.56 mmol), and sodium (32 mg, 1.4 mmol), and 3 M HCl (10 mL). Flash chromatography (20% EtOAc/hexanes) provided

a brown oil (16 mg, 43%) as a single diastereomer. Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.29 (m, 2H), 7.23 (m, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.06 (d, $J = 7.2$ Hz, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 3.78 (s, 3H), 3.50 (td, $J = 12.0, 6.0$ Hz, 1H), 3.44 (d, $J = 12.0$ Hz, 1H), 2.75-2.67 (m, 1H), 2.55-2.44 (m, 2H), 2.13-2.09 (m, 1H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 216.7, 158.3, 137.1, 133.6, 128.6, 128.5, 127.9, 126.9, 113.9, 63.0, 55.1, 49.6, 38.8, 29.6; **IR** (thin film, cm^{-1}) 3243, 2928, 2853, 2360, 2065, 1742, 1612, 1515, 1248, 1034; **TLC** (20% EtOAc/hexanes) $R_f = 0.26$; **LRMS** (ESI^+) Calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_2$: 267.14, Found: 267.11.



3-ethynyl-2-pentyl-3-phenylcyclopentan-1-one (1.68): The title compound was prepared according to General Procedure C using dimethyl 2-((*N*,4-dimethylphenyl)sulfonamido) -4- ethynyl-3-pentyl-4-phenylcyclopent-2-

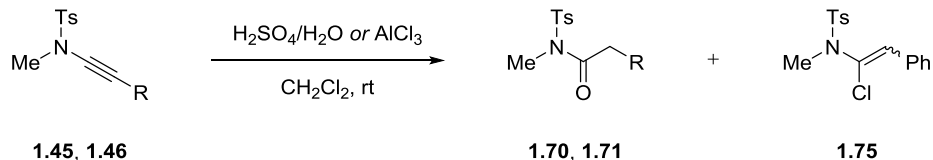
ene-1,1-dicarboxylate **1.62** (169 mg, 0.31 mmol), naphthalene (254 mg, 2.0 mmol), and sodium (114 mg, 4.9 mmol), and 3 M HCl (25 mL). Flash chromatography (10% EtOAc/hexanes) provided a brown oil (24 mg, 30%) as a single diastereomer. Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 (m, 2H), 7.40 (m, 2H), 7.31 (tt, $J = 7.2, 1.2$ Hz, 1H), 2.69-2.59 (m, 1H), 2.56-2.53 (m, 2H), 2.52 (s, 1H), 2.50-2.43 (m, 1H), 2.36-2.24 (m, 1H), 1.87-1.78 (m, 1H), 1.50-1.41 (m, 1H), 1.28-1.20 (m, 2H), 1.16-1.05 (m, 4H), 0.77 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 217.0, 141.6, 128.5, 127.2, 126.1, 84.1, 75.5, 60.2, 49.8, 37.9, 36.2, 31.7, 27.2, 26.4, 22.2, 13.9; **IR** (thin film, cm^{-1}) 3292, 3060, 2929, 2363, 1742, 1456, 1277, 1155, 744, 699; **TLC** (20% EtOAc/hexanes) $R_f = 0.52$; **LRMS** (ESI^+) Calcd. for $\text{C}_{18}\text{H}_{23}\text{O}$: 255.17, Found: 255.14. **NOESY data shown below:**



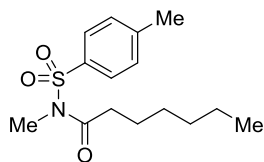
2-pentyl-3-phenylcyclopentan-1-one (1.69): The title compound was prepared according to General Procedure C using dimethyl 2-((*N*,4-dimethylphenyl)sulfonamido)-3-pentyl-4-phenylcyclopent-2-ene-1,1-

dicarboxylate **1.63** (0.38 g, 0.7 mmol), naphthalene (0.38 g, 3.0 mmol), and sodium (0.17 g, 7.4 mmol), and 3 M HCl (30 mL). Flash chromatography (20% EtOAc/hexanes) provided a dark yellow oil (70 mg, 41%) as a single diastereomer. Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.37 (t, *J* = 7.2 Hz, 2H), 7.31-7.26 (m, 3H), 3.04 (dt, *J* = 12.0, 6.4 Hz, 1H), 2.51 (dd, *J* = 16.4, 8.0 Hz, 1H), 2.29 (m, 3H), 2.00-1.84 (m, 1H), 1.59-1.47 (m, 2H), 1.36-1.28 (m, 1H), 1.25-1.11 (m, 5H), 0.82 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 219.0, 142.9, 128.4, 126.9, 126.5, 55.5, 48.4, 38.0, 31.6, 30.0, 27.7, 26.0, 22.1, 13.7; **IR** (thin film, cm⁻¹) 3496, 2957, 1735, 1652, 1265, 737, 700; **TLC** (20% EtOAc/hexanes) *R_f* = 0.51; **LRMS** (ESI⁺) Calcd. for C₁₆H₂₃O: 231.17, Found: 231.07.

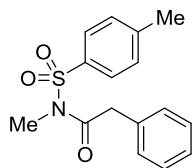
General Procedure D for the Preparation of Ynamide Hydrolysis Products (1.70, 1.71, 1.75)

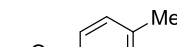


To 1 dram vials containing the ynamide (0.15 mmol) in CH₂Cl₂ (1 mL) was added the appropriate acid (30% H₂SO₄/H₂O or anhydrous AlCl₃). The reaction was allowed to stir at room temperature for 4 h, or until the reaction was deemed complete by TLC analysis. In the case of the hydrolysis products **1.70**, **1.71**, the organic layer was collected, dried over Na₂SO₄, filtered, and concentrated, providing analytically pure material. In the case of enamine **1.75**, the reaction was concentrated, and then purified by column chromatography (20% EtOAc/hexanes), yielding a single alkene isomer.

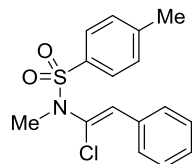


***N*-methyl-*N*-tosylheptanamide (1.70):** The title compound was prepared according to General Procedure D using *N*-(hept-1-yn-1-yl)-*N*,4-dimethylbenzenesulfonamide **1.45** (50 mg, 0.17 mmol) and 30% H₂SO₄ (1 mL). The reaction yielded a clear oil of good purity without further purification in quantitative yield. Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 3.01 (s, 3H), 2.64 (t, *J* = 7.4 Hz, 2H), 2.44 (s, 3H), 1.57 (m, 2H), 1.25 (m, 8H), 0.857 (t, *J* = 7.2 Hz, 3H).



 ***N*-methyl-2-phenyl-*N*-tosylacetamide (1.71):** The title compound was prepared according to General Procedure D using *N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide **1.46** (45 mg, 0.16 mmol) and 30% H₂SO₄ (1 mL). The reaction yielded a clear oil of good purity without further purification in quantitative yield. Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.21 (m, 5H) 7.05

(m, 2H), 3.96 (s, 2H), 3.20 (s, 3H), 2.36 (s, 3H); **LRMS** (ESI⁺) Calcd. for C₁₆H₁₈NO₃S: 304.10, Found: 304.10.



(Z)-N-(1-chloro-2-phenylvinyl)-N,4-dimethylbenzenesulfonamide (1.75):

The title compound was prepared according to General Procedure D using *N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide **1.46** (50 mg, 0.18 mmol) and AlCl₃ (1 equiv). Column chromatography yielded a white solid of good purity in near quantitative yield. Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.38 (m, 2H), 7.33 (m, 3H), 6.67 (s, 1H), 3.05 (s, 3H), 2.46 (s, 3H).

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CHAPTER TWO:
KINETIC SEPARATION AND ASYMMETRIC REACTIONS OF NORCARADIENE CYCLOADDUCTS:
FACILITATED ACCESS VIA H₂O-ACCELERATED CYCLOADDITION[†]

2.1 Introduction

Highly-substituted cyclohexanes comprise a large subset of valuable natural and laboratory-prepared molecules;¹ consequently, efficient assembly of these structural subunits remains a topic of great interest.² The impact of cycloaddition reactions on advances in this general area cannot be overstated;³ however, traditional cycloaddition approaches to the preparation of these functionalities are often constrained to specific substitution patterns, and stereochemistry is dictated by the nature of the starting materials employed.⁴ In this chapter, we utilize simple benzenoids as a platform for generating highly substituted cyclohexane derivatives. By initially disrupting aromaticity through an intermolecular Buchner reaction, we were able to generate norcaradienes (or their tautomeric cycloheptatrienes), as a mixture of regioisomers in the case of substituted aromatic substrates. Subsequent reaction with dienophiles allowed for the kinetic separation of many of the regioisomeric mixtures by exploiting the rate differences of the various regioisomers with dienophiles, facilitated by the rate acceleration of performing the cycloaddition reactions “on water.” The resultant *meso*-cycloadducts were successfully desymmetrized, providing up to seven contiguous stereocenters in three steps from commercial benzene.

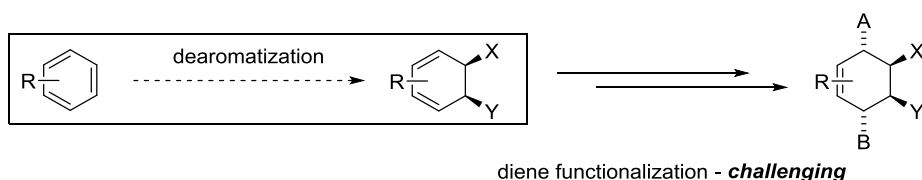
[†] Reprinted in part with permission from Mackay, W. D.; Johnson, J. S. *Org. Lett.* **2016**, *18*, 536–539.

2.2 Background

2.2.1 Importance and Application of Dearomatization in Synthesis

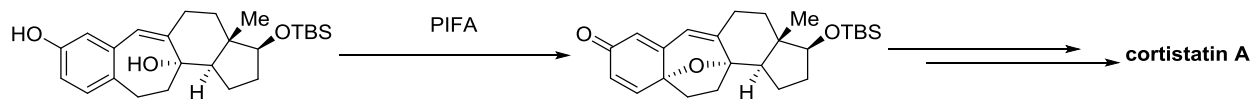
Despite their obvious potential in preparing substituted cyclohexanes, the direct manipulation of benzene derivatives in such endeavors remains an underutilized approach. As inexpensive commodity feedstock materials, benzene derivatives are frequently available in kilogram quantities and in a variety of substitution patterns.⁵ Furthermore, the pre-existing six-membered ring and latent unsaturation in benzene derivatives (enabling downstream functionalization) could streamline the preparation of stereodefined cyclohexanes (Scheme 2-1).

Scheme 2-1. Rapid Complexity-Building of Dearomatized 1,2-Disubstituted Cyclohexadienes



Of the extant methods for complexity-building dearomatizations of benzenes, arguably the most widely utilized are phenol oxidations.⁶ Treatment of phenols with highly oxidized metals and halogens (i.e., $\text{Pb}(\text{OAc})_4$,⁷ $\text{Cu}(\text{II})/\text{O}_2$,⁸ PIDA,⁹ NaIO_4 ,¹⁰ etc.) in the presence of an external or pendant nucleophile allows for rapid generation of both *p*- and *o*-quinones and their derivatives. Application of this chemistry has been applied towards the synthesis of numerous natural products (Scheme 2-2).¹¹

Scheme 2-2. Selected Example of Oxidative Dearomatization of Phenols in Synthesis

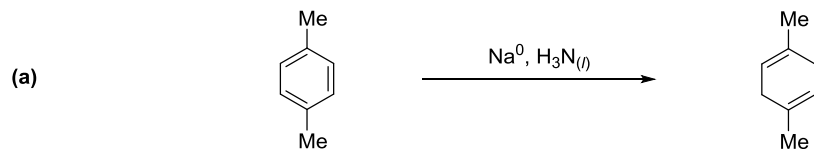


Aside from oxidative methods, reductive dearomatization (i.e., the Birch reduction) allows for the expedient synthesis of 1,4-dienes through the action of solvated electrons in liquid ammonia (Scheme 2-3a).¹² Harman has pioneered stoichiometric metal complexation as a means for

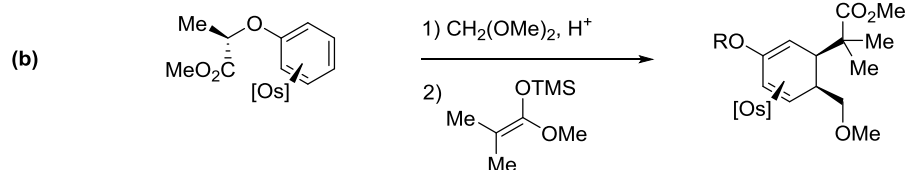
dearomatization, whereby strongly π -basic metals render aromatic rings nucleophilic (Scheme 2-3b).¹³ Along these lines, π -acidic metal complexation allows for facile nucleophilic attack of the metal-bound arene.^{13a,14} Enzymatic methods are to date the most effective method of generating enantioenriched cyclohexadiene intermediates directly from achiral aromatic substrates. The action of toluene dioxygenase in *Pseudomonas putida* allowing for the asymmetric dihydroxylation of toluene, is one pronounced example of such a transformation (Scheme 2-3c).¹⁵

Scheme 2-3. Other Selected Arene Dearomatization Reactions

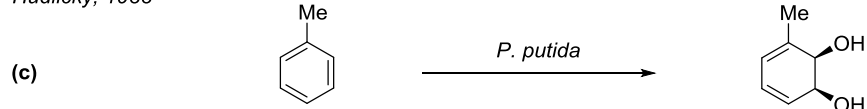
Birch, 1944



Harman, 2000



Hudlicky, 1988

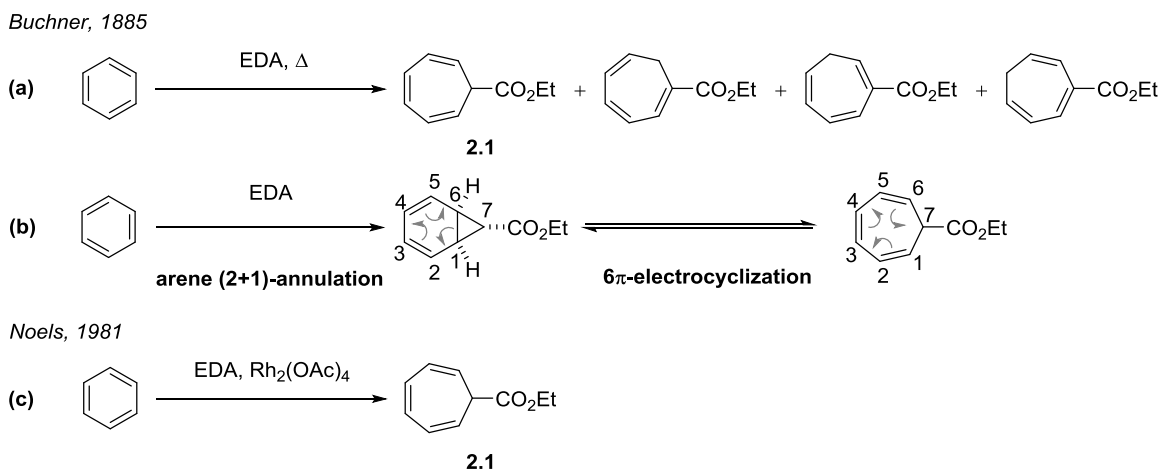


2.2.2 The Buchner Reaction

Of the extant methods of arene dearomatization, we were initially drawn towards direct benzene cyclopropanation—the Buchner reaction—that was first discovered in 1885 by the thermolysis of ethyl diazoacetate (EDA) in benzene.¹⁶ The products were found to be an inseparable mixture of cycloheptatriene (CHT) isomers that arose from successive 1,5-hydride shifts of the nascent cycloheptatriene **2.1** (Scheme 2-4a), formed from a 6π -electrocyclization of the initially formed norcaradiene (NCD; Scheme 2-4b); for a brief discussion on factors that influence the NCD/CHT equilibrium, see section 2.2.3. It was not until the discovery of transition

metal catalyzed arene cyclopropanation that single CHT isomers from benzene could be isolated (Scheme 2-4c).¹⁷

Scheme 2-4. Seminal Investigations into Benzene Cyclopropanation

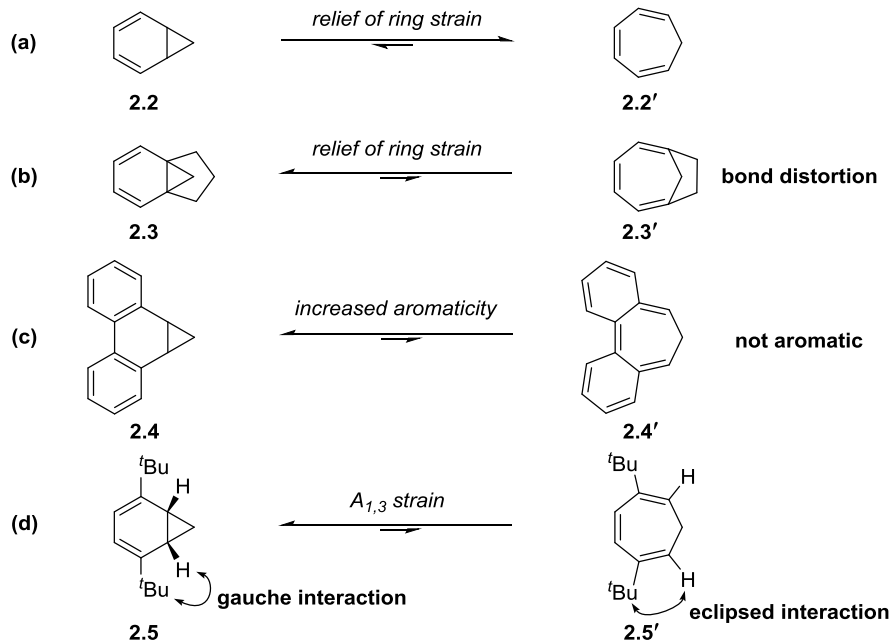


2.2.3 Factors Influencing the Norcaradiene/Cycloheptatriene Equilibrium

The direction of the NCD/CHT equilibrium has been a matter of significant investigation, and some of the many factors that are influential therein are summarized in Scheme 2-5. Devoid of substitution, the parent system ($\mathbf{2.2} \rightleftharpoons \mathbf{2.2'}$) natively favors the CHT, since the latent ring strain of the cyclopropyl ring (~ 27 kcal/mol) is relieved (Scheme 2-5a).¹⁸

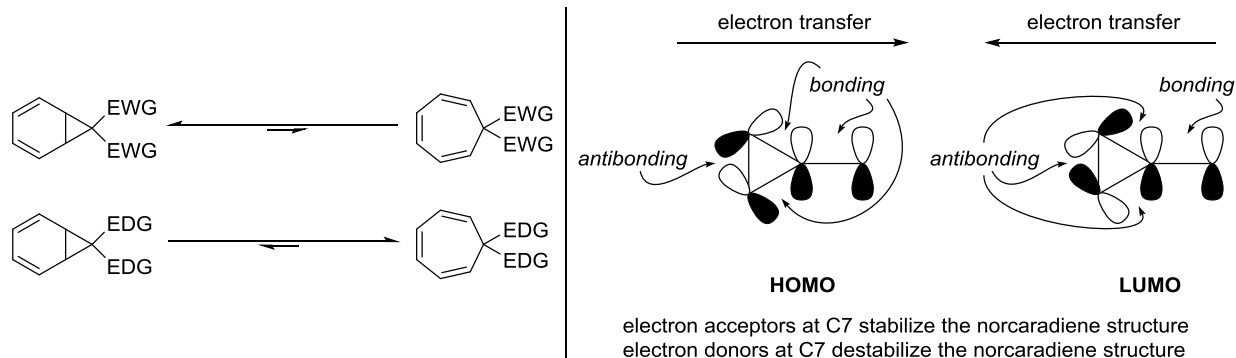
This ring-opening can be disfavored by tethering the C1 and C6 carbons in $\mathbf{2.3}$, thereby imposing significant bond distortion in the CHT form $\mathbf{2.3'}$ (Scheme 2-5b). The NCD isomer can also be favored by allowing for increased conjugation, as shown in Scheme 2-5c with the inclusion of two fused aromatic rings in $\mathbf{2.4}$, which are rendered non-aromatic in the CHT isomer $\mathbf{2.4'}$. Finally, bulky substitution at the C2 and C5 positions tends to favor the NCD isomer $\mathbf{2.5}$ due to relief of $A^{1,3}$ strain between the substituents at C1 and C2 in $\mathbf{2.5'}$ (Scheme 2-5d).¹⁸

Scheme 2-5. Influences of Substitution at C1-C6 on the NCD/CHT Equilibrium



The most general substitution pattern that affects the NCD/CHT equilibrium predictably is the inclusion of a π -acceptor at C7 (Scheme 2-6). Since the π -orbitals of the C7 substituents favorably overlap with the Walsh orbitals of the cyclopropyl ring of NCDs, the identity of a π -acceptor or donor at this position greatly influences the NCD/CHT equilibrium. In the case of π -acceptors, the NCD is more favorable through stabilization of the HOMO, concomitant with shortening of the C1–C6 bond; the same phenomenon is not observed with σ -acceptors (i.e., CF_3). Likewise, in the case of π -donors, the CHT is favored through stabilization of the LUMO, resulting in elongation of the C1–C6 bond. The inclusion of two electron-acceptors at C7 provides a significant stabilization effect, such that the parent benzene-derived NCD is the favored isomer without any other substitution.¹⁸

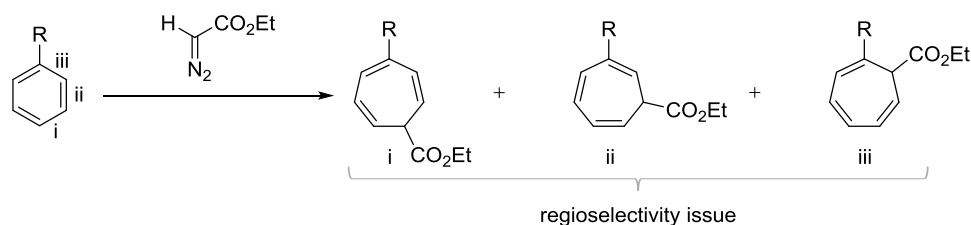
Scheme 2-6. Frontier Molecular Orbital Analysis of C7 Substitution to NCD/CHT Equilibrium



2.2.4 Comparison between the Intra- and Intermolecular Buchner Reaction

Although the initial reports of benzenoid cyclopropanation were performed intermolecularly, to date, there are limited examples of such dearomatized compounds as viable synthetic intermediates. A likely explanation of this phenomenon resides in controlling the regioselectivity of the Buchner reaction of substituted aromatic compounds. For monosubstituted benzene (i.e., toluene, chlorobenzene), three regioisomeric possibilities exist for the Buchner product identity via cyclopropanation at each site of unsaturation (Scheme 2-7);¹⁷ this problem is further complicated as the substitution pattern is increased.

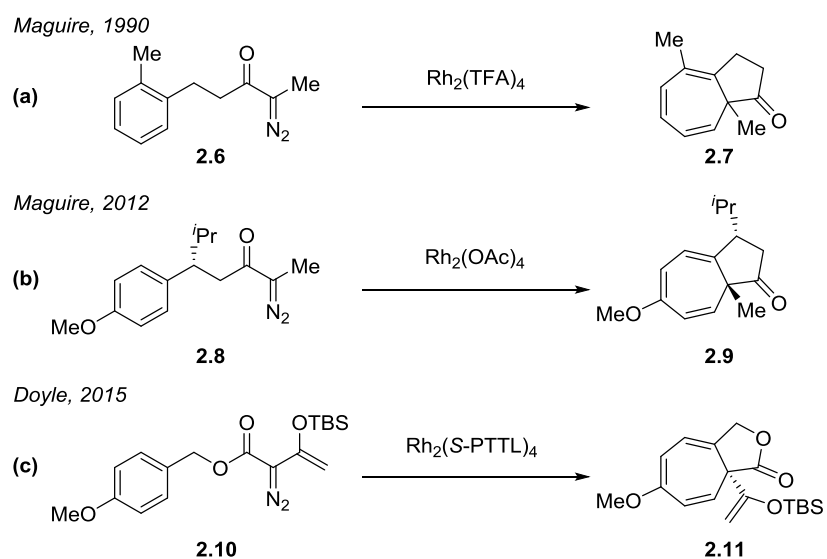
Scheme 2-7. Inherent Challenges Using Norcaradienes as Synthetic Intermediates



In prior art, this regiochemical preference has been biased by rendering the cyclopropanation intramolecular.¹⁹ Through the incorporation of a diazo moiety tethered to a substituted arene, the Buchner products can be obtained with high regioselectivity (Scheme 2-8). 2-Substituted aromatic compounds **2.6** can be selectively differentiated, whereby the least

sterically encumbered cycloheptatrienyl product **2.7** is formed (Scheme 2-8a).^{19a} Substitution at the benzylic position can effect high levels of diastereoselectivity, allowing for enantioenriched CHT products **2.9** from readily accessible materials (Scheme 2-8b).^{19d} Chiral rhodium(II) complexes are shown to enantioselectively desymmetrize symmetrically substituted aromatic compounds **2.10** (Scheme 2-8c), although the CHT products **2.11** tended to partially racemize upon prolonged reaction times.^{19f}

Scheme 2-8. Selected Examples of Intramolecular Buchner Reactions



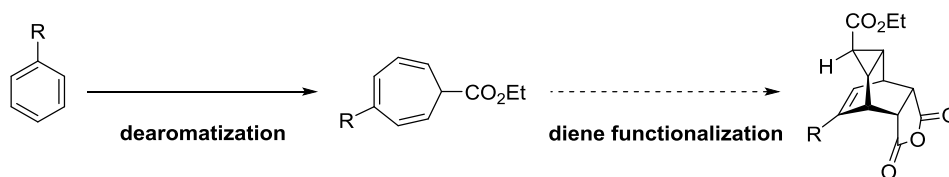
Despite the great strides that have been made in the intramolecular Buchner reaction, there currently exists no general regioselective method for the analogous *intermolecular* reaction.²⁰ The development of a regioselective intermolecular Buchner reaction would be inherently advantageous compared with the intramolecular reaction, since it would obviate the need for prefunctionalization of the aromatic substrate prior to the dearomatization reaction itself. Investigations into the regioselectivity issue will be addressed during the duration of this chapter and in Chapter Three.

2.3 Results and Discussion

2.3.1 Initial Reaction Design

As part of our ongoing studies in complexity generation via manipulation of strained carbocycles (see Chapter One for one such example),²¹ we envisioned the union of benzene dearomatization and cyclopropane annulation would provide expedient access to substituted cyclohexanes. This could be accomplished via the Buchner reaction—the (2+1)-annulation of carbenes with arenes—to access substituted NCDs (or their valence tautomeric CHTs).²² These intermediates would then be poised to participate in a variety of useful diene functionalizations (Scheme 2-9).

Scheme 2-9. Proposed Functionalization of Buchner Products



At least three barriers stand in the way of broader deployment of intermolecular Buchner adducts in synthesis: (1) the NCD products exist as a substrate-dependent equilibrating mixture of the NCD and the corresponding CHT adduct via electrocyclic ring opening and closure.¹⁸ Reactions must be developed in which only the NCD (and not the CHT) reacts productively to give the desired product; (2) the use of NCDs as Diels–Alder dienes is severely hindered by impractically slow reaction rates; and (3) from a practical standpoint, mixtures of isopolar constitutional isomers almost always present intractable separation/purification problems (*vide supra*).

2.3.2 Substrate Scope of the Intermolecular Buchner Reaction

In our initial screening using benzene, Rh₂(TFA)₄ was quickly identified as the optimal catalyst to generate high yields of the CHT product **2.1**, as rhodium diacetate dimers bearing electron-deficient ligands are reported to provide higher activity in the intermolecular Buchner reaction (Table 2-1, entry 1).¹⁷ Copper catalysts (entry 3) were ineffective at promoting this reaction.

Table 2-1. Optimization of the Buchner Reaction^a

entry	substrate	catalyst	product	yield (%)	rr
1	benzene	Rh ₂ (TFA) ₄		90	-
2		Rh ₂ (OAc) ₄	2.1	40	-
3		Cu(hfacac) ₂		<2	-
5	<i>p</i> -xylene	Rh ₂ (TFA) ₄		73	70:30
6		Rh ₂ (OAc) ₄		36	84:16
7		Rh ₂ (oct) ₄		15	93:7
8		Rh ₂ (esp) ₂	2.12a 2.12b	13	96:4

^aAll reactions were run on 1 mmol scale. Yields are ¹H NMR yields and were determined by ¹H NMR using 1,4-dimethylterephthalate as internal standard. Regioisomeric ratio (rr) was determined by ¹H NMR of the crude reaction mixture, and is a ratio of **2.12a**:**2.12b**.

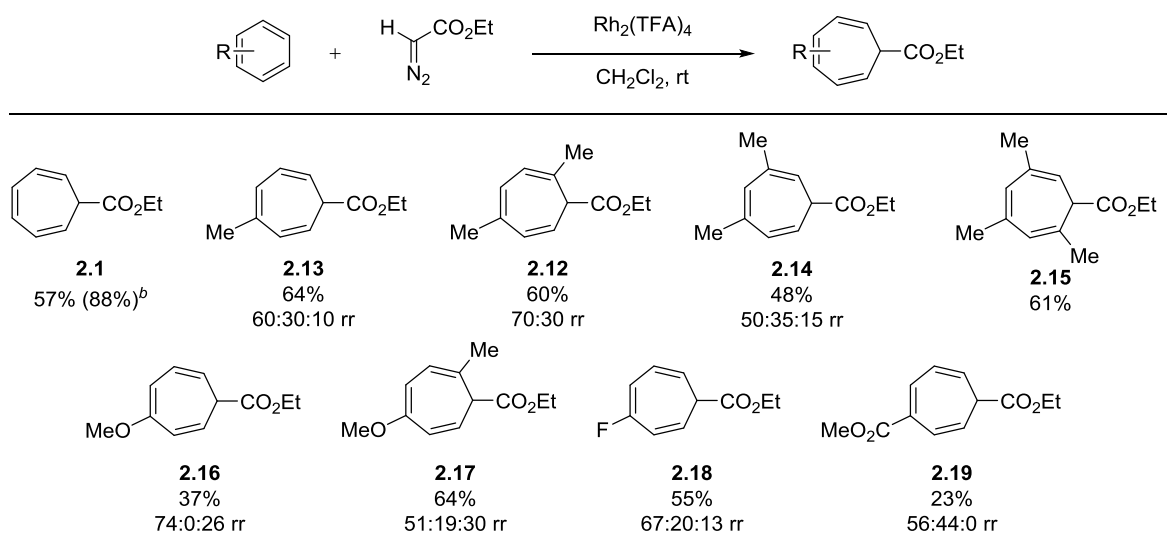
In order to investigate the role of the catalyst in the regioselectivity of the reaction, we focused on *p*-xylene as a model substrate, since only two possible regioisomers could arise (**2.12a/b**). As shown in Table 2-1, although more electron-deficient ligands provided higher yields in the Buchner reaction, lower rr was observed (entry 5). Conversely, using the electron-rich Rh₂(esp)₂ (entry 8), we observed excellent regioselectivity, albeit in prohibitively poor yields. Variation in reaction temperature, concentration, and catalyst loading were ineffective in providing

higher regioselectivity in the reaction. In light of these findings, we decided to use Rh₂(TFA)₄ throughout our screening, with the caveat that downstream separation of the multiple regioisomers would be required.

2.3.3 Substrate Scope of the Rh₂(TFA)₄ Catalyzed Buchner Reaction

Upon screening a variety of substituted benzene derivatives under the standard reaction conditions, moderate yields were observed for a variety of electron-rich systems. Diminished yields were observed for electron-deficient aromatic substrates, which is expected for reactions with highly electrophilic rhodium carbenoids. Isolation of the CHTs was complicated by appreciable instability of the Buchner products towards silica gel. Significant losses were observed upon each iteration of silica gel chromatography, as can be seen upon comparing the ¹H NMR yield of **2.1** and its isolated yield. Although the identity of the remaining mass balance was not determined, it is likely to result from rearomatization of the NCD intermediate. Therefore, in subsequent functionalization of the Buchner products, the crude material was carried forward without purification (*vide infra*).

Table 2-2. Substrate Scope of the Rh₂(TFA)₄ Catalyzed Buchner Reaction^a

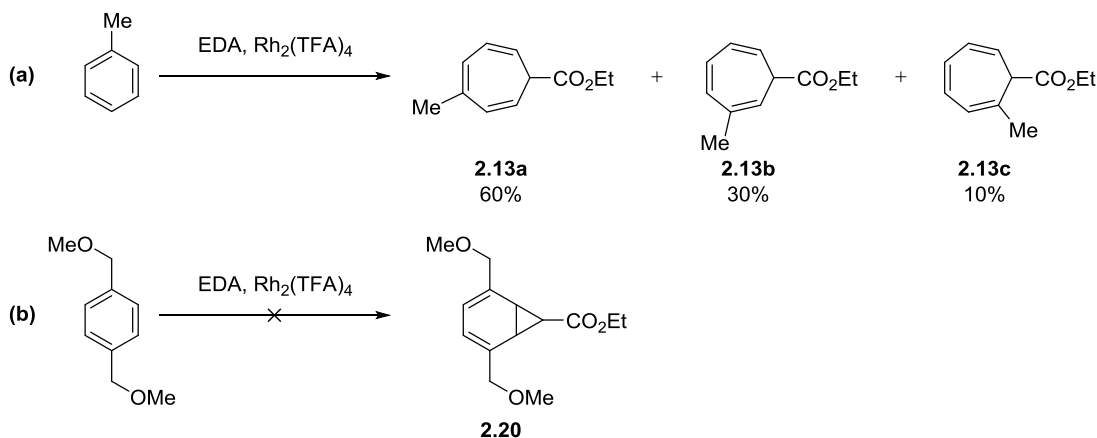


^aOnly the major regioisomer is shown. Yields are isolated yields. ^b¹H NMR yield.

2.3.4 Rationale for the Observed Regioselectivity in the Intermolecular Buchner Reaction

There were two key aspects to the factors that governed the regioselectivity of the Buchner reaction: steric and electronic effects. In alkyl substituted aromatic compounds, the steric effects seemed to govern the regioselectivity of the bond forming event. Using toluene to generate the cycloheptatriene mixture **2.13**, the least sterically encumbered site **2.13a** was the major product, with decreasing product yields approaching the methyl group (Scheme 2-10a). The Buchner reaction was so sensitive towards the steric impact of the substrates substituents such that 1,4-bis-hydroxymethyl-substituted arenes did not undergo the Buchner reaction, regardless of the protecting group on the primary alcohols (Scheme 2-10b).

Scheme 2-10. Steric Effects on the Regioselectivity of the Intramolecular Buchner Reaction



At the same time, a simple steric argument was insufficient to completely describe this reaction, since the non-symmetrical CHT **2.12a** was the major isomer using *p*-xylene as substrate, even when it appeared to arise from cyclopropanation at the more congested site.

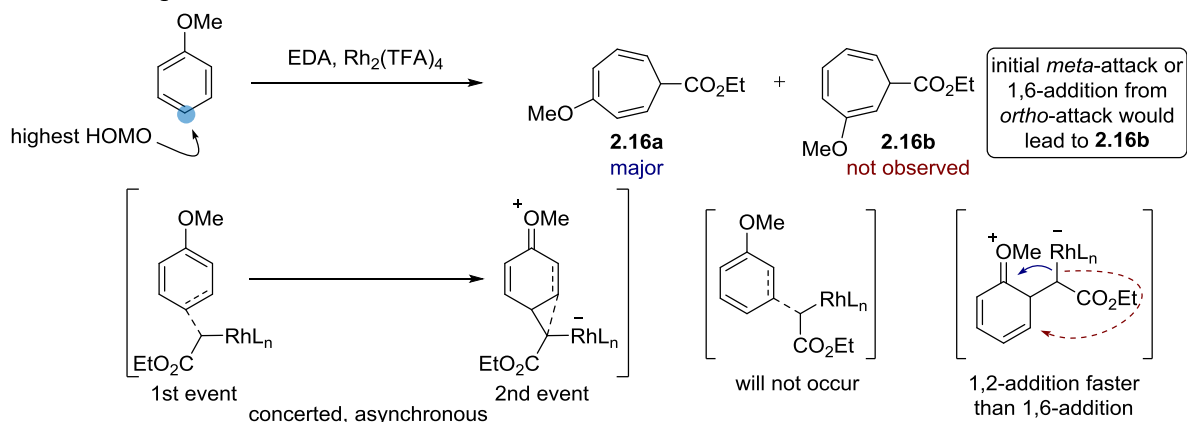
It has been suggested²⁰ that there is a significant electronic component to the regioselectivity of this reaction. Cyclopropanation reactions involving dirhodium carboxylate carbenoid intermediates are thought to proceed via a concerted process; however, the bond forming steps are not necessarily synchronous. In the context of this reaction, the mechanism of

cycloaddition was reasonable to consider a concerted, asynchronous process. With that in mind, the first bond forming “event” should occur at the position on the aromatic substrate with the highest HOMO, since the intermediate carbenoid was electrophilic. Upon reaction with anisole, one would expect initial addition to either the *ortho*- or *para*-positions. Initial attack at the *para*-position provided the major product (**2.16a**). Initial attack at the *ortho*-position, however, could result in either the 1,2-addition product (Scheme 2-11), providing **2.16c**, or the 1,6-addition product to give the 2-methoxy-substituted cycloheptatriene **2.16b**. Since the latter product was not observed, it was evident that the 1,2-addition pathway was significantly more facile than the 1,6-pathway.

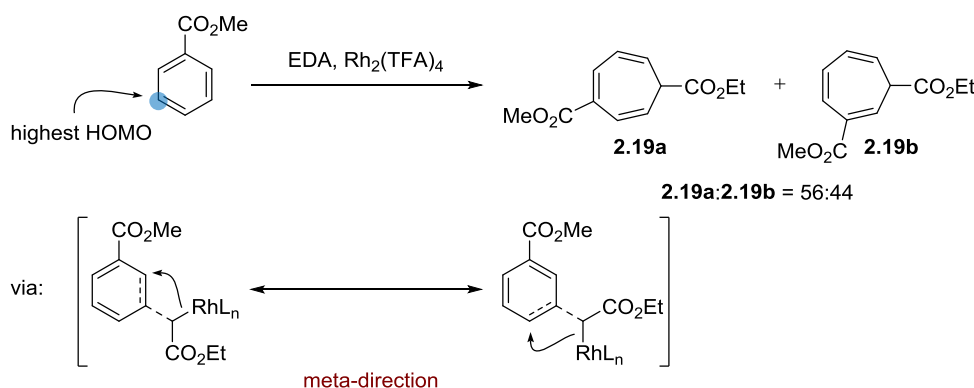
Along these lines, using an electron-deficient aromatic substrate, such as methyl benzoate, should provide a statistical mixture of the 2- and 3-substituted products, owing to the lack of direction by initial attack at the *meta*-position. In the event, we observed a 56:44 ratio of **2.19a/2.19b**, which was congruent with such an analysis.

Scheme 2-11. Electronic Effects on the Regioselectivity of the Intramolecular Buchner Reaction

Electron-donating substitution



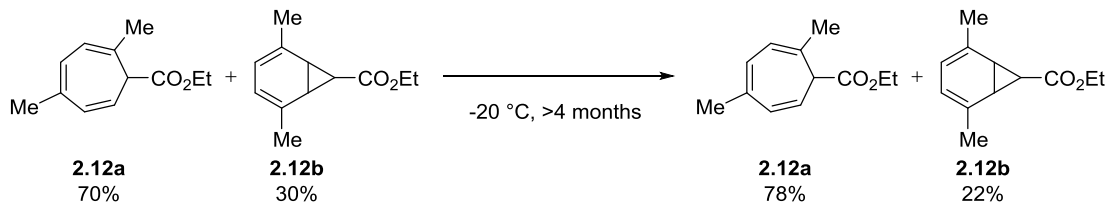
Electron-withdrawing substitution



2.3.5 Isomerization of Norcaradienes by Ring Walking

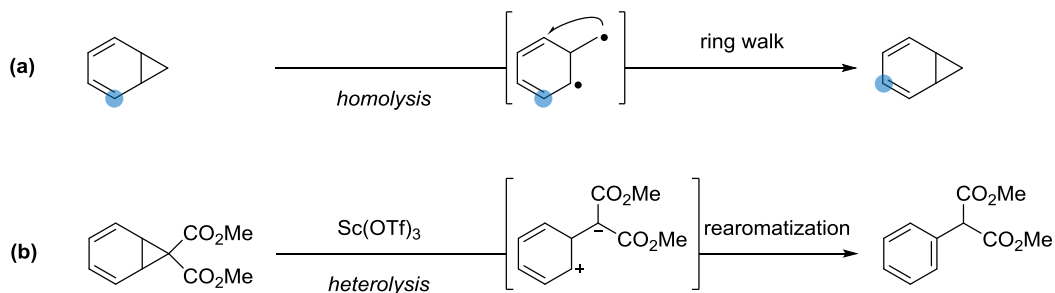
Although the CHT products were unable to be formed as single regioisomers, their fluxional nature provided us with ample opportunities to address this inconvenience. In one such instance, upon prolonged storage (>4 months), we noticed that the regioisomeric ratio of the Buchner products changed over time. As shown in Scheme 2-12, *p*-xylene derived CHT mixture **2.12** became slightly more enriched in CHT **2.12a** over this time; similar anomalies were observed for the other Buchner products. Since there was no evidence of degradation/rearomatization of the CHT, it was reasoned that the regioisomeric mixture was isomerizing.

Scheme 2-12. Isomerization of Regioisomeric Mixture upon Prolonged Storage

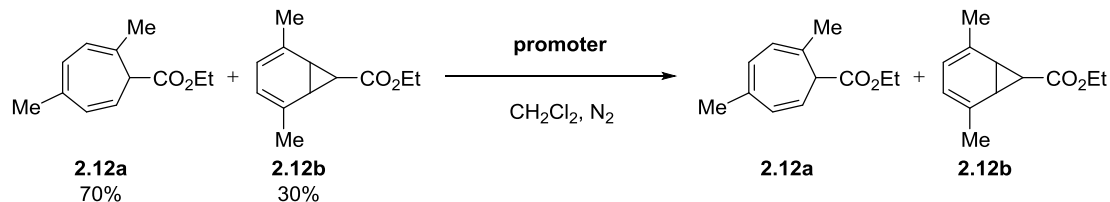


It is documented that NCDs and related compounds can isomerize via a ring-walking mechanism,^{23,24} as shown in Scheme 2-13a. Computational studies suggest that this ring walking proceeds through a biradical intermediate.²⁵ This mechanism is plausible in the case of **2.12**, since a polar mechanism would likely result in rearomatization (upon subjecting NCD diesters to Lewis acidic conditions, we observed complete rearomatization in under 5 min, Scheme 2-13b).

Scheme 2-13. Proposed Biradical Mechanism for Norcaradiene Ring Walk



We thought to probe the ring-walking phenomenon in hopes of quickly isomerizing the regioisomeric Buchner mixtures to single regioisomers. We probed a variety of Lewis acids and potential radical promoters for their ability to isomerize **2.12b** to **2.12a** some of which are included in Table 2-3.

Table 2-3. Ring Walk Promoter Screen

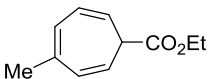
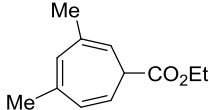
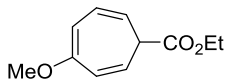
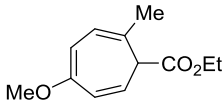
entry	promoter (x mol %)	temperature (°C)	time (h)	2.12a : 2.12b
1	n/a	23	0	70 : 30
2	n/a	-20	>3000	78 : 22
3	FeSO ₄ •7H ₂ O (10)	23	60	88 : 12
4	CuSO ₄ •5H ₂ O (10)	23	60	80 : 20
5	FeCl ₂ (10)	23	20	82 : 18
6	FeI ₂ (10)	23	20	97 : 3
7	I ₂ (3)	23	15	92 : 8
8	I ₂ (3)	4	15	>99 : 1
9	TEMPO (100)	23	17	>99 : 1

In the case of strong Lewis acids (i.e., BBr₃, FeCl₃), we observed significant rearomatization and other degradation products. However, when employing FeI₂, we observed near complete convergence to **2.12a**. Since older bottles of FeI₂ contain a significant portion of free I₂, we found that I₂ itself is competent at promoting the ring walk of **2.12**, with significantly higher selectivity at colder temperatures. To confirm that this reaction was proceeding via a biradical pathway, the addition of TEMPO provided complete convergence to **2.12a** upon stirring at room temperature overnight. While it is unclear the exact role of I₂ in the rearrangement, the homolysis of I₂ to generate I• is a likely mechanistic step to encourage the formation of the requisite biradical intermediate.

Although the isomerization of **2.12b** to **2.12a** was efficient, in cases where there were more than two regioisomeric products, the isomerization was not as clean (Table 2-4). Toluene-derived **2.13** did not experience significant changes in the relative amounts of the respective regioisomers.

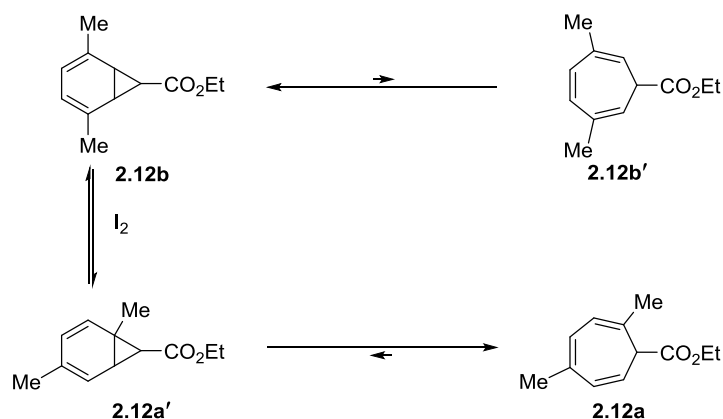
m-Xylene derived **2.14** saw an appreciable increase in the relative amounts of the 1,3-dimethyl **2.14b**, albeit with retention of appreciable levels of the remaining two regioisomers. Notably, methoxy-substituted **2.16** cleanly converted to the 1-methoxy CHT.

Table 2-4. Isomerization of Regioisomeric Buchner Products by I₂

				
	2.13	2.14	2.16	2.17
starting ratio:	60/27/13	50/35/15	74/26	51/38/12
16 h w/I ₂ @ 4 °C:	57/23/20	18/66/16	0/100	60/40/0

These results can be rationalized by the propensity of each regioisomer to exist as the NCD isomer. Since the ring walk occurs through NCD intermediates, regioisomers that readily convert to a NCD **2.12b** will undergo the ring walk at a faster rate than those that reside primarily as a CHT, resulting in an accumulation of the CHT isomer **2.12a** (Scheme 2-14).

Scheme 2-14. Rationale for Regioisomeric Distribution in Ring Walk Isomerizations



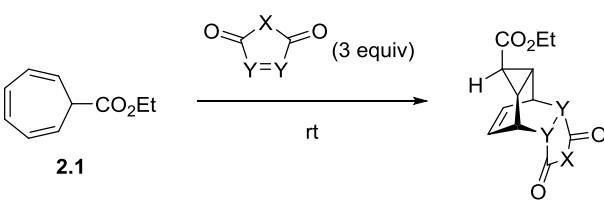
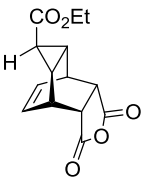
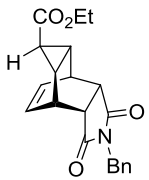
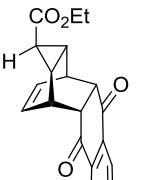
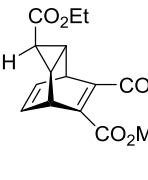
Incomplete isomerization to a single product was often observed in the trisubstituted CHTs (**2.13**, **2.14**, **2.17**, etc.). This is likely due to two of the CHTs having appreciable kinetic barriers to forming the requisite NCD for ring walking, resulting in multiple kinetic sinks. It may be possible to coerce the systems to converge to a singular product; however, practicality dictated alternative

methods for accessing regioisomerically enriched products (see Section 2.3.7 for one such discussion).

2.3.6 Further Functionalization of Buchner Products in Cycloaddition Reactions

In order to probe the utility of Buchner products **2.1** as viable synthetic intermediates, we first investigated their reactivity towards Diels–Alder cycloaddition, although they are known to react slowly with many dienophiles.²⁶ Central to confronting the Diels–Alder reaction rate problem was the recognition that conventional activation modes for accelerating Diels–Alder cycloaddition (e.g. Lewis acid catalysis) might be precluded by the tendency of the norcaradienes to rearomatize.^{18,27}

Table 2-5. Rate Enhancement on the Diels–Alder Reactions of **2.1** on Water

				
				
				
				
				
Et ₂ O, 3 h: >99%	Et ₂ O, 16 h: >99%	EtOAc, 16 h: >99% ^a	EtOAc, 1 h: <1 ^a (14 ^{a,b})%	
NaCl/H ₂ O, 90 s : >99%	NaCl/H ₂ O, 90 s : >99%	NaCl/H ₂ O, 90 s : >99% ^a	NaCl/H ₂ O, 1 h: 50 ^a (84 ^{a,b})%	

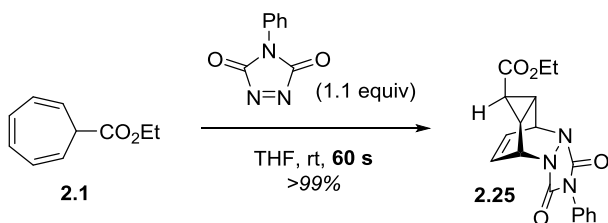
^aμwave, 100 °C; ^b10 equiv DMAD

While we continued to pursue reaction conditions that would have a lower propensity toward cyclopropane opening (e.g. iminium ion catalysis), in a parallel investigation we discovered a dramatic solvent effect that renders norcaradiene cycloadditions immediately more user friendly. Specifically, by using saturated aqueous NaCl as the reaction solvent, the reaction of cycloheptatriene **2.1** with a variety of activated carbon dienophiles (Table 2-5) led to exclusive

reaction via the norcaradiene isomer to providing *endo*-Diels–Alder products **2.21–2.24** as single diastereomers (via dienophile facial approach *anti* to the cyclopropyl moiety);²⁸ the structure was confirmed by an X-ray diffraction study of **2.21** (see section 2.5 for Experimental Details). Notably, the rate enhancement was significantly less pronounced using water without the added salt.

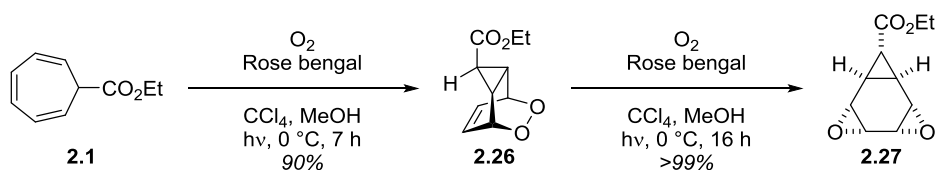
The rate increase for the aqueous Diels–Alder reaction was pronounced in the room temperature formation of **2.21** or **2.22** using maleic anhydride or *N*-benzyl maleimide, respectively, as the dienophiles (reaction times: **2.21** – Et₂O, 3 h; brine, 90 s; **2.22** – Et₂O, 16 h; brine, 90 s). The solvent effect was especially dramatic in the case of naphthoquinone: after stirring at room temperature in brine for 20 h, 22% conversion to **2.23** was observed with naphthoquinone as the dienophile. In diethyl ether under otherwise similar conditions, only trace product formation was observed. Under microwave irradiation (100 °C, 1 h) in brine, 95% conversion to the Diels–Alder product **2.23** was observed, whereas the use of ethyl acetate under the same conditions provided less than 2% conversion of **2.1**. Related reactions using naphthoquinone are reported to require prolonged heating (>120 °C, 7 d) to achieve suitable conversion.²⁹ Treating **2.1** with dimethyl acetylenedicarboxylate (DMAD)³⁰ under analogous microwave conditions provided **2.24** in 50% yield in brine, compared with trace product formation in EtOAc. The dramatic rate enhancements observed for these Diels–Alder reactions conducted in brine is most likely a manifestation of the hydrophobic effect.³¹

Scheme 2-15. Diels–Alder of **2.1** with PTAD



Hetero-Diels–Alder reactions also proceeded with the norcaradiene isomer of **2.1**. Treating **2.1** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in tetrahydrofuran provided complete conversion to the desired adduct **2.25** in under 60 s (Scheme 2-15).³² Photochemically-generated singlet oxygen³³ smoothly afforded the endoperoxide **2.26** in 7 h; however, this product was challenging to isolate when the reaction was further scaled as prolonged irradiation of **2.26** resulted in homolysis of the O–O bond and subsequent cyclization with the pendant alkene to provide the *syn*-bis-epoxide **2.27** (Scheme 2-16).³⁴ Productive reactivity with less reactive dienophiles (acrylates, acroleins, fumarates, etc.) in brine or organic solvents has been elusive to date; a screen of Lewis acid³⁵ or iminium³⁶ activators was ineffective.

Scheme 2-16. Photosensitized Singlet Oxygen Diels–Alder Reaction of **2.1**

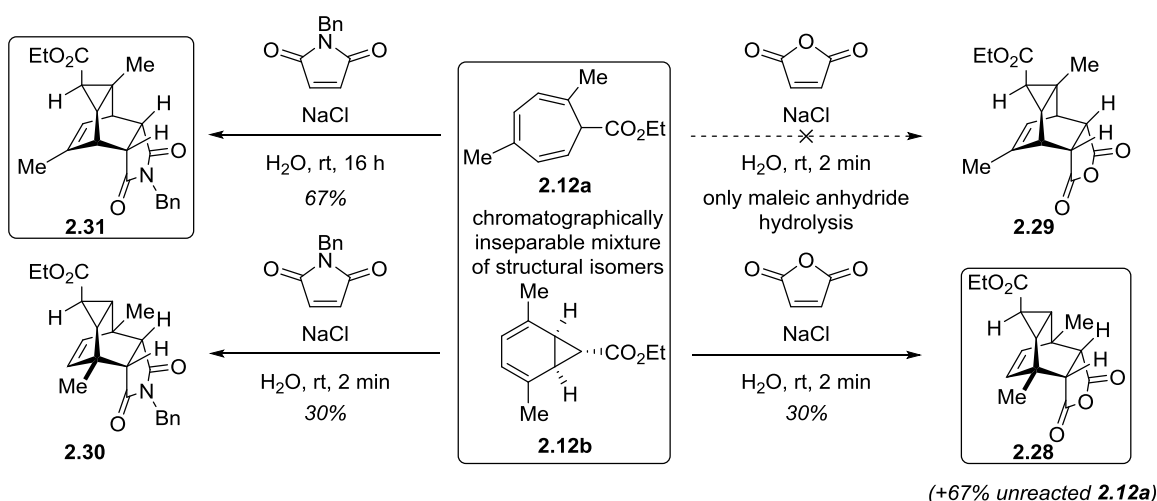


2.3.7 Investigations into the Kinetic Separation of Regioisomeric Mixtures

With proof-of-concept demonstrated for selective NCD (over CHT) reactivity Diels–Alder reactions, we turned our attention to expanding the scope of the reaction to encompass the regioisomerically impure substituted CHTs (Scheme 2-17). (For a description of the regioselectivity of the intermolecular Buchner reaction of substituted benzenes and the associated numbering scheme, see Section 2.5 for the Experimental Details.) In our initial screen with *p*-xylene-derived **2.12a/b** and maleic anhydride using brine as the reaction medium, we observed complete conversion of the stable NCD **2.12b** in under 2 min to **2.28**, while CHT **2.12a** failed to react prior to hydrolysis of maleic anhydride (<20 min). However, when *N*-benzylmaleimide (which exhibits increased hydrolytic stability relative to maleic anhydride) was employed, full

conversion to both regioisomeric products to **2.30/2.31** was realized upon prolonged stirring in brine (16 h). In light of these results and in order to resolve both product regioisomers, we envisioned a kinetic separation of the two isomers via successive treatment of the **2.12a/b** with maleic anhydride followed by *N*-benzylmaleimide in a one-pot procedure. While this approach was effective in delivering the desired orthogonal reactivity pattern, isolation of the two products **2.28/2.31** was complicated by challenges associated with their purification.

Scheme 2-17. Kinetic Separation of Chromatographically Inseparable Regioisomers^a

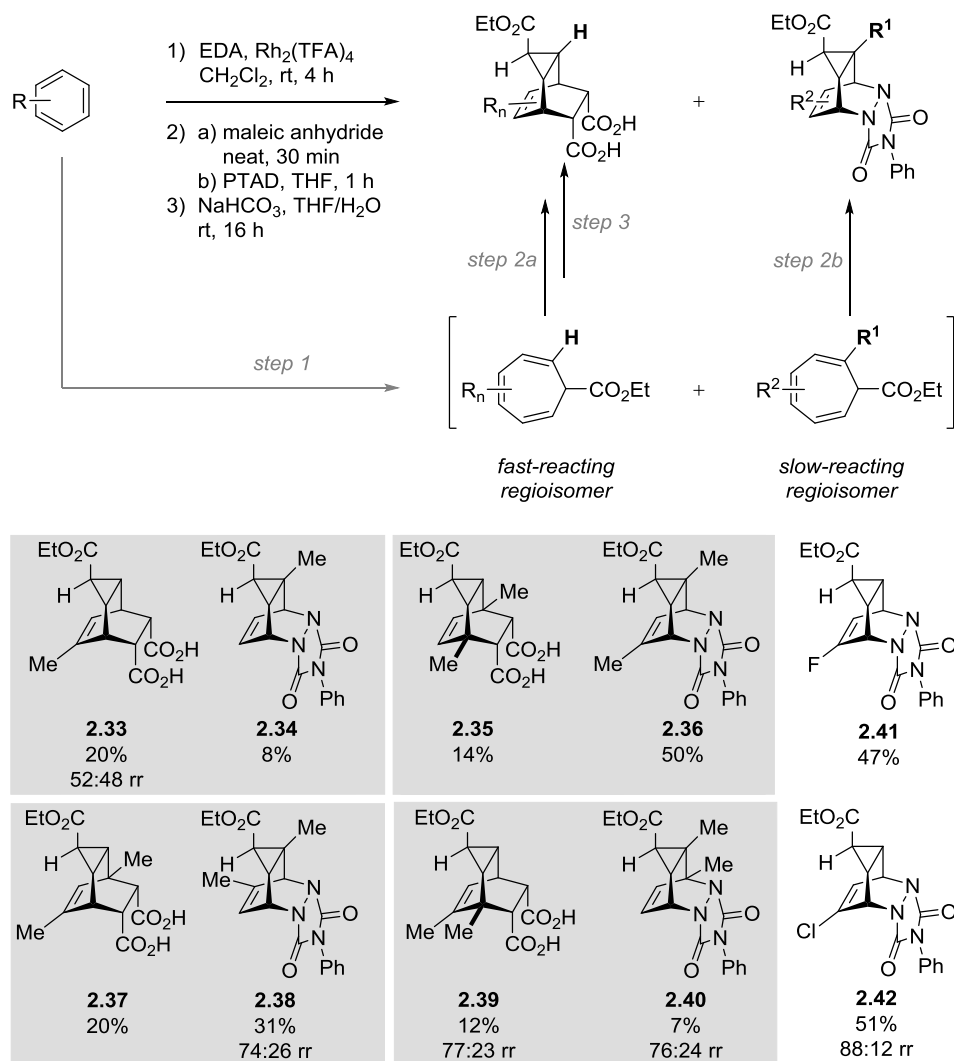


^aThe ^1H NMR yield was determined using 1,4-dimethylterephthalate as internal standard.

2.3.8 Optimized Multistep Route to Regioisomerically Enriched Buchner Products

To address these issues, we devised a two-step procedure to facilitate isolation and purification of both products. Two considerations were key to this endeavor: first, given that PTAD reacts with **2.1** more rapidly than *N*-benzylmaleimide, we transitioned to using the former as the second dienophile in the reaction sequence.

Table 2-6. Optimized Kinetic Separation via Buchner/Diels–Alder Reaction Sequence^a



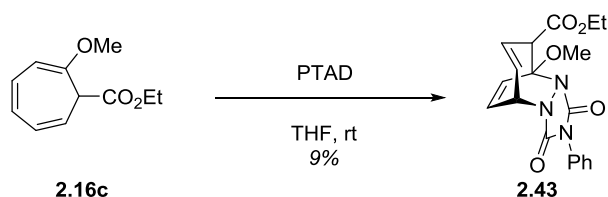
^aYields and regioisomeric ratios (rr) of the Diels–Alder products were determined by 1H NMR of the isolated products. In cases of regioisomeric mixtures, only the major regioisomer is shown (see Experimental Details in section 2.5 for a complete listing of the regioisomeric products).

Furthermore, the anhydride moieties of **2.21** could be selectively hydrolyzed in the presence of the urazoles **2.25** to generate diacids, which allowed for facile separation of the two products by an aqueous extraction (Table 2-6). We were, however, unable to isolate the diacids from 3-methoxy substituted cycloheptatrienes under this manifold, although the initial Diels–Alder adducts with maleic anhydride were readily identified by 1H NMR prior to hydrolysis. The halo-substituted cycloheptatrienes **2.18**, **2.32** were slow to react with maleic anhydride, and we

were only able to convert the 3-halo-substituted isomers to product using PTAD, with the other regioisomers being inert to the reaction conditions, even upon stirring for multiple days.

In our screening, we observed that the rate of the reaction of the dienes corresponded well with the position of the CHT/NCD equilibrium. While there are many factors that influence the equilibrium (see Section 2.2.3),¹⁸ in the context of this manuscript, substitution at the 1- or 6-position shifted the equilibrium toward the CHT. Notably, electron donating substituents at this position greatly favored the CHT, as evidenced by the isolation of **2.43**, resulting from the (4+2)-cycloaddition of the 1-methoxy-substituted CHT isomer **2.16c** (Scheme 2-18).

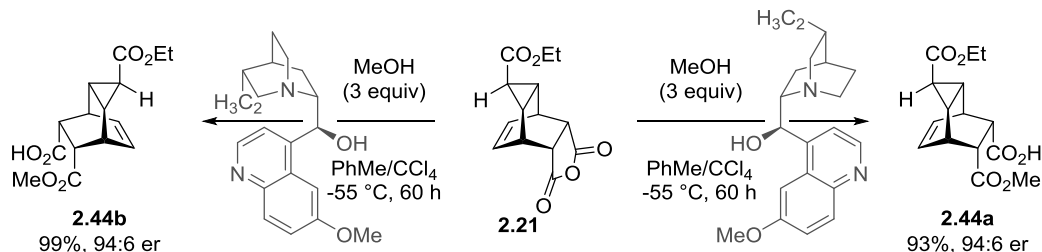
Scheme 2-18. Diels–Alder Reaction of 1-Methoxy-CHT **2.16c**



2.3.9 Desymmetrization of *meso*-[2.2.2]-Bicycles

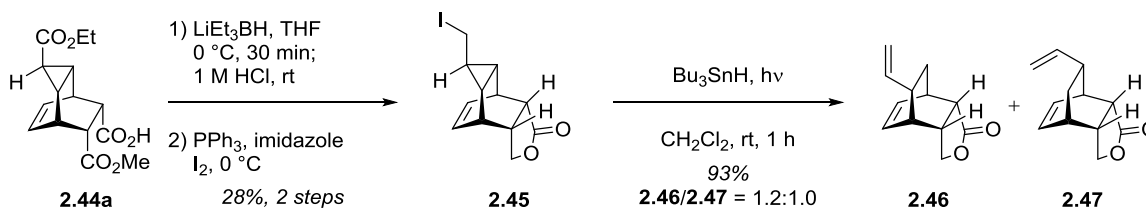
The benzene-derived norcaradiene Diels–Alder adducts are *meso* compounds containing six asymmetric centers. The viability of these products in stereoselective cyclohexane synthesis was explored in the context of a number of symmetry-breaking product manipulations. First, using cinchona alkaloids and alcoholic nucleophiles,³⁷ the anhydride **2.21** underwent enantiotopic group-selective nucleophilic acyl substitution, providing hemiesters **2.44a** and **2.44b** in 94:6 er with excellent diastereoselectivity (>20:1). Either enantiomer was accessible with comparable selectivity via appropriate selection of cinchona alkaloid promotor. Monoacids **2.44a/b** contain seven contiguous stereocenters—accessed from an achiral, *meso*-Diels–Alder adduct **2.21**—obtainable in three steps from benzene (Scheme 2-19).

Scheme 2-19. Anhydride Desymmetrization Using Cinchona Alkaloids



The hemiesters **2.44a/b** were then further manipulated towards the goal of cyclopropane ring-opening (Scheme 2-20). Accordingly, reduction of **2.44a** using LiEt₃BH followed by acid-promoted lactonization provided the cyclopropyl methanol, which could then be converted to the alkyl iodide **2.45** via Appel reaction. Photolysis of the alkyl iodide in the presence of Bu₃SnH revealed a primary cyclopropylmethyl radical that rearranged rapidly to form a secondary radical concomitant with cyclopropane ring-opening,³⁸ providing a regioisomeric mixture of **2.46** and **2.47** in 93% yield (Scheme 2-20).

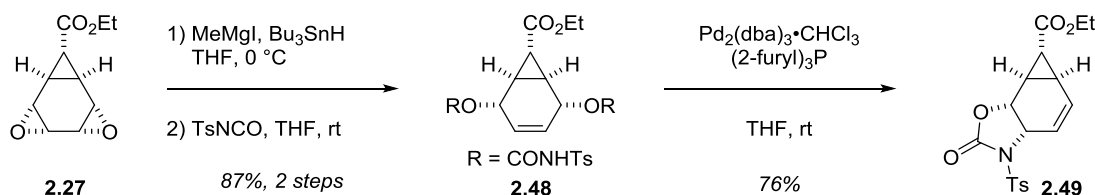
Scheme 2-20. Cyclopropane Ring-Opening of Desymmetrized Mono-Acid **2.44a**



Finally, *meso*-bis-epoxide **2.27** (derived from prolonged photolysis of endoperoxide **2.26**, *vide supra*) also may be converted to new chiral structures (Scheme 2-21). Reduction of **2.27** via treatment with MeMgI and SnBu₃H to afford the resulting *syn*-1,4-diol. Desymmetrization of the *meso*-diol was then accomplished in two steps via initial condensation with *p*-toluenesulfonyl isocyanate to provide the bis-carbamate **2.48** in 87% yield from **2.27**. Selective π -allyl displacement of the enantiotopic carbamates³⁹ under Pd(0) catalysis afforded the protected 1,2-

syn-aminoalcohol **2.49**. Extension of this methodology to enantioselective methods is well-precedented.⁴⁰

Scheme 2-21. Desymmetrization of *meso*-bis-Carbamate **2.48**



2.4 Conclusions

In conclusion, we have shown that inexpensive, commercially-available aromatic compounds may be deployed in the synthesis of complex cyclohexane derivatives in an expedient manner. As a means to independently isolate both regioisomers in the Buchner reaction of *p*-xylene (**2.12a/b**), the inseparable regioisomeric NCD/CHT mixture was kinetically resolved upon successive treatment with dienophiles of variable rates of reaction. Furthermore, enantioselective desymmetrization of *meso*-Diels–Alder products **2.21**, **2.27** enables access to up to seven stereocenters in a single operation from achiral materials. The present method should provide a new conceptual blueprint for the expedient assembly of complex carbocyclic structures. Additional improvements to Buchner reaction regioselectivity and further extension of CHT product transformations are reported in Chapter Three.

2.5 Experimental Details

Methods

Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on either a Bruker model DRX 400 or 600 spectrometer (^1H NMR at 400 or 600 MHz and ^{13}C NMR at 100 or 150 MHz) with solvent resonance as the internal standard (^1H NMR: CDCl_3 at 7.28 ppm and ^{13}C NMR: CDCl_3 at 77.0 ppm). ^1H 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, dddd = doublet of 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 and are uncorrected. 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 either the positive or negative ion mode. Samples were prepared in HPLC grade methanol. All reported masses obtained in the positive ion mode correspond to the protonated molecular ion ($\text{M}+\text{H}$) unless otherwise noted, and all reported masses obtained in the negative ion mode correspond to the deprotonated molecular ion ($\text{M}-\text{H}$), unless otherwise noted. High performance liquid chromatography (HPLC) was performed on a Perkin Elmer Flexar® HPLC system equipped with a Chiracel IA column. Samples were eluted with HPLC grade hexanes with the indicated percentage of $i\text{PrOH}$ 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. Microwave reactions were performed using a 300 W CEM Discover System with internal temperature monitoring via infrared sensing, in sealed 10 mL pressure vessels with a

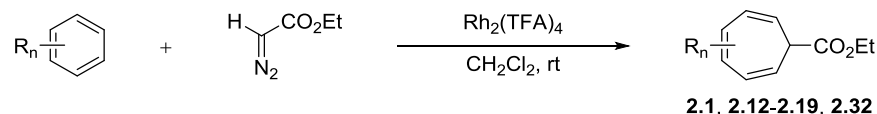
maximum ramp time of 2 min. Reactions performed “on water” were run in either conventional round-bottomed flasks or 1 or 5 dram vials with rapid agitation, either by vigorous manual shaking, or stirring (>900 rpm); we noticed no noticeable difference in the two methods. Thin layer chromatography (TLC) was performed on Sorbtech plastic-backed 0.20 mm silica gel 60 plates. Visualization was accomplished with UV light and either an aqueous ceric ammonium molybdate (CAM) or potassium permanganate (KMnO₄) solution, followed by heating. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 μ m) purchased from Silicycle. Unless otherwise specified, all crude materials were introduced to the chromatography column after dissolution in the specified eluent (plus a few drops dichloromethane, if required). Yields, regioisomeric ratios (rr’s) and diastereomeric ratios (dr’s) are reported herein for a specific experiment and as a result may differ slightly from those found in the tables, which are averages of at least two experiments.

Materials

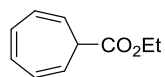
Nitrogen was dried by passage through anhydrous calcium sulfate with 3% cobalt chloride as indicator (commercial Drierite). Ethyl diazoacetate,⁴¹ *N*-benzylmaleimide,⁴² and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)⁴³ were prepared according to known literature procedures. The cycloheptatrienes **2.1**, **2.12-2.19**, **2.32** were prepared by a modified literature procedure.^{17,20} The ethyl diazoacetate was stored at room temperature as a solution (>80% w/w) in CH₂Cl₂ in a brown bottle to exclude light. **Caution:** While we experienced no difficulties in handling ethyl diazoacetate, care must be taken at all times when handling diazo compounds, as they are known to be explosive, especially upon heating during distillation.⁴¹ All aromatic substrates were purified by distillation prior to use. In all reactions run on water, solid reagents (maleic anhydride, *N*-

benzylmaleimide, naphthoquinone) were ground into fine powders prior to use. All other reagents and solvents were purchased from commercial sources and used as received.

General Procedure A for the Preparation of Cycloheptatrienes/Norcaradienes (2.1, 2.12-2.19, 2.32)

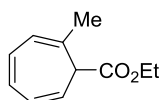
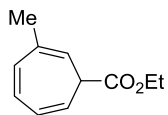
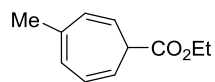


To a 25 mL round-bottomed flask charged with $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 equiv), the aromatic substrate (20 equiv), and CH_2Cl_2 (2.5 mL) was added a 2.5 mL solution of ethyl diazoacetate (114 mg, 1 mmol) in CH_2Cl_2 via syringe pump addition over 3 h. After complete addition, the brown solution was stirred for an additional hour at room temperature, at which time the CH_2Cl_2 was removed by rotary evaporation, and the excess arene was removed and could be recovered by distillation under reduced pressure with gentle heating ($<40^\circ\text{C}$). Analytically pure material was obtained following purification by silica gel chromatography. Complete analytical data are reported for new compounds; only ^1H NMR data are reported for known compounds. In cases where multiple regioisomers were formed, the isomers are listed in decreasing order of percent composition of the isolated mixture, and when possible, the resonances are identified for each isomer. The percentage shown in parentheses after identification of the regioisomer reflects the percent composition of that isomer in the regioisomeric mixture of the product mixture. Also indicated are the cases where the norcaradiene (NCD) is the predominant isomer by ^1H NMR analysis.



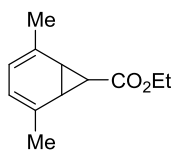
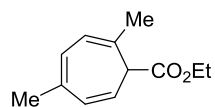
Ethyl cyclohepta-1,3,5-triene-7-carboxylate (2.1): The title compound was prepared according to General Procedure A using benzene (1.78 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear oil (94 mg, 57%). Analytical data: **^1H NMR** (600 MHz,

CDCl_3) δ 6.68 (m, 2H), 6.28 (m, 2H), 5.46 (dd, $J = 9.2, 5.6$ Hz, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 2.56 (t, $J = 5.6$ Hz, 1H), 1.33 (t, $J = 7.2$ Hz, 3H); **TLC** (20% EtOAc/hexanes) $R_f = 0.59$.



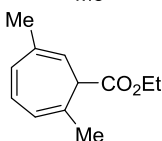
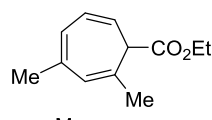
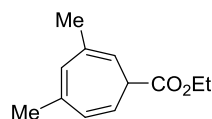
Ethyl 3-methylcyclohepta-1,3,5-triene-7-carboxylate (2.13): The title compound was prepared according to General Procedure A using toluene (2.13 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 1 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear oil (105 mg, 64%). Analytical data: **$^1\text{H NMR}$** (600 MHz, CDCl_3) δ (**2.13a, 3-Me, 60%**) 6.44 (m, 1H), 6.20 (m, 1H), 6.10 (m, 1H), 5.40 – 5.32 (m, 2H), 4.27 (q, $J = 7.2$

Hz, 2H), 2.57 (t, $J = 5.6$ Hz, 1H), 2.09 (s, 3H), 1.32 (t, $J = 7.2$ Hz, 3H); (**2.13b, 2-Me, 27%**) 6.44 (m, 2H), 6.20 (m, 1H), 5.05 (m, 1H), 4.75 (m, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.26 (t, $J = 5.2$ Hz, 1H), 1.97 (s, 3H), 1.32 (t, $J = 7.2$ Hz, 3H); (**2.13c, 1-Me, 13%**) 6.55 (m, 2H), 6.24 (dd, $J = 9.1, 4.8$ Hz, 1H), 6.12 (d, $J = 4.2$ Hz, 1H), 5.72 (dd, $J = 9.1, 7.0$ Hz, 1H), 5.36 (m, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 2.85 (d, $J = 7.0$ Hz, 1H), 1.99 (s, 3H), 1.32 (t, $J = 7.2$ Hz, 3H); **TLC** (20% EtOAc/hexanes) $R_f = 0.60$.



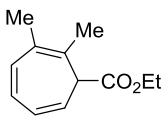
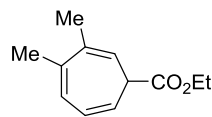
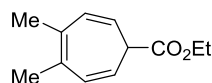
Ethyl 1,4-dimethylcyclohepta-1,3,5-triene-7-carboxylate (2.12): The title compound was prepared according to General Procedure A using *p*-xylene (2.47 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear oil (115 mg, 60%). Analytical data: **$^1\text{H NMR}$** (600 MHz, CDCl_3) δ (**2.12a, 1,4-Me, 70%**) 6.33 (d, $J = 3.2$ Hz, 1H), 6.07 (d, $J = 6.0$ Hz, 1H), 6.01 (d, $J = 3.2$ Hz, 1H), 5.69 (dd, $J = 6.0, 4.4$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 2.89 (d, $J = 4.4$ Hz, 1H), 2.05, (s, 3H), 1.95 (s, 3H), 1.31

(t, $J = 7.2$ Hz, 3H); (**2.12b, 2,5-Me (NCD), 30%**) 6.05 (s, 2H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.79 (br s, 2H), 1.97 (s, 6H), 1.59 (m, 1H), 1.31 (t, $J = 7.2$ Hz, 3H); **TLC** (20% EtOAc/hexanes) $R_f = 0.62$.



Ethyl 2,4-dimethylcyclohepta-1,3,5-triene-7-carboxylate (2.14): The title compound was prepared according to General Procedure A using *m*-xylene (2.47 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and Rh₂(TFA)₄ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear oil (93 mg, 48%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ (**(2.14a, 2,4-Me, 50%)** 6.16 (br s, 1H), 5.94 (br s, 1H), 4.73 (m, 1H), 4.43 (br s, 1H), 4.25

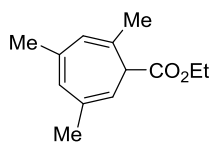
(q, *J* = 7.2 Hz, 2H), 2.11 (t, *J* = 5.2 Hz, 1H), 1.99 (s, 3H), 1.96 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); **(2.14b, 1,3-Me, 35%)** 6.36 (d, *J* = 5.6 Hz, 1H), 6.14 (m, 1H), 5.96 (br s, 1H), 5.65 (dd, *J* = 9.2, 6.7 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.89 (d, *J* = 6.7 Hz, 1H), 2.05 (s, 3H), 1.95 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); **(2.14c, 1,5-Me, 15%)** 6.44 (m, 2H), 6.01 (m, 1H), 5.47 (d, *J* = 6.8 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.84 (d, *J* = 6.8 Hz, 1H), 1.96 (s, 3H), 1.94 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); **TLC** (20% EtOAc/hexanes) R_f = 0.62.



Ethyl 3,4-dimethylcyclohepta-1,3,5-triene-7-carboxylate (2.50): The title compound was prepared according to General Procedure A using *o*-xylene (2.47 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and Rh₂(TFA)₄ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear oil (79 mg, 41%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ (**(2.50a, 3,4-Me, 42%)** 6.04 (d, *J* = 8.0 Hz, 2H), 4.79 (dd, *J* = 8.0, 5.6 Hz, 2H), 4.25 (q, *J* = 7.2

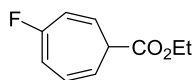
Hz, 2H), 2.25 (t, *J* = 5.6 Hz, 1H), 1.97 (s, 6H), 1.32 (t, *J* = 7.2 Hz, 3H); **(2.50b, 2,3-Me, 41%)** 6.32 (d, *J* = 6.4 Hz, 1H), 6.09 (t, *J* = 7.6 Hz, 1H), 5.05 (m, 1H), 4.82 (m, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 2.12 (t, *J* = 4.8 Hz, 1H), 2.03 (s, 3H), 1.95 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); **(2.50c, 1,2-Me, 17%)** 6.56 (d, *J* = 11.0 Hz, 1H), 6.48 (dd, *J* = 11.0, 5.4 Hz, 1H), 6.18 (dd, *J* = 9.6, 5.4 Hz, 1H), 5.77 (dd,

$J = 9.6, 6.8$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 2.69 (d, $J = 6.8$ Hz, 1H), 1.91 (s, 3H), 1.86 (s, 3H), 1.32 (t, $J = 7.2$ Hz, 3H); **TLC** (20% EtOAc/hexanes) $R_f = 0.62$.

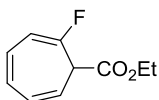


Ethyl 1,3,5-trimethylcyclohepta-1,3,5-triene-7-carboxylate (2.15): The title compound was prepared according to General Procedure A using mesitylene (2.78 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol).

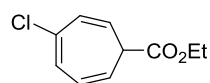
Flash chromatography (10% EtOAc/hexanes) provided a clear oil (129 mg, 62%). Analytical data: **^1H NMR** (400 MHz, CDCl_3) δ 6.25 (s, 1H), 5.84 (s, 1H), 5.38 (d, $J = 6.8$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 2.87 (d, $J = 6.8$ Hz, 1H), 2.01 (s, 3H), 1.93 (s, 3H), 1.90 (s, 3H), 1.30 (t, $J = 7.2$ Hz, 3H); **TLC** (20% EtOAc/hexanes) $R_f = 0.64$.



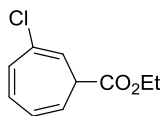
Ethyl 3-fluorocyclohepta-1,3,5-triene-7-carboxylate (2.18): The title compound was prepared according to General Procedure A using fluorobenzene (1.88 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear



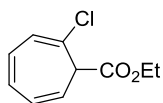
oil (99 mg, 54%). Analytical data: **^1H NMR** (600 MHz, CDCl_3) δ (**2.18a, 3-F, 67%**) 6.40 (m, 1H), 6.24 (m, 2H), 5.69 (m, 1H), 5.388 (dd, $J = 9.0, 5.4$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 2.69 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H); (**2.18b, 2-F, 20%**) 6.60 (ddd, $J = 10.8, 6.0, 4.2$ Hz, 1H), 6.40 (m, 1H), 6.17 (dd, $J = 9.6, 6.0$ Hz, 1H), 5.43 (dd, $J = 7.8, 6.0$ Hz, 1H), 5.03 (dd, $J = 12.6, 6.0$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 2.69 (m, 1H), 1.30 (t, $J = 7.2$ Hz, 3H); (**2.18c, 1-F, 13%**) 6.47 (dd, $J = 11.7, 5.7$ Hz, 1H), 6.34 (dd, $J = 9.6, 5.7$ Hz, 1H), 6.29 (ddd, $J = 12.9, 11.7, 6.6$ Hz, 1H), 6.06 (dd, $J = 12.9, 7.2$ Hz, 1H), 5.69 (m, 1H), 4.16 (m, 2H), 3.71 (dd, $J = 18.0, 7.8$ Hz, 1H), 1.24 (t, $J = 7.2$ Hz, 3H); **TLC** (20% EtOAc/hexanes) $R_f = 0.54$.



Ethyl 3-chlorocyclohepta-1,3,5-triene-7-carboxylate (2.32): The title compound was prepared according to General Procedure A using chlorobenzene

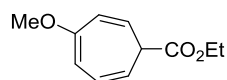


(2.03 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and Rh₂(TFA)₄ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear

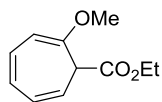


oil (113 mg, 57%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ (**2.32a, 3-Cl, 70%**) 6.82 (dd, *J* = 6.6, 1.2 Hz, 1H), 6.26 – 6.20 (m, 2H), 5.53 (dd, *J* = 9.6, 6.0 Hz, 1H), 5.50 (dd,

J = 9.6, 5.4 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.72 (dd, *J* = 6.0, 5.4 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); (**2.32b, 2-Cl, 18%**) 6.54 (dd, *J* = 10.2, 5.4 Hz, 1H), 6.50 (d, *J* = 10.2 Hz, 1H), 6.23 (m, 1H), 5.21 (m, 1H), 5.18 (ddd, *J* = 8.4, 5.4, 1.8 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 2.50 (dd, *J* = 6.6, 5.4 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H); (**2.32c, 1-Cl, 11%**) 6.61 (dd, *J* = 10.8, 5.4 Hz, 1H), 6.47 (d, *J* = 6.0 Hz, 1H), 6.42 (dd, *J* = 10.8, 6.6 Hz, 1H), 6.34 (dd, *J* = 9.6, 6.0 Hz, 1H), 5.78 (dd, *J* = 9.0, 7.8 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.48 (d, *J* = 7.8 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); **TLC** (20% EtOAc/hexanes) *R_f* = 0.54.

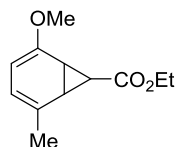
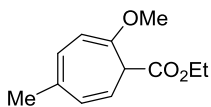
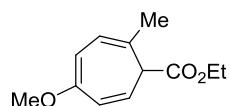


Ethyl 3-methoxycyclohepta-1,3,5-triene-7-carboxylate (2.16): The title compound was prepared according to General Procedure A using anisole (2.17



mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and Rh₂(TFA)₄ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes) provided a clear oil (73 mg, 37%).

Analytical data: ¹H NMR (400 MHz, CDCl₃) δ (**2.16a, 3-OMe, 74%**) 6.23 (m, 1H), 6.10 (dt, *J* = 10.0 Hz, 1.6 Hz, 1H), 5.89 (dd, *J* = 6.8, 2.0 Hz, 1H), 5.65 (m, 1H), 5.29 (m, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.69 (s, 3H), 2.71 (t, *J* = 5.6 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H); (**2.16c, 1-OMe, 26%**), 6.49 (dd, *J* = 10.8, 6.6 Hz, 1H), 6.36 (dd, *J* = 10.8, 5.7 Hz, 1H), 6.31 (dd, *J* = 9.3, 5.7 Hz, 1H), 5.66 (dd, *J* = 9.3, 7.2 Hz, 1H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 3.34 (d, *J* = 7.2 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H). **TLC** (20% EtOAc/hexanes) *R_f* = 0.51.

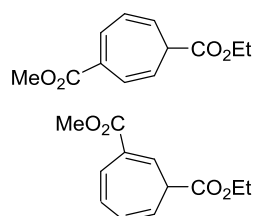


Ethyl 3-methoxy-6-methylcyclohepta-1,3,5-triene-7-carboxylate (2.17):

The title compound was prepared according to General Procedure A using 4-methylanisole (2.52 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol). Flash chromatography (10% EtOAc/hexanes)

provided a clear oil (95 mg, 46%). Analytical data: ^1H NMR (600 MHz, CDCl_3) δ (**2.17a**, **3-OMe**, **6-Me**, **51%**) 6.07 (d, $J = 9.9$ Hz, 1H), 6.01 (dd, $J =$

6.6, 1.2 Hz, 1H), 5.86 (dd, $J = 9.9, 7.2$ Hz, 1H), 5.77 (d, $J = 6.6$ Hz, 1H), 4.20 (d, $J = 7.2$ Hz, 2H), 3.64 (s, 3H), 2.91 (d, $J = 7.2$ Hz, 1H), 1.91 (s, 3H), 1.31 (t, $J = 7.2$ Hz, 3H); (**2.17b**, **1-OMe**, **4-Me**, **31%**) 6.24 (d, $J = 6.9$ Hz, 1H), 6.12 (d, $J = 9.6$ Hz, 1H), 5.64 (dd, $J = 9.6, 7.4$, 1H), 5.39 (d, $J = 6.9$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.61 (s, 3H), 3.31 (d, $J = 7.4$ Hz, 1H), 2.02 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); (**2.17c**, **2-OMe**, **5-Me** (NCD), **19%**) 5.83 (br s, 1H), 5.26 (br s, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.62 (s, 3H), 1.95 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (**2.17a**, **3-OMe**, **6-Me**) 172.2, 158.7, 124.9, 122.4, 122.3, 121.2, 103.9, 60.5, 54.7, 48.6, 20.0, 14.2; (**2.17b**, **1-OMe**, **4-Me**) 170.3, 148.1, 133.2, 129.8, 124.9, 117.4, 96.7, 60.8, 56.4, 48.5, 23.6, 14.1; IR (thin film, cm^{-1}) 2980, 2937, 2836, 1740, 1616, 1550, 1463, 1369, 1315, 1034; TLC (20% EtOAc/hexanes) $R_f = 0.54$; HRMS (ESI $^+$) Calcd. for $\text{C}_{12}\text{H}_{16}\text{NaO}_3$: 231.0992, Found: 231.0993.



7-ethyl 3-methyl cyclohepta-1,3,5-triene-3,7-dicarboxylate (2.19):

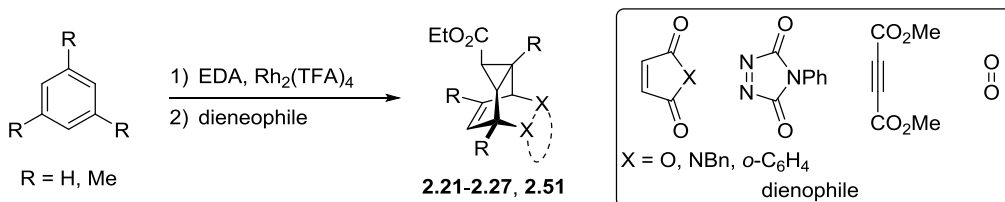
The title compound was prepared according to General Procedure A using methyl benzoate (2.51 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), and

$\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol). Flash chromatography (10%

EtOAc/hexanes) provided a colored oil (50 mg, 23%). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ (**2.19a**, **3-CO2Me**, **57%**) 7.63 (d, $J = 6.0$ Hz, 1H), 6.85 (d, $J = 9.6$ Hz, 1H), 6.42 (m, 1H), 5.55 (ddd, $J = 9.0, 5.4, 1.2$ Hz, 1H), 5.34 (ddd, $J = 9.0, 5.4, 1.2$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz,

2H), 3.85 (s, 3H), 2.42 (dd, $J = 5.4, 5.4$ Hz, 1H), 1.32 (t, $J = 7.2$ Hz, 3H); **(2.19b, 2-CO₂Me, 43%)**
 7.19 (d, $J = 10.2$ Hz, 1H), 6.64 (dd, $J = 10.2, 6.6$ Hz, 1H), 6.39 (m, 1H), 5.72 (ddd, $J = 5.4, 3.0, 1.0$ Hz, 1H), 4.82 (ddd, $J = 8.4, 5.5, 3.0$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 3.81 (s, 3H), 2.10 (dd, $J = 5.4, 5.4$ Hz, 1H), 1.33 (t, $J = 7.2$ Hz, 3H).

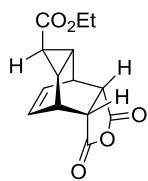
General Procedure B for the Buchner/Diels–Alder Sequence of Benzene and Mesitylene



To a 25 mL round-bottomed flask charged with $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 equiv), the aromatic substrate (20 equiv), and CH_2Cl_2 (2.5 mL) was added a 2.5 mL solution of ethyl diazoacetate (114 mg, 1 mmol) in CH_2Cl_2 via syringe pump addition over 3 h. After complete addition, the brown solution was stirred for an additional hour at room temperature, at which time the CH_2Cl_2 was removed by rotary evaporation, and the excess arene was removed and could be recovered by distillation under reduced pressure, yielding a brown oil. The following conditions were employed for the appropriate dienophile:

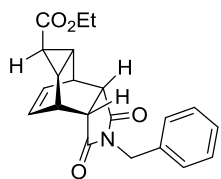
For maleic anhydride and *N*-benzylmaleimide: To the resultant oil was then added the dienophile (3 equiv) and saturated brine (NaCl) solution (10 mL), and the mixture was rapidly stirred at room temperature until the reaction was complete (2 – 30 min). The products were extracted with Et_2O (2×5 mL), dried over MgSO_4 , filtered, concentrated, and purified by chromatography. **For naphthoquinone:** To the resultant oil was then added naphthoquinone (3 equiv) and saturated brine (NaCl) solution (3 mL), and the mixture was heated under microwave irradiation (300 W, 100 °C, 1 h). Then the reaction mixture was diluted with EtOAc (25 mL), filtered through a short pad of activated charcoal and Celite, dried over MgSO_4 , filtered,

concentrated, and purified by chromatography. **For dimethyl acetylenedicarboxylate (DMAD):** To the resultant oil was then added DMAD (10 equiv) and saturated brine (NaCl) solution (3 mL), and the mixture was heated under microwave irradiation (300 W, 100 °C, 1 h). The products were extracted with EtOAc (2 × 10 mL), dried over Na₂SO₄, filtered, concentrated, and purified by chromatography. **For 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD):** To the resultant oil was then added PTAD (1.1 equiv) with 5 mL Et₂O. After stirring for 10 min, the solvent was removed by rotary evaporation, and the residue was purified by chromatography. **For O=O:** To the resultant oil was added rose bengal (0.01 equiv), and the mixture was dissolved in CCl₄/MeOH (20:1, 5 mL) and cooled to 0 °C. Then a steady stream of O₂ was bubbled through the solution and the mixture was irradiated with a Hg lamp with a Pyrex filter. After stirring for 7 – 24 h, the solvent was removed by rotary evaporation at room temperature, and the crude material was purified by chromatography.



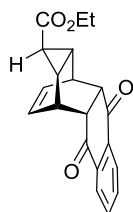
Ethyl 1,3-dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-1H-4,6-ethenocyclopropa-[f]isobenzofuran-5-carboxylate (2.21): The title compound was prepared according to General Procedure B using benzene (17.8 mL, 200 mmol), ethyl diazoacetate (1.14

g, 10 mmol), Rh₂(TFA)₄ (65.8 mg, 0.1 mmol), and maleic anhydride (2.94 g, 30 mmol). Flash chromatography (40% EtOAc/hexanes) provided a white solid (2.32 g, 88%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 5.97 (tt, *J* = 4.2, 3.6 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.57 (m, 2H), 3.32 (tt, *J* = 4.2, 1.8 Hz, 2H), 1.76 (dt, *J* = 2.7, 2.4 Hz, 2H), 1.38 (t, *J* = 2.7 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.7, 171.5, 129.1, 60.8, 45.2, 32.8, 20.3, 19.6, 14.1; **mp** 129–130 °C; **IR** (thin film, cm⁻¹) 2981, 1861, 1838, 1779, 1721, 1420, 1297, 1229, 1173, 926; **TLC** (20% EtOAc/hexanes) *R_f* = 0.07; **HRMS** (ESI⁻) Calcd. for C₁₄H₁₃O₅: 261.0768, Found: 261.0770.



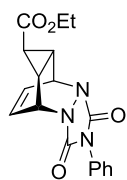
Ethyl -2-octyl-1,3-dioxo-1,2,3,3a,4,4a,5,5a,6,6a-decahydro-4,6-ethenocyclopropa-[f]isoindole-5-carboxylate (2.22): The title compound was prepared according to General Procedure B using benzene (1.8 mL, 20 mmol),

ethyl diazoacetate (114 mg, 1 mmol), $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and *N*-benzylmaleimide (234 mg, 1.25 mmol). Flash chromatography (30% EtOAc/hexanes) provided a white solid (260 mg, 74%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.29 – 7.22 (m, 5H), 5.69 (t, $J = 4.2$ Hz, 2H), 4.53 (s, 2H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.50 (br s, 2H), 3.01 (br s, 2H), 1.74 (dd, $J = 5.4$, 3.0 Hz, 2H), 1.35 (t, $J = 3.0$ Hz, 1H), 1.23 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 177.3, 17.2, 135.6, 128.5, 128.3, 128.2, 127.6, 60.6, 44.5, 42.0, 32.8, 20.3, 19.9, 14.1; **mp** 172–173 °C; **IR** (thin film, cm^{-1}) 2978, 1702, 1419, 1397, 1335, 1290, 1247, 1173, 1070, 910; **TLC** (20% EtOAc/hexanes) $R_f = 0.08$; **HRMS** (ESI^+) Calcd. for $\text{C}_{21}\text{H}_{22}\text{NO}_4$: 352.1543, Found: 352.1564.



Ethyl -3,8-dioxo-1a,2,2a,3,8,8a,9,9a-octahydro-1H-2,9-ethenocyclopropa-[b]anthracene-1-carboxylate (2.23): The title compound was prepared according to General Procedure B using benzene (1.8 mL, 20 mmol), ethyl diazoacetate (114 mg,

1 mmol), $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and naphthoquinone (474 mg, 3.0 mmol). Flash chromatography (20% EtOAc/hexanes) provided a brown solid (139 mg, 43%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.03 (dd, $J = 6.0$, 3.0 Hz, 2H), 7.71 (dd, $J = 6.0$, 3.0 Hz, 2H), 5.80 (dd, $J = 4.2$, 3.9 Hz, 2H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.76 (br s, 2H), 3.29 (s, 2H), 1.89 (dd, $J = 4.8$, 3 Hz, 2H), 1.26 (t, $J = 3.0$ Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 196.8, 172.9, 135.3, 134.2, 129.8, 126.9, 60.6, 49.5, 36.7, 20.6, 18.0, 14.2; **mp** 127–128 °C; **IR** (thin film, cm^{-1}) 3065, 2980, 1717, 1678, 1592, 1418, 1274, 1161, 709; **TLC** (20% EtOAc/hexanes) $R_f = 0.13$; **HRMS** (ESI^+) Calcd. for $\text{C}_{20}\text{H}_{17}\text{O}_4$: 321.1132, Found: 321.1144.

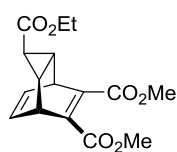


Ethyl

-1,3-dioxo-2-phenyl-2,3,5a,6,6a,7-hexahydro-1H,5H-5,7-

ethenocyclopropa[d][1,2,4]triazolo[1,2-a]pyridazine-6-carboxylate (2.25): The

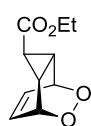
title compound was prepared according to General Procedure B using benzene (1.8 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and 4-phenyl-1,2,4-triazoline-3,5-dione (175 mg, 1.1 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white solid (241 mg, 71%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.43 (m, 4H), 7.35 (m, 1H), 6.17 (t, $J = 4.2$ Hz, 2H), 5.26 (m, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 2.23 (m, 2H), 1.45 (t, $J = 3.0$ Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 170.2, 156.4, 131.1, 129.0, 128.2, 126.0, 125.4, 61.1, 52.1, 23.5, 15.3, 14.0; **mp** 167–168°C; **IR** (thin film, cm^{-1}) 3066, 2982, 2937, 1770, 1715, 1503, 1407, 1319, 1235, 1177, 1048; **TLC** (20% EtOAc/hexanes) $R_f = 0.08$; **HRMS** (ESI^+) Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_4$: 340.1292, Found: 340.1311.



3-Ethyl-6,7-dimethyl-tricycle[3.2.2.0(2,4)]nona-6,8-diene-3,6,7-tricarboxylate

(2.24): The title compound was prepared according to General Procedure B using benzene (1.8 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), $\text{Rh}_2(\text{TFA})_4$ (6.6

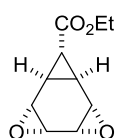
mg, 0.01 mmol), and dimethyl acetylenedicarboxylate (1.2 mL, 10 mmol). Flash chromatography (20% EtOAc/hexanes) provided a clear oil (178.2 mg, 58%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.16 (t, $J = 4.2$ Hz, 2H), 4.25 (m, 2H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 6H), 2.07 (dt, $J = 2.4, 2.4$ Hz, 2H), 1.76 (t, $J = 2.4$ Hz, 1H), 1.23 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 170.9, 166.2, 147.1, 130.8, 60.6, 52.3, 40.6, 30.6, 26.8, 14.1; **IR** (thin film, cm^{-1}) 3065, 2985, 2953, 2844, 1714, 1637, 1601, 1278, 1061, 731; **TLC** (20% EtOAc/hexanes) $R_f = 0.17$; **HRMS** (ESI^+) Calcd. for $\text{C}_{16}\text{H}_{19}\text{O}_6$: 307.1176, Found: 307.1176.



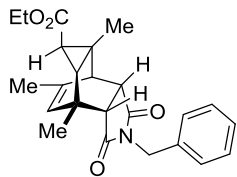
Ethyl-6,7-dioxatricyclo[3.2.2.0(2,4)]non-8-ene-3-carboxylate (2.26): The title

compound was prepared according to General Procedure B using benzene (1.8 mL, 20

mmol), ethyl diazoacetate (114 mg, 1 mmol), Rh₂(TFA)₄ (6.6 mg, 0.01 mmol), and rose bengal (10 mg, 0.01 mmol), under irradiation for 7 h. Flash chromatography (30% EtOAc/hexanes) provided a white solid (104 mg, 53%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 6.32 (t, *J* = 6.0 Hz, 2H), 4.98 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.24 (m, 2H), 1.29 – 1.22 (m, 4H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.3, 127.8, 72.0, 61.0, 21.7, 14.3, 14.1; **IR** (thin film, cm⁻¹) 2984, 1724, 1455, 1370, 1311, 1241, 1182, 1056, 877; **TLC** (20% EtOAc/hexanes) *R_f* = 0.15; **HRMS** (ESI⁺) Calcd. for C₁₀H₁₃NaO₄: 219.0628, Found: 219.0634.



Ethyl-3,6-dioxatetracyclo[6.1.0.0.2,4.0.5,7]nonane-9-carboxylate (2.27): The title compound was prepared according to General Procedure B using benzene (17.8 mL, 200 mmol), ethyl diazoacetate (1.14 g, 10 mmol), Rh₂(TFA)₄ (65.8 mg, 0.1 mmol), and rose bengal (103 mg, 0.1 mmol) under irradiation for 20 h. Flash chromatography (20% EtOAc/hexanes) provided a pink solid (976 mg, 49%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 4.19 (q, *J* = 7.2 Hz, 2H), 3.31 (s, 4H), 2.12 (d, *J* = 4.4 Hz, 2H), 1.76 (t, *J* = 4.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 171.1, 61.0, 47.4, 47.0, 22.6, 21.2, 14.0; **mp** 89–90 °C; **IR** (thin film, cm⁻¹) 2987, 1718, 1455, 1372, 1311, 1184, 1059, 1005, 945; **TLC** (20% EtOAc/hexanes) *R_f* = 0.05; **HRMS** (ESI⁺) Calcd. for C₁₀H₁₃NaO₄: 219.0628, Found: 219.0633.



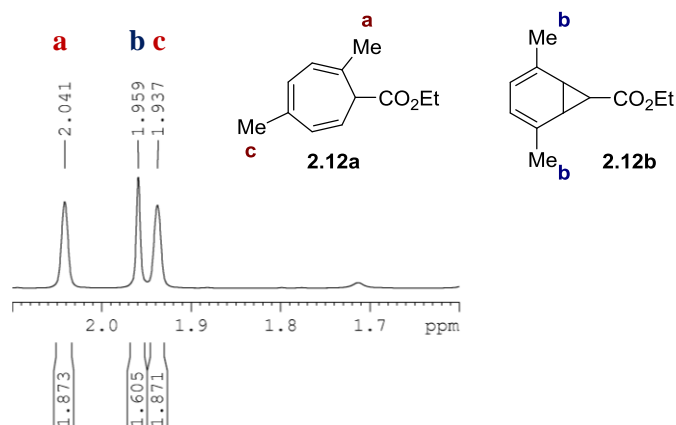
Ethyl -4,5a,7-trimethyl-2-octyl-1,3-dioxo-1,2,3,3a,4,4a,5,5a,6,6a-decahydro-4,6-ethenocyclopropa[f]isoindole-5-carboxylate (2.51): The title compound was prepared according to General Procedure B using mesitylene (2.78 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), Rh₂(TFA)₄ (6.6 mg, 0.01 mmol), and *N*-benzylmaleimide (562 mg, 3 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white solid (210 mg, 53%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.27 – 7.22

(m, 5H), 4.96 (s, 1H), 4.57 (d, $J = 14.1$ Hz, 1H), 4.48 (d, $J = 14.1$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.26 (dd, $J = 7.5, 3.6$ Hz, 1H), 2.94 (m, 1H), 2.65 (d, $J = 7.5$ Hz, 1H), 1.51 (s, 3H), 1.45 (d, $J = 1.2$ Hz, 3H), 1.38 (m, 2H), 1.29 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.5, 176.6, 171.6, 136.8, 135.8, 128.4, 128.3, 127.6, 125.9, 60.5, 49.0, 45.2, 43.8, 41.9, 39.9, 33.7, 24.6, 24.1, 21.5, 20.5, 14.2, 13.2; **mp** 134–135 °C; **IR** (thin film, cm^{-1}) 2933, 2874, 1770, 1698, 1397, 1327, 1180; **TLC** (20% EtOAc/hexanes) $R_f = 0.18$; **HRMS** (ESI^+) Calcd. for $\text{C}_{21}\text{H}_{22}\text{NO}_4$: 394.2013, Found: 394.2036.

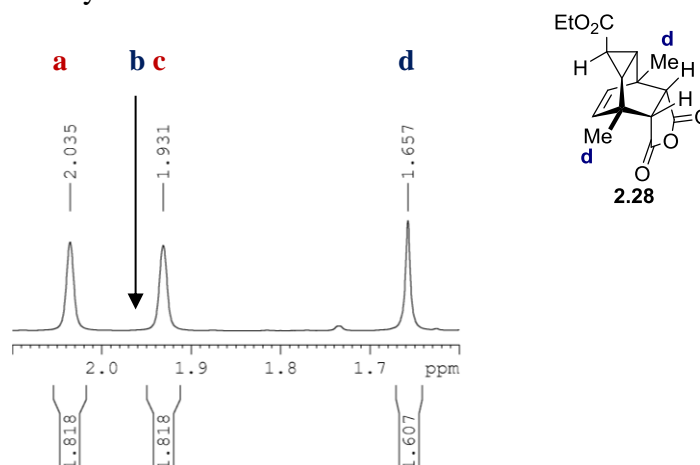
Separation difficulties for 2.28/2.31

Figure 2-1. Kinetic Separation of 2.12 Using Maleic Anhydride on Water

Before addition of maleic anhydride to 2.12

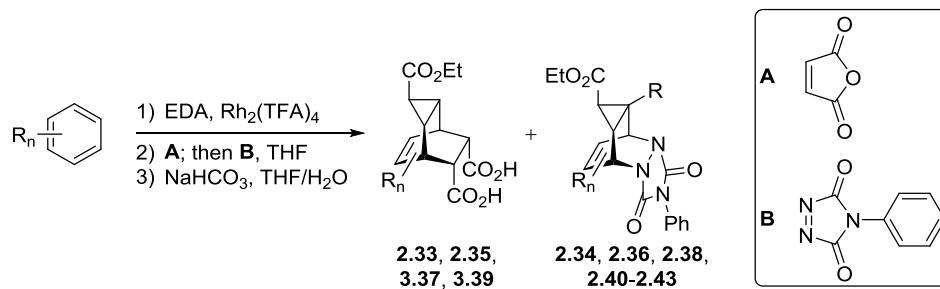


After 2 min in brine with maleic anhydride



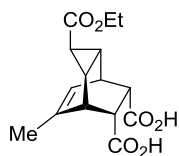
As shown in Figure 2-S1, treatment of the regioisomeric mixture **2.12** with maleic anhydride in brine provided complete conversion of **2.12b** in under 2 min, while only trace conversion of **2.12a** (<3%) was observed. While this analysis was feasible with any of the protons, the methyl peaks provided the cleanest separation. The vinyl protons in **2.12b** (6.03 ppm) and **2.28** (5.67 ppm) both overlap peaks in **2.12a**. 1,4-Dimethylterephthalate was used as an internal standard, with the resonance at 8.11 ppm (aryl C–H) set to 4.00, and the singlet at 3.96 ppm (–CO₂Me) provided internal consistency with an integration of 6.00.

General Procedure C for the Buchner/Diels–Alder/Hydrolysis Sequence



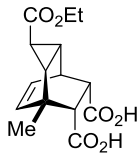
To a 25 mL round-bottomed flask charged with Rh₂(TFA)₄ (6.6 mg, 0.01 equiv), the aromatic substrate (20 equiv), and CH₂Cl₂ (2.5 mL) was added a 2.5 mL solution of ethyl diazoacetate (114 mg, 1 mmol) in CH₂Cl₂ via syringe pump addition over 3 h. After complete addition, the brown solution was stirred for an additional hour at room temperature, at which time the CH₂Cl₂ was removed by rotary evaporation, and the excess arene was removed and could be recovered by distillation under reduced pressure. At this point the crude mixture was analyzed by ¹H NMR spectroscopy to determine yield and regioisomeric ratio, using 1,4-dimethylterephthalate as an internal standard. To the brown oil was added finely ground maleic anhydride (300 mg, 3 equiv), and the neat mixture stood at room temperature for 30 min, after ensuring that the oil permeated the powder, after which, the mixture was dissolved in THF (5 mL) and treated with PTAD (1.1 equiv, relative to the regioisomers that had not reacted with maleic anhydride), and the

red solution was rapidly stirred for 1 h. After stirring for 1 h, brine was added (5 mL), and the mixture was rapidly stirred for 30 min. The products were extracted with EtOAc (2×10 mL), and washed with NaHCO_3 , water, and brine (1×10 mL ea), dried over MgSO_4 , filtered, and concentrated. The brown residue was subsequently partitioned between THF (10 mL) and saturated aqueous NaHCO_3 solution (10 mL) and rapidly stirred for 16 h, after which time the mixture was extracted with EtOAc (2×10 mL), and the combined organic layer was washed sequentially with NaHCO_3 , water, and brine (1×10 mL ea), dried over Na_2SO_4 , filtered, and concentrated, and then purified by chromatography, yielding the urazole. The aqueous washes were combined and cooled to 0°C and acidified with conc. HCl (about 7 mL). Then the acidic medium was extracted with Et_2O (3×25 mL), and the combined organic layer was dried over MgSO_4 , filtered, and concentrated. The solid residue was then triturated with CH_2Cl_2 , and the white, solid diacid was collected by vacuum filtration and dried in vacuo. **Note:** it was necessary to perform a preliminary aqueous workup to remove the maleic acid resulting from the hydrolysis of maleic anhydride in order to maximize the yield and purity of the diacid product. Maleic acid was not removed in the CH_2Cl_2 trituration, but it could be removed via trituration with EtOAc; however, the diacid products had higher solubility in EtOAc, so yields were diminished without removing the maleic acid halfway through the synthetic route. Notably, the anhydride in the Diels–Alder products was significantly more stable toward hydrolysis than maleic anhydride, so the maleic anhydride could be selectively hydrolyzed under the conditions reported. Below, in cases where an inseparable mixture of regioisomers were isolated, both structures are shown, and when possible, the resonances for both structures are identified. All spectra were recorded in CDCl_3 ; however, the diacids required approx. 10 drops of CD_3OD for dissolution.



3-(Ethoxycarbonyl)-8-methyltricyclo[3.2.2.0,2,4]non-8-ene-6,7-dicarboxylic

acid (2.33): The title compound was prepared according to General Procedure C using toluene (2.13 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol),



$\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and maleic anhydride (294 mg, 3 mmol), yielding

a white solid (54 mg, 20%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (**2.33a**,

47%) 5.51 (d, $J = 6.6$ Hz, 1H), 4.02 (q, $J = 7.2$ Hz, 2H), 3.12 – 2.92 (m, 4H), 1.71 (s, 3H), 1.58

(m, 1H), 1.36 (m, 1H), 1.19 (m, 1H), 1.18 (t, $J = 7.2$ Hz, 3H); (**2.33b**, **53%**) 5.93 (t, $J = 7.8$ Hz,

1H), 5.53 (d, $J = 7.8$ Hz, 1H), 4.02 (q, $J = 7.2$ Hz, 2H), 3.18 (br s, 1H), 3.12 – 2.92 (m, 2H), 1.58

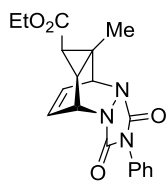
(m, 1H), 1.54 (m, 1H), 1.31 (m, 4H), 1.18 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ

(**2.33a**, **47%**) 175.1, 175.0, 173.5, 132.6, 120.8, 60.6, 53.6, 47.1, 38.8, 33.3, 21.7, 20.7, 20.1, 18.2,

13.9; (**2.33b**, **53%**) 174.9, 174.6, 173.5, 136.7, 127.3, 60.6, 50.2, 47.2, 38.8, 32.3, 26.7, 21.9, 21.5,

17.7, 13.9; **mp** 170–172 °C; **IR** (thin film, cm^{-1}) 3445, 1716, 1653, 1419, 1317, 1282, 1219, 1168;

HRMS (ESI) Calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_6$: 293.1031, Found: 293.1034.



Ethyl-5a-methyl-1,3-dioxo-2-phenyl-2,3,5a,6,6a,7-hexahydro-1H,5H-5,7-

ethenocyclopropa[d][1,2,4]triazolo[1,2-a]pyridazine-6-carboxylate (2.34): The

title compound was prepared according to General Procedure C using toluene (2.13

mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol) $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and 4-

phenyl-1,2,4-triazoline-3,5-dione (35 mg, 0.2 mmol). Flash chromatography (20%

EtOAc/hexanes) provided a white solid (36 mg, 8%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3)

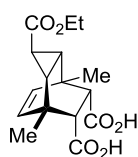
δ 7.45 (m, 4H), 7.38 (m, 1H), 6.27 (ddd, $J = 7.2, 5.1, 1.5$ Hz, 1H), 6.18 (ddd, $J = 7.2, 6.0, 1.2$ Hz,

1H), 5.24 (ddd, $J = 5.1, 4.5, 1.2$ Hz, 1H), 4.96 (dd, $J = 6.0, 1.5$ Hz, 1H), 4.18 (q, $J = 7.2$ Hz, 2H),

2.10 (dd, $J = 4.5, 3.9$ Hz, 1H), 1.61 (d, $J = 3.9$ Hz, 1H), 1.53 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C

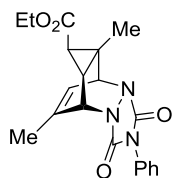
NMR (150 MHz, CDCl_3) δ 169.7, 157.1, 156.7, 131.2, 129.1, 128.3, 126.7, 125.7, 125.5, 61.1,

58.7, 52.7, 28.3, 20.4, 20.3, 14.2, 12.6; **mp** 140–142 °C; **IR** (thin film, cm⁻¹) 3065, 2982, 2932, 1774, 1715, 1503, 1405, 1335, 1232; **TLC** (20% EtOAc/hexanes) R_f = 0.13; **HRMS** (ESI⁺) Calcd. for C₁₉H₂₀N₃O₄: 354.1448, Found: 354.1469.



3-(Ethoxycarbonyl)-1,5-dimethyltricyclo[3.2.2.0,2,4]non-8-ene-6,7-dicarboxylic acid (2.35):

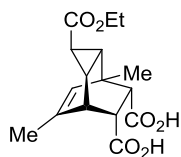
The title compound was prepared according to General Procedure C using *p*-xylene (24.6 mL, 200 mmol), ethyl diazoacetate (1.14 g, 10 mmol), Rh₂(TFA)₄ (65.8 mg, 0.1 mmol), and maleic anhydride (2.94 g, 30 mmol), yielding a white solid (409 mg, 14%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 5.57 (s, 3H), 3.98 (q, *J* = 7.2 Hz, 2H), 2.95 (s, 2H), 1.33, (d, *J* = 2.4 Hz, 2H), 1.31 (s, 6H), 1.30 (t, *J* = 2.4 Hz, 1H), 1.16 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 174.0, 173.7, 131.7, 60.6, 56.0, 38.0, 28.1, 21.7, 17.1, 13.8; **mp** 188–189 °C; **IR** (thin film, cm⁻¹) 3420, 2967, 1716, 1417, 1306, 1243, 1163; **HRMS** (ESI⁻) Calcd. for C₁₆H₁₉O₆: 307.1187, Found: 307.1191



Ethyl- 5a,9-dimethyl-1,3-dioxo-2-phenyl-2,3,5a,6,6a,7-hexahydro-1H,5H-5,7-ethenocyclopropa[d][1,2,4]triazolo[1,2-a]pyridazine - 6 - carboxylate (2.36):

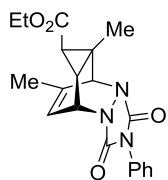
The title compound was prepared according to General Procedure C using *p*-xylene (24.6 mL, 200 mmol), ethyl diazoacetate (1.14 g, 10 mmol) Rh₂(TFA)₄ (65.8 mg, 0.1 mmol), and 4-phenyl-1,2,4-triazoline-3,5-dione (1.40 g, 8 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white solid (1.85 g, 50%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 7.46 (m, 4H), 7.37 (m, 1H), 5.83 (m, 1H), 5.00 (dd, *J* = 5.1, 1.8 Hz, 1H), 4.86 (d, *J* = 6.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.05 (dd, *J* = 5.1, 3.6 Hz, 1H), 1.88 (d, *J* = 1.8 Hz, 3H), 1.53 (d, *J* = 3.6 Hz, 1H), 1.51 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 169.8, 157.4, 156.9, 136.3, 131.3, 129.1, 128.2, 125.4, 118.5, 61.1, 59.6, 57.0, 28.0, 21.7, 20.0, 19.5, 14.2, 12.7; **mp** 126–127 °C; **IR** (thin film, cm⁻¹) 3063, 2981, 2935, 1772, 1716, 1504, 1404, 1227, 1158;

TLC (20% EtOAc/hexanes) R_f = 0.13; **HRMS** (ESI⁺) Calcd. for C₂₀H₂₂N₃O₄: 368.1605, Found: 368.1630.



3 - (Ethoxycarbonyl)-1,9-dimethyltricyclo[3.2.2.0,2,4]non-8-ene-6,7-dicarboxylic acid (2.37): The title compound was prepared according to General Procedure C using *m*-xylene (2.47 mL, 20 mmol), ethyl diazoacetate (114 mg, 1

mmol), Rh₂(TFA)₄ (6.6 mg, 0.01 mmol), and maleic anhydride (294 mg, 3 mmol), yielding a white solid (57 mg, 20%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 5.15 (s, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 3.05 (d, *J* = 9.9 Hz, 1H), 3.00 (br s, 1H), 2.90 (d, *J* = 9.9 Hz, 1H), 1.78 (s, 3H), 1.57 (br s, 1H), 1.30 (m, 1H), 1.26 (s, 3H), 1.21 – 1.15 (m, 4H); **¹³C NMR** (150 MHz, CDCl₃) δ 174.9, 174.6, 173.7, 135.9, 125.8, 60.6, 53.5, 49.8, 38.8, 37.3, 27.9, 21.9, 21.4, 20.5, 17.7, 13.9; **mp** 159–160 °C; **IR** (thin film, cm⁻¹) 3432, 2091, 1646, 1636, 1456, 1418, 1274, 1173; **HRMS** (ESI⁻) Calcd. for C₁₆H₁₉O₆: 307.1187, Found: 307.1192

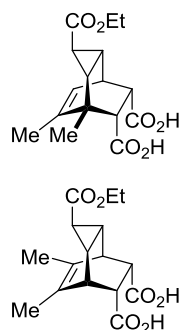


Ethyl -5a,10-dimethyl-1,3-dioxo-2-phenyl-2,3,5a,6,6a,7-hexahydro-1H,5H-5,7-ethenocyclopropa[d][1,2,4]triazolo[1,2-a]pyridazine - 6-carboxylate (2.38):

The title compound was prepared according to General Procedure C using *m*-xylene (2.47 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol) Rh₂(TFA)₄ (6.6 mg, 0.01 mmol), and 4-phenyl-1,2,4-triazoline-3,5-dione (105 mg, 0.6 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white solid (114 mg, 31%).

Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ (**2.38a, 74%**) 7.44 (m, 4H), 7.42 (m, 1H), 5.75 (d, *J* = 5.4 Hz, 1H), 5.14 (t, *J* = 5.4 Hz, 1H), 4.73 (s, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.05 (m, 1H), 1.92 (s, 3H), 1.52 (s, 3H), 1.49 (d, *J* = 3.6 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); (**2.38b, 26%**) 7.41 (m, 1H), 7.36 (m, 4H), 6.18 (dd, *J* = 7.5, 6.0 Hz, 1H), 5.99 (d, *J* = 7.5 Hz, 1H), 4.94 (d, *J* = 6.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.04 (s, 3H), 1.89 (d, *J* = 3.6 Hz, 1H), 1.59 (d, *J* = 3.6 Hz, 1H), 1.52 (s,

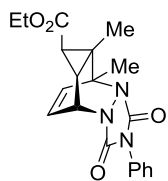
3H), 1.29 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ (**2.38a**, 74%) 169.8, 157.3, 156.9, 137.2, 131.2, 129.0, 128.2, 125.3, 117.7, 63.1, 61.0, 53.6, 27.7, 22.0, 20.0, 19.6, 14.2, 12.6; (**2.38b**, 26%) 169.8, 155.9, 155.4, 131.4, 131.2, 129.0, 128.2, 125.7, 125.0, 62.8, 61.0, 58.0, 28.0, 27.7, 21.8, 21.6, 14.2, 12.5; **mp** 110–112 °C; **IR** (thin film, cm^{-1}) 3064, 2980, 2934, 1771, 1716, 1504, 1404, 1227, 1173; **TLC** (20% EtOAc/hexanes) $R_f = 0.13$; **HRMS** (ESI^+) Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_4$: 368.1605, Found: 368.1628.



3-(Ethoxycarbonyl)-1,8-dimethyltricyclo[3.2.2.0^{2,4}]non-8-ene-6,7-

dicarboxylic acid (2.39): The title compound was prepared according to General Procedure C using *o*-xylene (2.47 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and maleic anhydride (294 mg, 3 mmol), yielding a white solid (37 mg, 12%). Analytical data: ^1H NMR (600 MHz, CDCl_3)

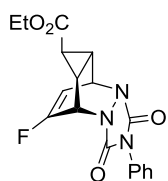
δ (**2.39a**, 77%) 5.58 (d, $J = 6.6$ Hz, 1H), 3.96 (q, $J = 7.2$ Hz, 2H), 3.08 (m, 1H), 2.96 (dd, $J = 10.8$, 1.2 Hz, 1H), 2.87 (d, $J = 10.8$ Hz, 1H), 1.56 (d, $J = 0.6$ Hz, 3H), 1.50 (m, 1H), 1.28 (dd, $J = 8.4$, 2.4 Hz, 1H), 1.25 (s, 3H), 1.16–1.12 (m, 4H); (**2.39b**, 23%) 3.96 (q, $J = 7.2$ Hz, 2H), 2.93 (br s, 2H), 2.89 (br s, 2H), 1.58 (s, 6H), 1.48 (m, 2H), 1.14 (t, $J = 7.2$ Hz, 3H), 0.96 (t, $J = 2.4$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ (**2.39a**, 77%) 174.8, 174.5, 173.7, 137.9, 121.2, 60.5, 53.8, 41.0, 32.0, 26.9, 21.9, 20.0, 18.1, 17.5, 16.8, 13.8; (**2.39b**, 23%) 175.0, 173.7, 127.4, 60.5, 47.0, 39.3, 21.6, 18.2, 13.8; **mp** 120–121 °C; **IR** (thin film, cm^{-1}) 3420, 1716, 1698, 1652, 1540, 1276, 1174; **HRMS** (ESI^-) Calcd. for $\text{C}_{16}\text{H}_{19}\text{O}_6$: 307.1187, Found: 307.1193.



Ethyl-5,5a-dimethyl-1,3-dioxo-2-phenyl-2,3,5a,6,6a,7-hexahydro-1H,5H-5,7-ethenocyclopropa[d][1,2,4]triazolo[1,2-a]pyridazine-6-carboxylate (2.40): The

title compound was prepared according to General Procedure C using *o*-xylene (2.47 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), Rh₂(TFA)₄ (6.6 mg, 0.01 mmol), and 4-phenyl-1,2,4-triazoline-3,5-dione (44 mg, 0.25 mmol), yielding a white solid (31 mg, 9%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ (**2.40a**,

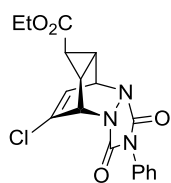
76%) 7.44 (m, 4H), 7.36 (m, 1H), 6.14 (dd, *J* = 7.8, 6.0 Hz, 1H), 6.04 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.23 (ddd, *J* = 6.0, 1.5, 1.5 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.12 (dd, *J* = 3.6, 1.5 Hz, 1H), 1.99 (s, 3H), 1.65 (d, *J* = 3.6 Hz, 1H), 1.43 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); (**2.40b**, 24%) 7.44 (m, 4H), 7.36 (m, 1H), 6.24 (dd, *J* = 4.2, 3.6 Hz, 1H), 4.90 (dd, *J* = 4.2, 3.6 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.65 (m, 5H), 1.50 (s, 3H), 1.30–1.27 (m, 4H); ¹³C NMR (150 MHz, CDCl₃) δ (**2.40a**, 76%) 169.9, 155.7, 155.4, 132.5, 131.3, 129.0, 128.2, 125.7, 124.7, 65.9, 61.1, 61.8, 28.2, 24.0, 22.7, 19.1, 14.2, 10.1; **mp** 131–132°C; **IR** (thin film, cm⁻¹) 2981, 2929, 1771, 1715, 1504, 1404, 1223, 1188; **TLC** (20% EtOAc/hexanes) R_f = 0.13; **HRMS** (ESI⁺) Calcd. for C₂₀H₂₂N₃O₄: 368.1605, Found: 368.1627.



Ethyl-9-fluoro-1,3-dioxo-2-phenyl-2,3,5a,6,6a,7-hexahydro-1H,5H-5,7-ethenocyclopropa[d][1,2,4]triazolo[1,2-a]pyridazine-6-carboxylate (2.41): The

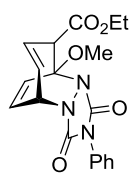
title compound was prepared according to General Procedure C using fluorobenzene (1.88 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), Rh₂(TFA)₄ (6.6 mg, 0.01 mmol), and 4-phenyl-1,2,4-triazoline-3,5-dione (193 mg, 1.1 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white solid (167 mg, 47%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.46 (m, 4H), 7.38 (m, 1H), 5.46 (m, 1H), 5.38 (m, 1H), 5.352 (ddd, *J* = 8.4, 5.4, 3.0, Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.30 (m, 1H), 2.22 (m, 1H), 1.61 (t, *J* = 2.7 Hz, 1H), 1.28

(t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.8, 156.4, 156.2 (d, $J = 3.3$ Hz), 154.2, 130.9, 129.1, 128.4, 125.3, 98.6 (d, $J = 3.5$ Hz), 61.4, 54.3 (d, $J = 26.7$ Hz), 52.7 (d, $J = 6.3$ Hz), 23.2, 16.8, 14.9 (d, $J = 2.6$ Hz), 14.0; **mp** 132–133°C; **IR** (thin film, cm^{-1}) 3064, 2987, 2932, 1717, 1663, 1404, 1226, 1165, 1050; **TLC** (20% EtOAc/hexanes) $R_f = 0.16$; **HRMS** (ESI^+) Calcd. for $\text{C}_{18}\text{H}_{17}\text{FN}_3\text{O}_4$: 358.1198, Found: 358.1217.



Ethyl -9-chloro-1,3-dioxo-2-phenyl-2,3,5a,6,6a,7-hexahydro-1H,5H-5,7-ethenocyclopropa[d][1,2,4]triazolo[1,2-a]pyridazine-6-carboxylate (2.42): The title compound was prepared according to General Procedure C using

chlorobenzene (2.03 mL, 20 mmol), ethyl diazoacetate (114 mg, 1 mmol), $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and 4-phenyl-1,2,4-triazoline-3,5-dione (193 mg, 1.1 mmol). Flash chromatography (20% EtOAc/hexanes) provided a white foam (191 mg, 51%). Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 7.46 (m, 4H), 7.39 (m, 1H), 6.13 (dd, $J = 6.6, 2.4$ Hz, 1H), 5.33 (dd, $J = 6.6, 5.8$ Hz, 1H), 5.30 (dd, $J = 4.8, 2.4$ Hz, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 2.31 (ddd, $J = 8.1, 4.8, 3.0$ Hz, 1H), 2.23 (ddd, $J = 8.1, 4.8, 3.0$ Hz, 1H), 1.52 (t, $J = 3.0$ Hz, 1H), 1.29 (t, $J = 7.2$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 169.8, 156.4, 156.0, 130.9, 129.1, 128.5, 128.4, 125.3, 120.8, 61.4, 59.1, 53.5, 23.3, 16.5, 15.3, 14.1; **IR** (thin film, cm^{-1}) 3065, 2981, 2932, 1772, 1716, 1646, 1505, 1404, 1224; **TLC** (20% EtOAc/hexanes) $R_f = 0.15$; **HRMS** (ESI^+) Calcd. for $\text{C}_{18}\text{H}_{17}\text{ClN}_3\text{O}_4$: 374.0902, Found: 374.0911.



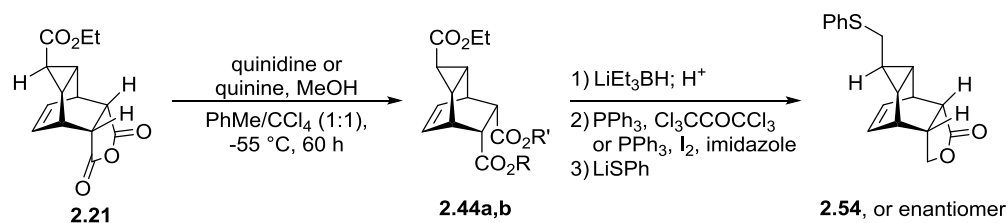
Ethyl -5-methoxy-1,3-dioxo-2-phenyl-2,3,6,9-tetrahydro-1H,5H-5,9-etheno[1,2,4]triazolo[1,2-a][1,2]diazepine-6-carboxylate (2.43): The title compound was prepared according to General Procedure C using anisole (2.17 mL, 20 mmol), ethyl

diazoacetate (114 mg, 1 mmol), $\text{Rh}_2(\text{TFA})_4$ (6.6 mg, 0.01 mmol), and 4-phenyl-1,2,4-triazoline-3,5-dione (53 mg, 0.3 mmol). Flash chromatography (20% EtOAc/hexanes) provided a yellow oil

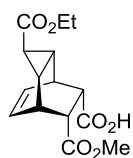
(34 mg, 9%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.53 (d, $J = 7.9$ Hz, 2H), 7.47 (dt, $J = 7.9, 7.3$ Hz, 2H), 7.38 (t, $J = 7.3$ Hz, 1H), 6.78 (dd, $J = 9.6, 7.2$ Hz, 1H), 6.34 (d, $J = 9.6$ Hz, 1H), 6.21 (ddd, $J = 11.1, 7.2, 2.4$ Hz, 1H), 5.77 (dd, $J = 11.1, 4.4$ Hz, 1H), 5.02 (dd, $J = 7.2, 7.2$ Hz, 1H), 4.28 (dd, $J = 4.4, 2.4$ Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 3.60 (s, 3H), 1.27 (m, 4H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 167.0, 154.4, 150.8, 132.5, 131.2, 131.1, 129.3, 129.0, 128.2, 126.5, 125.5, 91.2, 61.4, 53.7, 52.0, 50.3, 14.0; **IR** (thin film, cm^{-1}) 3067, 2981, 2938, 1772, 1715, 1498, 1409, 1247, 1187; **TLC** (20% EtOAc/hexanes) $R_f = 0.10$; **HRMS** (ESI^+) Calcd. for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}_5$: 370.1397, Found: 370.1419.

Further Transformations of Diels–Alder Products

Method to Obtain HPLC Traces of **2.44a,b**



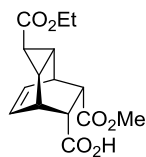
Note: The title procedure was required to assay the enantiomeric ratio (er) of the initial desymmetrization products **2.44a,b** owing to their poor UV activity. The desymmetrization could also be performed using benzyl alcohol without any loss in reactivity; however, this product was also poorly UV active. Furthermore, it was required to convert the hemiester into the respective lactone, since the acid functionality inhibited elution on silica. Due to the conformational rigidity of the hemiester, and the intermediates to **2.54**, we presume that no loss of enantiomeric purity was observed in this sequence.



(1S,2S,4R,5R,6R,7S)

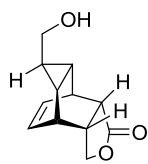
-3-(ethoxycarbonyl)-7-

(methoxycarbonyl)tricyclo[3.2.2.0^{2,4}] non-8-ene-6-carboxylic acid (2.44a/b):

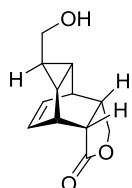


The anhydride (262 mg, 1 mmol) was added to a flame-dried round-bottomed flask containing the cinchona alkaloid (357 mg, 1.1 mmol), and the solid was suspended in 1:1 toluene/ CCl_4 (5 mL for quinidine, 20 mL for quinine). Then methanol (121 μL , 3 mmol) was added and the mixture was cooled to -55°C , where it stirred for 60

h. The mixture was warmed to room temperature and concentrated, and the residue was taken up in Et_2O (10 mL) and washed with 1 M HCl (3×10 mL). The combined aqueous layer was extracted with Et_2O (2×10 mL). **Note:** the cinchona alkaloid could be recovered from the acidic aqueous layer by basifying with Na_2CO_3 and extracting with Et_2O . The combined organic layer was then extracted with Na_2CO_3 (2×20 mL). The resultant aqueous layer was then acidified with conc. HCl (approx. 10 mL), and the organics were extracted with Et_2O (2×25 mL), washed with brine, dried over MgSO_4 , filtered, and concentrated, yielding a white solid of good purity: for quinine (**2.44a**, 272 mg, 93%), for quinidine (**2.44b**, 290 mg, 99%). Analytical data: **^1H NMR** (400 MHz, CDCl_3) δ 10.16 (br s, 1H), 6.01 (t, $J = 6.8$ Hz, 1H), 5.93 (t, $J = 6.8$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.59 (s, 3H), 3.30 (m, 2H), 3.17 (dd, $J = 10.4, 1.6$ Hz, 1H), 3.12 (dd, $J = 10.4, 2.0$ Hz, 1H), 1.67 (m, 2H), 1.37 (dd, $J = 2.8, 2.4$ Hz, 1H), 1.24 (t, $J = 7.2$ Hz, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 178.2, 173.0, 172.8, 128.7, 127.8, 60.6, 51.6, 47.4, 47.2, 33.8, 33.3, 20.3, 20.2, 18.4, 14.1; **mp** 114–116 $^\circ\text{C}$; **$[\alpha]_{\text{D}}$** = (**2.44a**) $+0.5^\circ$ ($c = 5.21$, CH_2Cl_2), (**2.44b**) -1.4° ($c = 11.79$, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3446, 2984, 1732, 1717, 1698, 1419, 1280, 1161, 1047; **HRMS** (ESI $^-$) Calcd. for $\text{C}_{15}\text{H}_{17}\text{O}_6$: 293.1031, Found: 293.1031.

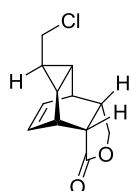


(3aS,4S,4aS,5aR,6R,6aR)-5-(hydroxymethyl)-3,3a,4,4a,5,5a,6,6a-octahydro-1H-4,6-ethenocyclopropa[f]isobenzofuran-1-one (2.52): The hemiester **2.44a**



(290 mg, 1 equiv) was added to a flame-dried 25 mL round-bottomed flask under nitrogen atmosphere and cooled to 0 °C. A solution of LiEt₃BH (1.0 M in THF, 6 mL, 6 equiv) was then added dropwise over 3 min. After stirred for 15 min at 0 °C, the ice bath was removed, and the solution warmed to room temperature while stirred

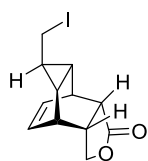
for 6 h. The reaction was then carefully quenched with 1 M HCl (10 mL) under nitrogen atmosphere, and the mixture stirred for an additional 2 h. The organics were then extracted with Et₂O (2 × 10 mL), dried over MgSO₄, filtered, and concentrated. The crude material was purified by column chromatography (40% EtOAc/hexanes), yielding a pungent smelling, white solid (132 mg, 71%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 5.99 (dd, *J* = 7.8, 6.6 Hz, 1H), 5.93 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.38 (dd, *J* = 9.6, 9.0 Hz, 1H), 3.89 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.51 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.45 (dd, *J* = 11.4, 7.2 Hz, 1H), 3.38 (m, 1H), 3.04 (m, 1H), 2.92 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.85 (dddd, *J* = 9.6, 9.6, 3.6, 3.6 Hz, 1H), 1.04 (ddd, *J* = 7.2, 3.0, 3.0 Hz, 1H), 0.97–0.91 (m, 2H); **¹³C NMR** (150 MHz, CDCl₃) δ 178.3, 130.8, 128.8, 71.8, 64.0, 45.7, 39.1, 34.5, 33.1, 20.3, 15.5, 15.4; **mp** 115–117 °C; [α]_D = (**2.52a**) +43.8° (*c* = 2.90, CH₂Cl₂), (**2.52b**) -53.6° (*c* = 6.27, CH₂Cl₂); **IR** (thin film, cm⁻¹) 3420, 2851, 1748, 1652, 1541, 1396, 1190, 1038; **TLC** (20% EtOAc/hexanes) *R_f* = 0.05; **HRMS** (ESI⁺) Calcd. for C₁₂H₁₅O₃: 207.1016, Found: 207.1021.



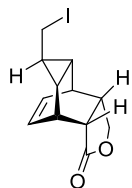
(3aS,4S,4aR,5aS,6R,6aR)-5-(chloromethyl)-3,3a,4,4a,5,5a,6,6a-octahydro-1H-4,6-ethenocyclopropa[f]isobenzofuran-1-one (2.53): Hexachloroacetone (0.6 mL,

6 equiv) was added to a 25 mL round-bottomed flask with 2 mL CH₂Cl₂, and the flask was cooled to 0 °C. Triphenylphosphine (185 mg, 1.1 equiv) was added, and the mixture stirred for 5 min. The intermediate alcohol **2.52** (132 mg, 1 equiv) was added in 3 mL CH₂Cl₂, and the

clear solution stirred for 5 min at 0 °C and 2 h at room temperature. The reaction was concentrated and immediately purified by column chromatography (20% EtOAc/hexanes), yielding a white solid (107 mg, 74%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.96 (dd, $J = 7.8, 6.6$ Hz, 1H), 5.92 (dd, $J = 7.8, 6.6$ Hz, 1H), 4.35 (t, $J = 9.6$ Hz, 1H), 3.85 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.45 (dd, $J = 10.8, 7.2$ Hz, 1H), 3.38 – 3.32 (m, 2H), 3.04 (m, 1H), 2.88 (dd, $J = 9.6, 3.6$ Hz, 1H), 2.82 (m, 1H), 1.13 (m, 1H), 1.06 – 0.99 (m, 2H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 178.0, 130.6, 128.8, 71.6, 46.8, 45.3, 38.8, 34.3, 33.0, 20.2, 18.1, 18.0; **mp** 99–100 °C; **IR** (thin film, cm^{-1}) 3050, 2934, 2867, 1759, 1636, 1377, 1182, 1007; **TLC** (20% EtOAc/hexanes) $R_f = 0.05$; **HRMS** (ESI^+) Calcd. for $\text{C}_{12}\text{H}_{14}\text{ClO}_2$: 225.0677, Found: 225.0677.



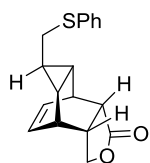
(3aS,4S,4aR,5aS,6R,6aR)- 5- (iodomethyl) - 3,3a,4,4a,5,5a,6,6a - octahydro - 1H - 4,6-ethenocyclopropa[f]isobenzofuran-1-one (2.45): A 25 mL round-bottomed



flask was charged with triphenylphosphine (412 mg, 2.05 equiv) and imidazole (261 mg, 5 equiv). The solids were dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Iodine (389 mg, 2 equiv) was added, and the yellow-orange solution stirred at 0 °C for 10 min. The intermediate alcohol **2.52** (158 mg, 0.8 mmol) was added in 10 mL of

CH_2Cl_2 , and the reaction was allowed to gradually warm to room temperature as it stirred for 16 h. Then the reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (8 mL), and the reaction was stirred at room temperature for 15 min. The product were then extracted with CH_2Cl_2 (3×10 mL), and washed with brine (1×20 mL), dried over Na_2SO_4 , filtered, and concentrated, and immediately purified by column chromatography (40% EtOAc/hexanes), yielding a white solid (88 mg, 36%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.96 (dd, $J = 7.2, 6.6$ Hz, 1H), 5.92 (dd, $J = 7.2, 6.6$ Hz, 1H), 4.34 (dd, $J = 9.6, 9.0$ Hz, 1H), 3.85 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.36 (m, 1H), 3.13 (dd, $J = 9.6, 7.2$ Hz, 1H), 3.07 – 2.99 (m, 2H), 2.87 (dd, $J = 9.6, 3.0$ Hz, 1H), 2.08 (dddd, $J = 9.6, 9.6,$

4.2, 4.2 Hz, 1H), 1.08 (m, 2H), 0.97 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.9, 130.6, 128.7, 71.5, 45.1, 38.6, 34.6, 33.3, 23.3, 23.0, 22.3, 9.4; **mp** 98–99 °C; $[\alpha]_{\text{D}} = (\mathbf{2.45a}) +47.3^\circ$ ($c = 2.00$, CH_2Cl_2), **(2.45b)** -43.0° ($c = 4.60$, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3054, 2859, 2359, 1756, 1484, 1437, 1182, 1119, 998, 750; **TLC** (20% EtOAc/hexanes) $R_f = 0.06$; **HRMS** (ESI^+) Calcd. for $\text{C}_{12}\text{H}_{14}\text{IO}_2$: 317.0033, Found: 317.0035.



(3aS,4S,4aR,5aS,6R,6aR)-5-((phenylthio)methyl)-3,3a,4,4a,5,5a,6,6a-

octahydro-1H-4,6-ethenocyclopropa[f]isobenzofuran-1-one (2.54): *n*-BuLi (2.61

M in hexanes, 0.36 mL, 2 equiv) was added dropwise to a flame-dried 25 mL round-

bottomed flask containing thiophenol (0.15 mL, 3 equiv) in anhydrous THF cooled

to 0 °C. After complete addition, the solution was warmed to room temperature,

where it stirred for 15 min. The alkyl chloride **2.53** (107 mg, 1 equiv) was added with

4 mL anhydrous THF, and the clear solution stirred until deemed complete by TLC

(16 h). The reaction was then concentrated and immediately purified by column chromatography

(20% EtOAc/hexanes), yielding a white solid (61 mg, 59%). The enantiomeric ratio (**2.54a**: 94:6;

2.54b, 6:94) was determined by chiral HPLC (column IA, 90:10 hexanes/*i*PrOH). Analytical data:

^1H NMR (600 MHz, CDCl_3) δ 7.35 (m, 2H), 7.29 (m, 2H), 7.21 (m, 1H), 5.94 (t, $J = 7.2$ Hz, 1H),

5.88 (t, $J = 7.2$ Hz, 1H), 4.35 (dd, $J = 9.6, 9.0$ Hz, 1H), 3.85 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.32 (m,

1H), 2.99 (m, 1H), 2.89 – 2.83 (m, 2H), 2.81 – 2.85 (m, 2H), 1.00 (ddd, $J = 7.5, 3.0, 3.0$ Hz, 1H),

0.91 (ddd, $J = 7.5, 3.6, 3.6$ Hz, 1H), 0.87 (dddd, $J = 6.6, 6.6, 3.6, 3.0$ Hz, 1H); ^{13}C NMR (150

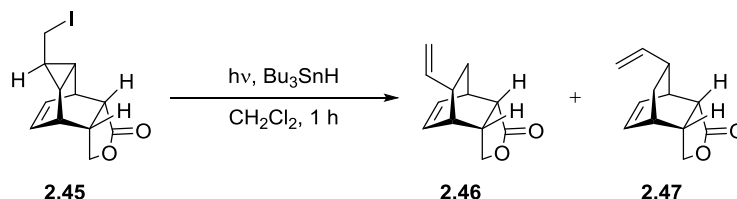
MHz, CDCl_3) δ 178.3, 136.2, 130.6, 130.0, 128.8, 128.7, 126.3, 71.7, 45.5, 38.9, 36.3, 34.6, 33.2,

18.04, 18.00, 17.5; **mp** 96–97 °C; $[\alpha]_{\text{D}} = (\mathbf{2.54a}) +22.5^\circ$ ($c = 0.98$, CH_2Cl_2), **(2.54b)** -21.0° ($c =$

0.18, CH_2Cl_2); **IR** (thin film, cm^{-1}) 3053, 2948, 1758, 1647, 1584, 1479, 1377, 1183, 1015; **TLC**

(20% EtOAc/hexanes) $R_f = 0.11$; **HRMS** (ESI⁺) Calcd. for C₁₈H₁₉O₂S: 299.1100, Found: 299.1110.

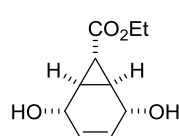
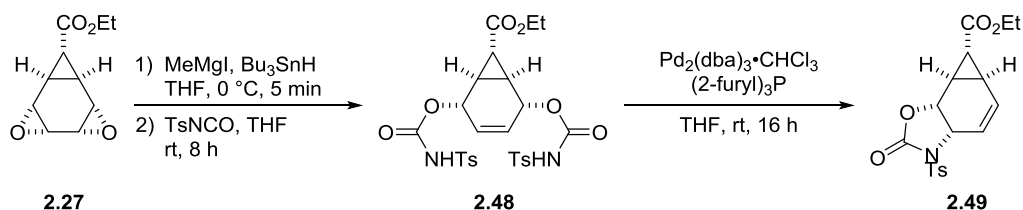
Cyclopropylmethyl Radical-Promoted Ring-Opening of **2.45**



9-vinyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1(3H)-one and 9-vinyl-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-3(1H)-one (2.46/2.47): The alkyl iodide **2.45** (38 mg, 0.12 mmol) was added to a flame-dried 5 dram vial under nitrogen atmosphere. Then the Bu₃SnH (0.13 mL, 4 equiv) was added, and the mixture was dissolved in anhydrous CH₂Cl₂ (10 mL). The vial was then subjected to irradiation by a Hg lamp/Pyrex filter for 1 h. After 1 h, the lamp was turned off and the reaction was concentrated and purified by column chromatography (20% EtOAc/hexanes), yielding a clear oil as a mixture of regioisomers (23 mg, >99%). Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ (**2.46**, **56%**) 6.42 (dd, $J = 7.2, 7.2$ Hz, 1H), 6.21 (dd, $J = 7.2, 7.2$ Hz, 1H), 5.56 (m, 1H), 4.98 (m, 1H), 4.91 (m, 1H), 4.37 (dd, $J = 9.0, 9.0$ Hz, 1H), 3.87 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.11 (m, 1H), 2.84 – 2.77 (m, 2H), 2.76 – 2.68 (m, 1H), 2.38 (m, 1H), 1.91 (ddd, $J = 12.6, 9.6, 2.4$ Hz, 1H), 1.19 (ddd, $J = 13.2, 4.8, 3.6$ Hz, 1H); (**2.47**, **44%**) 6.36 (dd, $J = 7.2, 7.2$ Hz, 1H), 6.26 (dd, $J = 7.2, 7.2$ Hz, 1H), 5.56 (m, 1H), 4.98 (m, 1H), 4.91 (m, 1H), 4.37 (dd, $J = 9.0, 9.0$ Hz, 1H), 3.87 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.07 (m, 1H), 2.87 (dd, $J = 10.2, 3.6$ Hz, 1H), 2.76 – 2.68 (m, 2H), 2.45 (m, 1H), 1.83 (ddd, $J = 12.6, 9.6, 2.4$ Hz, 1H), 1.15 (ddd, $J = 13.2, 5.4, 3.0$ Hz, 1H); **¹³C NMR** (150 MHz, CDCl₃) δ (**2.46**, **56%**) 179.1, 143.0, 134.9, 130.7, 113.5, 71.9, 44.1, 40.6, 39.4, 38.5, 32.3, 31.3; (**2.47**, **44%**) 178.9, 142.8, 133.2, 132.4, 113.6, 72.3, 45.1, 40.3, 37.4, 37.3, 34.0, 31.3; **IR** (thin film, cm⁻¹) 3048, 2934,

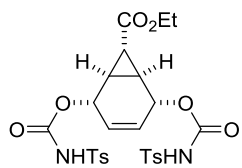
2867, 1759, 1636, 1377, 1182, 1007; **TLC** (20% EtOAc/hexanes) $R_f = 0.16$; **HRMS** (ESI⁺) Calcd. for C₁₂H₁₄NaO₂: 213.0886, Found: 213.0890.

Desymmetrization of bis-Epoxyde **2.27**



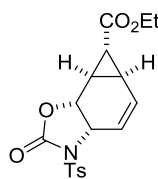
Ethyl -2,5-dihydroxybicyclo[4.1.0]hept-3-ene-7-carboxylate (2.55): The bis-epoxide **2.27** (250 mg, 1.3 mmol) and Bu₃SnH (1.4 mL, 4 equiv) were added to a

flame-dried 25 mL round-bottomed flask under nitrogen atmosphere and dissolved in anhydrous THF (10 mL). Then the reaction was cooled to 0 °C before the MeMgI (3.0 M in Et₂O, 0.53 mL, 1.25 equiv) was added dropwise over 5 min. After complete addition of MeMgI, the reaction was immediately quenched with saturated NH₄Cl (5 mL) under nitrogen atmosphere. The product was extracted with Et₂O (2 × 5 mL), dried over MgSO₄, filtered, and concentrated. The crude material was purified by column chromatography (50% EtOAc/hexanes → 100% EtOAc → 90% EtOAc/MeOH) yielding a golden oil (221 mg, 87%). **Note:** the reaction was slow to proceed if run in Et₂O, and it failed when MeMgBr was used instead. The inclusion of Bu₃SnH minimizes THF polymerization, although the reaction proceeds without it as an additive. Analytical data: **¹H NMR** (600 MHz, CDCl₃) δ 5.87 (br s, 2H), 4.42 (br s, 2H), 4.32 (br s, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 2.04 (d, $J = 4.2$ Hz, 2H), 1.38 (t, $J = 4.2$ Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H); **¹³C NMR** (150 MHz, CDCl₃) δ 172.8, 128.3, 61.8, 61.0, 25.9, 21.3, 14.2; **IR** (thin film, cm⁻¹) 3391, 2983, 2905, 1716, 1447, 1302, 1198, 1013, 801; **TLC** (20% EtOAc/hexanes) $R_f = 0.02$; **HRMS** (ESI⁻) Calcd. for C₁₀H₁₄NaO₄: 221.0784, Found: 221.0789.



Ethyl-2,5-bis((tosylcarbamoyl)oxy)bicyclo[4.1.0]hept-3-ene-7-carboxylate (2.48):

The diol **2.55** (53 mg, 0.26 mmol) was added to a flame-dried 10 mL round-bottomed flask under nitrogen atmosphere and dissolved in anhydrous THF (2.5 mL). The *p*-toluenesulfonyl isocyanate (81 μ L, 2.01 equiv) was then added, and the reaction was allowed to stir at room temperature for 8 h. The reaction was then concentrated and flushed through a short pad of silica first with 20% EtOAc/hexanes (40 mL) then with EtOAc (100 mL). The fractions containing the product were collected and concentrated, yielding a white solid (158 mg, >99%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.93 (m, 4H), 7.34 (m, 4H), 5.93 (br s, 2H), 5.42 (m, 2H), 4.13 (q, $J = 7.2$ Hz, 2H), 2.46 (s, 6H), 1.95 (m, 2H), 1.43 (t, $J = 4.2$ Hz, 1H), 1.25 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 171.2, 150.0, 145.2, 135.3, 129.6, 128.4, 127.4, 66.2, 61.4, 21.7, 21.4, 21.1, 14.1; **mp** 87–89 $^\circ\text{C}$; **IR** (thin film, cm^{-1}) 3248, 2985, 2875, 1716, 1597, 1456, 1353, 1161, 853; **TLC** (20% EtOAc/hexanes) $R_f = 0.01$; **HRMS** (ESI $^-$) Calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_{10}\text{S}_2^-$: 591.1113, Found: 591.1160.



Ethyl -2-oxo-3-tosyl-3,3a,5a,6,6a,6b-hexahydro-2H-cyclopropa[3,4]benzo[1,2-d]oxazole-6-carboxylate (2.49):

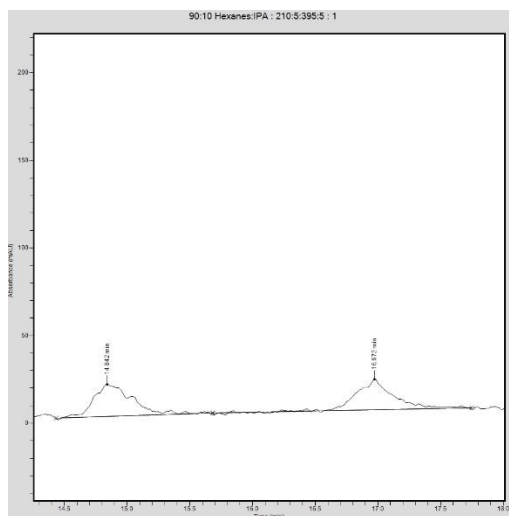
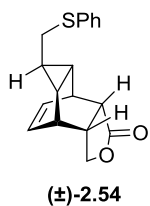
A flame-dried 10 mL round-bottomed flask was charged with $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (10 mg, 0.05 equiv) and tris-(2-furyl)phosphine (5 mg, 0.1 equiv) in a nitrogen-filled glovebox. The solids were then dissolved in anhydrous THF (2.5 mL), and the dark mixture stirred for 1 h. Then the bis-carbamate **2.48** (114 mg, 0.19 mmol) was added with anhydrous THF (2.5 mL), and the reaction was allowed to stir at room temperature for 16 h. Once the reaction was deemed complete by TLC analysis, the reaction was concentrated and immediately subjected to column chromatography (30% EtOAc/hexanes) to yield a white foam (55 mg, 76%). Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.96 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 6.28 (ddd, $J = 7.2, 5.4, 1.8$ Hz, 1H), 5.63 (ddd, $J = 7.2, 3.6, 1.8$ Hz, 1H), 5.14

(dd, $J = 7.8, 1.5$ Hz, 1H), 4.71 (ddd, $J = 7.8, 3.6, 1.8$ Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 2.46 (s, 3H), 2.28 (ddd, $J = 7.8, 4.8, 1.5$ Hz, 1H), 2.08 (ddd, $J = 7.8, 5.4, 3.6$ Hz, 1H), 1.56 (dd, $J = 4.8, 3.6$ Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 170.4, 150.7, 145.7, 135.3, 129.9, 129.1, 128.4, 119.5, 70.4, 61.4, 53.0, 29.7, 21.8, 20.2, 18.6, 14.2; IR (thin film, cm^{-1}) 3058, 2984, 1780, 1717, 1647, 1366, 1300, 1193, 1015, 814; TLC (20% EtOAc/hexanes) $R_f = 0.14$; HRMS (ESI $^+$) Calcd. for $\text{C}_{18}\text{H}_{19}\text{NNaO}_6\text{S}$: 400.0825, Found: 400.0851.

HPLC traces for **2.54a,b** (derived from hemiesters **2.44a,b**)

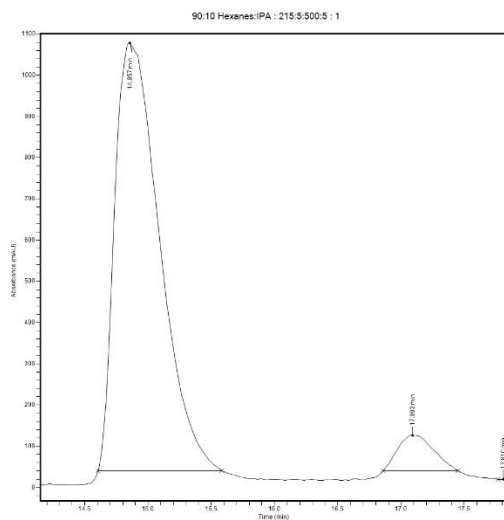
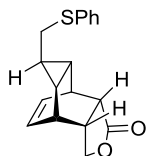
2.54 (rac):

peak #	RT (min)	area (mAU \times s)	height (mAU)	area(%)
1	14.842	390454.38	18414.06	52.9
2	16.972	347299.13	17470.47	47.1



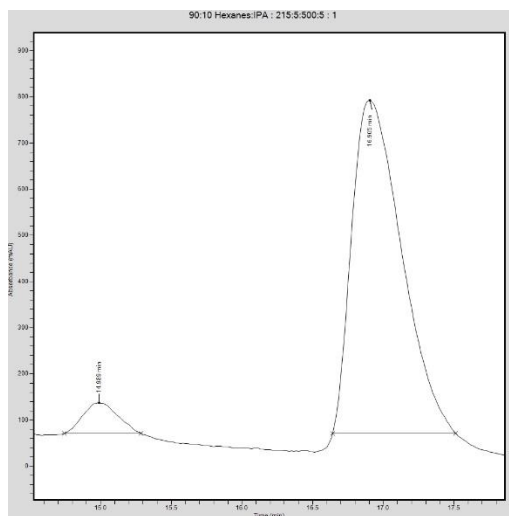
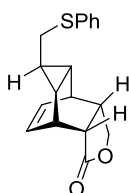
2.54a (quinine):

peak #	RT (min)	area (mAU × s)	height (mAU)	area(%)
1	14.857	25553519.61	1041017.51	93.7
2	17.093	1705684.86	86778.97	6.3



2.54b (quinidine):

peak #	RT (min)	area (mAU × s)	height (mAU)	area(%)
1	14.989	1182560.66	67685.57	6.3
2	16.905	17686664.05	724177.58	93.7



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CHAPTER THREE:
THE DEVELOPMENT OF REGIOISOMERICALLY ENRICHED BUCHNER PRODUCTS FOR USE AS
CYCLOHEXADIENYL SYNTHETIC INTERMEDIATES

3.1 Introduction

After our initial progress in showcasing norcaradienes (NCDs) as viable dienyl intermediates in the generation of highly substituted carbocyclic products (see Chapter Two),¹ the need for regioisomerically pure NCDs has become ever increasing. Although the kinetic separation of regioisomers was feasible in many cases, direct access to single regioisomers would not only offer an expedient route to valuable building blocks, but it would also be less wasteful in cases where a single regioisomer is desirable. Therefore, we endeavored to develop methods to provide such products.

There are two general methods for direct access to single regioisomeric NCDs: the development of a regioselective intermolecular Buchner reaction or an intramolecular Buchner reaction. Although there are currently no general methods for regioselective intermolecular Buchner reactions, intramolecular reactions have been shown to exhibit high levels of regioselectivity in many cases;² however, there are few examples of downstream applications to non-aromatic products.³ This chapter will be divided into two distinct, but related projects: discussed first will be our efforts towards the development of the first highly regioselective intermolecular Buchner reaction, and the utility of those intermediates in complex carbocycle synthesis. The second portion of the chapter will entail a discussion on the intramolecular Buchner reaction of benzyl cyanodiazooacetates and the functionalization of the resultant fused tricyclic NCDs. The initial investigations into both of these areas offer a firm foundation for the ultimate

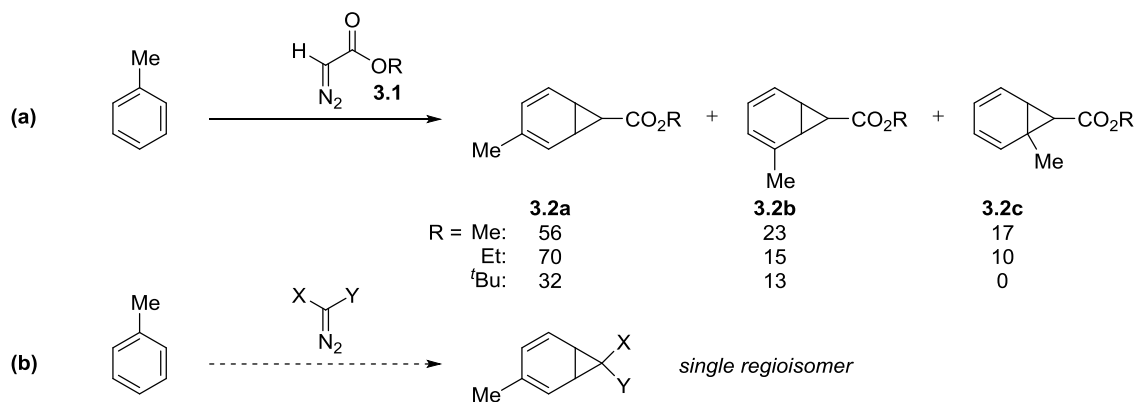
goal of generating single regioisomers of enantioenriched norcaradienyl intermediates for use in downstream functionalization towards complex carbocyclic materials.

3.2 Background

3.2.1 Poor Regioselectivity of Buchner Reactions Using Diazoacetates

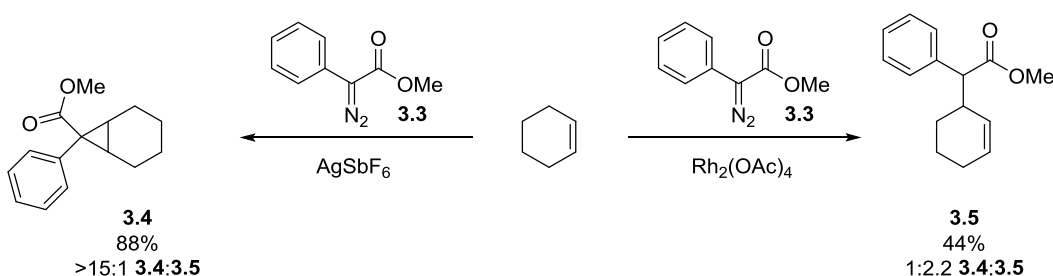
As discussed in depth throughout Chapter Two, there currently exists no highly regioselective intermolecular Buchner reaction. This is likely a result of the high energy barrier for dearomatization, coupled with the reactive carbenoid intermediates required for the transformation, providing poor discrimination between various sites of reactivity. Scheme 2-10 and 2-11 outlined the key stereoelectronic factors that affect the regioselectivity of the Buchner reaction, whereby the electronic factors dominated site selectivity in the case of highly activating or deactivating groups;^{1,4} at the same time, steric factors controlled arenes bearing simple aliphatic groups. Although the regioselectivity of the Buchner reaction employing simple diazoesters **3.1** can be partially modulated by varying the steric profile of the ester substituent (Scheme 1a),⁵ alteration of the identity of the diazo compound could offer a platform for absolute control over the reaction profile, such that the regioselectivity of the reaction could be adequately controlled (Scheme 3-1b).

Scheme 3-1. Controlling the Intermolecular Buchner Reaction through Steric Effects



To this end both the steric profile of the carbene and the identity of the catalyst could be manipulated to influence the regioselectivity of the transformation. There are a myriad of reports in the literature that outline the impact of catalyst variation on reaction outcome. In one related example, Davies showed how aryl diazoacetates **3.3** under Rh(II) catalysis are prone to insert into allylic C–H bonds to form **3.5**, rather than cyclopropane **3.4**; however, upon switching the catalyst to AgSbF₆, the C–H insertion pathway can be significantly suppressed (Scheme 3-2).⁶

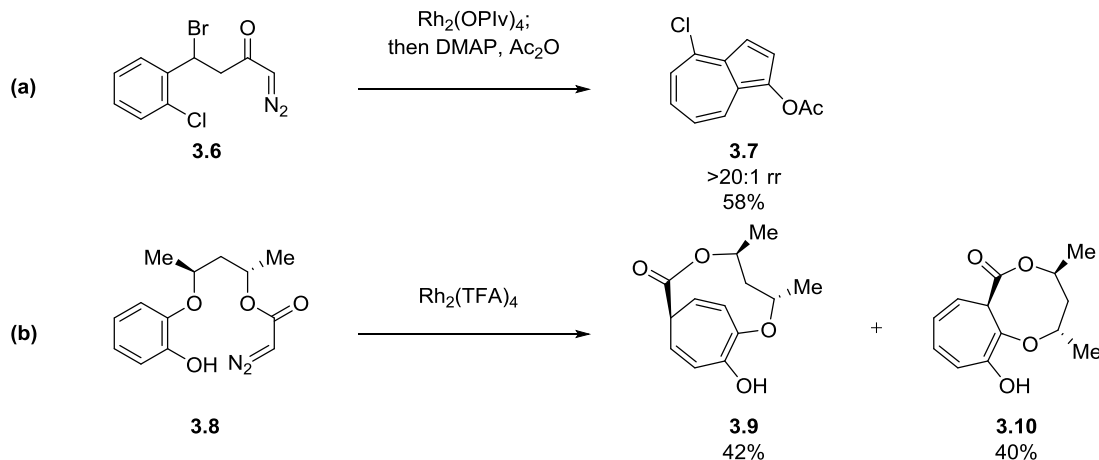
Scheme 3-2. Divergent Carbenoid Reactivity upon Variation of the Catalyst



3.2.2 Controlling Regio- and Enantioselectivity of Intramolecular Buchner Reactions

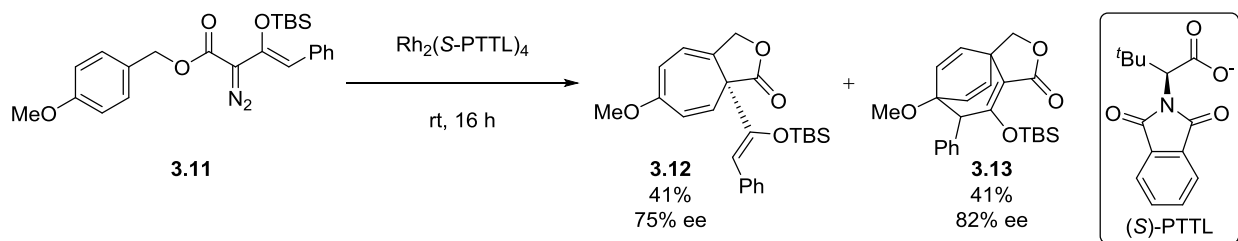
Another common way of rendering the Buchner reaction highly regioselective is through the incorporation of a tether. By forcing an intramolecular reaction with an appropriately sized tether, the reaction of **3.6** can only occur at a single site (Scheme 3-3a);^{2,7} however, if the tether is too long, as in the case of **3.8** (Scheme 3-3b), this constraint is relaxed and a mixture of regioisomeric products **3.9/3.10** can be observed.⁸

Scheme 3-3. Controlling the Intramolecular Buchner Reaction through Appropriately Sized Tethers



Aside from diastereoselective intramolecular Buchner reactions, there are examples of enantioselective variants.⁹ Doyle has shown that donor-acceptor diazo compounds **3.11** can undergo an enantioselective Buchner reaction generating **3.12**, followed by [3,3]-rearrangement to **3.13** using chiral rhodium carboxylate catalysts; however, isolation of the enantioenriched products **3.12** was challenging, due to facile racemization via a zwitterionic intermediate prior to Cope rearrangement (Scheme 3-4).¹⁰

Scheme 3-4. Enantioselective Intramolecular Buchner Reaction/[3,3]-Rearrangement



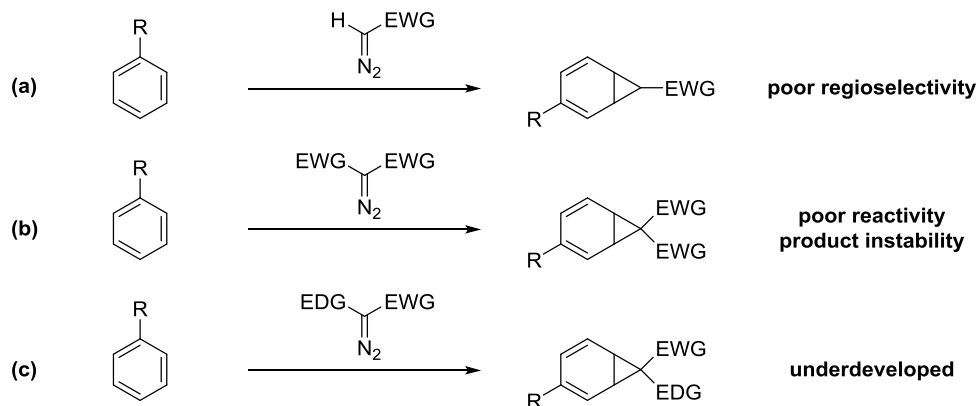
The above examples employing donor-acceptor diazo compounds and/or appropriately-sized tethers offered insight into direct ways to access regioisomerically pure NCDs. In the next section, we detail our efforts into not only gaining access to new regioisomerically pure NCDs, but also their utility in the synthesis of stereochemically complex carbocycles.

3.3 Results and Discussion

3.3.1 The Reactivity of Various Diazo Substitution Patterns towards the Buchner Reaction

After our initial investigations into intermolecular Buchner chemistry with ethyl diazoacetate (see Chapter Two),¹ we sought to discover conditions for a highly regioselective Buchner reaction. Since diazo compounds containing a single electron acceptor (Scheme 3-5a) result in poor regioselectivity regardless of identity,⁵ we began to explore diazo compounds bearing other substitution patterns. In our hands, acceptor-acceptor diazo compounds¹¹ (i.e., dimethyl diazomalonate) were plagued by lower reactivity than EDA and provided products that were prone towards rearomatization (Scheme 3-5b). Davies has pioneered donor-acceptor diazo compounds as selective and tunable carbene precursors;¹² however, there are few examples of using donor-acceptor diazo compounds for Buchner chemistry in the literature (Scheme 3-5c).¹³

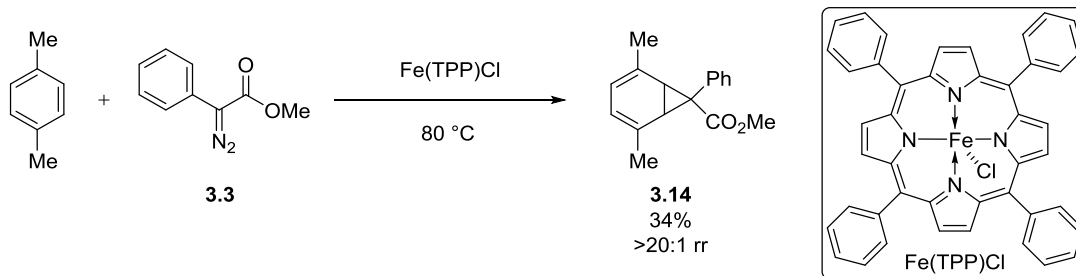
Scheme 3-5. The Shortcomings of Different Diazo Classes in Intermolecular Buchner Reactions



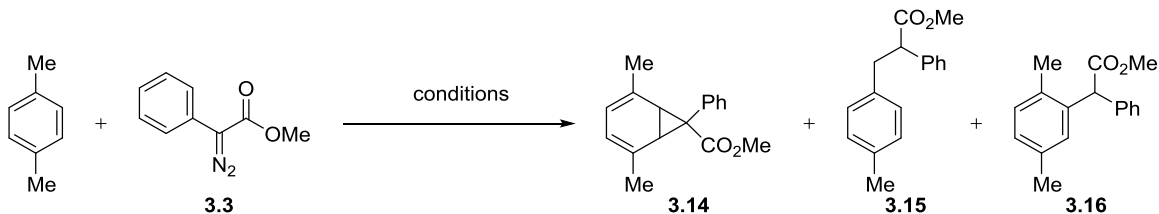
3.3.2 Iron Porphyrin Catalyzed Buchner Reaction

The most promising example using donor-acceptor diazo compounds was reported using the iron-porphyrin catalyzed decomposition of methyl phenyl diazoacetate **3.3**, which provided the stable norcaradiene **3.14** from *p*-xylene as a single regioisomer in modest yield (Scheme 3-6); the formation of this product was competitive with benzylic C–H insertion.^{13a,c}

Scheme 3-6. Fe(TPP)Cl-Catalyzed Intermolecular Buchner Reaction of *p*-Xylene



With this precedent in mind, we were interested in seeing if this catalyst, or variants thereof would promote this reaction for a range of substrates. Especially intriguing about this catalyst class is the possibility of substituting a chiral salen ligand for the porphyrin, since they are reported to behave analogously in many cases.¹⁴ In light of this, we screened a wide variety of conditions, varying both the ligand, metal source, and temperature (Table 3-1). Following the conditions reported by Mbuvi and Woo (entry 1),^{13c} we successfully isolated a modest yield of the desired product **3.14**, which existed exclusively as the *meso*-NCD. Starting with the *in situ*-generated Fe(II) porphyrin provided a modest increase in the yield of **3.14** (entry 2). Although cationic Fe(III) resulted in an increased reaction rate, the only product identified was the formal arene C–H insertion product **3.16**, that would arise from the rearomatization of **3.14**. Since iron salen complexes provided comparable results to that of Fe(TPP)Cl (entry 5), salen ligands were used in the remaining screening, since their synthesis was more modular. Notably, the reaction shut down when performed at temperatures lower than 80 °C (entry 6). Copper (II) and cobalt (II) salen complexes offered neither an improvement nor a detriment to the iron (II) catalyzed cases (entries 7-10).

Table 3-1. Catalyst Screen for Intermolecular Buchner Reaction of *p*-Xylene^a

entry	catalyst	temperature (°C)	time (h)	yield (%) ^b	3.14 : 3.15 ^c
1	Fe(TPP)Cl	80	16	16	2:1
2	Fe(TPP)Cl/CoCp ₂	80	16	34 (55) ^d	2:1
3	Fe(TPP)Cl/AgSbF ₆	80	16	0 (40) ^e	-
4	Fe(TPP)Cl/CoCp ₂ /AgSbF ₆	80	16	34	2:1
5	Fe(salen)Cl/CoCp ₂	80	16	38	2:1
6	Fe(salen)Cl/CoCp ₂	40	16	0	-
7	Cu(salen)	80	16	34	2:1
8	Cu(salen)	40	16	0	-
9	Cu(salen)	23	16	0	-
10	Co(salen)/CoCp ₂	80	16	36	2:1
11	CoCp ₂	80	16	42 ^d	2:1
12	-	80	16	41 ^d	2:1

^aReactions used 5 mol % catalyst, 100 equiv *p*-xylene. ^bYields are isolated yields of **3.14** unless otherwise noted. ^c**3.14**:**3.15** ratio was determined from the crude ¹H NMR. ^dDenotes ¹H NMR yield. ^eDenotes ¹H NMR yield of the rearomatization byproduct **3.16**.

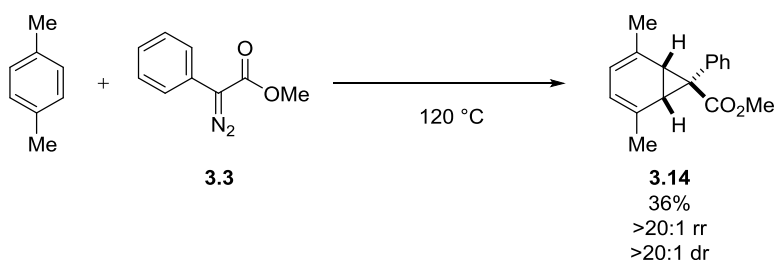
With minimal improvements to the reaction, we then tried to confirm that the catalyst was necessary for the transformation. Much to our chagrin, running the reaction at 80 °C in the absence of catalyst provided comparable results to the initial hit (entries 11, 12), indicating that the catalyst was not needed. It has been well-documented that aryl diazoacetates readily thermolyze at elevated temperatures.^{12b,13e}

3.3.3 Thermolysis of Phenyl Diazoacetates

In light of this, we found it operationally facile to simply thermolyze the diazo compound, providing access to the desired NCD in modest yields and high purity after a single recrystallization (Scheme 3-7). Although the thermolysis of **3.3** was limited to *p*-xylene, the ease

of accessing this material prompted us to investigate the utility of this norcaradiene in subsequent transformations.

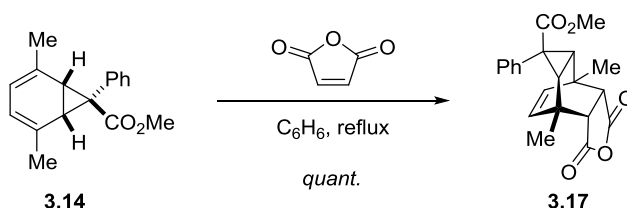
Scheme 3-7. Thermolysis of Methyl Phenyl Diazoacetate in *p*-Xylene



3.3.4 Functionalization of Norcaradienes through Cycloaddition Reactions

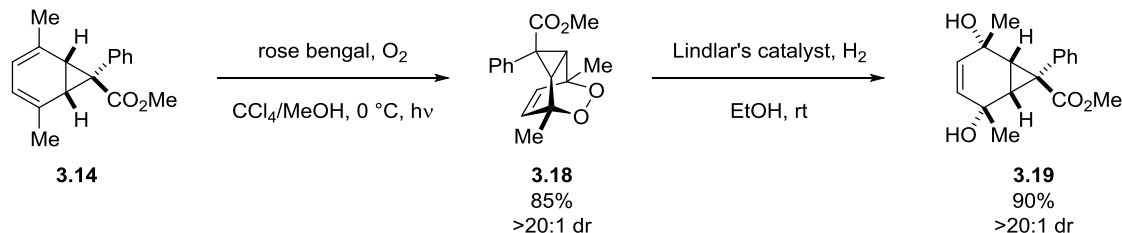
To probe its reactivity, NCD **3.14** was reacted with competent dienophiles, such as maleic anhydride, providing access to the expected [2.2.2]-bicyclic product in excellent yields (Scheme 3-8). We were excited about the possibility of expanding the scope of reactive dienophiles. If the rate limiting step of this Diels–Alder reaction is generation of the NCD (as opposed to the CHT), then having a stable norcaradiene such as **3.14**, would allow for the Diels–Alder reactions to proceed with less activated dienophiles. Unfortunately, this was not the case, as electron-deficient alkenes (i.e., acrolein, methyl acrylate, dimethyl fumarate, etc.) did not engage **3.14**.

Scheme 3-8. Diels–Alder Reactions of Norcaradiene **3.14**



Endoperoxide **3.18** was generated from the rose bengal sensitized singlet oxygen Diels–Alder reaction with **3.14**.¹⁵ Notably, this endoperoxide was isolable after silica gel chromatography. Reduction of the endoperoxide could be realized upon hydrogenolysis using Lindlar’s catalyst, providing the *syn*-1,4-diol **3.19** in excellent yield.

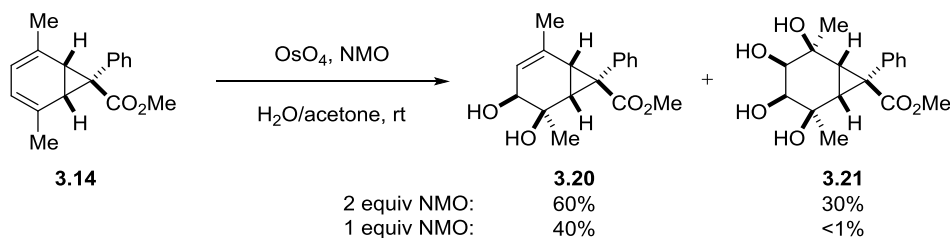
Scheme 3-9. Access to *syn*-1,4-Diol **3.19** from *meso*-Norcaradiene **3.14**



3.3.5 Non-Cycloaddition Transformations of Norcaradiene

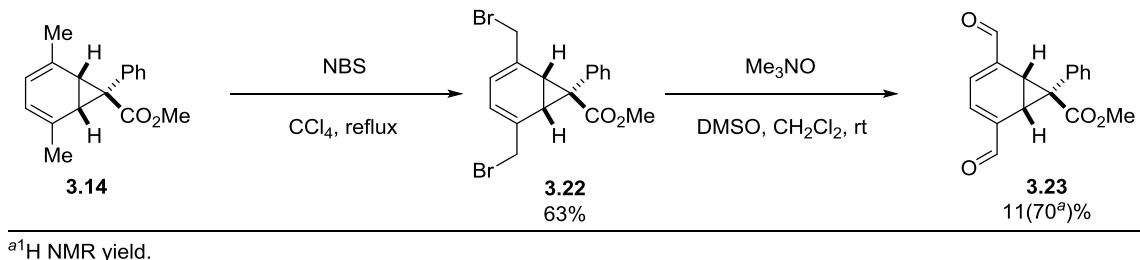
Direct, non-cycloaddition methods for functionalizing the norcaradienyl core proved to be challenging transformations. Of the multitude that were screened (e.g., hydroboration,¹⁶ hydrogenation,¹⁷ epoxidation,¹⁸ carbonyl ene,¹⁹ etc.) the only conditions that were successful in symmetry-breaking diene functionalization were simple dihydroxylations using OsO₄,²⁰ affording a mixture of mono-dihydroxylation **3.20** and bis-dihydroxylation **3.21** products. Controlling the stoichiometry of NMO succeeded in suppressing the formation of the **3.21**, albeit with incomplete conversion. Sharpless conditions for asymmetric dihydroxylation²¹ were unable to promote the desymmetrizing transformation, presumably due to the increased steric constraints imposed by the chiral ligand.

Scheme 3-10. Dihydroxylation of *meso*-Norcaradiene **3.14**

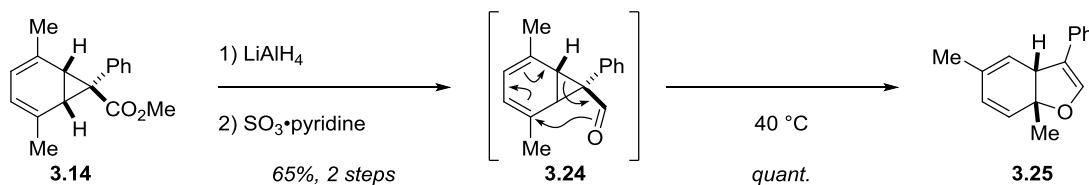


*¹H NMR yields, using mesitylene as internal standard.

The vinyl methyl groups could also be functionalized, as in the case of allylic bromination, providing the bis-bromide **3.22**. Kornblum oxidation²² of **3.22** allowed access to the bis-aldehyde **3.23** in good yield, although purification of the bis-aldehyde resulted in low mass recovery. This facile two-step route allows for the formal Buchner reaction on an electron-deficient arene.

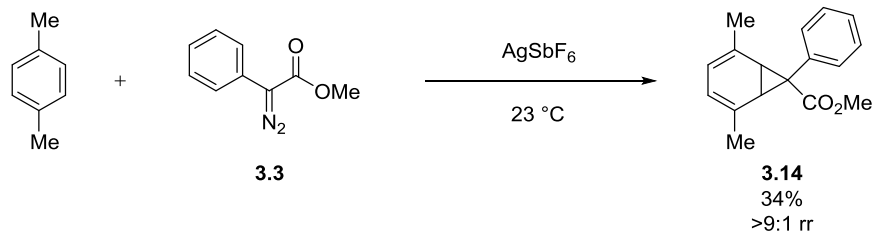
Scheme 3-11. Allylic Bromination and Kornblum Oxidation of *meso*-Norcaradiene

Rather than focus functionalizations on the diene portion of **3.14**, metal hydride reduction of the ester provided cycloheptatrienyl methanol. Parikh–Doering oxidation²³ of the intermediate allowed for formation of the aldehyde **3.24**, which was thermally unstable and gradually rearranged to the dihydrobenzofuran **3.25**.^{13a} This process proceeded slowly at room temperature, but was accelerated upon heating to 40 °C. Attempts to extend this methodology to dihydroindoles or dihydrobenzothiophenes, were unsuccessful; all attempts at substitution of the primary alcohol after initial reduction resulted in styrene products via rearomatization.

Scheme 3-12. Dihydrobenzofuran Synthesis from *meso*-Norcaradiene**3.3.6 Silver(I)-Catalyzed Buchner Reaction**

With the inherent limitations of the thermolysis method of generating norcaradienes, we further investigated transition metal catalyzed methods at lower temperatures. Neither Rh(II) carboxylates nor Cu(II) complexes were successful at providing meaningful yields of Buchner products with aryl diazoacetates; however, upon screening AgSbF₆, we were able to observe low yields of the desired product **3.14** in high regioselectivity with *p*-xylene.

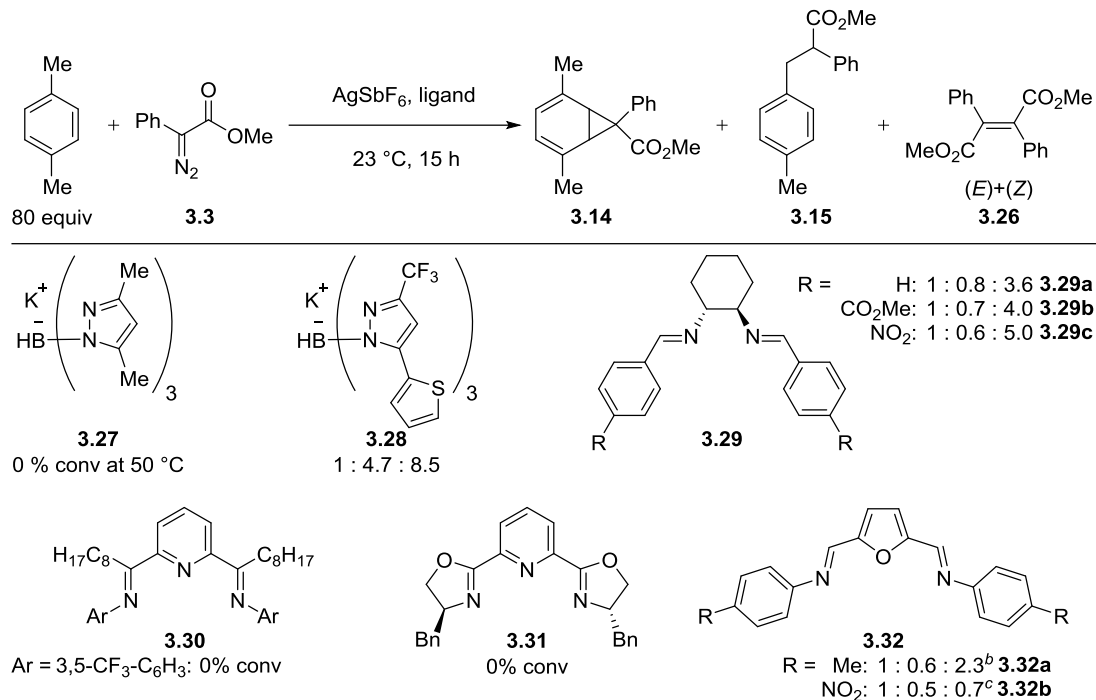
Scheme 3-13. AgSbF₆ Catalyzed Intermolecular Buchner Reaction of *p*-Xylene



Despite the diminished levels of regioselectivity relative to thermolysis (see Section 3.3.3), this initial hit encouraged us to further optimize this transformation, since the reaction could be performed at ambient conditions.

3.3.7 Ligand Screening for the Silver(I) Buchner Reaction

With the goal of accessing enantioenriched products, we began to screen various chelating ligands to probe their effect on the transformation. We began our screening with silver scorpionate catalysts since they have been effectively used in cyclopropanation reactions.²⁴ We found that electron rich ligands **3.27** completely suppressed the reaction, while electron deficient ligands **3.28** promoted the reaction, in poor selectivity over benzylic C–H insertion and carbene dimerization (Table 3-2). Switching to cyclohexyl diimine catalysts **3.29** showed a similar trend with imines bearing electron deficient groups providing higher selectivity for NCD **3.14**. While screening these ligands, however, we noticed that if the stoichiometry of the ligand was not carefully controlled, no conversion of the diazo compound would be observed. We attributed this suppression of reactivity to the formation of an inert 18-electron complex with two chelating ligands on silver.

Table 3-2. Ligand Screening in Ag(I)-Catalyzed Buchner Reaction of *p*-Xylene

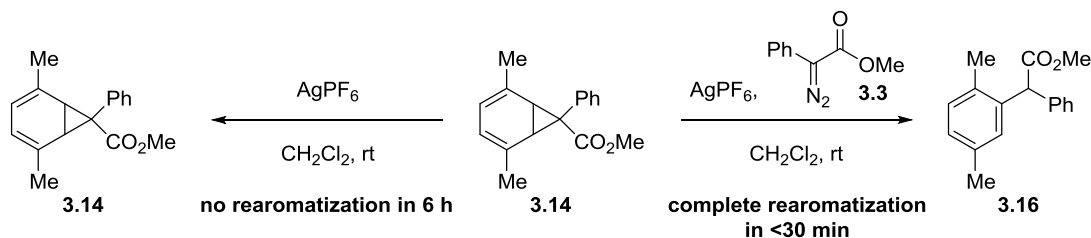
^aReaction conditions: AgSbF_6 (5 mol %), ligand (6 mol %), syringe pump addition of the diazo compound in 1 mL CH_2Cl_2 over 15 h. The ratio **3.14**:**3.15**:**3.26** was determined from the crude ^1H NMR spectra. Complete conversion was observed in all cases unless otherwise noted. ^bA normalized amount of 1.83 of the arene C–H insertion product **3.16** relative to the **3.14** was observed. ^cA normalized amount of 0.82 of the arene C–H insertion product **3.16** relative to the **3.14** was observed.

To avoid the possibility of this inert intermediate, we focused our attention on tridentate ligands, which would provide reactive 16-electron silver complexes. Much to our chagrin, using the strongly electron-deficient pyridyl ligand **3.30**, we were unable to complex the silver. Simple pybox ligands **3.31** were able to complex silver; although being electron rich, reactivity was shut down. It was not until switching the pyridyl backbone to a furyl group **3.32** that promising results were obtained. Using **3.32b**, high selectivity over both C–H insertion and dimerization was observed, albeit in low isolated yields (20%). Switching the diazo compound to the analogous 4-nitroaryl diazo acetate, dimerization could be completely suppressed, and a 4:1 **3.14**:**3.15** ratio could be obtained, though this iteration required >3 d at 40°C for complete conversion.

3.3.8 AgPF₆ Catalyzed Regioselective Intermolecular Buchner Reaction

Despite the promising levels of chemoselectivity using ligand **3.32b**, the extended reaction times and inability to impart enantioselectivity using the optimized system prompted us to probe the parent reactivity of the Ag(I) Buchner reaction. Over the course of these investigations, we discovered inauspicious product instability to the reaction conditions, with complete conversion of the NCD to the rearomatized product, which is likely a key factor in the formation of the formal arene C–H insertion product **3.16** observed above. Perhaps most striking is that NCD **3.14** was stable to both AgPF₆ and methyl phenyldiazoacetate **3.3** individually, but not the mixture of the two reagents, indicating that the mechanism for rearomatization is not a simple Lewis acid-promoted cyclopropyl ring opening and rearomatization (Scheme 3-14).

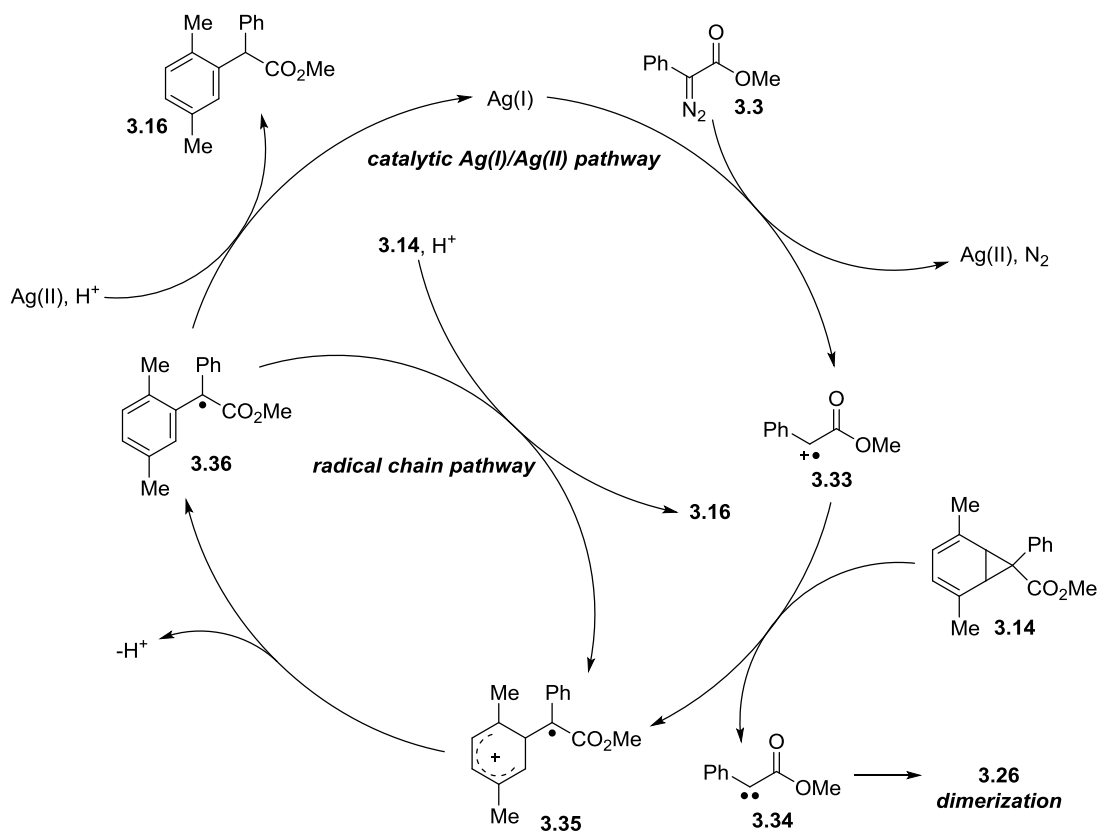
Scheme 3-14. Norcaradiene Instability to Methyl Phenyldiazoacetate and AgPF₆



The mechanism for rearomatization can be rationalized by invoking a single electron transfer from the diazo compound **3.3** to Ag(I), resulting in a radical cation intermediate that readily releases nitrogen.²⁵ This highly electrophilic intermediate **3.33** then engages the norcaradiene to provide radical cation intermediate **3.35**, which rapidly rearomatizes. Electron transfer and protonation produces the observed arene C–H insertion product **3.16** and regenerates Ag(I). Alternatively, a radical chain pathway could be initiated in the same manner, but propagates through electron transfer steps from the rearomatized intermediate **3.36** and another equivalent of **3.14** (Scheme 3-15). A radical pathway to generate carbene **3.34** could also be accessed upon treatment of diazo compound **3.3** with other radical initiators (i.e., AIBN/60 °C, Ru(bpy)₃Cl₂/hν,

SbCl₆N(4-Br-C₆H₄)₃); all of which either provided appreciable amounts of NCD **3.14**, arene C–H insertion **3.16**, or carbene dimerization **3.26**.

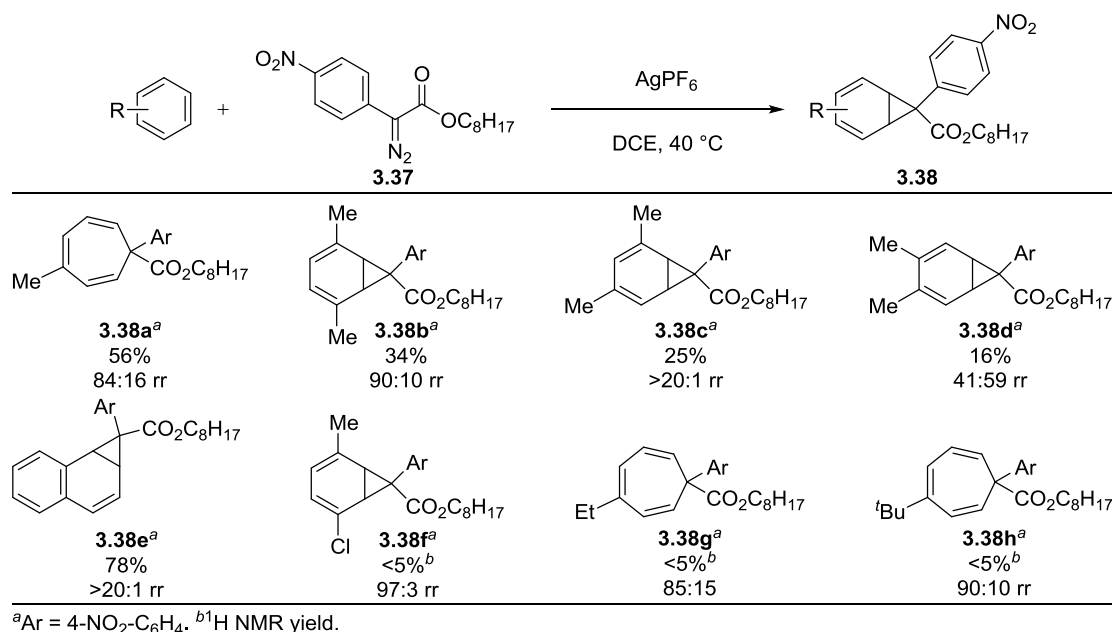
Scheme 3-15. Plausible Radical Cation Mechanism for Rearomatization of **3.14**



Such a treatment of the formation of the arene C–H insertion product **3.16** offers significant insight into the trends observed in the ligand screening. By including electron-withdrawing substitution on the ligands, the oxidation potential of Ag(I) increases, thereby slowing the rate of radical cation formation. Since silver carbenoids are known to selectively cyclopropanate over inserting into arene C–H bonds^{6a} (unlike gold carbenes²⁶), all observed arene C–H insertion products most likely arise from the mechanism outlined in Scheme 3-15. Therefore, to further disfavor this radical cation pathway, the addition of a strongly electron withdrawing substituent on the aryl diazoacetate would destabilize radical cation intermediate **3.33** and greatly suppress the undesired pathway.

In the event, we found that octyl 4-nitrophenyldiazoacetate **3.37** completely avoided the formation of the arene C–H insertion product, although heating was required to achieve reasonable reaction rates. As shown in Table 3-3, remarkable levels of regioselectivity were observed in many cases of aliphatic substituted arenes **3.38a-c**; however, for non-methyl substrates, or more electron-deficient arenes **3.38f-h**, the reactivity was significantly retarded. Notably, benzylic C–H insertion was not competitive in any case other than *p*-xylene—even for benzylic positions that are prone towards C–H insertion, such as ethyl benzene.^{13e}

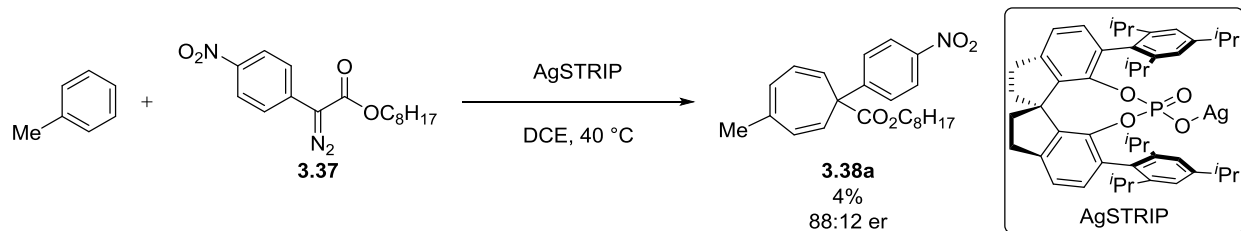
Table 3-3. Substrate Scope of AgPF₆-Catalyzed Buchner Reaction of *p*-Xylene



3.3.9 Efforts towards an Enantioselective Silver Buchner Reaction

Since we were precluded from using chiral ligands on silver to impart enantioselectivity upon the Buchner reaction, we identified two areas that might provide an enantioselective reaction. The first of these was based on the chiral anion approach. To this end, chiral phosphoric acid-derived AgSTRIP was prepared²⁷ and the Buchner reaction of toluene was investigated (Scheme 3-16).

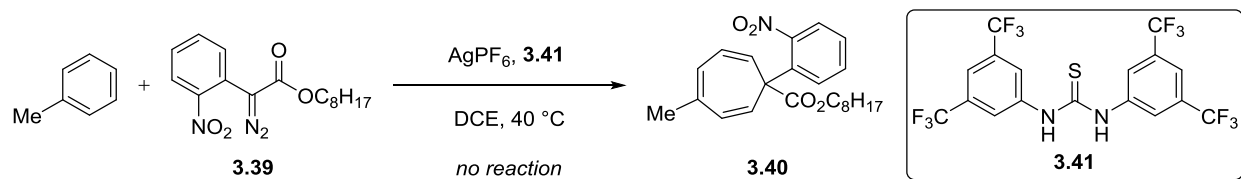
Scheme 3-16. AgSTRIP Catalyzed Enantioselective Buchner Reaction



In the event, we observed an 88:12 er under standard reaction conditions, albeit in low isolated yield of **3.38a**. The low yield could be explained by the fact that phosphates are more coordinating than PF_6^- . A strong correlation between the pK_a of the counterion and the yield of the reaction has been observed.^{6a} Nonetheless such a high initial hit for enantioselectivity could provide the foundation for an enantioselective silver Buchner reaction.

An alternative method that we tested was the union of chiral thiourea catalysis with silver(I) catalysis, since hydrogen bonding interactions between thioureas and nitro groups is well-documented.²⁸ In hopes of the thiourea catalyst affecting the transition state of the Buchner reaction, we moved the nitro group to the 2-position in **3.39** so it would be closer to the silver catalyst. However, in both the 2-nitro and 4-nitro cases, thiourea **3.41** was found to suppress reactivity, possibly through coordination with the silver. Due to these unavoidable detriments to reactivity, this path of investigation was abandoned.

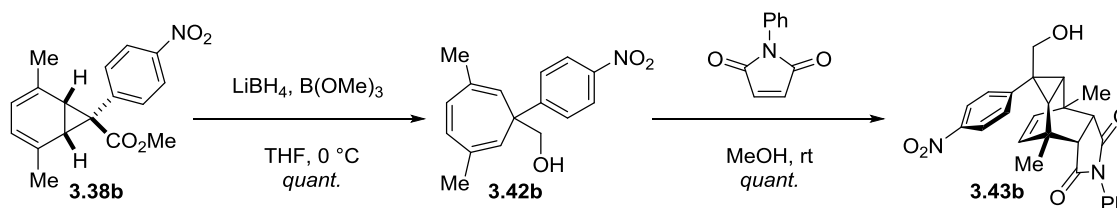
Scheme 3-17. Dual Catalytic Hydrogen Bond Donor/Silver(I) Catalytic System



3.3.10 Functionalization of Regioisomerically Enriched Norcaradienes

Many non-cycloaddition reactions on these intermediate NCDs were infeasible (i.e., epoxidation, (3+2)-annulation, carbonyl ene, Tsuji-Trost, etc.); however, treatment with *N*-phenylmaleimide on brine provided complete conversion to the desired Diels–Alder product.¹ Unfortunately, it seems that the formation of the Diels–Alder product is reversible, since attempts at purifying the [2.2.2]-bicyclic product resulted in quantitative recovery of the NCD **3.38b**. In an attempt to prevent this retro-Diels–Alder by disfavoring the reverse reaction, the ester was first reduced to the primary alcohol **3.42b**,^{29,30} which resulted in the CHT as the sole product. Treatment of CHT **3.42b** with *N*-phenylmaleimide resulted in quantitative conversion to the desired Diels–Alder product **3.43b** that was stable to silica gel chromatography.

Scheme 3-18. Selective Reduction and Diels–Alder of **3.38b**



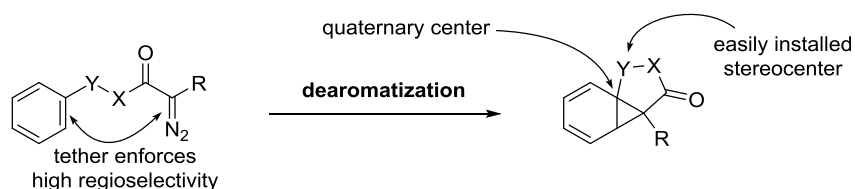
With this proof-of-concept, we have developed the first highly regioselective, metal-catalyzed intermolecular Buchner reaction. Although at this juncture the scope is limited, all of the products exist as stable norcaradienes that are amenable to further functionalization to deliver highly substituted cyclohexane cores. Efforts are ongoing in our lab to further exploit this reactivity.

3.3.11 Benefits of an Intramolecular Buchner Reaction

At this juncture, we transitioned our investigations towards intramolecular Buchner reactions. These intermediates offer several advantages over NCDs derived from an intermolecular process: (1) The inclusion of a tether strongly enforces high regioselectivity in the transformation;

(2) The Buchner reaction generates a quaternary stereocenter, which minimizes the propensity of the NCDs to rearomatize; (3) α -Chiral benzyl alcohols are easily prepared and readily available, allowing for diastereoselective transformations to generate enantioenriched NCDs.

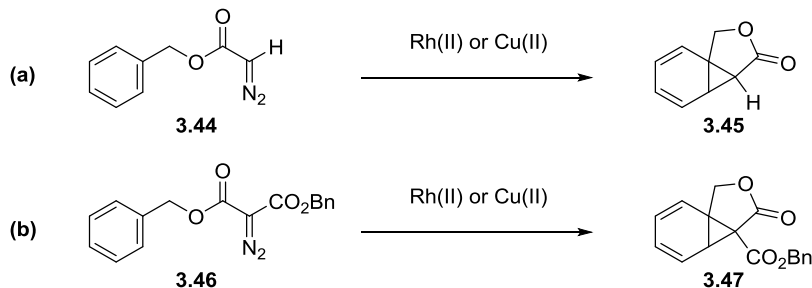
Scheme 3-19. Benefits of Using an Intramolecular Buchner Reaction



3.3.12 Initial Investigations into an Intramolecular Buchner Reaction

We began our investigations using simple benzyl diazoacetates **3.44**, which have been previously reported to undergo intramolecular Buchner reactions.^{2b} Despite this fact, there has been little utility of any of these intramolecular Buchner products as non-aromatic intermediates for downstream functionalization. Upon screening a variety of commercial Rh(II) and Cu(II) catalysts, we observed minimal formation of **3.45**. These poorly-yielding reactions coupled with instability of **3.44** towards storage prompted abandonment of this route. Dibenzyl diazomalonates **3.46** were slow to react under the screened conditions, a phenomenon that has been previously observed in intramolecular Buchner reactions.³¹

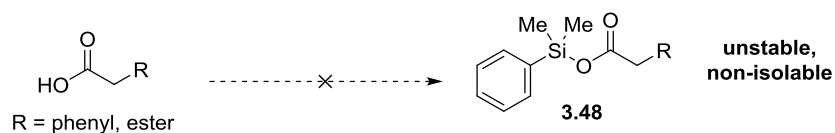
Scheme 3-20. Intramolecular Buchner Attempts with Diazoacetates and Malonates



Slowed by reactivity issues for known diazo substitution patterns, we became interested in the possibility of including a removable silicon tether between the diazo and aryl moieties. We

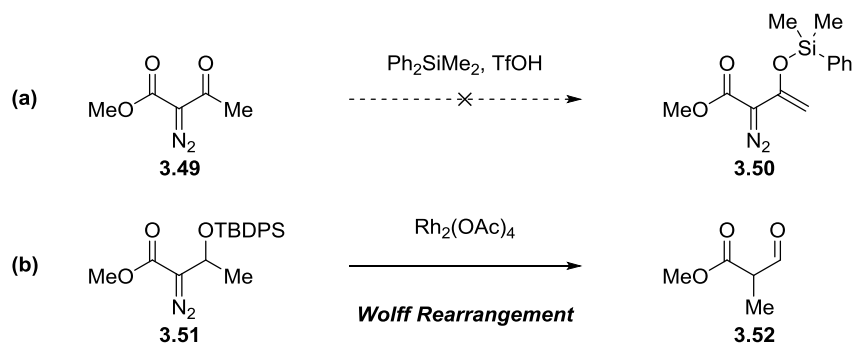
envisioned two possible locations for silicon incorporation: either directly bound to the acetate or included as a silyl enol ether, analogous to the donor-acceptor diazo compounds pioneered by Doyle.^{10,32} Attempts at generating the requisite diazo compounds were complicated by product instability. We were unable to append phenyl silanes onto carboxylic acids **3.48**, so attempts at making the related diazo compounds were not feasible.

Scheme 3-21. Non-Isolable Silyl Esters



Using Doyle's conditions,¹⁰ and variants thereof to access the desired donor-acceptor diazo compound, we were unable to form the silyl enol ether **3.50**. It seems that Doyle's TBS enol ether is the only silyl group that tolerates those conditions, as phenyl silanes returned starting material. The secondary alcohol resulting from reduction of the diazo ketone was able to be silicon protected with both dimethylphenylsilyl chloride and TBDPSCl; however, decomposition of **3.51** resulted only in Wolff rearrangement³³ to the trivial dicarbonyl **3.52**.

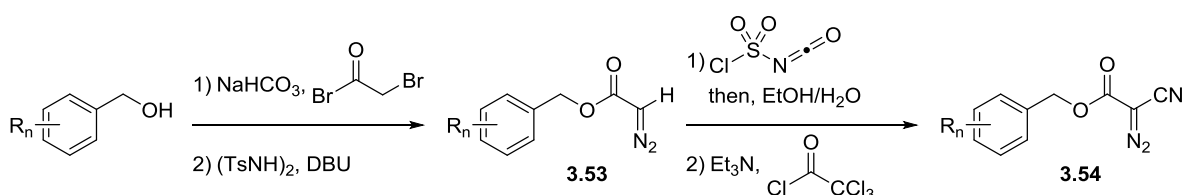
Scheme 3-22. Donor-Acceptor Diazo Compounds for Intramolecular Buchner Reactions



3.3.13 Development of an Expedient Route to Cyano Diazoacetates

At this critical impasse for the continuation of this project, we returned to the work by Reisman and the intramolecular Buchner reaction of cyanodiazoacetates she employed in her synthesis of salvileucalin B.^{3,31} Although she reports conventional Regitz diazo transfer to cyanoacetates, in our hands we found that such a procedure resulted in severe decomposition of the resultant diazo compound. To circumvent this, we developed a multistep route that allowed for reliable generation of a series of cyanodiazoacetates. The sequence was initiated by a method developed by Fukuyama,³⁴ where bis-tosylhydrazine converted an α -bromoester to α -diazoester **3.53** under basic conditions. This intermediate was then condensed with an isocyanate, providing the free primary amide upon hydrolysis.³⁵ This amide was dehydrated using trichloroacetyl chloride, cleanly providing cyano diazoacetate **3.54** in 25-45% yield over the five discrete steps. Although the route is longer than conventional methods, this route could be completed in just over a day and required only a single chromatographic operation. The 4-OMe substrate was unable to be prepared in this manner due to competing generation of quinone methide intermediates through elimination of the diazoacetate.

Scheme 3-23. Expedient Route to Benzyl Cyano Diazoacetates



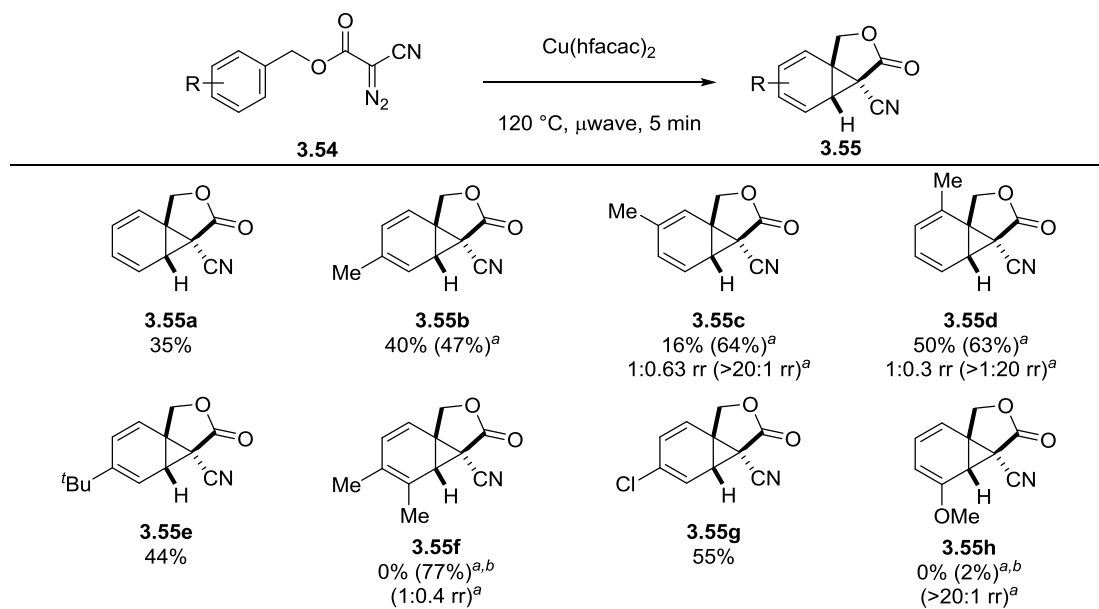
3.3.14 Substrate Scope of Intramolecular Buchner Reaction of Cyano Diazoacetates

With a number of diazo compounds in hand, the substrates were screened with typical reductive metals for carbene catalysis (i.e., $\text{Rh}_2(\text{OAc})_4$, $\text{Rh}_2(\text{TFA})_4$, $\text{Cu}(\text{hfacac})_2$, AgPF_6 , etc.) which were all met with discouraging results. Turning our attention to microwave heating,

however, provided efficient reactivity using Cu(hfacac)₂ as the metal catalyst at 120 °C for 2 min, providing NCDs **3.55** in high regioselectivity and diastereoselectivity (Table 3-4). The regioselectivity is exclusively controlled by steric effects; this bias is so strong that mesitylene-derived diazo compound **3.54i** (see Experimental Details, section 3.5) was unable to provide any meaningful levels of Buchner products, since both *ortho*-sites were blocked by the flanking methyl groups.

Notably, Rh₂(OPiv)₄ provided dramatically improved yields in many cases, concomitant with improved regioselectivity. This can be attributed to the suppression of Lewis acid assisted degradation and isomerization pathways of the initially formed norcaradiene **3.55**.

Table 3-4. Substrate Scope of Intramolecular Buchner Reaction under Microwave Heating



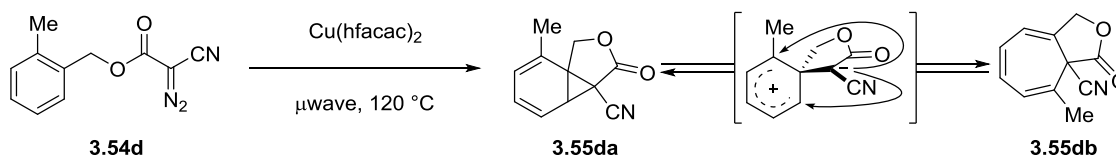
^aThe values in parentheses resulted from using 1 mol % Rh₂(OPiv)₄ at room temperature for 30 min. ^b¹H NMR yield.

Upon screening various copper sources under the standard microwave conditions, we found that cationic Cu(II)(pybox) systems could provide the desired NCD, albeit in lower yields than Cu(hfacac)₂. Despite this exciting possibility of an enantioselective transformation, we were unable to assay the product by HPLC. Fused norcaradienes are known to undergo reversible ring-

opening,¹⁰ concomitant with racemization; we are attributing the poor performance on the HPLC to rapid enantiomerization, resulting in a single peak on the HPLC trace. Therefore, although it may not be feasible to perform this Buchner reaction asymmetrically, it may be possible to perform a dynamic kinetic resolution (DKR) in subsequent manipulation of the NCDs (*vide infra*).

Along these lines, the poor regioselectivity in the case of **3.55d** can also be explained by this ring-opening pathway. Since the mesitylene-derived analogue **3.54i** failed to react (*vide supra*), it is reasonable to conclude that direct cyclopropanation of the fully-substituted site was unlikely to occur. Instead, initial formation of **3.55da** is kinetically favorable, followed by either a thermal or Lewis acid-promoted ring opening and closure event results in the regioisomeric scrambling (Scheme 3-24).

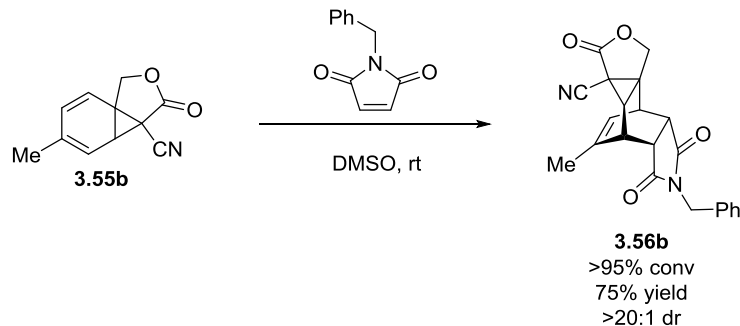
Scheme 3-24. Erosion of Regioselectivity via Zwitterionic Intermediates



3.3.15 Further Functionalization of Fused Norcaradienes

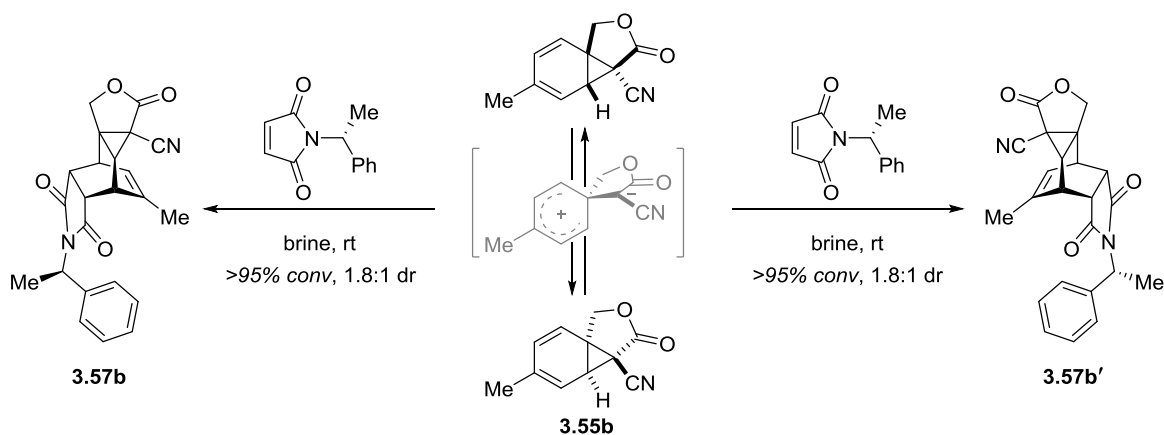
Having accessed a number of regioisomerically enriched norcaradienes, we turned our attention to functionalizing them to access complex carbocyclic products. As expected, Diels–Alder cycloaddition with *N*-benzylmaleimide smoothly provided the [2.2.2]-bicyclic product in high conversion to a single diastereomer of **3.56b**, with the maleimide approach *anti*- to the nitrile, although diminished yields were observed upon isolation (Scheme 3-25).

Scheme 3-25. Diels–Alder Cycloaddition of **3.55b** and *N*-Benzylmaleimide



To probe the possibility of a DKR of **3.55b** via an achiral zwitterionic intermediate, **3.55b** was treated with an *N*-chiral maleimide in brine at room temperature. Gratifyingly, the Diels–Alder product **3.57b/b'** was obtained in 1.8:1 dr (although the absolute configuration of the respective diastereomers was not definitively identified) at both partial and complete conversion, indicating that this result was not due to a simple kinetic resolution, but rather the desired racemization pathway was operative (Scheme 3-26). Further exploitation of this facile racemization is warranted.

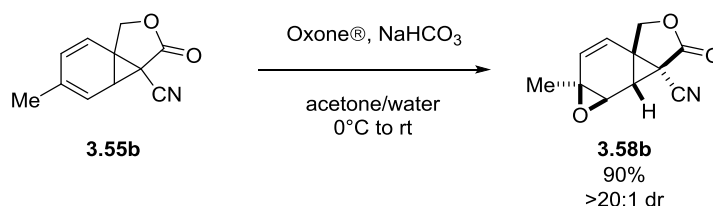
Scheme 3-26. Dynamic Kinetic Resolution of Fused Norcaradiene **3.55b**



Gratifyingly, we were also able to develop an efficient non-cycloaddition transformation of NCD **3.55b**. Treatment of **3.55b** with *in situ*-generated DMDO³⁶ provided a single diastereomer of the epoxide **3.58b** in excellent yield. Notably, the DMDO approached *anti*- to the nitrile,

signifying that the nitrile imposes a significant steric obstacle to the facial approach of electrophiles (Scheme 3-27). Efforts to extend this methodology to enantioselective epoxidations are ongoing.

Scheme 3-27. DMDO Epoxidation of Fused Norcaradiene 3.55b



3.4 Conclusions

We have performed initial investigations into methods to generate highly regioselective Buchner products. Silver(I) decomposition of electron deficient aryl diazoacetates provides the first example of a highly regioselective intermolecular Buchner reaction; however, this reaction is complicated by possible radical cation-initiated side reactions. Thermolysis of phenyl diazoacetates in *p*-xylene provided a single regioisomer of product and this intermediate was amenable to a number of complexity-building transformations.

A new method for the generation of cyanodiazooacetates has been developed, providing synthetically useful yields while requiring minimal purification. Intramolecular Buchner reactions can be efficiently performed using these benzyl cyanodiazooacetates under copper(II) catalysis and microwave irradiation to provide single regioisomers, favoring functionalization at the least sterically encumbered site. DMDO oxidation of the resultant norcaradiene provided a single diastereomer of product in high yield, signifying that these intermediates can be used to rapidly generate complex carbocycles without requiring cycloaddition transformations. Efforts to further expand the scope of downstream transformations and to generate the carbocyclic products asymmetrically through a DKR mechanism are currently underway.

3.5 Experimental Details

Methods

Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded on either a Bruker model DRX 400 or 600 spectrometer (^1H NMR at 400 or 600 MHz and ^{13}C NMR at 100 or 150 MHz) with solvent resonance as the internal standard (^1H NMR: CDCl_3 at 7.28 ppm and ^{13}C NMR: CDCl_3 at 77.0 ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, dq = doublet of quartets, t = triplet, and m = multiplet), coupling constant (Hz) and integration. Melting points (mp) were determined using a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. 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 either the positive or negative ion mode. Samples were prepared in HPLC grade methanol. All reported masses obtained in the positive ion mode correspond to the protonated molecular ion ($\text{M}+\text{H}$) unless otherwise noted, and all reported masses obtained in the negative ion mode correspond to the deprotonated molecular ion ($\text{M}-\text{H}$), unless otherwise noted. High performance liquid chromatography (HPLC) was performed on a Perkin Elmer Flexar® HPLC system equipped with a Chiracel IA column. Samples were eluted with HPLC grade hexanes with the indicated percentage of $i\text{PrOH}$ with an oven temperature of 40 °C. Microwave reactions were performed using a 300 W CEM Discover System with internal temperature monitoring via infrared sensing, in sealed 10 mL pressure vessels with a maximum ramp time of 2 min. Reactions performed “on water” were run in either conventional round-bottomed flasks or 1 or 5 dram vials with rapid agitation, either by vigorous manual shaking, or stirring (>900 rpm); we noticed no noticeable

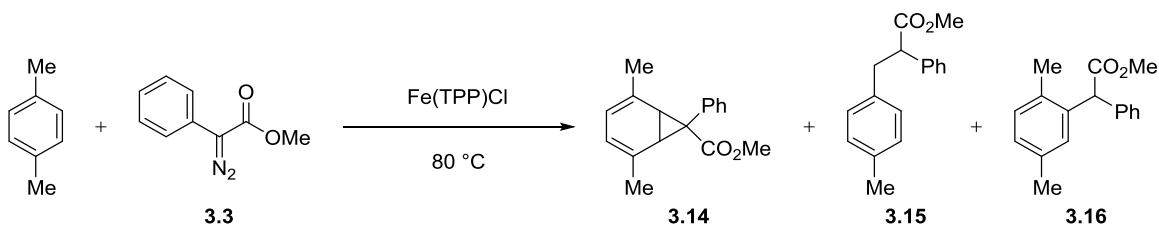
difference in the two methods. Thin layer chromatography (TLC) was performed on Sorbtech plastic-backed 0.20 mm silica gel 60 plates. Visualization was accomplished with UV light and either an aqueous ceric ammonium molybdate (CAM) or potassium permanganate (KMnO₄) solution, followed by heating. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 μ m) purchased from Silicycle. Unless otherwise specified, all crude materials were introduced to the chromatography column after dissolution in the specified eluent (plus a few drops dichloromethane, if required). Yields, regioisomeric ratios (rr's) and diastereomeric ratios (dr's) are reported herein for a specific experiment and as a result may differ slightly from those found in the tables, 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). Diazo compounds **3.3**, **3.37**, and **3.39** were prepared via slight modifications to known procedures.^{6,12} **Caution:** While we experienced no difficulties in handling the diazo compounds reported herein, care must be taken at all times when handling diazo compounds, as they are known to be explosive, especially upon heating during distillation. Simple acceptor diazo compounds, such as benzyl diazoacetate should be stored away from light, and cold to prevent decomposition. The following ligands were all prepared according to known procedures: salen,^{14,37} scorpionate **3.27/3.28**,³⁸ cyclohexyldiimine **3.29**,³⁹ 2,6-pyridyl diimine **3.30**,⁴⁰ pybox **3.31**,⁴¹ 2,5-furyl diimine **3.32**.⁴² The preparation of the carbene dimer **3.26** has been reported.⁴³ Diazo **3.51** was prepared via a modification of a known procedure.⁴⁴ Anhydrous Cu(hfacac)₂ was prepared from the commercial hydrate according to a known procedure, and was

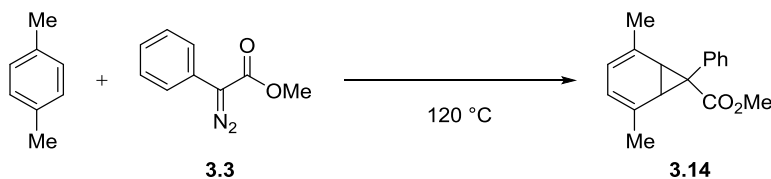
stored under anhydrous conditions.⁴⁵ All other reagents and solvents were purchased from commercial sources and used as received.

General Procedure A for the Fe(TPP)Cl Promoted Buchner Reaction of *p*-Xylene



To a flame-dried 1 dram vial in a nitrogen-filled glovebox was added Fe(TPP)Cl (2.8 mg, 0.004 mmol). The diazo compound **3.3** (35 mg, 0.2 mmol) was then transferred to the vial using *p*-xylene (2 mL, 16 mmol) via syringe. The vial was then placed in an oil bath preheated to 80 °C. After stirring at that temperature for 16 h, the reaction was removed from heat and allowed to cool to room temperature. The crude reaction mixture was flushed through a short pad of silica to remove the iron salts, and concentrated by rotary evaporation. The ratio between **3.14**, **3.15**, and **3.16** was then determined from the crude ¹H NMR. Isolation of **3.14** could be accomplished either through column chromatography using 20% EtOAc/hexanes as eluent, or by recrystallization from 10% EtOAc/hexanes.

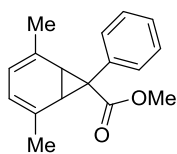
General Procedure B for the Thermolysis of **3.3** in *p*-Xylene



The *p*-xylene (270 mL, 2.18 mol) was added to a 500 mL round-bottomed flask with an attached addition funnel and heated to 120 °C under nitrogen atmosphere. Then the diazo compound **3.3** (19.2 g, 109 mmol) was diluted with 100 mL *p*-xylene and added dropwise over 3 h. The orange solution stirred at that temperature for 20 h. Upon completion of the reaction, the

solution had turned yellow, and the reaction was cooled to room temperature and concentrated.

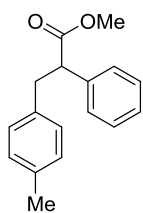
Note: the excess *p*-xylene could be easily recovered by distillation. The crude residue was triturated with 10% EtOAc/hexanes, and the resultant white solid was collected by filtration and dried in vacuo, providing a white solid (9.21 g, 33%).



Methyl 2,5-dimethyl-7-phenylbicyclo[4.1.0]hepta-2,4-diene-7-carboxylate

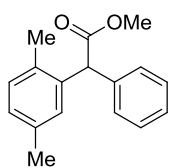
(3.14): The product was prepared according to either General Procedure A or B, yielding a white solid. Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.21 (m,

3H), 6.98 (m, 2H), 5.49 (s, 2H), 3.67 (s, 3H), 2.96 (s, 2H), 2.10 (s, 6H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 177.5, 132.9, 131.8, 130.4, 127.3, 126.9, 122.0, 52.9, 41.2, 26.0, 23.7.



Methyl 2-phenyl-3-(p-tolyl)propanoate (3.15): The product was prepared according to either General Procedure A or B, yielding a clear oil. Analytical data:

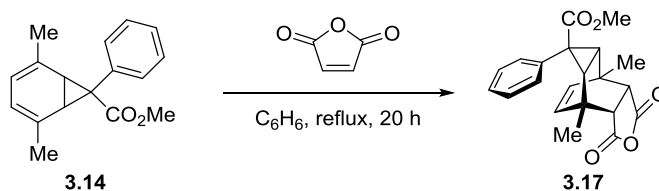
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35–6.95 (m, 5H), 3.85 (dd, J = 8.8, 6.8 Hz, 1H), 3.62 (s, 3H), 3.40 (dd, J = 13.8, 8.8 Hz, 1H), 3.00 (dd, J = 13.8, 6.8 Hz, 1H), 2.13 (s, 3H).

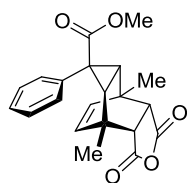


Methyl 2-(2,5-dimethylphenyl)-2-phenylacetate (3.16): The product was prepared according to either General Procedure A or B, yielding a clear oil.

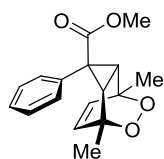
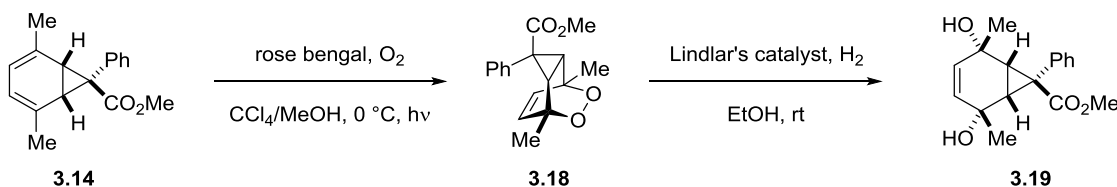
Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40–4.22 (m, 6H), 7.10–6.99 (m, 2H), 5.22 (s, 1H), 3.78 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H).

Transformations of *meso*-Norcaradiene 3.14



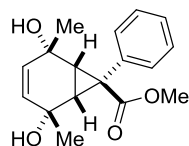


Methyl (3aR,4S,4aS,5aR,6R)-4,6-dimethyl-1,3-dioxo-5-phenyl-3,3a,4,4a,5,5a,6,6a-octahydro-1H-4,6-ethenocyclopropa[f]isobenzofuran-5-carboxylate (3.17): Norcaradiene **3.14** (10 mg, 0.04 mmol) and maleic anhydride (7.7 mg, 0.08 mmol) were combined in a 1 dram vial, dissolved in 0.5 mL C₆H₆ and heated to reflux for 20 h, at which point the reaction was cooled to room temperature and concentrated. The residue was subjected to column chromatography using 10% EtOAc/hexanes as eluent, yielding an off white solid (12 mg, 88%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.26 (m, 2H), 7.21 (m, 1H), 7.01 (m, 2H), 5.01 (s, 2H), 3.57 (s, 3H), 3.15 (s, 2H), 2.05 (s, 2H), 1.83 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 173.5, 169.9, 135.7, 133.6, 130.8, 128.4, 126.9, 53.0, 52.5, 39.7, 38.6, 37.0, 22.2.



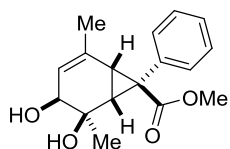
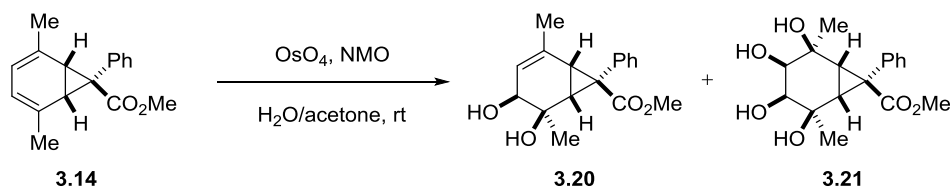
Methyl -1,5-dimethyl-3-phenyl-6,7-dioxatricyclo[3.2.2.0^{2,4}]non-8-ene-3-carboxylate (3.18): The norcaradiene **3.14** (896 mg, 3.52 mmol) and rose bengal (36 mg, 0.035mmol) were added to a 10 mL round bottomed flask and dissolved in 40 mL CCl₄/2 mL MeOH, and cooled to 0 °C. A steady stream of O₂ was then bubbled through the solution, and the pink mixture was irradiated with a medium pressure Hg lamp for 20 h. After completion, the lamp was turned off and the reaction was concentrated by rotary evaporation. The crude material was purified by column chromatography using 10%→20% EtOAc/hexanes as eluent, yielding a pinkish white solid of good purity (850 mg, 84%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.30–7.25 (m, 2H), 7.25–7.21 (m, 1H), 6.93 (m, 2H), 5.35 (s, 2H), 3.61(s,

3H), 2.43 (s, 2H), 1.65 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 173.3, 135.2, 132.1, 131.0, 128.4, 127.0, 77.1, 53.0, 35.7, 29.4, 22.1.



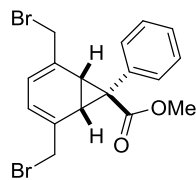
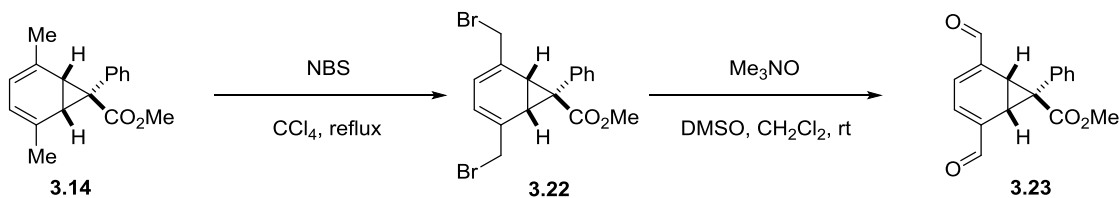
Methyl -2,5-dihydroxy-2,5-dimethyl-7-phenylbicyclo[4.1.0]hept-3-ene-7-carboxylate (3.19): The endoperoxide **3.18** (10 mg, 0.035 mmol) and Lindlar's catalyst (1 mg) were combined in a 1 dram vial that was purged with N_2 . Then the

vial was charged with 1 mL EtOAc and was purged with H_2 . The reaction stirred under H_2 for 40 min. After completion, the reaction was first purged with N_2 , then filtered through a short pad of Celite and concentrated, yielding a white solid of good purity (9 mg, 90%). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.19 (m, 3H), 7.12 (m, 2H), 5.31 (s, 2H), 3.56 (s, 3H), 2.39 (s, 2H), 1.61 (s, 3H). LRMS (ESI^+) Calcd. for $\text{C}_{17}\text{H}_{20}\text{NaO}_4$: 311.13, Found: 311.2.



Methyl -4,5-dihydroxy-2,5-dimethyl-7-phenylbicyclo[4.1.0]hept-2-ene-7-carboxylate (3.20): The norcaradiene **3.14** (10 mg, 0.04 mmol) and *N*-morpholine oxide (4.6 mg, 0.04 mmol) were combined in a 1 dram vial with 1 mL acetone/0.1 mL

water. Then a 3% w/w aqueous solution of OsO_4 (2.5 μL , 0.4 μmol) was added and the yellow solution stirred at room temperature for 16 h. The organics were then extracted with EtOAc (3×1 mL), and the combined organic layer was dried over Na_2SO_4 , filtered, and concentrated, yielding **3.20** (40%, ^1H NMR yield). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.47–7.21 (m, 4H), 7.04 (m, 1H), 5.11 (s, 1H), 3.63 (s, 3H), 2.88 (s, 1H), 2.58 (d, $J = 8.8$ Hz, 1H), 2.42 (s, 1H), 2.37–2.25 (m, 2H), 2.11 (br s, 3H), 1.55 (s, 3H).



Methyl -2,5-bis(bromomethyl)-7-phenylbicyclo[4.1.0]hepta-2,4-diene-7-

carboxylate (3.22): To a 50 mL round-bottomed flask was added **3.14** (254 mg,

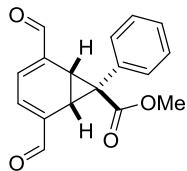
1 mmol) and *N*-bromosuccinimide (358 mg, 2.01 mmol). A reflux condenser was

then attached, and the mixture was then dissolved in 20 mL CCl_4 , purged with N_2 , and heated to

reflux for 16 h. The reaction was then cooled to room temperature and concentrated. The residue

was then purified by column chromatography using 10% EtOAc/hexanes as eluent, yielding a

white solid (259 mg, 63%). Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.21 (m, 3H), 7.16 (m, 2H), 5.87 (s, 2H), 4.36 (d, $J = 10.4$ Hz, 2H), 4.29 (d, $J = 10.4$ Hz, 2H), 3.71 (s, 3H), 3.36 (s, 2H).



Methyl -2,5-diformyl-7-phenylbicyclo[4.1.0]hepta-2,4-diene-7-carboxylate

(3.23): The bis-bromide **3.22** (250 mg, 0.61 mmol) was added to 25 mL round-

bottomed flask and diluted with 3 mL DMSO and 3 mL CH_2Cl_2 and cooled to 0

$^\circ\text{C}$. Then the trimethylamine *N*-oxide (810 mg, 7.3 mmol) was added, and the ice bath was

removed. The reaction was allowed to stir at room temperature for 2 h. Then the reaction was

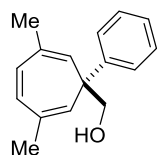
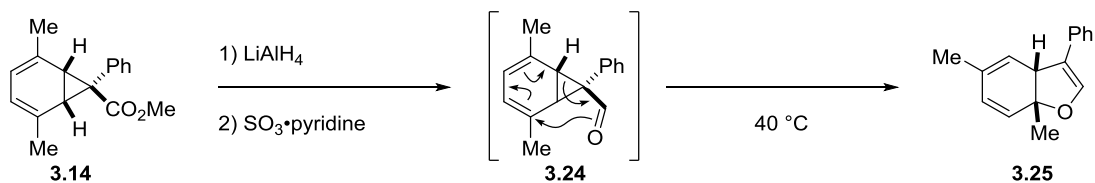
quenched with water (3 mL) and the organics were extracted with CH_2Cl_2 (2×3 mL). The

combined organic layer was washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4 ,

filtered, and concentrated. The crude material (70% by $^1\text{H NMR}$) was purified by column

chromatography using 20% \rightarrow 50% EtOAc/hexanes as eluent, yielding a yellow solid (18 mg,

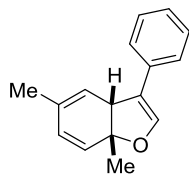
11%). Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.81 (s, 2H), 7.16 (m, 3H), 6.79 (s, 2H), 6.75 (m, 2H), 3.71 (s, 3H), 3.65 (s, 2H).



(3,6-Dimethyl-1-phenylcyclohepta-2,4,6-trien-1-yl)methanol (3.58): To a flame-

dried 25 mL round-bottomed flask under nitrogen atmosphere was added **3.14** (254 mg, 1 mmol) with 4 mL anhydrous THF. After cooling to 0 °C, the LiAlH₄ (2 M in

THF, 1 mL, 2 mmol) was added slowly, and the reaction stirred at that temperature for 30 min. The reaction was then quenched with careful, sequential addition of 0.1 mL water, 0.1 mL 10% KOH, and 0.3 mL water. The ice bath was then removed and the reaction stirred at room temperature for 30 min. The mixture was then diluted with Et₂O, and copious MgSO₄ was added, and the slurry was filtered through Celite and concentrated, yielding the cycloheptatrienyl methanol in excellent purity. Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.07 (m, 5H), 5.79 (s, 2H), 4.18 (s, 2H), 4.00 (br s, 2H), 2.02 (s, 6H).



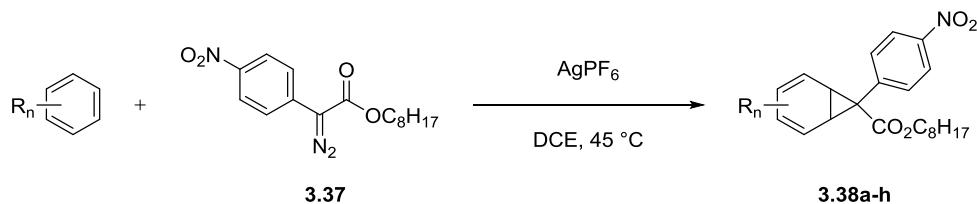
5,7a-Dimethyl-3-phenyl-3a,7a-dihydrobenzofuran (3.25): The clear oily

residue was then taken up in 10 mL CH₂Cl₂/DMSO (4:1), and treated with Et₃N (0.7 mL, 5 mmol). Meanwhile, a 2 mL DMSO solution of the SO₃•pyridine (480

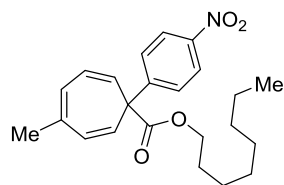
mg, 3 mmol) was prepared, and allowed to stir for 15 min prior to careful addition to the reaction mixture. After stirring at room temperature for 16 h, the reaction was quenched with water (10 mL) and diluted with CH₂Cl₂ (10 mL). The organics were separated, and washed with water (3 × 10 mL) and brine (10 mL), dried over Na₂SO₄, filtered, and concentrated, providing a mixture of **3.24** and **3.25**. The isomerization was completed upon gentle heating (40 °C) for 6 h. Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.00 (m, 5H), 6.86 (d, *J* = 2.4 Hz, 1H), 5.93 (d, *J* = 9.8

Hz, 1H), 5.79 (d, $J = 9.8$ Hz, 1H), 5.68 (br s, 1H), 3.82 (br s, 1H), 1.76 (dd, $J = 2.0, 2.0$ Hz, 3H), 1.50 (s, 3H).

General Procedure C for the Silver(I) Catalyzed Intermolecular Buchner Reaction



To a flame-dried 1 dram vial in a nitrogen filled glovebox was added either AgSbF_6 or AgPF_6 (0.05 equiv), then 0.5 mL anhydrous DCE and the arene (20 equiv) were added via syringe, and the vial was placed in an oil bath preheated to 45 °C, while excluded from light. A 1 mL solution of the diazo compounds (1 equiv) in anhydrous DCE was then added via syringe pump over 20 h. After complete addition, the reaction was allowed to stir for an additional hour before cooling to room temperature and concentration by rotary evaporation. The regioisomeric ratio was then determined from the crude ^1H NMR. The dearomatized products were then isolated after silica gel chromatography.



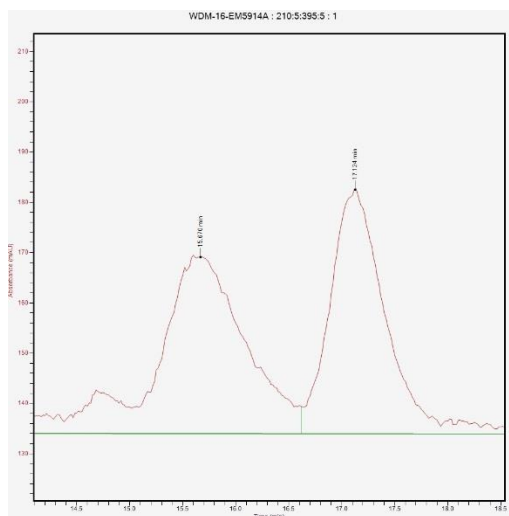
Octyl 4-methyl-1-(4-nitrophenyl)cyclohepta-2,4,6-triene-1-

carboxylate (3.38a): The product was prepared according to either

General Procedure C using toluene (0.21 mL, 2 mmol), octyl 4-nitrophenyl diazoacetate **3.37** (32 mg, 0.1 mmol), AgSbF_6 (1.7 mg, 0.005 mmol), and was purified using 5% EtOAc/hexanes yielding a yellow oil (21 mg, 56%). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, $J = 8.8$ Hz, 2H), 7.31 (d, $J = 8.8$ Hz, 2H), 6.23 (m, 1H), 6.02 (m, 1H), 5.77 (d, $J = 8.0$ Hz, 1H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.95 (m, 2H), 2.38 (s, 3H), 1.55–1.10 (m, 12H), 0.90 (t, $J = 7.2$ Hz, 3H).

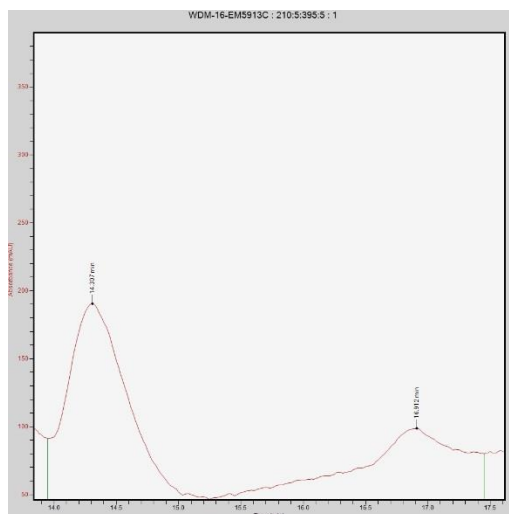
3.38a (racemic, using AgSbF₆):

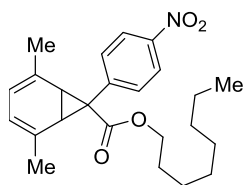
peak #	RT (min)	area (mAU × s)	height (mAU)	area(%)
1	15.634	2142781.65	35192.04	54.1
2	17.103	1820328.46	48431.79	45.9



3.38a (chiral, using AgSTRIP):

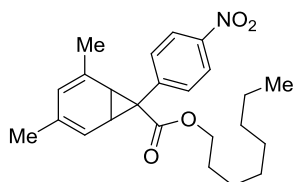
peak #	RT (min)	area (mAU × s)	height (mAU)	area(%)
1	14.321	4684159.27	180167.29	88.0
2	16.871	642460.12	78388.29	12.0





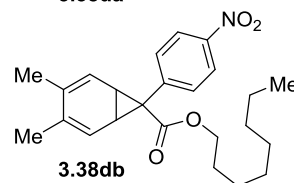
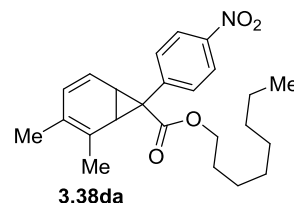
Octyl 2,5-dimethyl-7-(4-nitrophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (3.38b):

The product was prepared according to either General Procedure C using *p*-xylene (2.5 mL, 20 mmol), octyl 4-nitrophenyl diazoacetate **3.37** (319 mg, 1 mmol), AgSbF₆ (17 mg, 0.05 mmol), and was purified using 5% EtOAc/hexanes yielding a yellow oil (114 mg, 29%). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 8.05 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 5.48 (s, 2H), 4.06 (t, *J* = 6.6 Hz, 2H), 3.00 (s, 2H), 2.10 (s, 6H), 1.46 (m, 2H), 1.31–1.11 (m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 175.3, 146.6, 140.8, 132.6, 130.1, 122.5, 122.2, 65.9, 41.0, 31.6, 29.0, 28.9, 28.3, 25.6, 23.6, 22.5, 14.0.



Octyl 2,4-dimethyl-7-(4-nitrophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (3.38c):

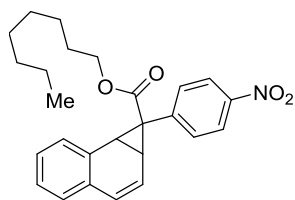
The product was prepared according to either General Procedure C using *m*-xylene (2.5 mL, 20 mmol), octyl 4-nitrophenyl diazoacetate **3.37** (319 mg, 1 mmol), AgSbF₆ (17 mg, 0.05 mmol), and was purified using 5% EtOAc/hexanes yielding a yellow oil (235 mg, 59%). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 5.80 (d, *J* = 6.4 Hz, 1H), 5.44 (dd, *J* = 6.4, 5.6 Hz, 1H), 4.07 (t, *J* = 6.4 Hz, 2H), 3.24 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.09 (d, *J* = 8.4 Hz, 1H), 2.11 (s, 3H), 1.52 (s, 3H), 1.51 (m, 2H), 1.40–1.15 (m, 10H), 0.91 (t, *J* = 7.2 Hz, 3H).



Octyl 2,3-dimethyl-7-(4-nitrophenyl)bicyclo[4.1.0]hepta-2,4-diene-7-carboxylate (3.38d):

The product was prepared according to either General Procedure C using *o*-xylene (2.5 mL, 20 mmol), octyl 4-nitrophenyl diazoacetate **3.37** (319 mg, 1 mmol), AgSbF₆ (17 mg, 0.05 mmol), and was purified using 5% EtOAc/hexanes yielding a yellow oil (232 mg, 58%, 59:41 rr). Analytical data: ¹H NMR (600 MHz, CDCl₃) δ

(**3.38da**, 59%) 8.04 (d, $J = 9.0$ Hz, 2H), 7.16 (d, $J = 9.0$ Hz, 2H), 6.01 (dd, $J = 9.3, 5.4$ Hz, 1H), 5.60 (d, $J = 9.3$ Hz, 1H), 4.04 (m, 2H), 3.25 (dd, $J = 9.0, 5.4$ Hz, 1H), 3.13 (d, $J = 8.0$ Hz, 1H), 2.08 (s, 3H), 1.52 (s, 3H), 1.51–1.1 (m, 12H), 0.88 (t, $J = 7.2$ Hz, 3H); (**3.38db**, 41%) 8.18 (d, $J = 9.0$ Hz, 2H), 7.25 (d, $J = 9.0$ Hz, 2H), 5.92 (t, $J = 3.0$ Hz, 2H), 4.16 (t, $J = 6.9$ Hz, 2H), 3.22 (dd, $J = 3.6, 2.4$ Hz, 2H), 2.25 (s, 6H); 1.63 (m, 2H), 1.32–1.11 (m, 10H), 0.88 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ (combined **3.38a** and **3.38b**) 175.1, 174.9, 135.3, 134.2, 133.4, 130.8, 130.0, 129.50, 129.48, 126.6, 125.6, 123.5, 122.1, 121.8, 121.23, 121.20, 65.8, 65.7, 65.6, 56.4, 31.63, 31.58, 29.1, 29.03, 29.00, 28.9, 28.4, 28.30, 28.27, 25.7, 25.6, 22.54, 22.52, 20.2, 19.8, 19.31, 19.25, 18.1, 14.00, 13.99.



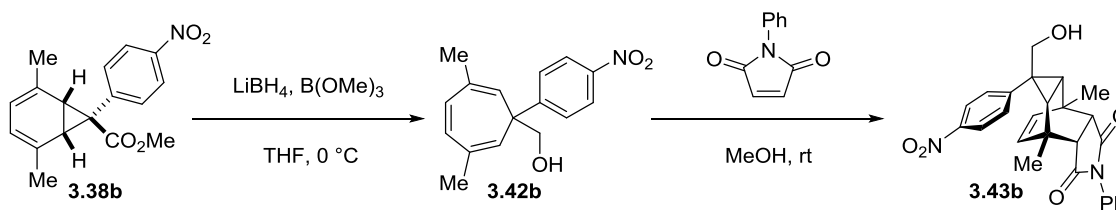
Octyl

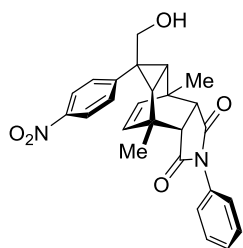
1-(4-nitrophenyl)-1a,7b-dihydro-1H-

cyclopropa[a]naphthalene-1-carboxylate (3.38e**):** The product was prepared according to either General Procedure C using naphthalene (128

mg, 1 mmol), octyl 4-nitrophenyl diazoacetate **3.37** (32 mg, 0.1 mmol), AgSbF_6 (1.7 mg, 0.005 mmol), and was purified using 5% EtOAc/hexanes yielding a yellow oil (33 mg, 78%). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.86 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 7.6$ Hz, 1H), 7.32 (m, 1H), 7.15 (m, 1H), 6.97 (br d, 8.4 Hz, 2H), 6.82 (d, $J = 7.6$ Hz, 1H), 6.20 (m, 2H), 4.09 (m, 2H), 3.69 (d, $J = 8.8$ Hz, 1H), 3.23 (ddd, $J = 8.8, 2.8, 2.8$ Hz, 1H), 1.50 (m, 2H), 1.35–1.11 (m, 10H), 0.89 (t, $J = 7.2$ Hz, 3H).

Subsequent Transformations of **3.38b**





5-(Hydroxymethyl)-4,6-dimethyl-5-(4-nitrophenyl)-2-phenyl-

4,4a,5,5a,6,6a-hexahydro-4,6-ethenocyclopropa[f]isoindole-

1,3(2H,3aH)-dione (3.43): The Buchner intermediate **3.38b** (38 mg, 0.12

mmol) was placed in a flame-dried 25 mL round-bottomed flask under

nitrogen atmosphere and dissolved in 10 mL anhydrous THF and cooled to 0 °C. Then the

trimethyl borate (1.3 μ L, 0.012 mmol) was added, followed by slow addition of LiBH₄ (1 M in

THF, 0.3 mL, 0.3 mmol). After complete addition, the reaction stirred at that temperature for 30

min. The reaction was quenched by dropwise addition of 0.03 mL water, 0.03 10% KOH, and 0.1

mL water. Then the reaction was warmed to room temperature and stirred for 30 min. MgSO₄ was

then added, and the reaction was filtered over Celite and concentrated, yielding the intermediate

3.42b. The residue was then treated with *N*-phenylmaleimide (22.8 mg, 0.13 mmol) and dissolved

in 10 mL MeOH, and the reaction stirred at room temperature for 16 h. Upon completion, the

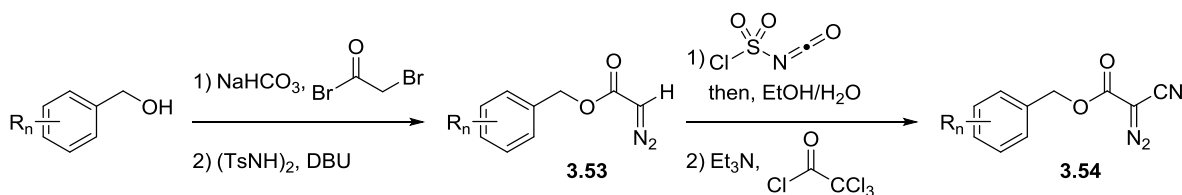
reaction was concentrated by rotary evaporation, and the resultant material was purified by column

chromatography (50% \rightarrow 100% EtOAc/hexanes), yielding a white solid. Analytical data: ¹H NMR

(400 MHz, CDCl₃) δ 8.07 (m, 2H), 7.36–7.25 (m, 3H), 7.21 (m, 2H), 6.98 (m, 2H), 5.01 (s, 2H),

3.34 (s, 2H), 2.93 (s, 2H), 1.78 (s, 6H), 1.50 (s, 2H).

General Procedure D for the Synthesis of Benzyl Cyanodiazooacetates



A 100 mL round-bottomed flask was charged with NaHCO₃ (3 equiv) and the benzyl alcohol (20 mmol, 1 equiv). The reagents were suspended in 15 mL MeCN and cooled to 0 °C.

Then the bromoacetyl bromide (1.5 equiv) was added slowly, and the reaction stirred at that temperature for 45 min. The reaction was then carefully quenched with water. After the gas evolution subsided, the organics were extracted with CH_2Cl_2 (2×10 mL), washed with NaHCO_3 (2×10 mL), and brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated, yielding a clear, colorless oil of the α -bromoester.

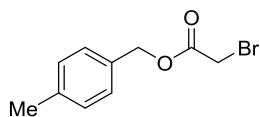
The bis-tosylhydrazine (1.5 equiv) was then added to the 250 mL round-bottomed flask containing the bromoester, and the reaction vessel was purged with nitrogen while cooling to 0°C , then 40 mL degassed THF was added. Then the DBU (4 equiv) was added slowly over 5 min, and the reaction stirred at that temperature for 40 min. Then the reaction was quenched with aqueous NaHCO_3 (50 mL), and the reaction was allowed to stir at room temperature for 30 min. **Note:** allowing the reaction to stir with NaHCO_3 was important to isolate the diazo compound cleanly without a column. After stirring for 30 min, the solid was removed by filtration through Celite, and the filtrate was transferred to a separatory funnel containing $\text{H}_2\text{O}/\text{Et}_2\text{O}$ (100 mL ea). The organics were collected, and the aqueous layer was further extracted with Et_2O (100 mL). The combined organic layer was washed with NaHCO_3 (100 mL), and brine (100 mL), dried over MgSO_4 , filtered, and concentrated by rotary evaporation. After ensuring all of the THF had been removed, the residue was then triturated with Et_2O , and filtered through a short pad of 3:1 Celite/silica and concentrated, yielding the diazo compound **3.53** in good purity.

The diazo compound **3.53** was then added to a flame-dried 100 mL round-bottomed flask under nitrogen atmosphere with 20 mL anhydrous Et_2O and cooled to -78°C . The isocyanate (1 equiv) was then added slowly over 30 min as a 10 mL solution in Et_2O . After complete addition, the reaction was maintained at -78°C for 3 h. Then the reaction was warmed to room temperature and concentrated by rotary evaporation. The residue was then taken up in EtOH (50 mL), and

water (15 mL) was then added forcefully to the solution, and the reaction was allowed to stand at room temperature overnight. **Note:** if upon standing, there is only a white solid, then the amide intermediate did not crystallize. If there is a yellow-colored solid, then that is the diazo compound. If the diazo compound solidified, then it can be isolated by filtration and washed with cold EtOH; otherwise, the ethanolic solution can be diluted with copious amounts of water (100 mL) and extracted with Et₂O (2 × 50 mL), dried over MgSO₄, filtered, and concentrated, yielding the diazo amide.

The amide was then transferred to a flame-dried 250 mL round-bottomed flask under nitrogen atmosphere with 40 mL anhydrous CH₂Cl₂ and cooled to 0 °C, followed by anhydrous Et₃N (3 equiv). Then the trichloroacetyl chloride (3.3 equiv) was added slowly. After stirring for 5 min, the reaction was carefully quenched with aqueous NaHCO₃ (50 mL). After gas evolution subsided, the reaction was transferred to a separatory funnel and the organics were collected. The aqueous layer was further extracted with CH₂Cl₂ (50 mL). The combined organic layer was then washed with NaHCO₃ (50 mL), water (50 mL), and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The orange residue was purified by column chromatography, yielding the desired product.

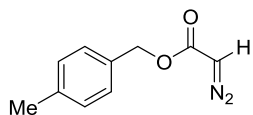
Note: This reaction sequence was performed without discrete isolation and characterization of the intermediates. Included below are representative ¹H NMR spectra of the intermediates towards **3.54b**, and the final cyanodiazooacetates **3.54a-i**.



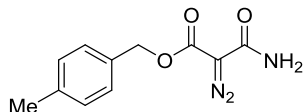
4-Methylbenzyl 2-bromoacetate (3.59b): The title compound was prepared according to General Procedure D using 4-methylbenzyl alcohol

(6.11 g, 50 mmol), sodium bicarbonate (12.6 g, 150 mmol), bromoacetyl bromide (6.5 mL, 75

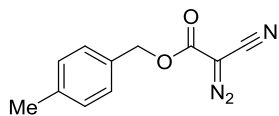
mmol), yielding a clear, colorless oil. Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.29 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 5.18 (s, 2H), 3.88 (s, 2H), 2.38 (s, 3H).



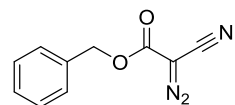
4-Methylbenzyl 2-diazoacetate (3.53b): The title compound was prepared according to General Procedure D using **3.59b** (11.5 g, 50 mmol) bis-tosylhydrazine (25.5 g, 75 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (30 mL, 200 mmol), yielding a bright red oil. Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.31 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 5.20 (s, 2H), 4.83 (br s, 1H), 2.40 (s, 3H).



4-Methylbenzyl 3-amino-2-diazo-3-oxopropanoate (3.60b): The title compound was prepared according to General Procedure D using **3.53b** (8.26 g, 43.4 mmol) chlorosulfonyl isocyanate (3.8 mL, 43.4 mmol), yielding a pale yellow solid. Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.78 (br s, 1H), 7.28 (s, 2H), 7.22 (s, 2H), 5.87 (br s, 1H), 5.25 (s, 2H), 2.39 (s, 3H).

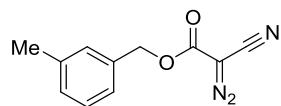


4-Methylbenzyl 2-cyano-2-diazoacetate (3.54b): The title compound was prepared according to General Procedure D using **3.60b** (3.20 g, 13.7 mmol) triethylamine (5.8 mL, 41.2 mmol) and trichloroacetyl chloride (5.1 mL, 45.3 mmol), yielding a yellow solid (1.96 g, 34%, 5 steps). Analytical data: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.30 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 5.28 (s, 2H), 2.39 (s, 3H).

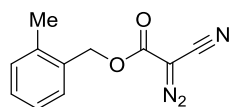


Benzyl 2-cyano-2-diazoacetate (3.54a): The title compound was prepared according to General Procedure D using benzyl alcohol (2.1 mL, 20 mmol), sodium bicarbonate (5.04 g, 60 mmol), bromoacetyl bromide (2.6 mL, 30 mmol), bis-tosylhydrazine (10.2 g, 30 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (12 mL, 80 mmol), chlorosulfonyl isocyanate (1.7 mL, 20 mmol), triethylamine (8.4 mL, 60 mmol) and trichloroacetyl

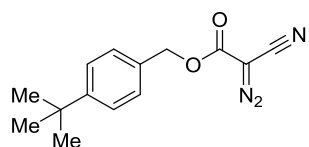
chloride (7.4 mL, 66 mmol), yielding a red oil (1.19 g, 30%, 5 steps). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.40 (s, 5H), 5.33 (s, 2H).



3-Methylbenzyl 2-cyano-2-diazoacetate (3.54c): The title compound was prepared according to General Procedure D using 3-methylbenzyl alcohol (1.2 mL, 10 mmol), sodium bicarbonate (2.52 g, 30 mmol), bromoacetyl bromide (1.3 mL, 15 mmol), bis-tosylhydrazine (5.1 g, 15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (6 mL, 40 mmol), chlorosulfonyl isocyanate (0.87 mL, 10 mmol), triethylamine (4.2 mL, 30 mmol) and trichloroacetyl chloride (3.7 mL, 33 mmol), yielding a yellow oil (653 mg, 30%, 5 steps). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.30 (m, 1H), 7.20 (m, 3H), 5.29 (s, 2H), 2.39 (s, 3H).

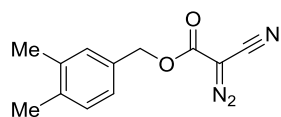


2-Methylbenzyl 2-cyano-2-diazoacetate (3.54d): The title compound was prepared according to General Procedure D using 2-methylbenzyl alcohol (1.22 g, 10 mmol), sodium bicarbonate (2.52 g, 30 mmol), bromoacetyl bromide (1.3 mL, 15 mmol), bis-tosylhydrazine (5.1 g, 15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (6 mL, 40 mmol), chlorosulfonyl isocyanate (0.87 mL, 10 mmol), triethylamine (4.2 mL, 30 mmol) and trichloroacetyl chloride (3.7 mL, 33 mmol), yielding a yellow solid (223 mg, 10%, 5 steps). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 7.32 (m, 2H), 7.24 (m, 2H), 5.36 (s, 2H), 2.40 (s, 3H).

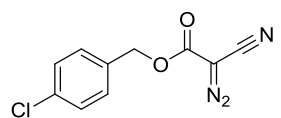


4-(tert-Butyl)benzyl 2-cyano-2-diazoacetate (3.54e): The title compound was prepared according to General Procedure D using 4-tert-butylbenzyl alcohol (1.77 mL, 10 mmol), sodium bicarbonate (2.52 g, 30 mmol), bromoacetyl bromide (1.3 mL, 15 mmol), bis-tosylhydrazine (5.1 g, 15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (6 mL, 40 mmol), chlorosulfonyl isocyanate (0.87 mL, 10 mmol), triethylamine (4.2 mL, 30

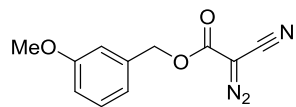
mmol) and trichloroacetyl chloride (3.7 mL, 33 mmol), yielding a yellow oil (333 mg, 13%, 5 steps). Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 5.29 (s, 2H), 1.35 (s, 9H).



3,4-Dimethylbenzyl 2-cyano-2-diazoacetate (3.54f): The title compound was prepared according to General Procedure D using 3,4-dimethylbenzyl alcohol (2.72 g, 20 mmol), sodium bicarbonate (5.04 g, 60 mmol), bromoacetyl bromide (2.6 mL, 30 mmol), bis-tosylhydrazine (10.2 g, 30 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (12 mL, 80 mmol), chlorosulfonyl isocyanate (1.7 mL, 20 mmol), triethylamine (8.4 mL, 60 mmol) and trichloroacetyl chloride (7.4 mL, 66 mmol), yielding a red oil (1.56 g, 34%, 5 steps). Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.15 (m, 3H), 5.26 (s, 2H), 2.30 (s, 6H).

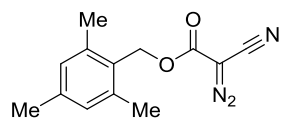


4-Chlorobenzyl 2-cyano-2-diazoacetate (3.54g): The title compound was prepared according to General Procedure D using 4-chlorobenzyl alcohol (1.43 g, 10 mmol), sodium bicarbonate (2.52 g, 30 mmol), bromoacetyl bromide (1.3 mL, 15 mmol), bis-tosylhydrazine (5.1 g, 15 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (6 mL, 40 mmol), chlorosulfonyl isocyanate (0.87 mL, 10 mmol), triethylamine (4.2 mL, 30 mmol) and trichloroacetyl chloride (3.7 mL, 33 mmol), yielding a yellow oil (177 mg, 8%, 5 steps). Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.39 (m, 2H), 7.34 (m, 2H), 5.28 (s, 2H).



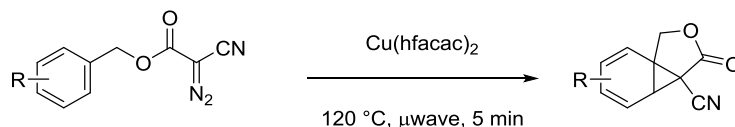
3-Methoxybenzyl 2-cyano-2-diazoacetate (3.54h): The title compound was prepared according to General Procedure D using 3-methoxybenzyl alcohol (3.21 g, 23.2 mmol), sodium bicarbonate (5.86 g, 70 mmol), bromoacetyl bromide (3.0 mL, 35 mmol), bis-tosylhydrazine (11.9 g, 35 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (14 mL, 93 mmol), chlorosulfonyl isocyanate (2.0 mL, 23.2 mmol), triethylamine (9.7 mL, 70 mmol) and

trichloroacetyl chloride (8.6 mL, 77 mmol), yielding a yellow oil (2.36 g, 44%, 5 steps). Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.30 (m, 1H), 7.00–6.85 (m, 3H), 5.29 (s, 2H), 3.84 (s, 3H).

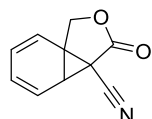


2,4,6-Trimethylbenzyl 2-cyano-2-diazoacetate (3.54i): The title compound was prepared according to General Procedure D using 2,4,6-trimethylbenzyl alcohol (3.00 g, 20 mmol), sodium bicarbonate (5.04 g, 60 mmol), bromoacetyl bromide (2.6 mL, 30 mmol), bis-tosylhydrazine (10.2 g, 30 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (12 mL, 80 mmol), chlorosulfonyl isocyanate (1.7 mL, 20 mmol), triethylamine (8.4 mL, 60 mmol) and trichloroacetyl chloride (7.4 mL, 66 mmol), yielding a red oil (1.12 g, 23%, 5 steps). Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 6.91 (s, 2H), 5.42 (s, 2H), 2.39 (s, 6H), 2.31 (s, 3H).

General Procedure E for the Intramolecular Buchner Reaction of Cyano Diazoacetates



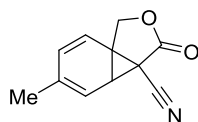
To a flame-dried 10 mL microwave reaction vessel in a nitrogen-filled glovebox was added anhydrous Cu(hfacac)₂ (0.2 equiv). The diazo compound (1 equiv) was then transferred with anhydrous DCE (0.1 M) via syringe. The reaction was then heated to 120 °C under microwave irradiation (2 min ramp, 5 min hold). After completion, the brown solution was cooled to room temperature, stirred with silica gel, and filtered over Celite and concentrated. The solid brown residue was then purified by either trituration with Et₂O or column chromatography, yielding the desired product in good purity.



3-Oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-carbonitrile (3.55a):

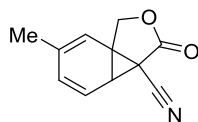
The title compound was prepared according to General Procedure E using benzyl 2-

cyano-2-diazoacetate **3.54a** (81 mg, 0.4 mmol) and Cu(hfacac)₂ (38 mg, 0.08 mmol), and was purified using 10% EtOAc/hexanes as eluent, yielding a clear oil (27 mg, 39%). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 6.67 (br s, 2H), 6.50 (br s, 1H), 6.38 (br s, 1H), 4.99 (br s, 1H), 4.72 (br s, 1H), 4.14 (br s, 1H).



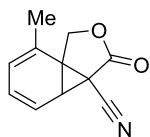
5-Methyl-3-oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-carbonitrile (3.55b): The title compound was prepared according to General

Procedure E using 4-methylbenzyl 2-cyano-2-diazoacetate **3.54b** (430 mg, 2 mmol) and Cu(hfacac)₂ (191 mg, 0.4 mmol), and was purified by trituration with Et₂O, yielding an off-white solid (118 mg, 32%). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 6.43 (d, *J* = 9.2 Hz, 1H), 6.20 (d, *J* = 9.2 Hz, 1H), 6.10 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 10.4 Hz, 1H), 4.49 (d, *J* = 10.4 Hz, 1H), 3.53 (d, *J* = 6.0 Hz, 1H), 2.08 (s, 3H).

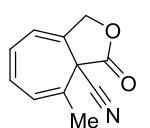


6-Methyl-3-oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-carbonitrile (3.55c): The title compound was prepared according to General

Procedure E using 3-methylbenzyl 2-cyano-2-diazoacetate **3.54c** (22 mg, 0.1 mmol) and Cu(hfacac)₂ (9.6 mg, 0.02 mmol), and was purified using 20% → 40% EtOAc/hexanes as eluent, yielding a white solid (3 mg, 16%). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 6.50 (br s, 1H), 6.37 (br s, 1H), 6.13 (d, *J* = 6.8 Hz, 1H), 4.77 (d, *J* = 9.0 Hz, 1H), 4.50 (d, *J* = 9.0 Hz, 1H), 3.30 (br s, 1H), 2.16 (s, 3H).

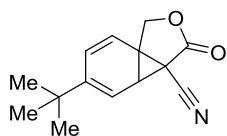


7-Methyl-3-oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-carbonitrile (3.55d): The title compound was prepared according to General



Procedure E using 2-methylbenzyl 2-cyano-2-diazoacetate **3.54d** (mg, mmol) and Cu(hfacac)₂ (mg, mmol), and was purified using 20% → 40% EtOAc/hexanes as eluent, yielding a brown oil (12 mg, 32%). Analytical data: ¹H NMR (600 MHz, CDCl₃, **3.55da**,

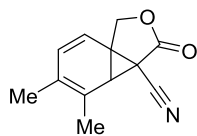
77%) δ 6.63 (dd, $J = 9.0, 7.5$ Hz, 1H), 6.54 (d, $J = 9.0$ Hz, 1H), 6.36 (d, $J = 7.5$ Hz, 1H), 5.02 (d, $J = 12.0$ Hz, 1H), 4.71 (d, $J = 12.0$ Hz, 1H), 4.39 (br s, 1H), 2.04 (s, 3H); (**3.55db**, 23%) 6.72 (m, 2H), 6.32 (m, 1H), 5.96 (br s, 1H), 5.10 (dd, $J = 12.6, 1.5$ Hz, 1H), 4.82 (dd, $J = 12.6$ Hz, 1.2 Hz, 1H), 1.93 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 170.4, 129.9, 129.5, 129.4, 127.5, 126.7, 120.7, 69.9, 69.6, 19.1, 18.9.



5-*tert*-Butyl-3-oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-

carbonitrile (3.55e): The title compound was prepared according to General

Procedure E using 4-*tert*-butylbenzyl 2-cyano-2-diazoacetate **3.54e** (26 mg, 0.1 mmol) and $\text{Cu}(\text{hfacac})_2$ (9.6 mg, 0.02 mmol), and was purified using 10% EtOAc/hexanes as eluent, yielding a white solid (10 mg, 44%). Analytical data: ^1H NMR (400 MHz, CDCl_3) δ 6.73 (br s, 1H), 6.39–6.20 (m, 2H), 4.79 (br s, 1H), 4.49 (br s, 1H), 3.47 (br s, 1H), 1.21 (s, 9H).

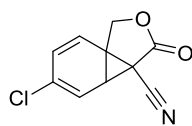


4,5-Dimethyl-3-oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-

carbonitrile (3.55f): The title compound was prepared according to General

Procedure E using 3,4-dimethylbenzyl 2-cyano-2-diazoacetate **3.54e** (46 mg, 0.2 mmol) and $\text{Rh}_2(\text{OPiv})_4$ (1.2 mg, 0.002 mmol), and was purified using 20% EtOAc/hexanes as eluent, yielding a clear oil as a 1:0.43 mixture of regioisomers (31 mg, 77%).

Analytical data: ^1H NMR (400 MHz, CDCl_3) δ (**3.55fa**, 70%) 6.38 (d, $J = 9.2$ Hz, 1H), 6.02 (d, $J = 9.2$ Hz, 1H), 4.63 (d, $J = 10.0$ Hz, 1H), 4.36 (d, $J = 10.0$ Hz, 1H), 3.07 (br s, 1H), 2.07 (s, 3H), 2.00 (s, 3H); (**3.55fb**, 30%) 6.08 (m, 1H), 5.93 (br s, 1H), 4.57 (d, $J = 9.6$ Hz, 1H), 4.33 (d, $J = 9.6$ Hz, 1H), 3.12 (d, $J = 5.2$ Hz, 1H), 2.05–2.01 (m, 6H).

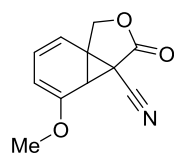


5-Chloro-3-oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-

carbonitrile (3.55g): The title compound was prepared according to General

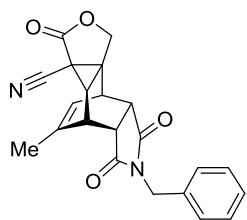
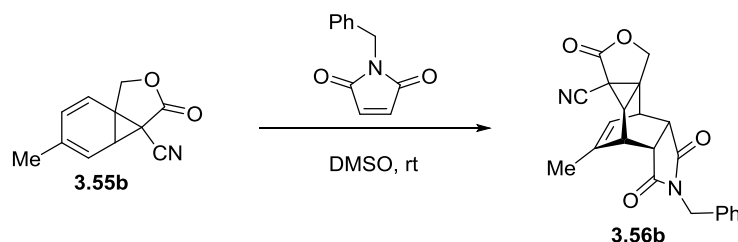
Procedure E using 4-chlorobenzyl 2-cyano-2-diazoacetate **3.54g** (47 mg, 0.2 mmol) and

Cu(hfacac)₂ (19 mg, 0.04 mmol), and was purified using 10% EtOAc/hexanes as eluent, yielding a brown solid (23 mg, 55%). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 6.72 (d, *J* = 6.0 Hz, 1H), 6.47 (d, *J* = 4.8 Hz, 1H), 6.35 (d, *J* = 6.0 Hz, 1H), 4.92 (d, *J* = 8.0 Hz, 1H), 4.67 (d, *J* = 8.0 Hz, 1H), 4.11 (br s, 1H).



6-Methoxy-3-oxo-1H,3H-benzo[1,3]cyclopropa[1,2-c]furan-3a(3bH)-carbonitrile (3.55h): The title compound was prepared according to General Procedure E using 3-methoxybenzyl 2-cyano-2-diazoacetate **3.54g** (23 mg, 0.1 mmol) and Rh₂(OPiv)₄ (0.6 mg, 0.001 mmol). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 6.38 (dd, *J* = 10.0, 1.2 Hz, 1H), 6.26 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.95 (s, 3H).

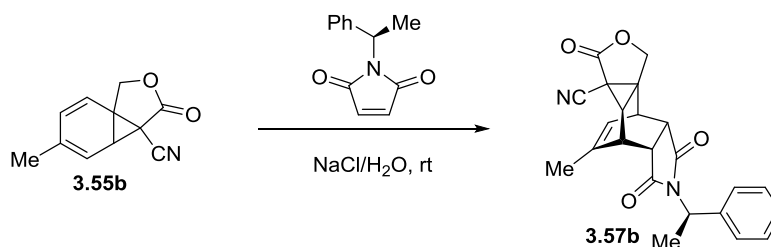
Subsequent Transformations of 3.55b



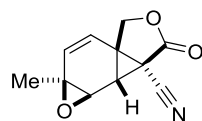
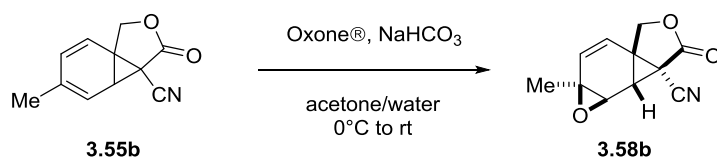
6-Benzyl-10-methyl-3,5,7-trioxo-3b,4,4a,5,6,7,7a,8-octahydro-1H-4,8-ethenofuro[3',4':1,3]cyclopropa[1,2-f]isoindole-3a(3H)-carbonitrile (3.56b):

In a 1 dram vial were combined **3.55b** (9.4 mg, 0.05 mmol) and *N*-benzylmaleimide (28 mg, 0.15 mmol) in DMSO (1 mL). The reaction was allowed to stir at room temperature for 3 d before the reaction was partitioned between EtOAc (1 mL) and water (1 mL). The aqueous layer was then extracted with EtOAc (4 × 1 mL). The combined organic layer was then washed with water (2 × 2 mL) and brine (1 × 2 mL), dried over Na₂SO₄, filtered, and concentrated. The solid residue was then triturated with Et₂O (2 mL), and the supernatant was

removed by suction. The solid was then washed with Et₂O (3 × 2 mL), and the residual solvent was removed *in vacuo*, providing a white solid in good purity as a single diastereomer (14 mg, 75%). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 5H), 5.61 (dq, *J* = 5.2, 1.6 Hz, 1H), 4.63 (d, *J* = 14.0 Hz, 1H), 4.54 (d, *J* = 14.0 Hz, 1H), 4.48 (d, *J* = 8.8 Hz, 1H), 4.30 (d, *J* = 8.8 Hz, 1H), 3.64–3.58 (m, 2H), 3.14 (dd, *J* = 8.0, 3.2 Hz, 1H), 3.06 (dd, *J* = 7.6, 3.2 Hz, 1H), 1.98 (d, *J* = 4.0 Hz, 1H), 1.52 (d, *J* = 1.6 Hz, 3H).



In a 1 dram vial were combined **3.55b** (9.4 mg, 0.05 mmol) and (*R*)-*N*-(1-phenylethyl)-maleimide (15.1 mg, 0.075 mmol). The mixture was then suspended in brine (1 mL) and the mixture was rapidly stirred for 16 h. After the reaction was complete by TLC, the organics were extracted with EtOAc (5 × 1 mL), dried over Na₂SO₄, filtered, and concentrated. The resultant solid was triturated with Et₂O, and washed with Et₂O (3 × 1 mL), yielding a white solid (16 mg, 81%, 1.8:1 dr). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 5H), 5.70 (m, 0.34H, minor), 5.62 (m, 0.64 H, major), 5.33 (m, 1H), 4.50 (m, 1H), 4.30 (m, 1H), 3.64 (m, 1H), 3.57 (m, 1H), 3.10 (m, 1H), 3.02 (m, 1H), 1.99 (m, 1H), 1.74 (m, 4.92H), 1.43 (br s, 1.02H, minor).



6a-Methyl-2-oxo-1a,6a-dihydro-2H,4H-oxireno[2'',3'':3',4']benzo[1',2':1,3]cyclopropa[1,2-c]furan-1c(1bH)-carbonitrile (3.58b)

carbonitrile (3.58b): The norcaradiene **3.55b** (10 mg, 0.05 mmol) and sodium bicarbonate (22 mg, 0.27 mmol) were added to a 1 dram vial and dissolved in 1:1 acetone/water (1 mL) and cooled to 0 °C. Then Oxone® (164 mg, 0.27 mmol) was added in one portion, and the reaction was allowed to gradually warm to room temperature over 22 h. Then the reaction was quenched with Na₂S₂O₃ (1 mL), extracted with CH₂Cl₂ (1 mL), dried over Na₂SO₄, filtered, and concentrated, yielding a clear oil in good purity as a single diastereomer (9 mg, 90%). Analytical data: ¹H NMR (400 MHz, CDCl₃) δ 6.09 (d, *J* = 5.8 Hz, 1H), 5.87 (d, *J* = 5.8 Hz, 1H), 4.44 (d, *J* = 9.8 Hz, 1H), 4.36 (d, *J* = 9.8 Hz, 1H), 3.56 (d, *J* = 2.0 Hz, 1H), 2.74 (d, *J* = 2.0 Hz, 1H), 1.50 (s, 3H).

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