DEAROMATIVE SPIROCYCLIZATIONS FOR THE PREPARATION OF
COMPLEX CARBO- AND HETEROCYCLES
AND
THE DEVELOPMENT OF A THERMODYNAMIC DIASTEREOMER ENRICHMENT OF
A FLUOROPHOSPHITE LIGAND

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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.

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ABSTRACT

Michael Francis McLaughlin: Dearomative Spirocyclizations for the Preparation of
Complex Carbo- and Heterocycles and the Development of a Thermodynamic
Diastereomer Enrichment of a Fluorophosphite Ligand
(Under the direction of Jeffrey S. Johnson)

I.   Enantioselective Phenolic α-Oxidation Using H_2O_2 via an Unusual Double Dearomatization Mechanism

We describe the oxidative dearomatizations of salicyl alcohols via their derived

bis(dichloroacetates) using hydrogen peroxide as a mild oxidant that intercepts a transient *ortho-*

quinone methide. A stereochemical study revealed that the reaction proceeds via a new mechanism

relative to other phenol dearomatizations and is complementary to extant methods that rely on

hypervalent iodine. Using a new chiral phase-transfer catalyst, the first asymmetric syntheses of

*ortho-*spiroepoxydienones were reported. The synthetic utility of the derived products is

demonstrated in a downstream complexity-generating transformation.
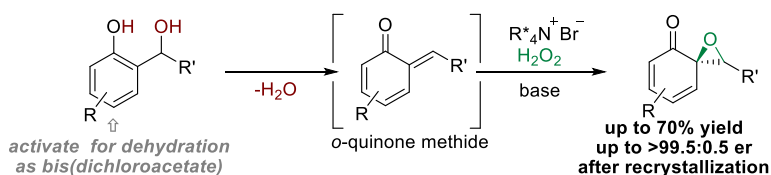
II.   Phenolic Oxidation Using H_2O_2 via in Situ Generated *para*-Quinone Methides for the Preparation of *para*-Spiroepoxydienones

We report an efficient preparation of dearomatized 1-oxaspiro[2.5]octa-4,7-dien-6-ones

(*para*-spiroepoxydienones) via the nucleophilic epoxidation of in situ generated *para*-quinone

methides from 4-(hydroxymethyl)phenols using hydrogen peroxide. The developed protocol

bypasses the need for stoichiometric bismuth reagents or diazomethane that are frequently

deployed for *p*-spiroepoxydienone preparation. The unusual reactivity of *p*-spiroepoxydienones is further explored in numerous downstream complexity-building transformations.
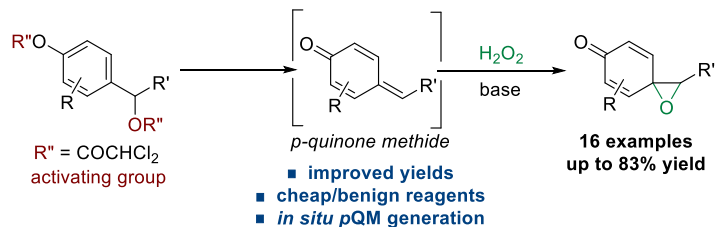
III. *N*-Heterospirocyclic Dienone Scaffolds via a One-Pot, Dearomative *ortho*-Semidine Rearrangement/Imine Hydrolysis
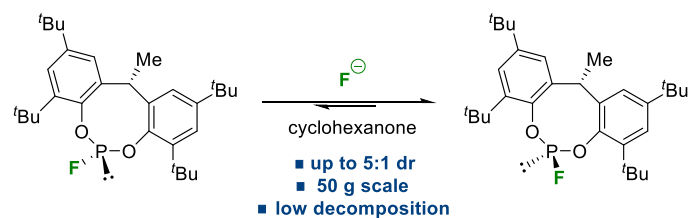
We have developed a one-pot, dearomative *ortho*-semidine rearrangement of tetrahydrodizocines and subsequent imine hydrolysis to afford synthetically useful dienone scaffolds with a heterospirocyclic tetrahydroisoquinoline moiety. These *N*-spirodienone scaffolds are used as linchpins for generation of downstream heterocyclic scaffolds via utilization of the spirocyclic nitrogen as a directing group.
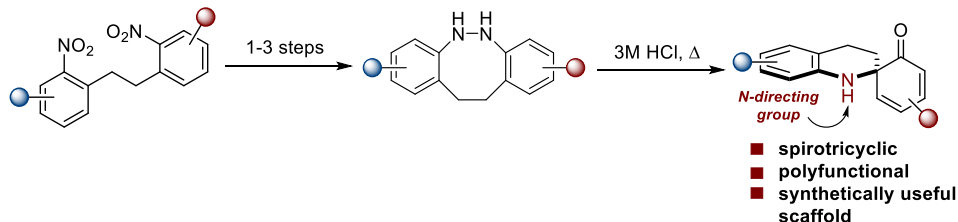
IV. The Development of a Thermodynamic Diastereomer Enrichment of a Fluorophosphite Ligand

We describe the development a thermodynamic diastereomer enrichment of a fluorophosphite ligand that exists as an initial 1:1 mixture of diastereomers. Using a fluoride source, the two diastereomers were readily interconverted. A solvent screen identified cyclohexanone as a privileged solvent for favoring formation of the anti isomer in ratios up to 5:1

dr at low temperatures. Reaction optimization and product isolation techniques were performed

for applicability to process scale-up. This work was conducted in collaboration with Eastman

Chemical Company.

My family has been my biggest support system throughout graduate school and throughout my entire life. To my grandparents, Manya and Babu, I am so thankful for all the times you let Sarah and I come to stay with you to crab and eat incredible food! To my parents in-law, Jack and Rosina Brinkman, and siblings in-law, David, Aly, and Eileen, thank you for being the best in-laws anyone could ask for and for always cheering me on! The family trips (Disney, Chicago, San Antonio, etc.) were always so much fun because of your love. Thank you also to my sister Mary Clare and her beautiful family and my sister Molly for their love!

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Finally, may all this work contained herein be used to glorify Jesus Christ and be used for the furthering of His Kingdom. For because of Him, this work has been made possible.

To my mom and dad,
for all the ways you have sacrificed for me
and
To my lovely wife, Sarah,
for all the times your love inspired me to persevere

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LIST OF ABBREVIATIONS AND SYMBOLS

%	percent
±	racemic
[O]	oxidant
$[\alpha]_D$	specific rotation
°C	degrees Centigrade
1,4-CHD	1,4-cyclohexadiene
^{13}C NMR	carbon nuclear magnetic resonance
1D	1-dimensional
2D	2-dimensional
^{19}F NMR	fluorine nuclear magnetic resonance
^{1}H NMR	proton nuclear magnetic resonance
^{31}P NMR	phosphorous nuclear magnetic resonance
α	alpha
Å	Angstrom
AcO	acetate
AcOH	acetic acid
Ag_2O	silver(II) oxide
AIBN	azobisisobutyronitrile
$AlCl_3$	aluminum trichloride
aq	aqueous
Ar	aryl
β	beta
B	boron
$Ba(OH)_2 \cdot H_2O$	barium hydroxide monohydrate

BINAM	2,2′-bis(diphenylphosphinoamino)-1,1′-binaphthyl
Bn	benzyl
Br	bromine
br s	broad singlet
C	carbon
calcd	calculated
CAM	cerium ammonium molybdate
cat	catalyst
CBr_4	carbon tetrabromide
CCl_4	carbon tetrachloride
CCDC	Cambridge crystallographic data center
$CDCl_3$	chloroform-d
$(CD_3)_2SO$	dimethylsulfoxide-d
CF_3	1,1,1-trifluoromethyl
$(CF_3)_2Ar$	bis(3,5-trifluoromethyl)aryl
CF_3CH_2OH	trifluoroethanol
CH_2Cl_2	dichloromethane
CH_2N_2	diazomethane
CH_3Cl	chloromethane
CH_3CN	acetonitrile
CH_3COOH	acetic acid
$CHCl_3$	chloroform
$(CH_2O)_n$	paraformaldehyde
CIDR	crystallization-induced dynamic resolution
Cl	chlorine

cm^{-1}	wavenumber
CN	cyano
CO$_2$Et	ethyl ester
CuOTf	copper(I) triflate
δ	chemical shift
Δ	heat
d	days
d	doublet
D	deuterium
DBU	1,8-diazobicyclo(5.4.0)undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
DFT	density functional theory
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
equiv	equivalents
er	enantiomeric ratio

ESI$^+$	electrospray ionization (positive mode)
Et	ethyl
Et$_2$O	diethyl ether
Et$_3$N	triethylamine
EtOH	ethanol
F	fluorine
FDA	U.S. Food and Drug Administration
Fe	iron
g	grams
h	hour
H	hydrogen
H$^+$	proton or generic acid source
H$_2$	hydrogen gas
H$_2$O	water
H$_2$O$_2$	hydrogen peroxide
H$_2$SO$_3$	sulfurous acid
H$_2$SO$_4$	sulfuric acid
H$_3$BO$_3$	boric acid
HCl	hydrochloric acid
HF	hydrofluoric acid
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz
I	iodine
^{i}PrOH	*iso*-propanol

IR	infrared
Ir	iridium
IRC	intrinsic reaction coordinates
J	coupling constant
K	potassium
K	Kelvin
K_2CO_3	potassium carbonate
kcal	kilocalories
KF	potassium fluoride
$KMnO_4$	potassium permanganate
KOCl	potassium hypochlorite
KOH	potassium hydroxide
LHMDS	lithium bis(trimethylsilane)amide
m	multiplet
M	molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeLi	methyllithium
MeMgBr	methylmagnesium bromide
MeOH	methanol
mg	milligram
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute

mL	milliliter
mmol	millimole
MnO_2	manganese dioxide
mol	mole
mp	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
N	nitrogen
Na	sodium
$NaBO_2 \cdot (H_2O)_4$	sodium metaborate tetrahydrate
$Na_2S_2O_3$	sodium thiosulfate
Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride
$NaBiO_3$	sodium bismuthate
NaH	sodium hydride
$NaIO_4$	sodium periodate
NaOH	sodium hydroxide
NBS	*N*-bromosuccinimide
n_F	non-bonding electrons of fluorine
NH_4Cl	ammonium chloride
NIS	*N*-iodosuccinimide
nOe	nuclear Overhauser effect
nOesy	nuclear Overhauser effect spectroscopy
O	oxygen
O_2	oxygen gas

OH	hydroxide
OMe	methoxy
*o*QM	*ortho*-quinone methide
o-	*ortho*-
OTs	tosylate
π	pi
p-	*para*-
Pb(OAc)$_4$	lead tetraacetate
PCl$_3$	phosphorous trichloride
Pd	palladium
Pd(PPh$_3$)$_4$	tetrakis(triphenylphosphine)palladium(0)
Pd/C	palladium on carbon
pH	potential hydrogen
Ph	phenyl
Ph$_2$O	diphenyl ether
PhB(OH)$_2$	phenyl boronic acid
PhMe	toluene
PhNCO	phenyl isocyanate
PIDA	(diacetoxydiodo)benzene
PPh$_3$	triphenylphosphine
ppm	parts-per-million
*p*QM	*para*-quinone methide
PTC	phase-transfer catalyst
qt	quartet
R$_f$	retention factor

rt	room temperature
s	seconds
s	singlet
S	sulfur
sept	septet
Si	silicon
t	triplet
TsNa	sodium p-toluenesulfinate
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBS	tetrabutylsilyl
^{t}Bu	*tert*-butyl
^{t}BuOK	potassium *tert*-butoxide
td	triplet of doublets
temp	temperature
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCF$_3$	trifluoromethyltrimethylsilane
TMSCN	trimethylsilyl cyanide
t_R	retention time
TS	transition state
Ts	tosyl

TsCl	tosic chloride
TsOH	tosic acid
tt	triplet of triplets
UHP	urea hydrogen peroxide
UV	ultraviolet
Zn	zinc

CHAPTER ONE:
ENANTIOSELECTIVE PHENOLIC α-OXIDATION USING H₂O₂ VIA AN UNUSUAL DOUBLE DEAROMATIZATION MECHANISM [*]

1.1 Introduction

Oxidative dearomatizations of feedstock arenes, including phenols, are useful in delivering functionalized, complex organic building blocks.[1] These processes often rely on excess, and in some cases costly, hypervalent iodine or heavy metal based (i.e., lead and bismuth) reagents that can give rise to hazardous byproducts;[2] a characteristic that can overshadow the benefit of using inexpensive feedstock precursors. Reactions using catalytic or heavy metal-free conditions with benign oxidants, such as hydrogen peroxide (H_2O_2), have seldom been explored, especially in asymmetric fashion.[3] In this chapter, we describe an oxidative dearomatization of salicyl alcohols via their derived bis(dichloroacetates) using H_2O_2 as a mild oxidant that intercepts a transient *ortho*-quinone methide. Herein, the first asymmetric syntheses of *ortho*-spiroepoxydienones are reported using a new chiral phase-transfer catalyst.

1.2 Background

1.2.1 Dearomatization

Highly substituted cyclohexane rings are important building blocks for the synthesis of complex scaffolds present in a variety of FDA-approved drugs (Figure 1-1);[4] therefore, efficient means of preparing these privileged ring systems remain a high priority for synthetic chemists.

Figure 1-1. FDA-Approved Drugs Containing Functionalized Cyclohexane Rings

Mavik[®]
trandolapril

Zemplar[®]
paricalictol

Lixiana[®]
edoxaban
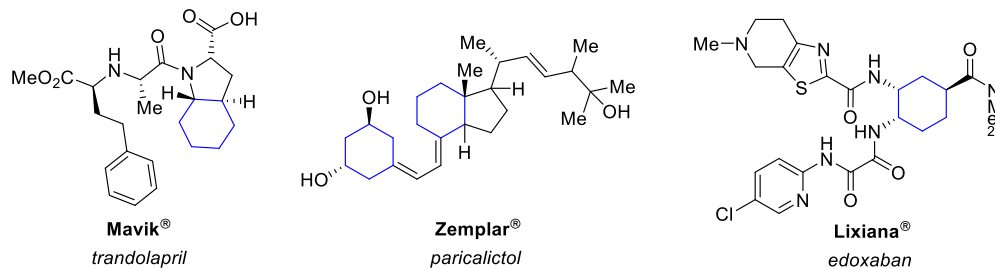
A streamlined approach to these complex ring systems could be envisioned through the direct manipulation of aromatic benzenoids. These benzenoids exhibit promising potential for complex cyclohexane preparation due to their latent unsaturation. Additionally, aromatic precursors are inexpensive feedstock chemicals that are commercially available in a wide array of substitution patterns.[5]

The key challenge in utilizing aromatics as source of complexity generation involves overcoming the strong aromatic stabilization energy of the benzenoid precursors. Consequently, dearomatization strategies have been developed to expose the latent diene functionality embedded within the aromatic core.[6] Subsequent deployment of established olefin functionalizations enables access to a wide number of highly substituted carbocycles (Scheme 1-1).

Scheme 1-1. Rapid Preparation of Complex Cyclohexanes via Dearomatization

Highly Substituted
Carbocycles
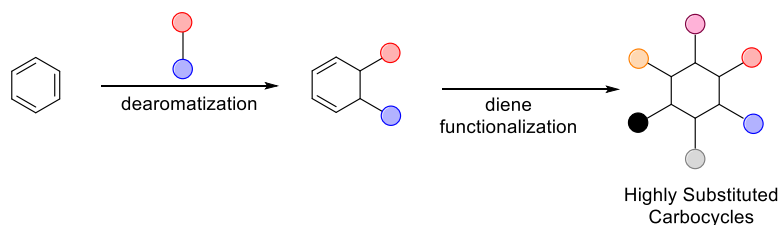
1.2.2 Oxidative Approaches to Dearomatization

Numerous dearomative methods have been developed in recent years using unactivated benzenoids;[7] however, the most common approach for dearomative complexity generation is through the oxidation of activated phenols.[8] These phenol oxidations frequently fall into three

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classifications contingent on the reagent used to enact the dearomatization: 1) biocatalysts; 2) heavy metal reagents; or 3) hypervalent iodine reagents (Scheme 1-2). The Narayan lab recently published an enzymatic oxidation of salicylaldehyde **1.1** to afford dearomatized dienone **1.2** in good yields and excellent enantioselectivities (Scheme 1-2a).[9] Historically, the Wessley oxidation has been employed for phenol oxidations via installation of an acetate at the more densely substituted *ortho*-position using stoichometric Pb(OAc)$_4$ to afford dienones (Scheme 1-2b).[10] The most prevalent method for dearomative phenol oxidations has been through use of hypervalent iodine reagents[11] (Scheme 1-2c). These reagents, such as (diacetoxyiodo)benzene (PIDA) **1.3**, are used frequently in natural product total synthesis, and, in recent years, enantioselective hypervalent iodine catalysts have been developed.[12]

Scheme 1-2. Selected Examples of Oxidative Dearomatization of Phenols
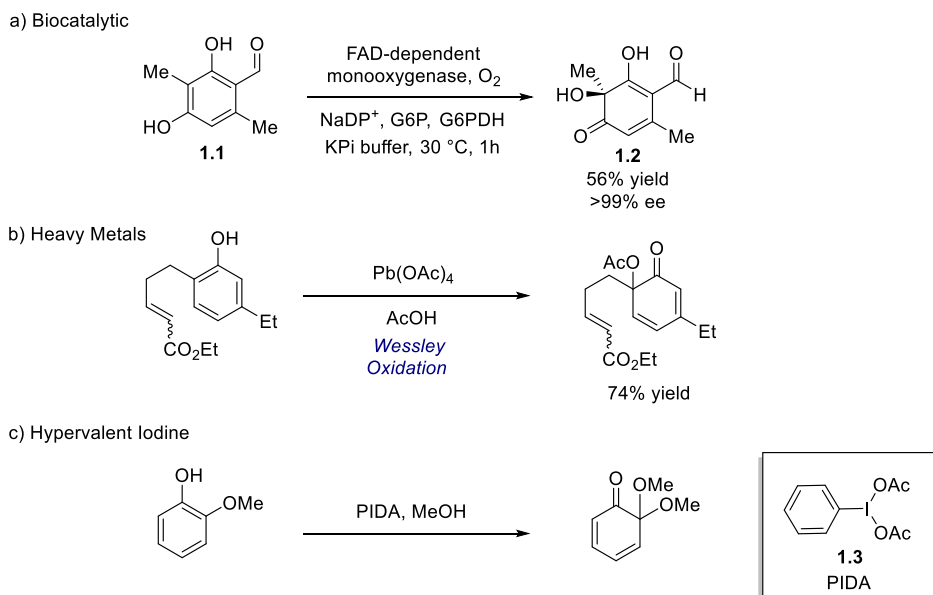
1.2.3 The Adler-Becker Oxidation

The Adler-Becker oxidation utilizes stoichiometric sodium metaperiodate (NaIO$_4$), a hypervalent iodine species, to convert 2-(hydroxymethyl)phenols **1.4**, also referred to as salicyl alcohols, into racemic, dearomatized 1-oxaspiro[2.5]-octa-5,7-dien-4-ones **1.5** (*ortho*-

spiroepoxydienones) (Scheme 1-3),[13] a motif readily found in a number of biologically active natural products (Figure 1-2).[14]

Scheme 1-3. The Adler-Becker Oxidation
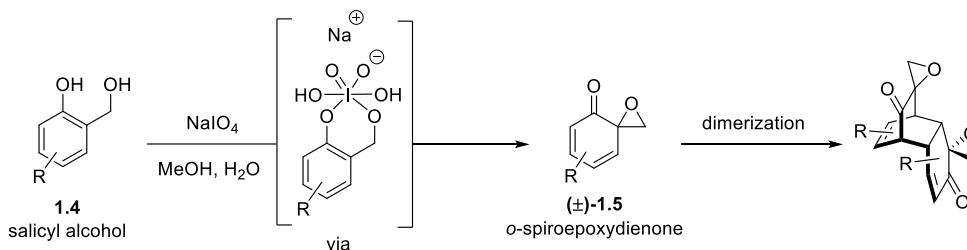
Figure 1-2. Representative Bioactive Compounds with *o*-Spiroepoxide Substructure

teucrolivin A   triptonide   epoxysorbicillinol
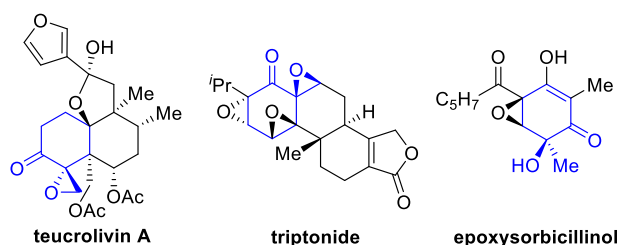
Since the development of the Adler-Becker reaction in 1971, these oxidation products have been broadly deployed due to their functionalizable dienone motif and proclivity to participate in a variety of cycloaddition reactions.[15] Most notably, Corey used the Adler-Becker oxidation as an enabling transformation in the synthesis of (±)-ovalicin **1.6**, a potent antitumor agent (Scheme 1-4a).[16] In this synthesis, NaIO$_4$ oxidation of 4-methoxysalicyl alcohol **1.7** afforded *ortho*-spiroepoxydienone **1.8** that enabled access to the resultant carbocyclic core of ovalicin. Another striking application of this methodology is found in Danishefsky's synthesis of (±)-calicheamicin **1.9** (Scheme 1-4b).[17] A key element of the construction of this natural product was the use of the Adler-Becker oxidation as a mechanism for advancing triol **1.10** to dienone **1.11**, an active electrophile for annulation with an enediyne.

Scheme 1-4. Selected Examples of Total Syntheses Employing the Adler-Becker Oxidation

a) *Corey, 1985*
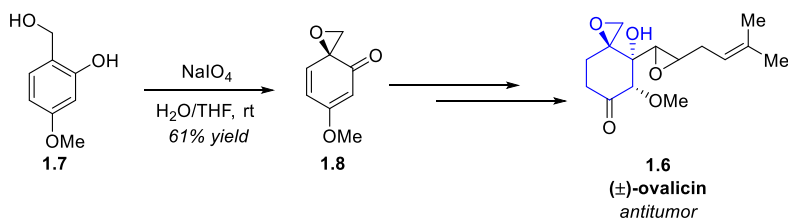
b) *Danishefsky, 1995*
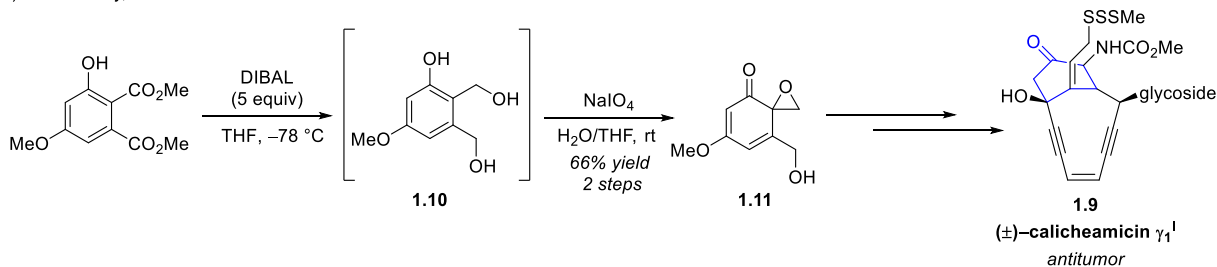
While these examples highlight the broad synthetic utility of *ortho*-spiroepoxydienones, a major roadblock in retrosynthetic analyses involving the Adler-Becker oxidation is the absence of a mechanism for stereocontrol of the resultant spiroepoxide. Furthermore, no alternative method existed for enantioenriched *ortho*-spiroepoxydienone preparation, ultimately limiting their applicability as building blocks in modern enantioselective syntheses.

1.2.4 Pettus Approach to *o*-Spiroepoxydienones

Pettus introduced a novel approach towards racemic spiroepoxydienone formation via epoxidation of substituted *ortho*-quinones (Scheme 1-5).[18] Using diazomethane and *ortho*-quinone **1.12**, he reported the formation of *o*-spiroepoxide **1.13** at low temperatures in good yields; however, further attempts to implement a copper-catalyzed cyclopropanation[19] resulted in isolation of rearomatized benzodioxole **1.14**, a known rearrangement of *o*-spiroepoxydienones. Absence of the copper catalyst resulted in isolation of spiroepoxide **1.13**.

5

Scheme 1-5. Pettus' Approach to *o*-Spiroepoxydienones
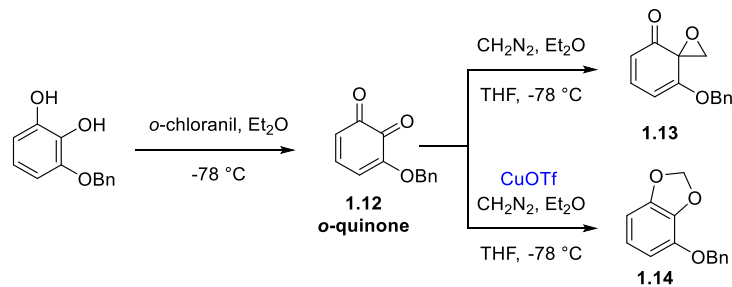
1.3 Nucleophilic Epoxidation of *ortho*-Quinone Methides

1.3.1 Motivation and Reaction Design

A recent report from these laboratories employed the Adler−Becker oxidation as the initiating step in a cascade sequence for the synthesis of highly functionalized heterocycles.[20] To prepare asymmetric variants of these heterocycles, a requirement would be the development of a method for accessing enantioenriched *o*-spiroepoxydienones. Our interest in this area led to the development of the hypothesis outlined in Scheme 1-6. The reaction design imagined an enabling and underexplored intersection between transient quinone methides and mechanistically validated asymmetric nucleophilic epoxidations using basic H_2O_2.[21]

Scheme 1-6 postulates that the reaction of nonstabilized,[22] ephemeral *ortho*-quinone methide **1.15** with H_2O_2 under basic conditions would initially re-establish aromaticity affording hydroperoxide **1.16** but concurrently set the stage for heterolytic O−O bond cleavage induced by engagement at the phenolic α-carbon, thereby breaking aromaticity for the second time in the sequence and creating the spiroepoxide substructure. Moreover, employing an asymmetric ion-pairing phase-transfer catalyst with phenoxide **1.16** could selectively facilitate the O−O bond cleavage, affording enantioenriched spiroepoxydienones (−)-**1.5**.

Scheme 1-6. Approach to Accessing Enantioenriched *o*-Spiroepoxydienones
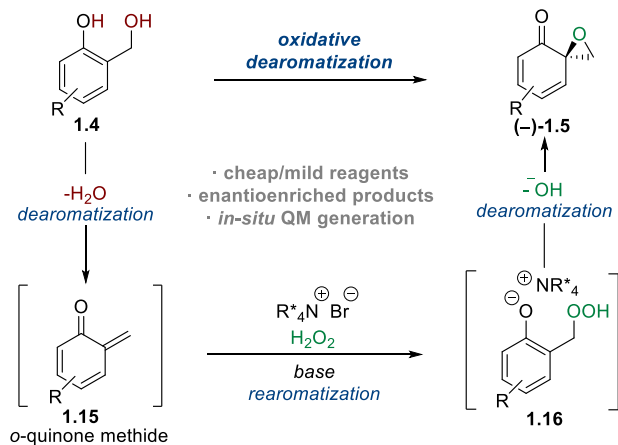
1.3.2 o*rtho*-Quinone Methides

The hypothesis in Scheme 1-6 hinged on the ability to generate and utilize a non-stabilized *ortho*-quinone methide intermediate. *ortho*-Quinone methides **1.15** (*o*QMs) are dearomatized species that have frequently been employed in forming complex natural products and synthetically useful building blocks (Scheme 1-7).[23] A strong driving force for rearomatization underlies the high reactivity of the exocyclic enone toward [4 + 2]-cycloadditions[24] and 1,4-conjugate additions.[25] In almost all cases, these transformations irreversibly reset the aromaticity of the resultant system, limiting further complexity-building transformations. Reactions involving *o*QMs resulting in isolable, dearomatized products are rare.[26]

Scheme 1-7. Select Examples of Reactions Involving *o*QM Intermediates
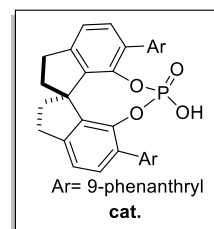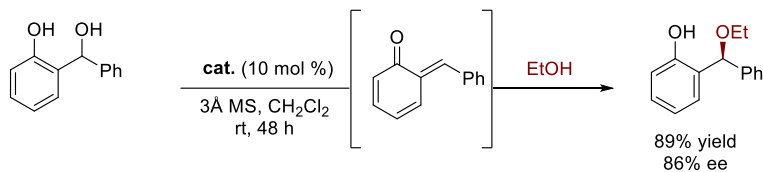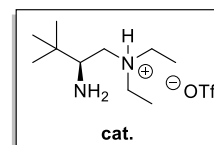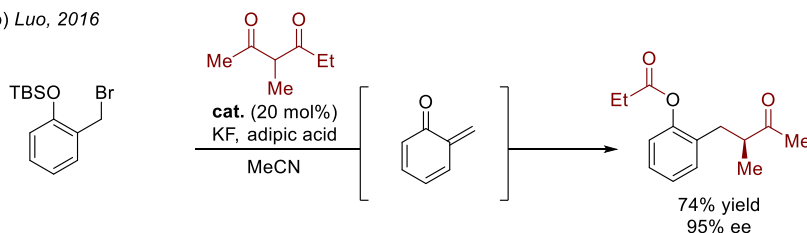
The high reactivity of *o*QMs require their generation and utilization in situ to prevent undesired dimer- and trimerization of the *o*QM monomer.[27] Stable *o*QMs **1.17** are often deployed as a way of mitigating the undesired oligomerization (Scheme 1-8); however, the scope of these species is highly limited.[28] Furthermore, the generation of stable *o*QMs requires superstoichiometric amounts of toxic metal oxidants (e.g. Ag_2O, MnO_2).

Scheme 1-8. Generation of Stable *o*-Quinone Methides

1.17
Stable
o-Quinone Methide
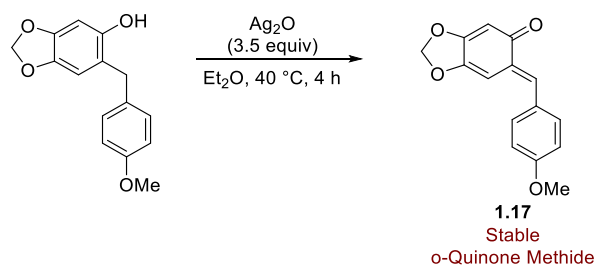
Under our proposed reaction scheme outlined in Scheme 1-6, phenol **1.4** is formally related to its derived *o*QM **1.15** by dehydration; therefore, a key challenge to achieving the title process would be the identification of conditions that facilitate dehydrative QM formation under basic conditions to promote a one-pot QM formation and subsequent nucleophilic epoxidation. Existing methods for QM generation using base were considered inadequate because of the poor scope or incompatibility with the known stability of the *o*-spiroepoxydienones;[29] a new method of QM generation was deemed to be a prerequisite for success of the project.

1.4 Development of a Novel Base-Promoted *o*QM precursor

1.4.1 Initial Attempts at Generating *o*QM Precursors

Considering the need for a base-promoted *o*QM precursor with a large substrate scope, our initial attempts focused on converting the benzylic alcohol of salicyl alcohols **1.4** into an active leaving group (Br, Cl, OTs). Preparation of the activated salicyl alcohol derivatives would ultimately enable *o*QM formation via deprotonation of the phenolic −OH followed by expulsion

of the benzylic leaving group to generate the active oQM transient species. Numerous methods for the direct conversion of benzylic alcohols into leaving groups exist in the literature.[30] Unfortunately, application of these methods to salicyl alcohols proved difficult in our hands due to significant decomposition upon attempted isolation (Scheme 1-9).

Scheme 1-9. Failed Initial Attempts at Salicyl Alcohol Activation
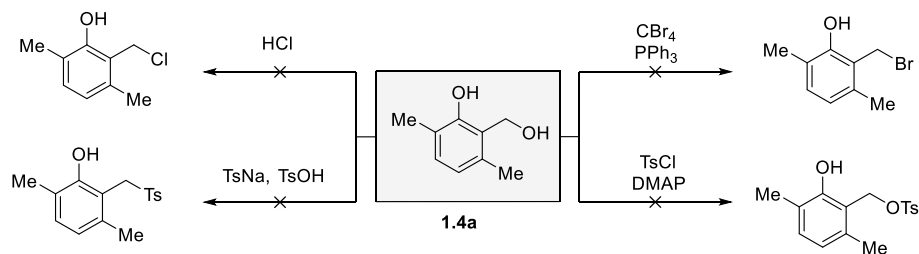
1.4.2 Identification and Optimization of an Activating Group for Quinone Methide Formation

Fortunately, we could convert benzylic alcohol **1.4a**[31] to its unstable monoacetate **1.18** in low yield. When phenol **1.18** was subjected to KOH and H_2O_2 in MeCN at −5 °C, the desired spiroepoxydienone **1.5a** was observed (Table 1-1, entry 1). Diacetate **1.19** was prepared in 70% yield and exhibited better stability than **1.18**. Diacetate **1.19** in turn gave **1.5a** in somewhat higher yield relative to the preparation from the monoacetate **1.18** (entry 2).

The efficiency of quinone methide formation could be affected by the rates of both the phenolic deacylation (loss of R^1) and expulsion of $^{(-)}OR^2$; the electronic characteristics of both groups should be critical. To accelerate both steps, the more electron-deficient mono- **1.20** and dichloroacetate **1.21** analogues were prepared and exhibited drastically improved intermediate and product yields (entries 3 and 4). Bis(trifluoroacetate) **1.22** performed at a modest level (entry 5); consequently, bis(dichloroacetate) analogue **1.21** was selected for deployment with additional phenols. Dichloroacetate merits some consideration of the molecular mass "sacrificed", but the attractiveness of this acid chloride as a dehydrating agent stems in no small part from its cheap

access on scale, high yields (>90%), and wide applicability and the fact that bis-(dichloroacetates) **1.21** are stable and often exist as easily handled white solids.

Table 1-1. Identification of an Optimal Activating Group for *ortho*-Quinone Methide Formation

entry	R^1	R^2	acetate product	yield **1.18-1.24** (%)[a]	yield **1.5a** (%)[b]	overall yield (%)
1	H	(C(=O)Me)	**1.18**	40	21	8
2	(C(=O)Me)	(C(=O)Me)	**1.19**	70	37	26
3	(C(=O)CH2Cl)	(C(=O)CH2Cl)	**1.20**	89	60	54
4	(C(=O)CHCl2)	(C(=O)CHCl2)	**1.21**	95	80	76
5	(C(=O)CF3)	(C(=O)CF3)	**1.22**	74	55	41

[a]Isolated yield. [b]^{1}H NMR yield versus internal standard

1.5 Racemic Reaction Scope

Using the optimized conditions identified in Table 1-1, alkyl-substituted salicyl alcohols **1.4a-c** afforded the highest yields of the desired racemic spiroepoxide products (Table 1-2, **1.5a-c**). Alkyl groups promote the formation of QMs while reducing the rate of detrimental dimerization processes.[32] Electron-withdrawing substituents and halogens are reported to inhibit QM formation[33] and lead to oligomerization under basic conditions;[27] however, when using difluorophenol **1.21e**, the desired product **1.5e** was obtained (47%). In contrast, difluorophenol **1.4e** failed to provide any discernible product when NaIO$_4$ was used, highlighting the complementary nature of this method relative to the Adler−Becker oxidation. Mixed alkyl and halogen substitution afforded similar yields when nine equivalents of peroxide were used (**1.5f**). Because benzylic substitution (R^5) often promotes facile rearrangement of spiroepoxydienones to

benzodioxoles,[13] we used bicyclic substrates **1.5g–h** to prevent rearrangement and observed good

yields with excellent diastereoselectivity in **1.5g**.

Table 1-2. Racemic Reaction Scope[a]
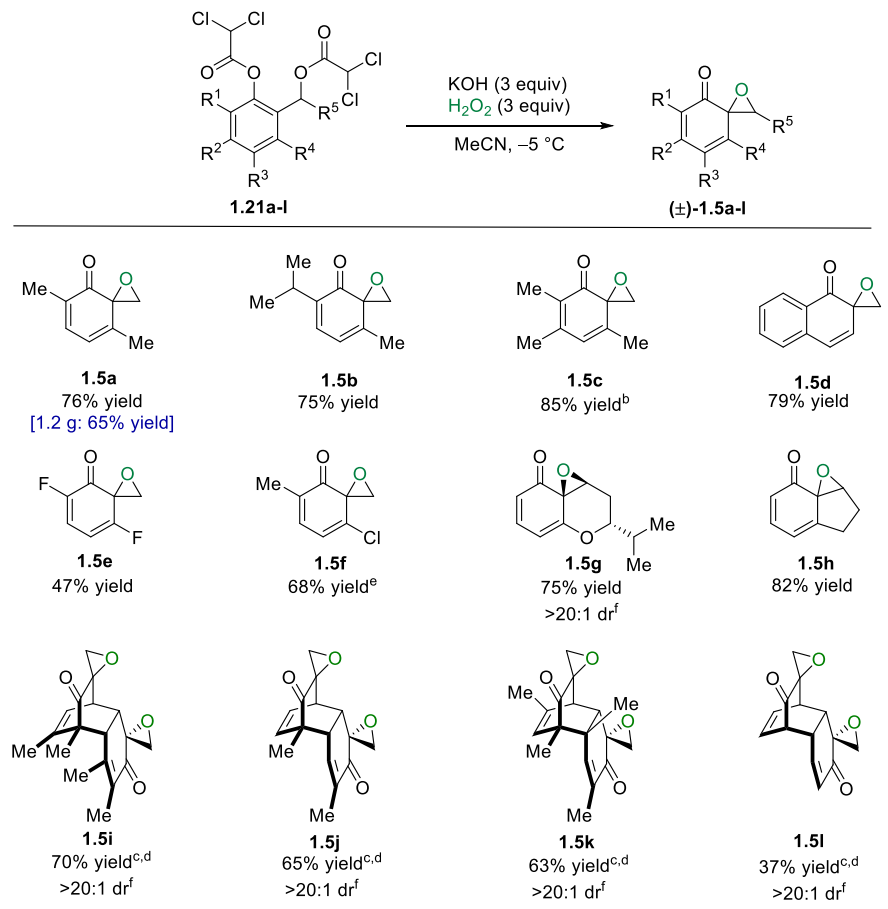
^aReactions performed with 1.0 equiv of **1.21** and 3.0 equiv of both H_2O_2 and KOH in MeCN
($[\mathbf{1.21}]_0 = 0.05$ M). Yields refer to isolated yields. ^b4 equiv of KOH were used. ^cProduct isolated
as dimer. ^dSlow addition of a solution of **1.21** and H_2O_2 over the course of 1 h. ^e9 equiv of H_2O_2
were used. ^fDetermined by ¹H NMR spectroscopic analysis.

The substitution pattern around the o-spiroepoxydienone was a critical determinant of

whether the product was isolated in monomeric or dimeric form.[33] Compounds **1.5i–l** with no

substitution at R⁴ generally favored dimerization upon isolation. Unsubstituted salicyl alcohol **1.4l**

afforded **1.5l** with low yield and resulted in a multitude of side products (i.e., oligomers, QM

dimers). Substrates prone to dimerization required that bis(dichloroacetate) **1.21** and H_2O_2 were

added over the course of 1 h to reduce excess QM accumulation in solution. Rapid addition (<1 min) of **1.21** and H_2O_2 to the KOH/MeCN mixture resulted in a 1:1 mixture of the dimer and chromane **1.23**, the product of trapping of the spiroepoxydienones with excess QM **1.15i** in solution (Scheme 2).

Scheme 1-10. Observed Competition Between Product Dimerization and Quinone Methide Trapping
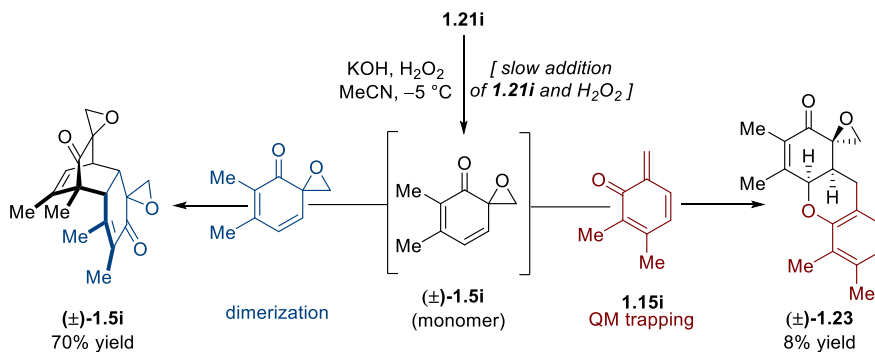
1.6 Approach to Enantioselective Variant

With a mechanistically distinct phenolic oxidation in hand, we became interested in developing an asymmetric variant of the title process. Enantioselective transformations utilizing *o*QMs lacking methide substitution under basic conditions are limited due to their high reactivity and propensity to dimerize rapidly in solution.[34] While asymmetric Weitz−Scheffer-type epoxidations are well-established for chalcones and other β-substituted enones using cinchona alkaloid phase-transfer catalysts (PTCs) (Scheme 1-11b),[35] asymmetric epoxidations of enones lacking β-substitution are rare.[36] Employing in situ-generated *o*QMs that lack substitution at the methide position presents a formidable challenge in controlling the stereochemistry of the resultant spiroepoxide. Toward this end, we envisioned employing an asymmetric ion-pairing PTC with phenoxide **1.16** as a method for controlling the facial selectivity of heterolytic O−O bond cleavage, a mechanism closely related to phase-transfer-catalyzed α-enolate substitution reactions (Scheme 1-11a).[37] Computational analyses of these enantioselective reactions have revealed tight catalyst

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control of the substrate and electrophile to direct the facial selectivity of the substitution.[38] While

PTC α-enolate substitution reactions frequently involve the coordination of external electrophiles,

more recent examples employ internal electrophiles using cinchona alkaloid PTCs bearing a free

hydroxyl group.[39]

Scheme 1-11. Selected Examples of Asymmetric Cinchona Alkaloid Phase-Transfer Reactions

a) Dolling, 1984

CH$_3$Cl (7 equiv)
cat. (10 mol %)

50% aq. NaOH
PhMe, 15 °C, 18 h

95% yield
92% ee

cat.

b) Corey, 1999

KOCl (5 equiv)
cat. (10 mol %)

PhMe, −40 °C, 12 h

96% yield
93% ee

cat.
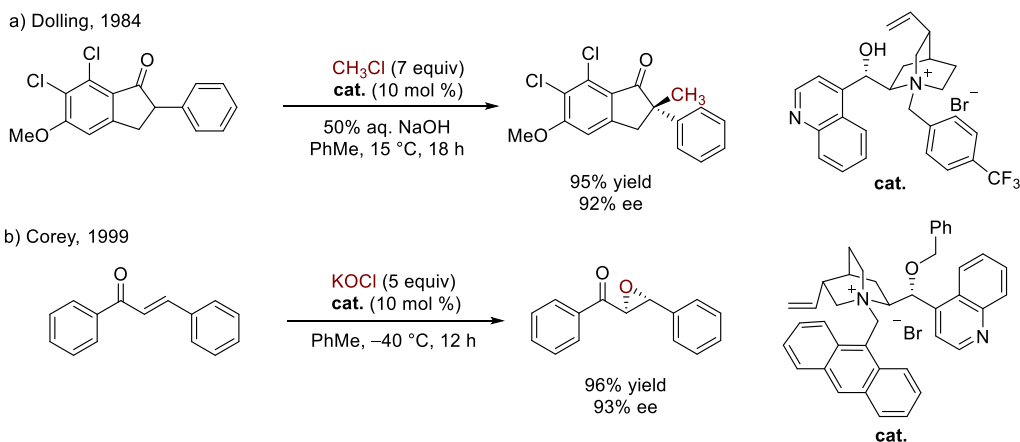
1.7 Enantioselective Reaction Optimization

We therefore began our catalyst screening by employing various cinchona alkaloid PTCs

with a free hydroxyl group. Gratifyingly, phase-transfer catalyst **1.24** with CH$_2$Cl$_2$ solvent using

30% aqueous H$_2$O$_2$ as the oxidant resulted in a 55:45 er (Table 1-3, entry 1). Further catalyst

optimization revealed that more electron-deficient benzyl groups (i.e., **1.26**) improved selectivity

(entry 3). Employing urea·H$_2$O$_2$ (UHP) to limit water content gave appreciable increases in

selectivities and yields (entry 4). Switching to quinine as the cinchona alkaloid (**1.27**) greatly

improved the er while affording mediocre yields (entry 5). Cooling the reaction temperature to −

20 °C resulted in lower yields and selectivities (entry 7). Dihydroquinine catalyst **1.28** was

investigated to minimize potential in situ derivatization of the catalyst's olefin via a Diels−Alder

cycloaddition with a transient quinone methide (entry 8). Disappointingly, this catalyst resulted in

the same yields and selectivities as **1.27**. Upon further analysis, increased catalyst loading resulted

in increased side product formation. Characterization revealed putative oxazonine **1.30** resulting

from nucleophilic attack on a generated QM by the catalyst's quinoline nitrogen followed by

cleavage of the quinuclidine core (Scheme 1-12a). To minimize the nucleophilicity of the

quinoline nitrogen while simultaneously providing steric hindrance,[40] catalyst **1.29** with a

trifluoromethyl group was developed[41] (30% yield over 3 steps from quinine *N*-oxide **1.31**, Scheme

1-13), that considerably improved yields while maintaining selectivities upon cooling to −40 °C

(entry 11; Scheme 1-12b).

Table 1-3. Optimization of Enantioselective Reaction[a]

entry	cat.	mol %	[O]	T (°C)	er[b]	yield (%)[c]
1	**1.24**	20	H_2O_2 (aq)	0	55:45	<10
2	**1.25**	20	H_2O_2 (aq)	0	50:50	<10
3	**1.26**	20	H_2O_2 (aq)	0	63:37	<10
4	**1.26**	20	UHP	0	69:31	33
5	**1.27**	20	UHP	0	85:15	50
6	**1.27**	20	UHP	−10	87:13	55
7	**1.27**	20	UHP	−20	80:20	43
8	**1.28**	20	UHP	−10	87:13	52
9	**1.29**	20	UHP	−10	85:15	70
10	**1.29**	20	UHP	−40	87:13	85
11	**1.29**	10	UHP	−40	87:13	86
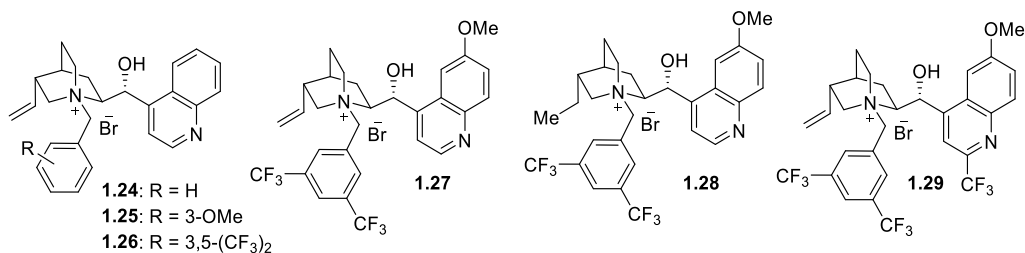
[a]Reactions were performed using **1.21a** (0.50 mmol), KOH (1.5 mmol), UHP (1.5 mmol), [**1.21a**]$_0$ = 0.05 M in CH_2Cl_2. 8a was added over the course of 2.5 h. [b]er was determined by chiral HPLC. [c]Isolated yields.

Scheme 1-12. Preventing Catalyst Decomposition
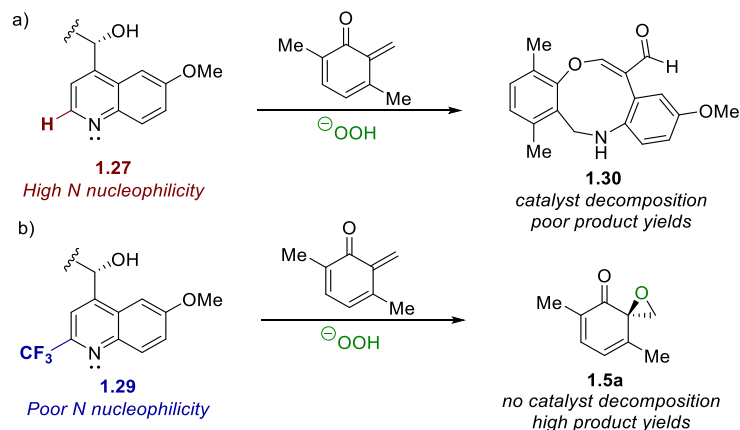
Scheme 1-13. CF₃-Quinine Phase-Transfer Catalyst **1.29** Synthesis
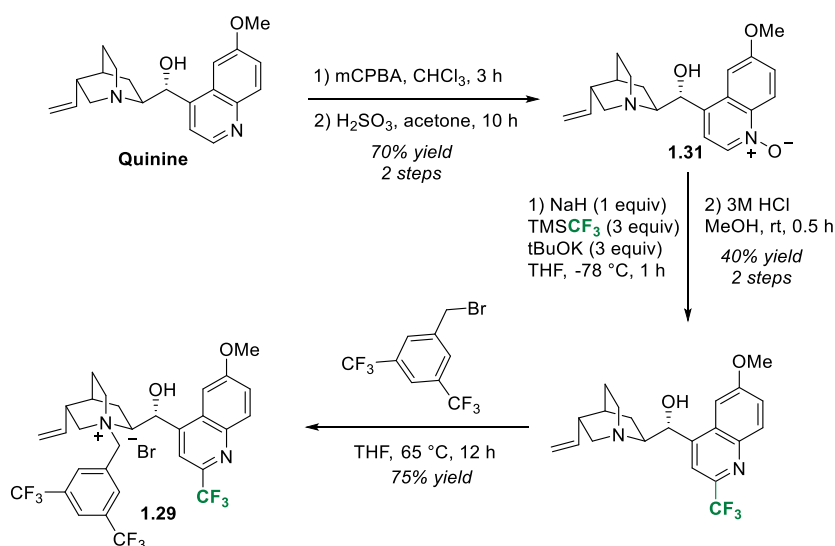
1.8 Enantioselective Reaction Scope

Using the optimized catalyst and reaction conditions, various bis(dichloroacetates) were evaluated for conversion to their derived enantioenriched epoxides (Table 1-4). Monomers **(–)-1.5a–d** were all found to afford modest selectivities with high yields; however, good to excellent enantioselectivities with good mass recovery could be achieved via a single recrystallization.[42] Similarly, dimer **(–)-1.5i** exhibited slightly diminished selectivities that could be upgraded by a

single recrystallization, affording excellent selectivities and modest recovery. It was quickly

apparent that the stability and substitution pattern of the generated QM were important factors in

influencing the yield and enantioselectivities of the reaction. Attempts to access the

enantioenriched unsubstituted dimer **(−)-1.5i** resulted in low yields of the racemic dimer due to

rapid QM oligomerization relative to epoxidation under the basic conditions. In contrast, bicyclic

substrate **(−)-1.5h** gave good yields but afforded poor selectivity, although a possible change in

the enantiodetermining step of the reaction should be noted with this β-substituted substrate.

Table 1-4. Enantioselective Reaction Scope[a,b,c]

1.5a 86% yield (70%) 87:13 er (95:5)	**1.5b** 85% yield (69%) 90:10 er (>99.5:0.5)

1.5a
86% yield (70%)
87:13 er (95:5)

1.5b
85% yield (69%)
90:10 er (>99.5:0.5)

1.5c
85% yield (59%)
80.5:19.5 er (93:7)

1.5d
81% yield (61%)
89:11 er (98.5:1.5)

1.5i[d]
65% yield (40%)
77:23 er (97:3)
>20:1 dr

X-ray structure

1.5h
80% yield
60:40 er

1.5I
15% yield
50:50 er
>20:1 dr
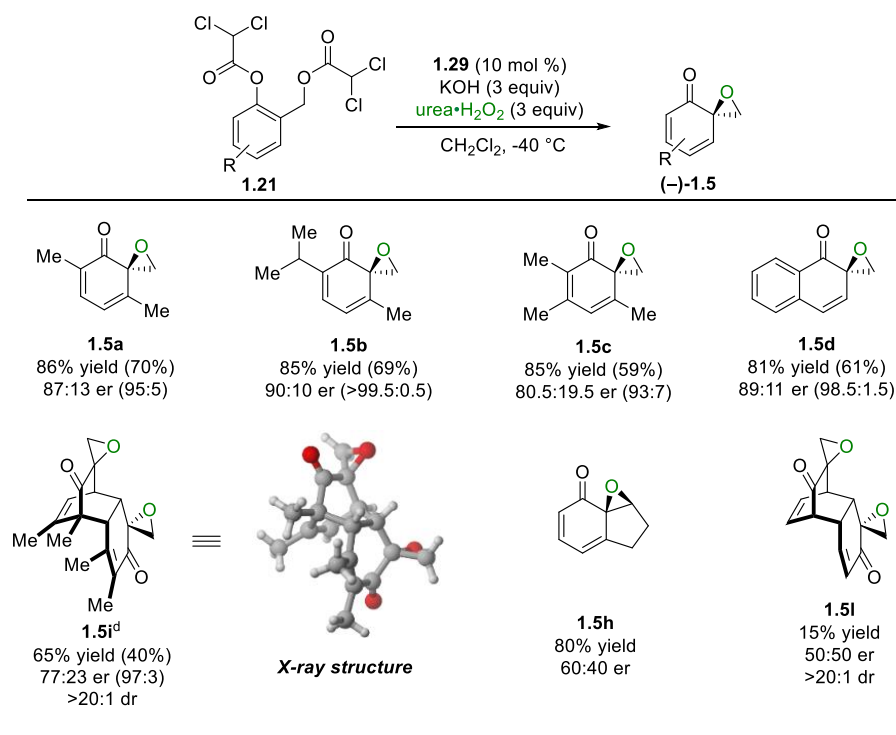
[a]Reactions were performed using **1.21** (0.50 mmol), QN-2 (10 mol%), KOH (1.5 mmol), UHP (1.5 mmol), [**1.21**] = 0.05 M in CH₂Cl₂, −40 °C. [b]er was determined by chiral HPLC. [c]Values in parentheses represent recrystallized yields and enantiomeric ratios. [d]20 mol% **1.29**.

1.9 Mechanistic Insights

An evaluation of the reaction mechanism was initiated by comparing the stereochemical

outcome of the H₂O₂-mediated oxidative dearomatization of **1.4g** to that when NaIO₄ was

employed (Scheme 1-14a). NaIO₄ oxidation proceeded with stereoretention (**1.32**), while Weitz−Scheffer epoxidation[21] of the planar QM intermediate proceeded with highly diastereoselective inversion at the benzylic position (**1.5g**). Based upon this observation, we propose the initial deacylation of the phenolic dichloroacetate **1.21a** to afford phenoxide **1.33** followed by formation of *o*QM **1.15a** via elimination of the benzylic dichloroacetate. Conjugate addition by the hydroperoxide affords rearomatized phenoxide **1.34** that attacks the hydroperoxide to give dearomatized epoxide (**−)-1.5a** (Scheme 1-14b).

Scheme 1-14. Mechanistic Insights and Proposed Mechanism
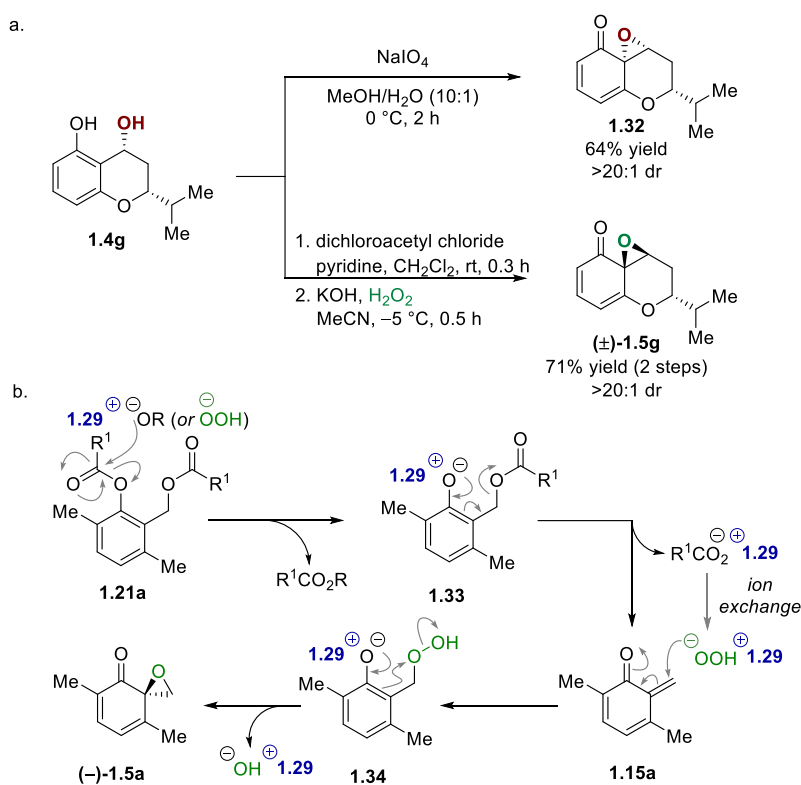
1.10 DFT-Optimized Transition States

The unique and critical role of PTC **1.29** in both QM generation and stereoselective epoxide formation is evident in this mechanism. To further understand the catalyst's role in promoting the observed stereoselectivity, the transition state of the epoxidation step between **1.29** and **1.15a** was

studied computationally using density functional theory (DFT) calculations at the level of M062X[43] approximate functional and a compound Pople basis set.[44] Upon analysis of the calculated major stereoisomer (Figure 1-3a), several important interactions emerge: (a) the hydroxide nucleofuge is stabilized by two significant hydrogen bonding interactions derived from the Ar–H on the electron-deficient $(CF_3)_2Ar$ ring (H$\cdots$O distance 2.06 Å) and the benzylic C–H in close proximity to the ammonium cation (H$\cdots$O distance 2.16 Å) as well as a weaker hydrogen bonding interaction from the C–H bond on the bridged quinuclidine (H$\cdots$O distance 2.67 Å);[45] (b) the catalyst −OH group forms a strong hydrogen bond (H$\cdots$O distance 1.83 Å) to the phenoxide of the substrate, orienting the hydroperoxide in close proximity to the three stabilizing hydrogen bond donors; and (c) the C-2 methyl group on **1.15a** experiences an attractive CH−π interaction with the quinoline ring (atom to plane distance of 2.50 Å).[46] The apparent synergistic role of the $R_3N^+CH_2$− cationic subunits and the $(F_3C)_2Ar$–H is to create an unconventional trifurcated oxyanion hole to stabilize and accommodate the nascent alkoxide during O−O scission (*vide infra*). Such interactions for nucleofuge stabilization have been previously identified via DFT calculations but arise principally or solely from the $R_3N^+CH_2$− cationic subunit.[38] We were interested in comparing the stereodetermining catalyst–substrate interactions leading to the formation of the minor enantiomer to those leading to major isomer formation. These interactions were calculated to be similar to the major isomer (Figure 1-3b), with the distinction being a ~90° rotation of the substrate's aromatic ring to afford the opposite epoxide facial selectivity. The transition state leading to minor enantiomer formation was calculated to be 0.84 kcal/mol greater in energy than the major enantiomer. This higher energy transition state can be explained by (a) the loss of the attractive CH−π interaction between the substrate C-2 methyl group and the quinoline ring and (b) the observed lengthening of the hydrogen bonding interaction between the hydroxide nucleofuge

and the benzylic C−H (2.36 Å versus 2.16 Å), mitigating, in part, the stabilization of the leaving group. The increased transition state barrier due to the loss of the methyl CH−π interaction is in accord with experimental evidence demonstrating reduced enantiocontrol with lack of alkyl substitution.

Figure 1-3. DFT-Optimized Stereodetermining Transition States of **1.29** and **1.15a**
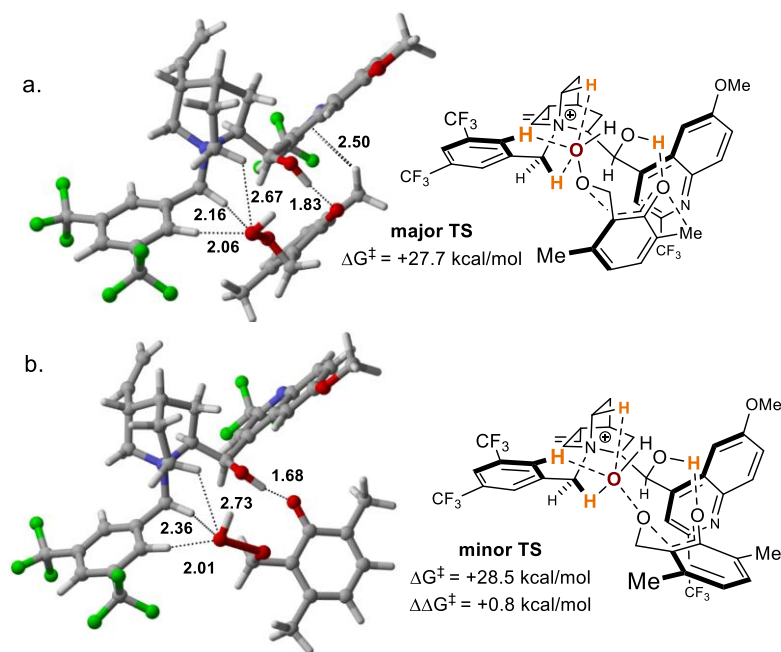
1.11 One-Pot Enantioselective Dearomatization/Acyl Nitroso Diels-Adler Cycloaddition

o-Spiroepoxydienones (**1.5**) are highly reactive species that readily participate in Michael additions,[47] dihydroxylation,[47] epoxide openings,[48] and cycloadditions.[49] To further highlight the synthetic utility of this reaction in complexity building transformations, enantioenriched spiroepoxydienone generation was merged with subsequent base promoted acyl-nitroso generation from **1.35**[50] to realize a one pot oxidative dearomatization/acyl-nitroso Diels−Alder cycloaddition. The derived tricyclic oxazinanone **1.36** (Scheme 1-15) was obtained with excellent enantio- and

diasteroselectivity after a single recrystallization. These tricyclic oxazinanones can be further elaborated to afford highly substituted cyclohexanone rings in a short number of synthetic steps.[20]

Scheme 1-15. One-Pot Enantioselective Oxidative Dearomatization/Acyl-Nitroso Diels-Alder Cycloaddition
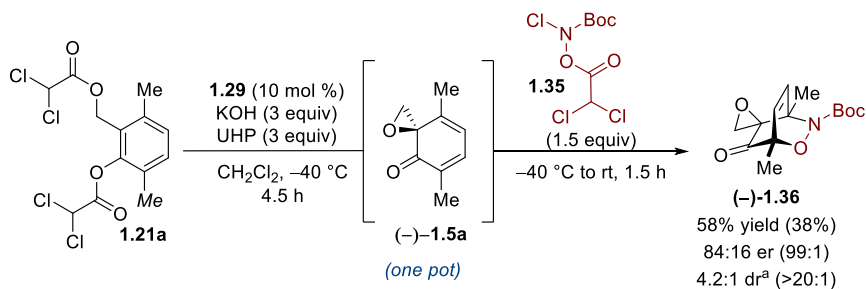
[a]Isolated as equilibrating mixture of diasteromers.[21] [b]Values in parentheses represent recrystallized yield, enantiomeric ratio, and diastereomeric ratio.

1.12 Conclusion

We have developed an enantioselective oxidative dearomatization of salicyl alcohols using H_2O_2 to afford stable, dearomatized *ortho*-spiroepoxydienones employing a base promoted in situ QM activation technique. By using a new cinchona alkaloid-derived phase-transfer catalyst, the reaction allows for access to enantioenriched *o*-spiroepoxydienones that were previously inaccessible via the Adler−Becker oxidation. DFT calculations revealed a highly organized transition state involving a unique tripartite stabilization of the hydroxide leaving group leading to the observed facial selectivity. The synthetic utility of this method for rapid complexity generation has been demonstrated by preparing an enantioenriched tricyclic oxazinanone. This chemistry demonstrates the potential for complementary enantioselective dearomative processes involving quinone methides, and our laboratory is currently exploring these possibilities.

1.13 Experimental Details

General 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 staining in an aqueous ceric ammonium molybdate (CAM) or potassium permanganate ($KMnO_4$) solution, followed by gentle heating. Flash chromatography was performed under positive nitrogen pressure using Siliaflash-P60 silica gel (40-63 μm) purchased from Silicycle. Yields and enantioselectivities are reported for a specific experiment and may differ slightly from those found in figures, which are averages of at least two experiments.

Instrumentation

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on either a Bruker model DRX 400, 500, or 600 (cryoprobe equipped) spectrometer. The spectra were calibrated using residual solvent resonances: ^{1}H NMR ($CDCl_3$ at 7.28 ppm, $(CD_3)_2SO$ at 2.50 ppm) and ^{13}C NMR ($CDCl_3$ at 77.0 ppm, $(CD_3)_2SO$ at 39.51 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, qt = quintet, sept = septet, and m = multiplet), coupling constants (Hz) and integration. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 1000 digital polarimeter. High resolution mass spectrometry (HRMS) was performed using a Thermo Scientific Q Exactive HF-X mass spectrometer with direct infusion in the positive ion mode. Samples were prepared in HPLC grade methanol. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier Transform Infrared Spectrometer. Enantiomeric ratios of enantioenriched products were determined by chiral HPLC analysis using

a chiral stationary phase (Daicel CHIRALPAK IC) on a Perkin Elmer Flexar® HPLC system. Yields refers to isolated yield of pure material unless otherwise noted.

Materials

Solvents were not dried prior to use unless specified as "anhydrous." Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (PhMe), diethyl ether (Et_2O) were dried by passage through a column of neutral alumina under nitrogen prior to use. All chemicals were purchased from either Fisher Scientific, Sigma-Aldrich, Alfa-Aesar, or Matrix Scientific and used as received. 2-(Hydroxymethyl)phenol (**1.4l**) and 6-hydroxy-3,4-dihydronaphthalen-1(2H)-one were purchased from Acros Organics and used as received. 1-(Bromomethyl)-3,5-bis(trifluoromethyl)benzene and catalyst **1.24** were purchased from Sigma-Aldrich and used as received. 2-(Hydroxymethyl)-6-isopropyl-3-methylphenol (**1.4b**)[51], 2-(hydroxymethyl)-6-methylphenol (**1.4j**)[52], 3,6-difluoro-2-(hydroxymethyl)phenol (**1.4e**)[52], 2-(hydroxymethyl)naphthalen-1-ol (**1.4d**)[53], 2,3-dihydro-1H-indene-1,7-diol (**1.4h**)[54], quinine N-oxide (**1.31**)[55], *tert*-butyl hydroxycarbamate[56], and *tert*-butyl hypochlorite[57] were prepared according to literature procedures. Catalysts **1.25**[58], **1.26**[59], **1.27**[60], and **1.28**[61] were all prepared according to literature procedures.

Experimental Procedures

Preparation of Salicyl Alcohols:

General Procedure A for Preparation of Salicyl Alcohols 1.4:
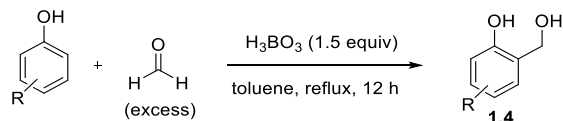
Hydroxymethylation of phenols was accomplished using a modified literature procedure.[51] To a flame-dried round-bottomed flask equipped with a stir bar was added the starting phenol (1.0 equiv), toluene ($[phenol]_0 = 0.2$ M), boric acid (1.5 equiv), and paraformaldehyde (1.25 equiv). The flask was equipped with a Dean-Stark condenser and heated at reflux until complete consumption of the phenol was observed as indicated by TLC. Every 4 h, a fresh portion of paraformaldehyde (0.25 equiv) was added. After the reaction completion, the reaction was cooled to room temperature, excess paraformaldehyde was removed by filtration, and the filtrate was concentrated. Water (1 mL/ mmol) was added to the yellow residue and the mixture was stirred vigorously for 1 h to ensure hydrolysis of the borate of the salicyl alcohol. The product was extracted thrice with ethyl acetate (3 x 40 mL/mmol) and the combined organic extracts were washed with water and then brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel to afford the desired alcohol **1.4**.
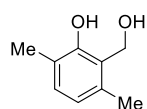
2-(hydroxymethyl)-3,6-dimethylphenol (1.4a): The title compound was prepared according to the General Procedure A using 2,5-dimethylphenol (2.00 g, 16.4 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 1.45 g (58%) of the title compound as a white solid. Analytical data: **^{1}H NMR** (400 MHz, (CD$_3$)$_2$SO) δ 8.84 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 4.65 (s, 2H), 2.19 (s, 3H), 2.10 (s, 3H); **^{13}C NMR** (151 MHz, (CD$_3$)$_2$SO) δ 154.1, 134.2, 128.9, 124.5, 122.1, 120.8,

57.5, 18.8, 16.2; **mp** 63-64 °C; **IR** (thin film, cm^{-1}): 3427, 2923; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.48; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_{12}$NaO$_2$: ([M+Na]): 175.0735, Found: 175.0730.
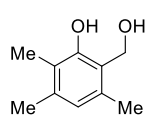
2-(hydroxymethyl)-3,5,6-trimethylphenol (1.4c): The title compound was prepared according to the General Procedure A using 2,3,5-trimethylphenol (3.50 g, 25.7 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 1.70 g (40%) of the title compound as a white solid. Spectroscopic properties were consistent to those previously reported.[48] Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.72 (s, 1H), 6.56 (s, 1H), 4.93 (d, *J* = 5.1 Hz, 2H), 2.24 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H).
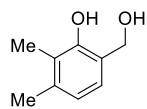
6-(hydroxymethyl)-2,3-dimethylphenol (1.4i): The title compound was prepared according the General Procedure A using 2,3-dimethylphenol (2.00 g, 16.4 mmol). The crude material was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 2.00 g (80%) of the title compound as a white solid. Analytical data: **^{1}H NMR** (400 MHz, (CD$_3$)$_2$SO) δ 8.32 (s, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 5.32 (s, 1H), 4.53 (s, 2H), 2.17 (s, 3H), 2.06 (s, 3H); **^{13}C NMR** (151 MHz, (CD$_3$)$_2$SO) δ 152.5, 135.6, 125.4, 124.1, 122.8, 120.6, 60.2, 19.9, 11.8; **mp** 64-65 °C; **IR** (thin film, cm^{-1}): 3366; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.42; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_{12}$NaO$_2$: ([M+Na]): 175.0735, Found: 175.0730.
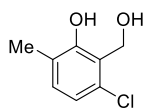
3-chloro-2-(hydroxymethyl)-6-methylphenol (1.4f): The title compound was prepared according to the General Procedure A using 5-chloro-3-methylphenol (3.00 g, 21.0 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 1.45 g (39%) of the title compound as a white solid. Analytical data: **^{1}H**

NMR (400 MHz, CDCl$_3$) δ 8.27 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 5.11 (d, J = 4.2 Hz, 2H), 2.57 (t, J = 4 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 155.5, 130.6, 129.4, 124.5, 120.8, 120.4, 62.0, 15.5; **mp** 49-50 °C; **IR** (thin film, cm^{-1}): 3336, 2926, 1466; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.40; **HRMS** (ESI$^+$) Calcd. for C$_8$H$_9$ClNaO$_2$: ([M+Na]): 195.0184, Found: 195.0184.

General Procedure B for Preparation of Salicyl Alcohols 1.4:
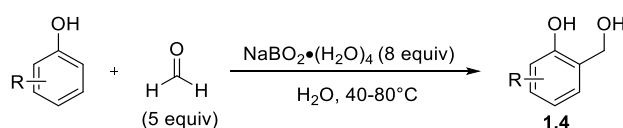
Hydroxymethylation of phenols was accomplished using a known literature procedure.[52] To a round-bottomed flask equipped with a magnetic stir bar was added the starting phenol (1.0 equiv), water ([phenol]$_0$ = 0.2 M), sodium metaborate tetrahydrate (8.0 equiv), and 37% aqueous formaldehyde (5.0 equiv). The reaction was stirred at 50 °C until disappearance of the starting phenol was observed by TLC analysis (usually 12-16 h). After completion, the reaction was cooled to room temperature and acidified with aqueous HCl (3 M) to pH of 4. The product was extracted thrice with ethyl acetate and the combined organic extracts were washed with water and then brine. The organic layer was dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel to afford the desired alcohol **1.4**.
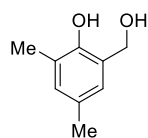
2-(hydroxymethyl)-4,6-dimethylphenol (1.4k): The title compound was prepared according to the General Procedure B using 2,4-dimethylphenol (3.00g, 24.6 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 2.60 g (70%) of the title compound as a white solid. Spectroscopic properties were

consistent with those previously reported.[62] Analytical data: **¹H NMR** (400 MHz, (CD₃)₂SO) δ 7.26 (s, 1H), 6.92 (s, 1H), 6.68 (s, 1H), 4.78 (s, 2H), 2.25 (s, 3H), 2.24 (s, 3H).
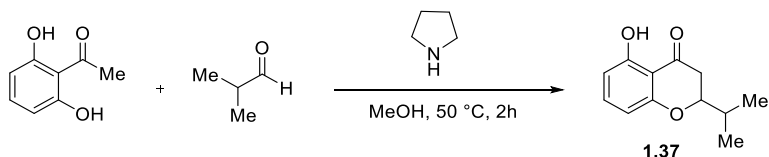
(±)-5-hydroxy-2-isopropylchroman-4-one (1.37): To a flame-dried round-bottomed flask equipped with a stir bar was added 1-(2,6-dihydroxyphenyl)ethan-1-one (1.0 g, 6.57 mmol) and anhydrous methanol (20 mL). Isobutyrlaldehyde (0.66 ml, 7.23 mmol) was added followed by pyrrolidine (0.27 ml, 3.29 mmol). The reaction was heated at 50 °C for 2 h. Excess methanol was removed *in vacuo* and the residue was dissolved in ethyl acetate and washed once with water (10 mL) and brine in a separatory funnel. The organic layer was dried with Na₂SO₄, filtered, and concentrated to afford a yellow oil which was purified by column chromatography on silica gel (30/70 ethyl acetate/hexanes) to afford 1.00 g (74% yield) of the title compound as a slightly yellow oil. **¹H NMR**: (600 MHz, CDCl₃): δ 11.71 (s, 1H), 7.36 (t, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 4.18 (ddd, *J* = 13.3, 5.9, 2.7 Hz, 1H), 2.79 (dd, *J* = 16.9, 13.3 Hz, 1H), 2.65 (dd, J = 16.9, 2.7 Hz, 1H), 2.06 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H); **¹³C NMR**: (151 MHz, CDCl₃): δ 199.1, 161.9, 138.1, 108.9, 108.1, 107.3, 82.0, 39.3, 32.0, 17.8, 17.8; **IR** (thin film, cm⁻¹): 2965, 1650, 1462, 1359, 1252, 1080; **TLC** (30/70 ethyl acetate/hexanes): R*f* = 0.68; **HRMS** (ESI⁺) Calcd. for C₁₂H₁₄NaO₃: ([M+Na]): 229.0841, Found: 229.0832.
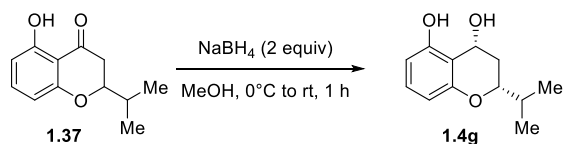
(±)-(2*R*,4*R*)-2-isopropylchromane-4,5-diol (1.4g): To a flame-dried flask was added **1.37** (737 mg, 3.57 mmol) and subsequently dissolved in 30 mL of anhydrous MeOH. The solution was cooled to 0 °C and NaBH$_4$ (270 mg, 7.15 mmol) was added in portions. The reaction was stirred for 10 min at 0 °C and then left to stir for 50 min at room temperature. The solution was cooled back to 0 °C and cold water was added to quench the reaction. The methanol was removed *in vacuo* and the residue was retaken up in ethyl acetate, washed with water and brine. The organic layer was dried using Na$_2$SO$_4$, filtered, then concentrated to afford **1.4g** as a colorless oil. A diastereomer ratio of 7:1 was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 3.85 (major diastereomer) and δ 3.76 (minor diastereomer). The oil was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 601 mg (81% yield) of the major diastereomer as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.81 (s, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.44 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.41 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.20 (dt, *J* = 10.6, 7.1 Hz, 1H), 3.83 (ddd, *J* = 11.7, 5.5, 1.3 Hz, 1H), 2.63 (d, *J* = 7.6 Hz, 1H), 2.36 – 2.27 (m, 1H), 2.02 – 1.90 (m, 1H), 1.86 – 1.76 (m, 1H), 1.04 (dd, J = 12.1, 6.8 Hz, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 156.5, 155.9, 128.7, 111.0, 108.6, 108.3, 79.3, 66.4, 34.0, 32.2, 17.9, 17.8; **mp** >300 °C; **IR** (thin film, cm^{-1}): 2957, 1467; **TLC** (30/70 Ethyl acetate/hexanes): R$_f$ = 0.46; **HRMS** (ESI$^+$) Calcd. for C$_{12}$H$_{16}$NaO$_3$: ([M+Na]): 231.0997, Found: 231.1000.

Optimization of Acetate Activation Group
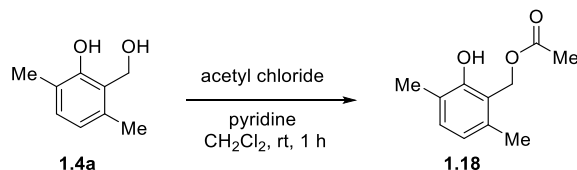
2-hydroxy-3,6-dimethylbenzyl acetate (1.18): To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added **1.4a** (200 mg, 1.31 mmol) and anhydrous CH_2Cl_2 (10 mL). Pyridine (0.120 mL, 1.48 mmol) was added to the solution and the reaction was stirred for 5 min after which time acetyl chloride (1.19 ml, 1.67 mmol) was added dropwise. The reaction was stirred for 1 h and then the solution was filtered through a plug of silica gel with CH_2Cl_2 as the eluent. The filtrate was concentrated and the oil was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 56.2 mg (40%) of acetate **1.18** as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 8.03 (s, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 5.21 (s, 2H), 2.39 (s, 3H), 2.25 (s, 3H), 2.12 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): 174.1, 154.2, 137.0, 131.6, 124.6, 121.8, 120.3, 60.4, 20.9, 19.1, 16.2; **IR** (thin film, cm^{-1}): 3306, 2924, 1714, 1283, 1242; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.64; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_{14}$NaO$_3$: ([M+Na]): 217.0841, Found: 217.0834.
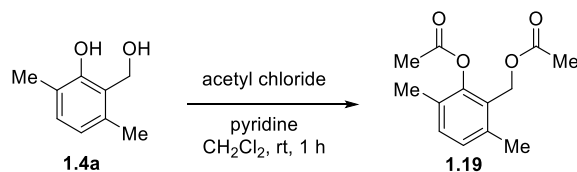
2-acetoxy-3,6-dimethylbenzyl acetate (1.19): To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added **1.4a** (200 mg, 1.31 mmol) and anhydrous CH_2Cl_2 (10 mL). Pyridine (0.240 mL, 2.97 mmol) was added to the solution and the reaction was stirred for 5 min after which time acetyl chloride (0.237 mL, 3.33 mmol) was added dropwise. The reaction was

stirred for 1 h and then the solution was filtered through a plug of silica gel with CH_2Cl_2 as the eluent. The filtrate was concentrated, and the oil was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 239 mg (70%) of diacetate **1.19** as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.15 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 5.12 (s, 2H), 2.40 (s, 3H), 2.36 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): 170.8, 169.0, 148.8, 137.1, 131.1, 128.2, 128.0, 126.1, 58.3, 20.7, 20.4, 18.9, 16.0; **IR** (thin film, cm^{-1}): 2977, 1774, 1165; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.58; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{16}$NaO$_4$: ([M+Na]): 259.0946, Found: 259.0948.
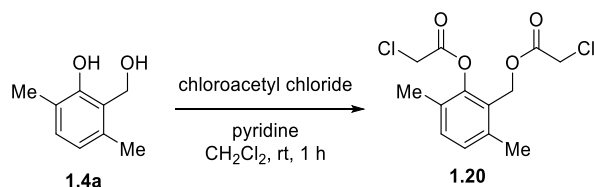
2-(2-chloroacetoxy)-3,6-dimethylbenzyl 2-chloroacetate (1.20): To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added **1.4a** (200 mg, 1.31 mmol) and anhydrous CH_2Cl_2 (10 mL). Pyridine (0.240 mL, 2.97 mmol) was added to the solution and the reaction was stirred for 5 min after which time chloroacetyl chloride (0.241 mL, 3.02 mmol) was added dropwise. The reaction was stirred for 30 min and then the solution was filtered through a plug of silica with CH_2Cl_2. The filtrate was concentrated, and the oil was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 356 mg (89%) of **1.20** as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.18 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 5.25 (s, 2H), 4.38 (s, 2H), 4.04 (s, 2H), 2.44 (s, 3H), 2.16 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): 167.1, 165.6, 148.4, 137.4, 131.7, 128.5, 128.1, 125.2, 59.7, 40.7, 40.5, 18.9, 15.9; **mp** 69-70; **IR** (thin film, cm^{-1}): 2961, 1757, 1171; **TLC** (20/80 ethyl acetate/hexanes): R$_f$ = 0.33; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{14}$Cl$_2$NaO$_4$: ([M+Na]): 327.0167, Found: 327.0161.
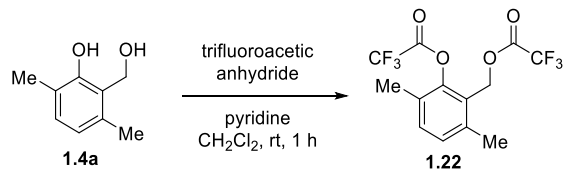
3,6-dimethyl-2-((2,2,2-trifluoroacetoxy)methyl)phenyl 2,2,2-trifluoroacetate (1.22): To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added **1.4a** (200 mg, 1.31 mmol) and anhydrous CH_2Cl_2 (10 mL). Pyridine (0.240 mL, 2.97 mmol) was added to the solution and the reaction was stirred for 5 min after which time trifluoroacetic anhydride (0.423 mL, 3.02 mmol) was added dropwise over the course of 1 min. The reaction was stirred for 30 min and then the solution was filtered through a plug of silica with CH_2Cl_2. The filtrate was concentrated and the oil was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 335 mg (74%) of **1.22** as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.27 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 5.40 (s, 2H), 2.47 (s, 3H), 2.18 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): 157.2 (q, J = 42.9 Hz), 155.1 (q, J = 43.5 Hz), 147.5, 137.9, 132.8, 129.6, 128.0, 123.5, 114.6 (q, J = 285.5 Hz), 114.3 (q, J = 285.6 Hz), 61.5, 18.9, 15.7.; **IR** (thin film, cm^{-1}): 2993, 1767, 1294, 1166; **TLC** (20/80 ethyl acetate/hexanes): R$_f$ = 0.74; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{10}$F$_6$NaO$_4$: ([M+Na]): 367.0381, Found: 327.0372.

30

Preparation of Bis(dichloroacetates) 1.21:
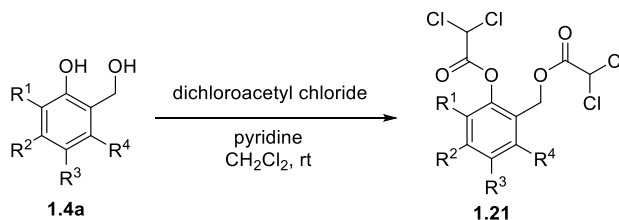
General Procedure D for Bis(dichloroacetate) Activation of Salicyl Alcohols: To a flame-dried round-bottomed flask was added the starting salicyl alcohol **1.4** (1.0 equiv) and anhydrous CH_2Cl_2 ([salicyl alcohol]$_0$ = 0.4 M). Pyridine (2.0 equiv) was added and the solution was stirred for 5 min, after which time dichloroacetyl chloride (2.2 equiv) was added dropwise. Once the acid chloride was fully added, the reaction mixture was stirred at room temperature for 20 min. The solution was directly filtered through a plug of silica gel with CH_2Cl_2 as the eluent. The filtrate was concentrated to afford the desired bis(dichloroacetate) product. These compounds were stored at −20 °C until used.

Note 1: For larger quantities of starting material (>500 mg), a noticeable exotherm is present upon addition of dichloroacetyl chloride. In these cases, the reaction should be cooled to 0 °C and left to stir at this temperature for 10 min after addition of the dichloroacetyl chloride then warmed to room temperature and allowed to stir for 20 min. This cooling does not negatively affect the outcome of the reaction or the purity of the product.

Note 2: When conducting the silica plug, the authors noticed a yellow/orange band would appear. For best purity, it was optimal to ensure that this band did not reach the collecting flask.

Note 3: When obtaining the HRMS data for the bis(dichloroacetate) compounds, two significant peaks appeared. One corresponding to [M+Na] and the other to the mass of the corresponding quinone methide derived from each bis(dichloroacetate).
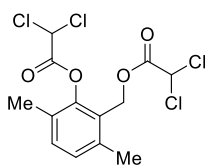
2-(2,2-dichloroacetoxy)-3,6-dimethylbenzyl 2,2-dichloroacetate (1.21a): The title compound was prepared according to General Procedure D using **1.4a** (200 mg, 1.31 mmol) to afford **1.21a** (477 mg, 1.28 mmol, 97% yield) as a white solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.23 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H), 5.92 (s, 1H), 5.32 (s, 2H), 2.45 (s, 3H), 2.20 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 164.3, 162.3, 148.0, 137.8, 132.3, 129.1, 128.2, 124.4, 64.0, 64.0, 61.1, 18.9, 15.8; **mp** 64-65 °C; **IR** (thin film, cm^{-1}): 2976, 1768, 1465, 1165; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.68; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{12}$Cl$_4$NaO$_4$: ([M+Na]): 394.9387, Found: 394.9386.
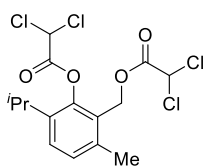
2-(2,2-dichloroacetoxy)-3-isopropyl-6-methylbenzyl 2,2-dichloroacetate (1.21b): The title compound was prepared according to General Procedure D using **1.4b** (200 mg, 1.11 mmol) to afford **1.21b** (435 mg, 1.08 mmol, 97% yield) as a colorless oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.27 (s, 1H), 5.93 (s, 1H), 5.31 (s, 2H), 2.96 (m, *J* = 6.8 Hz, 1H), 2.45 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 164.3, 163.0, 146.7, 138.5, 137.6, 129.5, 128.0, 124.5, 64.0, 64.0 61.2, 26.9, 18.9; **IR** (thin film, cm^{-1}): 1768; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.75; **HRMS** (ESI$^+$) Calcd. for C$_{15}$H$_{16}$Cl$_4$NaO$_4$: ([M+Na]): 422.9701, Found: 422.9697.
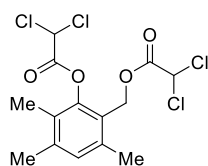
2-(2,2-dichloroacetoxy)-3,4,6-trimethylbenzyl 2,2-dichloroacetate (1.21c): The title compound was prepared according to General Procedure D using **1.4c** (200 mg, 1.20 mmol) to afford **1.21c** (434 mg, 1.12 mmol, 93% yield) as a

white solid. Analytical data: ^{1}**H NMR**: (600 MHz, CDCl$_3$): δ 7.04 (s, 1H), 6.25 (s, 1H), 5.9 (s, 1H), 5.29 (s, 2H), 2.41 (s, 3H), 2.31 (s, 3H), 2.08 (s, 3H). ^{13}**C NMR**: (151 MHz, CDCl$_3$): 164.4, 162.5, 147.9, 140.1, 136.8, 130.7, 126.8, 121.7, 64.1, 64.1, 61.3, 20.1, 18.8, 12.2; **mp** 80-81 °C; **IR** (thin film, cm^{-1}): 3013, 1766, 1156; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.73; **HRMS** (ESI$^+$) Calcd. for C$_{14}$H$_{14}$Cl$_4$NaO$_4$: ([M+Na]): 408.9544, Found: 408.9542.
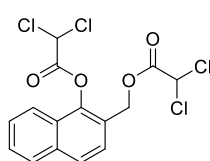
2-((2,2-dichloroacetoxy)methyl)naphthalen-1-yl   2,2-dichloroacetate (1.21d): The title compound was prepared according to General Procedure D using **1.4d** (300 mg, 1.72 mmol) to afford **1.21d** (650 mg, 1.72 mmol, 95% yield) as a white solid. Analytical data: ^{1}**H NMR**: (500 MHz, CDCl$_3$): δ 8.06 – 7.75 (m, 3H), 7.73 – 7.49 (m, 3H), 6.39 (s, 1H), 5.97 (s, 1H), 5.45 (s, 2H); ^{13}**C NMR**: (126 MHz, CDCl$_3$): δ 164.3, 162.7, 144.5, 134.9, 128.2, 127.7, 127.6, 127.6, 126.5, 126.2, 122.8, 120.8, 64.0, 64.0, 63.9; **mp** 81-82 °C; **IR** (thin film, cm^{-1}): 2359, 2341, 1768, 1168; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.65; **HRMS** (ESI$^+$) Calcd. for C$_{15}$H$_{10}$Cl$_4$NaO$_4$: ([M+Na]): 416.9231, Found: 416.9228.

2-(2,2-dichloroacetoxy)-3,6-difluorobenzyl 2,2-dichloroacetate (1.21e): The title compound was prepared according to General Procedure D using **1.4e** (500 mg, 3.12 mmol) to afford **1.21e** (1.17 g, 3.05 mmol, 98% yield) as a colorless oil. Analytical data: ^{1}**H NMR**: (600 MHz, CDCl$_3$): δ 7.34 (dd, J = 9.5, 6.3 Hz, 1H), 7.09 (dd, J = 8.8, 6.0 Hz, 1H), 6.22 (d, J = 0.5 Hz, 1H), 6.02 (d, J = 0.5 Hz, 1H), 5.35 (s, 2H); ^{13}**C NMR**: (151 MHz, CDCl$_3$): δ 164.1, 161.6, 155.9 (dd, J = 248.9, 2.8 Hz), 149.9 (dd, J = 249.0, 3.5 Hz), 137.9 (dd, J = 14.9, 11.3 Hz), 121.5 (dd, J = 16.8, 6.5 Hz), 117.9 (dd, J = 21.5, 4.5 Hz), 111.2 (d, J = 26.8 Hz), 63.8, 63.3, 61.6 (d, J = 2.0 Hz); ^{19}**F NMR:** (376 MHz, CDCl$_3$): -119.0 (d, J = 16.1 Hz),

-131.7 (d, J = 16.0 Hz); **IR** (thin film, cm^{-1}): 3014, 2360, 1765, 1510, 1159; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.56; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_6$Cl$_4$F$_2$NaO$_4$: ([M+Na]): 402.8886, Found: 402.8885.

3-chloro-2-((2,2-dichloroacetoxy)methyl)-6-methylphenyl 2,2- dichloro acetate (1.21f): The title compound was prepared according to General Procedure D using **1.4f** (200 mg, 1.16 mmol) to afford **1.21f** (420 mg, 1.06 mmol, 92% yield) as a white solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.35 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 6.25 (s, 1H), 5.93 (s, 1H), 5.42 (s, 2H), 2.22 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 164.3, 161.9, 148.5, 133.9, 133.1, 130.1, 128.3, 124.6, 63.9, 63.8, 61.0, 15.9; **mp** 65-66 °C; **IR** (thin film, cm^{-1}): 3518, 3013, 1769, 1467, 1294, 1177; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.65; **HRMS** (ESI$^+$) Calcd. for C$_{12}$H$_9$Cl$_5$NaO$_4$: ([M+Na]): 414.8836, Found: 414.8838.
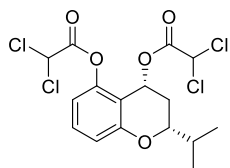
(±)-(2R,4R)-2-isopropylchromane-4,5-diyl bis(2,2-dichloroacetate) (8g): The title compound was prepared according to General Procedure D with the following modification: the solution was cooled to 0 °C before addition of acetyl chloride and left to stir for 10 min before warming up to room temperature using **1g** (100 mg, 0.480 mmol) to afford **8g** (197 mg, 0.458 mmol, 95% yield) as a colorless oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.33 (t, J = 8.3 Hz, 1H), 6.89 (dd, J= 8.1, 1.0 Hz, 1H), 6.80 (dd, J = 8.1, 1.0 Hz, 1H), 6.21 (t, J = 6.7 Hz, 1H), 6.13 (s, 1H), 5.95 (s, 1H), 3.86 (td, J = 8.1, 2.9 Hz, 1H), 2.51 (ddd, J = 14.4, 6.9, 3.0 Hz, 1H), 2.16 – 2.07 (m, 2H), 1.07 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 164.1, 162.5, 157.0, 149.3, 130.7, 116.2, 113.4,

112.1, 79.3, 66.9, 64.2, 64.1, 30.8, 29.3, 18.5, 18.5; **IR** (thin film, cm^{-1}): 2966, 1766, 1469; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.67; **HRMS** (ESI$^+$) Calcd. for C$_{16}$H$_{16}$Cl$_4$NaO$_5$: ([M+Na]): 450.9649, Found: 450.9641.
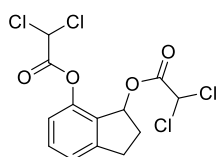
(±)-2,3-dihydro-1H-indene-1,7-diyl bis(2,2-dichloroacetate) (1.21h): The title compound was prepared according to General Procedure D using **1.4h** (400 mg, 2.66 mmol) to afford **1.21h** (917 mg, 2.46 mmol, 93% yield) as a yellow solid. Analytical data: **¹H NMR**: (600 MHz, CDCl$_3$): δ 7.45 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.10 (dd, J = 8.1, 0.9 Hz, 1H), 6.42 (dd, J = 7.1, 2.2 Hz, 1H), 6.21 (s, 1H), 5.91 (s, 1H), 3.26 (dt, J = 16.1, 7.9 Hz, 1H), 3.02 (ddd, J = 16.5, 9.0, 3.2 Hz, 1H), 2.61 (ddt, J = 14.6, 9.0, 7.3 Hz, 1H), 2.24 (dddd, J = 14.8, 8.4, 3.3, 2.3 Hz, 1H); **¹³C NMR**: (151 MHz, CDCl$_3$): δ 164.1, 162.6, 148.3, 147.1, 131.6, 130.6, 123.7, 119.5, 78.9, 64.3, 64.1, 31.9, 30.6; **mp** 72-73 °C; **IR** (thin film, cm^{-1}): 1761, 1472, 1295, 1232, 1171; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.67; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{10}$Cl$_4$NaO$_4$: ([M+Na]): 392.9231, Found: 392.9225.
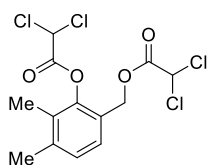
2-(2,2-dichloroacetoxy)-3,4-dimethylbenzyl 2,2-dichloroacetate (1.21i): The title compound was prepared according to General Procedure D using **1.4i** (400 mg, 2.63 mmol) to afford **1.21i** (915 mg, 2.45 mmol, 93% yield) as a white solid. Analytical data: **¹H NMR**: (600 MHz, CDCl$_3$): δ 7.25 (d, J = 7.7 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 6.25 (s, 1H), 5.92 (s, 1H), 5.23 (s, 2H), 2.35 (s, 3H), 2.13 (s, 3H); **¹³C NMR**: (151 MHz, CDCl$_3$): δ 164.2, 162.4, 147.2, 140.6, 129.6, 128.5, 128.2, 123.5, 64.6, 64.0, 64.0, 20.2, 12.3; **mp** 70-72 °C; **IR** (thin film, cm^{-1}): 2993, 1767, 1294, 1166; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.75; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{12}$Cl$_4$NaO$_4$: ([M+Na]): 394.9387, Found: 394.9386.
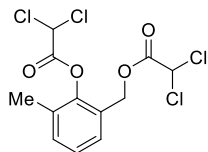
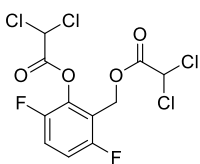**2-(2,2-dichloroacetoxy)-3-methylbenzyl 2,2-dichloroacetate (1.21j):** The title compound was prepared according to General Procedure D using **1.4j** (200 mg, 1.45 mmol) to afford **1.21j** (511 mg, 1.42 mmol, 98% yield) as a white solid.

Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.34 (t, J = 7.2 Hz, 2H), 7.27 (t, J = 7.8 Hz, 1H), 6.25 (s, 1H), 5.94 (s, 1H), 5.26 (s, 2H), 2.25 (s, 3H).**^{13}C NMR**: (151 MHz, CDCl$_3$): δ 164.2, 162.2, 147.2, 132.7, 131.1, 128.8, 127.2, 126.3, 64.3, 64.0, 64.0, 15.9; **mp** 70-71 °C; **IR** (thin film, cm$^-$^{1}): 3016, 1766, 1169; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.67; **HRMS** (ESI$^+$) Calcd. for C$_{12}$H$_{10}$Cl$_4$NaO$_4$: ([M+Na]): 380.9231, Found: 380.9229.

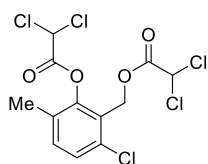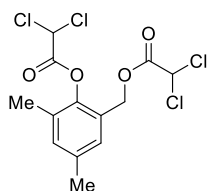**2-(2,2-dichloroacetoxy)-3,5-dimethylbenzyl 2,2-dichloroacetate (1.21k):** The title compound was prepared according to General Procedure D using **1.4k** (300 mg, 1.97 mmol) to afford **1.21k** (700 mg, 1.87 mmol, 95% yield) as a white solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.14 (s, 2H), 6.23 (s, 1H), 5.94 (s, 1H), 5.22 (s, 2H), 2.36 (s, 3H), 2.20 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 164.2, 162.4, 145.1, 137.0, 133.3, 130.6, 129.4, 125.8, 64.5, 64.0, 64.0, 20.8, 15.8; **mp** 76-77°C; **IR** (thin film, cm^{-1}): 1764; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.75; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{12}$Cl$_4$NaO$_4$: ([M+Na]): 394.9387, Found: 394.9385.
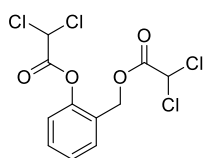
2-(2,2-dichloroacetoxy)benzyl 2,2-dichloroacetate (1.21l): The title compound was prepared according to General Procedure D using **1.4l** (500 mg, 4.03 mmol) to afford **1.21l** (1.34 g, 3.88 mmol, 96% yield) as a colorless oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.53 (d, J = 7.6 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 6.23 (s, 1H), 5.96 (s, 1H), 5.31 (s, 2H); **^{13}C**

NMR: (151 MHz, CDCl$_3$): δ 163.2, 162.6, 148.5, 131.1, 130.7, 127.3, 126.1, 121.9, 64.0, 64.0, 63.9; **IR** (thin film, cm^{-1}): 3014, 1767, 1297, 1179; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.64; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_8$Cl$_4$NaO$_4$: ([M+Na]): 366.9074, Found: 366.9071.

Racemic Reaction Scope for Preparation of *ortho*-Spiroepoxydienones 1.5
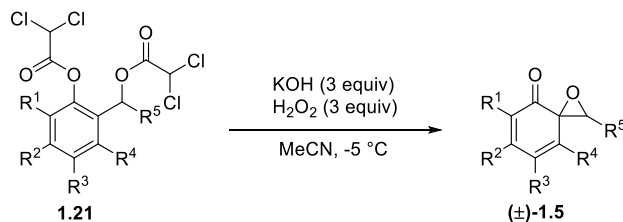
General Procedure E: To a vial equipped with a stir bar was added **1.21** (1.0 equiv) and MeCN

(4 mL/mmol). The resulting solution was cooled to −5 °C. Hydrogen peroxide (30% aqueous, 3.0

equiv) was added to the vial. The contents of the vial were added to a vigorously stirring, cooled

(−5 °C) slurry of powdered KOH (3.0 equiv) and MeCN ([**1.21**]$_0$ = 0.05 M after addition of the

bisdichloroacetate/H$_2$O$_2$) in a round-bottomed flask. The reaction was stirred at −5 °C until

complete disappearance of the starting material was observed by TLC analysis. The reaction was

stopped by decanting the contents of the flask into a separatory funnel and then diluting with ethyl

acetate and water. The organic layer was removed, and the aqueous layer was extracted with ethyl

acetate (3 x 40 mL/mmol). The organic layers were combined and washed once with a saturated

brine solution. The organic layer was removed, dried with Na$_2$SO$_4$, and concentrated. All products

were purified on silica gel via column chromatography to afford *ortho*-spiroepoxide **1.5**.

General Procedure F: To a vial equipped with a stir bar was added **1.21** (1.0 equiv) and MeCN

(4 mL/mmol). Hydrogen peroxide (30% aqueous, 3.0 equiv) was added to the vial. The contents

of the vial were added over the course of 1 h via syringe pump to a vigorously stirring, cooled (−5

°C) slurry of powdered KOH (3.0 equiv) and MeCN ([**1.21**]$_0$ = 0.05 M after addition of the

bisdichloroacetate/H$_2$O$_2$) in a round-bottomed flask. The reaction was stirred at −5 °C until

complete disappearance of the starting material was observed by TLC. The reaction was stopped

by decanting the contents of the flask into a separatory funnel and then diluting with ethyl acetate

and water. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 40 mL/mmol). The organic layers were combined and washed once with a saturated brine solution. The organic layer was removed, dried with Na_2SO_4, and concentrated. Residual solvent was removed by way of high vacuum. Et_2O (4 mL/mmol) was added to the residue which precipitated out the product. The vial was left at −20 °C for 30 min to complete precipitation. The solid was filtered and washed three times with cold Et_2O to afford desired spiroepoxide dimer **1.5**.

Note 1: For General Procedure F it is possible to observe and isolate small amounts (<20%) of the monomer before dimerization by forgoing addition of the Et_2O and immediately purifying the residue by column chromatography (30/70 ethyl acetate/hexanes). The monomer elutes very closely to the QM trapping product. For sake of yield and ease of isolation, the material was pushed to the dimer and yields given are of the dimer.

Note 2: For unsubstituted or halogenated substrates using procedure E the reaction was usually completed in <20 min whereas alkylated substrates were usually completed in 0.5-2 h.

Note 3: The monomer spiroepoxides often stained bright blue in a solution of cerium ammonium molybdate (CAM) upon gentle heating.
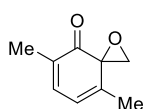
(±)-5,8-dimethyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5a): The title compound was prepared according to General Procedure E using **1.21a** (100 mg, 0.267 mmol). Flash chromatography (30/70 ethyl acetate/hexanes) afforded **(±)-1.5a** (30.5 mg, 0.203 mmol, 76% yield) as a bright yellow oil. Spectroscopic properties were consistent with those previously reported.[20] Analytical data: **¹H NMR**: (400 MHz, CDCl₃): δ 6.94 (d, J = 5.9 Hz, 1H), 6.26 (d, J = 5.6 Hz, 1H), 3.24 (d, J = 8.2 Hz, 1H), 3.17 (d, J = 8.2 Hz, 1H), 1.92 (s, 3H), 1.82 (s, 3H); **¹³C NMR**: (151 MHz, CDCl₃) 196.4, 144.7, 138.9, 131.8, 123.8, 58.7, 58.7, 16.1, 15.2.
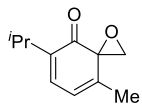
(±)-5-isopropyl-8-methyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5b): The title compound was prepared according to General Procedure E using **1.21b** (100 mg, 0.249 mmol). Flash chromatography (30/70 ethyl acetate/hexanes) afforded **(±)-1.5b** (33.4 mg, 0.187 mmol, 75% yield) as a bright yellow oil. Spectroscopic properties were consistent with those previously reported.[20] Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.89 (d, J = 6.4 Hz, 1H), 6.31 (d, J = 6.4 Hz, 1H), 3.23 (d, J = 8.2 Hz, 1H), 3.16 (d, J = 8.2 Hz, 1H), 2.94 (hept, J = 7.1, 1H), 1.82 (s, 3 H), 1.11-1.07 (m, 6H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 195.4, 144.4, 141.6, 135.6, 123.9, 59.0, 58.6, 26.1, 21.8, 21.6, 16.1.
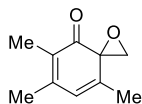
(±)-5,6,8-trimethyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5c): The title compound was prepared according to General Procedure E using **1.21c** (100 mg, 0.258 mmol) with the following modification: 4 equiv of KOH was used. Flash chromatography (30/70 ethyl acetate/hexanes) afforded **(±)-1.5c** (35.8 mg, 0.215 mmol, 85% yield) as a bright yellow solid. Spectral properties were consistent with those previously reported.[48] Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.20 (s, 1H), 3.20 (d, J = 8.2 Hz, 1H), 3.14 (d, J = 8.2 Hz, 1H), 2.09 (s, 3 H), 1.88 (s, 3 H), 1.80 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 194.8, 148.8, 142.6, 129.2, 128.0, 58.2, 57.6, 20.8, 16.0, 10.8.
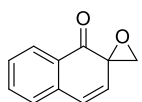
(±)-1H-spiro[naphthalene-2,2'-oxiran]-1-one (1.5d): The title compound was prepared according to General Procedure E using **1.21d** (100 mg, 0.254 mmol) to afford **(±)-1.5d** (28.3 mg, 0.166 mmol, 68% yield) as a white solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 8.11 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 9.9 Hz, 1H), 5.94 (d, J = 9.9 Hz, 1H), 3.48 (d, J = 7.6 Hz, 1H), 3.19 (d, J = 7.6 Hz, 1H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 193.4, 137.5, 135.1, 131.4, 131.1, 129.4, 128.5, 128.1, 126.9, 57.7, 55.8; **mp** 131-132 °C; **IR** (thin film, cm^{-1}): 1685, 1596, 1331; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.20; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_8$NaO$_2$: ([M+Na]): 195.0422, Found: 195.0429.
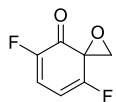
(±)-5,8-difluoro-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5e): The title compound was prepared according to General Procedure E using **1.21e** (100 mg, 0.262 mmol). Flash chromatography (20/80 ethyl acetate/hexanes) afforded **(±)-1.5e** (19.0 mg, 0.120 mmol, 47% yield) as a white semisolid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.28 (dd, J = 11.3, 5.9 Hz, 1H), 6.03 (dd, J = 9.3, 7.5 Hz, 1H), 3.71 (d, J = 5.9 Hz, 1H), 3.37 (d, J = 5.9 Hz, 1H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 178.7 (dd, J = 23.9, 16.8 Hz), 170.4 (dd, J = 287.9, 2.3 Hz), 155.8 (d, J = 269.7 Hz), 117.8 (dd, J = 18.2, 4.8 Hz), 112.5 (dd, J = 12.6, 4.2 Hz), 53.2 (d, J = 3.4 Hz), 51.8 (dd, J = 23.9, 11.1 Hz); **^{19}F NMR:** (376 MHz, CDCl$_3$): -105.1, -122.4; **IR** (thin film, cm^{-1}): 3078, 2342, 1686, 1640, 1161; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.35; **HRMS** (ESI$^+$) Calcd. for C$_7$H$_4$F$_2$NaO$_2$: ([M+Na]): 181.0077, Found: 181.0068.
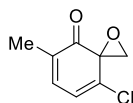
(±)-8-chloro-5-methyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5f): The title compound was prepared according to General Procedure E using **1.21f** (100 mg, 0.254 mmol) with the following modification: 9 equiv of H$_2$O$_2$ were used. Flash chromatography (30/70 ethyl acetate/hexanes) afforded **(±)-1.5f** (29.6 mg, 0.174 mmol, 68% yield) as a bright yellow solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.97 (d, J = 6.9 Hz, 1H), 6.61 (d, J = 6.9 Hz, 1H), 3.46 (d, J = 8.4 Hz, 1H), 3.29 (d, J = 8.4 Hz, 1H), 1.94 (s, 3 H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 193.6, 137.1, 137.1, 133.2, 125.8, 58.8, 57.9, 15.2; **mp** 70-71 °C; **IR** (thin film, cm^{-1}): 1665, 1563, 1286; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.56; **HRMS** (ESI$^+$) Calcd. for C$_8$H$_7$ClNaO$_2$: ([M+Na]): 193.0027, Found: 193.0027.
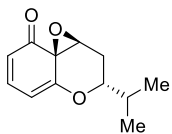
(±)-(1aS,3R,8aS)-3-isopropyl-1a,2-dihydro-3H,8H-oxireno[2,3-d]chromen-8-one (1.5g): The title compound was prepared according to General Procedure E using **1.21g** (100 mg, 0.233 mmol). Flash chromatography (30/70 ethyl acetate/hexanes) afforded **(±)-1.5g** (36.1 mg, 0.175 mmol, 75% yield) as a bright yellow oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.28 (m, 1H), 5.92 (d, J = 9.6 Hz, 1H), 5.80 (d, J = 7.2 Hz, 1H), 4.23 (ddd, J = 12.0, 5.8, 2.9 Hz, 1H), 4.08 (d, J = 2.8 Hz, 1H), 2.39 (dt, J = 15.0, 2.9 Hz, 1H), 1.92-1.80 (m, 2H), 0.99 (d, J = 6.9

Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 192.1, 161.7, 146.4, 117.8, 102.5, 77.4, 61.9, 54.2, 31.8, 26.6, 18.0, 17.7; **IR** (thin film, cm^{-1}): 2963, 1667, 1536; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.56; **HRMS** (ESI$^+$) Calcd. for C$_{12}$H$_{14}$NaO$_3$: ([M+Na]): 229.0841, Found: 229.0836.

(±)-2,3-dihydroindeno[1,7a-b]oxiren-7(1aH)-one (1.5h): The title compound was prepared according General Procedure E using **1.21h** (93 mg, 0.250 mmol). Flash chromatography (30/70 ethyl acetate/hexanes) afforded **(±)-1.5h** (31 mg, 0.209 mmol, 84% yield) as a yellow oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.11 (dd, J = 9.9, 5.9 Hz, 1H), 6.41-6.27 (m, 1H), 6.11 (d, J = 9.9 Hz, 1H), 4.30 (d, J = 1.5 Hz, 1H), 2.58-2.33 (m, 2H), 2.28 (ddd, J = 14.3, 7.7, 1.3, 1H), 2.00 (dtd, J = 14.2, 8.9, 1.6, 1H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 194.6, 155.2, 142.2, 124.6, 120.3, 70.3, 63.5, 28.0, 25.6; **IR** (thin film, cm^{-1}): 3457, 2932, 1737, 1477, 1261; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.30; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_9$O$_2$: ([M+H]): 149.0597, Found: 149.0599.
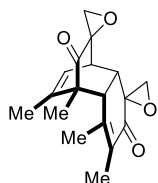
(±)-(1'R,4'R,4a'R,8a'R,10'R)-3',4',5',6'-tetramethyl-1',4',4a',8a'-tetrahydro-7'H-dispiro[oxirane-2,8'-[1,4]ethanonaphthalene-10',2''-oxirane]-7',9'-dione

(1.5i): The title compound was prepared according to General Procedure F using **1.21i** (100 mg, 0.267 mmol) to afford **(±)-1.5i** (28.3 mg, 0.094 mmol, 71% yield) as a white solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.33 (d, J = 6.1 Hz, 1H), 3.20 (d, J = 6.1 Hz, 1H), 3.05 (d, J = 8.9 Hz, 1H), 2.91 (d, J = 6.1 Hz, 1H), 2.86 (dd, J = 6.9, 3.0 Hz, 1H), 2.82 (s, 2H), 2.68 (dd, J = 9.0, 3.0 Hz, 1H), 2.09 (s, 3H), 1.84 (s, 3H), 1.60 (s, 3H), 1.35 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 205.4, 193.1, 149.1, 139.5, 136.2, 129.6, 59.9, 58.8, 57.6, 56.5, 53.5, 47.9, 40.4, 37.5, 24.4, 18.9, 14.8, 13.3; **mp** 118-119 °C; **IR** (thin film, cm^{-1}): 2915, 1731, 1681; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.15; **HRMS** (ESI$^+$) Calcd. for C$_{18}$H$_{20}$NaO$_4$: ([M+Na]): 323.1259, Found: 323.1257.
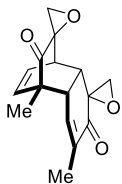
(±)-(1'R,4'S,10'R)-4',6'-dimethyl-1',4',4a',8a'-tetrahydro-7'H-dispiro[oxirane -2,8'-[1,4]ethanonaphthalene-10',2''-oxirane]-7',9'-dione (1.5j): The title compound was prepared according to General Procedure F using **1.21j** (100 mg, 0.278 mmol) to afford **(±)-1.5j** (24.7 mg, 0.907 mmol, 65% yield) as a white solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.59 (t, J = 7.4 Hz, 1H), 6.55 (d, J = 3.2 Hz, 1H), 5.79 (d, J = 8.1 Hz, 1H), 3.17 (d, J = 6.1 Hz, 1H), 3.15-3.12 (m, 1H), 2.94 (d, J = 6.1 Hz, 1H), 2.90 (d, J = 6.4 Hz, 2H), 2.85 (d, J = 6.5 Hz, 1H), 2.81 (d, J = 8.3 Hz, 1H), 1.88 (s, 3 H), 1.46 (s, 3H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 205.4, 193.3, 140.2, 139.4, 134.7, 133.4, 58.7, 58.4, 57.7, 54.9, 53.9, 42.3, 40.9, 39.7, 16.6, 15.4; **mp** 149-150 °C; **IR** (thin film, cm^{-1}): 2360, 1729, 1691; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.18; **HRMS** (ESI$^+$) Calcd. for C$_{16}$H$_{16}$NaO$_4$: ([M+Na]): 295.0947, Found: 295.0938.
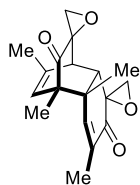
**(±)-(1'S,4'S,4a'S,8a'S,10'R)-2',4',4a',6'-tetramethyl-1',4',4a',8a'-tetrahydro-7'H-dispiro[oxirane-2,8'-[1,4]ethanonaphthalene-10',2''-oxirane]-7',9'-dione (1.5k):** The title compound was prepared according to General Procedure F using **1.21k** (100 mg, 0.267 mmol) to afford **(±)-1.5k** (25.1 mg, 0.0836 mmol, 63% yield) as a white solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.30 (s, 1H), 5.33 (3, 1H), 3.20 (d, J = 6.1 Hz, 1H), 2.97 (d, J = 6.1 Hz, 1H), 2.85 (d, J = 6.4 Hz, 1H), 2.83 (d, J = 6.4 Hz, 1H), 2.61 (d, J = 1.8 Hz, 1H), 2.27 (d, J = 1.8 Hz, 1H), 1.88 (s, 3 H), 1.85 (s, 3 H), 1.30 (d, J = 6.0 Hz, 6H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 205.6, 193.2, 146.3, 143.8, 136.7, 128.6, 58.6, 58.5, 58.3, 57.3, 52.9, 47.7, 45.8, 45.2, 23.9, 20.6, 16.3, 12.2; **mp** 115-116 °C; **IR** (thin film, cm^{-1}): 3008, 1769, 1674; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.2; **HRMS** (ESI$^+$) Calcd. for C$_{18}$H$_{20}$NaO$_4$: ([M+Na]): 323.1259, Found: 323.1259.
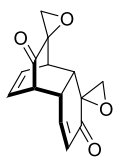
(±)-(1'R,4'S,4a'S,8a'R,10'R)-1',4',4a',8a'-tetrahydro-7'H-dispiro[oxirane-2,8'-[1,4]ethanonaphthalene-10',2''-oxirane]-7',9'-dione (1.5l): The title compound was prepared according to General Procedure F using **1.21l** (100 mg, 0.289 mmol) to afford **(±)-1.5l** (13.1

mg, 0.054 mmol, 37% yield) as a white solid. Spectral properties were consistent with those previously reported.[13] Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.71 (dd, J = 10.2, 4.0 Hz, 1H), 6.67 (t, J = 7.3 Hz, 1H), 6.25 (d, J = 10.2 Hz, 1H), 6.17 (t, J = 7.2 Hz, 1H), 3.59 (ddd, J = 9.2, 4.2, 2.1 Hz, 1H), 3.54-3.53 (m, 1H), 3.20 (m, 1H), 2.98 (d, J = 6.5 Hz, 1 H), 2.95 (d, J = 6.5 Hz, 2H), 2.89 (d, J = 6.5 Hz, 1H), 2.87 (d, J = 9.0, 1H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 203.5, 192.5, 146.9, 134.2, 131.3, 129.3, 58.9, 57.9, 57.6, 53.7, 53.0, 41.7, 38.9, 38.7.
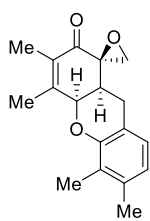
(±)-((2R,4a'R,9a'S)-3',4',5',6'-tetramethyl-9',9a'-dihydrospiro[oxirane-2,1'-xanthen]-2'(4a'H)-one (1.23): Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.80 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 5.30 (s, 1H), 3.03 (d, J = 6.4 Hz, 1H), 2.99 (d, J = 6.4 Hz, 1H), 2.86 (dd, J = 8.8, 3.2 Hz, 2H), 2.52 (ddd, J = 10.3, 7.7, 5.1 Hz, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H), 1.83 (s, 3H); **^{13}C NMR**: (150 MHz, CDCl$_3$): δ 192.2, 156.5, 150.1, 136.1, 132.9, 126.3, 124.3, 122.5, 116.9, 73.8, 60.2, 53.7, 37.7, 23.5, 19.9, 16.3, 11.5, 11.4; **IR** (thin film, cm^{-1}): 3583, 3055, 1665, 1624, 1298; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.47; **HRMS** (ESI$^+$) Calcd. for C$_{18}$H$_{20}$NaO$_3$: ([M+Na]): 307.1310, Found: 307.1304.
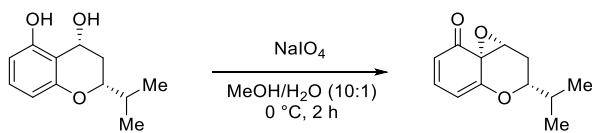
(±)-(1aR,3R,8aR)-3-isopropyl-1a,2-dihydro-3H,8H-oxireno[2,3-d]chromen-8-one (1.32): To a round-bottomed flask was added **1.4g** (80 mg, 0.384 mmol) and dissolved in MeOH (5 mL). The reaction was cooled to 0 °C and a solution of NaIO$_4$ in water (0.5 mL) was added dropwise to the reaction mixture, causing a bright yellow color to appear. The reaction was stirred for 2 h and then diluted with water. The contents were transferred to a separatory funnel and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined and washed brine, dried with Na$_2$SO$_4$,

filtered, and concentrated to afford 50.7 mg (64%) of epoxide **1.32** as a very bright yellow oil.

Analytical data: **¹H NMR**: (600 MHz, CDCl₃): δ 7.39 – 7.20 (m, 1H), 5.98 (d, J = 9.8 Hz, 1H), 5.94 (d, J = 6.7 Hz, 1H), 4.14 (s, 1H), 3.71 (dd, J = 12.9, 6.0 Hz, 1H), 2.38 (dd, J = 15.0, 6.8 Hz, 1H), 2.18 (dt, J = 15.1, 4.2 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.01 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H); **¹³C NMR**: (151 MHz, CDCl₃): δ 193.3, 161.9, 145.1, 119.8, 106.3, 84.7, 63.4, 52.6, 33.2, 26.3, 18.9, 18.3; **IR** (thin film, cm⁻¹): 3433, 1665, 1537; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.55; **HRMS** (ESI⁺) Calcd. for C₁₂H₁₄NaO₃: ([M+Na]): 229.0841, Found: 229.0835.
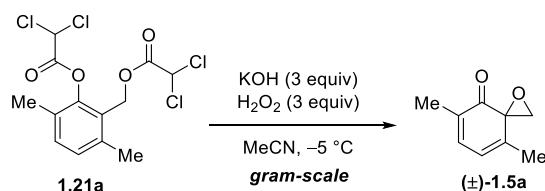
Gram-scale (±)-5,8-dimethyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5a): The title compound was prepared according to General Procedure E using **1.21a** (4.50 g, 12.0 mmol) with the following modifications: (a) [**1.21a**]₀ = 0.1 M after addition of **1.21a**/H₂O₂; (b) hydrogen peroxide was added rapidly to KOH/MeCN slurry followed by slow addition of **1.21a** (dissolved in MeCN) over the course of 5 min; (c) upon reaction completion, sat. aqueous Na₂S₂O₃ (5 mL) was slowly added over a period of 5 min and allowed to stir for another 5 min to quench the excess peroxide. Flash chromatography (30/70 ethyl acetate/hexanes) afforded epoxide **(±)-1.5a** (1.20 g, 7.99 mmol, 66% yield) as a yellow solid. Spectroscopic properties were consistent with those previously reported.[20]

Analytical data: **¹H NMR**: (400 MHz, CDCl₃): δ 6.94 (d, J = 5.9 Hz, 1H), 6.26 (d, J = 5.6 Hz, 1H), 3.24 (d, J = 8.2 Hz, 1H), 3.17 (d, J = 8.2 Hz, 1H), 1.92 (s, 3H), 1.82 (s, 3H); **¹³C NMR**: (151 MHz, CDCl₃) 196.4, 144.7, 138.9, 131.8, 123.8, 58.7, 58.7, 16.1, 15.2.

CF₃ Quinine Phase-Transfer Catalyst Synthesis

1.31 → **1.38** → **1.29**
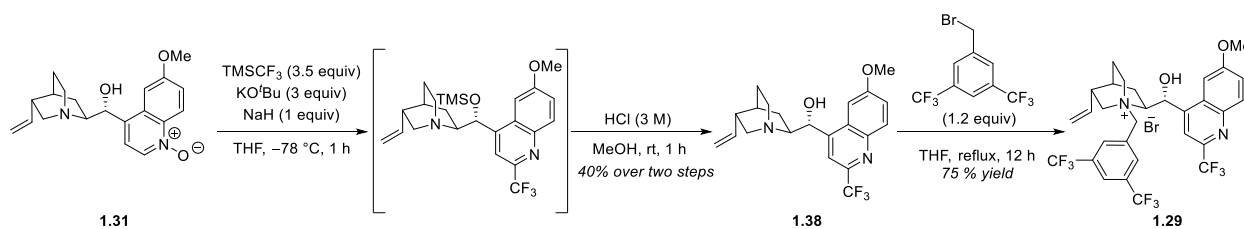
The following procedure is a modification to a previously reported procedure for the trifluoromethylation of quinolines.[41] To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added **1.31** (2.00 g, 5.88 mmol) and anhydrous THF (21 mL). The flask was purged with nitrogen and cooled to 0 °C, and NaH (235 mg, 5.875 mmol, 1 equiv) was added in portions and the flask was left to stir for 10 min. The flask was then cooled to −78 °C and TMSCF₃ (3.04 mL, 20.6 mmol, 3.5 equiv) was added in one portion. The flask was allowed to stir for 10 min followed by addition of KO^{t}Bu (1.98 g, 17.6 mmol, 3 equiv) in three equal portions over 30 min. After complete addition, the flask was allowed to stir for an additional 30 min. The reaction was quenched slowly with a saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The product was diluted with CH_2Cl_2 (100 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. The crude material was filtered through a silica plug (10/1 ethyl acetate/methanol) and concentrated to afford an orange/red solid. This solid was added directly to a round-bottomed flask equipped with a magnetic stir bar and diluted with MeOH (10 mL). HCl (3 M, 5 mL) was added and the contents of the flask were allowed to stir for 1 h. NaOH (10% aqueous) was added until the solution was pH 10. The contents of the flask were transferred to a separatory funnel, and the solution was diluted with CH_2Cl_2 (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (6 x 5 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. The crude product was

purified by column chromatography (5/1 ethyl acetate/methanol) to afford **1.38** (922 mg, 2.35

mmol, 40% yield over two steps) as a yellow solid. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$):

δ 8.14 (d, J = 9.2 Hz, 1H), 7.91 (s, 1H), 7.45 (dd, J = 9.3, 2.6 Hz, 1H), 7.27 (d, J = 2.7 Hz, 1H),

5.77 (ddd, J = 17.5, 10.3, 7.6 Hz, 1H), 5.60 (d, J = 3.8 Hz, 1H), 5.06 – 4.92 (m, 3H), 3.95 (s, 3H),

3.38-3.45 (m, 1H), 3.26 – 3.00 (m, 2H), 2.95 (s, 1H) 2.77 – 2.67 (m, 2H), 2.30 (s, 2H), 1.92 – 1.82

(m, 2H), 1.73 (q, J = 10.2, 7.9 Hz, 2H), 1.63 – 1.48 (m, 2H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ

159.2, 149.9, 145.2 (q, J = 34.3), 143.4, 141.7, 132.4, 127.5, 123.0, 122.0 (q, J = 275 Hz), 114.5,

114.2 (d, J = 2.1), 101.0, 72.1, 60.1, 57.0, 55.7, 43.3, 39.8, 27.7, 27.6, 21.6. **^{19}F NMR**: (376 MHz,

CDCl$_3$): −67.2 (s, 3F); **IR** (thin film, cm^{-1}): 2940, 1508, 1232, 1182, 1136, 1097; **mp** 185-186°C;

TLC (5/1 ethyl acetate/methanol): R$_f$ = 0.2; **HRMS** (ESI$^+$) Calcd. for C$_{21}$H$_{24}$F$_3$N$_2$O$_2$: ([M+H]):

393.1784, Found: 393.1787.

To a flame-dried round-bottomed flask equipped with a magnetic stir bar and reflux condenser

was added amine **1.38** (300 mg, 0.764 mmol), 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene

(0.168 mL, 0.917 mmol, 1.2 equiv) and THF (5 mL). The flask was stirred at reflux for 12 h then

allowed to cool to room temperature. The contents of the flask were slowly added to diethyl

ether/hexanes (3/1 mixture, 100 mL) with vigorous stirring. The mixture was stirred for 30 min

during which time a solid was formed. The solid was collected via vacuum filtration, washed with

cold diethyl ether, and dried under vacuum to afford **1.29** as a yellow solid (40 mg, 0.535 mmol,

75% yield). Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 8.66 (s, 1H), 8.07 (s, 1H), 8.02 (d, J

= 9.3 Hz, 1H), 7.94 (s, 1H), 7.30 – 7.25 (m, 1H), 7.18 (d, J = 2.0 Hz, 1H), 6.67 (d, J = 6.6 Hz, 1H),

6.34 (dd, J = 13.5, 9.6 Hz, 2H), 5.61 (ddd, J = 17.1, 10.5, 6.6 Hz, 1H), 5.54 (d, J = 11.9 Hz, 1H),

5.20 (d, J = 16.9 Hz, 1H), 5.02-4.93 (m, 2H), 4.31 (d, J = 9.6 Hz, 1H), 4.11 (t, J = 8.4 Hz, 1H),

3.91 (s, 3H), 3.29 (t, J = 11.7 Hz, 1H), 2.96 (q, J = 11.2 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.42-2.34

(m, 1H), 2.21 (dd, J = 11.7, 6.4 Hz, 1H), 2.11 − 2.04 (m, 1H), 1.81 (t, J = 10.5 Hz, 1H), 1.53 (t, J = 11.7 Hz, 1H); ^{13}**C NMR**: (151 MHz, CDCl$_3$): δ 159.8, 144.9, 144.8 (q, J = 36.2), 143.1, 135.6, 134.3, 134.3, 132.5, 132.4 (q, 34.7), 130.2, 126.6, 123.1 (q, 273.3 Hz), 122.3 (q, 273.3 Hz), 118.3, 116.3, 101.1, 69.2, 63.7, 60.6, 60.5, 56.4, 51.5, 37.8, 26.7, 24.7, 21.6; ^{19}**F NMR**: (376 MHz, CDCl$_3$): −62.76 (s, 6F); −67.11 (s, 3F); **mp** 167-168°C; **IR** (thin film, cm^{-1}): 3210, 2360, 1373, 1280; **HRMS** (ESI$^+$) Calcd. for C$_{30}$H$_{28}$F$_9$N$_2$O$_2$: ([M-Br]): 619.2007, Found: 619.1999. **[α]$_D$** = −107.8 (c = 0.05, CHCl$_3$).

Enantioselective Reaction Scope for Preparation of *ortho*-Spiroepoxydienones (−)-1.5
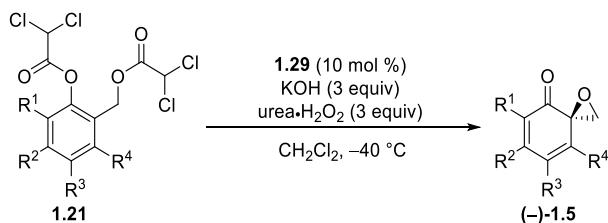
General Procedure G: To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added anhydrous CH_2Cl_2. The flask was cooled to −40 °C and KOH (3 equiv), **1.29** (10 mol %), and urea•hydrogen peroxide (3 equiv) were added. The starting bis(dichloroacetate) **1.21** was dissolved in CH_2Cl_2 ($[\mathbf{1.21}]_0 = 0.05$ M after addition of the bis(dichloroacetate)) and added to the mixture over the course of 2.5 h. Once added, the mixture was allowed to stir until complete disappearance of the starting material was observed by TLC (usually between 2-4 h after complete addition). The reaction was stopped by quenching with saturated aqueous sodium thiosulfate (1 ml/mmol) and the solution was decanted into a separatory funnel and diluted with water. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL/mmol). The organic layers were combined, dried with Na_2SO_4, and concentrated. The resultant compound was purified on silica by column chromatography. **Recrystallization:** The compound was dissolved in a mixture of boiling water and isopropanol. The resulting solution was allowed to cool to room temperature and then cooled at 0 °C for 24 h. If necessary, extra ice water was added to induce crystallization. After 24 hs, the supernatant was removed and the crystals were washed with cold water, retaken up in CH_2Cl_2, dried with Na_2SO_4, and concentrated to afford the recrystallized product **(−)-1.5**.

General Procedure H for Preparation of Enantioenriched Dimeric Species: To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added anhydrous CH_2Cl_2. The flask was cooled to $-40\ ^\circ C$ and KOH (3 equiv), **1.29** (20 mol %), and urea•hydrogen peroxide (3 equiv) were added. The starting bis(dichloroacetate) **1.21** dissolved in CH_2Cl_2 ($[\mathbf{1.21}]_0 = 0.05$ M after addition of the bisdichloroacetate) was added to the mixture over the course of 3 h. Once added, the mixture was allowed to stir vigorously until complete disappearance of the starting material was observed by TLC (usually between 2-4 h after complete addition). The reaction was stopped by quenching with saturated aqueous sodium thiosulfate solution and the solution was decanted into a separatory funnel and diluted with water. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL/mmol). The organic layers were combined, dried with Na_2SO_4, and concentrated. The crude product was passed through a silica plug using 50% ethyl acetate/hexanes to remove the catalyst and the filtrate was concentrated. Et_2O (4 mL/mmol) was added to the residue with gentle stirring which precipitated out the product. The vial was left at $-20\ ^\circ C$ for 30 min to complete precipitation. The solid was filtered and washed three times with cold Et_2O to afford the desired spiroepoxide dimer. **Recrystallization**: The compound was recrystallized by vapor diffusion. The compound was dissolved in a minimal amount of CH_2Cl_2 in a vial. The vial was placed in a larger vial with methyl *tert*-butyl ether (MTBE) and the large vial was closed and placed in the dark. After 24 h, the solvent was removed and the crystals were washed with cold MTBE and dried to afford the recrystallized dimer **(−)-1.5**.
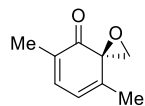
(*R*)-5,8-dimethyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5a): The title compound was prepared according to General Procedure G using **1.21a** (187 mg, 0.500 mmol). Flash chromatography (30/70 ethyl acetate/hexanes) afforded (−)-**1.5a** (64.4 mg, 0.43 mmol, 85% yield), as a yellow solid. The product was recrystallized using General Procedure G with a 10:1 water/isopropanol mixture affording crystalline (−)-**1.5a** (53.0 mg, 71% yield) enriched to 95:5 er. Analytical data (crude): **HPLC** (80/20 Hexanes/^{i}PrOH, Daicel CHIRALPAK IC): 87:13 er, t_R (major): 15.6 min, t_R (minor): 17.4 min. [α]$_D$ = −41.8 (c = 0.01, CHCl$_3$).
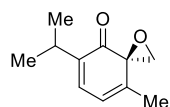
(*R*)-5-isopropyl-8-methyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5b): The title compound was prepared according to General Procedure G using **1.21b** (201 mg, 0.500 mmol) with the following modification: **1.21b** was cooled to −40 °C and added in one portion to the flask containing KOH, **1.29**, and UHP. Flash chromatography (20/80 ethyl acetate/hexanes) afforded (−)-**1.5b** (75.7 mg, 0.43 mmol, 85% yield) as a yellow solid. The product was recrystallized using General Procedure G using a 1.5:1 water/isopropanol mixture affording crystalline (−)-**1.5b** (61.1 mg, 69% yield) enriched to 99.8:0.2 er. Analytical data (crude): **HPLC** (80/20 Hexanes/^{i}PrOH, Daicel CHIRALPAK IC): 90:10 er, t_R (major): 9.3 min, t_R (minor): 11.0 min. [α]$_D$ = −37.2 (c = 0.03, CHCl$_3$).
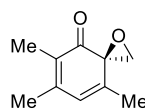
(*R*)-5,6,8-trimethyl-1-oxaspiro[2.5]octa-5,7-dien-4-one (1.5c): The title compound was prepared according to General Procedure G using **1.21c** (194 mg, 0.500 mmol). Flash chromatography (20/80 ethyl acetate/hexanes) afforded (−)-**1.5c** (71 mg, 0.43 mmol, 86%) as a yellow solid. The product was recrystallized using General Procedure G with a 1.5:1 water/isopropanol mixture affording crystalline (−)-**1.5c** (50.3 mg, 61% yield) enriched to

98:2 er. Analytical data (crude): **HPLC** (80/20 Hexane/^{i}PrOH, Daicel CHIRALPAK IC): 80.5:19.5 er, t_R (minor): 8.5 min, t_R (major): 9.4 min. **[α]$_D$** = −65.2 (c = 0.007, CHCl$_3$).

*Note: In order to aid in separation on the HPLC, **1.5c** was further derivatized to the bis-epoxide according to the reported procedure[47] affording the desired compound as single diasteromer.*
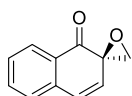
(**R**)-1H-spiro[naphthalene-2,2'-oxiran]-1-one (1.5d): The title compound was prepared according to General Procedure G using **1.21d** (198 mg, 0.500 mmol). Flash chromatography (20/80 ethyl acetate/hexanes) afforded **(−)-1.5d** (70 mg, 0.41 mmol, 81% yield) as a white solid. The product was recrystallized using a 1.5:1 water/isopropanol mixture affording crystalline **(−)-1.5d** (54 mg, 63% yield) enriched to 98.5:1.5 er. Analytical data: **HPLC** (80/20 Hexane/^{i}PrOH, Daicel CHIRALPAK IC): 89:11 er, t_R (major): 14.9 min, t_R (minor): 15.9 min. **[α]$_D$** = −17.2 (c = 0.01, CHCl$_3$).
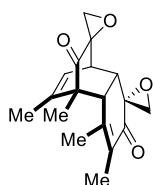
(1'**R**,2**R**,4'**R**,4a'**R**,8a'**R**,10'**S**)-3',4',5',6'-tetramethyl-1',4',4a',8a'-tetrahydro-7'H-dispiro[oxirane-2,8'-[1,4]ethanonaphthalene-10',2''-oxirane]-7',9'-dione (1.5i): The title compound was prepared according to General Procedure H using **1.21i** (194 mg, 0.500 mmol) to afford **(−)-1.5i** (49 mg, 0.16 mmol, 65% yield) as a white solid. The product was recrystallized using a CH$_2$Cl$_2$/MTBE mixture affording crystalline **(−)-1.5i** (30 mg, 40% yield) enriched to 97:3 er. Analytical data: **HPLC** (99/1 CH$_2$Cl$_2$/^{i}PrOH, Daicel CHIRALPAK IC): 77:23 er, t_R (major): 6.7 min, t_R (minor): 7.1 min. **[α]$_D$** = −5.3 (c = 0.01, CHCl$_3$).
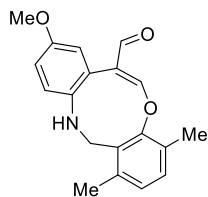
(E)-2-methoxy-7,10-dimethyl-5,6-dihydrodibenzo[b,f][1,5]oxazonine-13-carbaldehyde (1.30): **^{1}H NMR:** (600 MHz, CDCl$_3$) δ 9.79 (s, 1H), 7.79 (s, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.38 (s, 1H), 7.12 (d, J = 7.12 Hz, 1H), 7.01 (d, J = 8.9 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 5.33 (s, 2H), 5.14 (s, 1H), 3.91 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H). **^{13}C NMR**: 184.6, 156.7, 153.1, 137.7, 137.2, 132.7, 131.2, 126.2, 122.9, 120.7, 119.0, 117.6, 114.3, 111.0, 103.3, 55.8, 42.1, 19.2, 15.7; **mp** 194-195 °C; **IR** (thin film, cm^{-1}): 3423, 1773, 1725; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.3; **HRMS** (ESI$^+$) Calcd. for C$_{19}$H$_{19}$NNaO$_3$: ([M+Na]): 332.1262, Found: 332.1245.

One-Pot Acyl-Nitroso Diels-Alder Cycloaddition:
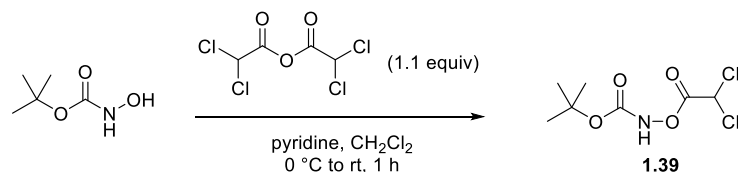
***tert*-butyl (2,2-dichloroacetoxy)carbamate (1.39)**: To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added benzyl hydroxycarbamate[56] (500 mg, 3.76 mmol) and anhydrous CH_2Cl_2 (15 ml). The solution was cooled to 0 °C and pyridine (0.320 ml, 3.94 mmol) was added. The solution was stirred for 5 min then dichloroacetic anhydride (0.629 mL, 4.13 mmol) was added dropwise. The reaction was stirred for 20 min at 0 °C and then 40 min at room temperature. The contents of the reaction were then filtered through a silica plug using CH_2Cl_2 as the eluent. The filtrate was concentrated to afford 813 mg (89% yield) of the title compound as a viscous, colorless oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 8.01 (s, 1H), 6.11 (s, 1H), 1.53 (s, 9H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 164.1, 154.6, 84.5, 62.0, 27.9; **IR** (thin film, cm^{-1}): 3315, 1739; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.63; **HRMS** (ESI$^+$) Calcd. for C$_7$H$_{11}$Cl$_2$NNaO$_4$: ([M+Na]): 265.9963, Found: 265.9969.
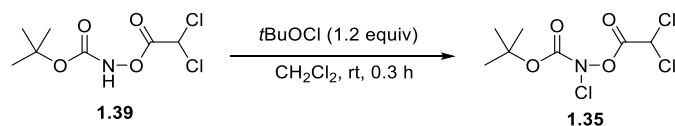
***tert*-butyl chloro(2,2-dichloroacetoxy)carbamate (1.35)**: To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added **1.39** (500 mg, 2.05 mmol) and anhydrous CH_2Cl_2 (5 mL). Freshly prepared *tert*-butylhypochlorite[57] (0.278 mL, 2.46 mmol) was added in the dark. The reaction was stirred for 20 min at room temperature then the solution was passed through a silica plug with CH_2Cl_2 and concentrated *in vacuo* to afford 217.5 mg (97%) of the title compound as a

colorless oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.04 (s, 1H), 1.56 (s, 9H). **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 161.3, 154.7, 88.2, 61.8, 27.6; **IR** (thin film, cm^{-1}): 3319, 1769, 1223; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.71; **HRMS** (ESI$^+$) Calcd. for C$_7$H$_{10}$Cl$_3$NNaO$_4$: ([M+Na]): 299.9573, Found: 299.9561.
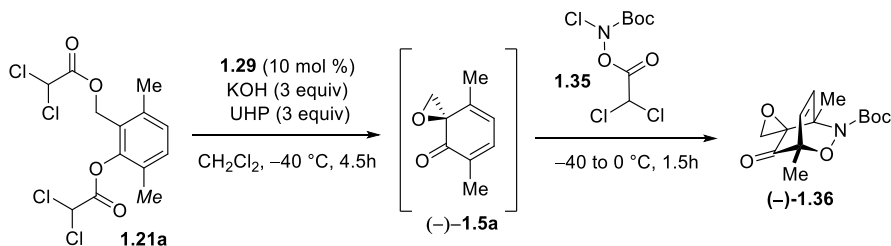
***tert*-butyl (1*R*,2*R*,4*S*)-1,4-dimethyl-3-oxo-5-oxa-6-azaspiro[bicyclo[2.2.2]octane-2,2'-oxiran]-7-ene-6-carboxylate ((−)-1.36):** To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added anhydrous CH$_2$Cl$_2$ (8 ml). The flask was cooled to −40 °C and powdered KOH (99 mg, 1.50 mmol), **1.29** (35 mg, 0.050 mmol), and urea•hydrogen peroxide (144 mg, 1.50 mmol) were added. Bis(dichloroacetate) **1.21a** (187 mg, 0.500 mmol) was dissolved in 2 mL of CH$_2$Cl$_2$ and subsequently added to the mixture over the course of 2.5 h via slow addition. Once fully added, the mixture was allowed to stir for 2 h. *N*-Chlorocarbamate **1.35** (209 mg, 0.750 mmol) was dissolved in 1 mL of CH$_2$Cl$_2$ and added to the reaction mixture over the course of an h. Once fully added, the reaction was allowed to warm to 0 °C and left to stir for an additional 30 min. The reaction was stopped by pouring the reaction mixture into a separatory funnel and diluted with water. The organic layer was removed and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 40 mL/mmol). The organic layers were combined, dried with Na$_2$SO$_4$, and concentrated. The resultant residue was redissolved in CH$_2$Cl$_2$ and passed through a silica plug (50/50 ethyl acetate/hexanes) to remove the catalyst. The filtrate was concentrated to afford oxazinanone **(−)-1.36**. An initial

diastereomer ratio of 4.2:1 (see Note 1 below) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 6.66 (major diastereomer) and δ 6.69 (minor diastereomer). Column chromatography (30/70 ethyl acetate/hexanes) afforded 82 mg (58%) of a 5:1 mixture of the major and minor diasteromers (see Note 2). **Recrystallization:** The compound was dissolved in boiling hexanes, allowed to cool to room temperature then cooled to 0 °C for 24 h. The supernatant was removed and the crystals were washed with cold hexanes affording crystalline **(−)-1.36** (54 mg, 38% yield) enriched to 99:1 er and >20:1 dr. Analytical data: Only definitively discernible peaks are reported in the ^{1}H NMR spectra for each isomer. **Major diasteromer ^{1}H NMR**: (600 MHz, CDCl$_3$): δ 6.70 (d, J = 8.2 Hz, 1H), 6.29 (d, J = 8.1 Hz, 1H), 3.12 (d, J = 5.7 Hz, 1H), 3.10 (d, J = 5.8 Hz, 1H), 1.67 (s, 6H), 1.49 (s, 9H). **Minor diastereomer ^{1}H NMR:** (600 MHz, CDCl$_3$): δ δ 6.71 (d, J = 8.8 Hz, 1H), 6.30 (d, J = 8.4 Hz, 1H), 3.20 (d, J = 5.7 Hz, 1H), 3.06 (d, J = 5.7 Hz, 1H), 1.76 (s, 3H), 1.65 (s, 3H), 1.48 (s, 9H). **IR** (thin film, cm^{-1}): 3033, 2995 1757, 1265; **TLC:** (30/70 ethyl acetate/hexanes): R$_f$ = 0.65; **HRMS** (ESI^{+}) = Cald. For C$_{14}$H$_{19}$NNaO$_5$: ([M+Na)]: 304.1161, found: 304.1167. **HPLC** (90/10 Hexane/^{i}PrOH, Daicel CHIRALPAK IC): 84:16 er, t_{R} (minor): 7.538 min, t_{R} (major): 9.258 min. **[α]$_D$** = −64.6 (c = 0.008, CHCl$_3$).

Note 1: An initial 2:1 dr was observed directly after the silica plug. However, because the Diels-Alder adduct is in an equilibrium of both diasteromers, after 24 h at room temperature, equilibrium was reached as 4.2:1 dr which is the reported value. This equilibrium does not change after 24 h.

*Note 2: The equilibrium of the two diasteromers occurs via a retro acyl-nitroso Diels Alder cycloaddition. Small amounts of **1.5a** can frequently be observed in the ^{1}H NMR spectra.*

Photochemical Stability of *ortho*-Spiroepoxydienones 1.5:

When 1-oxaspiro[2.5]octa-5,7-dien-4-ones (**1.5**) are exposed to light for extended periods of time, rearomatization to salicylaldehyde **1.40** is observed.[13] This rearomatization can be mitigated by storing the products at −20 °C in the dark.
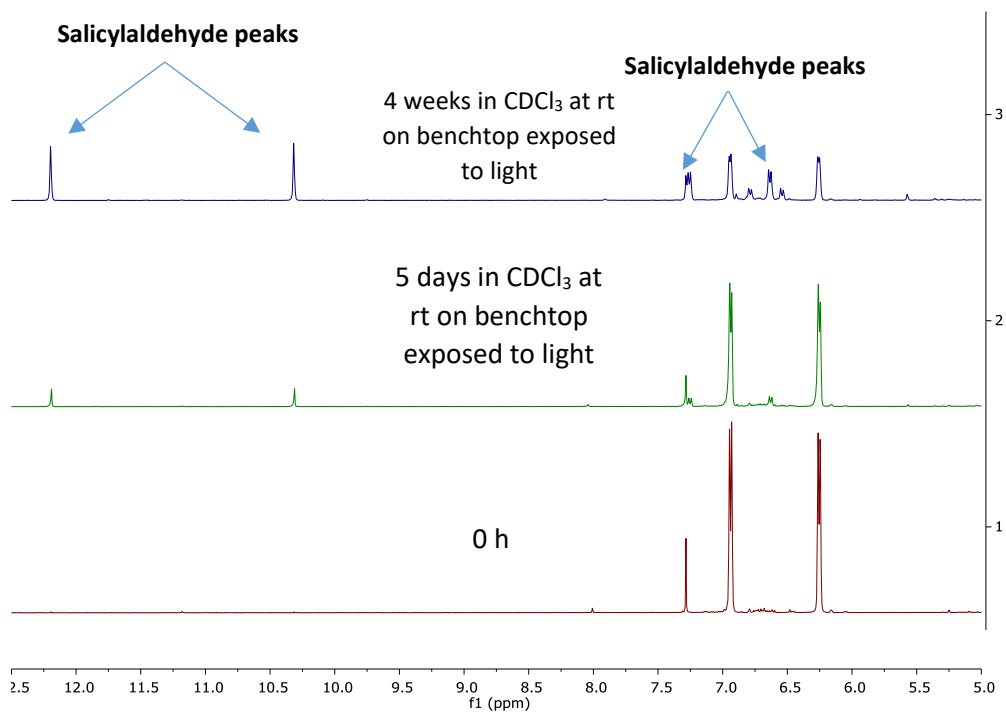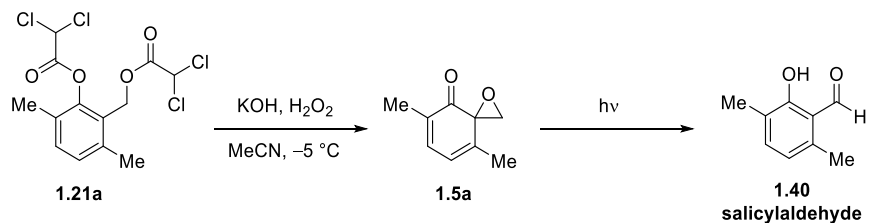
Stability of Aryl Substituted 1-Oxaspiro[2.5]octadienones:

For benzylic substiuted *o*-spiroepoxydienones, rapid rearrangement to benzodioxoles at temperatures above 0 °C has been reported.[13] Thus, when using our reaction conditions applied to a phenyl substituted compound, this rearrangement occurred (see reaction scheme below).
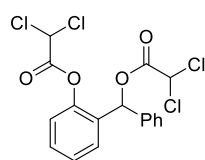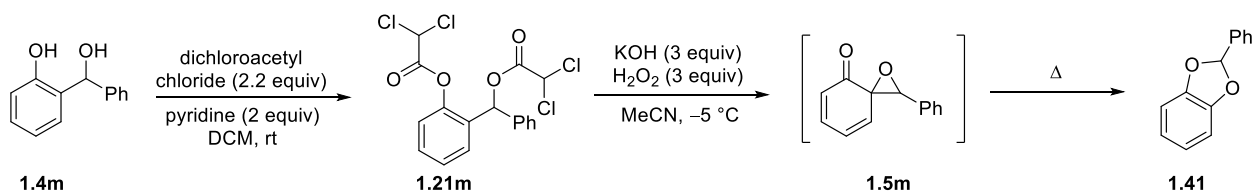
2-((2,2-dichloroacetoxy)(phenyl)methyl)phenyl 2,2-dichloroacetate (1.21m): The title compound was prepared according to General Procedure D using **1.4m** (300 mg, 1.50 mmol) to afford the title compound (583 mg, 1.38 mmol, 92% yield) as a colorless oil. Analytical data: **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.39 (dt, *J* = 11.8, 7.1 Hz, 6H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.18 (s, 1H), 6.10 (s, 1H), 6.04 (s, 1H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 163.1, 162.4, 147.5, 136.9, 130.2, 130.0, 128.8, 128.7, 127.2, 126.8, 122.0; 74.5, 64.2, 63.9; **IR** (thin film, cm^{-1}): 3583, 3055, 1665, 1624, 1298; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.67; **HRMS** (ESI$^+$) Calcd. for C$_{17}$H$_{12}$Cl$_4$O$_4$: ([M+Na]): 442.9388, Found: 442.9385.
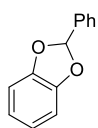
2-phenylbenzo[1,3]dioxole (1.41): The title compound was prepared according to the General Procedure E using **1.21m** (100 mg, 0.237 mmol). Flash chromatography (30/70 ethyl acetate/hexanes) afforded the title compound (24 mg, 0.121 mmol, 51% yield) as a white solid. Spectroscopic properties were consistent with those previously reported.[63] **^{1}H NMR**: (600 MHz, CDCl$_3$): δ 7.62-7.60 (m, 2H), 7.48-7.47 (m, 3H), 6.99 (s, 1H), 6.89 (s, 4H); **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 147.7, 136.4, 130.4, 128.9, 126.6, 121.9, 110.1, 108.8.

1D/2D NOESY correlations:

nOe observed

1.5i

nOe observed

1.23

*n*Oe observed

MeO

9.80

H 7.39

2.28

HN

5.34

Me

1.30
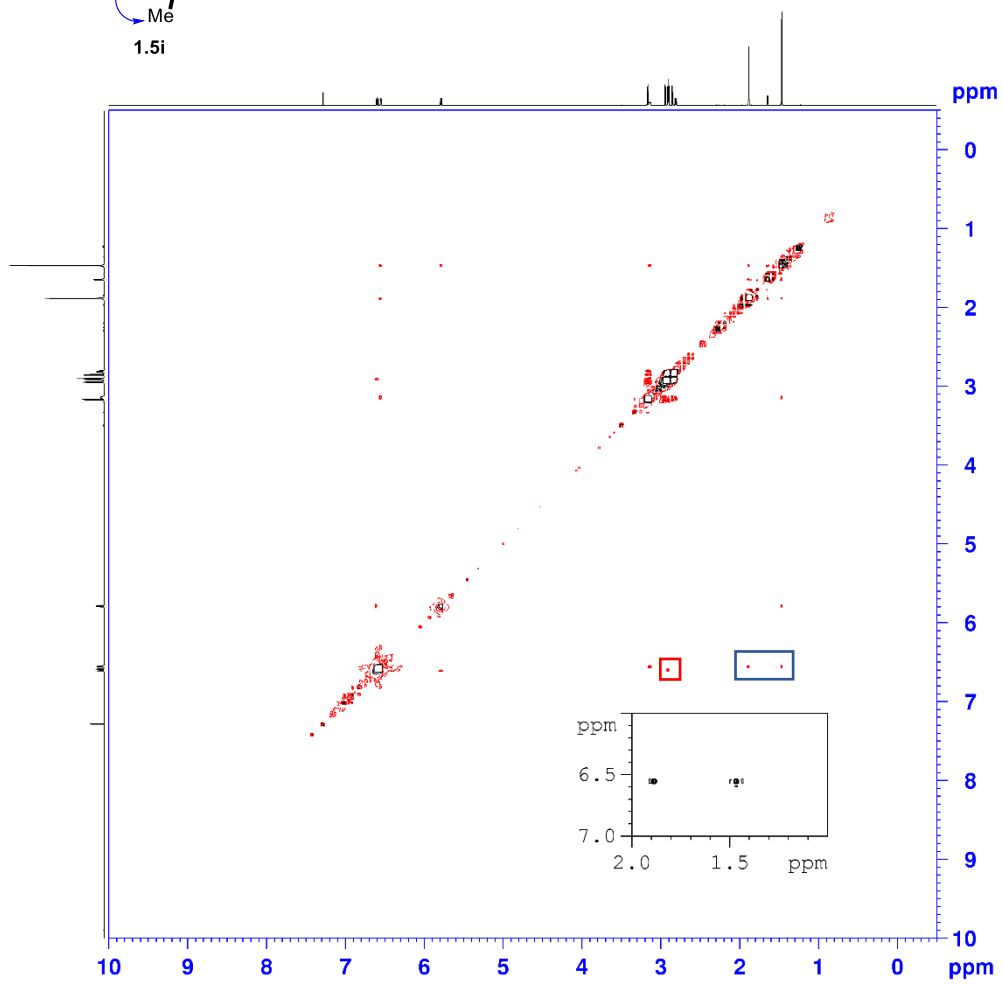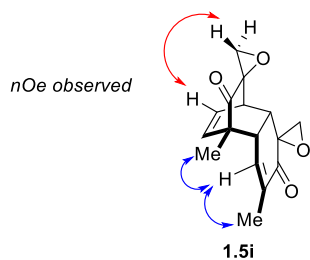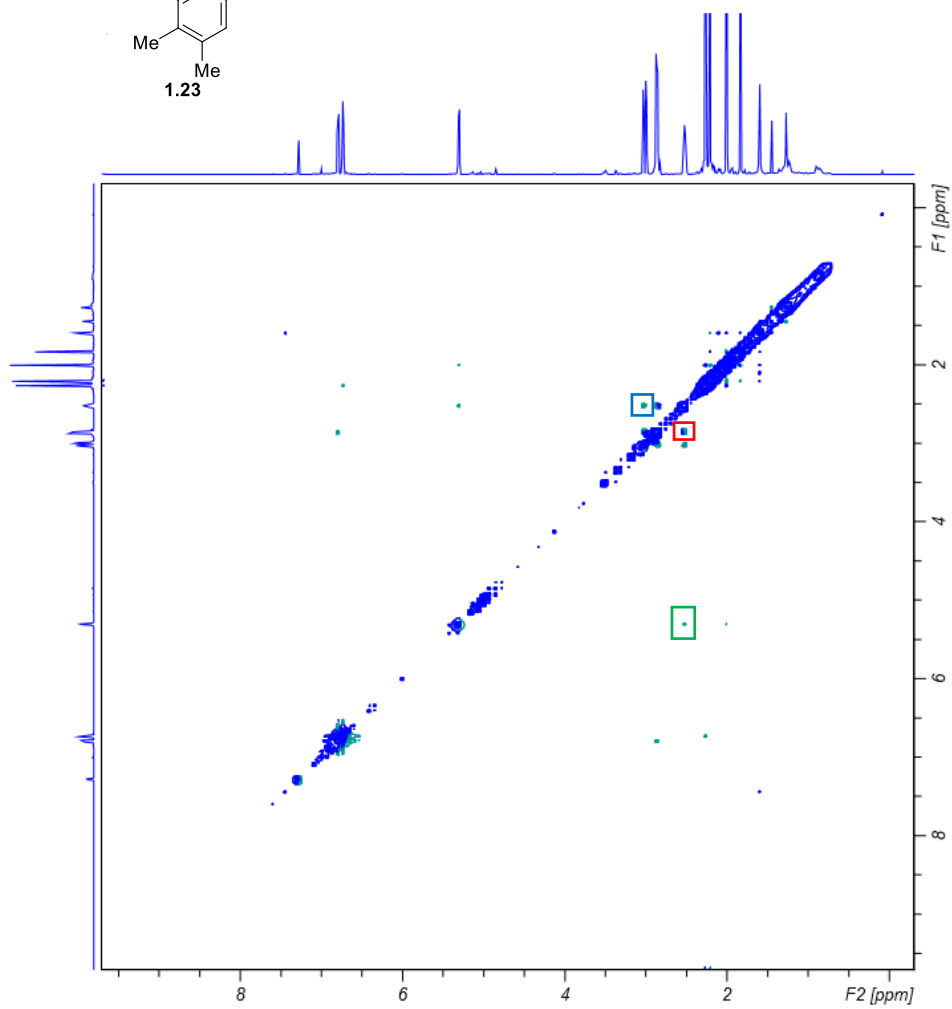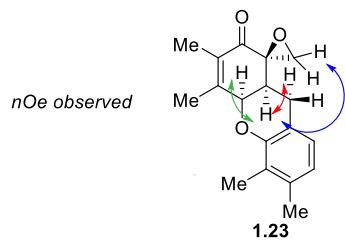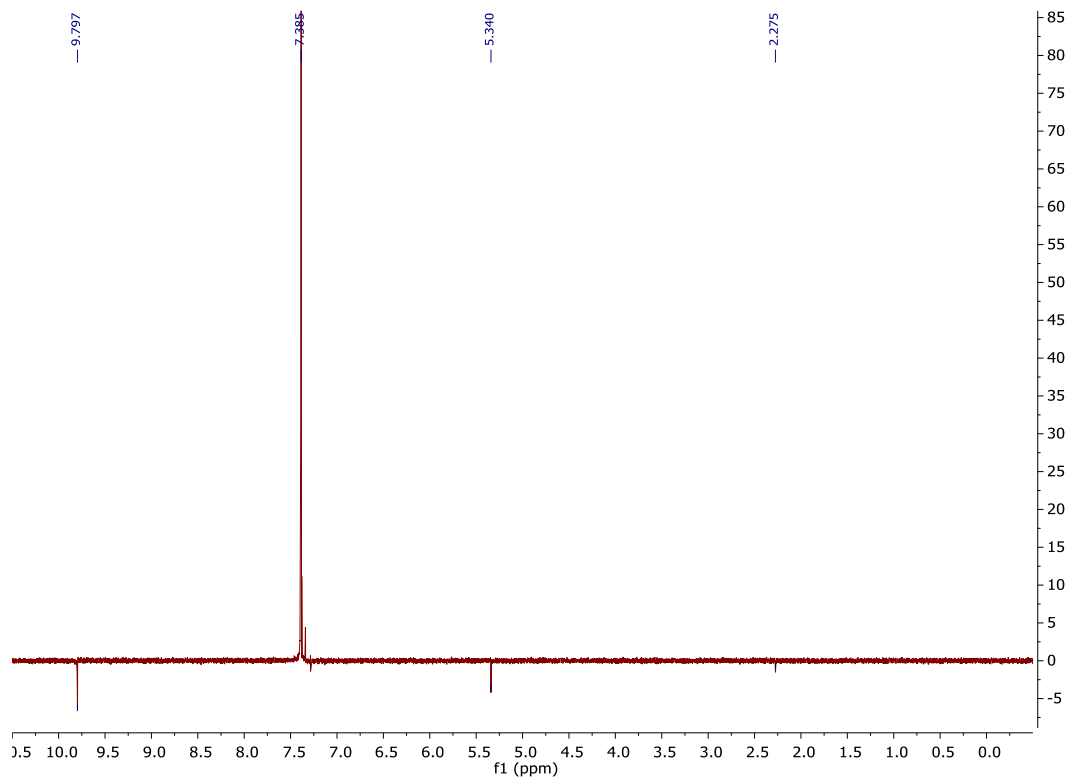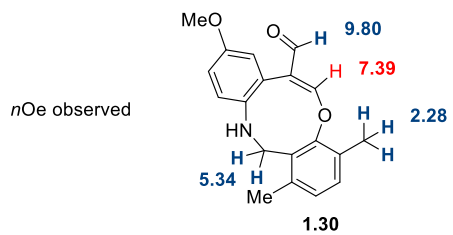
Computational Details

High-level density functional theory (DFT) calculations using the M06-2X[43] approximate exchange-correlation energy density functional have been performed with the standard Pople basis set 6-311+G(d)[44] for all electronegative elements such as N, O, and F, and 6-31G(d)[45] basis set for C and H elements. Calculations were performed in the gas phase at 0 K with tight SCF convergence and ultrafine integration grids. To simulate the solvent effect, the implicit solvent model of CPCM[64] has been employed for the solvent of dichloromethane. For stable structure optimizations, a single-point frequency calculation was carried out after each optimization to make sure that there is no negative frequency. For transition state structure searches, the single-point frequency calculation subsequently performed is to ensure that the final transition state structure obtained has only one imaginary frequency and the vibration mode of the negative frequency corresponds to the bond formation that is anticipated. In addition, intrinsic reaction coordinates (IRC)[28] were calculated to verify the relevance of transition-state structures. All calculations were performed with the package of Gaussian 16 version A03.[65]

Crystal Structure of (–)-1.5i
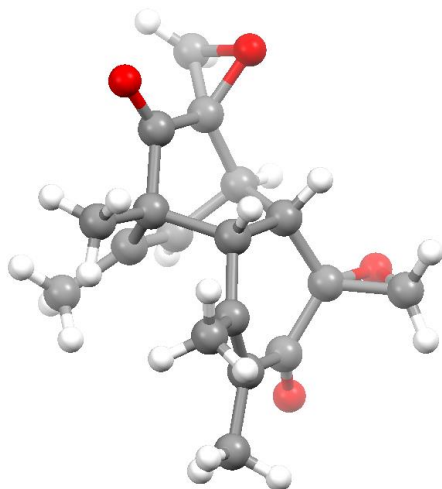
(–)-1.5i

(CCDC 1846094)

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PHENOLIC OXIDATION USING H₂O₂ VIA IN SITU GENERATED PARA-QUINONE METHIDES FOR THE PREPARATION OF PARA-SPIROEPOXYDIENONES *

2.1 Introduction

Phenols are attractive starting materials for the preparation of highly substituted cyclohexane rings via dearomative processes. In the previous chapter, we described the development of a novel oxidative dearomatization of salicyl alcohols via a nucleophilic epoxidation of in situ generated *o*-quinone methides to afford dearomatized *o*-spiroepoxydienones. To build upon and expand the impact of this new dearomative mechanism, herein we report an efficient preparation of dearomatized 1-oxaspiro[2.5]octa-4,7-dien-6-ones (*para*-spiroepoxydienones) via the nucleophilic epoxidation of in situ generated *para*-quinone methides from 4-(hydroxymethyl)phenols using aqueous H₂O₂. The developed protocol bypasses the need for stoichiometric bismuth reagents or diazomethane, which are frequently deployed for *p*-spiroepoxydienone preparation. The *p*-spiroepoxydienones are further elaborated in numerous downstream complexity-building transformations.

2.2 Background

2.2.1 Existing Methods for *p*ara-Spiroepoxydienone Preparation

In 1974, Adler described the preparation of dearomatized 1-oxaspiro[2.5]octa-4,7-dien-6-one (*p*-spiroepoxydienone) **2.1** via the oxidation of 4-(hydroxymethyl)phenol **2.2a** with sodium bismuthate (NaBiO₃) (Scheme 2-1a).[1] While novel, this approach required stoichiometric

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quantities of NaBiO₃ and afforded **2.1** in poor yield (20−30%).[2] Nevertheless, this method for the preparation of *p*-spiroepoxydienones **2.1** has been employed in the synthesis of bioactive and complex molecules.[3] The low yield obtained with NaBiO₃ has resulted in an alternative approach to synthesizing *p*-spiroepoxydienones. The addition of diazomethane (CH₂N₂) into highly substituted *para*-quinone derivatives **2.3** (Scheme 2-1b) affords improved yields of the desired product;[4] however, the dual quinone carbonyls present regioselectivity complications, and serious hazards associated with CH₂N₂ prevent its deployment on large scales. NaIO₄, an enabling reagent for the analogous oxidation of the *ortho*-isomer (Adler−Becker oxidation) has not, to the best of our knowledge, been successfully used for the *para*-isomer, indicating important structural or mechanistic differences.[1]

Scheme 2-1. Methods for Accessing *p*-Spiroepoxydienones and Current Approach
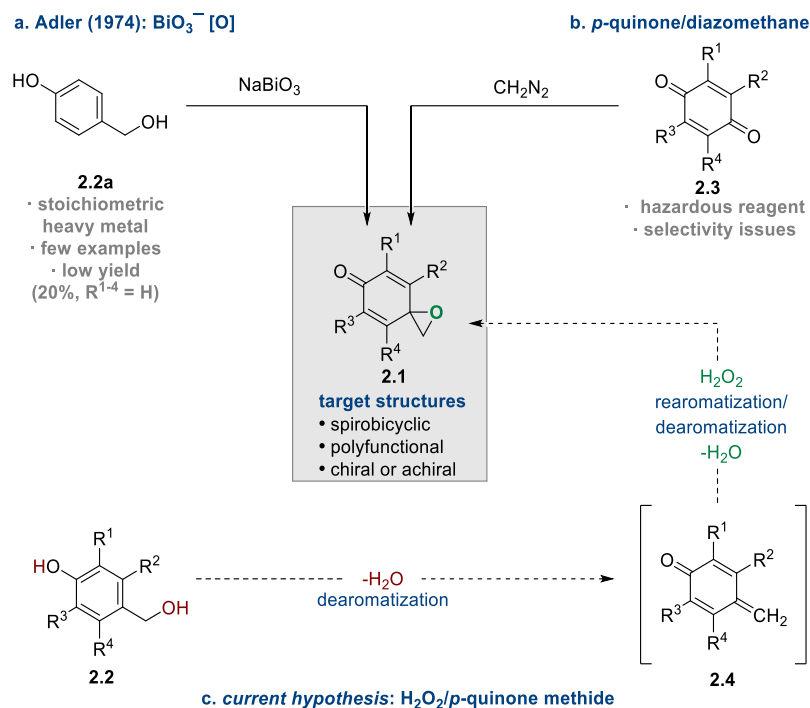
2.2.2 Reaction Design

Because of these limitations to the established methods for *p*-spiroepoxydienone generation as well as the prevalence of naturally occurring bioactive molecules bearing the *p*-spiroepoxide substructure (Figure 2-1),[5] we were interested in the development of a new approach to these privileged scaffolds.

Figure 2-1. Representative Bioactive Compounds Bearing *p*-Spiroepoxide Substructure

nyingchinoid B   ovalicin   isofruticolone
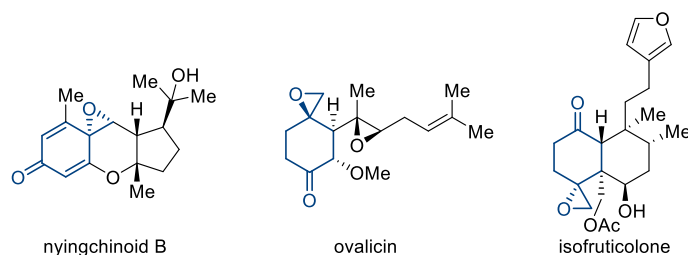
As shown in Chapter 1, the oxidative dearomatization of salicyl alcohol derivatives using H_2O_2 delivered *o*-spiroepoxydienones via a transient *ortho*-quinone methide.[6] Encouraged by the success of this approach, we proposed the reaction design outlined in Scheme 2-1c that accesses *p*-spiroepoxydienones **2.1** from 4-(hydroxymethyl)-phenols **2.2** via the intermediacy of a *para*-quinone methide **2.4**. *para*-Quinone methides **2.4** (*p*QMs) are highly reactive dearomatized intermediates that have been extensively explored in recent years due to their ability to form complex building blocks.[7] The inherent reactivity exhibited by *p*QMs is governed by the strong aromatic driving force, which has predicated numerous nucleophilic 1,6-conjugate additions to afford derivatized phenolic products.[8] Because of this aromatic driving force, transformations involving *p*QMs resulting in isolable, dearomatized building blocks for further elaboration are limited.[9]

2.2.3 *para*-Quinone Methides

Our working hypothesis, outlined in Scheme 2-1, required a resolution to a procedural

challenge in accessing the transient *p*QMs in situ. Because of the high reactivity of these ephemeral

species, a significant majority of methods involving *p*QM intermediates often rely on the prior

synthesis of stable derivatives.[10] Because of the ease of preparation and long shelf lives, these

stable *p*QMs **2.5** have been widely employed;[7,8] however, the strict substrate requirements of stable

*p*QMs **2.5** limit the scope of products available to these transformations (Scheme 2-2a). In contrast,

strategies for the in situ preparation of transient *p*QMs **2.4** using basic conditions have been

reported.[11] These approaches are usually restricted to benzylic aryl substitution, a characteristic

that is often incompatible with the stability of *p*-spiroepoxydienones **2.1** due to rapid

decomposition.[12]

Scheme 2-2. Methods for *p*-Quinone Methide Generation
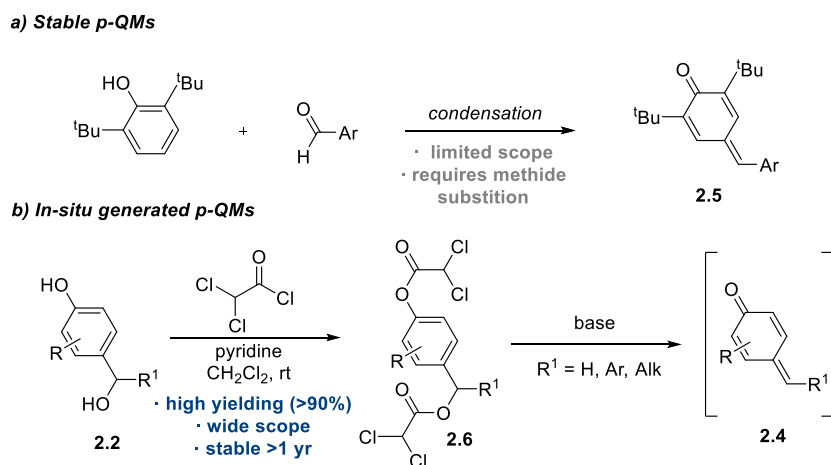
2.2.4 Development of an Efficeint Base-Promoted *para*-Quinone Methide Precursor

As demonstrated in Chapter 1, bis(dichloroacetate) esters of phenolic *o*-benzylic alcohols

are appropriately activated for *o*QM formation in the presence of [(−)]OOH.[6] This cheap and stable

activating group exhibited a wide substrate scope, and *o*QM formation could be easily achieved

via base-promoted phenolic deprotection, followed by the expulsion of the benzylic acetate. Considering the known differences in spiroepoxide synthesis from *ortho-* and *para*-benzylic alcohol phenols, it was an open question as to whether our previous method could be extended to the *para*-series. To test this hypothesis, we prepared a variety of 4-(hydroxymethyl)phenols **2.2** and activated them for projected *p*QM formation via the single-step preparation of heretofore unknown bis(dichloroacetates) **2.6** in high yield (>90%) (Scheme 2-2b).

2.3 Reaction Scope

Using optimized conditions, bis(dichloroacetates) **2.6** were evaluated as suitable reaction partners in the one-pot *p*QM formation and subsequent homo-Weitz−Scheffer epoxidation (Table 2-1).[13] Bis(dichloroacetate) **2.6a** afforded achiral *p*-spiroepoxide **2.1a** in 66% yield, a significant improvement over the NaBiO$_3$-based methodology.[1] Scaling up this dearomatization afforded 5.0 g of **2.1a** while maintaining practical yields. Benzylic alkyl substitution (R[5]) (**2.1b−d**) was tolerated, a trend that held true when employing (±)-synephrine as the phenolic precursor (**2.1c**).

Alkyl substitution (**2.1e−h**) provided for the highest yields due to the increased stability of the *p*QM intermediate.[14] Turning our attention to halogenated substrates, we found that similarly good yields could be obtained with chlorine substitution (**2.1i−k**); however, bromine and iodine were less tolerated under the optimized reaction conditions (**2.1l,m**). Tricyclic spiroepoxides (**2.1n−p**) were obtained in high yield. We identified a few limitations for this reaction. Highly electron-rich substrate **2.6q** was incompatible with the optimized reaction conditions due to the poor electrophilicity of the derived *p*QM. Additionally, we confirmed the instability of R[5] aryl substitution using our reaction conditions.[12] Subjecting bis(dichloroacetate) **2.6r** to the reaction conditions resulted in the isolation of hydroquinone and benzaldehyde, byproducts of the rapid decomposition of spiroepoxide **2.1r**.[1,12]

Table 2-1. Reaction Scope[a]

2.1a
66% yield
[5.0 g: 50% yield]

2.1b
64% yield

2.1c
56% yield

2.1d
69% yield

2.1e
77% yield

2.1f
83% yield[b]

2.1g
81% yield

2.1h
72% yield

2.1i
71% yield

2.1j
67% yield

2.1k
58% yield

2.1l
41% yield

2.1m
20% yield

2.1n
76% yield

2.1o
77% yield

2.1p
70% yield

Incompatible Substrates

2.1q
0% yield

2.1r
0% yield
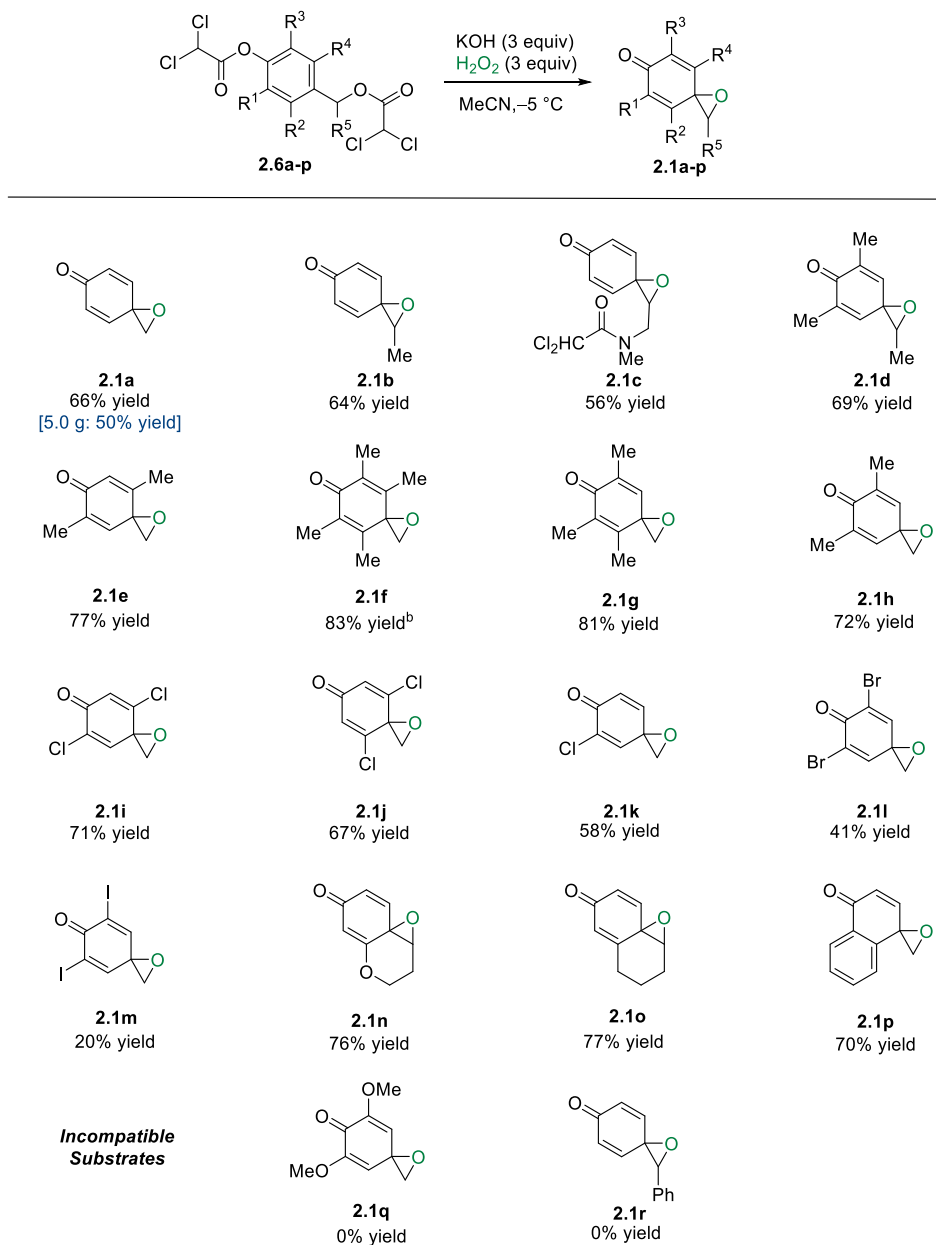
[a]Reactions performed with 1.0 equiv of **2.6** and 3.0 equiv of H_2O_2 and KOH in MeCN ([**2.6**]$_0$= 0.05 M). Isolated yields. [b]4.0 equiv of KOH was used.

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2.4 Synthetic Utility

1-Oxaspiro[2.5]octa-4,7-dien-6-ones **2.1** provide an interesting platform for further derivatization into complex organic frameworks. Until now, the reactivity of these compounds has been sparsely evaluated, presumably because of the lack of efficient preparation strategies. Accordingly, we sought to expand the reactivity profile of the dearomatized species (Scheme 2-3). Initial attempts at functionalizing *p*-spiroepoxydienones **2.1** revealed a unique reactivity as compared with *para*-quinols[15] or 1-oxaspiro[4.5]deca-6,9-dien-8-ones.[9] Namely, *p* spiroepoxydienones **2.1** demonstrated a high proclivity toward rearomatization under a variety of reaction conditions, partially ascribable to the highly strained spiroepoxide moiety. Several transformations such as direct epoxidation, 1,4- or 1,2- addition, and hydrogenation resulted in rearomatization to the parent phenolic compound, in agreement with previous literature;[3,4] however, the selective functionalization of **2.1a** could instead be achieved by accessing Diels−Alder cycloadduct **2.7**[2] using **2.1a** and cyclopentadiene, followed by functionalization of the enone and subsequent retro-Diels−Alder cycloaddition. Using this route, bis-epoxide **2.8** could be prepared as a single diastereomer. Alternatively, pentacycle **2.9** could be realized via the reaction of **2.7** with MeLi, followed by bromonium-promoted cyclization using *N*-bromosuccimide (NBS).[16]

To evaluate the unconventional electrophilic sites of the molecule, various nucleophiles were tested against *p*-spiroepoxydienones **2.1**. The reaction of spiroepoxide **2.1h** with MeMgBr resulted in nucleophilic attack on the epoxide oxygen attaching a pendant alkyl group while reestablishing the aromaticity to afford phenol **2.10**. Conversely, upon exposure to MeLi, spiroepoxide **2.1h** was converted to dearomatized dienone **2.11** via carbonyl addition, followed by a 1,2-alkyl shift to vinylogously open the strained spiroepoxide moiety. Taking advantage of the

new hydroxymethyl handle, the reaction of dienone **2.11** with phenyl isocyanate followed by iodolactamization resulted in spirocarbamate **2.12**. Thermal Diels−Alder cycloaddition between propargyl alcohol and dienone **2.11** afforded bicyclic diene **2.13** featuring two primary alcohols. *p*-Spiroepoxide **2.1a** was highly prone to rearomatization when treated with alkylmetal nucleophiles; however, employing trimethylsilyl cyanide (TMSCN), the 1,2-addition product was isolated as silyl ether **2.14**, preventing the 1,2-cyano shift to restore aromaticity.

Scheme 2-3. Chemoselective Transformations of *p*-Spiroepoxydienones
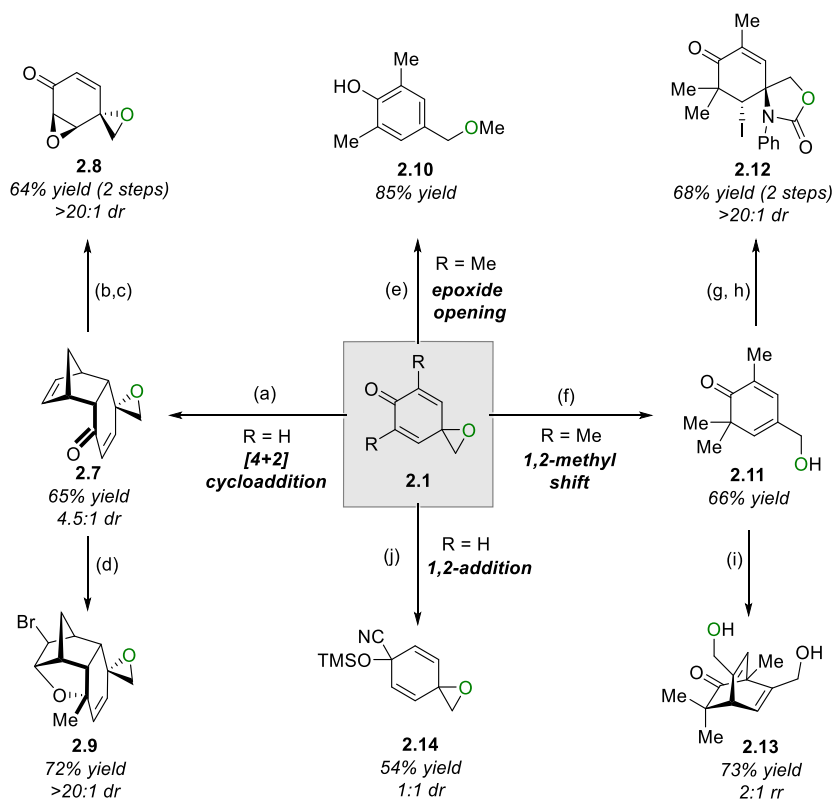
Conditions: [a]cyclopentadiene (3.0 equiv), TFE, 35 °C; [b]K_2CO_3 (50 mol %), 30% aq H_2O_2 (3.0 equiv), acetone, rt; [c]Ph_2O, 220 °C; [d]MeLi (1.1 equiv), THF, −78 °C, then NBS (1.1 equiv), CH_2Cl_2, rt; [e]MeMgBr (1.1 equiv), THF, −78 °C; [f]MeLi (1.0 equiv), THF, −78 °C; [g]PhNCO (1.1 equiv), DBU (1.0 equiv), CH_2Cl_2, rt; [h]NIS (4.0 equiv), MeCN, 50 °C; [i]propargyl alcohol (3.0 equiv), Ph_2O, 180 °C; [j]TMSCN (1.5 equiv), KF (10 mol %), MeCN, 0 °C to rt.

2.5 Failed Attempt at Enantioselective *para*-Epoxidation

Our previous success with developing an enantioselective nucleophilic epoxidation of *ortho*-quinone methides using a chiral phase-transfer catalyst inspired our attempt at preparing enantioenriched *para*-spiroepoxides.[6] Employing quinine-derived phase-transfer catalyst **2.15,** urea·H$_2$O$_2$ (UHP), and bis(dichloroacetate) **2.6e**, the enantioselective reaction was attempted. While the reaction proceeded in good yields, resultant spiroepoxide **2.1e** was racemic.

Scheme 2-4. Attempted Enantioselective Epoxidation Using Phase-Transfer Catalyst **2.15**
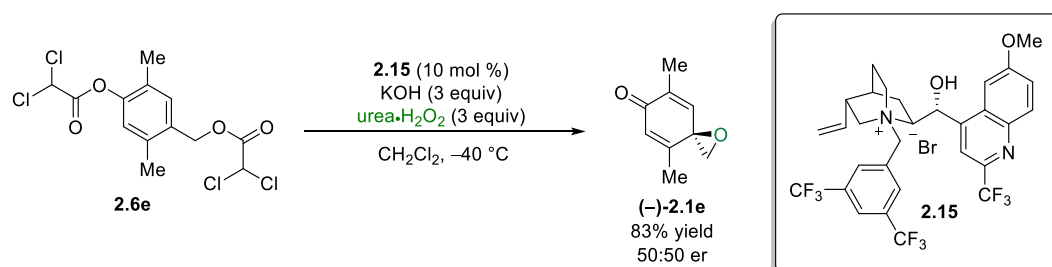
2.6 Conclusion

In conclusion, we have developed an efficient preparation for *p*-spiroepoxydienones that proceeds through an in situ generated *p*-quinone methide. This method bypasses the need for stoichiometric bismuth or hazardous diazomethane by using aqueous H$_2$O$_2$ as the oxidant while allowing superior yield and substrate scope. The unique reactivity these *p*-spiroepoxydienones exhibit was further explored via numerous complexity-building transformations. This methodology demonstrates the potential for complementary dearomative processes via *p*-quinone methide intermediates, and our laboratory is currently exploring these possibilities.

2.7 Experimental Details

General 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 staining in an aqueous ceric ammonium molybdate (CAM) or potassium permanganate (KMnO$_4$) solution, followed by gentle heating. Column chromatography was performed under positive nitrogen pressure using Siliaflash P60 silica gel (40-63 μm) purchased from Silicycle. Yields are reported for a specific experiment and may differ slightly from those found in figures, which are averages of at least two experiments.

Instrumentation

^{1}H NMR and ^{13}C NMR were recorded on either a Bruker model DRX 400, 500, or 600 (cryoprobe equipped) spectrometer. The spectra were calibrated using residual solvent resonances: ^{1}H NMR (CDCl$_3$ at 7.28 ppm, (CD$_3$)$_2$SO at 2.50 ppm) and ^{13}C NMR (CDCl$_3$ at 77.0 ppm, (CD$_3$)$_2$SO at 39.51 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td = triplet of doublets, tt = triplet of triplets, qt = quintet, sept = septet, and m = multiplet), coupling constants (Hz) and integration. High resolution mass spectrometry (HRMS) was performed using a Thermo Scientific Q Exactive HF-X mass spectrometer with direct infusion in the positive ion mode. Samples were prepared in HPLC grade methanol. Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier Transform Infrared Spectrometer. Yields refer to the isolated yield of pure material unless otherwise noted.

Materials

Solvents were not dried prior to use unless specified as "anhydrous." Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (PhMe), diethyl ether (Et_2O), dimethylsulfoxide, (DMSO), and acetonitrile (MeCN) were dried by passage through a column of neutral alumina under nitrogen prior to use. All chemicals were purchased from either Fisher Scientific, Sigma-Aldrich, Alfa-Aesar, or Oakwood and used as received. 2-(hydroxymethyl)-3,5,6-trimethylphenol,[6] 2,6-dibromo-4-(hydroxymethyl)phenol (**2.1l**),[17] and 2,6-diiodo-4-(hydroxymethyl)phenol[18] (**2.1m**) were prepared according to their respective literature procedures.

Experimental Procedures

Preparation of 4-(Hydroxymethyl)phenols 2.2:

General Procedure A for Preparation of 4-(Hydroxymethyl)phenols 2.2:
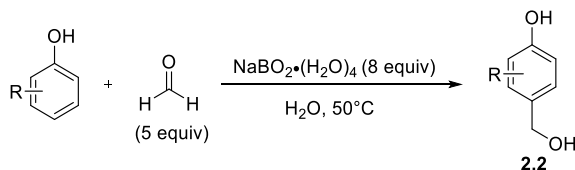
para-Hydroxymethylation of phenols was accomplished using a known literature procedure.[19] To a round-bottomed flask equipped with a magnetic stir bar was added the starting phenol (1.0 equiv), water ([phenol]$_0$ = 0.2 M), sodium metaborate tetrahydrate (8.0 equiv), and 37% aqueous formaldehyde (5.0 equiv). The reaction was stirred at 50 °C until disappearance of the starting phenol was observed by TLC analysis (usually 12-16 h). After completion, the reaction was cooled to room temperature and acidified with aqueous HCl (3 M) to pH 4. The product was extracted thrice with ethyl acetate and the combined organic extracts were washed with water and then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel to afford the desired (hydroxymethyl)phenol **2.2**.
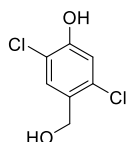
2,5-dichloro-4-(hydroxymethyl)phenol (2.2i): The title compound was prepared according to the General Procedure A using 2,5-dichlorophenol (1.00 g, 6.13 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 756 mg (64%) of the title compound as a white solid. Analytical data: **^{1}H NMR** (400 MHz, (CD$_3$)$_2$SO) δ 10.54 (br s, 1H), 7.42 (s, 1H), 6.97 (s, 1H), 5.31 (bs, 1H), 4.43 (s, 2H); **^{13}C NMR** (151 MHz, (CD$_3$)$_2$SO) δ 152.5, 131.1, 129.6, 129.1, 118.6, 116.6, 59.6; **mp** 144-145 °C; **IR** (thin

film, cm^{-1}): 3456, 3072, 2348; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.37; **HRMS** (ESI$^+$) Calcd. for $C_7H_6Cl_2NaO_2$: ([M+Na]): 214.9643, Found: 214.9635.
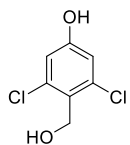
3,5-dichloro-4-(hydroxymethyl)phenol (2.2j): The title compound was prepared according to the General Procedure A using 3,5-dichlorophenol (1.00 g, 6.13 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 784 mg (66%) of the title compound as a white solid. Analytical data: **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ 10.34 (br s, 1H), 6.82 (s, 2H), 4.56 (s, 2H). **^{13}C NMR** (151 MHz, $(CD_3)_2SO$) δ 157.7, 135.7, 126.9, 115.4, 57.7. **mp** 169-171 °C; **IR** (thin film, cm^{-1}): 3389, 2959, 1572; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.33; **HRMS** (ESI$^+$) Calcd. for $C_7H_6Cl_2NaO_2$: ([M+Na]): 214.9643, Found: 214.9634.
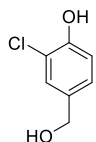
2-chloro-4-(hydroxymethyl)phenol (2.2k): The title compound was prepared according to the General Procedure A using 2-chlorophenol (5.00 g, 38.9 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 2.60 g (42%) of the title compound as a white solid. Spectroscopic properties were consistent with those previously reported.[20] Analytical data: **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 9.98 (s, 1H), 7.25 (s, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 5.10 (t, J = 5.7 Hz, 1H), 4.36 (d, J = 5.6 Hz, 2H).

General Procedure B for Preparation of 4-(Hydroxymethyl)phenols 2.2:
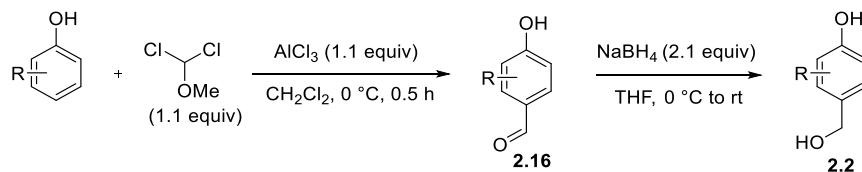
To a flame-dried round-bottomed flask equipped with a magnetic stir bar was added the starting

phenol (1.0 equiv) and CH_2Cl_2 ([phenol]$_0$ = 0.2 M). The solution was cooled to 0 °C and purged

with nitrogen. $AlCl_3$ (1.1 equiv) was added slowly in portions by spatula and the reaction was

stirred for a further 10 min. Dichloro(methoxy)methane (1.1 equiv) was added via syringe over 5

min. The reaction was stirred for 30 min. Excess $AlCl_3$ was quenched by slowly adding ice water

and the mixture was stirred for an additional 10 min. The product was diluted with water and the

organic layer was removed. The aqueous layer was extracted three times with CH_2Cl_2. The organic

layers were combined, washed with brine, dried with Na_2SO_4, filtered, and concentrated. Crude

2.16 was dissolved in anhydrous THF ([**2.16**]$_0$ = 0.2 M) and added to another flame-dried round-

bottomed flask. The solution was cooled to 0 °C. $NaBH_4$ (2.1 equiv) was added in portions and the

reaction was stirred at 0 °C for 20 min and then at room temperature for 20 min. The reaction was

cooled back to 0 °C and quenched by slowly adding ice water. The solution was acidified with

aqueous HCl (1 M) to pH 4. Excess THF was removed *in vacuo* and the product was extracted

three times with ethyl acetate. The organic layers were combined and washed with brine, dried

over Na_2SO_4, filtered, and concentrated. The crude material was purified by column

chromatography on silica gel to afford the desired (hydroxymethyl)phenol **2.2**.
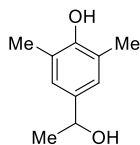
4-(1-hydroxyethyl)-2,6-dimethylphenol (2.2d): The title compound was prepared according to General Procedure B using 2,6-dimethylphenol (2.00, 16.4 mmol) with the following modification: MeMgBr (3.0 M in Et$_2$O, 12.0 mL, 36.1 mmol) was added to a solution of the crude aldehyde in THF at 0 °C and allowed to react for 40 min before following the quenching and workup procedure described in General Procedure B. The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 1.14 g (42% over two steps) of the title compound as a light orange solid. Analytical data: **^{1}H NMR** (600 MHz, (CDCl$_3$)) δ 7.01 (s, 2H), 4.80 (q, J = 6.4 Hz, 1H), 4.76 (bs, 1H), 2.27 (s, 6H), 1.49 (d, J = 6.4 Hz, 3H); **^{13}C NMR** (151 MHz, (CDCl$_3$)) δ151.5, 137.3, 125.7 (2C), 123.0 (2C), 70.1, 24.9, 16.0 (2C); **mp** 97-98 °C; **IR** (thin film, cm^{-1}): 3429, 1645; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.42; **HRMS** (ESI$^+$) Calcd. for C$_{10}$H$_{14}$NaO$_2$: ([M+Na]): 189.0892, Found: 189.0891.
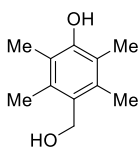
4-(hydroxymethyl)-2,3,5,6-tetramethylphenol (2.2f): The title compound was prepared according to the General Procedure B using 2,3,5,6-tetramethylphenol **2.17** (1.50 g, 10 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 1.12 g (64% over two steps) of the title compound as a white solid. Analytical data: **^{1}H NMR** (400 MHz, (CD$_3$)$_2$SO) δ 7.84 (s, 1H), 4.44 (s, 3H), 2.19 (s, 6H), 2.08 (s, 6H); **^{13}C NMR** (151 MHz, (CD$_3$)$_2$SO) δ 151.7, 133.3, 129.5, 120.5, 58.0, 15.7, 13.0; **mp** 168-169 °C; **IR** (thin film, cm^{-1}): 3436, 3281, 2916, 1573; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.42; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_{16}$NaO$_2$: ([M+Na]): 203.1048, Found: 203.1044.
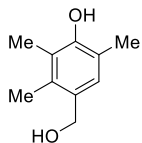
4-(hydroxymethyl)-2,3,6-trimethylphenol (2.2g): The title compound was prepared according to the General Procedure B using 2,3,6-trimethylphenol (3.00 g, 22.0 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 3.32 g (91% over two steps) of the title compound as a white solid. Analytical data: **^{1}H NMR** (600 MHz, (CD$_3$)$_2$SO) δ 7.94 (s, 1H), 6.83 (s, 1H), 4.78 – 4.69 (m, 1H), 4.35 (d, J = 5.2 Hz, 2H), 2.12 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H); **^{13}C NMR** (151 MHz, (CD$_3$)$_2$SO) δ 151.8, 132.5, 130.9, 127.6, 123.2, 120.5, 62.0, 16.7, 14.8, 12.5; **mp** 98-99 °C; **IR** (thin film, cm^{-1}): 3436, 3281, 2916, 1573; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.35; **HRMS** (ESI$^+$) Calcd. for C$_{10}$H$_{14}$NaO$_2$: ([M+Na]): 189.0892, Found: 189.0886.
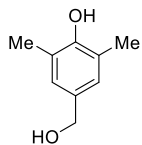
4-(hydroxymethyl)-2,6-dimethylphenol (2.2h): The title compound was prepared according to General Procedure B using 2,6-dimethylphenol (3.00 g, 24.6 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 3.30 g (88% over two steps) of the title compound as an orange solid. Analytical data: **^{1}H NMR** (600 MHz, (CD$_3$)$_2$SO) δ 8.04 (s, 1H), 6.84 (s, 2H), 4.88 (t, J = 5.7 Hz, 1H), 4.31 (d, J = 5.6 Hz, 2H), 2.14 (s, 6H); **^{13}C NMR** (151 MHz, (CD$_3$)$_2$SO) δ 151.9, 132.9, 126.9, 123.7, 62.9, 16.7; **mp** 103-104 °C; **IR** (thin film, cm^{-1}): 3340, 2900, 1364; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.3; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_{12}$NaO$_2$: ([M+Na]): 175.0735, Found: 175.0730.
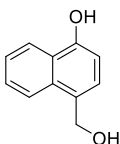
4-(hydroxymethyl)naphthalen-1-ol (2.2p): The title compound was prepared according to the General Procedure B using naphthalen-1-ol (2.00 g, 13.9 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 1.39 g (57% over two steps) of the title compound as a brown solid. Analytical data: **^{1}H**

NMR (400 MHz, (CD$_3$)$_2$SO) δ 10.03 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.54 – 7.41 (m, 4H), 7.29 (d, J = 7.7 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 5.06 (s, 1H), 4.82 (d, J = 3.6 Hz, 3H); **^{13}C NMR** (151 MHz, (CD3)$_2$SO) δ 152.7, 132.3, 128.2, 126.1, 125.8, 124.8, 123.4, 124.0, 122.4, 107.1, 61.4; **mp** 99-100 °C; **IR** (thin film, cm^{-1}): 3396, 2359; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.38; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_{10}$NaO$_2$: ([M+Na]): 197.0579, Found: 197.0574.

Miscellaneous Preparations of 4-(Hydroxymethyl)phenols 2.2:
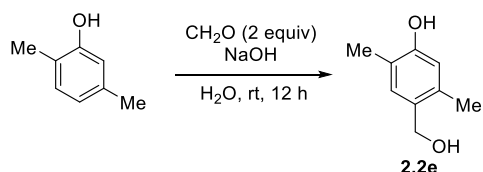
4-(hydroxymethyl)-2,5-dimethylphenol (2.2e): A round-bottomed flask equipped with a magnetic stir bar was charged with NaOH (327 mg, 8.19 mmol) and water (30 mL). 2,5-Dimethylphenol (1.0 g, 8.19 mmol) and formaldehyde (37% aqueous, 1.28 ml, 17.2 mmol) were added and the reaction was stirred for 12 h at room temperature. The reaction was quenched by acidifying with aqueous HCl (3 M) until pH 4 was reached and then extracting with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine, dried with Na$_2$SO$_4$ and filtered. The filtrate was concentrated to afford a colorless oil which was then purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 745 mg (60%) of the desired product as an off-white solid. Analytical data: **^{1}H NMR** (600 MHz, (CD$_3$)$_2$SO) δ 9.00 (s, 1H), 6.95 (s, 1H), 6.54 (s, 1H), 4.75 (t, J = 5.4 Hz, 1H), 4.32 (d, J = 5.3 Hz, 2H), 2.14 (s, 3H), 2.05 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 154.0, 133.6, 130.3, 120.1, 116.2, 61.1, 18.1, 15.6; **mp** 170-171 °C; **IR** (thin film, cm^{-1}): 3416, 3186; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.25; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_{12}$NaO$_2$: ([M+Na]): 175.0735, Found: 175.0730.
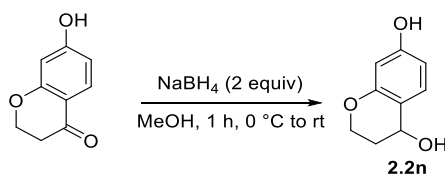
chromane-4,7-diol (2.2n): A flame-dried flask equipped with a magnetic stir bar was charged with 6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (200 mg, 1.22 mmol) and anhydrous MeOH (10 mL). The solution was cooled to 0 °C and NaBH$_4$ (92.2 mg, 2.44 mmol) was added in portions. The reaction was stirred for 10 min at 0 °C and then left to stir for 50 min at room temperature. Methanol was removed *in vacuo* and the residue was purified by column chromatography (40/60 ethyl acetate/hexanes to afford 85 mg (0.51 mmol, 42% yield) of the title compound as a colorless oil. Analytical data: **^{1}H NMR** (500 MHz, (CD$_3$)$_2$SO) δ 9.28 (s, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.29 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.12 (d, *J* = 2.4 Hz, 1H), 5.11 (d, *J* = 5.1 Hz, 1H), 4.49 (dd, *J* = 10.5 Hz, 4.2 Hz, 1H), 4.11 (dd, *J* = 8.3, 3.1 Hz, 3H), 1.91 (ddt, *J* = 13.6, 8.1, 4.8 Hz, 1H), 1.79 (ddd, *J* = 13.4, 9.0, 4.3 Hz, 1H); **^{13}C NMR** (126 MHz, (CD$_3$)$_2$SO) δ 157.7, 155.0, 130.8, 116.9, 107.9, 102.1, 61.8, 61.1, 31.4; **IR** (thin film, cm^{-1}): 3368; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.21; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_{10}$NaO$_3$: ([M+Na]): 189.0528, Found: 189.0526.

*Note: Compound **2.2n** is very prone to decomposition in the presence of acid or heat. Care should be taken to avoid these conditions during workup procedures.*
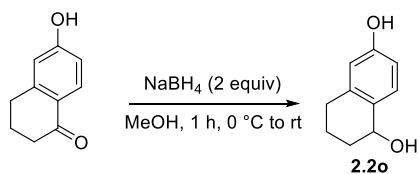
1,2,3,4-tetrahydronaphthalene-1,6-diol (2.2o): A flame-dried flask equipped with a magnetic stir bar was charged with 6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (1.50 g, 9.25 mmol) and anhydrous MeOH (40 mL). The solution was cooled to 0 °C and NaBH$_4$ (700 mg, 18.5 mmol) was

added in portions. The mixture was stirred for 10 min at 0 °C and then left to stir for 50 min at room temperature. The reaction was then cooled back to 0 °C and cold water was added to quench the reaction. Methanol was removed *in vacuo* and the residue was retaken up in ethyl acetate, washed with water (1 x 10 mL) and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford a colorless oil. The oil was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 254 mg (63%) of the title compound as a white solid. Analytical data: **¹H NMR** (600 MHz, $(CD_3)_2SO$) δ 9.12 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.56 – 6.51 (m, 1H), 6.42 (s, 1H), 4.85 (d, *J* = 5.8 Hz, 1H), 4.47 (dd, *J* = 10.2 ,4.8 Hz, 1H), 2.62 (dt, *J* = 16.4, 5.3 Hz, 1H), 2.57-2.51 (m, 1H), 1.90 – 1.74 (m, 2H), 1.72 – 1.51 (m, 2H); **¹³C NMR** (151 MHz, $(CD_3)_2SO$) δ 155.9, 137.6, 130.9, 129.8, 114.2, 113.1, 65.9, 32.7, 29.1, 18.9; **mp** 98-99 °C; **IR** (thin film, cm⁻¹): 3390; **TLC** (30/70 Ethyl acetate/hexanes): R_f = 0.43; **HRMS** (ESI⁺) Calcd. for $C_{10}H_{12}NaO_2$: ([M+Na]): 187.0735, Found: 187.0730.

*Note: Compound **2.2o** is very prone to decomposition in the presence of acid or heat. Care should be taken to avoid these conditions.*

2.17
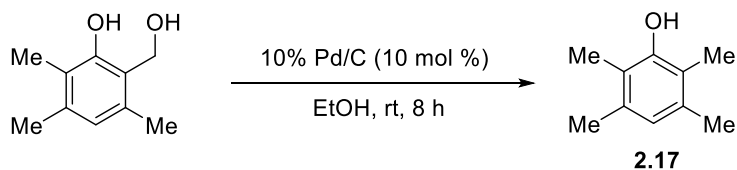
2,3,5,6-tetramethylphenol (2.17): A flame-dried round-bottomed flask equipped with a magnetic stir bar under nitrogen was charged with 10% Pd/C (256 mg, 2.4 mmol) and EtOH (40 mL). A solution of 2-(hydroxymethyl)-3,5,6-trimethylphenol[7] (2.00 g, 12.0 mmol) in EtOH (10 mL) was added and the reaction vessel was purged with hydrogen. The reaction was stirred under an atmosphere of H_2 (balloon) at room temperature for 8 h. The reaction vessel was purged with nitrogen and water (5 mL) was added. The reaction was filtered through a plug of Celite®. The

filtrate was transferred to a separatory funnel and the aqueous layer was removed. The organic layer was washed once with brine, dried over Na_2SO_4, filtered, and concentrated to afford 1.70 g (94%) of the title compound as a white solid. Spectral properties were consistent with those reported previously.[21] Analytical data: **¹H NMR** (400 MHz, $CDCl_3$) δ 6.63 (s, 1H), 4.62 (s, 1H), 2.24 (s, 6 H), 2.16 (s, 6 H).

Preparation of Bis(dichloroacetates) 2.6:
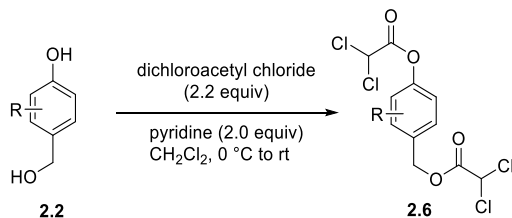
General Procedure C for Preparation of Bis(dichloroacetate)s 2.6: To a flame-dried round-bottomed flask was added the starting (hydroxymethyl)phenol **2.2** (1.0 equiv) and anhydrous CH$_2$Cl$_2$ ([**2.2**]$_0$ = 0.4 M). The flask was cooled to 0 °C and pyridine (2.0 equiv) was added. The solution was stirred for five min after which time dichloroacetyl chloride (2.2 equiv) was added dropwise. Once the acid chloride was fully added, the reaction mixture was stirred at room temperature for 20 min. The solution was directly filtered through a plug of silica gel with CH$_2$Cl$_2$ as the eluent. The filtrate was concentrated to afford the desired bis(dichloroacetate) product. These compounds were stored at −20 °C until used.

Note 1: When conducting the filtration over silica, the authors noticed a yellow/orange band would appear on the silica gel. For optimal purity, it was best to ensure that this band did not reach the collection flask.
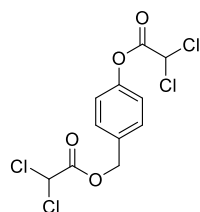
4-(2,2-dichloroacetoxy)benzyl 2,2-dichloroacetate (2.6a): The title compound was prepared according to General Procedure C using **2.2a** (400 mg, 3.28 mmol) to afford **2.6a** (1.06 g, 3.06 mmol, 95% yield) as a light yellow oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.18 (s, 1H), 6.00 (s, 1H), 5.31 (s, 2H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 164.2, 162.8, 150.3, 132.9, 129.9, 121.2, 68.1, 64.1, 64.0; **IR** (thin film, cm^{-1}): 3013, 1763, 1508, 1295, 1163; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.62; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_8$Cl$_4$NaO$_4$: ([M+Na]): 366.9074, Found: 366.907.
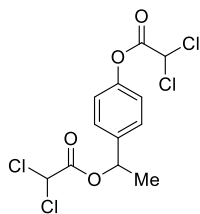
4-(1-(2,2-dichloroacetoxy)ethyl)phenyl 2,2-dichloroacetate (2.6b): The title compound was prepared according to General Procedure C using **2.2b** (255 mg, 1.85 mmol) to afford **2.6j** (650 mg, 1.81 mmol, 98% yield) as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.47 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 6.18 (s, 1H), 5.99 (q, J = 6.6 Hz, 1H), 5.97 (s, 1H), 1.66 (d, J = 6.6 Hz, 3H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 163.5, 162.9, 150.0, 138.5, 127.5, 121.0, 75.2, 64.3, 64.1, 21.8; **IR** (thin film, cm^{-1}): 2988, 1779, 1508, 1290, 1166; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.64; **HRMS** (ESI$^+$) Calcd. for C$_{12}$H$_{10}$Cl$_4$NaO$_4$: ([M+Na]): 380.9231, Found: 380.9230.

4-(2-(2,2-dichloro-N-methylacetamido)-1-(2,2-dichloroacetoxy)ethyl) phenyl 2,2-dichloroacetate (2.6c): The title compound was prepared according to General Procedure C using (±)-synephrine (500 mg, 2.99 mmol) with the following modification: 3.2 equiv. of dichloroacetyl chloride was used and reaction was cooled to 0 °C before addition of acetyl chloride. The reaction afforded **2.6c** (1.35 g, 2.70 mmol, 90% yield) as a white solid. A rotamer ratio of 7:1 was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 3.89 (major rotamer) and δ 4.08 (minor rotamer). Analytical data: **Major Rotamer ^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.50 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 6.24 (s, 1H), 6.20 – 6.12 (m, 2H), 5.99 (s, 1H), 3.89 (dd, J = 14.3, 3.7 Hz, 1H), 3.72 (dd, J = 14.3, 9.3 Hz, 1H), 3.30 (s, 3H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 164.0, 163.1, 162.8, 150.4, 134.5, 127.7, 121.4, 75.9, 65.0, 64.02, 63.99, 54.7, 37.9; **Minor Rotamer ^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.48 (s, 2H), 7.30 (d, J = 8.5 Hz, 2H), 6.33 (s, 1H), 6.16 (d, J = 3.6 Hz, 2H), 6.05 (dd, J = 9.1, 3.5 Hz, 1H), 6.00 (s, 1H), 4.08 (dd, J = 15.9, 9.1 Hz, 1H), 3.69 (s, 1H), 3.11 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ

163.9, 163.1, 162.7, 150.8, 133.7, 127.7, 121.9, 75.5, 64.6, 63.9, 63.7, 54.3, 36.0; **mp** 99-100 °C; **IR** (thin film, cm^{-1}): 1732, 1689; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.60; **HRMS** (ESI$^+$) Calcd. for C$_{15}$H$_{13}$Cl$_6$NNaO$_5$: ([M+Na]): 519.8823, Found: 519.8819.

1-(4-(2,2-dichloroacetoxy)-3,5-dimethylphenyl)ethyl 2,2-dichloroacetate (2.6d): The title compound was prepared according to General Procedure C using **2.2d** (500 mg, 3.00 mmol) to afford **2.6d** (1.06 g, 2.73 mmol, 91% yield) as an amorphous orange solid. Analytical data: ^{1}**H NMR** (600 MHz, CDCl$_3$): δ

7.12 (s, 1H), 6.22 (s, 1H), 5.97 (s, 1H), 5.91 (q, J = 6.6 Hz, 1H), 2.22 (s, 3H), 1.63 (d, J = 6.6 Hz, 2H); ^{13}**C NMR** (151 MHz, CDCl$_3$): δ163.6, 162.1, 147.1, 138.2, 130.4 (2C), 126.7 (2C), 75.4, 64.4, 63.4, 21.7, 16.1; **mp** 43-45 °C; **IR** (thin film, cm^{-1}): 3013, 1768, 1506, 1275, 1152; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.64; **HRMS** (ESI$^+$) Calcd. for C$_{14}$H$_{14}$Cl$_4$NaO$_4$: ([M+Na]): 408.9543, Found: 408.9538.
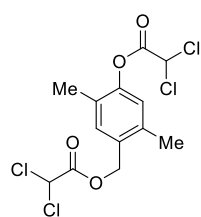
4-(2,2-dichloroacetoxy)-2,5-dimethylbenzyl 2,2-dichloroacetate (2.6e): The title compound was prepared according to General Procedure C using **2.2e** (400 mg, 2.63 mmol) to afford **2.6e** (907 mg, 2.42 mmol, 92% yield) as a white solid. Analytical data: ^{1}**H NMR** (600 MHz, CDCl$_3$): δ 7.28 (s, 1H), 6.98 (s, 1H), 6.21 (s, 1H), 6.00 (s, 1H), 5.28 (s, 2H), 2.37 (s, 3H), 2.23 (s, 3H); ^{13}**C NMR** (151 MHz, CDCl$_3$): δ 164.2, 162.7, 148.7, 136.8, 132.9, 130.9, 127.5, 123.0, 66.9, 64.1, 64.0, 18.5, 15.4; **mp** 43-45 °C; **IR** (thin film, cm^{-1}): 3013, 1768, 1506, 1275, 1152; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.64; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{12}$Cl$_4$NaO$_4$: ([M+Na]): 394.9387, Found: 394.9386.
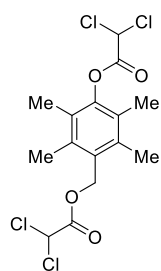
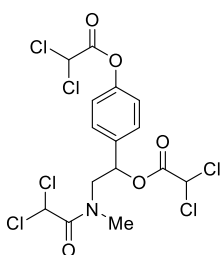**4-(2,2-dichloroacetoxy)-2,3,5,6-tetramethylbenzyl 2,2-dichloroacetate (2.6f):** The title compound was prepared according to General Procedure C using **2.2f** (200 mg, 1.11 mmol) to afford **2.6f** (419 mg, 1.04 mmol, 94% yield) as a white solid. Analytical data: ^{1}**H NMR**: (600 MHz, CDCl$_3$) δ 6.24 (s, 1H), 5.97 (s, 1H), 5.44 (s, 3H), 2.33 (s, 4H), 2.14 (s, 4H); ^{13}**C NMR**: (150 MHz, CDCl$_3$) δ 164.6, 162.4, 147.7, 136.4, 129.2, 126.4, 64.7, 64.2, 64.1, 16.0, 13.0; **mp** 109-110 °C; **IR** (thin film, cm^{-1}): 3434, 1752; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.73; **HRMS** (ESI$^+$) Calcd. for C$_{15}$H$_{16}$Cl$_4$NaO$_4$: ([M+Na]): 422.9701, Found: 422.9698.

4-(2,2-dichloroacetoxy)-2,3,5-trimethylbenzyl 2,2-dichloroacetate (2.6g): The title compound was prepared according to General Procedure C using **2.2g** (200 mg, 1.20 mmol) to afford **2.6g** (437 mg, 1.13 mmol, 94% yield) as a white solid. Analytical data: ^{1}**H NMR** (600 MHz, CDCl$_3$): δ 7.14 (s, 1H), 6.23 (s, 1H), 5.99 (s, 1H), 5.29 (s, 2H), 2.28 (s, 3H), 2.20 (s, 3H), 2.15 (s, 3H); ^{13}**C NMR** (150 MHz, CDCl$_3$): δ 164.3, 163.2, 147.6, 135.7, 130.6, 130.3, 129.5, 127.3, 67.9, 64.2, 64.0, 15.9, 15.4, 12.7; **mp** 75-76 °C; **IR** (thin film, cm^{-1}): 3014, 1764, 1479, 1157; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.73; **HRMS** (ESI$^+$) Calcd. for C$_{14}$H$_{14}$Cl$_4$NaO$_4$: ([M+Na]): 408.9544, Found: 408.9542.
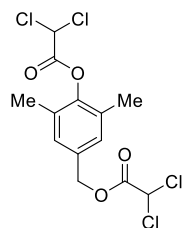
4-(2,2-dichloroacetoxy)-3,5-dimethylbenzyl 2,2-dichloroacetate (2.6h): The title compound was prepared according to General Procedure C using **2.2h** (500 mg, 3.29 mmol) to afford **2.6h** (1.18 g, 3.14 mmol, 96% yield) as a slightly yellow solid. Analytical data: ^{1}**H NMR** (600 MHz, CDCl$_3$): δ 7.14 (s, 2H), 6.23 (s, 1H), 6.00 (s, 1H), 5.24 (s, 2H), 2.23 (s, 6H); ^{13}**C NMR** (150 MHz, CDCl$_3$): δ 164.3, 152.1, 147.5, 132.6,

130.6, 129.0, 68.3, 64.1, 63.9, 16.1; **mp** 59-60 °C; **IR** (thin film, cm^{-1}): 1766; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.65; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{12}$Cl$_4$NaO$_4$: ([M+Na]): 394.9387, Found: 394.9390.

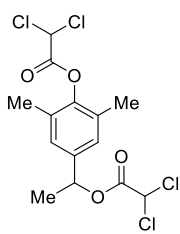**2,5-dichloro-4-((2,2-dichloroacetoxy)methyl)phenyl   2,2-dichloroacetate (2.6i):** The title compound was prepared according to General Procedure C using **2.2i** (125 mg, 0.648 mmol) to afford **2.6i** (256 mg, 0.617 mmol, 95% yield) as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.62 (s, 1H), 7.36 (s, 2H), 6.23 (s, 1H), 6.05 (s, 1H), 5.38 (s, 2H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 163.9, 161.6, 146.3, 132.4, 132.3, 131.1, 125.7, 124.3, 64.9, 63.9, 63.4; **IR** (thin film, cm^{-1}): 3012, 1770, 1595, 1572, 1459; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.46; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_6$Cl$_6$NaO$_4$: ([M+Na]): 434.8295, Found: 434.8293.

3,5-dichloro-4-((2,2-dichloroacetoxy)methyl)phenyl   2,2-dichloroacetate (2.6j): The title compound was prepared according to General Procedure C using **2.2j** (350 mg, 1.81 mmol) to afford **2.6j** (715 mg, 1.72 mmol, 95% yield) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.32 (s, 2H), 6.17 (s, 1H), 5.99 (s, 1H), 5.57 (s, 2H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 164.1, 162.0, 150.5, 137.8, 128.7, 121.4, 63.9, 63.6, 63.2; **mp** 61-62; **IR** (thin film, cm^{-1}): 1770; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.50; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_6$Cl$_6$NaO$_4$: ([M+Na]): 434.8295, Found: 434.8293.

2-chloro-4-((2,2-dichloroacetoxy)methyl)phenyl 2,2-dichloroacetate (2.6k): The title compound was prepared according to General Procedure C using **2.2k** (300 mg, 1.89 mmol) to afford **2.6k** (680 mg, 1.79 mmol, 95% yield) as a colorless oil. Analytical data: **¹H NMR** (600 MHz, CDCl₃): δ 7.55 (s, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 6.24 (s, 1H), 6.02 (s, 1H), 5.29 (s, 2H); **¹³C NMR** (150 MHz, CDCl₃): δ 164.1, 161.9, 146.2, 134.5, 130.4, 127.8, 127.1, 123.2, 67.2, 63.9, 63.6; **IR** (thin film, cm⁻¹): 1768; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.69; **HRMS** (ESI⁺) Calcd. for C₁₁H₇Cl₅NaO₄: ([M+Na]): 400.8684, Found: 400.8685.
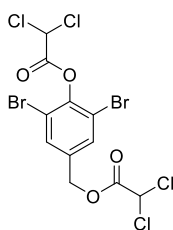
2,6-dibromo-4-((2,2-dichloroacetoxy)methyl)phenyl 2,2-dichloroacetate (2.6l): The title compound was prepared according to General Procedure C using **2.2l** (300 mg, 1.06 mmol) to afford **2.6l** (501 mg, 1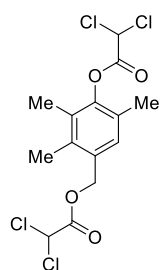.00 mmol, 94% yield) as a white solid. Analytical data: **¹H NMR** (600 MHz, CDCl₃): δ 7.64 (s, 2H), 6.28 (s, 1H), 6.03 (s, 1H), 5.26 (s, 2H); **¹³C NMR** (150 MHz, CDCl₃): δ 164.0, 160.6, 145.2, 135.8, 132.2 (2C), 117.4 (2C), 66.3, 63.8, 63.5; **IR** (thin film, cm⁻¹): 1772, 1241; **mp** 51-52°C**; TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.63; **HRMS** (ESI⁺) Calcd. for C₁₁H₆Br₂Cl₄NaO₄: ([M+Na]): 522.7285, Found: 522.7276.
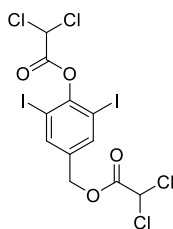
4-(2,2-dichloroacetoxy)-3,5-diiodobenzyl 2,2-dichloroacetate (2.6m): The title compound was prepared according to General Procedure C using **2.2m** (564 mg, 1.50 mmol) to afford **2.6m** (869 mg, 1.45 mmol, 97% yield) as a white solid. Analytical data: **¹H NMR** (500 MHz, CDCl₃): δ 7.87 (s, 2H), 6.28 (s, 1H), 6.03 (s, 1H), 5.22 (s, 2H); **¹³C NMR** (150 MHz, CDCl₃): δ 164.0, 160.6, 150.6, 139.5, 136.4 (2C), 89.4

(2C), 65.9, 64.1, 63.8; **IR** (thin film, cm^{-1}): 1770, 1295, 1227, 1160, 1122; **mp** 53-54°C**; TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.64; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_6$I$_2$Cl$_4$NaO$_4$: ([M+Na]): 618.7007, Found: 618.6999.
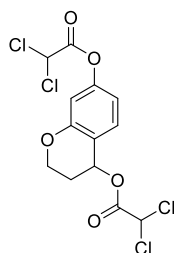
chromane-4,7-diyl bis(2,2-dichloroacetate) (2.6n): The title compound was prepared according to General Procedure C using **2.2n** (80.0 mg, 0.481 mmol) to afford **2.6n** (173 mg, 0.446 mmol, 93% yield) as a colorless oil. Analytical data: **¹H NMR** (600 MHz, CDCl$_3$): δ 7.38 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 8.4, 2.3 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.16 (s, 1H), 6.03 (dd, J = 3.3, 3.0 Hz, 1H), 5.97 (s, 1H), 4.39 (dt, J = 11.1, 3.6 Hz, 1H), 4.28 (td, J = 11.8, 2.4 Hz, 1H), 2.34 – 2.26 (m, 1H), 2.21 (ddd, J = 14.9, 6.3, 3.0 Hz, 1H).**¹³C NMR** (150 MHz, CDCl$_3$): δ 163.9, 162.7, 156.3, 151.5, 132.0, 117.1, 113.3, 109.9, 68.4, 64.3, 64.0, 61.9, 27.5; **IR** (thin film, cm^{-1}): 3016, 1761, 1255; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.58; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{10}$Cl$_4$NaO$_5$: ([M+Na]): 408.9180, Found: 408.9176.
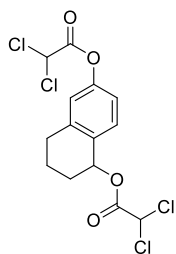
1,2,3,4-tetrahydronaphthalene-1,6-diyl bis(2,2-dichloroacetate (2.6o): The title compound was prepared according to General Procedure C using **2.2o** (150 mg, 0.914 mmol) to afford **2.6o** (336 mg, 0.870 mmol, 95% yield) as a colorless oil. Analytical data: **¹H NMR** (600 MHz, CDCl$_3$): δ 7.38 (d, J = 8.3 Hz, 1H), 7.10 – 6.91 (m, 2H), 6.17 (s, 1H), 6.08 (s, 1H), 5.96 (s, 1H), 2.93 (d, J = 17.1 Hz, 1H), 2.84-2.80 (m, 1H), 2.18 – 2.12 (m, 1H), 2.04 (dt, J = 20.7, 11.2 Hz, 2H), 1.91 (s, 1H); **¹³C NMR** (150 MHz, CDCl$_3$): δ 164.1, 162.9, 150.0, 140.3, 131.5, 131.2, 121.1, 118.8, 73.1, 64.5, 64.1, 28.8, 28.3, 18.1;

IR (thin film, cm^{-1}): 3013, 1756, 1266; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.59; **HRMS**

(ESI$^+$) Calcd. for C$_{14}$H$_{12}$Cl$_4$NaO$_4$: ([M+Na]): 406.9388, Found: 406.9386.
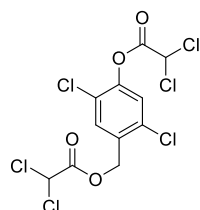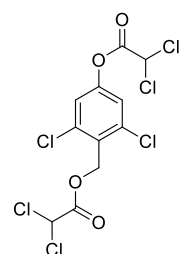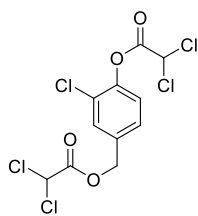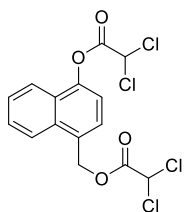
4-((2,2-dichloroacetoxy)methyl)naphthalen-1-yl 2,2-dichloroacetate (2.6p):
The title compound was prepared according to General Procedure C **2.2p** (200 mg, 1.15 mmol) to afford **2.6p** (425 mg, 1.08 mmol, 93% yield) as a red solid. Analytical data: **¹H NMR** (600 MHz, CDCl$_3$): δ 8.06 (dd, J = 14.8, 8.2 Hz, 2H), 7.71 – 7.63 (m,

3H), 7.37 (d, J = 7.7 Hz, 1H), 6.36 (s, 1H), 6.01 (s, 1H), 5.75 (s, 2H); **¹³C NMR** (150 MHz, CDCl$_3$):

δ 164.3, 162.8, 146.8, 132.6, 128.9, 127.8, 127.5, 127.3, 126.4, 123.7, 121.4, 116.8, 66.8, 64.2,

64.1; **mp** 53-54 °C ; **IR** (thin film, cm^{-1}): 3014, 1763, 1149; **TLC** (30/70 ethyl acetate/hexanes):

R$_f$ = 0.53; **HRMS** (ESI$^+$) Calcd. for C$_{15}$H$_{10}$Cl$_4$NaO$_4$: ([M+Na]): 416.9231, Found: 416.9228.

Preparation of *para*-Spiroepoxydienones 2.1:
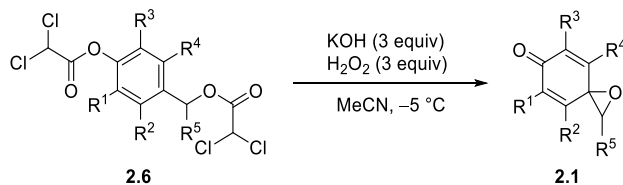
General Procedure D for Preparation of *para*-Spiroepoxydienones 2.1: To a vial equipped with a stir bar was added starting bis(dichloroacetate) **2.6** (1.0 equiv) and MeCN (4 mL/mmol). The resulting solution was cooled to −5 °C. Hydrogen peroxide (30% aqueous, 3.0 equiv) was added to the vial. The contents of the vial were added to a vigorously stirring, cooled (−5 °C) slurry of powdered KOH (3.0 equiv) and MeCN ([**2.6**)]$_0$ = 0.05 M after addition of the **2.6**/H$_2$O$_2$) in a round-bottomed flask. The reaction was stirred at −5 °C until complete disappearance of the starting material was observed by TLC analysis. Upon completion, the contents of the flask were decanted into a separatory funnel and then diluted with ethyl acetate and water. The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 40 mL/mmol). The organic layers were combined and washed once with a saturated brine solution. The organic layer was removed, dried over Na$_2$SO$_4$, and concentrated. All products were purified on silica gel via column chromatography.

Note 1: With unsubstituted or chlorinated substrates the reaction was usually completed in <20 min, whereas alkylated substrates or brominated/iodinated were usually completed in 0.5-2 h.

Note 2: A cooling bath comprised of equal portions of ice and saturated aqueous brine solution will cool the mixture to −5 °C.
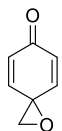
1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1a): The title compound was prepared according to General Procedure D using **2.6a** (100 mg, 0.289 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1a** (23.4 mg, 0.192 mmol, 66% yield) as a white solid. Spectral properties were consistent with those previously reported.[1] **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.52 (m, 4H), 3.37 (s, 2H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 185.4, 146.2, 133.7, 55.1, 53.7.
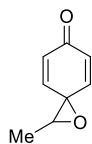
2-methyl-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1b): The title compound was prepared according to General Procedure D using **2.6b** (100 mg, 0.278 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1b** (25.0 mg, 0.184 mmol, 66% yield; the average yield of multiple experiments was 64%) as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.71 (dd, J = 10.3, 2.5 Hz, 1H), 6.55 (dd, J = 10.3, 1.9 Hz, 1H), 6.51-6.43 (m, 2H), 3.59 (q, J = 5.4 Hz, 1H), 1.55 (d, J = 5.4 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 185.4, 148.1, 143.6, 134.5, 132.9, 63.1, 57.3, 14.7; **IR** (thin film, cm^{-1}): 3323, 1654, 1597, 1509, 1240; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.30; **HRMS** (ESI$^+$) Calcd. for C$_8$H$_9$O$_2$: ([M+H]): 137.0597, Found: 137.0598.
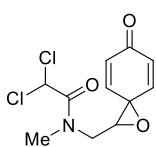
2,2-dichloro-N-methyl-N-(6-oxo-1-oxaspiro[2.5]octa-4,7-dien-2-yl)acet amide (2.1c): The title compound was prepared according to General Procedure D using **2.6c** (100 mg, 0.200 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1c** (31.9 mg, 0.115 mmol, 57% yield; the average yield of multiple experiments was 56%)) as a colorless oil. A rotamer ratio of 5:1 was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 4.26 (major rotamer) and δ 4.17 (minor rotamer). Analytical data: **Major rotamer ^{1}H NMR** (600 MHz,

CDCl$_3$):δ 6.68 (dd, J = 10.3, 2.6 Hz, 1H), 6.58 (d, J = 10.3 Hz, 1H), 6.50 (d, J = 10.1 Hz, 1H), 6.45 (dd, J = 10.1, 2.6 Hz, 1H), 6.29 (s, 1H), 4.26 (dd, J = 14.5, 3.4 Hz, 1H), 3.65 (dd, J = 7.2, 3.5 Hz, 1H), 3.38 – 3.30 (m, 4H); **^{13}C NMR** (150 MHz, CDCl$_3$): δ 185.0, 163.9, 146.5, 141.7, 135.1, 133.9, 64.9, 63.7, 56.3, 48.6, 36.8; **Minor rotamer ^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.65 (d, J = 2.2 Hz, 1H), 6.62 (d, J = 10.4 Hz, 1H), 6.53 (d, J = 10.2 Hz, 1H), 6.48 (s, 1H), 6.32 (s, 1H), 4.17 (dd, J = 15.4, 2.3 Hz, 1H), 3.75 (dd, J = 15.5, 7.1 Hz, 1H), 3.70 (dd, J = 7.1, 2.6 Hz, 1H), 3.10 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 184.7, 163.5, 146.1, 141.0, 135.5, 133.7, 65.3, 64.2, 56.6, 49.1, 35.2; **IR** (thin film, cm^{-1}): 3465, 1660; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.20; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_{11}$Cl$_2$NNaO$_3$: ([M+Na]): 298.0014, Found: 298.0009.

2,5,7-trimethyl-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1d): The title compound was prepared according to General Procedure D using **2.6d** (97.0 mg, 0.250 mmol). Column chromatography (20/80 ethyl acetate/hexanes) afforded **2.1d** (28.3 mg, 0.173 mmol, 69% yield) as a bright yellow solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$):δ 6.47 (s, 1H), 6.25 (s, 1H), 3.52 (q, J = 5.4 Hz, 1H), 2.00 (s, 3H), 1.96 (s, 3H), 1.52 (d, J = 5.4 Hz, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 186.6, 143.1, 141.2, 139.5, 138.2, 62.6, 57.0, 16.6, 16.0, 14.8; **mp** 62-63 °C; **IR** (thin film, cm^{-1}): 1635; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.52; **HRMS** (ESI$^+$) Calcd. for C$_{10}$H$_{13}$O$_2$: ([M+H]): 165.0915, Found: 165.0910.

4,7-dimethyl-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1e): The title compound was prepared according to General Procedure D using **2.6e** (100 mg, 0.267 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1e** (31 mg, 0.206 mmol, 77% yield) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.37 (s, 1H), 6.24 (s, 1H),

3.40 (d, J = 5.7 Hz, 1H), 3.20 (d, J = 5.7 Hz, 1H), 1.94 (s, 3H), 1.84 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 186.4, 154.1, 141.9, 140.2, 131.3, 55.0, 53.5, 16.0, 15.5; **mp** 63-64 °C; **IR** (thin film, cm^{-1}): 2923, 1668, 1637; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.51; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_{11}$O$_2$: ([M+H]): 151.0753, Found: 151.0754.

4,5,7,8-tetramethyl-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1f): The title compound was prepared according to General Procedure D using **2.6f** (100 mg, 0.249 mmol) with the following modification: 4 equiv of KOH were used. Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.6f** (36.8 mg, 0.206 mmol, 83% yield) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 3.17 (s, 2H), 1.95 (s, 6H), 1.78 (s, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 185.0, 147.3, 135.6, 55.7, 51.0, 12.5, 12.2; **mp** 69-70 °C; **IR** (thin film, cm^{-1}): 2923, 1672, 1376; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.62; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_{15}$O$_2$: ([M+H]): 179.1097, Found: 179.1068.

4,5,7-trimethyl-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1g): The title compound was prepared according to General Procedure D using **2.6g** (100 mg, 0.258 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1g** (34.1 mg, 0.208 mmol, 81% yield) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.25 (s, 1H), 3.34 (d, J = 5.7 Hz, 1H), 3.16 (d, J = 5.7 Hz, 1H), 1.96 (d, J = 3.4 Hz, 6 H), 1.76 (s, 3 H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 185.9, 147.1, 141.5, 139.5, 136.4, 54.5, 52.9, 16.1, 12.5, 12.1; **mp** 64-65 °C; **IR** (thin film, cm^{-1}): 3414, 2360, 1669, 1632, 1301; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.50; **HRMS** (ESI$^+$) Calcd. for C$_{10}$H$_{13}$O$_2$: ([M+H]): 165.0910, Found: 165.0910.
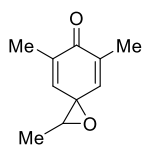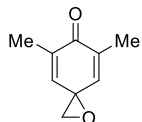
5,7-dimethyl-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1h): The title compound was prepared according to General Procedure D using **2.6h** (93.5 mg, 0.250 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1h** (27.0 mg, 0.180 mmol, 72% yield) as a pale yellow solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.28 (s, 2H), 3.29 (s, 2H), 1.97 (s, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 186.5, 141.2, 140.4, 54.9, 53.6, 16.2; **mp** 64-65 °C; **IR** (thin film, cm^{-1}): 2360, 1636; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.45; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_{11}$O$_2$: ([M+H]): 151.0753, Found: 151.0755.

Note: This compound is highly sensitive to rearomatization to the aldehyde upon exposure to light. Care should be taken to limit light when isolating and working with this compound.
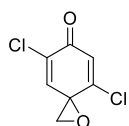
4,7-dichloro-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1i): The title compound was prepared according to General Procedure D using **2.6i** (100 mg, 0.241 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1i** (33.9 mg, 0.177 mmol, 74% yield; the average yield of multiple experiments was 71%)) as a white solid. Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$): δ 6.84 (s, 1H), 6.75 (s, 1H), 3.71 (d, J = 6.0 Hz, 1H), 3.35 (d, J = 6.0 Hz, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 177.0, 151.5, 141.1, 136.0, 131.3, 55.3, 54.4; **mp** 71-73 °C; **IR** (thin film, cm^{-1}): 1663; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.55; **HRMS** (ESI$^+$) Calcd. for C$_7$H$_5$Cl$_2$O$_2$: ([M+H]): 190.9661, Found: 190.9659.
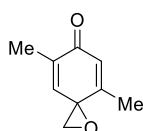
4,8-dichloro-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1j): The title compound was prepared according to General Procedure D using **2.6j** (100 mg, 0.241 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1j** (31.8 mg, 0.166 mmol, 68% yield; the average yield of multiple experiments was 67%)) as a white solid. Analytical data: **^{1}H NMR** (600

MHz, CDCl$_3$): δ 6.76 (s, 2H), 3.64 (s, 2H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 181.6, 150.3, 132.3, 55.6, 53.4; **mp** 98-99°C; **IR** (thin film, cm^{-1}): 3055, 1668, 1614, 1358, 1285; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.63; **HRMS** (ESI$^+$) Calcd. for C$_7$H$_5$Cl$_2$O$_2$: ([M+H]): 190.9661, Found: 190.9662.
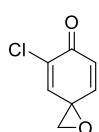
5-chloro-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1k): The title compound was prepared according to General Procedure D using **2.6k** (100 mg, 0.241 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1k** (24 mg, 0.153 mmol, 58% yield) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.71 (d, J = 2.4 Hz, 1H), 6.65-6.52 (m, 2H), 3.42 (s, 2H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 178.3, 146.6, 142.2, 136.3, 132.3, 55.1, 54.7; **mp** 89-91°C; **IR** (thin film, cm^{-1}): 3045, 1659, 1597; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.45; **HRMS** (ESI$^+$) Calcd. for C$_7$H$_6$ClO$_2$: ([M+H]): 157.0056, Found: 157.0052.
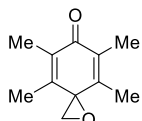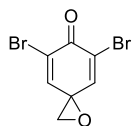
5,7-dibromo-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1l): The title compound was prepared according to General Procedure D using **2.6l** (126 mg, 0.250 mmol). Column chromatography (20/80 ethyl acetate/hexanes) afforded **2.1l** (28.2 mg, 0.100 mmol, 40% yield; the average yield of multiple experiments was 41%)) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.01 (s, 2H), 3.46 (s, 2H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 172.3, 146.8 (2C), 125.6 (2C), 56.2, 54.8; **mp** 98-99°C; **IR** (thin film, cm^{-1}): 1669; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.40; **HRMS** (ESI$^+$) Calcd. for C$_7$H$_4$Br$_2$NaO$_2$: ([M+Na]): 300.8476, Found: 300.8476.
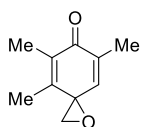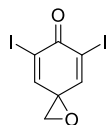
5,7-diiodo-1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1m): The title compound was prepared according to General Procedure D using **2.6m** (149.4 mg, 0.250 mmol). Column chromatography (20/80 ethyl acetate/hexanes) afforded **2.1m** (19.0 mg, 0.051 mmol, 20% yield) as a white solid. Spectral properties were consistent with those previously reported.[3] Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 7.33 (s, 2H), 3.44 (s, 2H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 173.6, 154.8 (2C), 101.6 (2C), 57.7, 54.5.
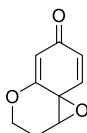
1a,2-dihydro-3H,6H-oxireno[2,3-d]chromen-6-one (2.1n): The title compound was prepared according to General Procedure D using **2.6n** (97 mg, 0.250 mmol). Column chromatography (20/80 ethyl acetate/hexanes) afforded **2.1n** (31.0 mg, 0.190 mmol, 76% yield) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.40 (dd, J = 9.9, 1.8 Hz, 1H), 6.21 (d, J = 9.9 Hz, 1H), 5.92 (d, J = 1.8 Hz, 1H), 4.46 (ddd, J = 13.4, 11.1, 3.3 Hz, 1H), 4.15 (dd, J = 10.9, 5.4 Hz, 1H), 3.94 (d, J = 2.9 Hz, 1H), 2.38 (dt, J = 15.1, 2.6 Hz, 1H), 2.28 (ddd, J = 15.1, 13.0, 5.4 Hz, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 187.2, 165.7, 140.1, 133.7, 110.3, 62.3, 59.0, 52.9, 23.5; **mp** 83-84°C; **IR** (thin film, cm^{-1}): 1652, 1594; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.40; **HRMS** (ESI$^+$) Calcd. for C$_9$H$_8$NaO$_3$: ([M+Na]): 187.0371, Found: 187.0368.
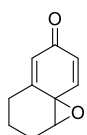
1a,2,3,4-tetrahydro-6H-naphtho[1,8a-b]oxiren-6-one (2.1o): The title compound was prepared according to General Procedure D using **2.6o** (100 mg, 0.259 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1o** (32.4 mg, 0.200 mmol, 83% yield; the average yield of multiple experiments was 77%)) as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.51-6.41 (m, 2H), 6.35 (s, 1H), 3.78 (d, J = 3.8 Hz, 1H), 2.64-2.50 (m, 1H), 2.30 (dt, J = 14.1, 4.1 Hz, 1H), 2.14 (ddd, J = 17.0, 10.3, 7.0 Hz, 1H), 2.07 (ddd, J = 14.7,

6.8, 3.3 Hz, 1H), 1.96-1.86 (m, 1H), 1.62-1.51 (m, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 186.4, 157.5, 146.0, 133.5, 128.4, 66.3, 56.1, 29.1, 23.2, 23.2; **IR** (thin film, cm^{-1}): 2996, 1655, 1291; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.46; **HRMS** (ESI$^+$) Calcd. for C$_{10}$H$_{11}$O$_2$: ([M+H]): 163.0759, Found: 163.0758.

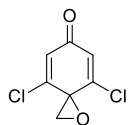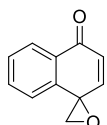**4H-spiro[naphthalene-1,2'-oxiran]-4-one (2.1p):** The title compound was prepared according to General Procedure D using **2.6p** (100 mg, 0.252 mmol). Column chromatography (30/70 ethyl acetate/hexanes) afforded **2.1p** (30.5 mg, 0.177 mmol, 70% yield) as a colorless oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 8.19 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 7.9 Hz, 1H), 6.67 (s, 2H), 3.49 (d, J = 5.7 Hz, 1H), 3.46 (d, J = 5.7 Hz, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 184.1, 147.5, 138.9, 133.2, 132.9, 132.8, 128.6, 127.0, 123.0, 58.3, 53.1; **IR** (thin film, cm^{-1}): 3583, 3055, 1665, 1624, 1298; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.51; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_8$NaO$_2$: ([M+Na]): 195.0422, Found: 195.0413.

Preparative Scale Procedures:
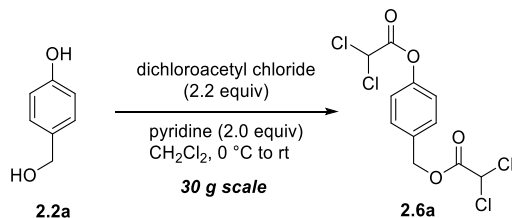
4-(2,2-dichloroacetoxy)benzyl 2,2-dichloroacetate (2.6a): To a flame-dried 1L round-bottomed flask was added 4-(hydroxymethyl)phenol **2.2a** (12.1 g, 95.0 mmol) and anhydrous CH_2Cl_2 (240 mL). The flask was cooled to 0 °C and pyridine (13.8 mL, 190.0 mmol) was added dropwise. The solution was stirred for five min, after which dichloroacetyl chloride (20.2 mL, 210.0 mmol) was added via addition funnel over the course of 20 min. Once the acid chloride was fully added, the reaction mixture was then stirred at room temperature for 30 min. The solution was directly filtered through a plug of silica gel with CH_2Cl_2 as the eluent (500 mL). The filtrate was concentrated to afford **2.6a** (31.2 g, 90.3 mmol, 95% yield) as a clear oil.
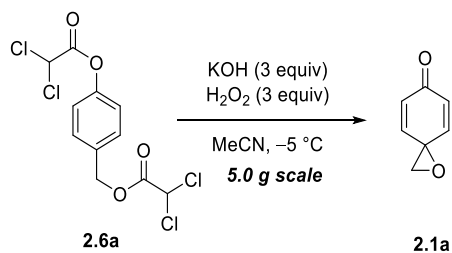
1-oxaspiro[2.5]octa-4,7-dien-6-one (2.1a): To a round-bottomed flask with MeCN (400 mL) cooled to −5 °C was added powdered KOH (85%, 16.9 g, 256 mmol). Hydrogen peroxide (30% aqueous, 26.2 mL, 256 mmol) was added via addition funnel over the course of 10 min. Once fully added, a solution of **2.6a** (29.5 g, 85.3 mmol) dissolved in MeCN (30 mL) was added via addition funnel over the course of 20 min. Once fully added, the reaction was allowed to stir at −5 °C for 10 m. The reaction was quenched by addition of a saturated aqueous sodium thiosuflate solution

(10 mL) over the course of 5 min. The contents of the flask were transferred to a separatory funnel followed by dilution with ethyl acetate (500 mL) and water (200 mL). The organic layer was removed and the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The organic layers were combined and washed once with a saturated brine solution (200 mL). The organic layer was removed, dried over Na_2SO_4, and concentrated. The product was purified via column chromatography (20/80 ethyl acetate/hexanes) to afford **2.1a** (5.23 g, 42.8 mmol, 50% yield) as a white solid.

Chemoselective Secondary Transformations:

2.1a   **2.7**
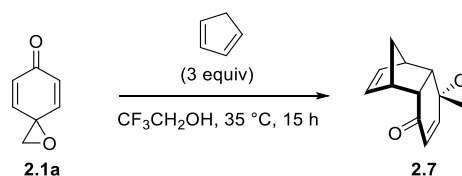
***rac*-(1'S,2R,4'R,4a'S,8a'R)-1',4',4a',8a'-tetrahydro-8'H-spiro[oxirane-2,5'-[1,4]methano naphthalen]-8'-one (2.7): 2.7** was prepared according to a modified literature procedure.[2] To a flame-dried flask was added **2.1a** (1.00 g, 8.19 mmol) and trifluoroethanol (30 mL). Freshly-distilled cyclopentadiene (2.07 mL, 24.6 mmol) was added dropwise and the flask was stirred at 35 °C for 15 h. Excess trifluoroethanol was removed *in vacuo*. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 3.44 (major diastereomer) and δ 1.34 (minor diastereomer). Column chromatography (20/80 ethyl acetate/hexanes) afforded the major diastereomer (1.02 g, 5.39, 69% yield; the average yield of multiple experiments was 65%) as a clear oil. Spectral properties were consistent with those previously reported.[2] Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 6.25 (dd, *J* = 5.4, 2.8 Hz, 1H), 6.04 (d, *J* = 10.2 Hz, 1H), 5.99 (d, *J* = 10.3 Hz, 1H), 5.97 (dd, *J* = 5.5, 2.8 Hz, 1H), 3.45 (s, 1H), 3.12 (s, 1H), 3.09 (d, *J* = 5.2 Hz, 1H), 3.04 (dd, *J* = 9.3, 4.1

Hz, 1H), 2.93 (d, J = 5.2 Hz, 1H), 2.79 (dd, J = 9.3, 3.7 Hz, 1H), 1.42 (d, J = 8.6 Hz, 1H), 1.28 (d, J = 8.6 Hz, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$): 199.6, 150.4, 136.0, 135.0, 133.9, 58.3, 55.2, 50.1, 48.3, 47.9, 47.0, 39.4.

2.7 → **2.18**

H$_2$O$_2$ (3 equiv)
K$_2$CO$_3$ (50 mol %)
acetone, 0 °C to rt
4 h
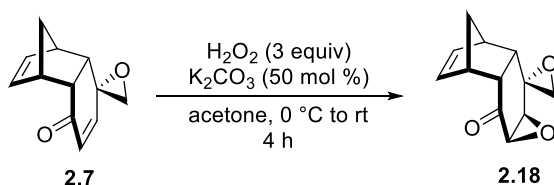
***rac*-(1a'S,2R,2a'S,3'R,6'S,6a'R,7a'R)-1a',2a',3',6',6a',7a'-hexahydro-7'H-spiro[oxirane-2,2'-[3,6]methanonaphtho[2,3-b]oxiren]-7'-one (2.18):** To a vial was added **2.7** (94.1 mg, 0.500 mmol) and acetone (2 mL) and the flask was cooled to 0 °C. K$_2$CO$_3$ (2.5 M in H$_2$O, 0.100 mL, 0.250 mmol) and H$_2$O$_2$ (30% in H$_2$O, 0.152 mL, 1.50 mmol) were added. The reaction was allowed to warm up to room temperature and stirred for 4 h. The reaction was quenched with a saturated aqueous sodium thiosulfate solution (0.25 mL) and the product extracted with ethyl acetate (3 x 10 mL) and washed with water (5 mL). The combined organic layers were washed with a saturated brine solution (5 mL), dried over MgSO$_4$, filtered, and concentrated to afford **2.18** (77.0 mg, 0.380 mmol, 75% yield) as a single diastereomer as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 6.12 (dd, J = 4.8 Hz, 2.4 Hz, 1H), 6.05 (dd, J = 4.8 Hz, 2.4 Hz, 1H), 3.35 (d, J = 3.9 Hz, 1H), 3.25 – 3.20 (m, 2H), 3.11 (dd, J = 10.7, 3.4 Hz, 1H), 3.01 (d, J = 4.5 Hz, 1H), 2.93 (d, J = 4.5 Hz, 1H), 2.89 (d, J = 3.9 Hz, 1H), 2.69 (s, 1H), 1.39 (d, J = 8.4 Hz, 1H), 1.23 (d, J = 8.4 Hz, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$): 206.3, 135.8, 134.7, 59.1, 55.2, 55.1, 50.6, 50.5, 47.2, 43.5, 43.2, 41.8.; **mp** 74-75°C; **IR** (thin film, cm^{-1}): 2974, 1715; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.50; **HRMS** (ESI$^+$) Calcd. for C$_{12}$H$_{12}$NaO$_3$: ([M+Na]): 227.0684, Found: 227.0681.

2.18 → **2.8**
Ph₂O, 220 °C, 1 h
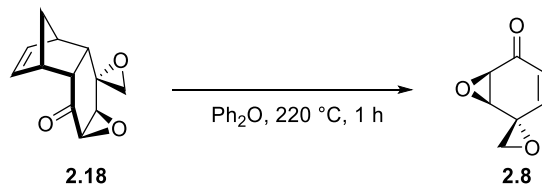
rac-(1S,2R,6R)-7-oxaspiro[bicyclo[4.1.0]heptane-2,2'-oxiran]-3-en-5-one (2.8): To a flame-dried vial was added **2.18** (51.0 mg, 0.250 mmol) and Ph₂O (1 mL). The vial was heated at 220 °C for 1 h. The flask was allowed to cool to room temperature and the crude contents were purified by column chromatography (20/80 ethyl acetate/hexanes) to afford **2.8** (30.0 mg, 0.217 mmol, 87% yield; the average yield of multiple experiments was 85%) as a single diastereomer as a white solid. Analytical data: ^{1}**H NMR** (400 MHz, CDCl₃): δ 6.21 (dd, J = 0.5, 1.8 Hz, 1H), 6.12 (dd, J = 10.5, 2.5 Hz, 1H), 3.61 (dd, J = 3.6, 1.9 Hz, 1H), 3.41 (d, J = 4.7 Hz, 1H), 3.34 (dd, J = 3.6, 2.4 Hz, 1H), 3.14 (d, J = 4.7 Hz, 1H); ^{13}**C NMR** (151 MHz, CDCl₃): δ 191.9, 143.4, 131.4, 57.8, 53.4, 52.9, 52.0; **mp** 55-57°C; **IR** (thin film, cm^{-1}): 1683; **TLC** (30/70 ethyl acetate/hexanes): R_f = 0.31; **HRMS** (ESI⁺) Calcd. for $C_7H_6NaO_3$: ([M+Na]): 161.0214, Found: 161.0212.

2.7 → [**2.19**] → **2.9**
MeLi (1.1 equiv), THF, −78 °C
NBS (1.1 equiv), CH₂Cl₂, rt
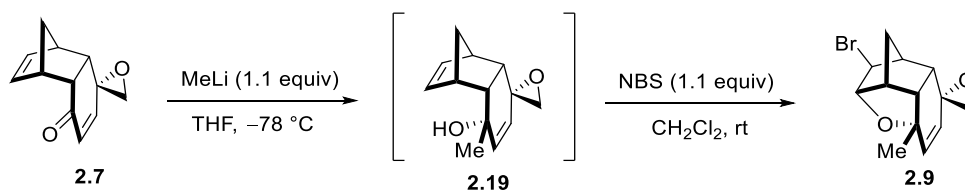
rac-(2R,2'S,2a'S,2a1'S,7a'S)-8'-bromo-7a'-methyl-2a',2a1',3',4',4a',7a'-hexahydro-2'H-spiro[oxirane-2,5'-[2,4]methanoindeno[7,1-bc]furan] (2.9): To a flame-dried vial was added **2.7** (47.1 mg, 0.250 mmol) and anhydrous THF (2 mL) and the flask was cooled to −78 °C. MeLi (1.6 M, 0.172 mL, 0.275 mmol) was added dropwise. The reaction was stirred for 30 min and quenched with a saturated aqueous ammonium chloride solution (1 mL). The crude product was

extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with a saturated brine solution (5 mL), dried over MgSO$_4$, filtered, and concentrated to afford crude **2.19**. The crude tertiary alcohol was immediately redissolved in anhydrous CH$_2$Cl$_2$ (2 mL) and *N*-bromosuccinimide (NBS, 49.0 mg, 0.275 mmol) was added in portions. The reaction was stirred for 30 min and the solvent was removed *in vacuo* to afford the crude material. Column chromatography (10/90 ethyl acetate/hexanes) afforded **2.9** (51.0 mg, 0.180 mmol, 72% yield) as white amorphous solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$ δ 6.04 (d, *J* = 10.1 Hz, 1H), 5.21 (d, *J* = 10.1 Hz, 1H), 4.64 (d, *J* = 4.7 Hz, 1H), 4.17 (d, *J* = 2.2 Hz, 1H), 3.06 (ddt, J = 4.9, 3.4, 1.4 Hz, 1H), 2.92 (d, *J* = 5.2 Hz, 1H), 2.87 (d, *J* = 5.2 Hz, 1H), 2.59 (dd, *J* = 3.5, 1.7 Hz, 1H), 2.40 (dd, *J* = 10.5, 5.1 Hz, 1H), 2.21 (dd, *J* = 10.4, 3.5 Hz, 1H), 2.15 (d, *J* = 11.1 Hz, 1H), 1.53 (dq, *J* = 11.1, 1.9 Hz, 1H), 1.33 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 138.7, 129.1, 90.7, 77.3, 57.5, 54.6, 54.4, 49.5, 47.4, 43.9, 41.6, 33.9, 28.7; **IR** (thin film, cm^{-1}): 2973, 1690, 1049; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.62 (not UV active, stains in KMnO$_4$); **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{15}$BrNaO$_2$: ([M+Na]): 305.0153, Found: 305.0149.
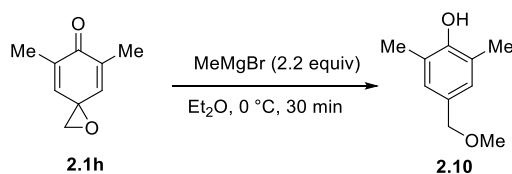
4-(methoxymethyl)-2,6-dimethylphenol (2.10): To a flame dried vial was added **2.1h** (50.0 mg, 0.333 mmol) and Et$_2$O (4 mL). The vial was cooled to 0 °C and MeMgBr (3.0 M in Et$_2$O, 0.244 mL, 0.732 mmol) was added dropwise. The vial was allowed to stir for 30 min at 0 °C. The reaction was quenched by addition of saturated aqueous NH$_4$Cl (1 mL). The organic layer was separated and the aqueous layer was washed with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (1 x 5 mL), saturated brine solution (1 x 5 mL), dried with MgSO$_4$,

filtered, and concentrated. Column chromatography afforded **2.10** (47.0 mg, 0.283 mmol, 85%

yield) as a yellow oil. Spectral properties were consistent with those previously reported.[22]

Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$): δ 6.98 (s, 2H), 4.74 (bs, 1H), 4.34 (s, 2H), 3.38 (s,

3H), 2.26 (s, 6H). **^{13}C NMR**: (151 MHz, CDCl$_3$): δ 151.8, 129.6, 128.6 (2C), 122.9 (2C), 74.6,

57.8, 15.9 (2 C).
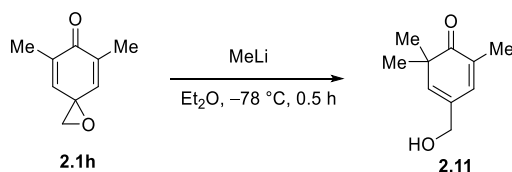
4-(hydroxymethyl)-2,6,6-trimethylcyclohexa-2,4-dien-1-one (2.11): To a flame-dried vial were

added **2.1h** (37.5 mg, 0.250 mmol) and anhydrous Et$_2$O (5 mL). The vial was purged with nitrogen

and cooled to −78 °C. MeLi (1.6 M in Et$_2$O, 0.234 mL, 0.375 mmol) was added dropwise over the

course of 10 min and the reaction was stirred at -78 °C for 20 min. The reaction was quenched

with a saturated aqueous ammonium chloride solution (3 mL) and allowed to warm to room

temperature. The contents of the flask were transferred into a separatory funnel and 5 mL of water

was added. The product was extracted with ethyl acetate (3 x 10 mL) and the organic layers were

combined and washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated to afford a slightly

yellow oil. Purification by column chromatography (30/70 ethyl acetate/hexanes) afforded **2.11**

(27.5 mg, 0.175 mmol, 66%) as a colorless oil. Analytical data: **^{1}H NMR**: (400 MHz, CDCl$_3$): δ

6.91 (s, 1H), 6.10 (s, 1H), 4.26 (s, 2H), 1.93 (s, 3H), 1.21 (s, 6H). **^{13}C NMR**: (151 MHz, CDCl$_3$):

δ 206.1, 141.2, 138.5, 133.1, 130.2, 64.7, 45.9, 25.9, 15.6; **IR** (thin film, cm^{-1}): 3418, 2925, 1666;

TLC (30/70 ethyl acetate/hexanes): R$_f$ = 0.21; **HRMS** (ESI$^+$) Calcd. for C$_{10}$H$_{14}$NaO$_2$: ([M+Na]):

189.0892, Found: 189.0888.

2.11 → **2.20**

PhNCO (1.2 equiv)

DBU (0.2 equiv)
CH$_2$Cl$_2$, rt, 3 h
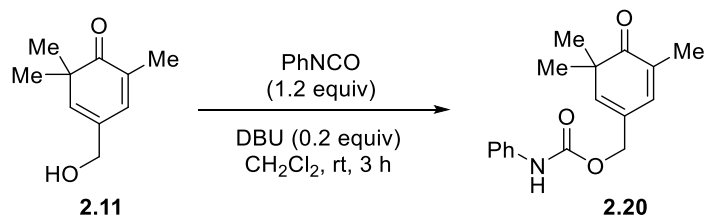
(3,3,5-trimethyl-4-oxocyclohexa-1,5-dien-1-yl)methyl phenylcarbamate (2.20): To a flame-dried vial was added allylic alcohol **2.11** (50.0 mg, 0.301 mg) and CH$_2$Cl$_2$ (3.0 mL). DBU (0.0075 mL, 0.060 mmol) and phenyl isocyanate (0.0391 mL, 0.358 mmol) were added and the reaction was stirred at room temperature for 3 h. The reaction was quenched by the addition of 1 M HCl (0.5 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (1 x 2 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. Column chromatography (20/80 ethyl acetate/hexanes) afforded **2.20** (82.3 mg, 0.289 mmol, 96% yield) as a clear oil. A rotamer ratio of 4:1 was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 6.20 (major rotamer) and δ 5.86 (minor rotamer). Analytical data: **Major Rotamer** ^{1}**H NMR**: (600 MHz, CDCl$_3$): δ 7.44 (d, J = 6.1 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 6.95 (bs, 1H), 6.89 (s, 1H), 6.21 (s, 1H), 4.77 (s, 2H), 1.93 (s, 3H), 1.23 (s, 6H).^{13}**C NMR**: (151 MHz, CDCl$_3$): δ 205.6, 144.3, 138.3, 13.4, 129.1 (4C), 126.4, 123.6, 120.0, 66.4, 46.2, 25.8 (2C), 15.7; **Minor Rotamer** ^{1}**H NMR**: (600 MHz, CDCl$_3$):δ 10.80 (bs, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.27 (dd, J = 8.4, 1.8 Hz, 2H), 6.52 (s, 1H), 5.88 (s, 1H), 4.74 (s, 2H), 1.87 (s, 3H), 1.14 (s, 6H); ^{13}**C NMR**: (151 MHz, CDCl$_3$): δ 205.3, 143.4, 137.7, 133.4, 129.1 (2C), 129.0 (2C), 125.1, 124.2, 120.7, 67.6, 46.1, 25.7 (2C), 15.6; **mp** 114-116 °C; **IR** (thin film, cm^{-1}): 3316, 1733, 1541, 1217; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.49; **HRMS** (ESI$^+$) Calcd. for C$_{17}$H$_{19}$NNaO$_3$: ([M+Na]): 308.1263, Found: 308.1260.

2.20 → **2.12**

NIS (4 equiv)

MeCN, 50 °C, 24 h
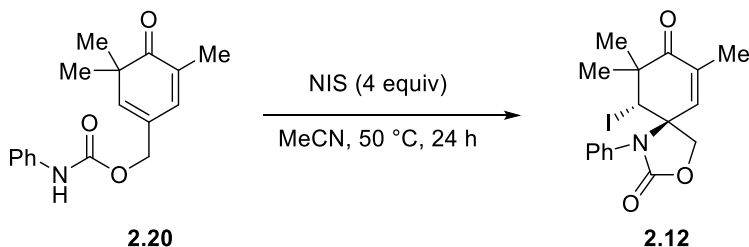
rac-(5S,10R)-10-iodo-7,9,9-trimethyl-1-phenyl-3-oxa-1-azaspiro[4.5]dec-6-ene-2,8-dione

(2.12): To a flame-dried flask was added **2.20** (71.3 mg, 0.250 mmol) and anhydrous MeCN (5 mL). *N*-iodosuccinimide (225 mg, 1.00 mmol) was added and the reaction was heated at 50 °C for 24 h. The reaction was cooled to rt and concentrated. Excess Et_2O was added which precipitated out excess NIS and succinimide. Column chromatography (10/90 ethyl acetate/hexanes) afforded oxazolidinone **2.12** (73.0 mg, 0.178 mmol, 71% yield; the average yield of multiple experiments was 68%) as a clear oil as a single diastereomer. Analytical data: **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.45-7.41 (m, 5 H), 7.12 (s, 1H), 4.96 (d, *J* = 9.2 Hz, 1H), 4.52 (d, *J* = 9.2 Hz, 1H), 4.44 (s, 1H), 1.93 (s, 3H), 1.28 (s, 3H), 1.16 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$): δ 206.1, 141.2, 138.5, 133.1, 130.2, 64.7, 45.9, 25.9, 15.6; **IR** (thin film, cm^{-1}): 1761, 1683; **TLC** (30/70 ethyl acetate/hexanes): R_f = 0.65; **HRMS** (ESI$^+$) Calcd. for $C_{17}H_{18}INNaO_3$: ([M+Na]): 434.0229, Found: 434.0230.

2.11 → **2.13a** + **2.13b**

(3 equiv)

Ph_2O, 180 °C, 1 h
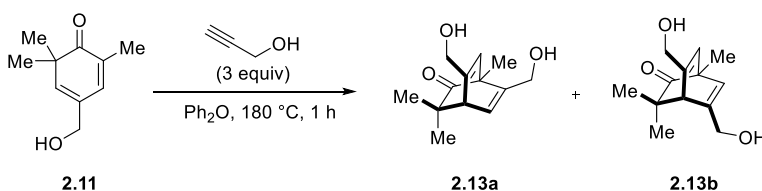
rac-(1S,4S)-5,7-bis(hydroxymethyl)-1,3,3-trimethylbicyclo[2.2.2]octa-5,7-dien-2-one **(2.13a)** and *rac*-(1s,4s)-5,8-bis(hydroxymethyl)-1,3,3-trimethylbicyclo[2.2.2]octa-5,7-dien-2-one **(2.13b) :** To a flame-dried flask was added **2.11h** (41.6 mg, 0.250 mmol), propargyl alcohol (0.014 mL, 0.250 mmol), and Ph_2O (1 mL). The vial was heated at 180 °C for 1 h. The vial was cooled

to room temperature. The mixture was passed through a silica plug (30/70 ethyl acetate/hexanes) to remove the diphenylether then flushed with ethyl acetate to elute the product. The regioisomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 3.54 (**2.13a**, **major**) and δ 3.38 (**2.13b**, **minor**). Column chromatography (100% ethyl acetate) afforded **2.13a/b** (41.0 mg, 0.180 mmol, 74% yield; the average yield of multiple experiments was 73%) as an inseparable mixture of regioisomers as a clear oil. Analytical data: **^{1}H NMR 2.13a (major)** (600 MHz, CDCl$_3$): δ 6.4 (d, J = 6.2 Hz, 1H), 5.83 (s, 1H), 4.31 (d, J = 12.8 Hz, 2H), 4.27 (d, J = 11.4 Hz, 2H), 3.35 (dd, J = 6.2, 2.1 Hz, 1H), 1.50 (s, 2H), 1.08 (s, 3H), 1.08 (s, 3H); **^{13}C NMR 2.13a (major)** (151 MHz, CDCl$_3$): δ 210.9, 150.1, 149.9, 132.5, 127.3, 64.2, 64.1, 60.8, 49.7, 41.2, 28.5, 26.8, 12.5; **^{1}H NMR 2.13b (minor)** (600 MHz, CDCl$_3$): δ 5.86 (s, 2H), 4.23 (s, 4H), 3.38 (t, J = 2.0 Hz, 2H), 1.47 (s, 3H), 1.07 (s, 6H).**^{13}C NMR 2.13b (minor)** (151 MHz, CDCl$_3$): δ 210.9, 144.2 (2C), 129.2 (2C), 60.8 (2C), 56.6, 52.0, 40.9, 27.0 (2C), 15.5; **IR** (thin film, cm^{-1}): 3335, 2360, 1683; **TLC** (100% ethyl acetate): R$_f$ = 0.63; **HRMS** (ESI$^+$) Calcd. for C$_{13}$H$_{18}$NaO$_3$: ([M+Na]): 245.1154, Found: 245.1152.
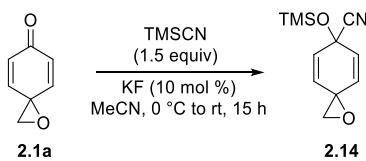
6-((trimethylsilyl)oxy)-1-oxaspiro[2.5]octa-4,7-diene-6-carbonitrile (2.14): To a flame-dried flask was added **2.1a** (122.2 mg, 1.00 mmol) and anhydrous MeCN (6 mL). The flask was cooled to 0 °C and TMSCN (0.188 mL, 1.50 mmol) and KF (5.80 mg, 0.100 mmol) were added sequentially. The reaction was stirred for 12 h during which time the flask was warmed to room temperature. The reaction mixture was filtered over silica with CH$_2$Cl$_2$ and the filtrate was concentrated. The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the

crude reaction mixture by comparison of the integration of the resonances at δ 3.15 (Isomer A) and δ 3.13 (Isomer B). Column chromatography afforded **2.14** (120 mg, 0.54 mmol, 54% yield) as a white solid. Analytical data: **Isomer A ^{1}H NMR**: (600 MHz, CDCl$_3$) δ 6.27 (d, J = 10.0 Hz, 1H), 5.71 (d, J = 10.0 Hz, 1H), 3.15 (s, 1H), 0.25 (s, 9H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 132.2 (2C), 131.6 (2C), 118.9, 63.5, 54.8, 51.7, 1.7 (3C); **Isomer B ^{1}H NMR** (600 MHz, CDCl$_3$):δ 6.21 (d, J = 10.0 Hz, 1H), 5.68 (d, J = 10.0 Hz, 1H), 3.12 (s, 1H), 0.24 (s, 5H); **^{13}C NMR** (151 MHz, CDCl$_3$): δ 131.4 (2C), 130.6 (2C), 119.0, 63.7, 55.6, 51.7, 1.8 (3C); **mp** 40-41°C; **IR** (thin film, cm^{-1}): 3502, 1255, 1089; **TLC** (30/70 ethyl acetate/hexanes): R$_f$ = 0.53; **HRMS** (ESI$^+$) Calcd. for C$_{11}$H$_{15}$N NaO$_2$Si: ([M+Na]): 244.0770, Found: 244.0768.

Photochemical Stability of *para*-Spiroepoxydienones:

When *para*-spiroepoxydienones (**2.1**) are exposed to light for extended periods of time, rearomatization to 4-hydroxybenzaldehyde **2.21** is observed. This rearomatization can be mitigated by storing the products at −20 °C in the dark.

Stability of Aryl Subtituted *para*-Spiroepoxydienones
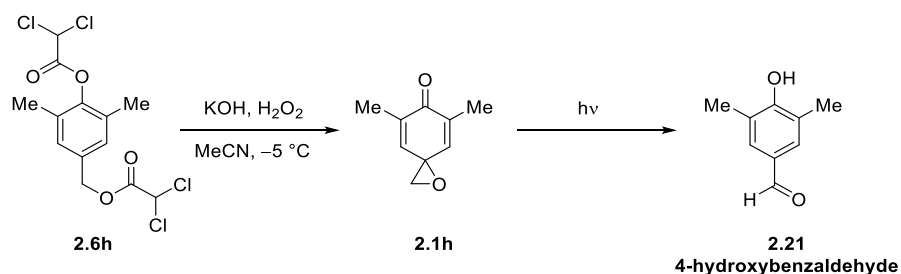
Attempts to form aryl substituted *para*-spiroepoxydienone **2r** resulted in complete isolation of the corresponding hydroquinone **2.23** and arylaldehyde **2.24**. This most likely proceeds via the shown zwitterionic species **2.22** which then reacts with water to afford the shown rearomatized products.[12]
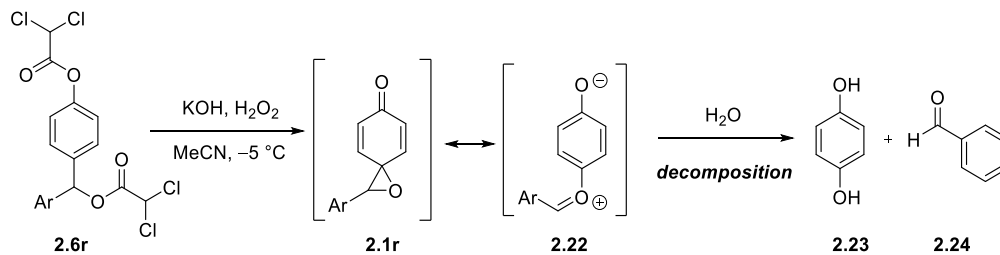
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3.1 Introduction

Heterospirocyclic scaffolds are broadly present in drug-like molecules.[1] Consequently, new methods for the preparation of these scaffolds, especially nitrogen containing scaffolds, are of utmost importance for the synthetic community. In this chapter, we describe the preparation of *N*-heterospirocyclic spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-ones via the development of a one-pot, dearomative *ortho*-semidine rearrangement of tetrahydrodiazocines and subsequent imine hydrolysis. The *N*-spirodienone is used as a linchpin for the preparation of additional heterocycles and the spirocyclic nitrogen is employed as a directing group for highly diastereoselective transformations.

3.2 Background

3.2.1 Heterospirocycle Preparation

The importance of new methodology development for heterocycle preparation cannot be overstated. The prevalence of these molecules in FDA-approved drugs and naturally-occurring biologically active molecules ensure their continued interest by synthetic chemists.[2] Nitrogen-containing heterocycles hold a primary position within this class, as >50% of all FDA-approved drugs contain at least one nitrogen heterocycle.[3]

A privileged class of heterocycles are *N*-heterospirocycles. These frameworks present unique preparative challenges due to their spiroquaternary atom and exhibit promising bioactivities

in natural products (Figure 3-1).[4] Similar to $C(sp^3)$-rich cycloalkanes or aromatic platforms, these heterospirocycles are useful scaffolds to probe various binding site interactions via differentiation of their ring characteristics, such as substituent identity, electronic effects, or size. Consequently, these *N*-heterospirocycles are important tools for lead compound generation.

In recent years, there has been a resurgence in preparatory methods for these *N*-heterospirocyclic frameworks.[5] Notable examples include work by Gaunt who reported a method for accessing a broad number of $C(sp^3)$-rich *N*-heterospirocycles via a radical cyclization of α-imino radical intermediates (Scheme 3-1a).[6] The Martin group recently demonstrated a diversity-oriented aza-Sakurai cyclization of cyclic ketones and amino-allyl silanes (Scheme 3-1b).[7] The derived *N*-spirocycles acted as linchpins for the preparation of numerous bioactive compounds. Dearomative spirocyclizations have also been used to access these *N*-heterospirocycles. The Bower group prepared numerous *N*-spiropyrrolidines via a dearomative metal-free C-N coupling (Scheme 3-1c).[8]

Scheme 3-1. Selected Examples of *N*-Heterospirocycle Preparation
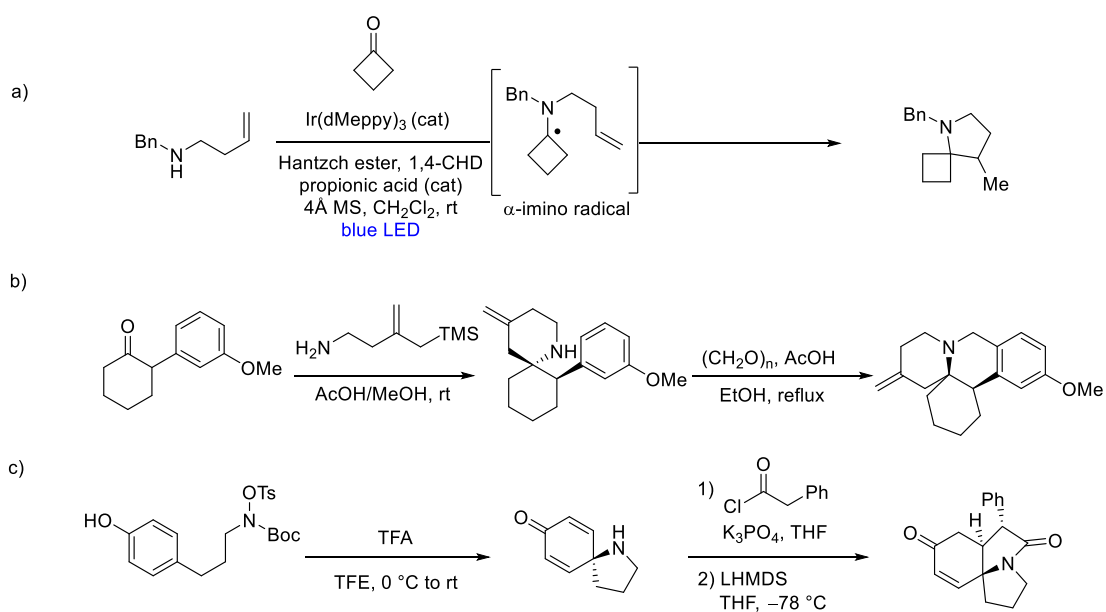
3.2.2 The Benzidine Rearrangement

The rearrangement of diphenylhydrazine **3.1** under acidic conditions has been known for over a century.[9] This conversion of aryl hydrazines to diaminobiaryls and aminodiarylamines has been collectively referred to as the "benzidine rearrangement". Using hydrochloric acid or other strong acids, the diphenylhydrazine **3.1** undergoes a [5,5]-sigmatropic rearrangement to afford *para*-benzidine **3.2** in good yields; however, a closer analysis of the side products in the reaction reveals the formation of four other rearrangement products: diphenyline **3.3**, *ortho*-benzidine **3.4**, *para*-semidine **3.5**, and *ortho*-semidine **3.6** (Scheme 3-2).[10] Diphenyline **3.3** is the result of a tandem N[1,3]/[3,3]rearrangement while *ortho*-benzidine **3.4** is the result of a [3,3]sigmatropic rearrangement. *para*-Semidine **3.5** results from a tandem N[1,3]/[1,3]rearrangement, and the *ortho*-semidine **3.6** comes from a N[1,3]-shift.

Scheme 3-2. The Benzidine Rearrangement
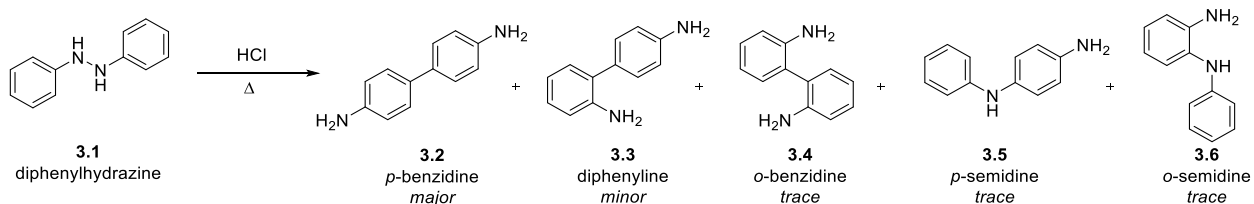
Numerous efforts have been undertaken to design substrates or reaction conditions that selectively favor the product distribution away from the most stable *para*-benzidine rearranged product.[11] These efforts have elucidated a product distribution dependence on the electronic and steric environment of the two aryl rings;[12] however, in almost every case, *para*-benzidine remains the major product. A significant synthetic challenge is the development of methods that selectively afford single regioisomers without the presence of *para*-benzidine formation.

Various methodologies in recent years have achieved this goal of selective rearrangement to create synthetically useful and elaborate scaffolds. Most notably, in 2013, List reported the first

example of a catalytic asymmetric benzidine rearrangement of dinaphthylhydrazines that was selective for the *ortho*-benzidine product (Scheme 3-3).[13] Using chiral phosphoric acid **3.9** and acidic resin (CG-50), dinaphthylhydrazine **3.7** afforded BINAM **3.8** in excellent enantioselectivities via a [3,3]rearrangement.

Scheme 3-3. List's Catalytic Asymmetric *ortho*-Benzidine Rearrangement

3.7

3.8
85% yield
96:4 er

Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
3.9
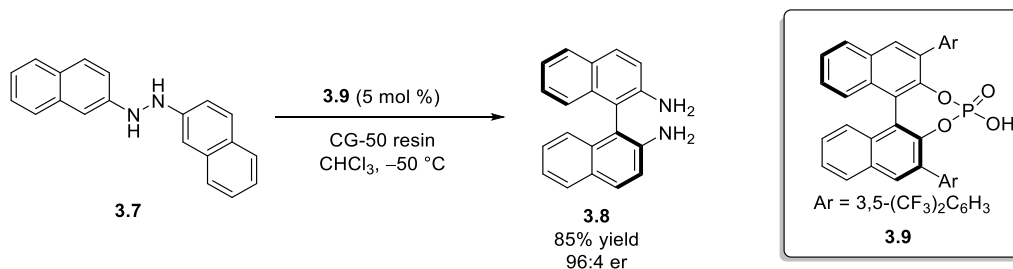
While the benzidine rearrangement has been extensively studied, a conclusive mechanism has not been agreed upon.[10] The debate surrounding this mechanism has resulted in several theories regarding the nature of the protonated transition state of the hydrazine either as a mono-protonated, bis-protonated, or bis-protonated radical cation (Scheme 3-4).[10] Several kinetic analyses of unsubstituted benzidine rearrangements have demonstrated a broad second-order dependence on acid indicating a bis-protonated state;[14] however, these kinetic studies also reveal impressive substituent effects on the acid dependence. Naphthyl or methyl substitution exhibits a first-order dependence on acid due to their ability to stabilize the charged transition state.[15] More recent literature reports have used DFT-calculations to explore the rearrangement and have suggested a first-order or near first order acid dependence via a mono-protonated transition state.[16]

Scheme 3-4. Proposed Transition States for Benzidine Rearrangement

3.1
diphenylhydrazine

mono-protonated   bis-protonated   bis-protonated
radical cation

3.2
benzidine
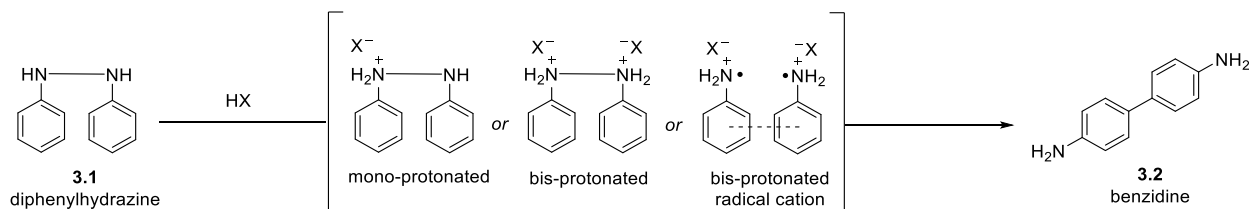
3.2.3 Paudler Dearomative *ortho*-Semidine Rearrangement

In an attempt to favor the selective formation of the *ortho*-semidine product over the other observed regioisomers, Paudler, in 1973, reported the first example of a selective and stable *ortho*-semidine rearrangement using a class of cyclic aryl hydrazines known as tetrahydrodiazocines **3.10**.[17] This dearomative reaction proceeded in the presence of concentrated HCl to afford *N*-spiro-1,2,3,4-tetrahydroquinoline derivative **3.11**. While this seminal work represented an important step in the understanding of *ortho*-semidine rearrangements, the full synthetic potential of this rearrangement was not ascertained due to a lack of scope and demonstrated secondary transformations. A possible reason for this lack of exploratory work could be due to the poor stability of the derived *N*-spiroimine **3.11** structure which, in our hands, was found to be prone to rapid decomposition upon isolation. Consequently, expanding its synthetic utility by elaboration of this scaffold was unable to be realized due to the poor stability.

3.3 Reaction Design

Considering the stability limitations of *N*-spiroimine **3.11**, we hypothesized that acid hydrolysis of the imine would afford more stable 2,4-cyclohexadienone **3.12** (Scheme 3-5). 2,4-Cyclohexadienones are valuable motifs due to their versatile nature and synthetic utility.[18] Generation of *N*-spirodienone **3.12** could therefore act as a linchpin for preparation of additional valuable *N*-heterospirocyclic scaffolds in a short number of steps (Scheme 3-5). Moreover, the nitrogen of the *N*-spirodienone could potentially act as a directing group to enable highly diastereoselective transformations, such as 1,2-carbonyl additions and Diels-Alder cycloadditions.

Scheme 3-5. One-Pot, Dearomative *ortho*-Semidine Rearrangement/Imine Hydrolysis
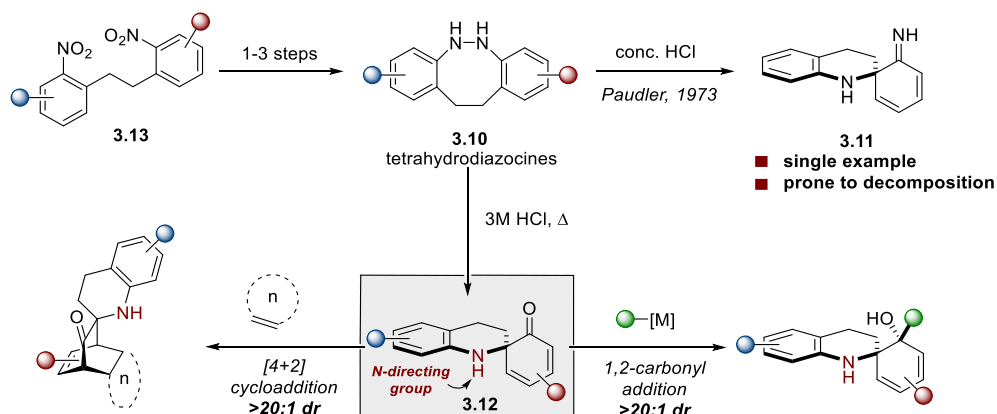
3.4 Preparation of Tetrahydrodiazocines 3.10

The lack of efficient literature preparations of tetrahydrodiazocines **3.10** caused a significant obstacle in the development of this proposal. The cyclic diazocine scaffolds were prepared via two separate approaches based on the functional groups present on the aryl rings: reductive cyclization of bis(nitrophenyl)ethane derivatives **3.13**[19] and dihydrodiazocine **3.15** reduction (Scheme 3-6). The former method exhibits mediocre yields in comparison to dihydrodiazocine reduction, and labile functional groups (i.e. halogens) were not tolerated. Nevertheless, reductive cyclization was decidedly more direct than its counterpart, which required several steps to access dihydrodiazocines **3.15**. During this project, several methods for the preparation of substituted dihydrodiazocines **3.15** were published.[20] Most notably is Trauner's oxidative coupling of dianilines **3.14** using *m*CPBA and acetic acid (Scheme 3-6, conditions d).[20a] Using both approaches, various electronically distinct tetrahydrodiazocines **3.10** were prepared.

Scheme 3-6. Tetrahydrodiazocine Preparation[a]

3.14

3.13

3.15
dihydrodiazocine

3.10
tetrahydrodiazocine
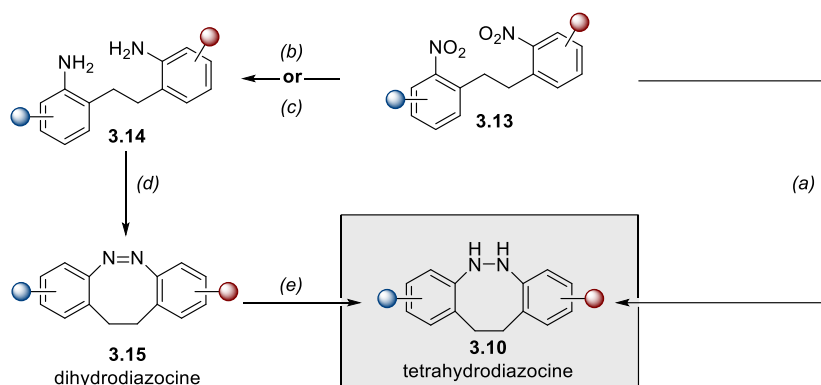
[a]Conditions: (a) Zn (12 equiv), Ba(OH)$_2$·H$_2$O (3 equiv), EtOH, reflux, 16 h; (b) Pd/C (10 mol %), H$_2$ (1 atm), DCE/MeOH (1:4), 60 °C, 16 h; (c) Fe powder (10 equiv), aq. NH$_4$Cl/EtOH (1:8), 50 to 70 °C;, 5 h. (d) *m*CPBA (2 equiv), CH$_3$COOH/CH$_2$Cl$_2$ (1:3), rt, 7 h; (e) Zn (15 equiv), 10% aq. NaOH (15 equiv), EtOH, 40 °C, 2h.

3.5 Optimization

With tetrahydrodiazocines **3.10** in hand, we began optimization on our hypothesized one-pot *ortho*-semidine rearrangement/imine hydrolysis to afford *N*-spirodienone **3.12a** using cyclic hydrazine **3.10a** (Table 3-1). An initial screen of solvent systems revealed that the presence of an organic co-solvent inhibits complete hydrolysis of imine **3.11a** and results in lower conversions as compared to using HCl as the solvent (entries 1-3). Switching to 3M H$_2$SO$_4$ as the acid source failed to increase conversions or yields (entry 4). Heating the reaction to 55 °C afforded full imine hydrolysis and gave a 75% ^{1}H NMR yield (entry 5). Increasing the temperature to 65 °C resulted in a significant loss in product yield (entry 6). Varying the acid concentration had negative effects on either conversion (lower [acid]) (entry 7) or yields (higher [acid]) (entry 8). In both cases, the conversion-to-yield ratio dramatically decreased. Attempts to run the reaction more concentrated resulted in poor conversion (most likely due to the poor solubility of the hydrazine in the reaction medium) (entry 9). Further dilution has minimal effect on yields (entry 10).

Table 3-1. Reaction Optimization[a]
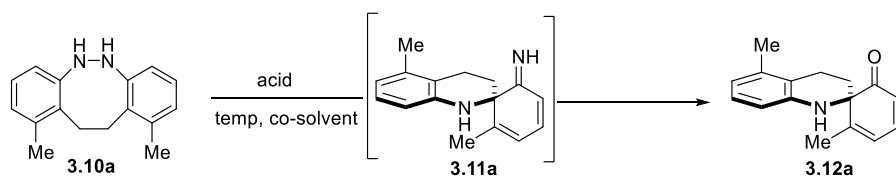
entry	acid	temp (°C)	co-solvent	3.11a hydrolysis (%)[b]	3.12a ^{1}H NMR yield (%)
1	3M HCl	0 to 40	MeOH	57	36
2	3M HCl	0 to 40	acetone	34	22
3	3M HCl	0 to 40	none	77	54
4	3M H$_2$SO$_4$	0 to 40	none	75	40
5	3M HCl	0 to 55	none	100	75
6	3M HCl	0 to 65	none	100	43
7	2M HCl	0 to 55	none	92	55
8	4M HCl	0 to 55	none	100	58
9[c]	3M HCl	0 to 55	none	80	48
10[d]	3M HCl	0 to 55	none	100	71

[a]Reactions performed using **3.10a** (0.10 mmol) with [**3.10a**] = 0.025M for 5h. [b]Determined by ^{1}H NMR spectroscopic analysis. [c][**3.10a**] = 0.05M. [d][**3.10a**] = 0.0125M.

3.6 Reaction Scope

With our optimized reaction conditions in hand, tetrahydrodiazocines **3.10** were evaluated as reaction partners (Table 3-2). Because unsubstituted 2,4-cyclohexandienones are known to rapidly dimerize, substitution at the 3-position of the aryl ring was initially evaluated to afford 5-substituted dienones that do not readily undergo dimerization.[21] Various electronically distinct functional groups were found to afford the *N*-spirodienones in modest to good yields. Brominated **3.10b** and 3-methoxyphenyl **3.10c** exhibited sluggish imine hydrolysis as compared to methyl **3.10a** to afford dienones **3.12b** and **3.12c**, respectively. To accommodate this reduced reactivity, longer reaction times and higher temperatures were required. In contrast, *para*-brominated substrate **3.10d** readily underwent dearomatization and imine hydrolysis to afford dienone **3.12d** in excellent yields, which did not have a propensity to dimerize. The presence of additional Lewis

basic sites such as methoxy and benzyloxy led to reactions exhibiting mixed results. Methoxy hydrazine **3.10e** readily underwent dearomatization and imine hydrolysis; however, the acidic reaction medium resulted in methyl ether cleavage affording bis-carbonyl **3.12e** as the major product. To prevent this cleavage, benzyloxy **3.10f** was employed; however, this substrate failed to advance to either the imine intermediate or the dienone under the optimized reaction conditions. We hypothesized that substrates lacking substitution at the 4- or 5-position of the dienone would readily dimerize exemplifying this notion. Unsubstituted tetrahydrodiazocine **3.10g** underwent the *o*-semidine rearrangement and subsequent hydrolysis to afford dienone dimer **3.12g** in modest yields.

Table 3-2. Reaction Scope[a]

3.10a-g → **3.12a-g**

3M HCl
0 to 55 °C, 5 h

3.12a
70% yield

3.12b[b]
61% yield

3.12c[c]
52% yield
Ar = 3-OMe-C$_6$H$_3$

3.12d
90% yield

3.12e
51% yield

3.12f
0% yield

3.12g
52% yield
>20:1 dr[d]
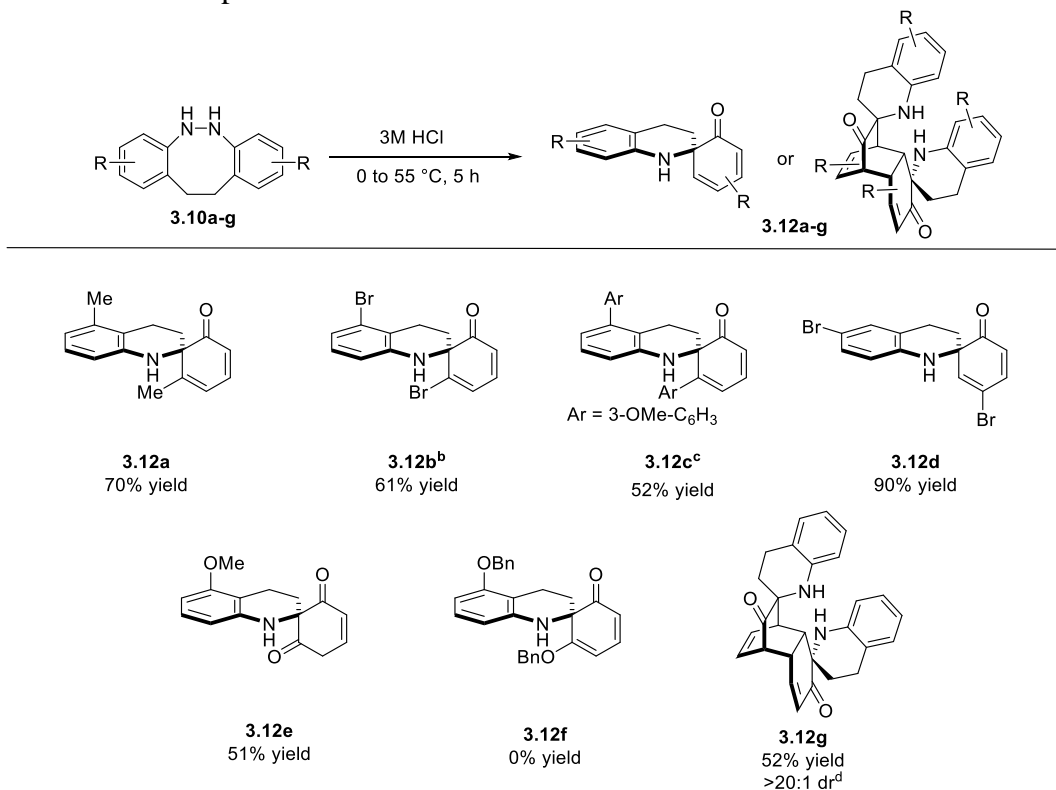
[a] Reactions performed with **3.10** (0.25 mmol) and 3M HCl [[**3.10**] = 0.025M]. Yields refer to isolated yields. [b] 8 h at 60 °C. [c] 16 h at 65 °C. [d] Determined by ^{1}H NMR spectroscopic analysis.

3.7 Synthetic Utility

The addressable functional groups in derived *N*-spirodienones **3.12** present numerous opportunities for synthetic elaboration; accordingly, several secondary transformations were carried out using **3.12a** (Scheme 3-7). We first explored the directing group ability of the nitrogen for nucleophilic attack on the carbonyl. Sodium borohydride (NaBH$_4$) was highly selective for reduction of the carbonyl and proceeded in good yields and excellent diastereoselectivity to afford secondary alcohol **3.16**. Similar selectivity was observed when employing alkyl metal species such as methyl lithium or allyl magnesium bromide to afford tertiary alcohols **3.17** and **3.18**, respectively. In all cases, nOe analysis indicated approach of the nucleophile from the same face as the nitrogen indicating the directing nature of the nitrogen atom. 2,4-Cylohexadienones are active dienes in numerous cycloaddition reactions.[18,21] Taking advantage of the activated *N*-spirodienone 2,4-dienone moiety, **3.12a** underwent a Diels-Alder cycloaddition with maleic anhydride to afford cycloadduct **3.19** as a single diastereomer. nOe analysis indicated approach of the dienophile from the same face as the nitrogen.

During the reaction optimization, we noticed the presence of a new product forming upon basification (pH >9) of the reaction mixture at room temperature. Subjecting *N*-spirodienone **3.12a** to NaH resulted in rearrangement to azepinone **3.20** in good yields. We propose this rearrangement proceeds through the mechanism outlined in Scheme 3-8.[22] Initial deprotonation of *N*-spirodienone followed by intramolecular attack on the carbonyl affords sprioaziridine **3.25**. 6π-electrocyclic ring opening gives azepine **3.26** followed by tautomerization to afford azepinone **3.20**. Azepinone **3.20** resisted diene isomerization attempts to establish conjugation with the carbonyl; however, similar azepinone systems in the literature report similar difficulties and propose that the obtained deconjugated diene is more thermodynamically stable.[23]

Attempts to epoxidize dienone **3.12a** using nucleophilic epoxidation conditions resulted in rearomatized tricycle **3.21**.[24] The aniline moiety embedded in *N*-spirocycle **3.12** enables further arene functionalization. Taking advantage of this functional group, selective mono-bromination with NBS followed by Suzuki cross-coupling with phenyl boronic acid afforded bis-aryl **3.22**. Using an electrophilic chlorinating reagent,[25] bis-chlorination of the aryl ring was accomplished to afford **3.23**.

Scheme 3-7. Synthetic Utility of *N*-Spirodienones[a]

3.16
72% yield
>20:1 dr

3.23
75% ^{1}H NMR yield

(h)

(a)

(b)

3.17
43% yield
>20:1 dr

3.22
47% yield
(2 steps)

(g)

3.12a

(c)

3.18
86% yield
>20:1 dr

(f)

(e)

(d)

3.21
73% yield

3.20
53% yield

3.19
83% yield
>20:1 dr
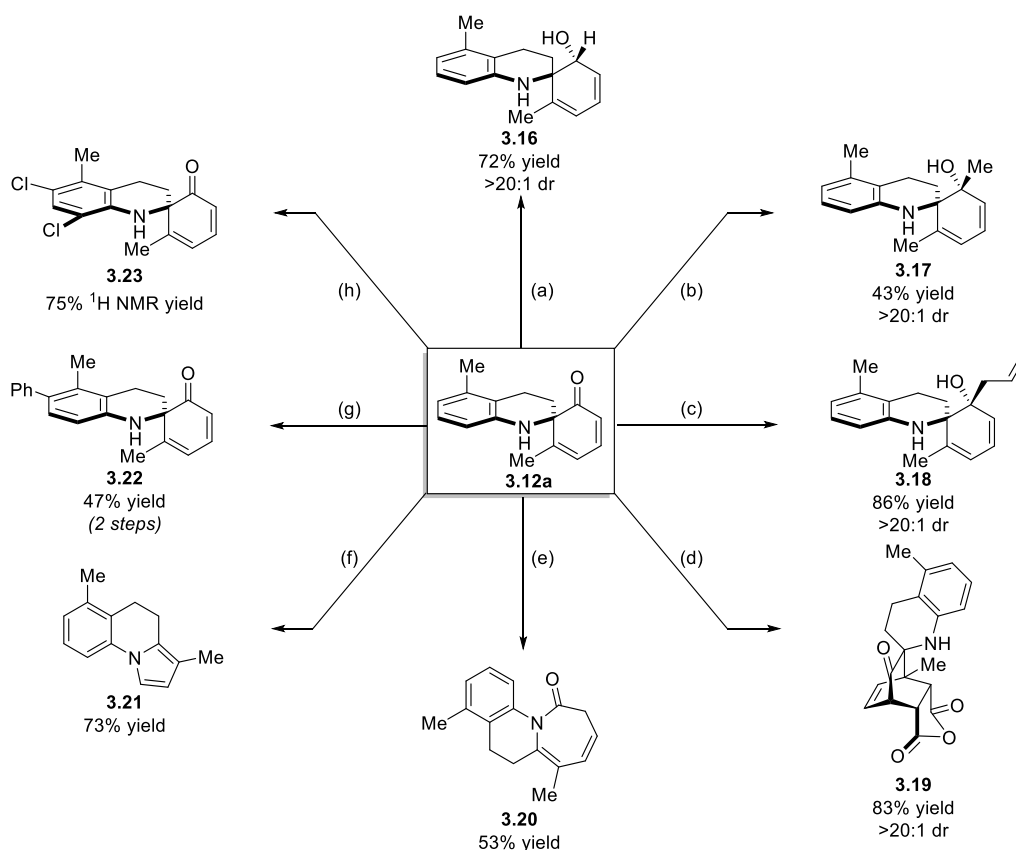
[a]Conditions: (a) NaBH$_4$ (2 equiv), MeOH, 0 °C to rt, 0.5 h; (b) MeLi (2 equiv), THF, −78 °C, 0.5 h; (c) allylmagnesium bromide (2 equiv), −78 °C, 0.5 h; (d) maleic anhydride (2 equiv), DCE, 75 °C, 48 h; (e) NaH (2 equiv), THF, 0 °C to rt, 16 h; (f) H$_2$O$_2$ (3 equiv), KOH (3 equiv), MeOH, rt, 2h; (g) (1) NBS (1 equiv), DMSO, rt, 24 h. (2) Pd(PPh$_3$)$_4$ (10 mol %), PhB(OH)$_2$ (1.1 equiv), K$_2$CO$_3$ (3 equiv), PhMe, 80 °C, 48 h; (h) CBzN(Cl)O$_2$CCHCl$_2$ (2 equiv), DMAP (10 mol %), CH$_2$Cl$_2$, 0 °C

Scheme 3-8. Proposed Mechanism for Rearrangement to Azepinone **3.20**
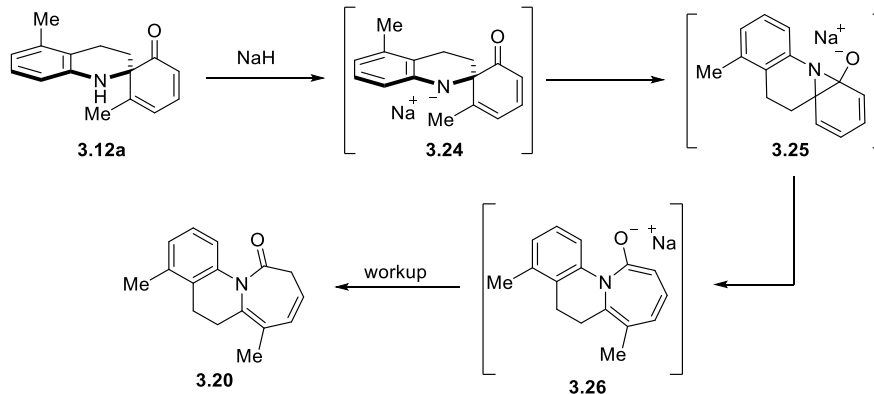
3.8 Conclusion

In conclusion, we have developed a one-pot, dearomative *ortho*-semidine rearrangement/ and subsequent imine hydrolysis of tetrahydrodiazocines to afford *N*-spirodienones **3.12**. The synthetic utility of these heterospirocyclic compounds is demonstrated in numerous secondary transformations. The directing group ability of the spirocyclic nitrogen is employed in several highly diastereoselective 1,2-carbonyl additions and a Diels-Alder cycloaddition. Additionally, the *N*-spirodienone **3.12** is readily converted into other nitrogen-containing heterocycles.

3.9 Experimental Details

General 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 staining in an aqueous ceric ammonium molybdate (CAM) or potassium permanganate ($KMnO_4$) solution, followed by gentle heating. Column chromatography was performed under positive nitrogen pressure using Siliaflash P60 silica gel (40-63 μm) purchased from Silicycle. Yields are reported for a specific experiment and as a result may differ slightly from those found in figures, which are averages of at least two experiments.

Instrumentation

^{1}H NMR and ^{13}C NMR were recorded on either a Bruker model DRX 400, 500, or 600 (cryoprobe equipped) spectrometer. The spectra were calibrated using residual solvent resonances: ^{1}H NMR ($CDCl_3$ at 7.28 ppm) and ^{13}C NMR ($CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, t = triplet, and m = multiplet), coupling constants (Hz) and integration. Yields refer to the isolated yield of pure material unless otherwise noted.

Materials

Solvents were not dried prior to use unless specified as "anhydrous." Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene (PhMe), dimethylformamide (DMF) and dimethylsulfoxide (DMSO), and were dried by passage through a column of neutral alumina under nitrogen prior to use. All chemicals were purchased from either Fisher Scientific, Sigma-Aldrich, Alfa-Aesar, or Oakwood and used as received.

Experimental Procedures

General Procedure A for the Preparation of 1,2-bis(2-nitroaryl)ethanes (3.13):
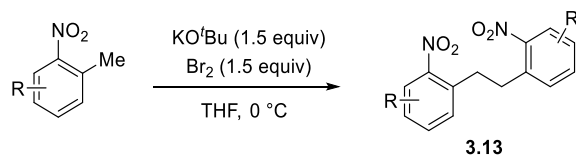
The preparation of 1,2-bis(2-nitroaryl)ethanes **3.13** was accomplished following a known procedure.[19] A flame-dried flask equipped with a magnetic stir bar was charged with the nitrotoluene and THF (0.25 M). The solution was cooled to 0 °C and KO^{t}Bu (1.5 equiv) was added in one portion. The mixture was vigorously stirred for 1 min and then Br$_2$ (1.5 equiv) was added dropwise over the course of 1 min. After addition, the mixture stirred at 0 °C for 1 min and warmed and stirred at room temperature for 10 min. The contents of the flask were poured into ice water, vigorously shaken, and the resulting suspension was filtered. The icy filter cake was washed with copious amounts of water and a saturated aqueous sodium thiosulfate solution. The filter cake was redissolved in CH$_2$Cl$_2$, dried with MgSO$_4$, and passed though a silica plug with CH$_2$Cl$_2$. The filtrate was concentrated and the product was purified by column chromatography or recrystallization in hot ethanol to afford the desired 1,2-bis(2-nitrophenyl)ethane.

Note: During filtration, the filter funnel is prone to clogging. Filtration should be conducted via slow addition of the icy mixture to the filter funnel. If the funnel becomes clogged, the cake can be washed with CH$_2$Cl$_2$ into a separate flask and then reused to finish the filtration.
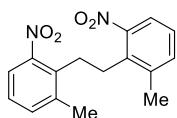
1,2-bis(2-methyl-6-nitrophenyl)ethane (3.13a): The title compound was prepared according to the General Procedure A using 1,2-dimethyl-3-nitrobenzene (5.00 g, 4.43 mL, 33.1 mmol). The crude material was purified by column chromatography (10/90

ethyl acetate/hexanes) to afford 3.87 g (77%) of the title compound as a light brown solid.

Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.57 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H),

7.28 (dd, J = 7.8, 7.8 Hz, 2H), 3.11 (s, 4H), 2.44 (s, 6H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 151.3

(2C), 139.8 (2C), 134.5 (2C), 132.4 (2C), 126.9 (2C), 121.9 (2C), 28.0 (2C), 19.7 (2C)
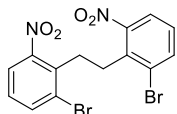
1,2-bis(2-bromo-6-nitrophenyl)ethane (3.13b): The title compound was prepared according to the General Procedure A using 2-bromo-6-nitrotoluene (5.00

g, 23.1 mmol). The crude material was purified by column chromatography (10/90 ethyl

acetate/hexanes) to afford 3.31 g (66%) of the title compound as a brown solid. Analytical data:

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.26 (dd, J = 8.1,

8.1 Hz, 2H), 3.43 (s, 4H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 151.5 (2C), 137.1 (2C), 133.6 (2C),

128.5 (2C), 127.2 (2C), 123.6 (2C), 30.6 (2C).

1,2-bis(2-methoxy-6-nitrophenyl)ethane (3.13e): The title compound was prepared according to the General Procedure A using 1-methoxy-2-methyl-3-

nitrobenzene (5.35 g, 32.0 mmol). The crude material was of sufficient purity after the silica plug

and was not purified further to afford 4.43 g (83%) of the title compound as a light yellow solid.

Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.31 (dd, J = 7.8, 6.9 Hz, 2H), 7.27 (d, J = 8.1 Hz,

2H), 7.01 (d, J = 7.9 Hz, 2H), 3.84 (s, 6H), 3.16 (s, 4H).**^{13}C NMR** (151 MHz, CDCl$_3$) δ 158.5

(2C), 151.2 (2C), 127.4 (2C), 124.4 (2C), 115.5 (2C), 113.6 (2C), 56.0 (2C), 24.7 (2C).
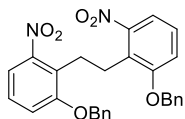
1,2-bis(2-(benzyloxy)-6-nitrophenyl)ethane (3.13f): The title compound was prepared according to the General Procedure A using 1-(benzyloxy)-2-methyl-3-

nitrobenzene (5.00 g, 23.1 mmol). The crude material was purified by column chromatography

(10/90 ethyl acetate/hexanes) to afford 3.25 g (65%) of the title compound as a light orange solid.

Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.41 – 7.32 (m, 12H), 7.24 (d, J = 8.1 Hz, 2H),

7.21 (dd, J = 8.1, 8.1 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 4.96 (s, 4H), 3.33 (s, 4H). **^{13}C NMR** (151

MHz, CDCl$_3$) δ 157.5 (2C), 151.2 (2C), 126.3 (2C), 128.6 (4C), 128.0 (2C), 127.3 (2C), 127.2

(4C), 124.6 (2C), 115.9 (2C), 115.0 (2C), 70.5 (2C), 24.7 (2C).

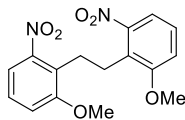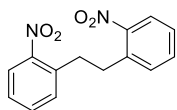**1,2-bis(2-methyl-6-nitrophenyl)ethane (3.13g):** The title compound was prepared according to the General Procedure A using 1,2-dimethyl-3-nitrobenzene (14.0 g, 12.1 mL, 0.102 mol). The crude material was sufficiently pure after the silica plug and was not purified further to afford to afford 10.2 g (68%) of the title compound as a light brown solid. Spectroscopic properties were consistent with those previously reported.[19] Analytical data:

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, J = 8.1 Hz, 2H), 7.57 (dd, J = 7.5, 7.5 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.41 (dd, J = 7.7, 7.7 Hz, 2H), 3.27 (s, 4H).

Preparation of Bis(anilines) 3.14:
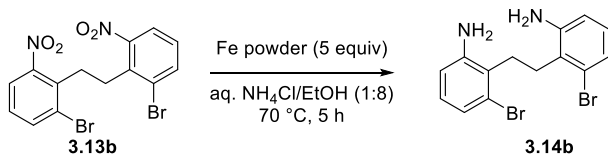
2,2'-(ethane-1,2-diyl)bis(3-bromoaniline) (3.14b): The following preparations of bis(anilines) were accomplished following a modified literature procedure.[26] A round-bottomed flask under N_2 and equipped with a magnetic stir bar was charged with 1,2-bis(2-nitrophenyl)ethane **3.13b** (2.00 g, 4.65 mmol), a saturated aqueous NH_4Cl solution (15 mL), and EtOH (120 mL). The solution was heated to 50 °C and Fe powder (1.30 g, 23.3 mmol) was added. The mixture was vigorously stirred for 5 h at 70 °C. The reaction was cooled to room temperature and the mixture was passed through Celite®. EtOH was removed *in vacuo* and the crude product was extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with water (15 mL) and brine, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the crude product was recrystallized from hot EtOH to afford 1.10 g (64%) of the title compound as a light brown solid. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.01 (d, J = 7.9 Hz, 2H), 6.91 (dd, J = 7.9, 7.9 Hz, 2H), 6.65 (d, J = 7.9 Hz, 2H), 4.09 (s, 4H), 2.93 (s, 4H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 146.2 (2C), 128.4 (2C), 125.8 (2C), 124.5 (2C), 122.6 (2C), 114.9 (2C), 29.4 (2C).
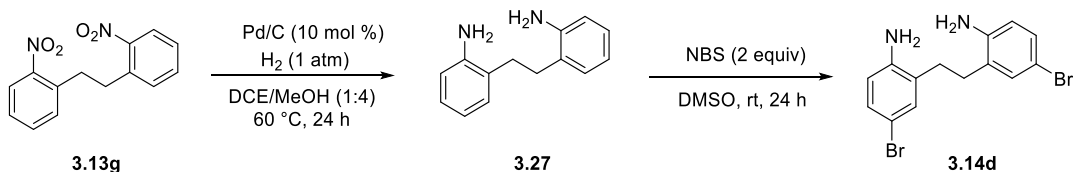
2,2'-(ethane-1,2-diyl)dianiline (3.27): A flame-dried round-bottomed flask equipped with a magnetic stir bar under N_2 was charged with 10% Pd/C (580 mg, 0.55 mmol), DCE (10 mL), and EtOH (40 mL). 1,2-bis(2-nitrophenyl)ethane **3.13a** (1.50 g, 5.51 mmol) was added and the reaction

vessel was purged with hydrogen. The reaction stirred under an atmosphere of H_2 (balloon) at 60 °C for 24 h. The reaction was cooled, purged with nitrogen, and water (5 mL) was added. The reaction was filtered through a plug of Celite®. The filtrate was concentrated, and the crude product was purified by silica gel column chromatography (40/60 ethyl acetate/hexanes) to afford 1.00 g (86%) of **3.27** as a light brown solid. Spectroscopic properties were consistent with those previously reported.[20a] Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.18 – 6.98 (m, 1H), 6.79 (dd, J = 7.4, 7.4 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 2.99 (s, 4H), 2.83 (s, 1H).

2,2'-(ethane-1,2-diyl)bis(4-bromoaniline) (3.14d): The following preparation was accomplished following a modified literature procedure.[20a] A flame-dried round-bottomed flask equipped with a stir bar under N_2 was charged with **3.27** (1.90 g, 8.95 mmol) and anhydrous DMSO (35 mL). NBS (3.19 g, 17.9 mmol) was added in three portions within 10 min and the mixture stirred for 24 h at room temperature. Water (30 mL) and CH_2Cl_2 (15 mL) were added and the contents of the flask were transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined and washed with water (3 x 30 mL) and brine (3 x 10 mL), dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* to afford the crude product. The product was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 850 mg (26%) of **3.14d** as a light brown solid. The contents of the vial were transferred to a separatory funnel and diluted with CH_2Cl_2 (5 mL) and water (10 mL). Spectroscopic properties were consistent with those previously reported.[20a] **¹H NMR** (600 MHz, CDCl₃) δ 7.20 – 7.14 (m, 4H), 6.58 (d, J = 8.3 Hz, 2H), 3.65 (s, 4H), 2.74 (s, 4H).

General Procedure B for the Preparation of Dihydrodiazocines:

3.14   **3.15**
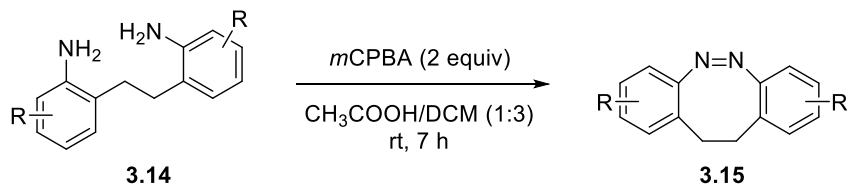
The following preparations of bis(anilines) **3.14** were accomplished via a modified literature procedure.[20a] A round-bottomed flask equipped with a magnetic stir bar was charged with the starting bis-aniline **3.14** (1 equiv) and a CH_3COOH/CH_2Cl_2 solution (1:3, 0.05 M). A solution of *m*CPBA (75%, 2 equiv) in CH_3COOH (0.6 M) was added to the solution over the course of 6 h. After addition, the solution was stirred for an additional 1 h. The solution was concentrated *in vacuo* and the residue was redissolved in EtOAc (100 mL), washed with saturated aqueous sodium bicarbonate solution (3 x 100 mL), water (100 mL), and brine. The solution was dried using $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography to afford the desired dihydrodiazocine **3.15**.
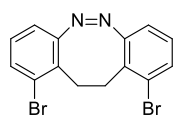
(Z)-1,10-dibromo-11,12-dihydrodibenzo[c,g][1,2]diazocine (3.15b): The title compound was prepared according to the General Procedure B using bis(aniline) **3.14b** (1.30 g, 3.51 mmol). The crude material was purified by column chromatography (5/95 to 10/90 gradient ethyl acetate/hexanes) to afford 720 mg (56%) of the title compound as an orange solid. Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.35 (dd, J = 8.0, 0.9 Hz, 2H), 7.02 (dd, J = 7.9, 7.8 Hz, 2H), 6.79 (dd, J = 7.6, 0.8 Hz, 2H), 3.48-2.73 (m, 4H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 155.9 (2C), 131.4 (2C), 127.7 (2C), 127.6 (2C), 125.2 (2C), 117.9 (2C), 30.3 (2C).
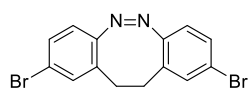
(Z)-2,9-dibromo-11,12-dihydrodibenzo[c,g][1,2]diazocine (3.15d): The title compound was prepared according to the General Procedure B using bis-aniline **2.3a** (1.10 g, 2.97 mmol). The crude material was purified by column chromatography (5/95 to 10/90 gradient ethyl acetate/hexanes) to afford 455 mg (41%) of the title compound as a bright yellow solid. Spectroscopic properties were consistent with those previously reported.[20a] Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.31 (d, *J* = 8.3 Hz, 2H), 7.19 (s, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 3.02-2.68 (m, 4H).
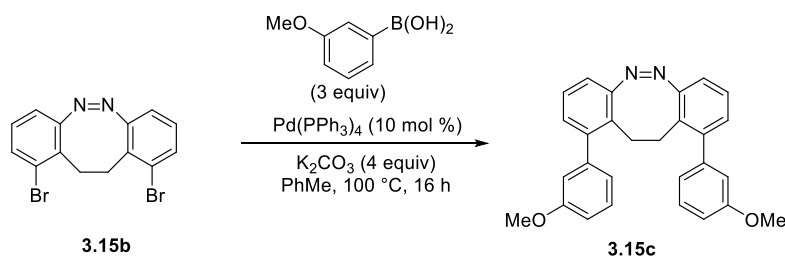
(Z)-1,10-bis(3-methoxyphenyl)-11,12-dihydrodibenzo[c,g][1,2]diazocine (3.15c): A flame-dried round-bottomed flask equipped with a stir bar was charged with Pd(PPh$_3$)$_4$ (158 mg, 0.137 mmol), (2-methoxyphenyl)boronic acid (623 mg, 4.10 mmol) and K$_2$CO$_3$ (755 mg, 5.46 mmol). Dibromide **3.15b** (50 mg, 1.37 mmol) dissolved in anhydrous PhMe (15 mL) was added to the flask. The mixture was heated at 100 °C for 16 h. The mixture was passed through a silica plug with CH$_2$Cl$_2$ as the eluent. The filtrate was concentrated, and the crude product was purified by silica gel column chromatography (5/95 to 10/90 gradient ethyl acetate/hexanes) to afford 276 mg (48%) of the title compound as a bright yellow oil. Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.20 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.14 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 7.9 Hz, 2H), 6.70 (s, 2H), 6.61 (d, *J* = 7.6 Hz, 2H), 3.78 (s, 6H), 2.71 (d, *J* = 4.2 Hz, 4H).

General Procedure C for the Preparation of Tetrahydrodiazocines 3.10:
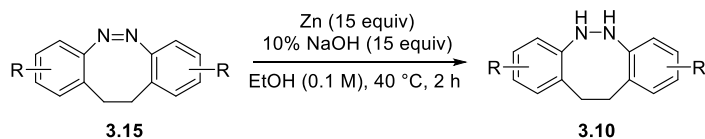
A round-bottomed flask equipped with a magnetic stir bar was charged with starting diazocine **3.15** (1 equiv), EtOH (0.1 M), and NaOH (10% aqueous, 15 equiv). Zinc (15 equiv, unactivated) was added and the mixture stirred at 40 °C for 2 h. The mixture was cooled to room temperature and filtered through Celite®. The filtrate was extracted with CH_2Cl_2, washed with water (x3) and brine (x2). The solution was dried with $MgSO_4$, filtered, and concentrated under a steady stream of N_2 to afford the desired product.

Note: The authors noticed that tetrahydrodiazocines 3.10 are very prone to oxidation under air and heat back to the corresponding dihydrodiazocine 3.15. Caution should be taken to avoid heat after purification to prevent impurities from forming.
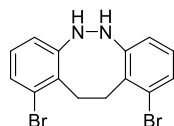
 1,10-dibromo-5,6,11,12-tetrahydrodibenzo[c,g][1,2]diazocine (3.10b): The title compound was prepared according to the General Procedure C using dihydrodiazocine **3.15b** (500 mg, 1.37 mmol) to afford 234 mg (47%) of the title compound as a light orange solid. Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 7.22 (dd, *J* = 8.0, 1.2 Hz, 2H), 6.90 (dd, *J* = 7.9, 7.8 Hz, 2H), 6.70 (dd, *J* = 7.8, 1.2 Hz, 2H), 5.62 (s, 2H), 3.45 (s, 4H); **¹³C NMR** (101 MHz, CDCl₃) δ 147.2 (2C), 132.4 (2C), 127.4 (2C), 126.2 (2C), 118.0 (2C), 76.7 (2C), 29.7 (2C).
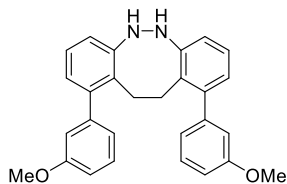
1,10-bis(3-methoxyphenyl)-5,6,11,12-tetrahydrodibenzo[c,g]

[1,2]diazocine (3.10c): The title compound was prepared according to the General Procedure C using dihydrodiazocine **3.15c** (150 mg, 0.36 mmol) to afford 3.12 g (62%) of the title compound as a white foam. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.21 (dd, J = 8.0, 8.0 Hz, 2H), 7.11 (dd, J = 7.7, 7.7 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 6.80 (m., 6H), 5.77 (s, 2H), 3.79 (s, 6H), 3.05 (s, 4H).

2,9-dibromo-5,6,11,12-tetrahydrodibenzo[c,g][1,2]diazocine

(3.10d): The title compound was prepared according to the General Procedure C using dihydrodiazocine **3.15d** (183 mg, 0.500 mmol) to afford 159 mg (86%) of the title compound as a white solid. Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.27 (d, J = 2.1 Hz, 2H), 7.19 (dd, J = 8.2, 2.2 Hz, 2H), 6.60 (d, J = 8.2 Hz, 2H), 5.55 (s, 2H), 3.16 (s, 4H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 145.3 (2C), 135.1 (2C), 133.5 (2C), 129.2 (2C), 118.9 (2C), 114.6 (2C), 30.7 (2C).

General Procedure D for the Preparation of Tetrahydrodiazocines 3.10:
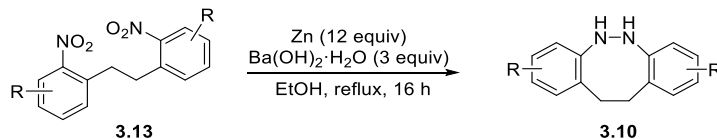
The following preparations of tetrahydrodiazocines **3.10** were accomplished using a modified literature procedure.[19b] A round-bottomed flask equipped with a magnetic stir bar was charged with the starting 1,2-bis(2-nitrophenyl)ethane **3.13** (1 equiv) and EtOH (0.05 M). The solution was heated to 95 °C and a hot solution of $Ba(OH)_2 \cdot H_2O$ (3 equiv) in H_2O (0.50 M) was added. Zinc dust (12 equiv, unactivated) was added in portions over 10 min with vigorous stirring. The mixture stirred for 16 h at reflux and cooled to room temperature. The mixture was cooled further to 0 °C via addition of ice to the flask and the mixture was then filtered through Celite®. The filtrate was concentrated to remove the EtOH. The residue was redissolved in CH_2Cl_2 and washed with water (3x) and brine. The organic layer was dried using $MgSO_4$, filtered, and concentrated. The product was purified by silica gel column chromatography and concentrated under a steady stream of N_2 to afford the desired tetrahydrodiazocine **3.10**.

*Note: The authors noticed that tetrahydrodiazocines **3.10** are very prone to oxidation under air and heat back to the corresponding dihydrodiazocine **3.15**. Caution should be taken to avoid heat after purification to prevent impurities from forming.*
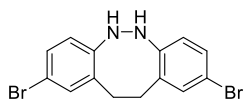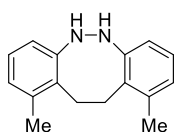

1,10-dimethyl-5,6,11,12-tetrahydrodibenzo[c,g][1,2]diazocine (3.10a): The title compound was prepared according to the General Procedure D using 1,2-bis(2-nitrophenyl)ethane **3.13a** (2.20 g, 7.34 mmol). The crude material was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 750 mg (43%) of the title compound as a white solid. Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 6.95 (dd, *J* = 7.6, 7.6 Hz, 2H), 6.81

(d, J = 7.4 Hz, 2H), 6.64 (d, J = 7.7 Hz, 2H), 5.54 (s, 2H), 3.26 (s, 4H), 2.34 (s, 6H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 146.0 (2C), 136.9 (2C), 131.8 (2C), 125.9 (2C), 125.0 (2C), 117.4 9 (2C), 25.9 (2C), 20.3 (2C).
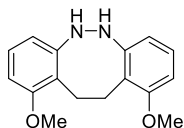
1,10-dimethoxy-5,6,11,12-tetrahydrodibenzo[c,g][1,2]diazocine

(3.10e): The title compound was prepared according to the General Procedure D using 1,2-bis(2-nitrophenyl)ethane **3.13e** (3.00 g, 9.03 mmol). The crude material was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 454 mg (19%) of the title compound as a light yellow solid. Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.01 (dd, J = 8.0, 8.0 Hz, 2H), 6.54 (d, J = 8.2 Hz, 2H), 6.42 (d, J = 7.8 Hz, 2H), 5.58 (s, 2H), 3.81 (s, 6H), 3.25 (s, 4H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 157.8 (2C), 147.4 (2C), 126.3 (2C), 121.9 (2C), 111.8 (2C), 105.4 (2C), 55.9 (2C), 21.8 (2C).
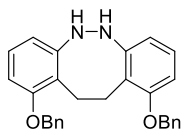
1,10-bis(benzyloxy)-5,6,11,12-tetrahydrodibenzo[c,g][1,2]diazocine (3.10f): The title compound was prepared according to the General Procedure D using 1,2-bis(2-nitrophenyl)ethane **3.13f** (2.50 g, 5.16 mmol). The crude material was purified by column chromatography (15/85 to 30/70 gradient ethyl acetate/hexanes) and concentrated to afford 250 mg (12%) of the title compound as a bright yellow solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.58 – 7.30 (m, 10H), 6.98 (dd, J = 11.5, 8.0 Hz, 2H), 6.60 (d, J = 8.1 Hz, 1H), 6.45 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 6.28 (d, J = 8.0 Hz, 1H), 5.62 (s, 1H), 5.03 (d, J = 10.6 Hz, 4H), 3.38 (s, 1H), 3.36 (s, 2H), 2.67 (s, 2H). **^{13}C NMR** (151 MHz, CDCl$_3$) δ 157.3, 156.9, 147.4, 145.7, 137.4, 137.2, 128.6 (2C), 128.5 (2C), 128.2 (2C), 128.1, 127.7, 127.1 (2C), 127.0, 126.5, 122.5, 114.7, 112.6, 108.8, 107.0, 101.5, 70.5, 70.3, 23.0, 22.2.
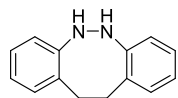
5,6,11,12-tetrahydrodibenzo[c,g][1,2]diazocine (3.10g): The title compound was prepared according to the General Procedure F using 1,2-bis(2-nitrophenyl)ethane **3.13g** (2.00 g, 7.35 mmol) with the following modification: the reaction stirred for 5 h. The crude material was purified by column chromatography (10/90 ethyl acetate/hexanes) and concentrated to afford 1.05 g (68%) of the title compound as a white solid. Spectroscopic properties were consistent with those previously reported.[19] Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.14 (d, J = 7.4 Hz, 2H), 7.09 (dd, J = 7.6, 7.6 Hz, 2H), 6.93 (dd, J = 7.4, 7.4 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 5.57 (s, 2H), 3.25 (s, 4H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 146.4 (2C), 133.4 (2C), 130.9 (2C), 126.5 (2C), 122.4 (2C), 117.7 (2C), 21.4 (2C).

Dearomative One-Pot *ortho*-Semidine Rearrangement/Imine Hydrolysis

General Procedure E for the Preparation of *N*-Spirodienones 3.12:
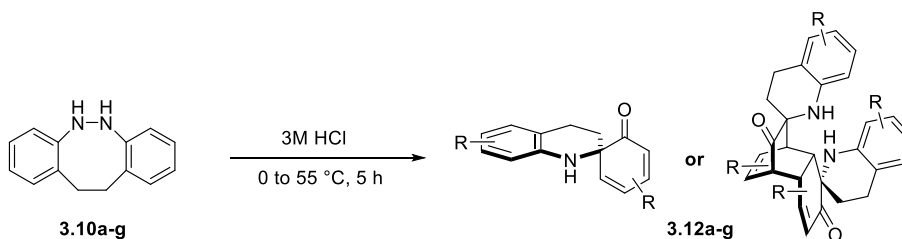
A round-bottomed flask equipped with a magnetic stir bar was charged with the starting tetrahydrodiazocine **3.10** (0.250 mmol). The solid was cooled to 0 °C and placed under a constant stream of N_2 and equipped with an outlet needle. HCl (3M, aq., 10 mL, precooled to 0 °C) was added in one portion under vigorous stirring and the mixture stirred for 15 min. The mixture was heated to 55 °C and stirred for 4.75 h. The solution was cooled to 0 °C and CH_2Cl_2 (2 mL) was added. The solution was quenched with 10% NaOH until neutral pH. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was purified via silica gel column chromatography to afford the desired *N*-spirodienone **3.12**.

*Note: Over basification (pH > 9) of the reaction mixture at warm temperatures using 10% NaOH can result in partial rearrangement to **3.20** and diminished product yields.*
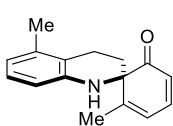
 (*rac*)-2,5'-dimethyl-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-one (3.13a): The title compound was prepared according to the General Procedure E using dihydrodiazocine **3.10a** (60 mg, 0.25 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 43 mg (72%) of the title compound as a bright orange oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 6.97 (t, *J* = 7.7 Hz, 1H), 6.91 (dd, *J* = 9.8, 6.0 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.04 (d,

J = 6.0 Hz, 1H), 6.00 (d, *J* = 9.8 Hz, 1H), 4.11 (s, 1H), 2.68 (ddd, *J* = 16.6, 5.2, 4.8 Hz, 1H), 2.54 (ddd, *J* = 16.2, 10.1, 5.4 Hz, 1H), 2.20 (s, 3H), 2.13 (ddd, *J* = 13.3, 10.1, 5.1 Hz, 1H), 2.00 (d, *J* = 1.5 Hz, 3H), 1.92 (ddd, *J* = 13.3, 5.3, 4.8 Hz, 1H); **13C NMR** (151 MHz, CDCl₃) δ 206.6, 157.8, 143.7, 140.7, 136.2, 126.5, 122.5, 119.3, 119.1, 118.0, 112.4, 67.5, 30.6, 20.2, 20.1, 19.3.

(***rac***)-2,5'-dibromo-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-one (3.13b): The title compound was prepared according to the General Procedure E using dihydrodiazocine **3.10b** (92 mg, 0.25 mmol) with the following modification: the reaction stirred for 8 h at 60 °C. The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 57 mg (62%) of the title compound as a bright red oil. Analytical data: **1H NMR** (400 MHz, CDCl₃) δ 6.90-6.85 (m, 2H), 6.88 (dd, *J* = 9.8, 6.6 Hz, 1H), 6.69 (d, *J* = 6.5 Hz, 1H), 6.61 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.16 (d, *J* = 9.7 Hz, 1H), 4.26 (s, 1H), 3.00 (dd, *J* = 17.0, 4.8, 4.8 Hz, 1H), 2.65 (ddd, *J* = 16.7, 10.8, 5.3 Hz, 1H), 2.21 (ddd, *J* = 13.6, 10.8, 5.0 Hz, 1H), 1.98 (ddd, *J* = 14.3, 4.9, 4.9 Hz, 1H); **13C NMR** (151 MHz, CDCl₃) δ 202.5, 144.2, 141.8, 139.6, 128.0, 126.0, 124.9, 124.1, 121.6, 119.0, 113.2, 68.4, 30.1, 22.4.
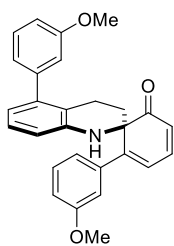
(***rac***)-2-(3-methoxyphenyl)-5'-(3-methoxyphenyl)-3',4'-dihydro-1'H-spiro [cyclohexane-1,2'-quinoline]-2,4-dien-6-one (3.13c): The title compound was prepared according to the General Procedure E using tetrahydrodiazocine **3.10c** (106 mg, 0.25 mmol) with the following modification: the reaction stirred for 16 h at 65 °C. The crude material was purified by column chromatography (20/80 ethyl acetate/hexanes) to afford 57 mg (54%) of the title compound as an orange solid. Analytical data: **1H NMR** (600 MHz, CDCl₃) δ 7.25-7.20 (m, 2H), 7.15 (s, 1H), 7.12-7.06 (m, 2H), 6.90-6.86 (m,

3H), 6.71 (dd, J = 4.4, 2.4 Hz, 1H), 6.62 (dd, J = 15.4, 7.8 Hz, 2H), 6.36 (d, J = 6.2 Hz, 1H), 6.16 (d, J = 9.8 Hz, 1H), 4.37 (s, 1H), 3.81 (s, 3H), 3.69 (s, 3H), 2.57-2.44 (m, 2H), 2.24 (ddd, J = 13.7, 8.7, 5.1 Hz, 1H), 1.98 (ddd, J = 12.7, 5.7 Hz, 1H); ^{13}C NMR (151 MHz, CDCl$_3$) δ 204.9, 159.0, 157.1, 143.5, 142.9, 141.7, 140.5, 139.9, 129.0, 128.8, 126.6, 125.8, 123.3, 121.5, 121.5, 120.7, 118.9, 117.5, 114.5, 114.4, 114.1, 113.8, 112.4. 68.1, 55.2, 55.1, 32.1, 21.9.
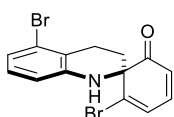
(*rac*)-3,6'-dibromo-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-one (3.12d): The title compound was prepared according to the General Procedure E using tetrahydrodiazocine **3.10d** (92 mg, 0.25 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 83 mg (90%) of the title compound as an orange solid. Analytical data: ^{1}**H NMR** (600 MHz, CDCl$_3$) δ 7.20-7.11 (m, 1H), 6.98 (dd, J = 10.2, 2.6 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.53 (d, J = 9.1 Hz, 1H), 6.05 (d, J = 10.1 Hz, 1H), 4.19 (s, 1H), 2.86-2.72 (m, 2H), 2.12 (ddd, J = 13.1, 5.8, 5.8 Hz, 1H), 1.84 (ddd, J = 13.0, 8.1, 6.6 Hz, 1H); ^{13}**C NMR** (151 MHz, CDCl$_3$) δ 201.5, 144.2, 143.3, 140.7, 131.6, 130.1, 125.9, 121.6, 117.0, 114.3, 110.0, 65.2, 31.2, 23.3.
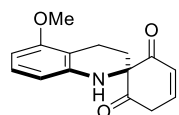
(rac)-5'-methoxy-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinolin]-3-ene-2,6-dione (3.12e): The title compound was prepared according to the General Procedure E using tetrahydrodiazocine **3.10e** (68 mg, 0.25 mmol). The crude material was purified by column chromatography (40/60 ethyl acetate/hexanes) to afford 33 mg (51%) of the title compound as a light orange oil. Analytical data: ^{1}**H NMR** (600 MHz, CDCl$_3$) δ 7.10 (ddd, J = 10.3, 4.9, 2.9 Hz, 1H), 7.05 (dd, J = 8.1, 8.1 Hz, 1H), 6.47 (d, J = 8.1 Hz, 1H), 6.36 (ddd, J = 10.3, 3.3, 1.0 Hz, 1H), 6.29 (dd, J = 8.1 Hz, 1H), 4.77 (s, 1H), 3.79 (s, 3H), 3.68 (ddd, J = 21.6, 3.1, 3.0 Hz, 1H), 3.34 (ddd, J = 21.6, 4.9, 1.0 Hz, 1H), 2.71 (ddd, J = 16.9, 7.2, 5.1 Hz, 1H), 2.57 (ddd, J

= 16.9, 8.5, 5.2 Hz, 1H), 2.21 (ddd, *J* = 12.5, 7.2, 5.2 Hz, 1H), 2.15 (ddd, *J* = 13.2, 8.5, 5.2 Hz, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 201.8, 196.7, 157.1, 143.2, 142.2, 128.0, 127.4, 108.4, 107.2, 99.7, 76.3, 55.2, 39.2, 30.0, 18.2.
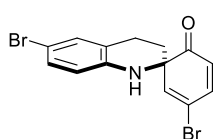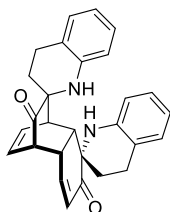

(*rac*)-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-one dimer (3.12g): The title compound was prepared according to the General Procedure E using tetrahydrodiazocine **3.10g** (52.6 mg, 0.250 mmol). The crude material was purified by column chromatography (30/70 ethyl acetate/hexanes) to afford 27 mg (51%) of the title compound as clear oil. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 6.95-6.84 (m, 4H), 6.64 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.62-6.58 (m, 2H), 6.48 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.45 (dd, *J* = 10.1, 4.0 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 6.15 (dd, *J* = 10.1, 1.7 Hz, 1H), 6.03 (ddd, *J* = 7.9, 6.0, 1.7 Hz), 4.49 (s, 1H), 3.72 (s, 1H), 3.40 (ddd, *J* = 8.3, 4.0, 2.1 Hz, 1H), 3.37 (ddd, *J* = 6.1 Hz, 2.5 Hz, 1.4 Hz, 1H), 3.34 (dd, *J* = 8.4, 1.8 Hz, 1 H), 3.29 (ddd, *J* = 6.7, 1.8, 1.8 Hz, 1H), 2.89 (ddd, *J* = 16.3, 11.0, 5.2 Hz, 1H), 2.72-2.63 (m, 3H), 2.04 (ddd, *J* = 13.0, 4.9, 4.9 Hz, 1H), 1.91 (ddd, *J* = 13.0, 4.9, 4.9 Hz, 1H), 1.74 (ddd, *J* = 13.0, 11.0, 4.9 Hz, 1H), 1.65 (ddd, *J* = 13.0, 10.0, 6.5 Hz, 1H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 213.4, 200.3, 144.3, 142.7, 141.9, 134.9, 129.0, 128.7, 128.5, 126.3, 127.1, 126.9, 121.3, 120.3, 118.4, 117.9, 116.3, 115.5, 61.4, 60.6, 53.4, 43.4, 40.9, 40.4, 33.7, 29.8, 23.3, 23.1.

Secondary Transformations:

3.12a → **3.16**

NaBH₄ (2 equiv)
MeOH, 0.5 h, 0 °C to rt
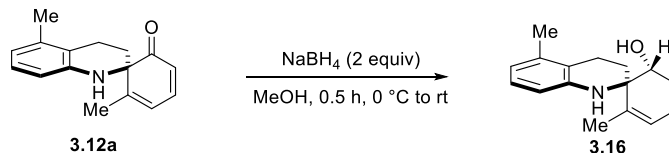
(*rac*)-(1R,6R)-2,5'-dimethyl-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-ol (3.16): A flame-dried 4-dram vial equipped with a stir bar and under N_2 was charged with *N*-spirodienone **3.12a** (25 mg, 0.10 mmol) and anhydrous MeOH (2.5 mL). The solution was cooled to 0 °C, and NaBH₄ (7.9 mg, 0.20 mmol) was added portionwise over the course of 1 min. The mixture stirred at 0 °C for 5 min then stirred at room temperature for 25 min. The mixture was concentrated to dryness *in vacuo*. A saturated aqueous ammonium chloride solution (2 mL) and EtOAc (5 mL) were added to the vial. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic extracts were combined, washed with water (2 mL) and brine, dried with MgSO₄, and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography (20/90 ethyl acetate/hexanes) to afford **3.16** (21 mg, 0.087 mmol, 83% yield, >20:1 dr) as a white solid. Analytical data: **¹H NMR** (400 MHz, CDCl₃) δ 6.93 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 5.96 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.87 (dd, *J* = 9.5, 4.0 Hz, 1H), 5.78 (dq, *J* = 5.6, 1.7 Hz, 1H), 4.27 (d, *J* = 4.0 Hz, 1H) 3.61 (s, 1H), 2.79-2.67 (m, 2H), 2.31 (ddd, *J* = 12.8, 6.2, 6.2 Hz, 1H), 2.22 (s, 3H), 2.01 (ddd, *J* = 13.3, 9.1, 5.9 Hz, 1H), 1.85 (d, *J* = 5.4 Hz, 1H), 1.81 (s, 3H); **¹³C NMR** (151 MHz, CDCl₃) δ 144.0, 142.9, 136.8, 126.8, 126.4, 124.9, 120.5, 119.8, 119.1, 112.5, 71.0, 57.2, 22.8, 21.5, 19.4.
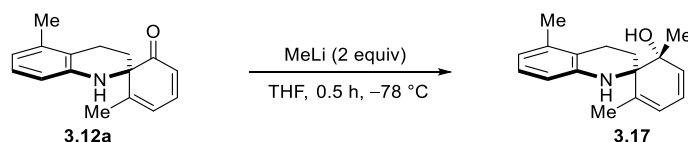
(*rac*)-(1R,6R)-2,5',6-trimethyl-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-ol (3.17): A flame-dried 4-dram vial equipped with a stir bar and under N_2 was charged *N*-spirodienone **3.12a** (11 mg, 0.05 mmol) and anhydrous THF (2 mL). The solution was cooled to −78 °C, and MeLi (1.6 M in Et_2O, 57 μL, 0.10 mmol) was added dropwise over the course of 1 min. The solution stirred at −78 °C for 0.5 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (1 mL) and warmed to room temperature. The reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, washed with water (2 mL) and brine, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography (10/90 ethyl acetate/hexanes) to afford **3.17** (5.0 mg, 0.02 mmol, 43% yield, >20:1 dr) as a yellow oil. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 5.75 (dd, *J* = 9.7, 4.9 Hz, 1H), 5.68 (d, *J* = 9.5 Hz, 1H), 5.59 (dq, *J* = 4.9, 1.6 Hz, 1H), 3.89 (s, 1H), 2.75 (ddd, *J* = 16.4, 5.2, 5.2 Hz, 2H), 2.51 (ddd, *J* = 16.5, 10.7, 5.6 Hz, 1H), 2.34 (ddd, *J* = 13.2, 10.8, 5.5 Hz, 1H), 2.26-2.18 (m, 4H), 2.04 (s, 1H), 1.72 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 146.7, 144.9, 136.6, 133.7, 126.4, 122.3, 120.7, 119.4, 119.2, 112.6, 77.4, 62.1, 24.7, 22.2, 21.0, 20.5, 19.3.
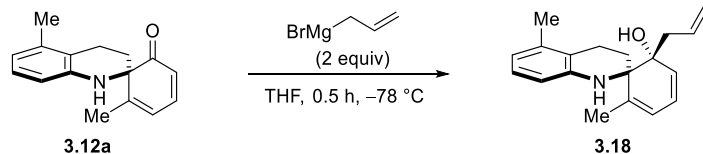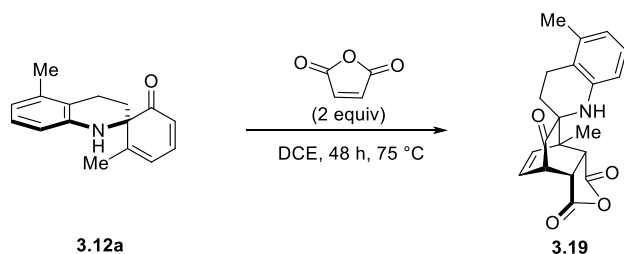
(*rac*)-(1R,6R)-6-allyl-2,5'-dimethyl-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-ol (3.18): A flame-dried 4-dram vial equipped with a stir bar and under N_2 was charged with *N*-spirodienone **3.12a** (40 mg, 0.17 mmol) and anhydrous THF (2.5 mL). The solution was cooled to −78 °C, and allyl magnesium bromide (1.0 M in Et_2O, 0.33 mL, 0.10 mmol) was added dropwise over the course of 1 min. The solution stirred at −78 °C for 0.5 h. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (1 mL) and warmed to room temperature. The reaction mixture was extracted with EtOAc (3 x 5 mL). The organic extracts were combined, washed with water (2 mL) and brine, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography (10/90 ethyl acetate/hexanes) to afford **3.18** (40 mg, 0.14 mmol, 85% yield, >20:1 dr) as a yellow oil. Analytical data: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.59 (d, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.3, 7.2 Hz, 1H), 5.82 (dd, *J* = 9.8, 5.1 Hz, 1H), 5.72-5.60 (m, 2H), 5.20-5.10 (m, 2H), 3.99 (s, 1H), 2.82-2.70 (m, 2H), 2.52 (ddd, *J* = 16.4, 5.2, 5.2 Hz, 1H), 2.42 (dd, *J* = 14.5, 6.3 Hz, 1H), 2.37 (ddd, *J* = 14.5, 5.7, 3.6 Hz, 1H), 2.21 (s, 3H), 2.16 (ddd, *J* = 13.4, 5.5, 5.5 Hz, 1H), 2.08 (s, 1H), 1.72 (s, 3H).

3.12a   **3.19**

(*rac*)-(2S,3a'R,4'R,7'S,7a'R)-4',5-dimethyl-3,3a',4,4',7',7a'-hexahydro-1H-spiro[quinoline-2,9'-[4,7]ethanoisobenzofuran]-1',3',8'-trione (3.19): A flame-dried 4-dram vial equipped with a stir bar and under N$_2$ was charged with *N*-spirodienone **3.12a** (24 mg, 0.10 mmol), maleic anhydride (20 mg, 0.20 mmol), and anhydrous DCE (5 mL). The solution stirred at 75 °C for 48 h. The reaction was cooled to room temperature, and the organic layer was washed with water (3 x 2 mL) and brine, dried with MgSO$_4$, and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography (20/90 ethyl acetate/hexanes) to afford **3.19** (40 mg, 0.14 mmol, 85% yield, >20:1 dr) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 6.96 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.66 (d, *J* = 7.4 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 6.40-6.30 (m, 2H), 3.75 (ddd, *J* = 5.8, 4.3, 2.0 Hz, 1H), 3.57 (dd, *J* = 9.0, 3.1 Hz, 1H), 3.53 (s, 1H), 3.46 (d, *J* = 9.1 Hz, 1H), 2.79 (ddd, *J* = 15.7, 9.3, 5.8 Hz, 1H), 2.69 (ddd, *J* = 16.5, 5.6, 5.6 Hz, 1H), 2.22 (s, 3H), 2.00 (ddd, *J* = 14.7, 9.5, 5.5 Hz, 1H), 1.78 (ddd, *J* = 13.2, 5.8, 5.8 Hz, 1H), 1.67 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 208.1, 170.0, 168.3, 142.5, 140.8, 136.3, 126.5, 126.4, 120.4, 120.0, 113.1, 59.5, 49.1, 48.4, 44.7, 43.5, 28.0, 21.3, 19.2, 15.3.
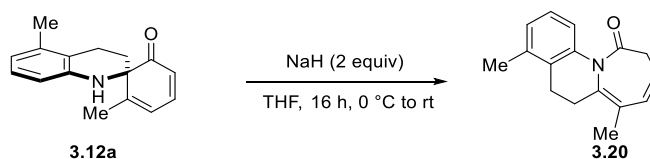
4,7-dimethyl-6,10-dihydroazepino[1,2-a]quinolin-11(5H)-one (3.20): A flame-dried 4-dram vial equipped with a stir bar and under N_2 was charged with *N*-spirodienone **3.12a** (24 mg, 0.10 mmol) and anhydrous THF (2.5 mL). The solution was cooled to 0 °C, and NaH (60% suspension, 8.0 mg, 0.20 mmol) was added. The mixture was stirred for 16 h during which time the reaction warmed to room temperature. The mixture was diluted with EtOAc (10 mL) and water (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The organic extracts were combined, washed with water (3 x 2 mL) and brine, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography (20/90 ethyl acetate/hexanes) to afford **3.20** (12.7 mg, 0.053 mmol, 53% yield) as a white solid. Analytical data: **^{1}H NMR** (600 MHz, CDCl$_3$) δ 7.21 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.13 (d, *J* = 9.3 Hz, 1H), 5.85 (dt, *J* = 9.2, 6.8 Hz, 1H), 3.34 (br s, 1H), 3.03 (br s, 1H), 2.95 (br s, 1H), 2.78 (br s, 1H), 2.53 (br s, 2H), 2.35 (s, 3H), 1.83 (s, 3H); **^{13}C NMR** (151 MHz, CDCl$_3$) δ 168.9, 137.9, 135.1, 134.2, 132.6, 132.0, 127.2, 125.9, 123.6, 122.6, 121.8, 37.5, 31.3, 22.1, 19.2, 18.0.
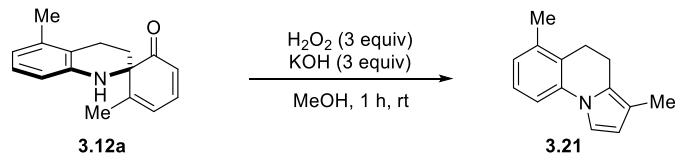
3,6-dimethyl-4,5-dihydropyrrolo[1,2-a]quinoline (3.21): A 4-dram vial equipped with a stir bar was charged with *N*-spirodienone **3.12a** (24 mg, 0.10 mmol) and MeOH (2 mL). KOH (85% powder, 21 mg, 0.30 mmol) and H_2O_2 (30% aqueous, 9.6 µL, 0.30 mmol) were added. The mixture stirred for 1 h. The solvent was removed *in vacuo*, and the crude product was diluted with EtOAc (5 mL) and water (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 2.5 mL). The organic extracts were combined, washed with water (2 mL) and brine, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* to afford **3.21** (15.3 mg, 0.073 mmol, 73% yield) as a clear oil. Analytical data: **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.20 (d, *J* = 7.2 Hz, 1H), 7.16 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.95 (d, *J* = 7.1 Hz, 1H), 6.15 (d, *J* = 2.9 Hz, 1H), 2.84 (s, 2H), 2.84 (s, 2H), 2.36 (s, 3H), 2.11 (s, 3H); **^{13}C NMR** (101 MHz, CDCl$_3$) δ 136.8, 136.5, 126.5, 125.9, 125.5, 125.2, 113.8, 113.7, 112.9, 111.3, 22.8, 19.9, 19.7, 10.8.
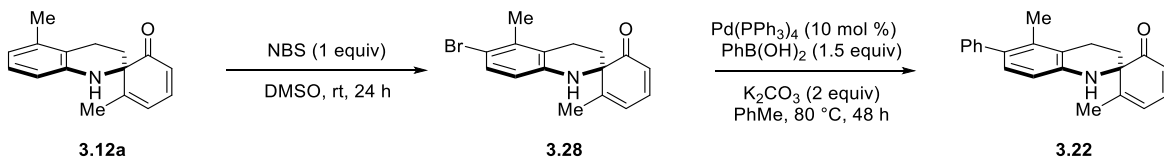
(*rac*)-2,5'-dimethyl-6'-phenyl-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-one (3.22): A flame-dried 1-dram vial equipped with a stir bar was charged with *N*-spirodienone **3.12a** (60 mg, 0.25 mmol) and anhydrous DMSO (1.5 mL). NBS (44 mg, 0.25 mmol) was added and the solution stirred for 24 h. The contents of the vial were transferred to a separatory funnel and diluted with CH_2Cl_2 (5 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, washed with

water (3 x 5 mL) and brine (3 x 5 mL), dried with MgSO₄, and filtered. The solvent was removed to afford crude **3.28** that was used directly in the next step.

A flame-dried 1-dram vial equipped with a stir bar under N_2 was charged with Pd(PPh₃)₄ (15 mg, 0.0125 mmol, PhB(OH)₂ (46 mg, 0.38 mmol), and K_2CO_3 (69 mg, 0.50 mmol). Crude aryl bromide **3.28** dissolved in anhydrous PhMe (1.5 mL) was added to the vial. The mixture stirred at 80 °C for 48 h. The mixture was cooled to room temperature, and the contents of the vial were filtered through a silica plug using 50/50 ethyl acetate/hexanes as the eluent. The filtrate was concentrated *in vacuo*, and the crude material was purified by silica gel column chromatography (20/80 ethyl acetate/hexanes) to afford **3.22** (37 mg, 0.12 mmol, 47% yield over two steps) as a light brown oil.

Analytical data **3.22**: **¹H NMR** (600 MHz, CDCl₃) δ 7.39 (dd, *J* = 7.6 Hz, 7.6 Hz, 2H), 7.35 – 7.28 (m, 3H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.93 (dd, *J* = 9.8, 6.0 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.07 (d, *J* = 6.0 Hz, 1H), 6.02 (d, *J* = 9.7 Hz, 1H), 4.14 (s, 1H), 2.75 (ddd, *J* = 16.7, 4.9, 4.9 Hz, 1H), 2.58 (ddd, *J* = 16.4, 10.6, 5.3 Hz, 1H), 2.17 (ddd, *J* = 13.5, 10.7, 5.1 Hz, 1H), 2.12 (s, 3H), 2.04 (s, 3H), 2.05-1.90 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 206.7, 157.6, 142.9, 142.8, 140.8, 133.5, 131.9, 129.8 (2C), 128.5, 127.8 (2C), 125.9, 122.6, 119.5, 118.2, 112.0, 67.3, 30.4, 20.8, 20.0, 16.7.
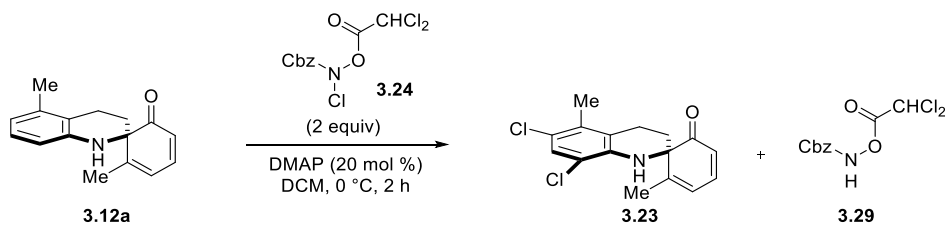
(*rac*)-6',8'-dichloro-2,5'-dimethyl-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinoline]-2,4-dien-6-one (3.23): A flame-dried 4-dram vial equipped with a stir bar was charged with *N*-spirodienone **3.12a** (50 mg, 0.21 mmol) and anhydrous CH_2Cl_2 (5 mL). The solution was cooled to 0 °C, and *N*-chlorocarbamate **3.24**[24] (98 mg, 0.31 mmol) and DMAP (5.1 mg, 0.042 mmol) were added. The reaction was stirred for 2 h at 0 °C. A saturated aqueous ammonium chloride solution (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, washed with water (3 x 2 mL) and brine, dried with $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the crude material was purified by silica gel column chromatography (20/90 ethyl acetate/hexanes) to afford a 3:1 inseparable mixture of **3.23** (75% ^{1}H NMR yield) and **3.29**[24]. Analytical data **3.23**: **^{1}H NMR** (600 MHz, CDCl₃) δ 7.22 (s, 1H), 6.95 (dd, *J* = 9.8, 6.0 Hz, 1H), 6.10 (d, *J* = 5.9 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 4.55 (s, 1H), 2.74 (ddd, *J* = 16.6, 4.4, 4.4 Hz, 1H), 2.56 (ddd, 11.2, 5.6, 5.6 Hz, 1H), 2.24 (s, 3H), 2.02 (s, 3H), 2.05-1.90 (m, 2H); **^{13}C NMR** (101 MHz, CDCl₃) δ 205.5, 156.0, 141.0, 138.6, 132.3, 126.7, 122.6, 122.0, 120.5, 120.1, 116.1, 66.6, 29.0, 21.0, 19.5, 15.7.

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CHAPTER FOUR:
THE DEVELOPMENT OF A THERMODYNAMIC DIASTEREOMER ENRICHMENT OF A FLUOROPHOSPHITE LIGAND

4.1 Introduction

Dynamic processes enable efficient access to stereoenriched materials in high yields.[1] While these stereoenrichments have been broadly employed for carbon stereocenters, rarely has this approach been applied towards non-chiral phosphorous or nitrogen heteroatoms. In this chapter, we report a thermodynamic diastereomer enrichment of a fluorophosphite ligand that exists as an initial 1:1 mixture of diastereomers. Using a fluoride source, the two diastereomers were readily interconverted. A solvent screen identified cyclohexanone as a privileged solvent for favoring enrichment of one diastereomer in ratios of up to 5:1 dr. Reaction optimization and product isolation techniques were performed for applicability to process scale-up. This work was done in collaboration with Eastman Chemical Company.

4.2 Background

4.2.1 Fluorophosphite Ligand

As part of an integral program to develop novel trivalent phosphorous ligands for hydroformylation reactions, Eastman Chemical Company found cyclic fluorophosphite **4.1** to be an active ligand.[2] Ligand **4.1** is prepared on process-scale via a two-step procedure (Scheme 4-1). The first step involves preparation of chlorophosphite **4.3** using phosphorous trichloride (PCl_3) and bis-phenol **4.2**. Fluoride substitution of chlorophosphite **4.3** affords fluorophosphite **4.1**.

Scheme 4-1. Preparation of Fluorophosphite **4.1**
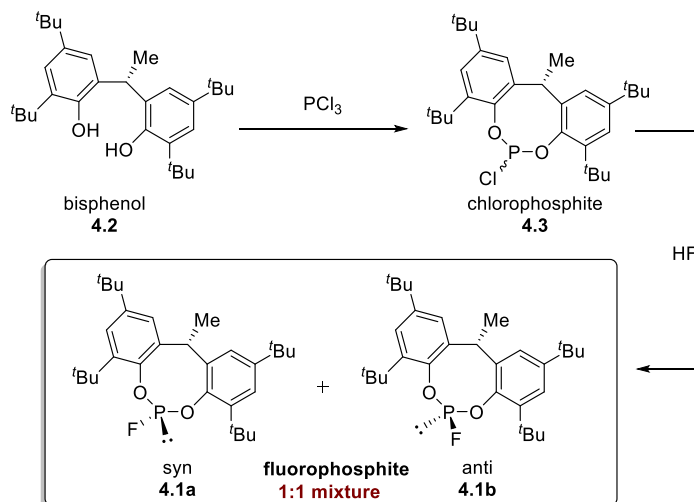
This preparatory method affords fluorophosphite **4.1** as roughly a 1:1 mixture of diastereomers **4.1a** (syn) and **4.1b** (anti). Phosphorous halides are resistant to pyramidal inversion as inversion barriers exceed 30 kcal/mol;[3] therefore, under ambient conditions, diastereomers **4.1a** and **4.1b** do not interconvert. This resistance to interconversion is observed even upon heating the isomers to temperatures above 100 °C. The restricted interconversion is of consequence when coupled with the fact that the two fluorophosphite isomers exhibit unique ligand properties based on the orientation of the phosphorous lone pair. As a result, methods for the interconversion of isomer **4.1a** to isomer **4.1b** were attempted internally at Eastman with limited success.

4.2.2 Reaction proposal

Our lab approached this challenge with an initial focus on using an additive to facilitate interconversion between the two isomers based, in part, on a literature report that found addition of excess [18]fluoride to fluorophosphite ligand **4.1** resulted in significant ^{18}F incorporation.[4] Inspired by this knowledge, we hypothesized that the use of a fluoride catalyst could help promote interconversion between the two isomers under certain experimental conditions. Taking advantage of this interconversion and potential solubility differences between the two isomers, tested in a

range of solvents, this could allow for selective precipitation of one isomer, funneling the fluorophosphite diastereomixture to an enriched isomer via crystallization-induced dynamic transformation (Scheme 4-2).[5]

Scheme 4-2. Proposed Crystallization-Induced Dynamic Diastereoseparation of Fluorophosphite
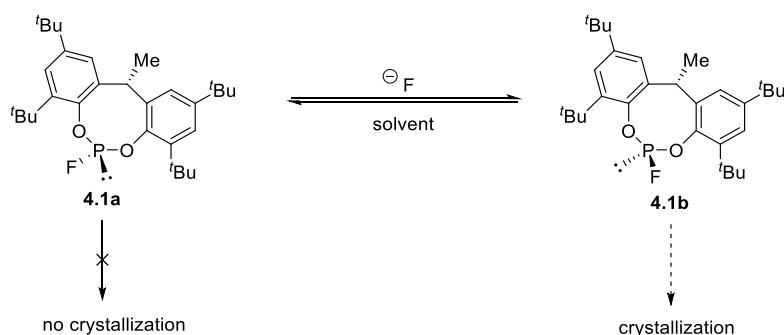
An alternative variant of this proposed approach would focus on identifying reaction conditions, principally through temperature or solvent selection, under which fluorophosphite diastereomer interconversion does not occur, but chlorophosphite **4.3** (or more promisingly, ephemeral bromophosphite or iodophosphite) interconversion does occur. In this scenario, equilibration of the starting material isomers (or their bromo- or iodo variants) would be desired, and kinetically selective fluorophosphite formation "locks in" one isomer. The plausibility of such a scenario would be linked to the reduced nucleofugality in the series ($I^- < Br^- < Cl^- < F^-$).

4.2.3 Crystallization-Induced Dynamic Resolution

As not to disrupt the established process for fluorophosphite **4.1** preparation, we decided to focus our initial approach on the development of a crystallization-induced dynamic resolution of the fluorophosphite ligand using a fluoride source to interconvert the isomers while simultaneously screening various crystallization solvents. Crystallization-induced dynamic resolution (CIDR) is a variant of a dynamic resolution that can afford, in principle, quantitative yields of a single isomer from a mixture of enantiomers or diastereomers via a resolving process

followed by crystallization (Scheme 4-2).[5] These processes require 1) crystalline products and 2) interconvertible isomers at temperatures below the melting point of the products.

Multiple CIDRs have been developed for compounds with carbon stereocenters; fewer examples have been accomplished using heteroatoms such as nitrogen or phosphorous.[6] An important example of a CIDR using a tertiary phosphine was developed by Vedejs (Scheme 4-3).[7] In this work, the authors realized an interconversion pathway for phosphines **4.4** and **4.5** using catalytic iodine via pentavalent transition state **4.6**. Using this iodine-catalyzed epimerization, the initial isomeric mixture (3:1 mixture **4.4** to **4.5**) was converted to a single diastereomer (>20:1) by slow evaporation crystallization from MeCN.

Scheme 4-3. Vedejs CIDR of Tertiary Phosphines
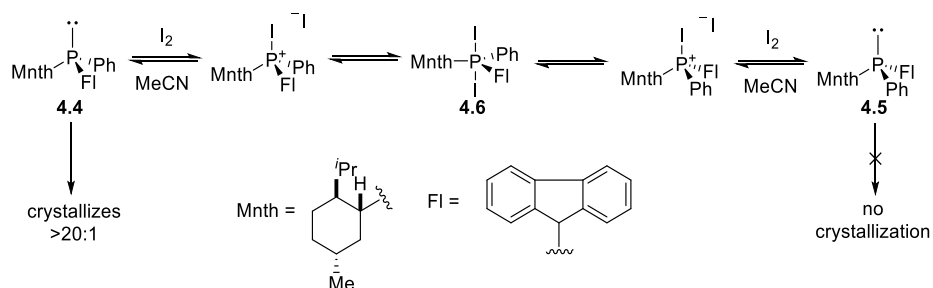
4.3 Fluoride-Promoted Isomer Interconversion

Inspired by the work demonstrated by Vedejs, our approach focused on interconverting fluorophosphite isomers **4.1a** and **4.1b** during crystallization to achieve a CIDR. This approach required initial proof-of-concept of isomer interconversion using a fluoride additive. Accordingly, pure syn **4.1a** and anti **4.1b** were independently isolated using column chromatography. Subjecting **4.1b** to 10 mol % solid tetrabutylammonium fluoride hydrate (TBAF) in MeCN at 60 °C resulted in a 1:1 ratio of **4.1a** and **4.1b** (Table 4-1, entry 1). A fluoride loading screen in acetone revealed that loadings as low as 1 mol % resulted in formation of **4.1a** (entries 2-5). Using KF as the anhydrous fluoride source also resulted in formation of **4.1a**, although in lower quantities due the

poor solubility of the fluoride source in acetone. In a similar way, pure syn **4.1a** was converted to a 1:1 mixture of isomers when subjected to TBAF (10 mol %) in MeCN.

Table 4-1. Fluoride-Catalyzed Isomer Interconversion[a]
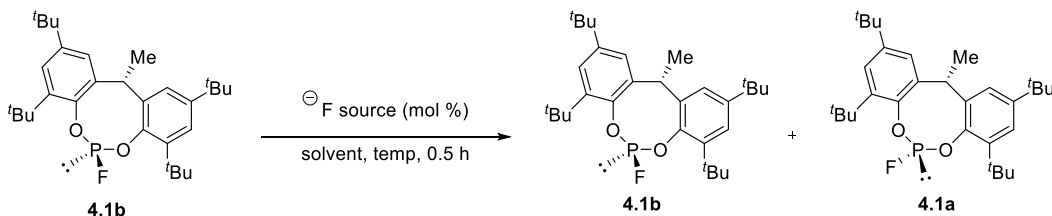
entry	fluoride source	mol %	solvent	temp	isomer ratio (4.1b:4.1a)[b,c]
1	TBAF	10	MeCN	60	1:1
2	TBAF	10	acetone	45	1:1
3	TBAF	10	acetone	rt	3:2
4	TBAF	1	acetone	rt	3:2
5	TBAF	50	acetone	rt	1:1
6	KF	10	acetone	rt	8:1
7	KF	50	acetone	rt	3:1

[a]Reactions run using **4.1b** (0.25 mmol) and [**4.1b**] = 0.2M. [b]Determined by ^{1}H NMR analysis. [c]Decomposition of **4.1a** not calculated into isomer ratios.

4.4 Attempted Crystallization-Induced Dynamic Resolution

4.4.1 Solvent Screening

With the method for isomer interconversion in hand, we then turned towards application of the methodology to a CIDR using slow evaporation of the solution. Various solvent classifications (non-polar, polar aprotic, polar protic) were employed (Table 4-2, entries 1-8). In every case, modest stereoenrichment favoring anti **4.1b** was observed.

Acetone provided the highest ratio of **4.1b** to **4.1a** (entry 8); therefore, we screened various cyclic and acyclic ketones using the same reaction conditions (Table 4-2, entries 9-12) that revealed cyclohexanone as demonstrating a distinct and unique preference for **4.1b** with a 4.8:1 anti:syn ratio. Similar derivatives to cyclohexanone such as cycloheptanone, cyclopentanone, and

cyclobutanone were also screened (entries 13-15) but performed disappointingly in comparison to cyclohexanone.

Table 4-2. Representative Solvent Screen for CIDR[a]
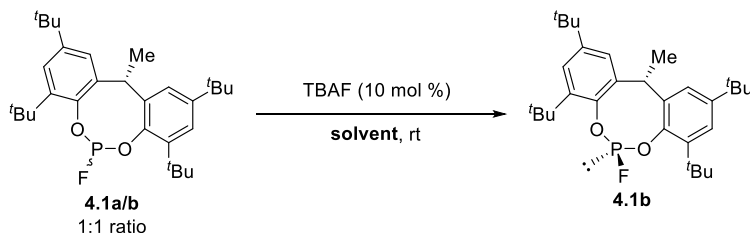
entry	solvent	isomer ratio (4.1b:4.1a)[b,c]
1	PhMe	1.2:1
2	DCM	1.6:1
3	hexanes	1.3:1
4	1,4-dioxane	1.7:1
5	THF	1.7:1
6	DMF	1.9:1
7	isopropanol	1.5:1
8	acetone	2.1:1
9	methyl isopropyl ketone	2.8:1
10	pentanone	1.9:1
11	2-butanone	1.7:1
12	cyclohexanone	4.8:1
13	cyclobutanone	1.8:1
14	cyclopentanone	1.5:1
15	cycloheptanone	1.2:1

[a]Reactions run using 1:1 mixture **4.1a/b** (0.25 mmol) and TBAF (10 mol %) with [**4.1**] = 0.2M using slow evaporation. [b]Determined by ^{1}H NMR analysis. [c]Decomposition of **4.1a** not calculated into isomer ratios.

### 4.4.2 Decomposition of Fluorophosphite

This preference for **4.1b** is due in part to the isomer's resistance to decomposition in comparison to **4.1a**. Water from the TBAF hydrate promotes hydrolysis of flurophosphite **4.1a** affording bisphenol **4.2**. As a result, the observed ratios were elevated to favor **4.1b** due to this

decomposition. When taking this decomposition of **4.1a** into account,[8] cyclohexanone maintained

a >3:1 **4.1b**:**4.1a** ratio at room temperature. This was superior to other solvents that all failed to

achieve greater than a 2.2:1 **4.1b**:**4.1a** ratio.

4.4.3 Failure of CIDR

Diastereoenriched fluorophosphite **4.1** obtained from the cyclohexanone was not

crystalline due to the difficulty in completely removing the cyclohexanone solvent; therefore, we

explored slow cooling crystallization using cyclohexanone as the solvent to crystallize the

fluorophosphite without employing fluoride (Table 4-3, entry 1). In every case, the obtained

crystals were enriched with **4.1a** over **4.1b**. This preference for **4.1a** upon crystallization was

incompatible with the observed selectivity for **4.1b** using fluoride. Additionally, **4.1a** was favored

when varying the solvent choice (entries 2-5). As a result, we determined that a CIDR would not

be possible to obtain the desired selectivities.

Table 4-3. Slow Cooling Crystallization of Fluorophosphite[a]
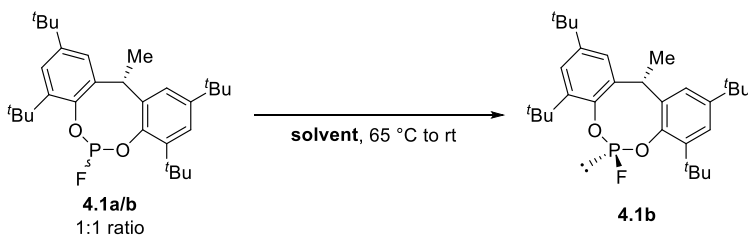
entry	solvent	isomer ratio (4.1b:4.1a)[b]
1	cyclohexanone	1:1.4
2	acetone	1:1.2
3	methyl isopropyl ketone	1:1.1

[a]Reaction run using 1:1 mixture **4.1a/b** (0.25 mmol). [b]Determined by ^{1}H NMR analysis.

4.5. Optimization of Isomer Ratios

While a CIDR was not feasible, our ability to access and isolate diastereoenriched fluorophosphite **4.1** in a >3:1 **4.1b**:**4.1a** ratio using cyclohexanone prompted further optimization of this enrichment to increasingly favor the more thermodynamically stable isomer **4.1b** (Scheme 4-4). Specifically, we focused on optimization of the reaction temperature, fluoride source, reaction time, and isolation technique. In parallel, these initial analyses also focused on mitigation of ligand hydrolysis.

Scheme 4-4. Proposed Thermodynamic Diastereomer Enrichment of Fluorophosphite
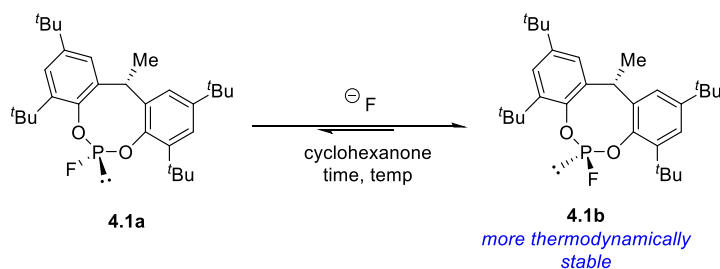
4.5.1 Fluoride Source Optimization

As a control experiment, stirring the fluorophosphite in a 5:1 mix of cyclohexanone and water for 5 d at room temperature resulted in no observable decomposition to bisphenol **4.2** (Scheme 4-5). When conducting the same experiment using 10 mol % of solid TBAF hydrate, significant levels of decomposition were observed. We therefore hypothesize that this decomposition results from fluoride-promoted hydrolysis of the fluorophosphite. Various anhydrous fluoride sources were explored (Table 4-4, entries 2-5). In every case, the fluoride sources either failed to achieve the same B:A ratio or resulted in higher amounts of decomposition as compared to TBAF.

Scheme 4-5. Stability of Fluorophosphite in Cyclohexanone/Water Mixture
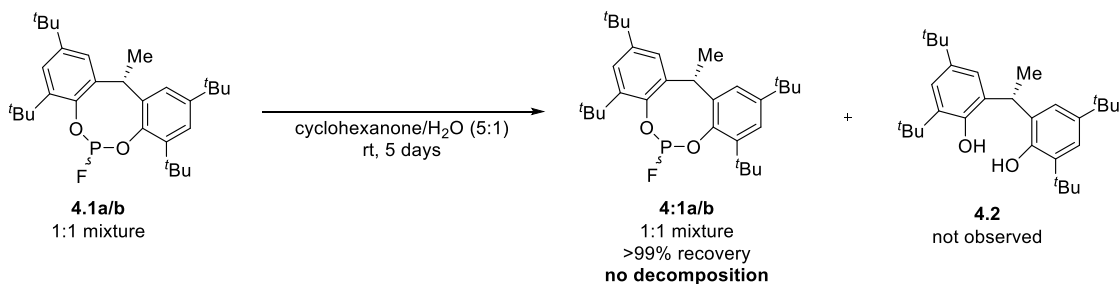
Table 4-4. Fluoride Source Optimization[a]
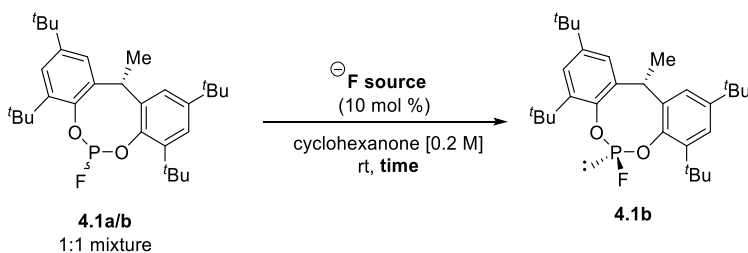
entry	fluoride source	time (h)	isomer ratio (4.1b:4.1a)[b,c]	decomp (%)
1	TBAF	1	3.2:1	6.0
2	fluoride (polymer supported)	48	1.4:1	3.0
3	KF, 18-crown-6	24	3.0:1	13.0
4	TBAT	1	2.9:1	4.7
5	Silica TBAF	24	2.2:1	1.5
6	dried TBAF	24	3.3:1	3.5

[a]Reaction run using 1:1 mixture **4.1a/b** (0.25 mmol). [b]Determined by ^{1}H NMR analysis.
[c]Decomposition of **4.1a** is calculated into isomer ratios.

Solid TBAF is commercially sold as the hydrate due to the unstable nature of pure anhydrous TBAF. Fortunately, we found that partial removal of water from the TBAF hydrate could be accomplished via desiccating the TBAF over Drierite® for 48 h without decomposition. Utilizing dried TBAF in the reaction gave similar ratios to non-desiccated TBAF and significantly reduced the ligand decomposition, although longer reaction times were required to achieve similar **4.1b**:**4.1a** ratios (Table 4-4, entry 6).

4.5.2 Temperature Optimization

Because **4.1b** is more thermodynamically stable than **4.1a**, we hypothesized that lowering the temperature of the reaction could slow isomer **4.1b** conversion to isomer **4.1a** ultimately increasing ratios. Simultaneously we believed that lower temperatures would reduce decomposition. Using dried TBAF, we explored the effects of temperature on the interconversion efficiency (Table 4-5). This screening indicated that lowering the temperature of the reaction generally decreased decomposition of fluorophosphite **4.1a** while also increasing the **4.1b**:**4.1a** ratio. At −20 °C a ratio of 4.9:1 **4.1b**:**4.1a** and only 2.9% decomposition was obtained after 24 h. Further cooling of the reaction mixture was not possible as the mixture began to freeze at temperatures near −25 °C.

Table 4-5. Temperature Optimization[a]
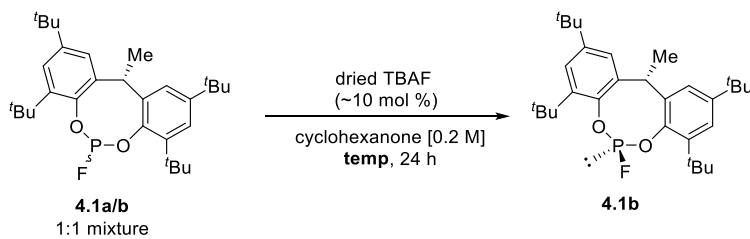
entry	temp (°C)	isomer ratio (4.1b:4.1a)[b,c]	decomp (%)
1	rt	3.3:1	3.5
2	15	3.4:1	3.4
3	0	4.0:1	3.2
4	−10	4.2:1	3.0
5	−20	4.9:1	2.9

[a] Reaction run using 1:1 mixture **4.1a/b** (0.25 mmol). [b] Determined by ^{1}H NMR analysis. [c] Decomposition of **4.1a** is calculated into isomer ratios.

4.5.3 Reaction Time Optimization

During these optimization experiments, we observed significant varying of the B:A ratio and decomposition levels when altering the reaction time. Accordingly, we screened the effect of

reaction time at −20 °C (Table 4-6). As expected, longer times resulted in higher levels of ligand decomposition; however, **4.1b**:**4.1a** ratios were significantly increased even when accounting for this higher decomposition level. After 48 h, the **4.1b**:**4.1a** ratio was 5.2:1 with 3.1% decomposition (entry 6).

Table 4-6. Reaction Time Optimization[a]

4.1a/b
1:1 mixture

4.1b
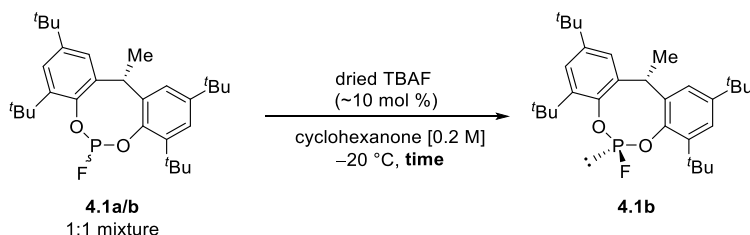
entry	time (h)	isomer ratio (4.1b:4.1a)[b,c]	decomp (%)
1	0.2	1.1:1	0.5
2	0.5	1.2:1	0.5
3	1	1.4:1	1.2
4	12	2.4:1	1.4
5	24	4.9:1	2.9
6	48	5.2:1	3.1
7	72	5.1:1	5.1

[a] Reaction run using 1:1 mixture **4.1a/b** (0.25 mmol). [b] Determined by ^{1}H NMR analysis. [c] Decomposition of **4.1a** is calculated into isomer ratios.

4.6 Isolation Technique

An important step in the reaction optimization was identification of an appropriate isolation technique. Two main factors had to be considered when discussing isolation. Firstly, removing the fluoride source was imperative to prevent undesired equilibration and decomposition upon warming the solution. Secondly, solvent removal at near-ambient temperatures was required since heating the solution even after fluoride removal resulted in increased decomposition levels. To address the first factor, we observed via ^{1}H NMR that complete removal of the TBAF could be accomplished by passing the reaction mixture through a silica plug; however, the complete

removal of TBAF was dependent on the wash solvent. Washing the silica plug with excess cyclohexanone or other polar solvents resulted in TBAF in the filtrate; therefore, hexanes was employed to prevent TBAF leaching while allowing for efficient recoveries of fluorophosphite **4.1**.

The removal of the solvent presented a unique challenge since the boiling point of cyclohexanone is 155 °C. This high temperature limited available solvent removal methods for complete drying of the ligand without significant levels of heat. Fortunately, we found that removal of the cyclohexanone could be achieved by concentrating the solution under a steady stream of nitrogen. For larger amounts of solvent, the solution was heated to 40 °C to increase the rate of solvent removal while avoiding detrimental decomposition.

4.7 Process-Scale Optimization

4.7.1 Factors to Consider for Process-Scale

With a consistent method for preparation and isolation of a >4:1 fluorophosphite **4.1b**:**4.1a** mixture in hand, we began to adapt the optimized conditions towards process-scale limitations at Eastman. These adaptations consisted of five main areas: 1) increasing the reaction temperature to accommodate the reactor capabilities, 2) lowering the TBAF catalyst loading, 3) decreasing reaction time, 4) increasing reaction concentration, and 5) precipitation of the ligand from the cyclohexanone.

4.7.2 Process-Scale Temperature and Catalyst Loading Optimization

We further refined our optimized conditions to higher temperatures while simultaneously lowering the catalyst loadings (Table 4-7). We also increased the scale of the reaction to 10 g of starting material. As expected, increasing the temperature to 0 °C lowered the **4.1b**:**4.1a** ratio and significantly increased the decomposition levels (entry 1). Lowering the catalyst loading to 5 mol

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% resulted in lower decomposition levels while maintaining the isomer ratios (entry 2); however, dropping the catalyst loading to 2.5% diminished the ratios (entry 3). Switching to 4 mol % maintained product ratios while further decreasing decomposition (entry 4). Increasing the temperature to 15 °C and room temperature using 4 mol % of dried TBAF lowered the product ratios but maintained minimal decomposition levels.

**Table 4-7.** Process-Scale Temperature and Catalyst Loading Optimization[a]
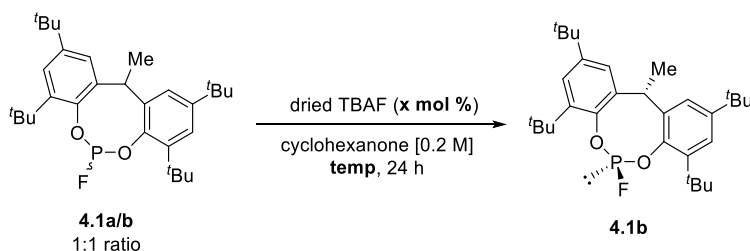
entry	temp (°C)	mol %	isomer ratio (4.1b:4.1a)[b,c]	decomp %
1	0	10	4.0:1	7.2
2	0	5	4.1:1	4.4
3	0	2.5	2.5:1	2.5
4	0	4	4.0:1	3.4
5	15	4	3.2:1	4.3
6	rt	4	2.6:1	4.3

[a] Reaction run using 1:1 mixture **4.1a/b** (20.5 mmol). [b] Determined by ^{1}H NMR analysis. [c] Decomposition of **4.1a** is calculated into isomer ratios.

4.7.3 Process-Scale Reaction Time Optimization

Further optimization at 15 °C was conducted as this temperature was ideal for reactor capabilities and maintained good ratios and minimal decomposition levels. To reduce reaction time, the ratios and decomposition levels at various time points were taken (Table 4-8). Increasing reaction time elevated **4.1b**:**4.1a** ratios and increased decomposition that leveled off around 8 h (entries 1-3). Longer reaction times past 24 h did not increase the ratios and slightly increased decomposition levels (entry 6).

**Table 4-8.** Process-Scale Reaction Time Optimization
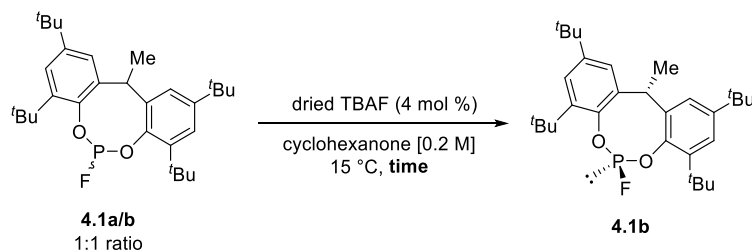
entry	time (h)	isomer ratio (4.1b:4.1a)[b,c]	decomp %
1	1	2.4:1	2.5
2	4	2.7:1	3.2
3	8	3.1:1	4.0
4	20	3.2:1	4.2
5	24	3.2:1	4.3
6	48	3.2:1	4.8

[a] Reaction run using 1:1 mixture **4.1a/b** (20.5 mmol). [b] Determined by ^{1}H NMR analysis. [c] Decomposition of **4.1a** is calculated into isomer ratios.

4.7.4 Reaction Concentration Optimization

We explored increasing reaction concentration due to the cost of obtaining cyclohexanone on process-scale (Table 4-9). Fluorophosphite **4.1** has modest solubility in cyclohexanone; increasing the reaction concentration past 0.3 M resulted in a slurry. At 0.3 M, the reaction exhibited similar **4.1b**:**4.1a** ratios and decomposition as 0.2 M (entry 2). Increasing to 0.4 M resulted in a slurry; however, enrichment was still observed, although in lower ratios.

Table 4-9. Process-Scale Concentration Optimization
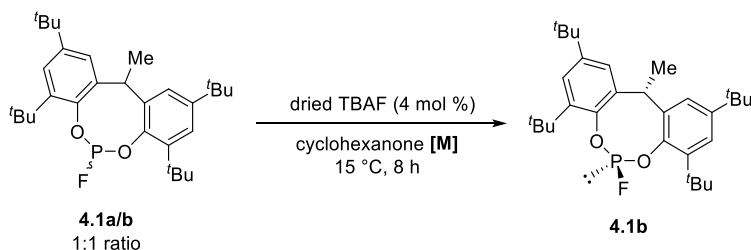
entry	[M]	isomer ratio (4.1b:4.1a)[b,c]	decomp %
1	0.2	3.1:1	4.0
2	0.3	3.0:1	4.1
3	0.4 (slurry)	2.7:1	4.1

[a] Reaction run using 1:1 mixture **4.1a/b** (20.5 mmol). [b] Determined by ^{1}H NMR analysis. [c] Decomposition of **4.1a** is calculated into isomer ratios.

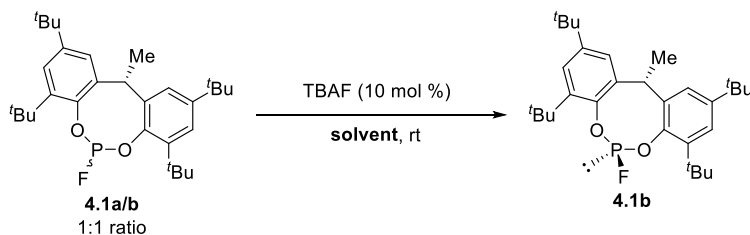### 4.7.5 Precipitation of Fluorophosphite from Cyclohexanone

Removal of cyclohexanone via evaporation on a large scale was deemed impractical. Accordingly, initial studies were undertaken to precipitate out fluorophosphite **4.1** using an antisolvent. Previous work determined methanol as an appropriate antisolvent for the reaction. Two approaches were developed to precipitate out the fluorophosphite. The first approach focused on precipitation of the ligand by adding MeOH (3:1 ratio MeOH: cyclohexanone) directly to the reaction flask at 15 °C followed by filtration. The second approach consisted of adding silica gel directly to the reaction flask to adsorb the TBAF catalyst followed by filtration of the silica gel and subsequent precipitation of the fluorophosphite from the filtrate with MeOH (3:1 ratio MeOH:cyclohexanone). In both cases, these isolation methods resulted in modestly reduced ratios (<5%) as compared to evaporation of the cyclohexanone and decomposition levels were similar. Recoveries for both procedures were >70%.

4.8 Project Completion/Future Efforts

At the project closeout, the described protocols for diastereomer enrichment and isolation were provided to Eastman Chemical Company for further optimization and scale-up. Our laboratory has successfully demonstrated these protocols up to a 50 g scale.

4.9 Commentary on Cyclohexanone

The unique role cyclohexanone exhibits in favoring isomer **4.1b** is currently not well understood. During the reaction optimization, various steps were attempted to quantify this selectivity with little success. As earlier mentioned, various similar solvent choices such as cycloheptanone, cyclopentanone, and cyclobutanone were employed using the reaction conditions; however, these solvents failed to provide significant levels of stereoenrichment. Similarly, trying other cyclohexanone or cyclohexane derivatives failed to achieve stereoenrichment (Table 4-10).

Table 4-10. Effect of Cyclohexanone/Cyclohexane Derivatives on Isomer Ratios

entry	solvent	isomer ratio (4.1b:4.1a)[b,c]	entry	solvent	isomer ratio (4.1b:4.1a)[b,c]
1	(cyclohexanone)	4.8:1	5	(substituted cyclohexanone)	1.9:1
2	(cyclohexane)	1.0:1.1	6	(substituted cyclohexanone)	1.6:1
3	(cyclohexene)	N/A[d]	7	(4-methylcyclohexanone)	1.6:1
4	(cyclohexenone)	1.9:1	8	(tetrahydropyranone)	N/A[e]

[a] Reaction run using 1:1 mixture **4.1a/b** (0.25 mmol). [b] Determined by ^{1}H NMR analysis. [c] Decomposition of **4.1a** not calculated into isomer ratios. [d] Complete decomposition of **4.1a** and poor recoveries. [e] **4.1a/b** not soluble in solvent.

The solvent screen indicates that minute structural changes to cyclohexanone has a significant impact on isomer ratios suggesting important solvent-substrate interactions. While we have been unsuccessful to date in preparing an X-ray quality crystal of **4.1b** in cyclohexanone, we obtained crystals of **4.1b** (Figure 4-1) prepared in acetone and **4.1a** prepared in cyclohexanone (Figure 4-2). Analysis of both crystal structures does not reveal an apparent increased stability in isomer **4.1b**; however, fluorophosphite **4.1b** co-crystallized with acetone. Analysis of this solvent-fluorophosphite interaction indicates there is a $n_F \rightarrow \pi^*_{C=O}$ interaction (3.1 Å) between the fluorophosphite fluoride and the carbonyl of acetone.[10] If this solvent-fluorophosphite interaction occurs in the solution phase, we hypothesize that this interaction could stabilize **4.1b**. When

extrapolating this interaction to cyclohexanone as a solvent, additional stabilizing solvent-fluorophosphite interactions could occur. For example, weak H-bonding interactions between the methylene hydrogens of cyclohexanone and the fluorophosphite oxygens would further stabilize, and therefore favor, the anti isomer **4.1b** (Figure 4-3). Structural changes to the cyclohexanone ring could negatively affect these stabilizing interactions.

Conversely, the structural conformation of **4.1a** would prevent significant solvent-fluorophosphite interactions. Indeed, in Figure 4-2, there is no observed co-crystallization between the solvent (cyclohexanone) and the fluorophosphite. These differences in solvent-fluorophosphite interaction between the two isomers could give rise to an explanation for the marked increased in **4.1b**:**4.1a** ratios demonstrated by ketone solvents (Table 4-2).
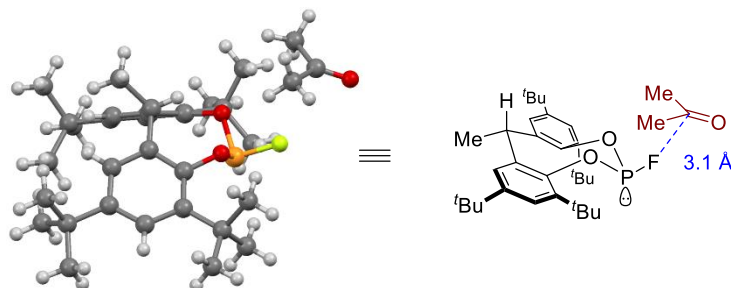
Figure 4-1. Crystal of **4.1b** Prepared in Acetone

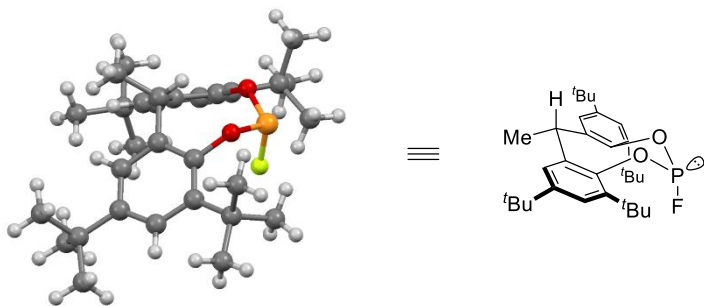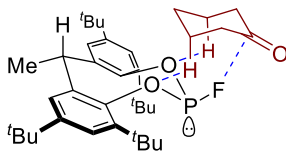**Figure 4-2.** Crystal of **4.1a** Prepared in Cyclohexanone

Figure 4-3. Possible Stabilizing Interactions Between Cyclohexanone and **4.1b**

4.10 Conclusion

A thermodynamic diastereomer enrichment of a 1:1 mixture of a fluorophosphite ligand has been developed to afford isomer **4.1b** enriched up to 5:1 dr. By using a fluoride source, we developed a method for isomer interconversion between **4.1a** and **4.1b**. Using a dried TBAF catalyst and cyclohexanone as a privileged solvent at low temperatures, isomer **4.1b** was enriched while the fluorophosphite decomposition was kept to a minimum. Additional experiments were undertaken to modify the optimized procedure for process scale. The optimized protocols were provided to Eastman Chemical Company.

4.11 Experimental Details

General 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 staining in a potassium permanganate (KMnO$_4$) solution, followed by gentle heating. Column chromatography was performed under positive nitrogen pressure using Siliaflash P60 silica gel (40-63 μm) purchased from Silicycle.

Instrumentation

^{1}H NMR and ^{13}C NMR were recorded on either a Bruker model DRX 400, 500, or 600 (cryoprobe equipped) spectrometer. The spectra were calibrated using residual solvent resonances: ^{1}H NMR (CDCl$_3$ at 7.28 ppm) and ^{13}C NMR (CDCl$_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (abbreviations: s = singlet, d = doublet, q = quartet, and m = multiplet), coupling constants (Hz) and integration.

Materials

Solvents were not dried prior to use unless specified as "anhydrous." Anhydrous tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), toluene (PhMe), and acetonitrile (MeCN) were dried by passage through a column of neutral alumina under nitrogen prior to use. All chemicals were purchased from either obtained directly from Eastman Chemical Company or purchased from Fisher Scientific, Millipore-Sigma, Alfa-Aesar, or Oakwood Chemical Company and used as received. Dried TBAF was accomplished by placing TBAF in a plastic flask inside a desiccator (Drierite®) for at least 48 h. Pure fluorophosphite **4.1a** and **4.1b** were separated via silica gel column chromatography (100% petroleum ether).

Experimental Procedures

Optimized Procedures for Fluorophophshite 4.1b Diastereomer Enrichment

4.1a/b
1:1 ratio

dried TBAF (4 mol %)

cyclohexanone [0.2M]
−20 °C, 48 h

4.1b
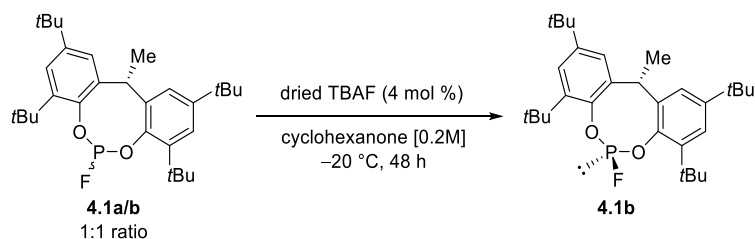
For best ratios and recoveries:

To a flame dried flask under N$_2$ was added the fluorophosphite ligand (1:1 **4.1a/b**) and cyclohexanone [0.2M]. Once fully dissolved, the flask was cooled to −20 °C. Solid TBAF hydrate (~4 mol %, desiccated for at least 48 h using Drierite®) was then added quickly to the flask. The reaction stirred for 48 h at −20 °C after which the mixture was filtered through a silica plug and washed with hexanes. The resultant solution was concentrated under a stream of nitrogen to afford the enriched fluorophosphite (5:1 **4.1b**:**4.1a**). Removal of bisphenol **4.2** can be accomplished by stirring the product in MeOH and filtering.

*Note: The diastereomer ratio of 5:1 was determined by ^{1}H NMR spectroscopic analysis of the reaction mixture by comparison of the integration of the resonances at δ 4.94 (**4.1b**) and δ 4.69 (**4.1a**).*


4.1a/b
1:1 ratio
>10 g

dried TBAF (4 mol %)

cyclohexanone [0.3M]
15 °C, 8 h

4.1b
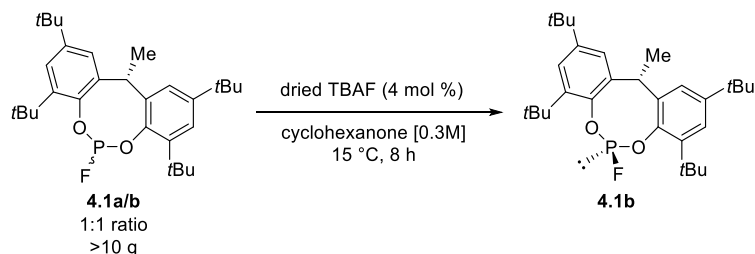
For preparative/process-scale:

To a flame dried flask under N$_2$ was added the fluorophosphite ligand (1:1 ratio **4.1a/b**) and cyclohexanone [0.3 M]. Once fully dissolved, the solution was cooled to 15 °C. Solid TBAF

hydrate (~4 mol %, desiccated for at least 48 h with Drierite®) was then added quickly to the flask. The reaction stirred for 8 h at 15 °C after which MeOH (3:1 MeOH:cyclohexanone ratio) was added to induce precipitation of the ligand. Once fully precipitated, the enriched fluorophosphite (3:1 **4.1b**:**4.1a**) was filtered and dried.
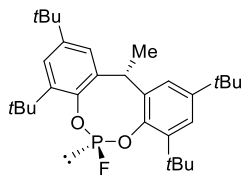
Fluorophosphite 4.1b: Analytical data: **¹H NMR** (400 MHz, CDCl₃): δ 7.44 (s, 2H), 7.28 (s, 2H), 4.94 (q, *J* = 7.6 Hz, 1H), 1.65 (d, *J* = 7.5 Hz, 3H), 1.45 (s, 18H), 1.34 (s, 18H); **¹³C NMR** (151 MHz, CDCl₃): δ 147.5 (2C), 142.7 (2C), 141.3 (2C), 140.4 (2C), 122.7 (2C), 121.2 (2C), 35.1 (2C), 34.8 (2C), 31.5 (12C), 30.9, 20.0; **³¹P NMR** (162 MHz, CDCl₃): δ 132.2 (d, *J* = 1260 Hz); **¹⁹F NMR** (376 MHz, CDCl₃): δ −73.3 (d, *J* = 1260 Hz); **TLC** (100% petroleum ether): R*f* = 0.42.
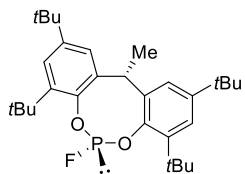
Fluorophosphite 4.1a: Analytical data: **¹H NMR** (400 MHz, CDCl₃): δ 7.32 (s, 2H), 7.23 (s, 2H), 4.69 (q, *J* = 7.3 Hz, 1H), 1.69 (d, *J* = 7.2 Hz, 3H), 1.43 (s, 18H), 1.32 (s, 18H); **¹³C NMR** (151 MHz, CDCl₃): δ 146.7 (2C), 145.7 (2C), 139.6 (2C), 136.5 (2C), 122.5 (2C), 120.9 (2C), 35.0 (2C), 34.7 (2C), 31.5 (12C), 30.8, 19.5; **³¹P NMR** (162 MHz, CDCl₃): δ 106.9 (d, *J* = 1254 Hz); **¹⁹F NMR** (376 MHz, CDCl₃): δ −62.0 (d, *J* = 1254 Hz); **TLC** (100% petroleum ether): R*f* = 0.48.

Decomposition Calculation:

The decomposition percentage is reported as the total decomposition using the integration of the resonances at 4.48 (bisphenol **4.2**), δ 4.94 (fluorophosphite **4.1b**), and δ 4.69 (fluorophosphite **4.1a**). The percentage was approximated using the following equation based on the integrations:

Decomposition % = (∫**4.2**)÷(∫**4.2** + ∫**4.1b** + ∫**4.1a**) x 100. For an example, see below:

Decomposition % = (0.12) ÷ (0.12 + 3.44 +1.00) x 100 = 2.63% decomposition
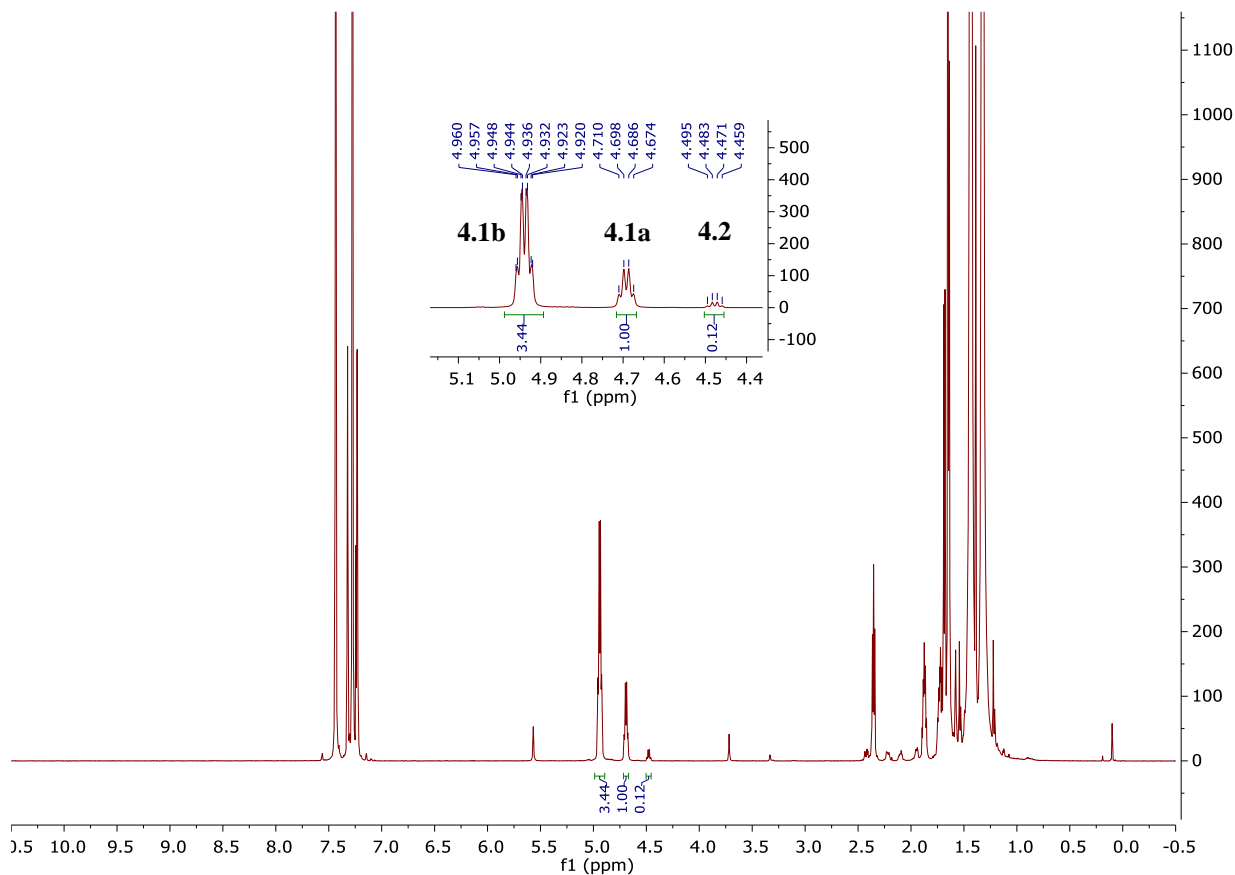
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(8)   See **Decomposition Calculation** in the Experimental (Chapter 4.11).

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