Developing Novel Synthetic Methodologies Using Hypervalent

Iodine(III) Reagents and Diazonium- or Iodonium Ylides

by

Jason Tao

A thesis

presented to the University of Waterloo

in fulfillment of the

thesis requirement for the degree of

Doctor of Philosophy

in

Chemistry

Waterloo, Ontario, Canada, 2018

Examining Committee Membership

The following served on the Examining Committee for this thesis. The decision of the Examining Committee is by majority vote.

External Examiner   Viktor V. Zhdankin
                                                      Professor, University of Minnesota Duluth

Supervisor   Graham K. Murphy
                                                      Associate Professor, University of Waterloo

Internal Member   J. Michael Chong
                                                       Professor, University of Waterloo

Internal Member   Sonny C. Lee
                                                       Associate Professor, University of Waterloo

Internal Member   Adrian L. Schwan
                                                      Professor, University of Guelph

Internal-external Member   Praveen P. N. Rao
                                                  Associate Professor, University of Waterloo

Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including

any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Hypervalent iodine compounds have been established as useful reagents in synthetic chemistry due to their ease of handling and wide range of chemical reactivity under mild reaction conditions.

Reported within are studies into the development of new *gem*-difunctionalization reactions using hypervalent iodine(III) compounds. To this end, classic or modern hypervalent iodine reagents such as $PhICl_2$, $TolIF_2$, $PhI(OAc)_2$, and 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one were reacted with either a diazonium ylide or an iodonium ylide. Oftentimes, catalytic amounts of additives served to activate the iodane and provide increased yields, faster reaction times, and higher chemoselectivity.

In Chapter 2, the halogenation of diazo compounds using $PhICl_2$ or $TolIF_2$ is described. The primary research objective was to develop a robust method for the activation of these iodanes towards geminal double ligand transfer reactions. A majority of the research efforts was placed into understanding aspects of the geminal dichlorination of phenyldiazoacetate derivatives using $PhICl_2$. A key finding was that the inclusion of 1–5 mol% of a Lewis-basic additive, such as pyridine, allowed for efficient transfer of the chloride ligands of the iodane onto the diazo compound. Reaction optimization studies allowed for the identification of conditions that provided the desired *gem*-dichlorinated compounds in good yields (typically >75%) with high functional group tolerance. The desire to use the reaction between diazo compounds and $PhICl_2$ or $TolIF_2$ to create C–C bonds led to studying tandem halogenation/semi-pinacol reactions of β-hydroxy-α-diazoesters. The chlorination/semi-pinacol reactions were found to occur readily under Lewis base catalysis while Rh-catalyzed conditions were found to provide the analogous fluorinated compounds in moderate yield (51%).

In Chapter 3, the first study into *gem*-difunctionalization reactions of iodonium ylides and hypervalent iodine(III) reagents is described. Specifically, it outlines the extension of *gem*-dichlorination reactions discussed in Chapter 1 to the *gem*-dichlorination of phenyliodonium ylides of 1,3-dicarbonyl compounds. This study found that treating phenyliodonium ylides with PhICl$_2$ can provide *gem*-dihalogenated products in high yield (up to 94%), which confirmed that these types of ylides are suitable for geminal double ligand transfer reactions. Probing the reaction between these types of reagents allowed for the discovery that, in the presence of PhICl$_2$, the phenyliodonium ylide of methyl benzoylacetate can engage with styrene in a cyclopropanation reaction. The diastereoselectivity of this reaction was observed to be complementary to the selectivity when the same cyclopropane was generated via the rhodium carbenoid.

In Chapter 4, as a result of the observation described above, a study of intermolecular cyclopropanation between iodonium ylides and alkenes under metal-free conditions was performed. These studies allowed for the identification of various iodine-containing reagents (e.g., *n*-Bu$_4$NI, *n*-Bu$_4$NI$_3$, and 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one) that can be used to promote (or enhance) a cyclopropanation reaction. A majority of the research efforts were placed into performing cyclopropanations in the presence of a mixture of PhI(OAc)$_2$ and *n*-Bu$_4$NI. In the presence of this mixture of reagents, various alkenes (e.g., styrenes, 3-alkylidene-2-oxidoles, 1,1-enediones, 1,2-diones) were found to be able to undergo cyclopropanation with the phenyliodonium ylide of dimedone and/or the phenyliodonium of dimethyl malonate in up to 97% yield.

Acknowledgements

First and foremost, I would like to thank Prof. Graham Murphy for allowing me to work in his lab. I would specifically like to thank him for all of the encouragement that inspired me to pursue my Ph.D. studies. His knowledge and guidance during this this time has allowed for me to attend conferences, apply for scholarships/awards, and strive to become a better scientist. I also thank him for his patience throughout the years and ask for forgiveness for all of my bad jokes, antics, and other actions that leads a person to shake their head as they place it into the palm of their hand.

I would like to thank my committee members Profs. Michael Chong, Sonny Lee, and Adrian Schwan for all of the guidance they have provided me. Special thanks goes out to Prof. Chong, for innumerable loans of chemicals, glassware, and equipment. I would like to thank him for his invaluable expertise, time, and patience as I have spent countless hours in his office discussing chemistry with only minor diversions to related topics such as how to quantify the hardness of sample wood.

I would like to thank the research groups of Profs. Michael Chong, Gary Dmitrienko, Eric Fillion, Sonny Lee, Adrian Schwan, and Scott Taylor for access to various chemicals, equipment, and/or instrumentation.

I also thank the members of the Murphy group, past and present, for making the lab an enjoyable environment. I would like to thank the fellow students with whom I have co-authored publications, it was a pleasure. Special thanks goes out to former group member Richard Tran for his eagerness to lend a helping hand, regardless the situation. He had taken responsibility of the management of many lab chores (and other thankless work) and this has been much appreciated. A single person would struggle to shoulder his duties and his recent departure leaves a large void that remains to

Table of Contents

List of Tables

List of Schemes

List of Figures

List of Abbreviations

[O]	oxidation
ABX	1-azido-1,2,benziodoxol-3-(1H)-one
Ac	acetyl
aq.	aqueous
Ar	aryl
BHT	butylated hydroxytoluene
Bu	butyl
Bn	benzyl
BO	bond order
Boc	*tert*-butyloxycarbonyl
br	broad
BX	benziodoxole
Bz	benzoyl
C	Celcius
calcd	calculated
cat.	catalytic
CBX	1-cyano-1,2-benziodoxole-3-(1H)-one
Cbz	carboxybenzyl
cf.	confer (compare)
cm^{-1}	reciprocal centimetre
concd	concentrated
concn	concentration
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DART	direct analysis in real time
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	1,2-dichloroethane
(DHQD)₂PHAL	hydroquinidine 1,4-phthalazinediyl diether
DMAP	4-(dimethylamino)pyridine
DMP	Dess-Martin periodinane
DME	1,2-dimethoxyethane
DNPH	2,4-dinitrophenylhydrazine
dr	diastereomeric ratio
E	electrophilicity parameter
EDG	electron donating group
ee	enantioexcess
e.g.	exempli gratia ("for example")

eq	equation
equiv	equivalent(s)
ESI	electrospray ionization
ESR	electron spin resonance
Et	ethyl
et al.	et alia (and others)
etc	et cetera (and so forth)
EWG	electron withdrawing group
FCC	flash column chromatography
h	hour
HMDSO	hexamethyldisiloxane
HRMS	high resolution mass spectrometry
HTIB	hydroxy(tosyloxy)iodobenzene
HVI	hypervalent iodine
Hz	Hertz
i	iso
IBX	2-iodoxybenzoic acid
i.e.	*id est* (that is)
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
$k_{20\ °C}$	rate constant (determined at 20 °C)
g	gram
GC	gas chromatography
Gem	geminal
GP	general procedure
k	rate constant
L	ligand
	litre
LG	leaving group
	nucleofugal substituent
m	metre
	multiplet
m	meta
M	metal
	molar
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl

mg	milligram
MHz	megaHertz
min	minute(s)
MIRC	Michael-initiated ring closure
mL	millilitre
mmol	millimole
MO	molecular orbital
mp	melting point
mol	mole
MS	mass spectrometry
m/z	mass to charge ratio
μL	microliter
μm	micrometre
μmmol	micromole

n	normal
N	nucleophilicity parameter
N	normal
nb	nonbonding
NBS	*N*-bromosuccinimide
ND	not determined
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMPI	*N*-methylpyridinium iodide
NMR	nuclear magnetic resonance
NR	no reaction
Nuc	nucleophile

o	*ortho*
oct	octanoyl

p	*para*
pABSA	4-acetamidobenzensulfonyl azide
PFA	perfluoroalkoxy alkane
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
Pr	propyl
py	pyridine

q	quartet

R	substituent
rt	room temperature

s	singlet
sat.	saturated
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
sep	septet
s_N	nucleophile-dependent sensitivity parameter
S_N2	bimolecular nucleophilic substitution
R_f	retention factor
rt	room temperature
t	triplet
t	*tert*
TBA	tetrabutylammonium
TBAC	tetrabutylammonium chloride
TBAI	tetrabutylammonium iodide
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFA	trifluoroacetyl
TFE	2,2,2-trifluoroethanol
TIPS-EBX	triisopropylsilyl-ethynylbenziodoxolone
TLC	thin layer chromatography
THF	tetrahydrofuran
TMS	trimethylsilyl
Tf	triflyl
Tol	4-tolyl
Ts	4-tosyl
TTBP	2,4,6-tri-*tert*-butylpyrimidine
v	volume
VBX	vinylbenziodoxolone
VSEPR	valence shell electron pair repulsion
vs	versus
wt	weight
X	electronegative group or atom

List of Symbols

°	degrees
Δ	heat
δ	chemical shift
δ^-	slightly negative
δ^+	slightly positive
μ	micro
ν	frequency
§	section
σ	sigma bonding orbital
σ*	sigma antibonding orbital
ψ	pseudorotation
>	greater than
≥	greater than or equal to
<	less than
=	equal to
~	approximately

1. **Introduction**

1.1. **Iodine**

Iodine is the heaviest, naturally occurring stable halogen. It was discovered in 1811 by Bernard Courtois who noticed dark crystals forming from violet vapors during the production of saltpeter from seaweed.[1] After it was identified as a new element, Guy-Lusaac used the colour of its vapor as inspiration for the name "iodine", originating from the Greek word for violet.

Today, iodine-containing salts are manufactured from brines, oilfields, and caliche. The world's leading producers of iodine are Chile, followed by Japan, then the United States of America. Iodine plays an important part in our world as its many forms have industrial, medical, and biological applications.[2] For example, iodide (I^-), is metabolized by humans to form thyroid hormone triiodothyronine and prohormone thyroxine, which regulate many biochemical processes of human metabolism.[3] As such, a deficiency of bioavailable iodine in humans is linked to the thyroid-related diseases such as goitre.[4]

Iodine plays important roles in organic chemistry as well. Being the largest, most polarizable of the common halogens, iodine can be incorporated into many different kinds of reagents which participate in a wide variety of chemical reactions. For example, introductory organic chemistry courses often present alkyl iodides as prototypical electrophiles in the S_N2 reaction, while an inorganic source of iodine, periodate (e.g., $NaIO_4$), is often introduced to effect the oxidative cleavage of the carbon-carbon bond of 1,2-diols. This reaction holds historic significance due to its use in the structural analysis of carbohydrates.[5] As demonstrated by these examples, iodine can exist in both inorganic and organic compounds and in varying oxidation states. The nomenclature reflects the oxidation state of the iodine. Inorganic iodine-containing compounds are called iodides

(-I), hypoiodites (I), iodites (III), iodates (V), and periodate (VII). Compounds containing a C–I bond are called organoiodine compounds. Monovalent organoiodine compounds are called organoiodides, however, the similar electronegativity between carbon and iodine[6,7] leads to ambiguity when assigning oxidation states. As such, the oxidation state of iodine is considered to be (-I) or (I) depending on whether iodine or carbon is considered the more electronegative atom, respectively. For the purposes of this thesis, as described by IUPAC,[8] oxidation states will be calculated using Allen electronegativities,[7] where carbon is more electronegative than iodine. Higher valent organoiodine compounds are called iodinanes (III) and periodinanes (VI). Compounds containing iodine with oxidation state > 1 look seemingly peculiar as typical structural representations depict more than eight electrons around iodine, violating the well-known Lewis octet rule.[9] Chemists have come to refer to these compounds as "hypervalent iodine" containing compounds. Hypervalency is an important concept to understand to help appreciate the chemistry of high-oxidation state iodine containing compounds.

1.2. Hypervalency

The term "hypervalent" was first used by Musher to describe molecules and ions "formed by elements in Groups V–VIII of the periodic table in any of their valences other than their lowest stable chemical valence of 3, 2, 1 and 0, respectively".[10] Today, IUPAC defines hypervalency as "the ability of an atom in a molecular entity to expand its valence shell beyond the limits of the Lewis octet rule"[11] while a "hypervalent compound" is a molecule which contains a hypervalent atom. Musher's definition of hypervalency classifies atoms using their "valence state" (i.e., oxidation state), while the IUPAC definition considers the number of valence electrons. As a system to classify compounds, the IUPAC definition of hypervalency is useful and more comprehensive than Musher's definition. However, due to its dependency on the Lewis octet rule

(which was conceived before the advent of quantum mechanically correct chemical bonding models), the definition of hypervalency recommended by IUPAC cannot —and should not— be used to infer any information about the electronic structure of qualifying molecules.

The desire to have a physically-meaningful definition of "hypervalency" has made this topic controversial among some scientists.[12–14] Argument of the appropriateness of the term "hypervalent" arises when chemists question whether or not "hypervalent" atoms truly have more than eight valence electrons. The principles of chemical bonding dictate that main group elements satisfying the Lewis octet rule have fully occupied orbitals originating from the valence s, and p orbitals. In order for an atom to accept more electrons (thereby becoming hypervalent), an additional empty orbital is needed to engage in bonding. This originally led to the invocation of d orbital participation to justify the apparent violation of the Lewis octet rule. However, for many hypervalent molecules, ab initio calculations have revealed that d orbital participation to be negligible as the vacant d orbitals are too high in energy to engage significantly in chemical bonding.[12,15,16] Therefore, the IUPAC definition of "hypervalency" appears to be a misnomer. This has led some members of the scientific community to suggest more appropriate terms to call these molecules, such as "hypercoordinate". However, the majority of the synthetic community has long accepted use of the term "hypervalent" when naming these molecules. This thesis will continue to refer these molecules as "hypervalent" in order to align with the nomenclature used by the majority of the current literature.

Many elements are capable of forming hypervalent compounds. In fact, hypervalent compounds are relatively common (Figure 1-1).[17] While larger elements form stable hypervalent compounds more readily, compounds containing hypervalent second row elements, such as boron[18] and carbon,[19] have been synthesized, isolated, and characterized.

3
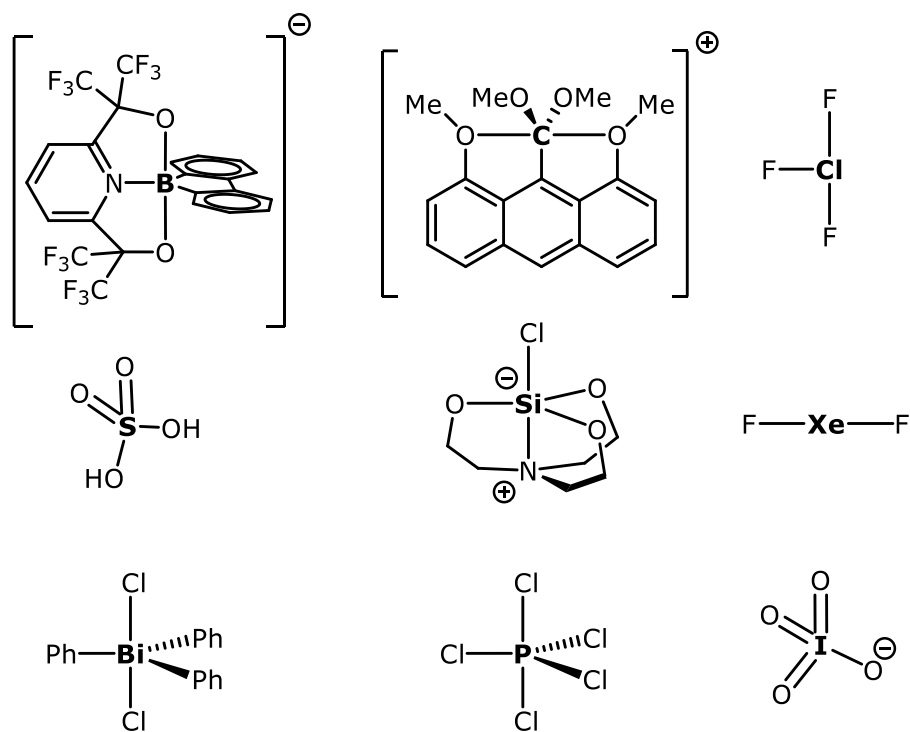
Figure 1-1. Examples of hypervalent molecules. The hypervalent atom appears in bold.

While hypervalent molecules share some structurally similarities, they can exhibit a diverse set of chemical reactivity. The use of hypervalent iodine (HVI) compounds as versatile reagents in synthetic chemistry has become increasingly popularly in the last few decades. Developing new synthetic methods using HVI reagents has been the focus of this thesis. The following section provides an introduction to pertinent fundamental chemical concepts of HVI chemistry and their applications to synthetic organic chemistry.

1.3. Hypervalent Iodine

Iodine is the largest, most polarizable element amongst the common halogens and therefore forms the most stable complexes past its standard coordination number. The synthesis of the first organic hypervalent iodine compound was reported in 1886 by Willgerodt who passed chlorine gas into a solution of iodobenzene (**1.1**) in chloroform, yielding iodobenzene dichloride (**1.2**, eq 1.1).[20]

$$\text{1.1} \xrightarrow[\text{CHCl}_3]{\text{Cl}_2} \text{1.2} \tag{1.1}$$
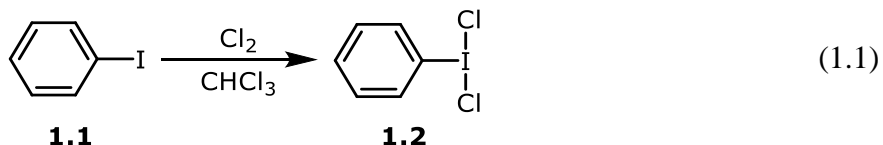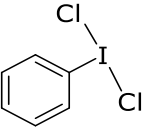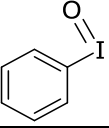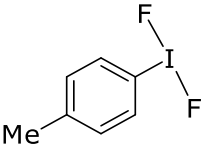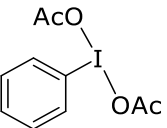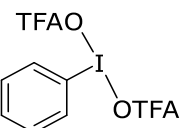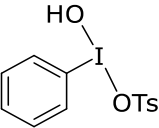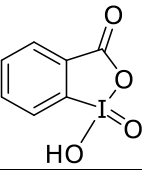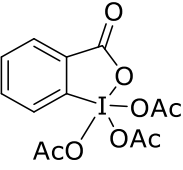
During the first half of the 20th century, relatively limited progress was made in the synthesis of HVI reagents and the study of their applications to organic synthesis. In recent decades, interest in HVI chemistry has been re-kindled due to their wide range of chemical reactivity (often under mild reaction conditions), ease of handling, and potentially recyclable by-products. Currently, research into HVI reagents is quite vibrant and has been the subject of many reviews[21–24] and books.[25–29] There is also a biennial international conference dedicated to HVI chemistry: the International Conference on Hypervalent Iodine Chemistry.

In naming hypervalent compounds, IUPAC recommends the use of λ-notation in which the hypervalent atom is preceded by λ^n and is followed by the suffix "-ane", where n is the bonding number in a parent hydride. In practice, the IUPAC nomenclature is used inconsistently throughout the scientific literature and some compounds are often referred to by many different names. For example, acceptable IUPAC names for $PhICl_2$ are "dichloro(phenyl)-λ^3-iodane" or "(dichloro-λ^3-iodanyl)benzene", but these are rarely used in comparison to the names "iodobenzene dichloride" or "(dichloroiodo)benzene". A wide variety of HVI reagents are used in organic synthesis. Classic examples of popular HVI reagents (and their common names) are shown in Table 1-1. A common structural feature of these reagents is the aryl group bound onto the iodine, and as such, they belong to a class of HVI reagents known as aryl-λ^3-iodanes. These compounds are relatively stable reagents and, oftentimes, can be isolated and stored at reasonable temperatures (0–25 °C). On the other hand, alkyl-λ^3-iodanes are very reactive compounds and are typically only formed as transient intermediates during reactions.[25] This has led to the preference of aryl-λ^3-iodanes over alkyl-λ^3-iodanes for use as reagents in both organic and inorganic synthesis.

Table 1-1. Examples of Common Organic Hypervalent Iodine Reagents

	Dichloro(phenyl)-λ^3-iodane (Dichloroiodo)benzene Iodobenzene dichloride
	Iodosylbenzene Iodosobenzene
	Difluoro(p-tolyl)-λ^3-iodane p-(Difluoroiodo)toluene (DFIT) p-Iodotoluene difluoride (TolIF$_2$)
	Diacetoxy(phenyl)-λ^3-iodane (Diacetoxy)iodobenzene (DIB) Phenyliodine(III) diacetate (PIDA) Iodobenzene diacetate
	Ditrifluoroacetoxy(phenyl)- λ^3-iodane Bis(trifluoroacetoxy)iodobenzene (BTI) Phenyliodine(III) bistrifluoroacetate (PIFA)
	Hydroxy(tosyloxy)iodobenzene (HTIB) Koser's Reagent
	1-Hydroxy-1-λ^5-2-benziodoxol-1,3-dione 2-Iodoxybenzoic acid (IBX)
	1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2- benziodoxol-3-(1H)-one Dess-Martin Periodinane (DMP)

Aryl-λ^3-iodanes in which the iodine is part of a heterocycle are a prominent subclass of compounds. Of the many types of hypervalent iodine(III)-containing heterocycles that have been synthesized, a majority of the research efforts has gone into investigating the synthetic applications

of benziodoxolones and benziodoxoles. As seen in Figure 1-2, for these compounds, one of the ligands on the iodine is endocyclic while the other ligand is exocyclic. Benziodoxolones are easily synthesized from commercially available 2-iodobenzoic acid, providing easy access to HVI reagents which exhibit remarkable thermal stability. They are used in reactions that transfer the exocyclic ligand (e.g., trifluoromethyl-,[30] alkynyl-,[31] azido-,[32,33] alkenyl-,[34] trifluoroethyl-,[35,36] and cyano[37] groups) onto organic substrates.
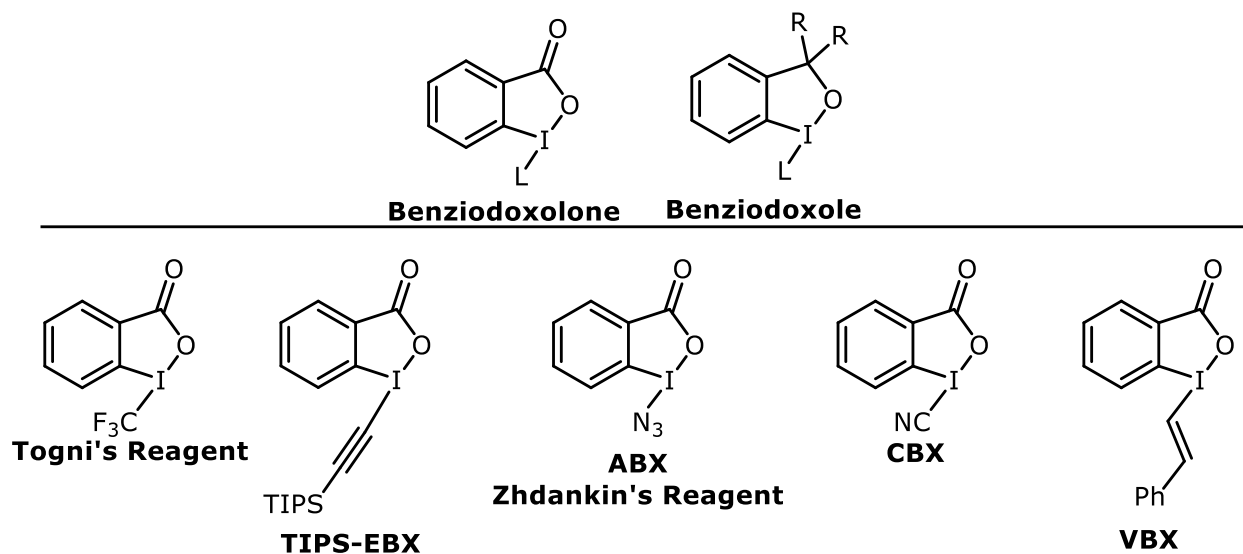
Figure 1-2. Examples of heterocyclic hypervalent iodine reagents.

One advantage of using benziodoxolones as reagents in chemical reactions is that the by-product of their reaction, 2-iodobenzoic acid, is the original precursor to these reagents and can be easily removed by aqueous extraction, recovered, and recycled.[38] Moreover, benziodoxolones (and benziodoxoles) are typically more thermally stable than their acyclic counterparts, allowing for ease of storage and handling. They are, generally, solids that can be isolated and stored, typically, at room temperature or in a refrigerator for relatively long periods of time. This stability has been rationalized due to the so-called "five-member ring effect", where a significant increase in stability

7

is observed through the bidentate binding of the iodine,[39] which places the lone-pair electrons of iodine in conjugation with the π-system of the benzene ring for further stabilization.[40]

1.3.1. Synthesis

There are few convenient preparatory methods for the direct introduction of the iodanyl group onto an arene. Methods typically employ the use of an oxidant with a reagent acting as a source of iodine. This strategy has, for example, been applied to the syntheses of (diacetoxy)iodoarenes (eq 1.2),[41,42] hydroxy(tosyloxy)iodanes (eq 1.3),[43] (difluoroiodo)arenes (eq 1.4),[41] and symmetrical diaryliodonium salts (eq 1.5).[44–46]

$$\text{Ar-H} \xrightarrow[\substack{\text{or} \\ \text{Selectfluor} \\ \text{I}_2, \\ \text{MeCN, AcOH}}]{\substack{\text{K}_2\text{S}_2\text{O}_8,\ \text{I}_2 \\ \text{DCE} \\ \text{AcOH, H}_2\text{SO}_4 \\ 40\ °\text{C}}} \text{Ar-I(OAc}_2) \tag{1.2}$$

$$\text{Ar-H} \xrightarrow[\text{DCM/TFE}]{\substack{m\text{CPBA, I}_2 \\ \text{TsOH}\bullet\text{H}_2\text{O}}} \text{Ar-I(OH)OTs} \tag{1.3}$$

$$\text{Ar-H} \xrightarrow[\substack{\text{Et}_3\text{N}\bullet3\text{HF} \\ \text{MeCN}}]{\substack{\text{Selectfluor} \\ \text{I}_2}} \text{Ar-IF}_2 \tag{1.4}$$

$$\text{Ar-H} \xrightarrow[\text{DCM/TFE}]{\substack{m\text{CPBA, I}_2 \\ \text{TfOH}}} (\text{Ar})_2\text{IOTf} \tag{1.5}$$
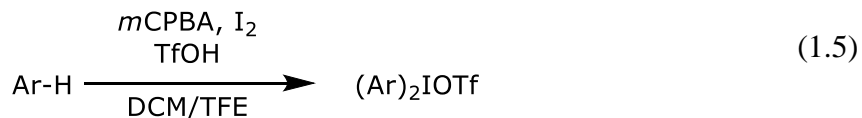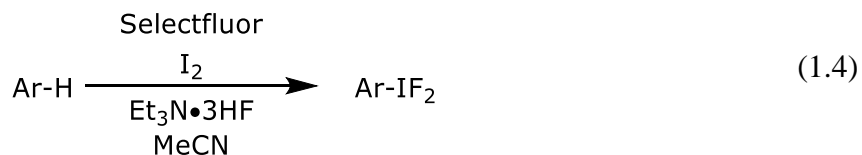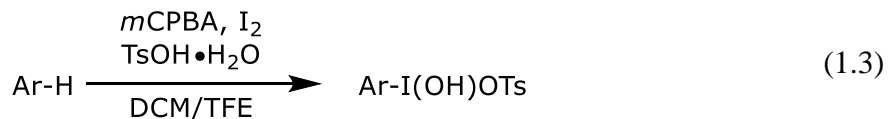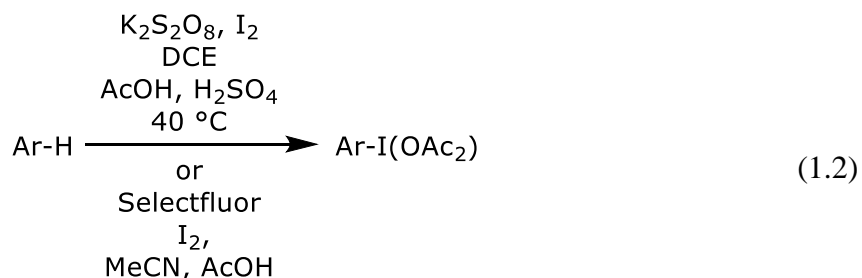
It is often easier to synthesize, purify, and isolate aryl-λ^3-iodanes by first oxidizing the respective aryl iodides and then performing metathesis reactions to obtain the desired ligand(s).

8

For example, iodoarenes can be oxidized to directly provide the corresponding dichlorides (e.g.,

1.2), difluorides (e.g., **1.3**), and diacetates (e.g., **1.4**) using Cl$_2$,[20,47,48] a mixture of Selectfluor and

F$^-$,[49] or AcOOH, [50] respectively (Scheme 1-1). Interconversion of these iodanes can be

accomplished by first hydrolyzing the iodanes and then treating the resulting iodosoarenes (e.g.,

1.6) with mineral acid/acetic acid. Iodobenzene diacetate (**1.4**) is an important bench-stable HVI

reagent and its ligands can exchanged with other carboxylic acids to give

bis(acyloxy)iodobenzenes (**1.5**).[51–54]

Scheme 1-1. Examples of the Syntheses of Various Hypervalent Iodine(III) Compounds
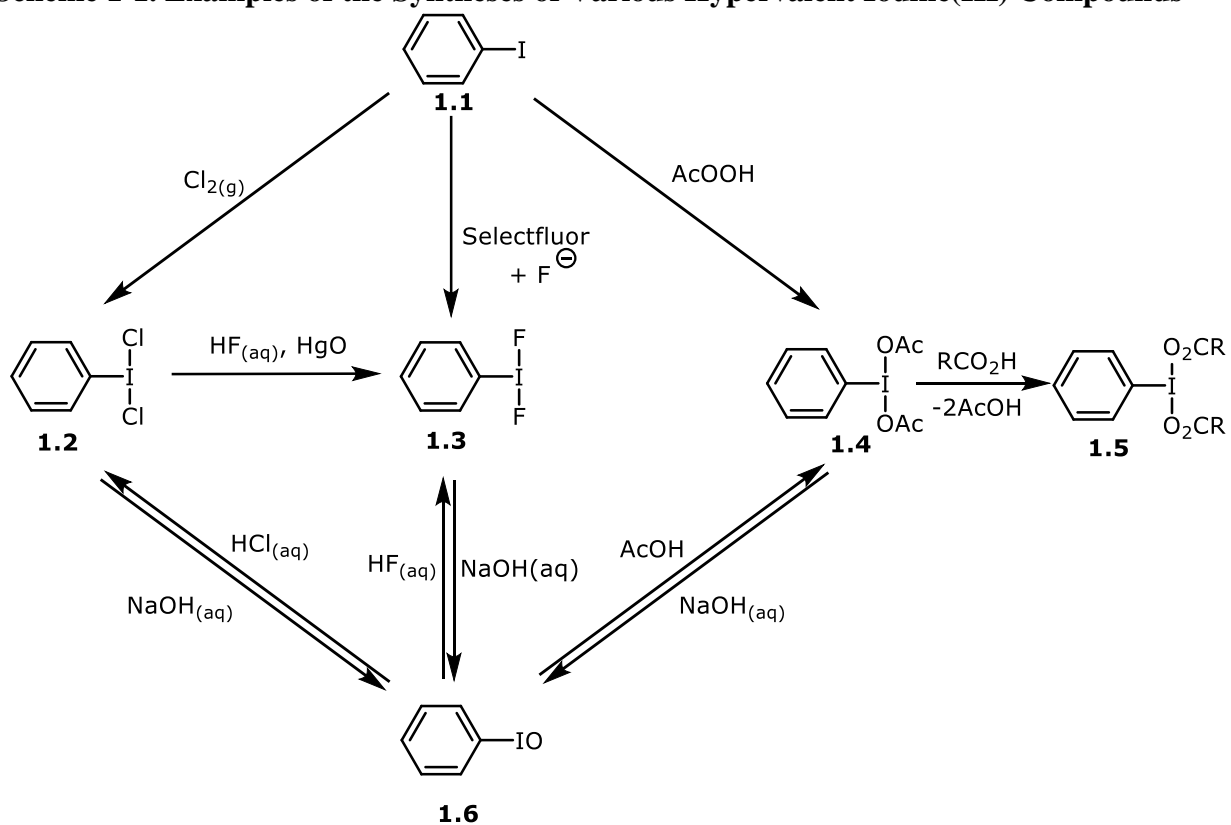
1.3.2. Structure and Bonding

A common structural feature found in hypervalent molecules is a bond between three near-

collinear atoms, such as the L–I–L triad of **1.7** (Figure 1-3), and has been termed the "hypervalent

bond". The electronegativity of most ligands found in aryl-λ^3-iodanes are higher than that of the

carbon of the aryl group. VSEPR theory therefore predicts the lowest energy conformation of aryl-λ^3-iodanes to be the one that places the ligands (L) in the apical positions of a T-shaped geometry (Figure 1-3). This geometry is regularly observed in the X-ray crystal structures of aryl-λ^3-iodanes such as $PhICl_2$,[55] $TolIF_2$,[41] and $PhI(OAc)_2$.[56] Analysis of the structure and bonding of various aryl-λ^3-iodanes gives us insight into their reactivity.

A simplistic description of the bonding in aryl-λ^3-iodanes can be seen in Figure 1-3. As discussed in §1.2, for iodine, the only orbitals available for bonding are the 5s and three 5p valence orbitals. Two orbitals are used to hold the two pairs of valence electrons of iodine, leaving two orbitals available to bond between the three substituents (i.e., one Ar and two L's). Therefore, the larger, more electropositive Ar group occupies the equatorial position while the two ligands occupy the apical positions and overlap with one 5p orbital on the iodine. This can be represented by drawing the aryl-λ^3-iodane as a hybrid of two resonance forms (i.e., **1.7a** and **1.7b**), both containing one ionic and one covalent L–I bond.
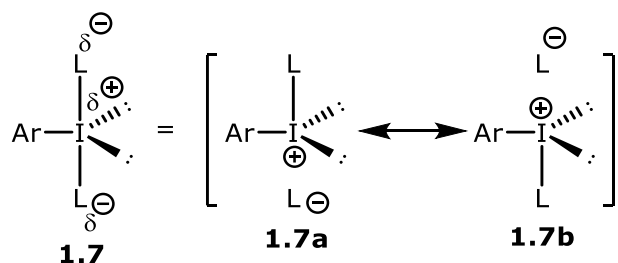
Figure 1-3. Valence bond description of the hypervalent bond of aryl-λ^3-iodanes.

Another view of the hypervalent bond can be obtained using molecular orbital (MO) theory (Figure 1-4), which combines one empty orbital from iodine and one filled orbital from each of the L's to produce 3 MOs: one bonding (σ), one nonbonding (nb), and one antibonding (σ^*).
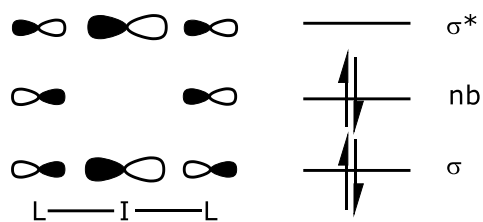
Figure 1-4. MO description of the hypervalent bond of aryl-λ^3-iodanes.

Interpretation of this diagram generates the same qualitative conclusions as the approach using valence bond theory. The L–I–L triad forms a closed-shell system with an overall bond order of BO = 1 shared between the three atoms. Each individual I–L bond, has a BO = 0.5. Therefore, this model also predicts longer, weaker I_{λ^3}–L bonds when compared to the corresponding I–L bonds for monovalent iodine containing compounds. For example, the crystal structure of $PhICl_2$ shows I–Cl bonds (2.45 Å)[55] that are significantly longer than the interhalogen bond found in iodine monochloride (2.32 Å).[57] These weak, hypervalent bonds have become an attractive target for homolysis, allowing chemical reactions through radical processes.[58] It is noteworthy that in both bonding models, there is no participation of d orbitals.

The T-shaped geometry of **1.7** provides little hindrance to the positively charged iodine, allowing nucleophiles to interact with the C–I σ* orbital. Meanwhile, analysis of the HOMO reveals that electron density is concentrated on the ligands. As such, these molecules can be expected to be electrophilic at iodine, while the ligands can act as Lewis basic sites. This can be seen in practice as HVI reagents can be considered ambiphilic in nature, able to react with both electrophiles and nucleophiles, contributing to their broad reactivity profile.

1.3.3. Reactivity

In general, HVI-containing compounds undergo three fundamental processes that are similar to ones encountered in transition metal chemistry and share the same names: ligand

exchange, pseudorotation, and reductive elimination (Scheme 1-2). As mentioned in §1.3.1, the process of ligand exchange can be used to interconvert between different iodanes. In solution, the geometry of aryl-λ^3-iodanes is dynamic and the word *pseudorotation* is used to describe the process(es) in which the positions of the ligands can be exchanged. The name *reductive elimination* is given to processes that expel an iodine-containing species of while lowering the oxidation state of iodine (e.g., Scheme 1-2c). Processes are especially useful when generating reactive iodanes which can undergo further reactions in situ, typically ending with the reductive elimination of an aryl iodide.

Scheme 1-2. Fundamental Reactions and Processes of Aryl-λ^3-iodanes

a) Ligand Exchange
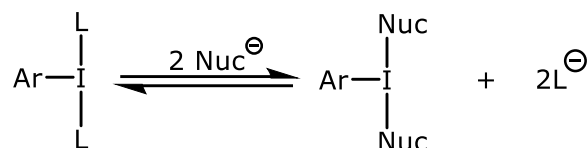
b) Pseudorotation
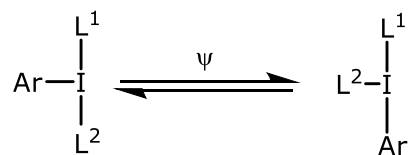
c) Reductive Elimination
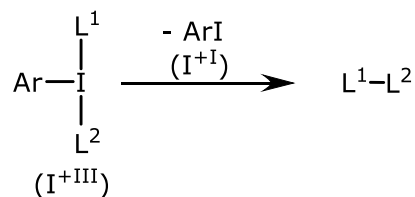
Reductive elimination is thermodynamically favorable: Ochiai et al. have quantified the leaving group ability of PhI to be ~10^{12} times higher than that of I^- and 10^6 times higher than even the so-called "super-leaving group", triflate (TfO$^-$).[59] This was done by measuring the rate of solvolysis of alkenyl(phenyl)iodonium salts (**1.8**, Scheme 1-3). After acidic work-up, these

reactions provided 4-*tert*-butylcyclohexanone (**1.10**), presumably via vinyl cation **1.9**. They found iodonium salts **1.8** underwent solvolysis 10^6 times faster than the analogous vinyl triflate.[60]

Scheme 1-3. Solvolysis of Cyclohexenyliodonium Salts
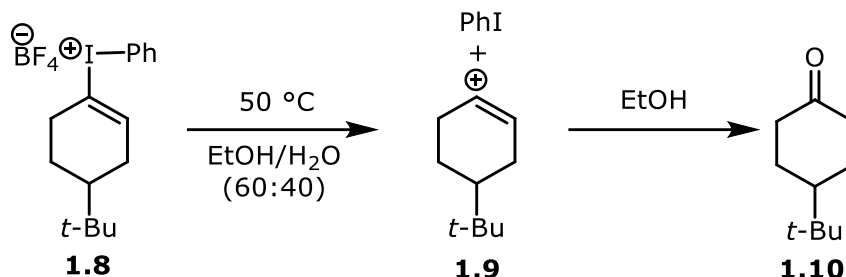
Support for the intermediacy of a vinyl cation intermediate (e.g, **1.9**) was obtained when **1.11** provided cyclopentylmethyl ketone **1.14** upon solvolysis (Scheme 1-4). This transformation was rationalized by the rearrangement of endocyclic vinyl cation **1.12** to a linear cation (**1.13**).[59]

Scheme 1-4. Evidence for the Formation of a Vinyl Cation
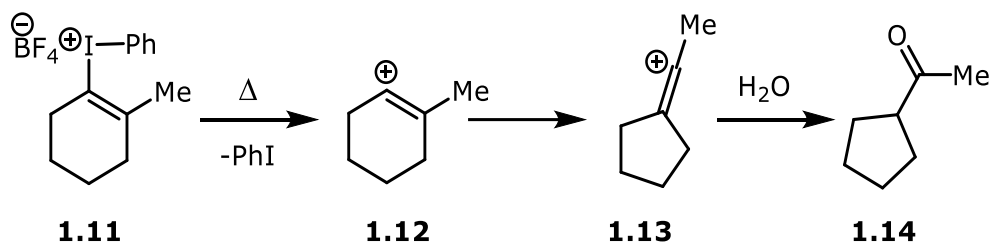
Exceptionally high nucleofugality is not limited to hypervalent iodine containing groups. This property extends to groups containing other hypervalent atoms as well. For example, the reductive elimination of aryl bromides from aryl-λ^3-bromanes occurs even more readily than the analogous aryl-λ^3-iodanes. In another study, Ochiai et al. found bromane **1.15** was able to undergo solvolysis (eq 1.6)[61] while both the corresponding vinyl iodane and vinyl triflate (**1.18**) were completely stable under the same conditions (eq 1.7).[62]

13

$$(1.6)$$

$$(1.7)$$
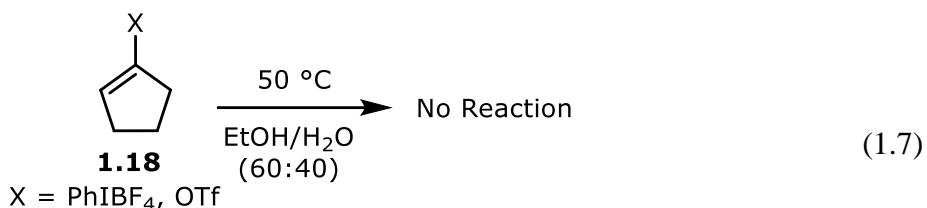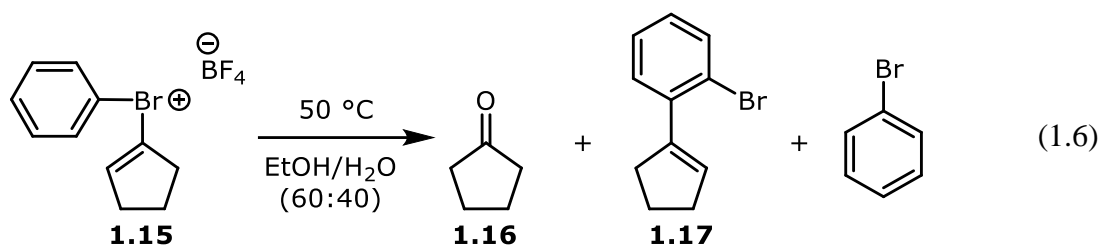
The tendency of various hypervalent moieties to possess extremely high nucleofugality led to Ochiai introducing the term *hypernucleofuge*,[17] referring to a hypervalent group that has a higher leaving group ability than triflate. While the chemistry of hypervalent bromine compounds is interesting, it is unfortunately out of the scope of this thesis.

The processes of ligand exchange, pseudorotation, and reductive elimination are important for the interconversion of iodanes and their use in synthetic organic chemistry. Iodanes can undergo ligand exchange with a carbon-based nucleophile (e.g., **1.19**, Scheme 1-5) to give alkyl-, alkenyl-, or alkynyliodanes. Subsequent reactions of these transient intermediates can provide synthetically useful transformations. For example, the leaving group ability of PhI allows alkyl(aryl)-λ^3-iodanes to undergo classic substitution (i.e., S_N1 and S_N2) and elimination (i.e., E1 and E2) chemistry. The ability of HVI-containing compounds to undergo ligand exchange with carbon nucleophiles has allowed for their use in substitution reactions to form carbon–carbon or carbon–heteroatom bonds. Common functional groups appearing as ligands on aryl-λ^3-iodanes include trifluoromethyl-, fluoro-, chloro-, hydroxy-, acetoxy-, and tosyloxy- groups. Once displaced, the ligands can then act as nucleophiles or as Brønsted bases to perform substitution

Scheme 1-5. Pathways for Reductive Elimination of ArI from Aryl-λ^3-iodanes

a) Substitution

b) Elimination

X= O, NH, S, C$^{\ominus}$,
etc.
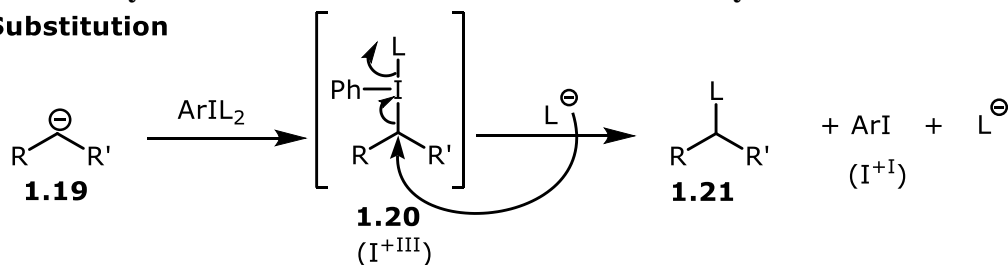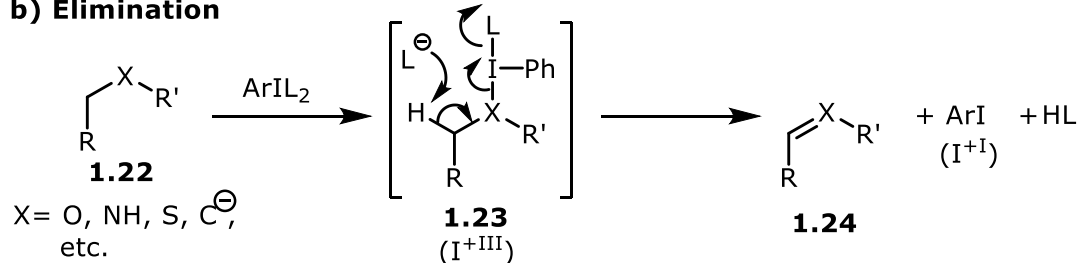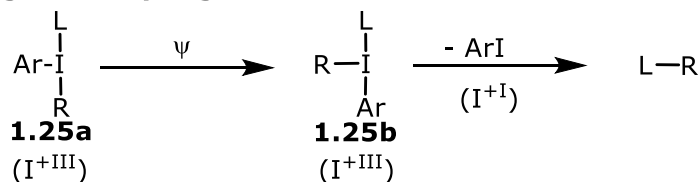
c) Ligand Coupling

reactions (e.g., **1.20** to **1.21**, Scheme 1-5a) or elimination reactions (e.g., **1.23** to **1.24**, Scheme 1-5b), respectively. Another avenue towards the reductive elimination of aryl iodide is through ligand coupling. A pseudorotation (ψ) can occur to bring the ligands into the required *cis*-orientation (**1.25a** to **1.25b**, Scheme 1-5c) to allow for the coupling to occur. Substitution reactions utilize aryl-λ^3-iodanes as a formally electrophilic source of one of their ligands. These ligands, typically, originate from nucleophilic species prior to their incorporation into an HVI reagent. This reversal of reactivity has led HVI chemistry to be associated with umpolung chemistry. In a simplistic approach, aryl-λ^3-iodanes can be viewed as a source of one nucleophilic ligand, while the other ligand, when coupled to the reductive elimination of an aryl iodide, is formally electrophilic.

15

The synthetic applications of the general reaction pathways shown above in Scheme 1-5a–b can be seen in the illustrative examples of Scheme 1-6. Treatment of acetophenone derivatives (**1.26**) with PhIO in MeOH/KOH affords α-hydroxylated dimethyl ketals (**1.28**, Scheme 1-6a). Moriarty et al. rationalized the hydroxylation as occurring through the substitution of the iodanyl group via a ring-closure of hemi-ketal **1.27**.[63] An example of the reductive elimination of PhI occurring through an elimination pathway is when α-phenylsulfanylacetates (**1.29**) are fluorinated by TolIF$_2$ (Scheme 1-6b).[64] Despite TolIF$_2$ possessing two equivalents of fluoride, only monofluorination occurs when using 1 equivalent of this reagent. This is because the reaction occurs through a fluoro-Pummerer rearrangement where the fluorination event (**1.31** to **1.32**) happens after TolIF$_2$ oxidizes **1.29** to a sulfonium ion (**1.31**). A second equivalent of TolIF$_2$ can be used to achieve a second fluorination (i.e., **1.32** to **1.33**).

Scheme 1-6. Examples of Substitution and Elimination Reactions Promoted by Hypervalent Iodine(III) Reagents

16
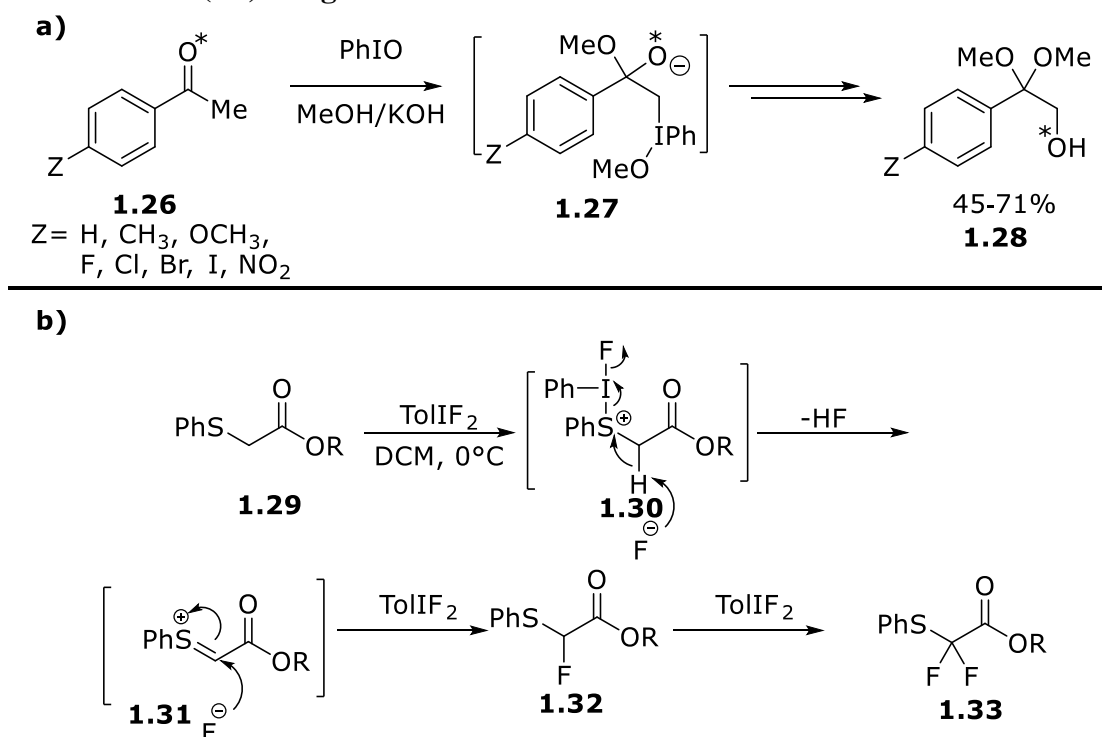
α-Carbonyl functionalization is an important application of hypervalent iodine chemistry.[65,66] Achieving a single α-carbonyl functionalization per equivalent of aryl-λ^3-iodane is typical. This process uses only one of the two heteroatom ligands of the iodane or an external nucleophile. Examples of this reactivity include the fluorination[67] and oxyfunctionalization[68] of β-dicarbonyl compounds (**1.34**) using TolIF$_2$ (eqs 1.8 and 1.11, respectively).

$$\text{(1.8)}$$

$$\text{(1.9)}$$

X= MeO, EtO, *i*-PrO,
(PhO)$_2$PO$_2$, TsO, MsO
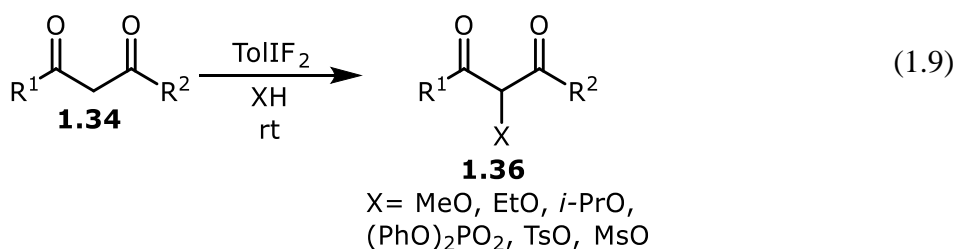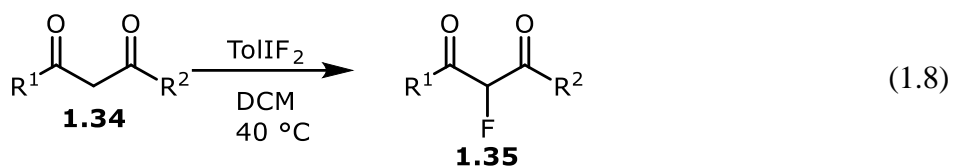
Ligand transfer reactions involving HVI reagents and organic substrates can utilize one or two ligands and typically involve the functionalization of 2 different (often adjacent) carbon atoms. We wondered if we could design a system that would allow for the transfer of both ligands of an aryl-λ^3-iodane onto the same carbon, thereby performing a *gem*-difunctionalization. Based on the reactivity patterns for the α-functionalization of enolates (Scheme 1-7a), we devised a strategy for the α,α-difunctionalization of carbonyl compounds using aryl-λ^3-iodanes (Scheme 1-7b). In typical α-carbonyl functionalization chemistry, only the formally electrophilic ligand of the iodane reacts with the nucleophilic enolate, leaving by behind the second, nucleophilic, ligand. It was postulated that if the enolate already possesses a nucleofugal substituent (LG) at the α-position, such as in the case of **1.39**, then the displaced ligand could return and replace LG, providing the *gem*-difunctionalization. Structure **1.39** is an ylide and it was rationalized that this class of chemical

17

compounds may contain members suitable to investigate *gem*-difunctionalization reactions using

HVI reagents. The following section provides a brief description of ylides and rationalization of

why they are candidates for *gem*-difunctionalization.

**Scheme 1-7. Schematic Representation of Hypervalent Iodine Reagent Based Strategies for
a) α-Functionalization of Enolates and b) α,α-Difunctionalization of Ylides**
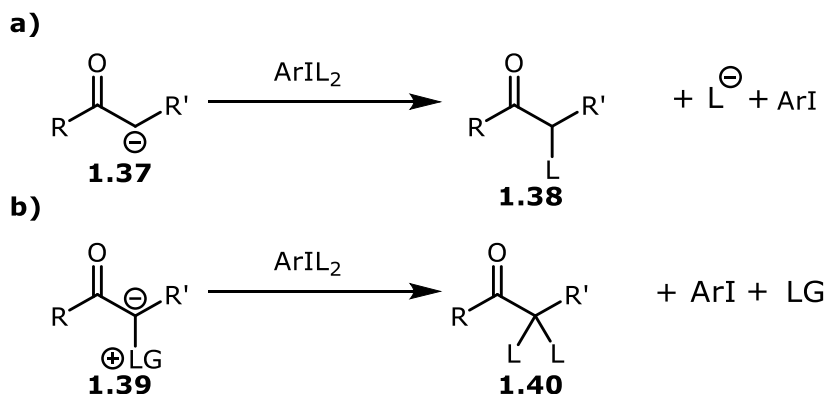
1.4. Ylides

Ylides are a subclass of zwitterionic molecules which contain an anionic carbon covalently

bonded to a cationic heteroatom.[69] The word "ylide" (or "ylid") was coined by Nobel laureate

Georg Wittig, who combined two suffixes used in chemical nomenclature: "-yl" and "-ide".[70]

These suffixes were used to denote a "homopolar valence" (i.e., covalent bond) and a "heteropolar

binding" (i.e., ionic interaction), respectively, and aptly describes the functionality. Typical

chemical structures used to represent these compounds include resonance contributors known as

the neutral "ylene form" (**1.41a**) and the dipolar "ylide form" (**1.41b**) (eq 1.10).

(1.10)
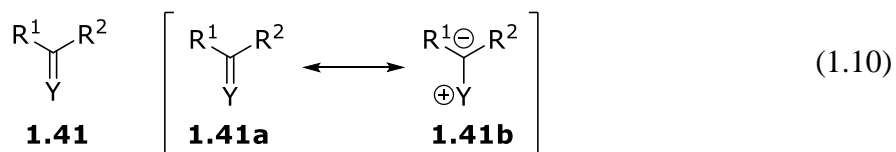
Ylides represent an important class of chemical compounds that are used for many different

transformations in synthetic organic chemistry.[71] While many types of ylides have been

synthesized, the ylides pertinent to this thesis include phosphonium- (**1.42**), diazonium- (**1.43**), and iodonium ylides (**1.44**). General structures of these ylides are shown in Figure 1-5. While the definition of an ylide implies that the molecule possesses a dipolar structure, ylides are often drawn in the neutral ylene form for the purposes of convenience and clarity of presentation. This thesis will continue the practice of representing such compounds in the ylene form with full understanding that the dipolar (or zwitterionic, if applicable) form is an important resonance contributor to the overall electronic structure of the molecule. The dipolar nature of phosphonium ylides is illustrated in the well-known Wittig reaction (eq 1.11). Matching the dipoles of phosphonium ylides to the opposing dipoles of the carbonyl correctly predicts the regiochemistry of the reaction that provides oxaphosphatane **1.46**.
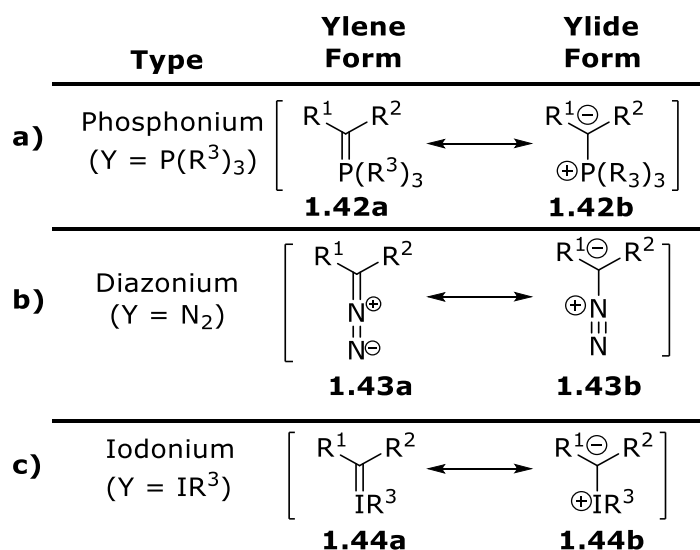
Figure 1-5. Ylene and ylide resonance forms of phosphonium-, diazonium-, and iodonium ylides.

$$(1.11)$$

19
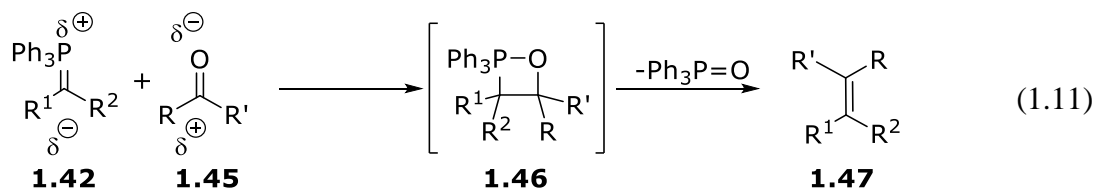
1.5. Reactions of Ylides and Hypervalent Iodine(III) Reagents

Although ylides and HVI reagents have been known for over a century, there have been few reports of their reactions with each other. Of these, the most studied has been between reactions of phosphonium ylides and aryl-λ^3-iodanes. These reactions, however, do not substitute the PPh_3 group with a ligand from the iodane. For example, $PhICl_2$ has been reported to react with **1.48** to initially generate α-chlorinated phosphonium salt **1.49** which is deprotonated to afford a α-chlorophosphonium ylide (**1.50**, Scheme 1-8).[72] Additionally, $PhICl_2$ can be used to chlorinate the oxidoylide (**1.53**) generated in the Schlosser modification of the Wittig olefination, ultimately providing Z-chloroalkenes (**1.55**, Scheme 1-9).[73]

Scheme 1-8. Chlorination of Phosphonium Ylides Using $PhICl_2$
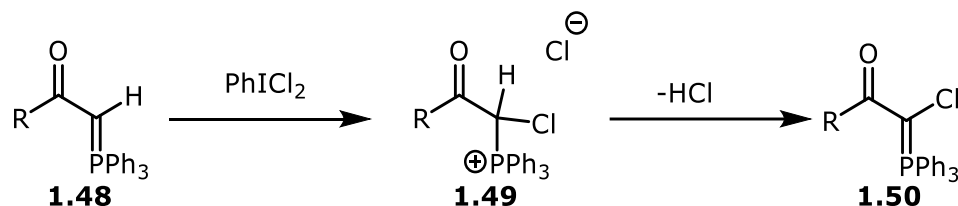
Scheme 1-9. Chlorination of the Oxidoylide During the Schlosser-modified Wittig Olefination
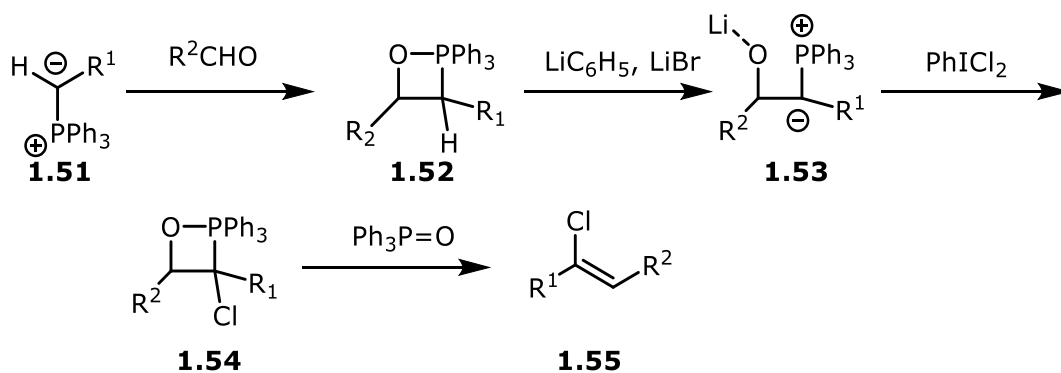
Phosphonium ylides **1.48** react with $PhI(OAc)_2$ and HBF_4 to give mixed phosphonium-iodonium salts (**1.56**, eq 1.12).[74,75] Similar salts with counterions such as TfO^- or TsO^- can be obtained by treating **1.48** with $PhI(OTf)_2 \cdot 2Py$ or $PhI(OH)OTs$, respectively.[74]

20

$$
\text{1.48} \quad \xrightarrow[\text{HBF}_4]{\text{PhI(OAc)}_2} \quad \text{1.56} \tag{1.12}
$$
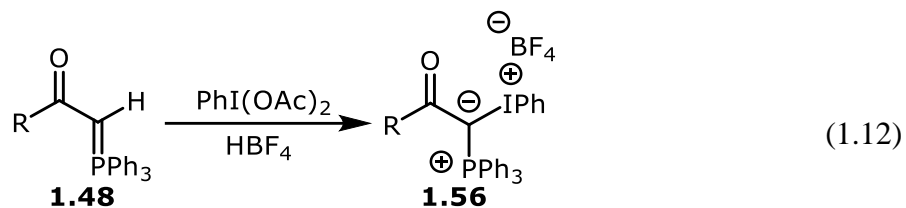
The inability for PPh_3 to act as a leaving group in the reaction of phosphonium ylides and aryl-λ^3-iodanes led us to consider other structures for ylides **1.39**, where LG has greater nucleofugality than PPh_3. We rationalized if LG possessed high nucleofugality, ylidic structure **1.39** could be a carbene precursor. Diazonium ylides (i.e., diazo compounds, LG = N_2) possess a potential leaving group, dinitrogen, which is considered one of the best leaving groups in organic chemistry. The expulsion of dinitrogen from diazo compounds has been used as a thermodynamic driving force in the generation of high-energy intermediates such as free carbenes and metallocarbenes.[76,77]

At the onset of our investigation, there were very few examples of diazo compounds reacting with HVI reagents. For instance, Varvoglis et al. have reported the reaction of aryldiazoethanes or aryldiazomethanes (**1.57**) with $PhI(OTFA)_2$ provides a range of oxygenated products (eq 1.13).[25] The authors suspected **1.59** arose from the hydrolysis of the corresponding acylals (**1.59'**). In another example, Roedig et al. found polychlorinated α-diazo-*β*-ketoesters (e.g., **1.60**) reacted with a slight excess of $PhICl_2$ to generate *gem*-dichlorinated products (e.g., **1.61**) upon heating in carbon tetrachloride (eq 1.14).[78]

$$
\underset{\substack{\textbf{1.57} \\ \text{R = Me, H}}}{\overset{N_2}{\underset{Ar}{\bigwedge}}R} \quad \xrightarrow{\text{PhI(OTFA)}_2} \quad \underset{\textbf{1.58}}{\overset{OTFA}{\underset{Ar}{\bigwedge}}R} + \underset{\textbf{1.59}}{\overset{O}{\underset{Ar}{\bigwedge}}R} \quad \left[\overset{\text{via}}{\underset{\textbf{1.59'}}{\overset{TFAO\ OTFA}{\underset{Ar}{\bigwedge}}R}} \right] \tag{1.13}
$$

$$(1.14)$$
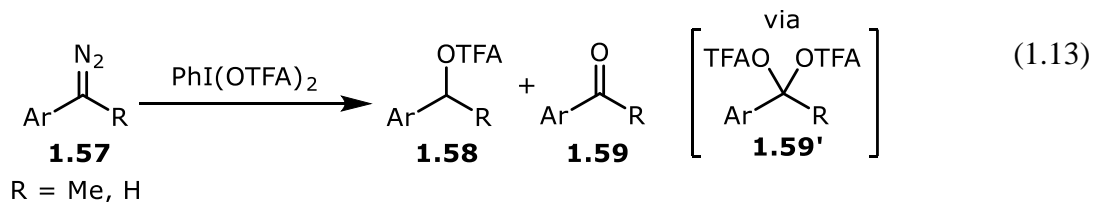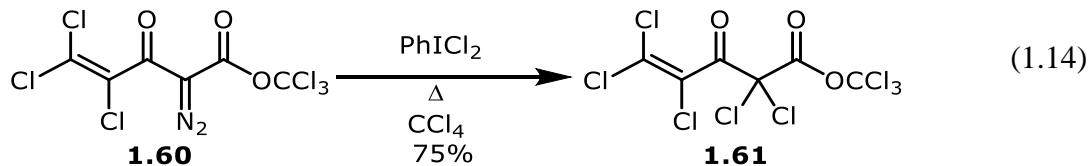
These examples demonstrate the reaction of diazo compounds and aryl-λ^3-iodanes can lead to *gem*-difunctionalized products. However, products of *gem*-difunctionalization in reactions of the type shown in eq 1.14 were not directly observed as the proposed bis(trifluoromethyl)acylals are likely unstable. The reaction conditions of eq 1.14 suggests that geminal double ligand transfer from PhICl$_2$ onto the ylidic carbon of **1.60** is occurring. However, these conditions are of low synthetic utility as they likely provide non-specific chlorination of a variety of functional groups, which may be why the authors used polychlorinated substrates. Heating PhICl$_2$ in refluxing CCl$_4$ has been suggested to provide homolysis of the I–Cl bonds, generating radicals which can even react with typically inert functionalities, such as alkanes.[79]

1.6.   Safety Considerations

It should be remembered that both diazo compounds and hypervalent compounds are high-energy compounds. Members of these two classes of compounds have gained notoriety as being explosive hazards. For diazo compounds, diazomethane and related diazoalkanes are likely responsible for the explosive reputation of diazo compounds.[80]

With respect to the handling of aryl-λ^3-iodanes: in general, the more I–O bonds an iodane possesses, the more explosive the compound will be. It is important to bear in mind that HVI compounds are potentially impact and thermally sensitive, possibly exploding if mishandled. This is especially true if the iodine bears multiple ligands of high *trans*-influence.[81] It should be known that, despite the discussion of the relative stability of hypervalent iodine heterocycles,

benziodoxoles/benziodoxolones are potential hazards as well.[82] Accounts of explosions involving 2-iodoxybenzoic acid (IBX),[83] Togni's reagent,[84] and Zhdankin's reagent have been reported.[82] Despite the potential dangers related to diazo compounds and HVI reagents, there has been no unexpected explosion during the course of the work described below.

1.7. Scope of Thesis

The purpose of this thesis was to investigate the reactions of various ylides with aryl-λ^3-iodanes that can allow for *gem*-difunctionalization. Literature precedent suggests diazo compounds are suitable ylides for this purpose.

Chapter 2 describes studies of the reactions of diazo compounds and hypervalent iodine(III) reagents. There has been one report in the literature of the *gem*-dichlorination of diazo compounds using PhICl$_2$. However, their methods likely lead to low chemoselectivity. We decided to initiate our studies with the dichlorination of aryldiazoesters using PhICl$_2$. The first objective was to determine whether milder, more practical conditions could be developed. Once new conditions were found and optimized, studies to investigate mechanistic details and synthetic utility were performed. Brief studies into interrupting the double ligand transfer were also undertaken. We found β-hydroxy-α-diazoesters can react with PhICl$_2$ or TolIF$_2$ and undergo a tandem halogenation/semi-pinacol rearrangement when the iodane is activated with a suitable catalyst. Lewis bases such as pyridine and 2,6-lutidine were found to activate PhICl$_2$ to various chlorination reactions while rhodium carboxylate complexes were found to react with TolIF$_2$ to generate adducts which rapidly decomposed a β-hydroxy-α-diazoester and provided the respective product of a fluorination/semi-pinacol rearrangement. This reagent mixture was then applied to an aryldiazoacetate to see its viability for *gem*-difluorination.

Chapter 3 describes the reaction of iodonium ylides of 1,3-dicarbonyl compounds with $PhICl_2$ that provides dichlorination of the ylidic carbon. This study found that the dichlorination occurs much more readily than with the analogous diazo compounds. Differences in the dichlorination of diazonium- versus iodonium ylides were observed and ultimately led to the discovery that the mixture of iodonium ylides and $PhICl_2$ could provide cyclopropanation of styrene. This resulted in a systematic study of metal-free methods for promoting intermolecular cyclopropanation of alkenes using iodonium ylides of 1,3-dicarbonyl compounds.

Chapter 4 describes studies into cyclopropanation reactions of iodonium ylides. These studies were inspired by the observation made in Chapter 3 that, in the presence of styrene, the reaction of the phenyliodonium ylide of methyl benzoylacetate and $PhICl_2$ affords a cyclopropane. The diastereomeric ratio of the cyclopropane generated from this reaction favoured the opposite diastereomer when compared to metal-catalyzed methods. At the outset of our investigation, there were very few reports of using iodonium ylides of 1,3-dicarbonyl compounds in intermolecular cyclopropanation reactions under metal-free conditions. We therefore conducted a study to provide such methods, focusing on using hypervalent iodine(III) reagents to effect this transformation. While the majority of the work was focused on using a mixture if $PhI(OAc)_2$ and TBAI, a variety of metal-free reagents were also found to promote cyclopropanation reaction of iodonium ylides.

2. **Halogenation of Diazonium Ylides**

2.1. **Diazonium Ylides – Introduction**

Diazonium ylides (i.e., diazo compounds, **2.1a–b**, eq 2.1) are compounds used in organic chemistry as synthetic intermediates or reagents.[76,77] Diazo compounds have high-value synthetic applications due to their ability to generate free carbenes (**2.2**) or carbenoid intermediates (e.g., metallocarbenoids **2.3**). The high leaving group ability of N_2 allows for diazo compounds to act as carbene precursors via a process known as α-elimination (Scheme 2-1). This decomposition pathway can be promoted by metal-catalyzed-, photochemical-, or thermal conditions. In addition, metallocarbenes (**2.3**) generated by the decomposition of diazo compounds via a metal catalyst can be used as more controllable carbenoid intermediates.

$$(2.1)$$

2.1a   **2.1b**
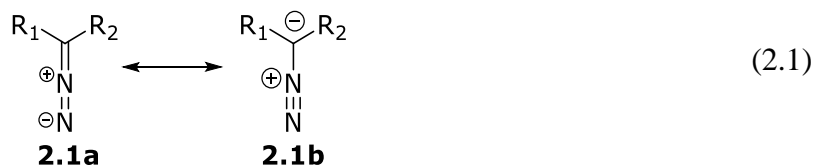
Scheme 2-1. Generation of Free Carbene and Metallocarbenes From Diazo Compounds
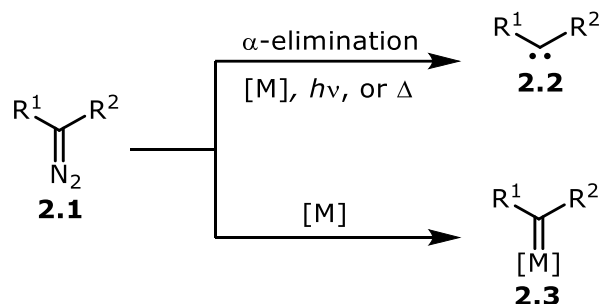
Carbene and carbenoid intermediates have been used to form products of rearrangements (**2.5**), ylide formation (**2.6**), cyclopropanation (**2.7**), and X–H insertions (**2.8**, X = C, N, O, etc.) (Scheme 2-2).[76]

Scheme 2-2. Prototypical Reactions of Carbene and Carbenoid Intermediates
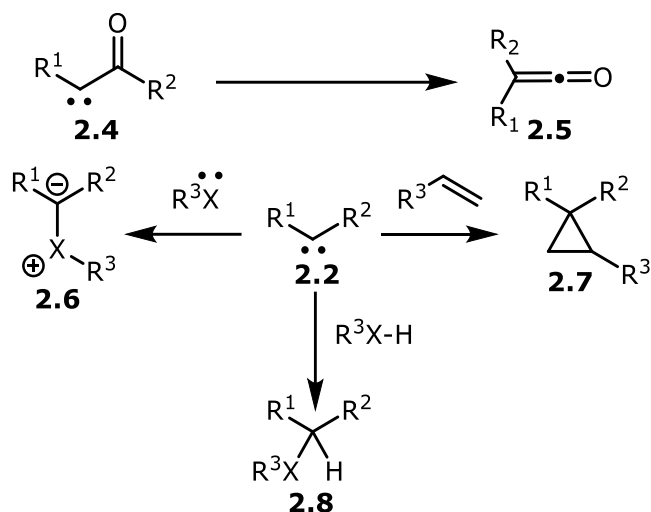
The carbanionic character of a diazo compound's ylidic resonance form (**2.1b**) correctly describes the nucleophilic character of the ylidic carbon. As such, diazo compounds have been commonly used in reactions where the diazo compound reacts with a suitable electrophile. One example is the Büchner–Curtius–Schlotterbeck reaction in which a diazo compound performs a nucleophilic attack onto an aldehyde or a ketone (Scheme 2-3).[85] After the ylidic carbon attacks the carbonyl carbon, the zwitterion (**2.10**) can decompose via either a cyclization or a semi-pinacol rearrangement and the concomitant expulsion of dinitrogen allows for the formation of epoxides (**2.11**) or homologated ketones (**2.12**).

Scheme 2-3. The Büchner–Curtius–Schlotterbeck Reaction
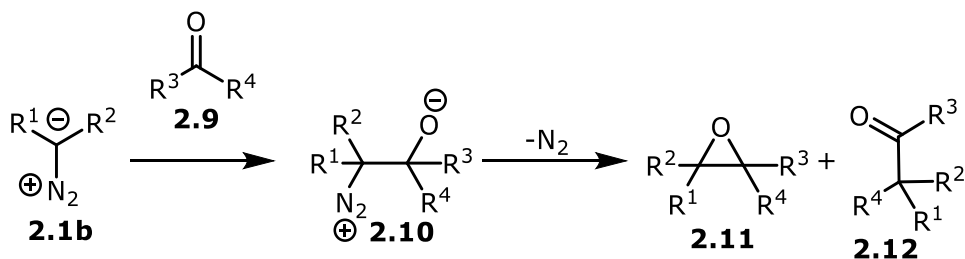
Electrophilic halogenating agents can be used to halogenate diazo compounds at the ylidic carbon. For example, *gem*-dihalogenation can be afforded through the reaction of diazo compounds and dihalogens (F_2,[86] Cl_2,[87–89] Br_2,[90] I_2[91]). Additionally, reaction of diazo compounds

with a mixture of an electrophilic halogenating agent and a nucleophilic halide, such as a mixture of NBS/HF,[92] can be used to convert a diazo group to a dihalomethylene group bearing two different halogens. Schematically, (dihaloiodo)arenes such as TolIF$_2$ and PhICl$_2$ can be regarded as surrogates to the respective dihalogens for the use in dihalogenation reactions. An example of this is the previously mentioned *gem*-dichlorination of polychlorinated 2-diazo-1,3-dicarbonyl compounds reported by Roedig and Aman using PhICl$_2$ in refluxing CCl$_4$ (see §1.5).[78] The high reactivity of PhICl$_2$ with various organic functionalities[93] was likely the reason why the reported substrate scope was limited to polychlorinated carbonyl compounds. At the outset of our investigation, we saw great potential for the reaction of diazo compounds and PhICl$_2$ that would allow for geminal dichlorination reactions to occur. The goal was to develop new synthetic methodologies based on the interaction of HVI reagents and diazo compounds that allow for the transfer of *both* ligands of the iodane onto the same carbon. We, therefore, decided to investigate reactions of PhICl$_2$ and various diazo compounds in the hopes of developing general geminal difunctionalization methodologies that could be applied to other HVI reagents or substrates.

2.2. Geminal Dichlorination

The diazo compounds used in this study were synthesized via different methods depending on their carboskeleton. The majority of this work was performed using diazo compounds derived from substituted phenylacetates synthesized from various arylacetates (**2.14**) originating from either commercially available carboxylic acids or acyl chlorides (**2.13**, eq 2.2). The diazo functionality was introduced onto these substates via a Regitz diazo transfer[94] using a protocol similar to what has been reported by Davies et al.[95] (eq 2.3). Methyl phenyldiazoacetate (**2.15a**, Z = H, R = Me) was chosen as our model substrate for a majority of the reaction optimization studies and mechanistic investigations.

$$(2.2)$$

R₃ = OH, Cl

$$(2.3)$$
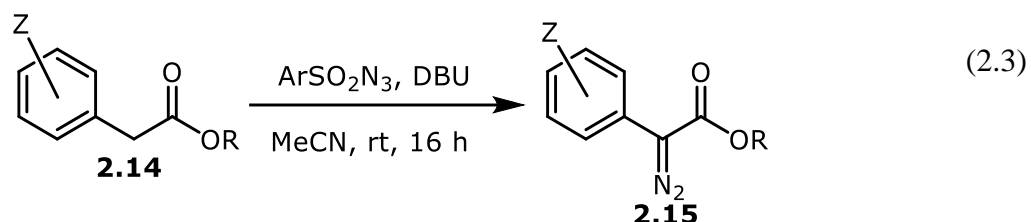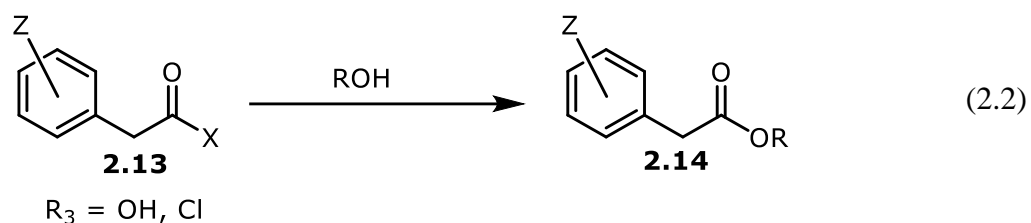
In our hands, these diazo transfer conditions typically gave incomplete reactions. Purification of diazo ester **2.15**, via flash column chromatography (FCC), often proved challenging due to partial co-elution of the parent ester (**2.14**). Attempts to consume the starting material by pushing the reaction to completion by performing the reaction with longer reaction times (up to 72 h), using elevated reaction temperatures, or adding excess sulphonyl azide provided no improvement. FCC could be used to obtain serviceable amounts of the pure diazo compound, although careful choice of column purification conditions (e.g., mobile phase and flow rate) was required. In some cases, when the diazo compound and its parent ester completely co-eluted using FCC, radial chromatography was able to provide adequate separation. Purification via trituration or recrystallization was used in cases where the solubility of the diazo compound was very different than the parent ester.

PhICl₂ was synthesized by the direct chlorination of iodobenzene. A convenient method to synthesize PhICl₂ was reported by Zhao and Zhang[48] and was used throughout these studies.

$$(2.4)$$
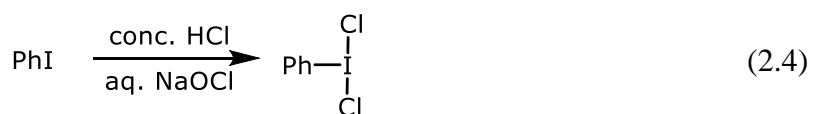
This method involves the generation of chlorine gas via a dropwise addition of concd hydrochloric acid to a suspension of PhI in solutions of household bleach (eq 2.4). In our hands, to generate $PhICl_2$ in reproducibly good yield, stability, and solubility, several reaction parameters of this heterogeneous reaction were controlled. Ultimately, we found the synthesis was best performed on a 10.0 mmol scale (2.17 g of PhI) in a 250 mL or 300 mL round bottom flask with vigorous stirring of the reaction mixture. The exothermic addition of hydrochloric acid to the suspension of $PhICl_2$ was only problematic if the addition was performed too quickly. As other research groups have found, the quality of $PhICl_2$ was influenced by the bleach used during this reaction.[96] Of the various solutions of bleach available at local grocery stores, we found No Name bleach solutions provided more reproducible quality of $PhICl_2$ when compared to formulations manufactured by Old Dutch and Chlorox.[96] Only regular, non-scented formulations of bleach solutions were investigated for our syntheses of $PhICl_2$. As it has been reported that (dichloroiodo)arenes slowly decompose during storage,[25] an additional effort was taken to ensure reproducibility of the chlorination reactions by storing $PhICl_2$, away from light, in a desiccator (over $CaSO_4$). Furthermore, any reagent that had aged over one week was discarded and a fresh batch was prepared.

2.2.1. Initial Studies and Optimization

Initial studies into the *gem*-dichlorination of diazo compounds were performed by adding solid $PhICl_2$, in one portion, to a solution of methyl phenyldiazoacetate (**2.15a**) and 2,6-lutidine dissolved in DCM at room temperature (eq 2.5). 2,6-Lutidine was originally added as a preventive measure to sequester trace HCl lingering on the $PhICl_2$ from its synthesis. Mixture of the three reagents yielded a rapid reaction in which rapid gas evolution was observed while the colour of the solution changed from orange to faintly yellow. Products of dichlorination (**2.16a**),[97]

monochlorination (**2.17a**),[98] and oxygenation (**2.18a**)[99] were observed and confirmed via comparisons of their NMR spectra to the ones reported in the literature.
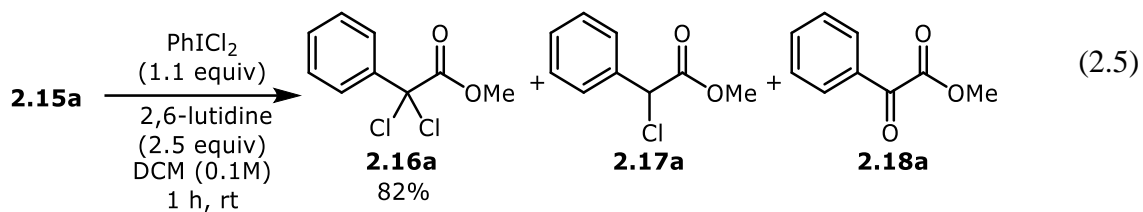
Using the conditions shown in eq 2.5, the dichlorinated product **2.16a** was obtained in 82% yield relative to **2.15a** and 72% yield relative to PhICl$_2$, indicating that double ligand transfer was occurring. Upon purification of the crude reaction mixture by FCC, chlorinated products **2.16a** and **2.17a** were recovered as a partially separable mixture. Subsequent reactions were performed to optimize for the yield of **2.16a** and for its selective formation over monochloride **2.17a**. The ratio of the two products were determined by analyzing the mixture of the two compounds, recovered after FCC, via ^{1}H NMR spectroscopy. Screening various reaction solvents (Table 2-1) found halogenated solvents such as dichloromethane and 1,2-dichloroethane provided the highest yields of **2.16a** in the shortest reaction times (79–82% yield, entries 1–3). Ethereal solvents (i.e., DME and THF) were found to be inefficient reaction solvents, providing lower yields of **2.16a** (51% and 23%, Table 2-1, entries 4–5). The dichlorination of **2.15a** occurred very slowly in non-polar solvents such as toluene and hexanes (48 and 16 h, respectively) and, interestingly, gave high yields of **2.16a**, (81% and 77%, entries 6–7). A rapid reaction was observed when acetonitrile was used as the reaction solvent, albeit providing lower amounts of **2.16a** (65% yield, entry 8). When DMSO was used as the reaction solvent, rapid decomposition of PhICl$_2$ was observed upon its addition accompanied by the observation of grey vapours above the surface of the reaction

Table 2-1. Solvent Effects Upon the Reaction Between Methyl Phenyldiazoacetate and PhICl$_2$[a]

entry	solvent	time (h)	concn (M)	yield[b] 2.16a (%)	yield[b] 2.17a (%)
1	DCM	1	0.1	82	16
2	DCM	0.33	0.2	81	12
3	DCE	1	0.1	79	15
4	DME	5	0.1	51	7
5	THF	16	0.1	23	0
6	Toluene	48	0.1	81	15
7	Hexanes	16	0.1	77	4
8	MeCN	0.1	0.1	65	9
9	DMSO	16	0.1	0	0
10[c]	DCM	16	0.2	ND[d]	ND

[a]General conditions: **2.15a** (50 mg), PhICl$_2$ (1.1 equiv), 2,6-lutidine (2.5 equiv) in solvent (0.1 or 0.2 M) at rt. [b] Isolated yield after column chromatography, recovered as a mixture of the two chlorinated products. [c]Reaction contained no 2,6-lutidine. [d]Not determined, reaction was incomplete.

mixture. Unsurprisingly, dichlorination did not occur in this case and the diazo compound appeared to remain unreacted (entry 9). 2,6-Lutidine was soon found to play an important role in the dichlorination of aryldiazoesters. For example, when performing the reaction in DCM in the absence of 2,6-lutidine, there was very little colour change and no gas evolution was observed. Even after allowing the mixture to stir for 16 hours at room temperature, analysis of the reaction mixture, using TLC, suggested significant amounts of **2.15a** remained in solution (entry 10) the formation of only small amounts of **2.16a**. In contrast, the addition of excess 2,6-lutidine into a pre-mixed suspension of PhICl$_2$ and **2.15a** in DCM resulted in rapid gas evolution and product formation. These reactions typically completed within a few minutes. This rate enhancement was rationalized by hypothesizing that 2,6-lutidine activates PhICl$_2$ in a similar manner to that observed for the pyridine-accelerated chlorination of alkenes and oxidation of alcohols using PhICl$_2$.[100] It

has been proposed that pyridine can activate PhICl$_2$, via ligand exchange, generating the more electrophilic iodane **2.19** (eq 2.6).[25]

$$\text{Ph}-\overset{\overset{\text{Cl}}{|}}{\underset{\underset{\text{Cl}}{|}}{\text{I}}} \quad \underset{}{\overset{\text{Py}}{\rightleftharpoons}} \quad \text{Ph}-\overset{\overset{\text{py}^{\oplus}}{|}}{\underset{\underset{\text{Cl}}{|}}{\text{I}}} \quad + \text{Cl}^{\ominus} \qquad (2.6)$$

2.19
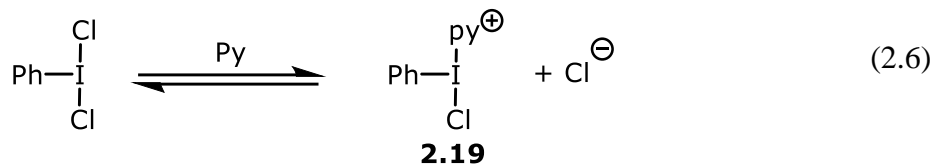
We postulated that 2,6-lutidine, despite the steric hindrance about the Lewis basic nitrogen, was still able to perform a nucleophilic attack onto the iodine of PhICl$_2$, generating a more reactive iodane analgous to **2.19**. Activation of PhICl$_2$ would allow its facile reaction with the diazo compound and thereby promote the dichlorination reaction. This prompted a reaction optimization study to determine the effects of using various pyridine analogs as Lewis basic additives (Table 2-2). Lowering the loading of 2,6-lutidine from 2.5 equiv to 0.05 equiv was found to increase selectivity of dichlorination versus monochlorination from 88:12 to 98:2 (entries 1–4). Pyridine and 4-(dimethylamino)pyridine (DMAP) were also capable of promoting the reaction as well. When these pyridines were used, a marked increase in reaction rate —which positively correlated to the nucleophilicity of the pyridine— was observed. Under the same catalytic loading, an approximate 4-fold increase in reaction rate was observed when 2,6-lutidine was replaced with pyridine (Table 2-2, entries 4 vs 5). Another 4-fold increase was observed when changing from pyridine to DMAP (entries 6 vs 7). Conversely, using the extremely sterically-hindered 2,4,6-tri-*tert*-butylpyrimidine (TTBP, developed by Crich et al. as a cost-effective alternative to 2,6-di-*tert*-butylpyridine)[101,102] showed incomplete reaction (Table 2-2, entry 8), similar to that observed when the Lewis base was absent (Table 2-1, entry 10), indicating that it may be possible to prevent interaction of the nitrogens of the pyrimidine and the iodane via steric bulk. From this study, we determined that 5 mol% pyridine gave the best yields of **2.16a** and lowered formation of **2.17a** to amounts nearly undetectable by ^{1}H NMR spectroscopy. Using catalytic amounts of pyridine-type

bases provided **2.16a** in ≥79% yield. When acetonitrile was used as the reaction solvent, inclusion of 5 mol% of 2,6-lutidine or pyridine was found to produce rapid (within 10 minutes) formation of **2.16a** in good yields as well (Table 2-2, entries 9–10). Based on the yield of **2.16a**, the conditions shown in Table 2-2, entry 5, were considered to be the "standard conditions" for the dichlorination of diazo compounds and were used in a subsequent study scope of diazo compounds that this reaction was applicable to.

Table 2-2. Comparing Various Pyridine Analogs[a]

entry	solvent	additive	mol%	time (min)	yield 2.16a[a] (%)	eatio (2.16a:2.17a)
1	DCM	2,6-lutidine	250	20	81	88:12
2	DCM	2,6-lutidine	25	30	83	94:6
3	DCM	2,6-lutidine	10	40	84	97:3
4	DCM	2,6-lutidine	5	45	79	98:2
5[b]	DCM	pyridine	5	10	90	97:3
6	DCM	pyridine	1	50	87	98:2
7	DCM	DMAP	1	12	86	98:2
8	DCM	TTBP	10	16 h	ND[c]	ND
9	MeCN	2,6-lutidine	5	10	83	98:2
10	MeCN	pyridine	5	2	79	99:1

[a]General conditions: **2.15a** (50 mg), solvent (1.4 mL), and additive (1–250 mol%), and PhICl₂ (1.1 equiv).[b]These conditions are considered the "standard conditions".[c]Not determined, reaction was incomplete.

2.2.2. Substrate Scope Studies

Studies into the functional group tolerance and the substrate scope of the dichlorination of diazo compounds using PhICl₂/Py were investigated by applying the standard dichlorination conditions to various compounds that were analogous to our model system, **2.15a**. The successful

Table 2-3. Dichlorination of Aryldiazoacetate Derivatives[a]

product	Z	R	time (min)	yield (%)[b]
2.16a	H	Me	10	90
2.16b	H	i-Pr	10	88
2.16c	H	Bn	10	95
2.16d	H	$3,4$-$(OCH_3)_2C_6H_3$	15	96
2.16e	H	allyl	10	89
2.16f	NHAc	Me	5	78
2.16g	OMe	Me	20	79
2.16h	OTs	Me	120	89
2.16i	Br	Me	10	87
2.16j	NO_2	Me	50	45

[a]General conditions: **2.15** (50 mg, 1.0 equiv), pyridine (5 mol%) in DCM (1.4 mL), at rt.[b]Isolated yields after column chromatography.

dichlorination of various aryldiazoesters (**2.15b–j**) demonstrated that a variety of functional groups tolerate the reaction conditions (Table 2-3). These diazo compounds were subjected to the standard dichlorination conditions and were allowed to stir until analysis via TLC indicated complete consumption of the diazo compound. At this point, the reaction mixtures ceased gas evolution and remained a constant colour and were considered complete. Various ester substituents were well-tolerated as diazo groups conjugated to carbomethoxy-, carboisopropoxy-, and carbobenzyloxy groups (**2.15a–e**) were dichlorinated in excellent yields (**2.16a–c**, 90%, 88%, and 95%, respectively). When chlorinating **2.15d–e**, the dichlorination of the ylidic carbon occurred chemoselectively over the chlorination of an electron rich aromatic ring or an allyl group, furnishing high amounts of dichlorides **2.16d–e** (96% and 89% yield, respectively). Substitutions at the 4-position of the benzene ring of **2.15** with acetamido-, methoxy-, tosylate-, bromo-, or nitro groups were also investigated (entries **2.16f–j**). Dichlorination of these compounds proceeded

smoothly and provided the respective dichlorides in good to excellent yields (>75%), with the exception of methyl (4-nitrophenyl)diazoacetate (**2.15j**), which only provided 45% yield of **2.16j** due to the formation of approximately equal amounts of an isomeric dichloride (see §2.2.3 for discussion).

This work led to the investigation of the dichlorination of other diazo compounds in which the diazo group was stabilized by a carbonyl- or aryl groups (Table 2-4). These diazo compounds are relatively non-explosive and the stability conferred by these groups allows for these compounds to be isolated and stored for short-to-long periods of time. In a preliminary study, another member of the Murphy group (L. Vanderzwet) found that subjecting diazo esters containing a methine or a methylene group adjacent to the diazo carbon (e.g., **2.20**, R^1 = alkyl or phenyl, R^2 = Me) to the standard dichlorination conditions generated a complex mixture of products. Chloroalkene **2.21** (eq 2.7) was identified from this mixture, and it was presumed to be formed via elimination pathways. As a result, similar diazo esters and diazoalkanes were not investigated.

$$\text{(2.7)}$$
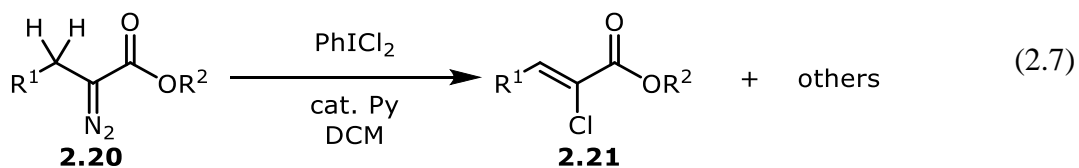
When treated with $PhICl_2$/Py, benzyl diazoacetate (**2.22**, R^1 = H, R^2 = CO_2Bn) and diphenyldiazomethane (**2.22**, $R^1 = R^2 = Ph$) were dichlorinated in 71% and 70% yield, respectively. Other members of the Murphy group found 2-diazo-1,3-dicarbonyl compounds[103] and 3-diazo-2-oxindoles could be dichlorinated as well.[104] These examples demonstrate the robustness of the standard dichlorinations, and it appears that compounds without C–H bonds adjacent to the diazo group undergo dichlorination without difficulty. The formation of dichlorides **2.25** and **2.27**

demonstrates that the diazo group does not need to be at the benzylic position to undergo dichlorination. Similarly, the successful dichlorination of diphenyldiazomethane illustrates that the presence of a carbonyl conjugated to the diazo group is not essential for the reaction to occur.

Table 2-4. Summary of Successfully Dichlorinated Diazo compounds using PhICl$_2$/Py^a
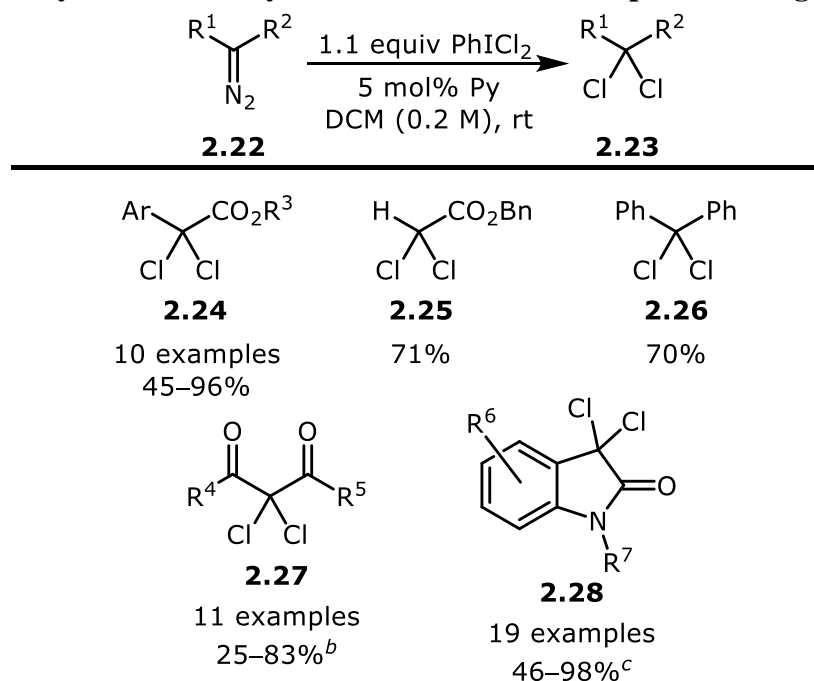
^{a}Reaction used 1.0 equiv PhICl$_2$. ^{b}See Coffey and Murphy.[103] ^{c}Reactions were performed at refluxing temperatures, see Murphy et al.[104]

2.2.3. Side Product Analysis

As mentioned in §2.2.1, the reaction of methyl phenyldiazoacetate (**2.15a**) generated monochlorinated (**2.17a**) and oxygenated (**2.18a**) side products. The observation of **2.17a** was interesting because the source of the hydrogen of the chloromethylene group was not obvious. An investigation was performed to probe the source of this hydrogen. In separate control reactions, replacing pyridine with pyridine-d_5, CH$_2$Cl$_2$ with CD$_2$Cl$_2$, or PhICl$_2$ with PhICl$_2$-d_5 found no deuterium incorporation into **2.17a**. Water was investigated as a potential source of the hydrogen by performing various reactions in the presence of added H$_2$O or D$_2$O. As discussed in the previous section, the standard reaction conditions provided **2.17a** in trace amounts (~2% yield). Therefore,

in order see a larger effect in the probing reactions, higher loadings of the Lewis base were used to increase the amount of **2.17a** (or **2.17a-***d*) generated. In these reactions (Table 2-5), the ratios of **2.16a**, **2.17a**, and **2.18a** were obtained via ^{1}H NMR spectroscopy using the methyl signal of the respective compounds. Initial reactions were performed by adding water to a miscible solvent, MeCN. However, no **2.17a** was observed using a vast excess of H_2O or D_2O (18.5 equiv) when performing dichlorinations with 50 mol% pyridine in MeCN (entries 1 and 2). When DCM was used as the reaction solvent, dichlorinations using 2.5 equiv of 2,6-lutidine, in absence of added water, unexpectedly generated slightly more **2.17a** than reactions in which 5 equivalents of D_2O were allowed to mix with the diazo compound and solvent before the addition of 2,6-lutidine and PhICl$_2$ (entry 3 vs 4). No significant differences were observed when using freshly distilled 2,6-lutidine (entry 5–6). Conditions shown in Table 2-5, entries 4 and 6, provided **2.17a** with approximately 20% deuterium incorporation. These results suggest that water can be a source of the hydrogen, but it may not be the main source.

Table 2-5. Probing the Effect of Water Upon the Dichlorination of Methyl Phenyldiazoacetate
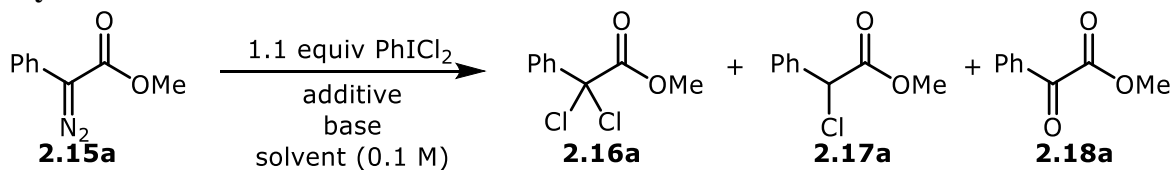
entry	solvent	base (equiv)	additive (equiv)	ratio (2.16a:2.17a:2.18a)[a]
1	MeCN	Pyridine (0.5)	H_2O (18.5)	63:trace:37
2	MeCN	Pyridine (0.5)	D_2O (18.5)	63:trace:37
3	DCM	2,6-lutidine (2.5)	None	84:13:3
4	DCM	2,6-lutidine (2.5)	D_2O (5)	82:8[b]:10
5	DCM	2,6-lutidine[c] (2.5)	None	85:13:2
6	DCM	2,6-lutidine[c] (2.5)	D_2O (5)	82:10[d]:8

[a]General conditions: **2.15a** (50 mg), solvent (1.4 mL), base and additive, at rt. Ratios determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures.[b]22% deuterium incorporation.[c]Freshly distilled.[d]20% deuterium incorporation.

The reaction of **2.15a** with PhICl$_2$ to provide **2.17a** bears resemblance to a reaction Varvoglis et al. reported when treating aryldiazoethanes with PIFA. Similar to our study, they found these diazo compounds (e.g., **2.29**-*d₃*) reacted and provided a product with a hydrogen introduced at the, formerly ylidic carbon (Scheme 2-4).[105] The results of their probing reactions also suggested that the source of the hydrogen was unlikely to be from either water or from the solvent. During this study, they investigated the possibility that the hydrogen originated from the aryldiazoethane by determining the amount of deuterium incorporation at the benzylic position of the product (**2.30**-*d₄*) arising from the reaction of deuterium-enriched diazo compound **2.29**-*d₃* with PIFA. When they subjected **2.30**-*d₄* to mass spectrometric analysis, examination of the isotopic distribution pattern of fragment ion **2.31** revealed ~33% deuterium incorporation. This observation led the authors to suggest that an intermolecular reaction between an adduct formed from PIFA and **2.29**-*d₃* with another molecule of **2.29**-*d₃* led to the formation of **2.30**-*d₄*.

Scheme 2-4. Isotopic Labeling Experiment Performed by Varvoglis et al.
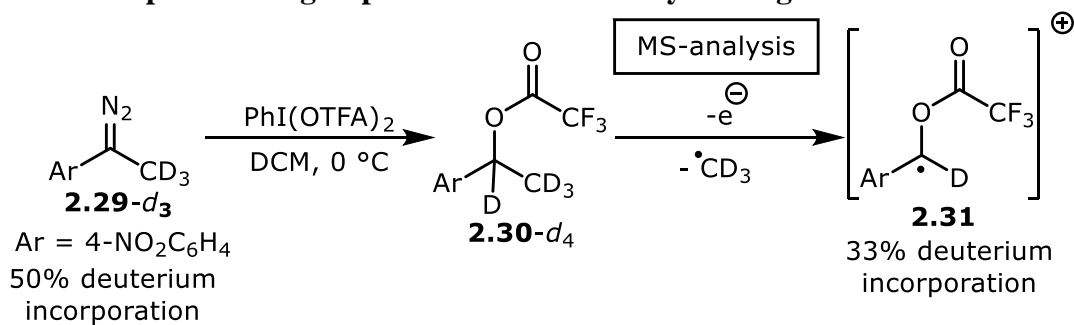
An analogous mechanism may not be operative in the reactions where we observed **2.17a** because **2.15a** does not have a methyl group adjacent to the diazo group. However, this leads us to question the possibility of hydrogen-transfer from **2.15a** as a potential pathway to **2.17a**. In the investigative reactions probing the dichlorination of **2.15a** with PhICl$_2$/Py, the only C–H bonds that have not been replaced with C–D bonds are the ones belonging to the methyl and the phenyl

groups of **2.15a**. However, as described in §2.2.1, the formation of the **2.17a** could be mostly avoided through the use of small, catalytic loadings of a Lewis base. Therefore, the selectivity of **2.16a** versus **2.17a**, and the origin of **2.17a** became insignificant and research priority was given to investigating other aspects of the dichlorination chemistry.

Another interesting side product was observed during the *gem*-dichlorination of **2.15j**. When this diazo compound was subjected to the standard dichlorination conditions, analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed a 2:1 mixture of **2.16j** and a constitutional isomer in which chlorination occurred on the aromatic ring (**2.16j'**, eq 2.8). These two isomers were initially recovered as an inseparable mixture after FCC using mixtures of EtOAc/hexanes as the mobile phase. Interestingly, despite the inability to resolve the isomers, they were obtained in a 1:1 ratio after FCC. These isomers were later partially separated via FCC using benzene as the mobile phase.

2:1 ratio (crude)
1:1 ratio (after column chromatography)
89% combined yield
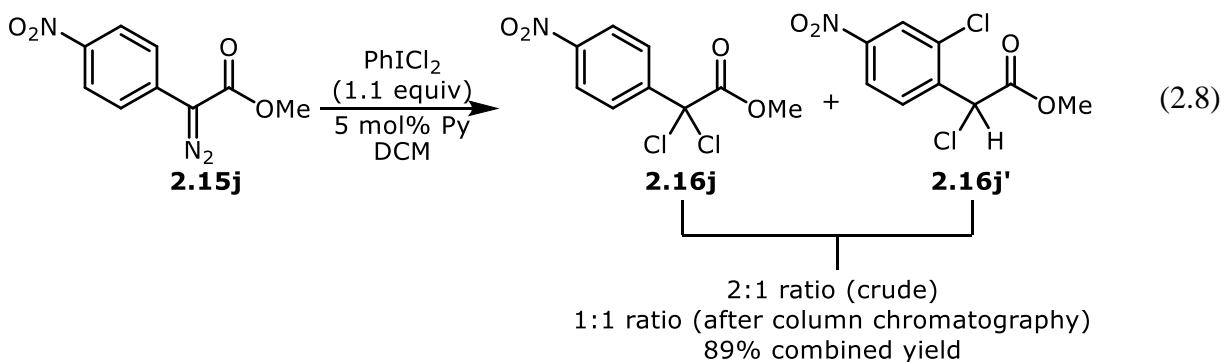
The change in the isomeric ratio before and after FCC can be due to the decomposition of **2.16j** or the chromatographic separation of **2.16j** and **2.16j'**. These options were deemed unlikely due to the high yield of the combined mixture of the dichlorides (89%) and the difficulty related to the separation of the isomers using FCC. Instead, it was initially believed that, in the presence of silica gel, **2.16j** isomerized into **2.16j'** during chromatography. However, subjecting pure **2.16j** to the same chromatography conditions led to its recovery, unchanged. This observation led to

suspicion that **2.16j**, and possibly **2.16j'**, were reactive towards silica gel when present in the crude reaction mixtures in which they were formed. This led to an investigation to determine if the ratio between **2:16j** and **2.16j'**, observed in the crude reactions mixtures, could be affected by adding silica gel to reaction mixtures in which **2.15j** was reacting with $PhICl_2$/Py. This study revealed the presence of silica gel, and the time of its addition, had a significant effect on the outcome of the dichlorination of **2.15j**. For example, adding 150 mg of silica gel to a reaction mixture in which **2.16j** had been reacting with $PhICl_2$ under the standard dichlorination conditions for 45 minutes led to the observation of a 1:2 mol ratio of **2.16j**:**2.16j'** in the ^{1}H NMR spectrum of the crude reaction mixture. If silica gel was added five minutes after the addition of $PhICl_2$, **2.16j** was the major product and no detectable amount of **2.16j'** was observed in the ^{1}H NMR spectrum of the crude material. After small modifications to the reaction conditions, it was found that using DMAP as the activator and adding silica gel 5 minutes after the addition of $PhICl_2$ allowed for the isolation of **2.16j** in 67% yield (eq 2.9).

$$(2.9)$$
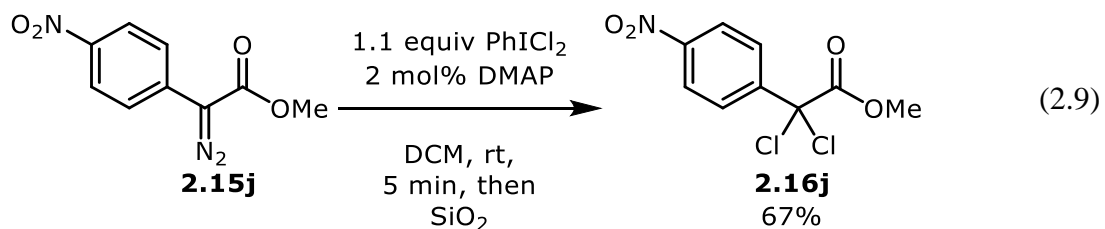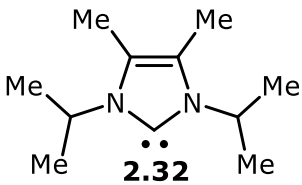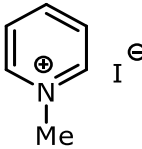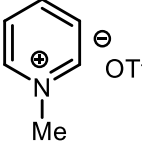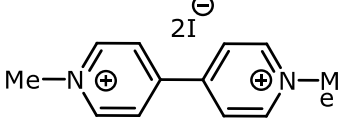
This was the only example of chlorination of the benzene ring in the study of the *gem-*dichlorination of aryldiazoesters. Later, another member of the Murphy group (I. Wang) dichlorinated (4-nitrophenyl)diazoacetamides and did not observe any chlorination of the aromatic ring, indicating that this type of reactivity may be specific to diazoacetates. Further investigations into this reactivity were not performed.

2.2.4. Other Activators of PhICl$_2$

With the observation that Lewis basic pyridine bases played a critical role in the dichlorination of **2.15a**, other Lewis basic additives were screened as potential catalysts. The goal of this study was to identify other possible methods of activating PhICl$_2$ towards the dichlorination of diazo compounds. First, under the standard reaction conditions, replacing pyridine with other nitrogenous bases such as trimethylamine, diisopropylethylamine, DBU, or 2,2,6,6,-tetramethylpiperidine caused decomposition of PhICl$_2$, but not **2.15a**. Using a catalytic amount of imidazole allowed for partial decomposition of **2.15a**, with limited amount of dichlorination occurring. From the above examples it appeared that nitrogenous bases which contained either a N$_{sp^3}$–H bond or an amine capable of being oxidized to an iminium were unable to efficiently activate PhICl$_2$ towards the dichlorination of **2.15a**. Bearing these two points in mind, other reagents used in nucleophilic catalysis/organocatalysis were screened as potential activators. This study identified various additives that, when used in catalytic amounts, promoted dichlorination in yields comparable to the pyridine-based compounds discussed previously (Table 2-6, entries 1–4, 84–90%). We found 1,4-diazabicyclo[2.2.2]octane (DABCO, entry 5), NHC **2.32** (entry 6), and TBAI (entry 7) provided rapid reaction. Interestingly, 5 mol% *N*-methylpyridinium iodide (entry 8) was found to provide the highest yield/selectivity of **2.16a**. A negative control was performed, using *N*-methylpyridinium triflate, proved the iodide participated in the dichlorination reaction (entry 9). Use of *N,N'*-dimethylviologen diiodide provided a very slow reaction, despite possessing twice as much iodide per equivalent of molecule. We rationalized its low solubility in the reaction solvent lowered its availability to activate PhICl$_2$. Finally, Lewis acids were investig-

Table 2-6. Comparing Various Additives[a]
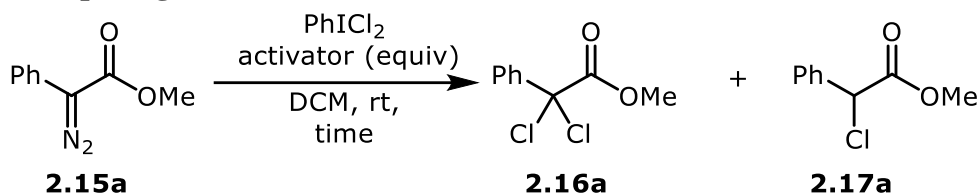
entry	activator	equiv (mol%)	time (min)	yield 2.16a (%)	ratio (2.16a:2.17a)
1	2,6-lutidine	5	45	79	98:2
2	pyridine	5	10	90	97:3
3	pyridine	1	50	87	98:2
4	DMAP	1	12	86	98:2
5	DABCO	1	4	84	99:1
6	2.32	1	6	89	>99:1
7	TBAI	5	3	84	95:5
8		5	6	90	99:1
9		5	7 h	ND[b]	ND
10		5	5 h	85	94:6
11	AlCl$_3$	5	80	72	88:12
12	BF$_3$•OEt$_2$	1	50	ND[c]	ND

[a]General conditions: **2.15a** (50 mg), DCM (1.4 mL), and activator, and PhICl$_2$ (1.1 equiv) at rt. Isolated yields after column chromatography are shown.[b]Not determined; the reaction was incomplete.[c] Not determined, ^{1}H NMR analysis of the crude reaction mixture revealed an intractable mixture.

ated, and we found the use of 5 mol% of AlCl$_3$ was able to provide **2.16a** (entry 11), albeit in a yield lower (72%) than most other additives. The use of 1 mol% BF$_3$•OEt$_2$ as an activator led to the formation of an intractable mixture of products.

2.2.5. Mechanistic Discussion

The experimental data discussed in §2.2.1–§2.2.4 were taken into consideration when attempting to provide a mechanistic route for the dichlorination of the diazo compounds shown in Table 2-4. The possibility of radical intermediates was briefly investigated by attempting to affect the chlorination of **2.15a** through the addition of a radical inhibitor, BHT, to the standard dichlorination conditions. However, no effect with regards to the yield of **2.16a** or the ratio between **2.16a**:**2.17a** was observed when using up to 1.0 equiv of BHT, suggesting that radical intermediates are not involved. A possible ionic mechanism for the dichlorination reaction is shown in Scheme 2-5. First, exchange of a chloride ligand with pyridine generates a more reactive iodane (**2.19**). The diazo compound can then displace the pyridinium of **2.19**, generating iodane

Scheme 2-5. Possible Mechanism for the Dichlorination Diazo Compounds Using PhICl$_2$
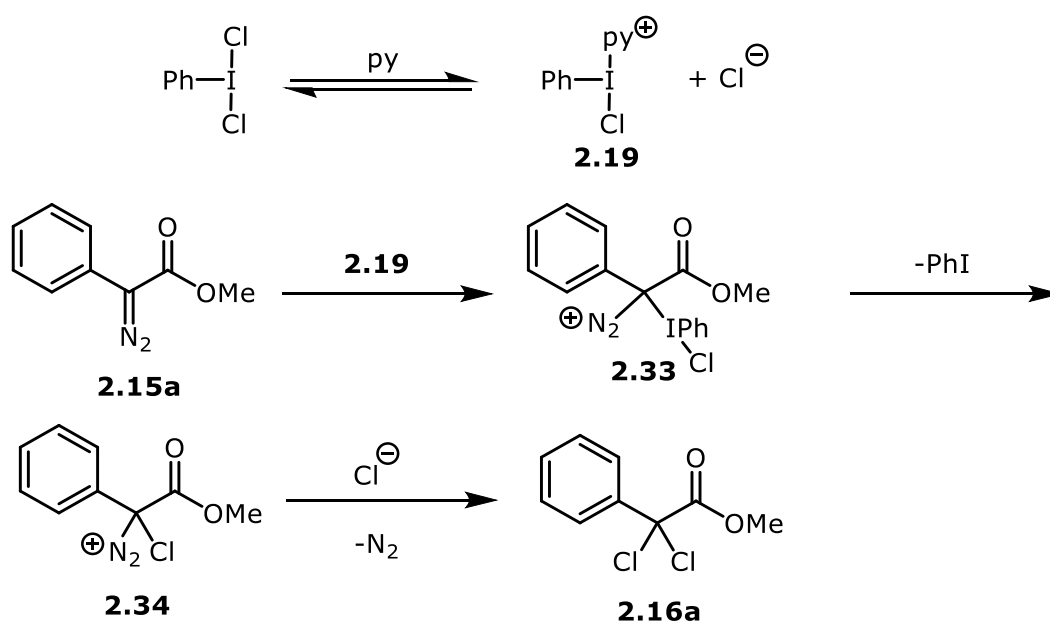
2.33. Chlorine atom transfer via ligand coupling with the concomitant reductive elimination of iodobenzene results in the first chlorination, while the second chlorination would accompany the expulsion of dinitrogen.

Mechanisms involving the direct chlorination of the ylidic carbon of the diazo compounds via $PhICl_2 \cdot Py$ or the generation of carbene intermediates have not been ruled out. Regardless, the mechanism shown above was used as the working hypothesis to investigate other reactions of (dihaloiodo)arenes that led to reactions altering the carboskeleton of diazo compounds.

2.3. Tandem Halogenation/Semi-pinacol Rearrangements

The desire to forge C–C bonds using the reaction between diazo compounds and a (dihaloiodo)arene led to the investigation of β-hydroxy-α-diazoesters (**2.35**) as potential substrates. We sought to interrupt the geminal double ligand transfer (discussed in the previous section) using a semi-pinacol rearrangement (Scheme 2-6). It was rationalized that the reaction of **2.35** and (dihaloiodo)arenes could generate an intermediate (**2.36**) in which leaving group ability of either N_2 or ArI would be sufficient to allow for the rearrangement to occur.

Scheme 2-6. Hypothetical Mechanistic Pathway for Halogenation/Semi-pinacol Rearrangement

LG= N_2, ArIX
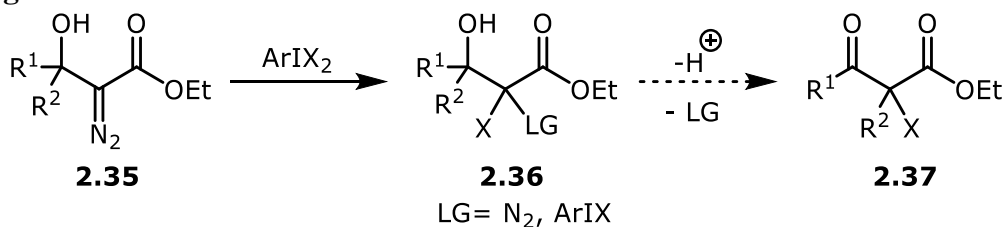
In the desired reaction, $ArIX_2$ would act as an electrophilic halogenating agent. Common electrophilic halogenation reagents used in organic chemistry include N–X (X = F, Cl, Br, I) reagents such as *N*-haloimides. Zhu et al. have recently demonstrated the ability of *N*-chloro- and

N-bromo- hydantoins (**2.38**, X = Cl or Br) and *N*-iodosuccinimide (NIS) to react with **2.35** to

provide tandem halogenation/semi-pinacol rearrangements (Scheme 2-7).[106]

Scheme 2-7. Halogenation/Semi-pinacol Reactions Using N-X reagents
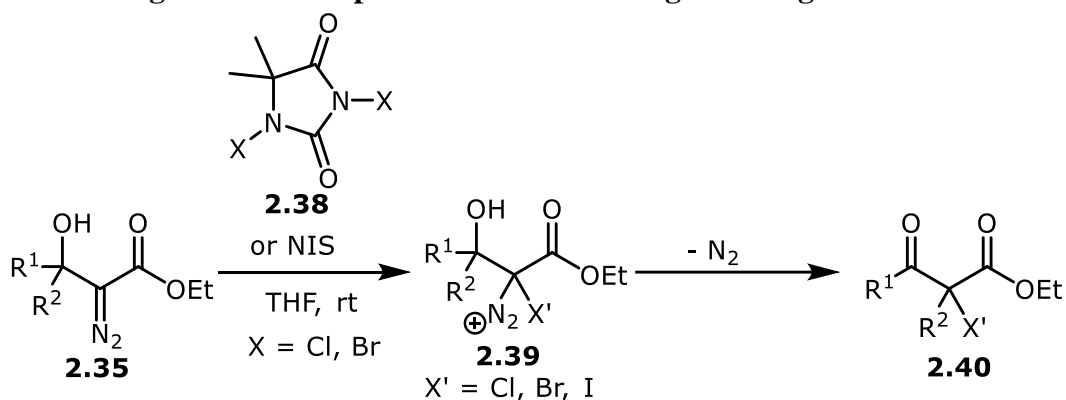
Our study utilized a two-step procedure to synthesize the necessary diazo compounds.

First, glycine ethyl ester was subjected to diazotization conditions to yield ethyl diazoacetate (**2.42**,

eq 2.10). Subsequent addition of **2.42** into various ketones (**2.43**) furnished the β-hydroxy-α-diazo

esters (**2.35**, eq 2.11).

(2.10)

(2.11)
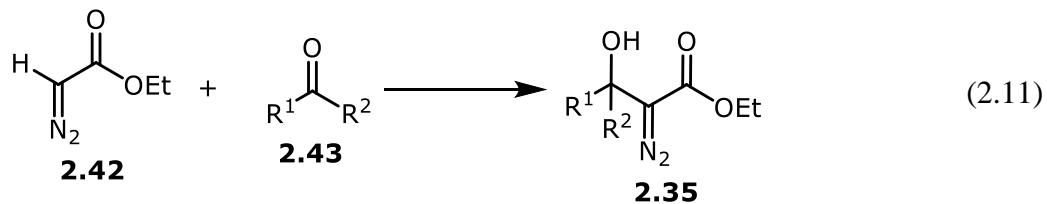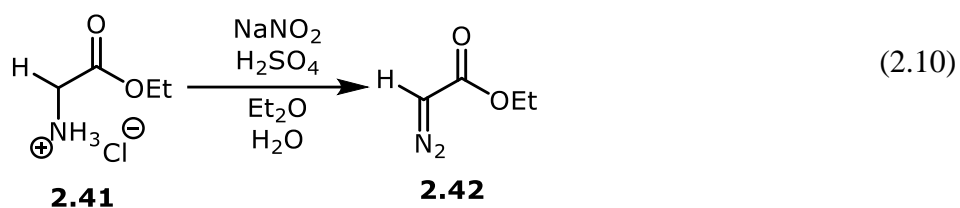
2.3.1. Chlorination/Semi-pinacol Rearrangement

In un-optimized conditions, subjecting β-hydroxy-α-diazoester **2.44** to a mixture of PhICl$_2$/2,6-lutidine in acetonitrile afforded the desired product (**2.45**) in 42% NMR yield (eq 2.12). This product was confirmed by a comparison with the ^{1}H NMR spectral data reported in the literature.[106] β-hydroxy-α-diazoester **2.46** reacted under similar conditions to provide a tandem chlorination/semi-pinacol rearrangement, featuring a ring expansion, furnishing ketone hydrate **2.47**, after FCC, in 73% yield (eq 2.13).

$$(2.12)$$

$$(2.13)$$
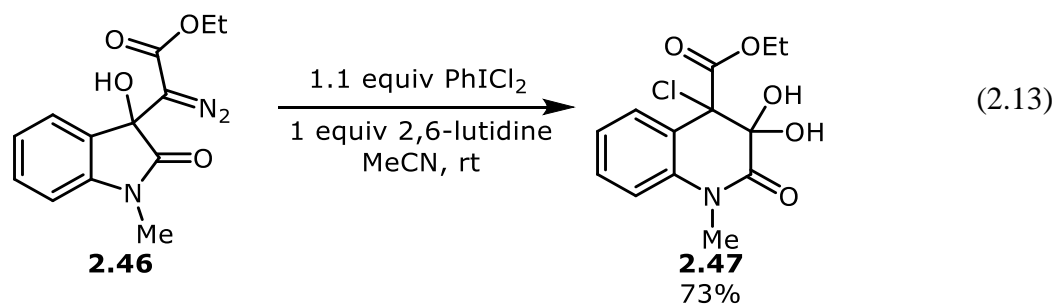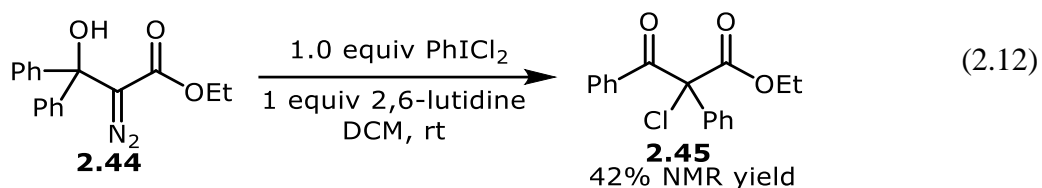
These reactions are interesting for two reasons: first, they demonstrate that it is possible for intramolecular processes to interrupt the dichlorination process and, second, these transformations place two different groups onto the formerly ylidic carbon, one of which is a carbon-based group. This creates a new stereocenter and future research using chiral hypervalent iodine reagents may allow for an asymmetric reaction.

2.3.2. Fluorination/Semi-pinacol Rearrangement

The chlorination of **2.44** using PhICl$_2$ demonstrated that halogenation/semipinacol reactions of these diazo compounds can be effected by a (dihaloiodo)arene. We desired to use

TolIF$_2$ to perform the analogous fluorination/semipinacol rearrangement using β-hydroxy-α-diazoesters (e.g., **2.35**) to provide **2.48** (eq 2.14). Tuning TolIF$_2$ to react with **2.35** and provide products of halogenation/rearrangement was expected to be more difficult than the analogous reactions using PhICl$_2$. This is because typical conditions for the fluorination of diazo compounds using TolIF$_2$ requires the use of elevated temperatures (70–110 °C) and the use of Lewis acids which would likely decompose the diazo compound. Therefore, this study was undertaken with the mindset that it would lead to the discovery of a new method of activating TolIF$_2$ towards fluorination chemistry.

(2.14)
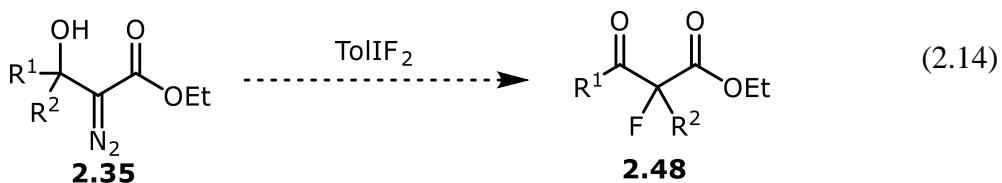
To expedite the screening process, β-hydroxy-α-diazoester **2.44** was used as the model substrate and the ^{19}F NMR spectroscopic signal of the desired product (**2.50**) was obtained by analyzing an authentic sample synthesized via a two-step process: acid-promoted semi-pinacol rearrangement followed by electrophilic fluorination, using TolIF$_2$,[107] of the resulting β-ketoester **2.49** (Scheme 2-8).

Scheme 2-8. Two-Step Synthesis of Ethyl 2-Fluoro-3-oxo-2,3-diphenylpropanoate
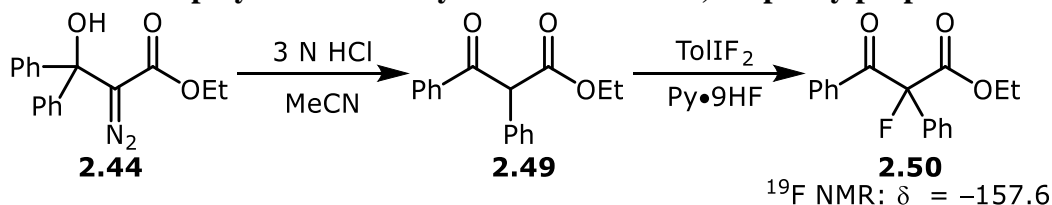
Unsurprisingly, Lewis-acidic conditions used in the fluorination of other diazo compounds only formed traces of **2.50** (eq 2.15). Heating a mixture of **2.44** and TolIF$_2$ in refluxing toluene

$$\textbf{2.44} \xrightarrow[\substack{[M] \\ \text{DCE, reflux} \\ [M]= \text{BF}_3\text{·Et}_2\text{O, FeF}_3, \\ \text{TiF}_4, \text{TiF}_3, \text{etc.}}]{\text{TolIF}_2}$$

2.50
trace

(2.15)
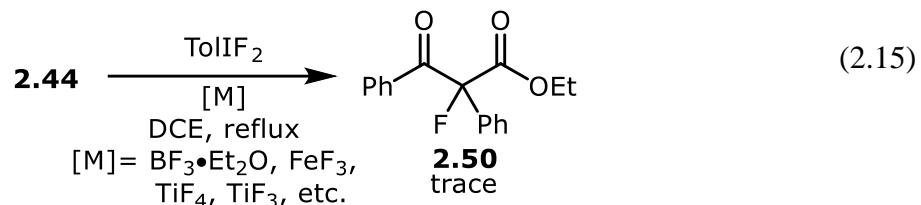
or 1,3,5-mesitylene led to the formation of significant amounts of either benzaldehyde or 3,5-dimethylbenzaldehyde as detected in the ^{1}H NMR spectra of the respective crude reaction mixtures (eq 2.16). While benzylic oxidation reactions have been reported with other HVI reagents such as IBX[108,109] and iodoxybenzene,[110] to our knowledge, this type of reaction has not been reported using TolIF$_2$. Simply heating TolIF$_2$ in refluxing toluene does not generate benzaldehyde, suggesting the participation of the diazo compound is required to allow for the oxidation to occur. This type of reactivity was not investigated further.

$$\textbf{2.44} \xrightarrow[\substack{\text{toluene or} \\ 1,3,5\text{-mesitylene} \\ \text{reflux}}]{\text{TolIF}_2}$$

2.51   **2.52**

(2.16)
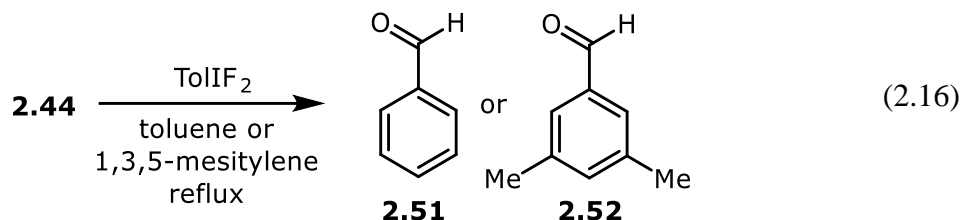
Eventually, we found rhodium carboxylate complexes were able to furnish the desired fluorination/semipinacol rearrangement product even at room temperature. In un-optimized conditions, both dirhodium tetraacetate and dirhodium tetrakis(2,4-dichlorobenzoate), when used in catalytic amounts, granted **2.50** in 27% and 52% yield, respectively.

(2.17)

2.44

2.50
L = OAc, 27%
L = 2,4-Cl$_2$C$_6$H$_3$CO$_2$, 52%
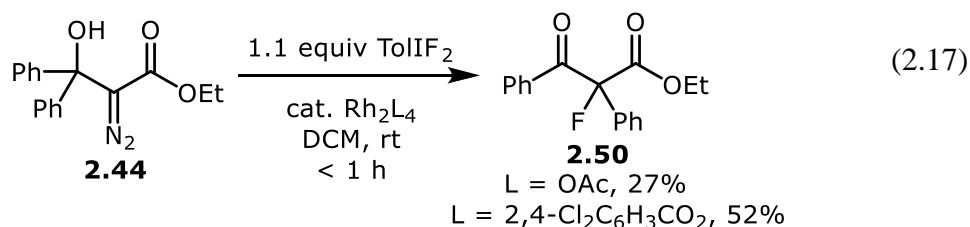
The mechanistic rationale for this transformation is shown in Scheme 2-9. This hypothesis involves a rhodium carbenoid (**2.53**) undergoing electrophilic trapping of a fluoride ligand from

TolIF$_2$, which oxidizes the rhodium complex (**2.53** to **2.54**). Subsequent semi-pinacol rearrangement would allow for the reductive elimination and regeneration of Rh$_2$L$_4$, furnishing the desired product (**2.48**).

Scheme 2-9. Initial Mechanistic Rationale for the Fluorination/Semi-pinacol Rearrangement
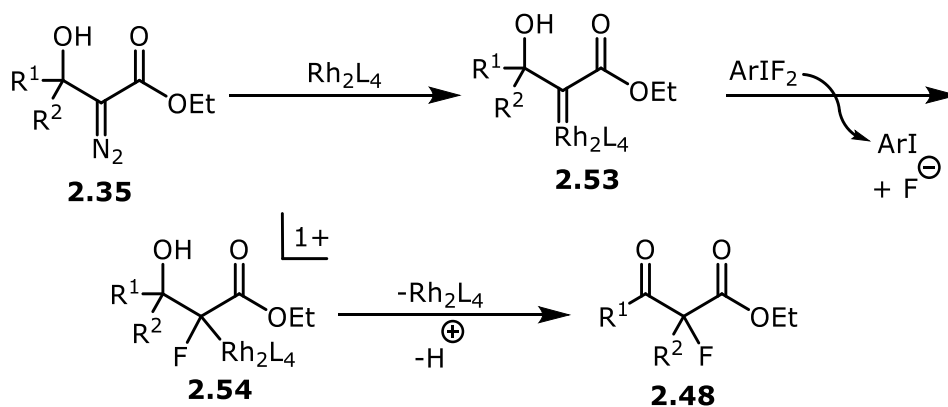
It is also possible that the reaction may occur through a one-pot, tandem version of Scheme 2-8, with rhodium taking the place of HCl in the semi-pinacol rearrangement that furnishes β-ketoester **2.49** and, subsequently, electrophilic fluorination using TolIF$_2$ provides **2.48**. However, this pathway was found to be unlikely as a control reaction revealed, in the absence of TolIF$_2$, the dirhodium tetraacetate catalyzed semi-pinacol rearrangement of **2.44** is much slower than the overall reaction of eq 2.17, which is consistent to what has been reported in the literature.[111] This observation led us to believe that TolIF$_2$ had an effect on the phenyl-migration. Additional experiments showed little reaction between TolIF$_2$ and **2.44** in the absence of any additives. This led to the suspicion that the decomposition of **2.44** is initiated via a reaction between an adduct arising from the reaction of Rh$_2$(OAc)$_4$ and TolIF$_2$, as opposed to Rh$_2$(OAc)$_4$ by itself. This inspired the investigation of a potential reaction between Rh$_2$(OAc)$_4$ and TolIF$_2$ which would promote the fluorination/pinacol rearrangement reaction. An experiment performed by treating a suspension of Rh$_2$(OAc)$_4$ in DCM with TolIF$_2$ converted the solid from green to brown. This new

material showed little-to-no solubility in most common organic solvents, even at elevated temperatures. The insolubility of this adduct prevented the acquisition of structural information. Regardless of its identity, this adduct was qualitatively investigated as a potential catalyst in the decomposition of **2.44**. This study found that, even at room temperature, the addition of $Rh_2(OAc)_4 \cdot TolIF_2$ to a solution **2.44** in DCM induced rapid decomposition of the diazo compound. After consumption of **2.44**, the reaction mixture took on a more greenish hue, similar to the colour when $Rh_2(OAc)_4$ is dissolved in DCM. In another qualitative experiment, a solution of **2.44** in DCM was added dropwise, over the course of 1 h, to a mixture of $TolIF_2$ and $Rh_2(OAc)_4$ in DCM. At the beginning of the addition, each drop of the solution containing **2.44** caused the solution localized near the surface to briefly turn green before returning to a brownish colour until the next drop entered solution. However, as the reaction progressed the solution remained brown in colour even when more drops of the solution containing **2.44** was added. Dissolution of $Rh_2(OAc)_4$ in non-Lewis basic solvents without any Lewis basic additives are often green in colour. This qualitative observation suggests that reaction of **2.44** and the adduct between $TolIF_2$ and $Rh_2(OAc)_4$ regenerates $Rh_2(OAc)_4$. Investigations into the mode of activation of dimeric rhodium complexes using $TolIF_2$ were not performed.

While the reaction of $Rh_2(OAc)_4$ and $TolIF_2$ has not been reported, it is worth mentioning that examples of *gem*-difunctionalization reactions involving diazo compounds, HVI reagents, and rhodium- or copper catalysts have been recently reported. Szabó et al. have reported the oxyfluorination or oxytrifluoromethylation of diazo compounds using catalytic amounts of $Rh_2(OAc)_4$ and either a fluorobenziodoxole (e.g., eq 2.18) or Togni's reagent, respectively.[112]

$$(2.18)$$
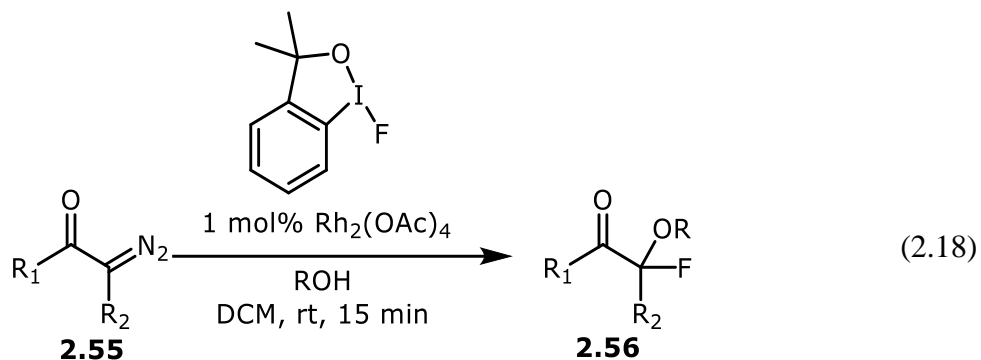
Additionally, Waser reported that copper-catalyzed decomposition of various diazo compounds allowed oxy-alkynylation reactions when using TIPS-EBX.[113] The authors reported that attempts to use $Rh_2(OAc)_4$ to catalyze this reaction failed. In the reactions of eqs 2.18 and 2.19, the authors' proposed mechanisms for their reactions in which the participation of the HVI reagent occurs after the metallocarbene is generated.

$$(2.19)$$
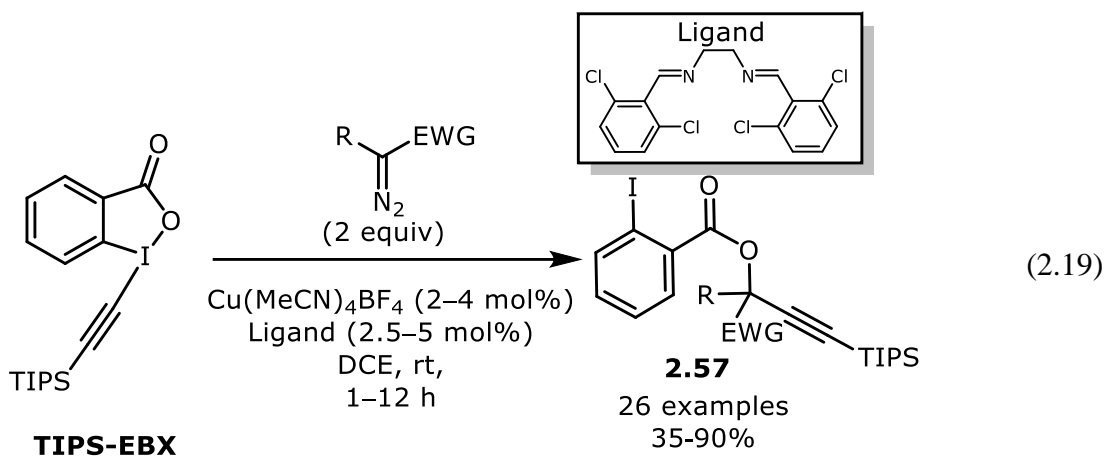
Therefore, the activation of rhodium carboxylates using a hypervalent iodine reagent, such as $TolIF_2$, may be a novel interaction and future investigations into this chemistry may lead to interesting synthetic applications.

2.4. Geminal Difluorination

The geminal difluorination of diazo compounds was developed by other members of the Murphy group (i.e., G. Murphy and R. Tran) at approximately the same time as the chlorination

reactions described in §2.2 and §2.3. When compared to the *gem*-dichlorination reactions using

PhICl$_2$, they found optimized reaction conditions allowing for the *gem*-difluorination using TolIF$_2$

required stronger activation of the iodane and higher reaction temperatures. Attempting Lewis

basic activation of TolIF$_2$ using pyridine-type bases proved futile in providing difluorination. Thus,

early reactions used a Lewis acid (i.e., 1 mol% BF$_3$•Et$_2$O) to activate TolIF$_2$ and provided *gem*-

difluorination reactions of aryldiazoesters **2.15**, furnishing the desired *gem*-difluorinated products

in 17–79% yield (eq 2.20). These conditions are much harsher than the standard *gem*-

dichlorination conditions (Table 2-2, entry 6) and, when examining the same phenyldiazoacetate

derivatives (**2.15**), the *gem*-difluorination reactions typically proceeded in lower yields. Lower

functional group tolerance was also observed as aryldiazoesters bearing an aryl ether, an

acetamido-, or an allyl group furnished little to no difluorinated product.
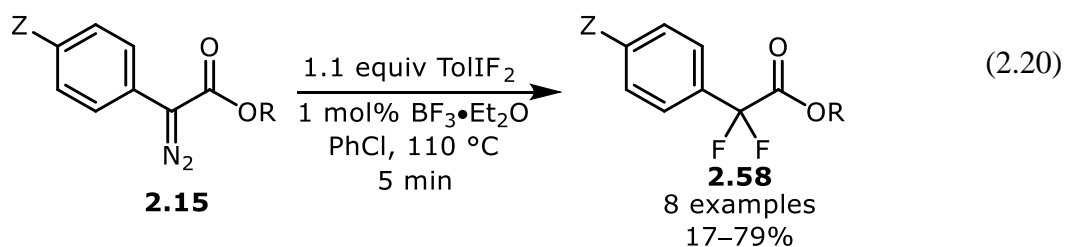
Eventually, G. Sinclair and R. Tran found that withholding BF$_3$•Et$_2$O from the reaction

mixture (i.e., simply heating the aryldiazoacetate and TolIF$_2$ solution in a glass vessel) allowed for

the respective *gem*-difluorides (**2.58**) to be obtained in higher yields. Heating the reagent mixture

in reaction vessels composed of PFA or silanized glass provided little-to-no reaction unless

borosilicate glass was added. It was hypothesized that the borosilicate present in standard

laboratory glassware was acting as a Lewis acid to activate TolIF$_2$, similar to the reaction of glass

with another hypervalent polyfluoride reagent, XeF$_2$.[114–116] Applying the borosilicate glass-

activation of TolIF$_2$ to the *gem*-difluorination of aryldiazoacetates found that the reproducibility of

this reaction was dependent on the purity of TolIF$_2$. During the investigation of the tandem fluorination/semi-pinacol reaction (§2.3.2), the experimental protocol for the synthesis of TolIF$_2$ was optimized to reproducibly afford the reagent in high purity. This material was obtained as white needles, typically with a 1–2 °C melting point range that occurred between 98–102 °C. In contrast, the batches of TolIF$_2$ that were used in original difluorination study, consisted of white-yellow material with a melting point of 88–90 °C, indicating possible impurities. In both of these batches, the ^{1}H and ^{13}C NMR spectra do not show observable impurities. However, when using borosilicate glass to activate TolIF$_2$, the discoloured material provided inconsistent reactions with various aryldiazoesters. For example, the reactions might occur rapidly within 10 minutes after mixing all the reagents together at the reaction temperature, or the reaction mixture would show no visible signs of reaction for approximately 3 hours and then, seemingly, spontaneous rapid gas evolution would be observed. The synthesis of TolIF$_2$ may be challenging considering other research groups have recently reported the synthesis of TolIF$_2$ and obtained the reagent as an off-white or yellow solid.[117,118]

Other members of the group (G. Sinclair and R. Tran) found that performing the difluorination of aryldiazoesters in borosilicate vials using high-purity TolIF$_2$ led to the respective difluorinated products to be obtained in reproducible reaction times and yields (eq 2.21). These conditions proved to be higher yielding and had higher tolerance to functionalities such as alkenes and aryl ethers than when BF$_3$•Et$_2$O was used as a Lewis acid (cf. eqs 2.20 and 2.21).[119]

$$(2.21)$$
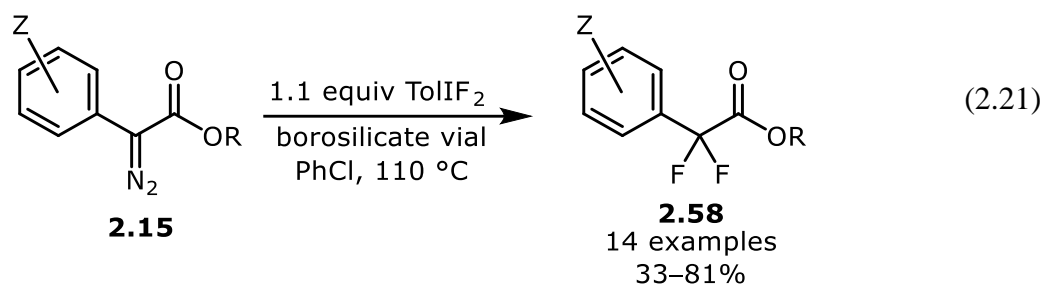
A three-step synthetic pathway for the reproducible synthesis high-quality $TolIF_2$ was developed (Scheme 2-10) based on modifications of literature protocols for the syntheses of $TolICl_2$,[48] $TolIO$,[120] and $TolIF_2$.[120] The synthesis starts with the chlorination of TolI using a mixture of bleach and concentrated HCl, followed by hydrolysis to provide *p*-iodosotoluene (TolIO). This polymeric material is then suspended in $CHCl_3$ and treated with concd HF to afford $TolIF_2$.

Scheme 2-10. Synthesis of *p*-Iodotoluene Difluoride from *p*-Iodotoluene
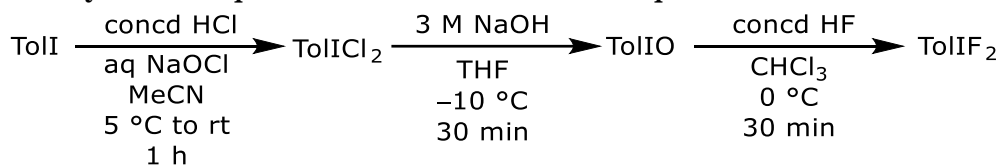
Proceeding through $TolICl_2$ as a synthetic intermediate provides a synthetic pathway with features advantages such as: fast reaction times, inexpensive/readily available reagents, and because all reactions are conducted using aqueous media, strict drying of the synthetic intermediates is not required. The entire synthetic route can be completed well-within one working day, allowing for isolation of $TolIF_2$ within 5 hours. Another pathway, which proceeds through the intermediacy of $TolI(OAc)_2$ (instead of $TolICl_2$) was considered. However, the oxidation of TolI to $TolI(OAc_2)_2$ using a solution of peracetic acid, generated from the mixture of Ac_2O and H_2O_2, was considered too cumbersome due to the reaction procedure requiring long reaction times (> 16 h) with precise temperature control (40 °C ± 2°C) to be maintained during this time.[26] In addition, there was a report in 2010 that an attempt to synthesize a (diacetoxyiodo)arene using

54

AcOOH, generated from the mixture of H_2O_2 and Ac_2O, resulted in the reaction mixture detonating, leading to serious injury to the chemist.[121] In general, the main modifications to the experimental procedures reported in the literature include: 1) management of the exothermic reactions by placing the respective reaction vessels in a cooling bath during each of the three steps 2) thorough rinsing of TolIO during filtration to remove traces of THF and 3) drying of $TolIF_2$ within a vacuum chamber (< 0.1 torr). The first point is thought to increase reaction yields by preventing side reactions from occurring while the latter points were found to minimize the amount of yellow impurity present in the $TolIF_2$. Batches of $TolIF_2$ generated by this method could be stored for over 1 year in a –20 °C freezer, remaining visibly unchanged and no detectable amounts of decomposition was observed by ^1H NMR spectroscopic analysis of the material.

The applicability of $TolIF_2 \cdot Rh_2(OAc)_4$ (see §2.3.2 for a discussion on the discovery that this mixture promoted rapid decomposition of diazo compounds) to the difluorination of diazo ester **2.15h** was investigated. Interestingly, a small amount of difluoride **2.58h** was formed even at room temperature (13% yield, eq 2.22). Optimization studies for Rh-catalyzed difluorinations were not pursued.

$$(2.22)$$
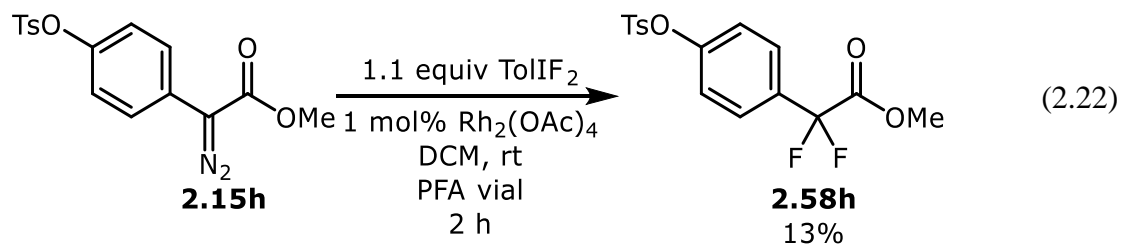
2.5. Concluding Remarks

In this chapter it was found that geminal double ligand transfer reactions are possible through the reaction of various diazo compounds and (dihaloiodo)arenes. The dichlorination of methyl

phenyldiazoacetates using $PhICl_2$ proceeded under mild conditions when using small, catalytic loadings of additives that may react with $PhICl_2$ to generate iodanes which were more reactive towards diazo compounds. Some Lewis-basic additives, which have been used as nucleophilic catalysts in other organic transformations, were also found to able to successfully promote the dichlorination reaction. Using 5 mol% pyridine allowed for the dichlorination of aryldiazoesters to occur in up to 96% yield. The functional group tolerance was determined to be fairly high. Dichlorination of the diazo group appears to take precedence over reactive groups such as an allyl group or electron rich benzene rings. The Lewis acid, $AlCl_3$, was found to allow for *gem*-dichlorination to occur but less efficiently than most Lewis bases.

In the case of β-hydroxy-α-diazo-esters, it was found that the dichlorination reaction can be interrupted via a semi-pinacol rearrangement. Tertiary alcohols adjacent to the diazo carbon were shown to be capable of undergoing a phenyl shift to generate α-chloroketones when treated with $PhICl_2$/Py or $PhICl_2$/2,6-lutidine. This transformation generates a stereogenic center, and it may be possible to render this reaction stereoselective. The use of hypervalent iodine reagents in stereoselective reactions has received significant attention recently.[24] One possible method for doing so would use a chiral nucleophilic catalyst, such as the cinchona alkaloid-derived catalysts developed for the Sharpless asymmetric dihydroxylation reaction. One of these catalysts (i.e., $(DHQD)_2PHAL$) has been used in conjugation with an *N*-bromoimide to form an asymmetric bromination/semi-pinacol rearrangement (eq 2.23).[106]

2.59

(0.2 equiv x 6)
(DHQD)$_2$PHAL
(20 mol%)
DCM, -20°C

2.60
86% yield
72% ee

(2.23)
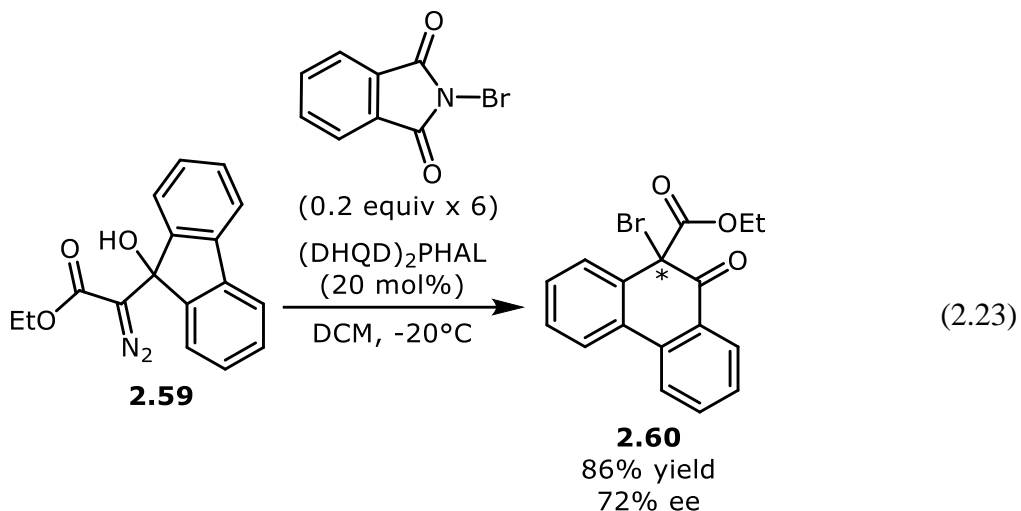
Additionally, there is precedent for the use of (DHQ)$_2$PHAL and PhICl$_2$ in asymmetric chlorination reactions, such as the asymmetric *vic*-dichlorination of allylic alcohols (eq 2.24).[96] Nicolaou et al. proposed a stereoinductive model in which the nitrogen on the quinuclidine portion of the molecule performs a ligand exchange with one of the ligands of PhICl$_2$ and a hydrogen bonding interaction between the allylic alcohol and a nitrogen of the phthalazine guides the stereochemical approach of the alkene to the iodane. Similar to the Sharpless asymmetric epoxidation, this chlorination required an unprotected alcohol for optimal asymmetric induction. β-Hydroxy-α-diazoesters have a nearby unprotected hydroxyl group which may be able to participate an interaction with a chiral catalyst as well.

2.61

(DHQ)$_2$PHAL (20 mol%)

ArICl$_2$ (1.6 equiv)
DCM, -78 °C

2.62
12 examples
35-84% yield
25-81% *ee*

(2.24)
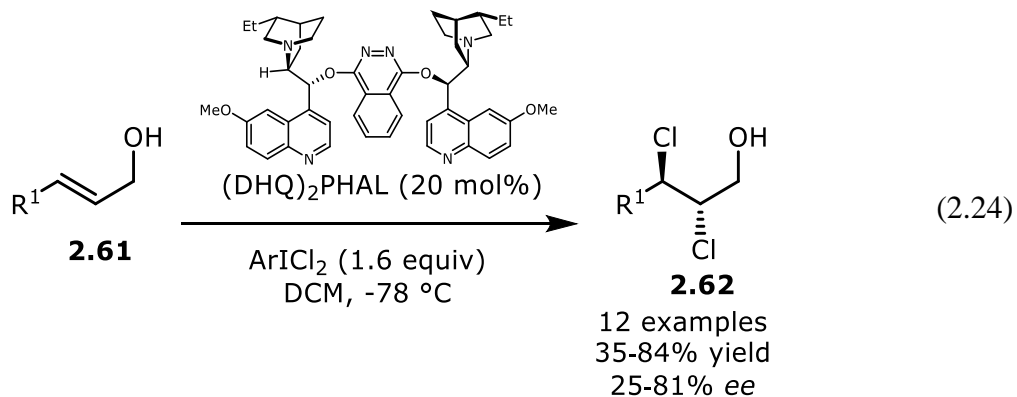
The chlorination/semi-pinacol rearrangement was used as a proof-of-concept to establish that the double ligand transfer reaction can be interrupted by an intramolecular process. An analogous fluorination/semi-pinacol reaction was shown to be possible using TolIF$_2$ when used in conjunction with dirhodium tetracarboxylate catalysts. A novel interaction between TolIF$_2$ and the Rh-catalysts was observed and is believed to generate a catalyst that is more reactive in the decomposition of diazo compounds than the parent rhodium catalyst.

These studies revealed that a variety of diazo compounds were able to undergo reactions with (dihaloiodo)arenes. As a further test of our hypothesis that an ylidic structure with a cationic portion bearing excellent leaving group (Scheme 1-7) allows for the possibility of gem-difunctionalization using HVI reagents, we began looking at the use of iodonium ylides as potential reaction partners. The results of which are the subject to the next chapter of this thesis.

2.6. Experimental

All reactions were performed using oven-dried or flame-dried glassware under a positive pressure of nitrogen unless otherwise stated. Dry DCM, THF, DCE, toluene, and Et$_2$O were obtained from a JC Meyer solvent purification system,[122] and were used without further purification. Anhydrous MeCN and DMSO were obtained by storing the solvents over activated 3 Å or 4 Å molecular sieves (respectively) overnight and were used without further purification. Molecular sieves were activated by heating the sieves to 150–300 °C under high vacuum (0.1–0.05 torr) overnight. 2,4,6-tri-*tert*-butylpyrimidine,[101] *N*-methylpyridinium iodide,[123] *N*-methylpyridinium triflate,[124] *N,N'*-dimethylviologen diiodide,[125] and ditosylhydrazine[126] were synthesized via literature procedures. NHC **2.32** was received from the lab of Prof. S. Lee. 5.25% NaOCl solution (No Name brand) was purchased from The Real Canadian Superstore and Zehrs. All other solvents and reagents were obtained from commercial sources (e.g., Sigma-Aldrich, Oakwood Chemical, etc.) and were used

without further purification unless otherwise stated. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm Kieselgel 60 F254 (Merck). Unless otherwise stated, flash chromatography columns were packed with 230–400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.0 ppm). Positive ion electrospray ionization (+ESI) mass spectrometry, negative ion electrospray ionization (-ESI) mass spectrometry or direct analysis in real time (DART) mass spectrometry were performed with a Thermo Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. For ESI, samples were infused at 10 µL/min in either 1:1 CH_3OH/H_2O+0.1% formic acid or 1:1 CH_3OH/H_2O+0.2% NH_4OH. IR spectroscopy was perofmred using aPerkinElmer Spectrum Two FT-IR spectrometer.

General Procedure 2.1 (GP2.1) – Diazo Transfer Reaction

Based on a modified protocol reported by Davies et al.[127] To a stirring solution of arylacetate (1.0 equiv) was added TsN$_3$[128] (1.0 equiv) or pABSA[129] (1.0 equiv). The reaction mixture was then cooled to 0 °C in an ice-water bath, and DBU (1.35 equiv) was added. The reaction mixture was allowed to stir overnight at room temperature, after which it was concentrated and re-suspended in ethyl acetate, washed three times with a solution of sat. NH_4Cl, then with brine. The organic extracts were then dried over $MgSO_4$, filtered, and concentrated. The resultant residue was triturated with 1:1 hexanes:Et$_2$O and filtered. The filtrate was concentrated in vacuo and the residue was purified using flash column chromatography.

General Procedure 2.2 (GP2.2) – Dichlorination of Diazo Compounds

In a 10 mL round bottom flask was added diazo ester **2.15** (50 mg, 1.0 equiv), CH_2Cl_2 ([**2.15**] = 0.2 M), then pyridine in CH_2Cl_2 (10% v/v solution, 5.0 mol%). $PhICl_2$ (1.1 equiv) was then added in one portion. The mixture was stirred until TLC analysis indicated the complete consumption of starting material. The reaction mixture was concentrated in vacuo and the resulting crude material was purified using flash chromatography.

Iodobenzene Dichloride (PhICl₂)[48]
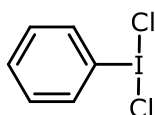
In ambient atmosphere, a 250 mL round bottom flask, iodobenzene (2.0 g, 9.8 mmol, 1.0 equiv) was suspended in 5.25% aq NaOCl solution (60 mL, 42.3 mmol, 4.3 equiv) and was stirred vigorously at room temperature. Concd HCl (20 mL, 248 mmol, 25.3 equiv) was then added dropwise to the flask via a graduated cylinder over 2 minutes. The flask was sealed with a cap and allowed to stir for 5 minutes. The solid was collected by filtration and washed with water (200 mL × 2) and then hexanes (50 mL). The solid was then transferred into a 50 mL beaker and stored in a desiccator in the dark overnight to yield the title compound as a pale yellow solid (2.5 g, 93% yield). mp 110–112 °C.

p-Iodotoluene Difluoride (TolIF₂)[120]
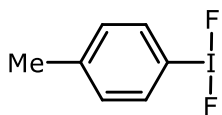
In ambient atmosphere, a 1 L round-bottomed flask with a 29/34 ground glass joint was charged with a 6 cm long Teflon-coated, ellipsoidal, magnetic stir bar and *p*-iodotoluene (10.9 g, 50.0 mmol, 1.0 equiv). The flask was then charged with acetonitrile (100 mL) and the mixture was stirred to give a colourless solution. The flask was cooled in a 5 °C water bath and charged with 5.25% aq NaOCl solution (300 mL, 211 mmol, 4.2 equiv). The flask was equipped with a 125 mL pressure-equilibrating addition funnel charged with concd HCl (100

mL, 1.2 mol, 24.8 equiv). The solution HCl was then added dropwise over 30 minutes to the vigorously stirring reaction mixture. After complete addition of the solution of HCl, the reaction mixture was allowed to stir for an additional 30 minutes. The water bath was allowed to warm naturally over the course of the reaction. The mixture was then filtered through a 350 mL medium porosity sintered glass funnel and the filtrate was discarded. The filter cake was washed with deionized water (200 mL × 3), and then with hexanes (50 mL × 3). The yellow solid (commonly 15.35–16.10 g) was immediately transferred into a 300 mL, single-necked, round bottom flask with a 24/40 joint, equipped with a 4 cm long Teflon-coated ellipsoidal magnetic stir bar. Tetrahydrofuran (100 mL) was used to assist in this transfer. The flask was cooled to <–10 °C in an ice/salt-water bath and equipped with a 125 mL pressure-equilibrating addition funnel charged with 3 N NaOH (50 mL, 150 mmol, 3.0 equiv). The NaOH solution was added to the flask dropwise over 5 minutes, and the reaction mixture was allowed to stir for an additional 30 minutes. At this time, dichloromethane (100 mL) was added to the reaction flask and the resulting suspension was stirred for an additional 2 minutes prior to being filtered through a 350 mL medium porosity sintered glass funnel. The filter cake was then washed with water (30 mL × 5) and dichloromethane (30 mL × 3), and the resulting wet, pale yellow paste was transferred (without weighing) to a 250 mL Teflon beaker (6 cm diameter) equipped with 5 cm long magnetic stir bar. The beaker was charged with chloroform (80 mL) and the resulting suspension was stirred. The reaction vessel was cooled in a 0 °C ice-water bath and six portions of concd HF (2.5 mL × 6, 69 mmol × 6, 1.4 equiv × 6) was added dropwise to the beaker via a 3 mL graduated polypropylene pipette. After the addition, the mixture was stirred for 30 minutes, after which solid *p*-iodosotoluene was no longer visible and the reaction mixture consists of two colourless phases. The reaction vessel was removed from the cooling bath and the top layer of the biphasic mixture

was removed using a 3 mL polypropylene pipette. The beaker was then placed in a water bath maintained at 40 °C and stirred while being concentrated to approximately 25% of its original volume using a gentle stream of dinitrogen. Crystallization of *p*-iodotoluene difluoride was induced by slowly adding hexanes (100 mL) via a graduated cylinder into the Teflon beaker over 1 minute. The resulting mixture was concentrated to approximately 25% of its original volume by a gentle stream of dinitrogen. The resulting slurry was cooled to 0 °C, decanted, and the white solid adhering to the side of the Teflon beaker was quickly scraped down into the bulk of the material using a metal spatula. This material was washed hexanes (50 mL × 2), decanting in between washes. The resulting white solid was transferred to a 10 dram Teflon or polypropylene vial and the vessel was placed into a 40 °C water bath, and excess hexanes was evaporated by using a gentle stream of nitrogen gas. The vial containing the white needles was then deposited into a vacuum chamber and dried under high vacuum (<0.1 torr) until a constant weight was achieved. This procedure typically afforded *p*-iodotoluene difluoride (8.2–9.2 g, 64–72% yield over 3 steps) as white needles and this reagent was stored in a −20 °C freezer under an atmosphere of nitrogen gas. mp 99–101°C; IR (ATR) 1478, 1380, 1208, 1001, 789 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.83 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 142.3, 132.1, 130.2, 120.8 (t, ^{2}J = 11 Hz), 21.1 ppm. These data match those reported in the literature.

Note: *p*-Iodotoluene was purchased from the following chemical suppliers: Sigma-Aldrich, Matrix Scientific, or Oakwood Chemical. Although pure *p*-iodotoluene is a white solid, different batches of *p*-iodotoluene (even from the same chemical supplier) were often discoloured and contained yellow-brown patches. It is presumed that traces of diiodine are the cause of this discolouration. Using exceptionally impure *p*-iodotoluene for the synthesis of TolIF$_2$ led to the iodane to be

recovered as light yellow solid although there were no impurities present in the ^{1}H NMR spectrum of this material. Severely yellow or brown batches of *p*-iodotoluene were decolourized by dissolving the material in hexanes and treating the resultant solution with a dilute solution of sodium thiosulfate until both layers of the biphase mixture became colourless. It is worth mentioning that R. Tran had found that treating a solution of *p*-iodotoluene in EtOAc with a dilute solution of sodium thiosulfate did not decolourize the material.

3,4-Dimethoxybenzyl 2-phenylacetate (2.14d)[130]
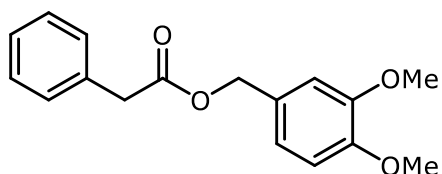
To a stirred solution of 3,4-dimethoxybenzyl alcohol (3.9 g, 19.4 mmol, 1.2 equiv) in DCM (40 mL) were added pyridine (1.85 g, 23.3 mmol, 1.2 equiv) and DMAP (237 mg, 10 mol%). The mixture was cooled to 0 °C and phenylacetyl chloride (3.0 g, 19.4 mmol, 1.0 equiv) was added dropwise over 1 minute. The reaction mixture was allowed to stir for 16 h (the reaction was not monitored), then partitioned between EtOAc (150 mL) and sat. NH$_4$Cl solution (50 mL). The organic layer was separated and washed, sequentially, with a sat. NaHCO$_3$ solution (50 mL), H$_2$O (50 mL), and brine (50 mL). The organic layer was then separated and dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (10% EtOAc/hexanes) to yield the title compound as a white solid (4.4 g, 77% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.96 (d, *J* = 1.8, 1H), 6.88 (d, *J* = 8.1, 1H), 5.90 (s, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 3.67 (s, 2H),. The spectral data is consistent with those reported in the literature.

3,4-Dimethoxybenzyl 2-diazo-2-phenylacetate (2.15d)
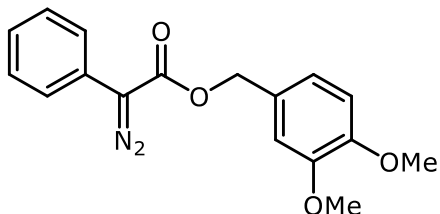
The title compound was synthesized via **GP2.1** using 3,4-dimethoxybenzyl 2-phenylacetate (**2.14d**) (3.25 g, 11.4 mmol) and TsN_3 (1.0 equiv). Purification via flash column chromatography (10% EtOAc/hexanes then 20% EtOAc/hexanes) afforded the title compound as an orange solid (1.48 g, 42% yield). $R_f = 0.40$ (20% EtOAc/hexanes, UV active); mp 42–44 °C; IR (film cast) 2957, 2087, 1699, 1518, 1499, 1242, 1160, 1028 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.49 (d, $J = 7.6$ Hz, 2H), 7.38 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.18 (t, $J = 7.6$ Hz, 1H), 6.98 (dd, $J = 8.2$ Hz, 1.6 Hz, 1H), 6.94 (d, $J = 1.6$ Hz, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 5.25 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.0, 149.17, 149.0, 128.8, 128.4, 125.9, 125.5, 123.9, 121.2, 111.7, 111.0, 66.6, 55.9, (C=N$_2$ not observed; one OMe not resolved); HRMS (DART) m/z: [M+H-N$_2$]$^+$ calcd for C$_{17}$H$_{17}$O$_4$, 354.0420; found 354.0415.

Methyl 2-diazo-2-(4-(tosyloxy)phenyl)acetate (2.15h)
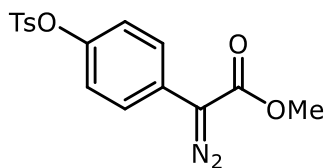
To a 100 mL round bottom flask, DBU (4.5 mL, 30 mmol, 3.0 equiv) was added dropwise to a stirring solution of methyl 2-(4-hydroxyphenyl)acetate[131] (1.66 g, 10.0 mmol, 1.0 equiv) in MeCN (30 mL) at room temperature. TsCl (1.9 g, 10 mmol, 1.0 equiv) was then added portionwise and the resulting mixture was stirred for 30 minutes, after which TLC analysis showed complete consumption of the starting material. The reaction mixture was cooled to 0 °C in an ice-water bath and TsN$_3$ (1.5 mL, 10 mmol, 1.0 equiv) was added dropwise to the solution and the mixture was allowed to warm to ambient temperature overnight. The reaction mixture was concentrated in

vacuo, dissolved in Et$_2$O (80 mL) and sequentially washed with sat. NH$_4$Cl (80 mL × 3) and brine (80 mL), dried over MgSO$_4$, filtered, and then concentrated to dryness in vacuo. The orange solid was dissolved in a minimal amount of DCM, cooled to 0 °C and filtered. The filtrate was concentrated and purified by column chromatography (15% EtOAc/hexanes), which afforded the title compound as an orange solid (1.61 g, 46% yield). R_f = 0.46 (20% EtOAc/hexanes, UV active, stains in *p*-anisaldehyde); mp 97–99 °C; IR (film cast) 2093, 1704, 1505, 1374, 1249, 1179, 1156, 862, 737 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.41–7.37 (m, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.01–6.96 (m, 2H), 3.85 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.3, 147.4, 145.6, 132.2, 129.8, 128.7, 124.9, 123.0, 52.3, 21.9 (C=N$_2$ not observed, one C=<u>C</u> not resolved); HRMS (+ESI) *m/z*: [M+H-N$_2$]$^+$ calcd for C$_{16}$H$_{15}$O$_5$S, 319.0635; found 319.0633.

Methyl 2-(4-acetamidophenyl)-2-diazoacetate (2.15f)
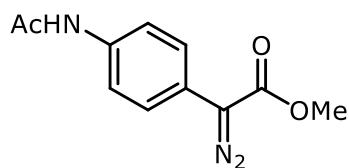
To a 50 mL round bottom flask containing a stirring solution of methyl 2-(4-acetamidophenyl)acetate[132] (1.30 g, 6.27 mmol, 1.0 equiv) in MeCN (19 mL) was added TsN$_3$ (1.24 g, 6.27 mmol, 1.0 equiv), in one portion, and reaction vessel was cooled to 0 °C in an ice-water bath. DBU (1.31 g, 8.46 mmol, 1.35 equiv) was added dropwise to this mixture and the flask was allowed to warm to ambient temperature overnight, after which the mixture was concentrated in vacuo, re-dissolved in EtOAc (50 mL) then washed sequentially with sat. NH$_4$Cl (50 mL × 3) and brine (50 mL), then dried over MgSO$_4$, filtered, and then concentrated to dryness in vacuo. The crude solid material was triturated with 0 °C DCM to yield the title compound as an orange solid (480 mg, 37% yield). R_f = 0.43 (75% EtOAc/hexanes, UV active); mp 122–124 °C; IR (film cast) 3584, 2953, 1699, 1596, 1530, 1430, 1156 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.44 (br s, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.5,

166.0, 136.1, 124.9, 124.9, 121.0, 120.6, 52.2, 24.7 (C=N$_2$ not observed); HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{11}$H$_{12}$N$_3$O$_3$, 234.0873; found 234.0873.

Methyl 2,2-dichloro-2-phenylacetate (2.16a)[97]
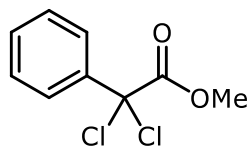
The title compound was synthesized according to **GP2.2** using diazo ester **2.15a**.[95] Purification via flash chromatography column (5% EtOAc/hexanes then 10% EtOAc/hexanes) afforded the title compound as a clear, colourless oil (56 mg, 90% yield). R_f = 0.42 (10% EtOAc/hexanes, UV active); IR (film cast) 2956, 1759, 1467, 1240, 1198, 1108, 1007, 832 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73–7.69 (m, 2H), 7.45–7.40 (m, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.6, 138.7, 129.8, 128.5, 126.4, 84.6, 54.9; HRMS (DART) calcd for C$_9$H$_{12}$^{35}Cl$_2$NO$_2$ [M+NH$_4$]$^+$ 236.0240; found 236.0237. These data correspond to those reported in the literature.

Isopropyl 2,2-dichloro-2-phenylacetate (2.16b)
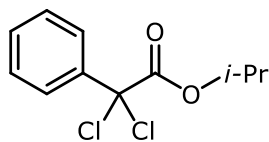
The title compound was synthesized according to **GP2.2** using diazo ester **2.15b**.[95] Purification via flash column chromatography (5% EtOAc/hexanes then 10% EtOAc/hexanes) afforded the title compound as a clear, colourless oil (53 mg, 88% yield). R_f = 0.58 (10% EtOAc/hexanes, UV active); IR (film cast) 3066, 2956, 1759, 1637, 1448, 1240, 1198, 1008, 832, 734 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.72–7.69 (m, 2H), 7.34–7.38 (m, 3H), 5.10 (sep, J = 6.3 Hz, 1H), 1.26 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.5, 139.1, 129.8, 128.4, 126.5, 84.7, 72.68, 21.3; HRMS (DART) *m/z*: [M+H]$^+$ calcd for C$_{11}$H$_{13}$^{35}Cl$_2$O$_2$, 247.0287; found 247.0282.

Benzyl 2,2-dichloro-2-phenylacetate (2.16c)

The title compound was synthesized according to **GP2.2** using diazo ester **2.15c**.[133] Purification via flash column chromatography (5% EtOAc/hexanes then 10% EtOAc/hexanes) afforded the title compound as a clear, colourless oil (56 mg, 95% yield). $R_f = 0.47$ (10% EtOAc/hexanes, UV active); IR (film cast) 3066, 2962, 1756, 1447, 1220, 1001, 831, 732, 692 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73–7.65 (m, 2H), 7.43–7.38 (m, 3H), 7.37–7.31 (m, 3H), 7.30–7.25 (m, 2H), 5.28 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.8, 138.7, 134.5, 129.9, 128.8, 128.7, 128.5, 128.1, 126.6, 84.8, 69.6; HRMS (DART) *m/z*: [M+NH$_4$]$^+$ calcd for C$_{15}$H$_{16}$^{35}Cl$_2$NO$_2$, 312.0553; found 312.0547.

3,4-Dimethoxybenzyl 2,2-dichloro-2-phenylacetate (2.16d)

The title compound was synthesized according to **GP2.2** using diazo ester **2.15d**. Purification via flash column chromatography (20% EtOAc/hexanes then 40% EtOAc/hexanes) afforded the title compound as yellow oil (55 mg, 96% yield). $R_f = 0.23$ (20% EtOAc/hexanes, UV active); IR (film cast) 2960, 1754, 1594, 1518, 1463, 1448, 1265, 1161, 1028, 735 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.67–7.62 (m, 2H), 7.39–7.35 (m, 3H), 6.86 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 0.7 Hz, 1H), 5.21 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.9, 149.6, 149.15, 138.9, 129.9, 128.6, 127.0, 126.6, 121.4, 111.5, 111.1, 85.6, 69.8, 56.1, 56.0; HRMS (DART) *m/z*: [M$^{+•}$]calcd for C$_{17}$H$_{16}$^{35}Cl$_2$O$_4$, 354.0420; found 354.0415.

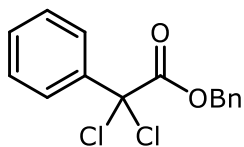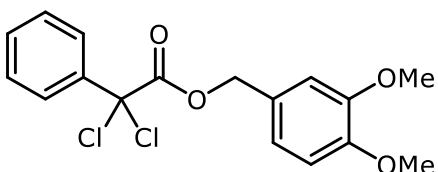**Allyl 2,2-dichloro-2-phenylacetate (2.16e)**

The title compound was synthesized according to **GP2.2** using diazo ester **2.15e**.[134] Purification via flash column chromatography (2.5% EtOAc/hexanes to 10% EtOAc/hexanes) afforded the title compound as clear, colourless oil (54 mg, 89% yield). $R_f = 0.52$ (10% EtOAc/hexanes, UV active); IR (film cast) 2985, 1758, 1448, 1373, 1240, 1047, 988, 834, 735 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.77–7.68 (m, 2H), 7.47–7.36 (m, 3H), 5.90 (ddt, J = 17.2, 10.4, 5.4 Hz, 1H), 5.32 (ddt, J = 17.1, 10.8, 5.6 Hz, 1H), 5.28 (d, J = 10.5 Hz, 1H), 4.76 (d, J = 5.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.7, 138.8, 130.5, 129.9, 126.6, 84.8, 68.4; HRMS (DART) m/z: [M+NH$_4$]$^+$ calcd for C$_{11}$H$_{14}$^{35}Cl$_2$NO$_2$, 262.0396; found 262.0393.

Methyl 2-(4-acetamidophenyl)-2,2-dichloroacetate (2.16f)
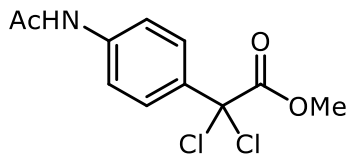
The title compound was synthesized following **GP2.2** using diazo ester **2.15f**. Purification was attempted via flash column chromatography (50% EtOAc/hexanes then 75% EtOAc/hexanes) provided 50 mg of a partially separable mixture of the title compound and glyoxylate in a 9:1 mol ratio (78% corrected yield). An analytic sample of the title compound was obtained, as a white solid, through radial chromatography (50% to 75% EtOAc/hexanes). mp 118–121 °C; $R_f = 0.51$ (75% EtOAc/hexanes, UV active); IR (film cast) 3584, 2957, 1748, 1670, 1601, 1532, 1406, 1248, 1182, 1004 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.65 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.35–7.28 (br s, 1H), 3.86 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.5, 166.6, 139.3, 134.2, 127.6, 119.2, 85.5, 55.0, 24.8; HRMS (DART) m/z: [M+H]$^+$ calcd for C$_{11}$H$_{12}$^{35}Cl$_2$NO$_3$, 276.0189; found 276.0184.

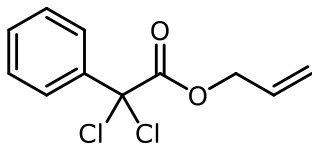## Methyl 2,2-dichloro-2-(4-methoxyphenyl)acetate (2.16g)

The title compound was synthesized according to **GP2.2** using diazo ester **2.15g**.[95] Purification via flash column chromatography (7.5% EtOAc/hexanes then 15% EtOAc/hexanes) afforded the title compound as a yellow oil (48 mg, 79% yield). R_f = 0.29 (10% EtOAc/hexanes, UV active); IR (film cast) 1755, 1608, 1511, 1463, 1258, 1177, 1006, 762 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.65–7.61 (m, 2H), 6.93–6.88 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.8, 160.7, 130.9, 128.2, 113.8, 84.8, 55.6, 55.0; HRMS (DART) m/z: [M$^{+\bullet}$] calcd for C$_{10}$H$_{10}$^{35}Cl$_2$O$_3$, 248.0002; found 247.9997.

## Methyl 2,2-dichloro-2-(4-(tosyloxy)phenyl)acetate (2.16h)
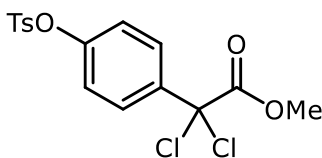
The title compound was synthesized according to **GP2.2** using diazo ester **2.15h**. Purification via flash column chromatography (10% EtOAc/hexanes then 25% EtOAc/hexanes) afforded the title compound as a white solid (100 mg, 89% yield). mp 56–59 °C; R_f = 0.48 (30% EtOAc/hexanes, UV active); IR (film cast) 1762, 1642, 1377, 1180, 1158, 865 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.67–7.63 (m, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.07–7.02 (m, 2H), 3.85 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.2, 150.5, 145.8, 137.5, 132.3, 130.0, 128.6, 128.4, 122.4, 83.7, 55.1, 21.9; HRMS (DART) m/z: [M+NH$_4$]$^+$ calcd for C$_{16}$H$_{18}$^{35}Cl$_2$NO$_5$S, 406.0277; found 406.0272.
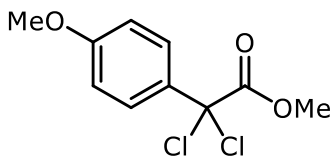
Methyl 2-(4-bromophenyl)-2,2-dichloroacetate (2.16i)
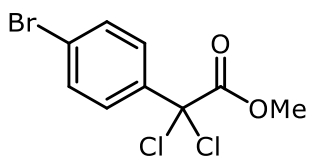
The title compound was synthesized according to **GP2.2** using diazo ester **2.15i**.[95] Purification via flash column chromatography (5% EtOAc/hexanes then 10% EtOAc/hexanes) afforded the title compound as a clear, colourless oil (51 mg, 87 yield). R_f = 0.47 (10% EtOAc/hexanes, UV active); IR (film cast) 2955, 1758, 1586, 1485, 1395, 1238, 1198, 1010, 846, 764 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.58 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.2, 137.9, 131.8, 128.4, 124.5, 84.0, 55.1; HRMS (DART) m/z: [M+NH$_4$]$^+$ calcd for C$_9$H$_{11}$^{79}Br^{35}Cl$_2$NO$_2$, 313.9345; found 313.9340.

Methyl 2,2-dichloro-2-(4-nitrophenyl)acetate (2.16j)
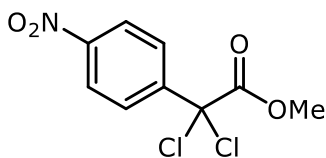
Using diazo ester **2.15j**,[135] the title compound was synthesized following **GP2.2** with the exception that DMAP (0.5 mg, 1.8 mol%) instead of pyridine and after the reaction was complete (40 minutes), 30 mg of silica was added to the reaction mixture and allowed to stir for 5 minutes. Purification via flash column chromatography (benzene) afforded the title compound as an off-white solid (40 mg, 67% yield). mp 67–70 °C; R_f = 0.55 (benzene, UV active); IR (film cast) 3110, 2958, 1759, 1527, 1351, 1258, 1008, 849, 735 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.27 (d, J = 8.9 Hz, 2H), 7.91 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.7, 148.6, 144.9, 128.2, 123.7, 82.9, 55.4; HRMS (DART) m/z: [M+NH$_4$]$^+$ calcd for C$_9$H$_{11}$^{35}Cl$_2$N$_2$O$_4$, 281.0090; found 281.0086.

**Methyl 2-chloro-2-(2-chloro-4-nitrophenyl)acetate (2.16j')**
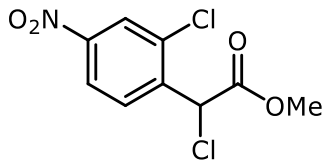
The title compound was synthesized according to **GP2.2** using diazo ester **2.15j** (65 mg, 0.30 mmol). Purification via column chromatography (benzene) allowed for partial separation of **2.15j** and **2.15j'**, yielding the title compound as a faintly yellow liquid (22 mg, 28% yield). R_f = 0.48 (benzene, UV active); IR (ATR) 3104, 2957, 1750, 1524, 1348, 1165 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.28 (d, J = 2.2 Hz, 1H), 8.19 (dd, J = 8.6, 2.2 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 5.86 (s, 1H), 3.82, (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 167.2, 148.4, 140.3, 134.3, 130.9, 124.3, 122.3, 54.3, 53.9; HRMS (-ESI) *m/z*: [M-H]$^-$ calcd for C$_9$H$_6$^{35}Cl$_2$NO$_4$, 261.9668; found 261.9684.

Benzyl 2,2-dichloroacetate (2.25)
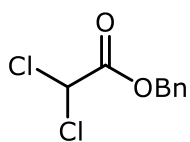
The title compound was synthesized according to **GP2.2** using benzyl diazoacetate.[126] Purification was attempted via flash column chromatography (5% EtOAc/hexanes then 10% EtOAc/hexanes) and provided 46 mg of a colourless oil containing a partially separable mixture the title compound and α-chlorobenzylacetate in a 7:1 mol ratio (71% corrected yield). R_f = 0.45 (10% EtOAc/hexanes, UV active); IR (film cast) 2960, 1754, 1594, 1518, 1463, 1448, 1265, 1161, 1028, 735 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$), 7.42–7.34 (m, 5H), 5.98 (s, 1H), 5.29 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 164.5, 134.3, 129.0, 128.9, 128.6, 69.2, 64.39; HRMS (DART) *m/z*: [M+NH$_4$]$^+$ calcd for C$_9$H$_{12}$^{35}Cl$_2$NO$_2$, 236.0240; found 236.0237.

Dichlorodiphenylmethane (2.26)[136]
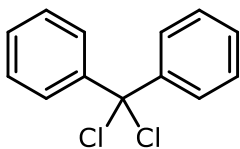
Using diphenyldiazomethane,[137] the title compound was synthesized according to **GP2.2** with the exception that using 1.0 equiv of PhICl₂ was. The reaction mixture was concentrated in vacuo and then place under hi vacuum to remove the volatiles to yield 71 mg of a colourless oil containing a 2:1 mol ratio of the title compound (41 mg, 70% corrected yield) and iodobenzene. The spectral data matches those reported in literature.

Ethyl 2-chloro-3-oxo-2,3-diphenylpropanoate (2.45)[106]
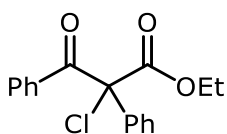
Diazo ester **2.44**[111] (30 mg, 0.10 mmol, 1.0 equiv) was dissolved in DCM (1 mL) and 2,6-lutidine (11 mg, 0.10 mmol, 1.0 equiv) was added as the mixture was stirred at room temperature. PhICl₂ (27 mg, 0.10 mmol, 1.0 equiv) was added and the mixture was allowed to stir for 5 minutes. The volatiles were removed in vacuo and HMDSO (3.0 μL, 0.024 mmol) was added and the mixture dissolved in CDCl₃. The NMR yield (39% yield) was obtained by a comparison with the doublet at $\delta = 7.85$ with the signal of HMDSO.

Ethyl 2-diazo-2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acetate (2.46)
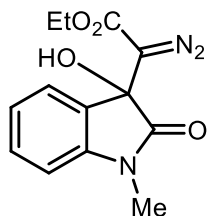
In a 100 mL round bottom flask, *N*-methylisatin[138] (1.61 g, 10 mmol, 1.0 equiv) was dissolved in absolute EtOH (50 mL) at room temperature. DBU (228 mg, 1.5 mmol, 15 mol%) and ethyl diazoacetate (1.37 g, 12.0 mmol, 1.2 equiv) was added to the reaction vessel and the mixture was stirred for 3 h at room temperature. The solvent was concentrated on a rotary evaporator and the residue was recrystallized in EtOH to provide the title compound as a yellow solid (2.08 g, 76% yield). mp 100–102 °C (EtOH); $R_f = 0.24$ (40% EtOAc/hexanes, UV active); IR (ATR) 3260 (br), 2977, 2102, 1687, 1612, 1471, 1371, 1097, 1130

cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50 (d, J = 7.4 Hz, 1H), 7.40 (dd, J = 7.8 Hz, 7.8 Hz, 1H), 7.14 (dd, J = 7.5 Hz, 7.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 4.18 (br q, 2H), 3.45 (s, 3H), 1.20 (br t, 3H); ^{13}C NMR (125 MHZ, CDCl$_3$) δ 175.2, 165.3, 143.6, 130.8, 128.2, 124.6, 123.5, 108.8, 71.3, 61.2, 26.5, 14.2 (C=N$_2$ not observed); HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{13}$H$_{14}$N$_3$O$_4$, 276.0979; found 276.0979.

Ethyl 4-chloro-3,3-dihydroxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinoline-4-carboxylate (2.47)
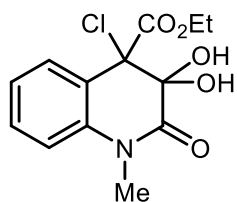
To a stirred room temperature solution of diazo ester **2.46** (157 mg, 0.60 mmol, 1.0 equiv) in anhydrous DCM (6 mL) were added 2,6-lutidine (65 mg, 0.60 mmol, 1.0 equiv) and PhICl$_2$ (247 mg, 0.90 mmol, 1.5 equiv) and the mixture was allowed to stir for 20 min at room temperature. At this time, TLC analysis indicated complete consumption of the diazo compound. The reaction was concentrated and the residue was purified by column chromatography (10% then 40% EtOAc/hexanes) to yield the title compound as an orange yellow which foamed when dried under high vacuum (131 mg, 73% yield). R$_f$ = 0.20 (EtOAc/hexanes, UV active, stains in DNPH); IR (ATR) 3407 (br), 2984, 1756, 1682, 1600, 1472, 1224, 1109, 1019 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.50–7.40 (br s, 1H), 7.43 (dd, J = 8.0, 8.0 Hz, 1H), 7.16 (dd, J = 7.7, 7.5 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 4.65–4.28 (br s, 1H), 4.34–4.22 (br q, 2H), 3.47 (s, 3H), 1.30–1.22 (br t, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 167.0, 166.0, 138.3, 130.6, 127.4, 124.1, 116.0, 90.6, 63.7, 30.7, 13.7 (C(OH)$_2$ and one =C-H not observed); HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{13}$H$_{15}$^{35}ClNO$_5$, 300.0633; found 300.0633.

Ethyl 2-fluoro-3-oxo-2,3-diphenylpropanoate (2.50)
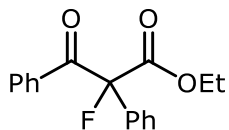
To a room temperature solution of diazo ester **2.44**[135] (59 mg, 0.20 mmol, 1.0 equiv) dissolved in DCM (2 mL) were added TolIF$_2$ (56 mg, 0.22 mmol, 1.1 equiv) and dirhodium tetrakis(2,4-dichlorobenzoate) (1 mg, 1 μmol, 0.5 mol%), and the resulting mixture was stirred for 40 minutes. The reaction mixture was concentrated in vacuo and the residue was purified via flash column chromography (5% then 10% EtOAc/hexanes) to yield the title compound as a faintly yellow liquid (30 mg, 52% yield). $R_f = 0.30$ (10% EtOAc/hexanes, UV active); IR (ATR) 2954, 1754, 1737, 1687, 1597, 1448, 1255, 1200, 1014, cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, J = 8.1 Hz, 2H), 7.63–7.38 (m, 8H), 4.36 (q, J = 7.1 Hz, 2H), 1.31 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) 191.5 (d, ^2J = 26.5 Hz), 166.5 (d, ^2J = 26.3 Hz), 133.8, 133.6 (d, ^2J = 21.8 Hz), 133.4 (d, ^4J = 3.6 Hz), 130.2, 130.1 (d, ^3J = 4.8 Hz), 129.1, 128.5 (d, ^4J = 1.4 Hz), 125.6 (d, ^2J = 8.5 Hz), 99.5 (d, ^1J = 200.1 Hz), 62.0, 13.9; ^{19}F NMR (470 MHz, CDCl$_3$) δ −157.6.

3. Dichlorination of Iodonium Ylides

3.1. Iodonium Ylides – Introduction

3.1.1. Structure and Stability

Iodonium ylides (e.g., **3.1.1** or **3.1.2**) are a subclass of hypervalent iodine containing compounds with the general structure shown in eq **3.1**. These compounds are typically used as reactive intermediates or reagents with many synthetic applications to organic chemistry. Iodonium ylides often exhibit low stability and typically participate in reactions as transient intermediates. The simplest iodonium ylide, methyliodonium methanylide (**3.3**), is believed to be generated by the deprotonation of dimethyliodonium hexafluoroantimonate (**3.2**) using NaH (Scheme 3-1).[139] This reaction led to the detection of ethane, presumably formed by two-step sequence: first, a [1,2]-rearrangement (or methylation of **3.3** using **3.2**), followed by a nucleophilic attack by NaH.

$$\left[\begin{array}{c} R^1 \diagdown \diagup R^2 \\ \overset{|}{I}R^3 \\ \textbf{3.1.1} \end{array} \quad \longleftrightarrow \quad \begin{array}{c} R^1 \overset{\ominus}{\diagdown} R^2 \\ \oplus \overset{|}{I}R^3 \\ \textbf{3.1.2} \end{array} \right] \tag{3.1}$$
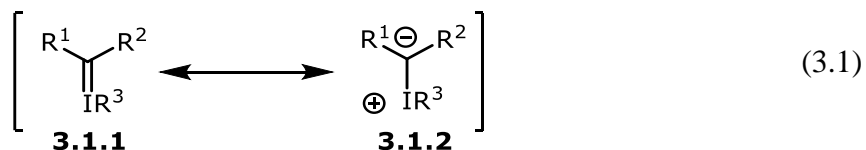
Scheme 3-1. In situ generation of Methyliodonium Methanylide

$$\underset{\textbf{3.2}}{Me_2\overset{\oplus}{I}\ \overset{\ominus}{SbF_6}} \quad \xrightarrow[-78\ °C]{NaH} \quad \left[\underset{\textbf{3.3}}{Me\diagup\overset{\oplus}{I}\diagdown\overset{\ominus}{CH_2}} \right] \quad \longrightarrow \quad C_2H_6 + others$$
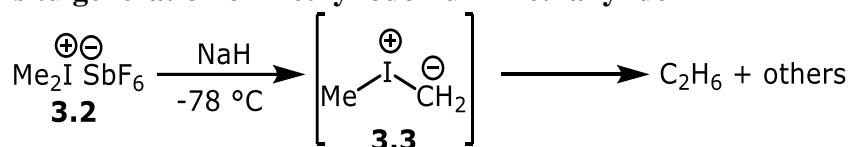
Reactive alkenyl- or alkyliodonium ylides (e.g., **3.5**) can be generated by trapping a metallocarbene with an organoiodide. These transient iodonium ylides can undergo rearrangement reactions. For example, allyl iodides (**3.4**) can trap copper or rhodium carbenoids (generated from the metal-catalyzed decomposition of diazo esters) and the resulting iodonium ylides can participate in [1,2]- or [2,3]-rearrangements (Scheme 3-2).[140–143] Tambar and Xu have found that

the choice of ligand for copper-catalyzed reactions can be used to tune the selectivity for [1,2]-rearrangement versus [2,3]-rearrangement.[144]

Scheme 3-2. Rearrangements of Transient Iodonium Ylides
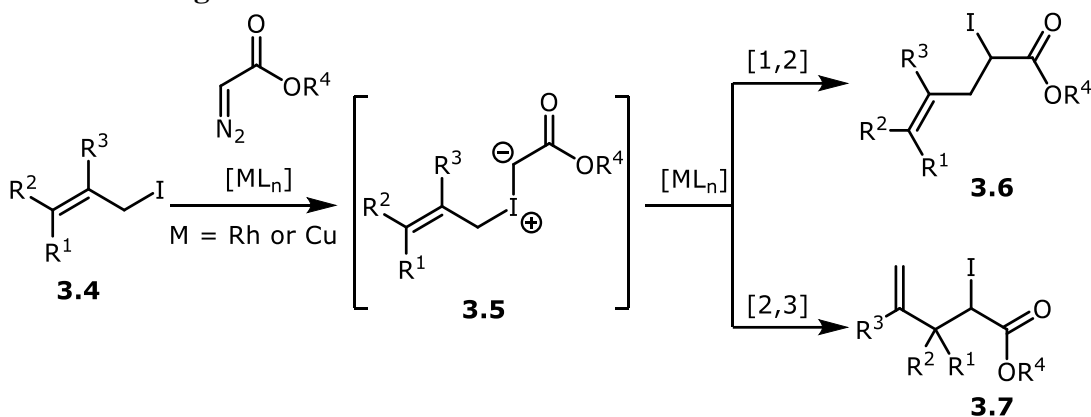
Relatively stable iodonium ylides (see Figure 3-1) can be derived from aryl-λ^3-iodanes and active methylene compounds. Of these, the phenyliodonium ylides adjacent to carbonyl or sulfonyl groups have received significant attention from the scientific community.[145]
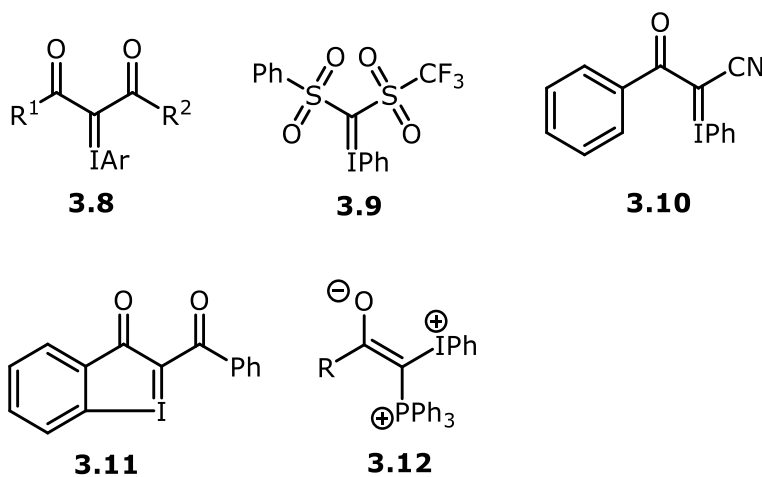
Figure 3-1. Examples of relatively stable iodonium ylides.

Conjugation of the ylidic carbon to these electron withdrawing groups stabilizes the ylide through delocalization of the anion, giving rise to zwitterionic forms such as **3.8.2** and **3.8.3** (eq

76

3.2). The contribution of these resonance forms varies depending on the parent active methylene compound.

$$R^1 \underset{\overset{|}{\oplus \bar{I}Ar}}{\overset{O \quad O}{\underset{C}{\bigominus}}} R^2 \longleftrightarrow R^1 \underset{\overset{|}{\oplus \bar{I}Ar}}{\overset{O \quad \overset{\ominus}{O}}{\underset{C}{}}} R^2 \longleftrightarrow R^1 \underset{\overset{|}{\oplus \bar{I}Ar}}{\overset{\overset{\ominus}{O} \quad O}{\underset{C}{}}} R^2 \qquad (3.2)$$

3.8.1   **3.8.2**   **3.8.3**
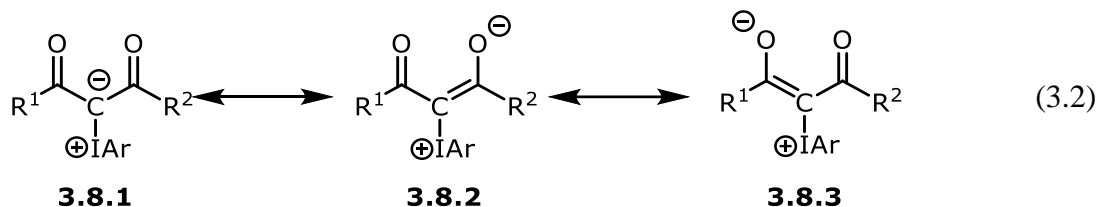
An example in which the ylidic resonance form plays a significant role in the description of the electronic structure is the phenyliodonium ylide of bis(triflyl)methane ($Tf_2C^- - I^+Ph$). The X-ray crystal structure of this ylide reveals the $C^- - I^+$ bond length is 1.89 Å, which is much shorter than the typical $C_{sp^3} - I$ bond length (2.14 Å) and even shorter than the $C_{sp} - I$ bond length (1.99 Å) indicating some double-bond character between $C^- - I^+$.[146] However, in the case of iodonium ylides of 1,3-dicarbonyl compounds, the $C^- - I^+$ bond lengths are typically much longer, 2.04–2.10 Å,[147–149] indicating higher zwitterionic character. In addition, when analyzed by IR spectroscopy, the carbonyl stretches of ylides **3.8** occur at frequencies significantly lower than their parent 1,3-dicarbonyl compounds.[25] For example, the C=O stretching frequency of dimedone is $v = 1627$ cm^{-1},[150] while in the corresponding phenyliodonium ylide, the C=O stretching frequency is $v = 1530$ cm^{-1}.[151]

The studies described below were mainly focused on the chemistry of phenyliodonium ylides of 1,3-dicarbonyl compounds (**3.8**). These compounds are typically solids with moderate thermal stability that can be stored for short periods of time (approximately a few weeks in a –20 °C freezer) without significant detectable decomposition. The first isolable iodonium ylide was reported by Neilands et al., who synthesized the phenyliodonium ylide of dimedone using $PhIF_2$ and dimedone.[152] Since then, numerous iodonium ylides of 1,3-dicarbonyl compounds have been

synthesized and used as reagents or synthetic intermediates.[145] The general procedure for

synthesizing and isolating iodonium ylides of 1,3-dicarbonyl compounds is typically a

modification of the procedure reported by Schank and Lick in which the parent 1,3-dicarbonyl

reacts with an (diacetoxyiodo)arene in alcoholic alkali.[153] The resulting ylides, once isolated, are

generally sparingly soluble in most common organic solvents, although some ylides may be fairly

soluble in DMSO or in chlorinated solvents such as dichloromethane and chloroform. The

zwitterionic character of these compounds likely contributes to the insolubility of these ylides by

providing a high degree of intermolecular secondary bonding between oxygen and iodine atoms.

This type of secondary bonding is present in many aryl-λ^3-iodanes and disrupting this interaction

has proved to be an effective strategy to increase solubility of these compounds.[154] For example,

HVI reagents derived from aryl iodides bearing a Lewis basic substituent *ortho* to the iodo group

possess an intramolecular interaction between the Lewis basic atom and the iodine atom which

out-competes the intermolecular interaction.[154–156] Zhdankin et al. have applied this concept to

iodonium ylides and designed (2-alkyloxyphenyl)iodonium ylides of dimedone (**3.13**)[149] and

dimethyl malonate (**3.14**)[148] which are significantly more soluble than the analogous

phenyliodonium ylides.

3.13   **3.14**

R = Me, *n*-Pr, *i*-Pr, *n*-Bu   R = Me, *n*-Pr, *i*-Pr, *n*-Bu
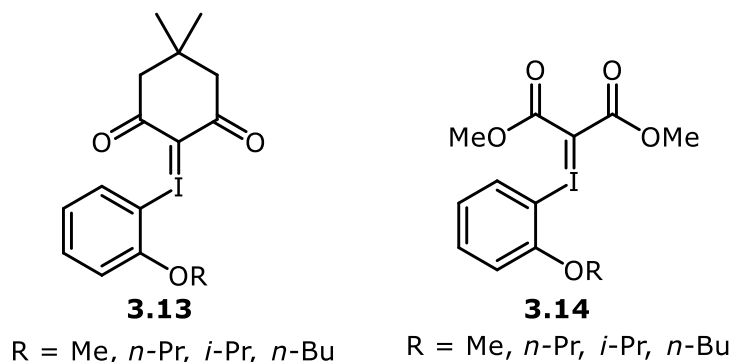
Figure 3-2. Examples of highly soluble (2-alkyloxyphenyl)iodonium ylides.

3.1.2. General Reactivity Patterns of Iodonium Ylides

Iodonium ylides of 1,3-dicarbonyl compounds have a broad reactivity profile. The zwitterionic/dipolar nature of iodonium ylides allows them to react with both nucleophiles[157,158] and electrophiles.[159] The ylidic and zwitterionic resonance structures (**3.8.1–3**) show potential nucleophilic sites to be the ylidic carbon and the oxygens of the carbonyl groups. As such, iodonium ylides can act as both Brønsted bases and Lewis bases. Reactions between iodonium ylides and Brønsted acids (HX) initially yield iodonium salts that are typically unstable and decompose through the displacement of the aryliodide by the counter-ion (X⁻). In some cases, if the counter-ion is relatively non-nucleophilic, the iodonium salt can be isolated and subjected to reactions with a variety of nucleophiles. Examples of this type of reactivity are shown in Scheme 3-3.[160]

Scheme 3-3. Substitution Reactions of Iodonium Salts
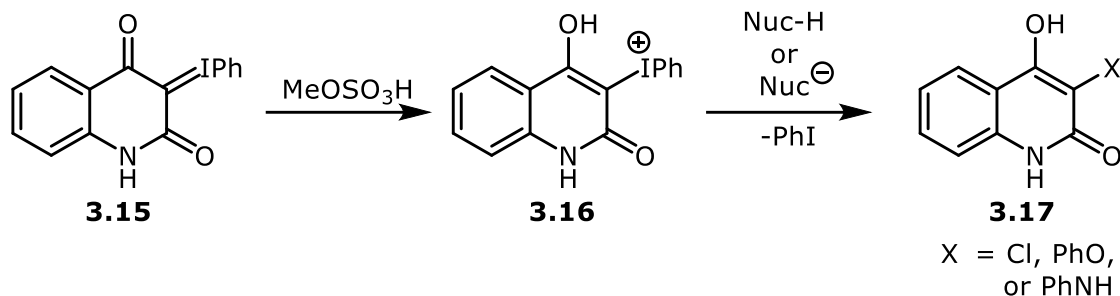
When reacting with carbon-based electrophiles, the iodonium ylides of 1,3-dicarbonyl compounds typically react predominantly at the oxygen. For example, benzoyl chloride and triethyloxonium tetrafluoroborate either acylate[161] or alkylate,[162] respectively, at the oxygen of the phenyliodonium ylide of dimedone (**3.8a**, eq 3.3).

$$(3.3)$$

3.8a → **3.18**
R = Bz or Et
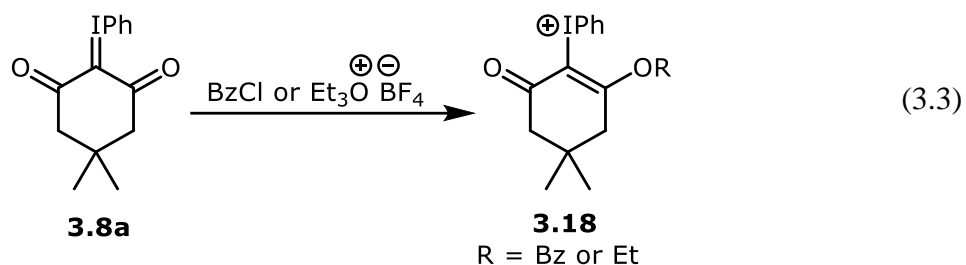
Mayr et al. recently reported an investigation of the nucleophilicity of a few phenyliodonium ylides of cyclic 1,3-dicarbonyl compounds.[163] This study quantified the nucleophilicity of these ylides with respect to the Mayr-Patz equation, $\log (k_{20\ °C}) = s_N (N + E)$,[164] where $k_{20\ °C}$ is the rate constant of the reaction (determined at 20 °C), s_N is the nucleophile-dependent sensitivity parameter, N is the nucleophilicity parameter, and E is the electrophilicity parameter. Using benzhydrylium cations (**3.19**), they determined the nucleophilicity parameters for ylides **3.8a–d** to be within the range $4 < N < 8$ (Figure 3-3).

	3.8a	**3.8b**	**3.8c**	**3.8d**
$N=$	6.18	4.67	4.36	7.98
$s_N=$	0.81	0.92	1.06	0.71
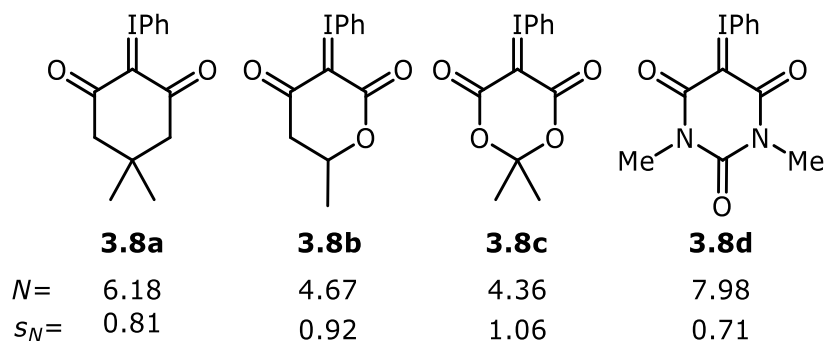
Figure 3-3. Nucleophilicity parameters of phenyliodonium ylides of cyclic 1,3-dicarbonyl compounds.

They also found that these benzhydrylium cations ($E > -10$), prefer to react at the ylidic carbon (Scheme 3-4)[163] and hypothesized that stronger electrophiles ($E > 0–4$) prefer to react at oxygen.

Scheme 3-4. Evidence for C-alkylation of Iodonium Ylides
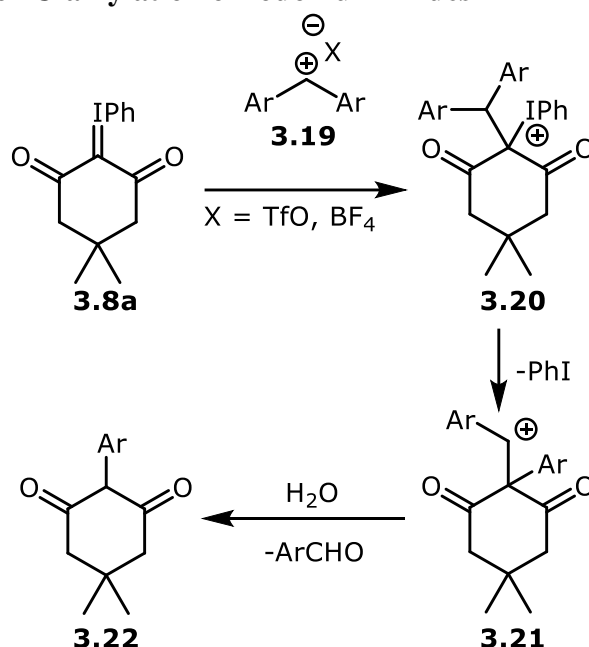
Apart from their use in nucleophilic substitution reactions, iodonium ylides have received attention for their use in carbenoid reactions. They can be used to generate carbenoid intermediates via thermal,[165] photochemical,[166,167] or metal-catalyzed processes.[167–170] This type of chemistry has been summarized in numerous reviews.[171–173] Iodonium ylides have been used in carbenoid reactions that generate products of C-H insertion,[174] cyclopropanation,[175–177] ylide formation,[170] and rearrangements.[178] The versatility of iodonium ylides in these reactions led to them being regarded as viable alternatives to diazonium ylides (i.e., diazo compounds) as metallocarbene precursors. When comparing these two ylides as carbene precursors for synthetic applications, iodonium ylides have some advantages over the analogous diazo compounds. For example, diazo compounds have gained notoriety as potential explosion hazards. On the other hand, iodonium ylides are less explosive and analysis via differential scanning calorimetry has found that they release much less energy upon thermal decomposition when compared to the corresponding diazo compounds.[176] Iodonium ylides are also more reactive than the analogous diazo compounds. For example, diazomalonates were found to struggle to undergo copper- or rhodium-catalyzed

81

decomposition to the respective metallocarbenoids under mild conditions,[172] and the reaction mixture were required to be heated (60–100 °C) in order to facilitate the decomposition. However, these conditions led to poor enantioselectivities when attempting asymmetric cyclopropanation using chiral metal catalysts. In contrast, the iodonium ylides are easily decomposed at room temperature by both copper and rhodium catalysts to provide carbenoid reactions with good enantioselectivities.[172] An illustrative example of the difference in reactivity between the iodonium ylides and diazo compounds can be seen when compared to the notably stable ylides of Meldrum's acid. Müller et al. found the phenyliodonium ylide of Meldrum's acid (**3.8c**) undergoes facile decomposition using $Rh_2(OAc)_4$, at room temperature, and can be used in cyclopropanation reactions of styrene to provide **3.24c** in quantitative yield (eq 3.4). However, under the same conditions, the analogous diazo compound (**3.23c**) failed to react. Müller et al. noted that heating **3.23c** to 80–90 °C in fluorobenzene was required to obtain yields of cyclopropanation comparable to the reaction performed using **3.8c**. A subsequent study performed by Lee et al. found $Rh_2(OPiv)_4$ superior to $Rh_2(OAc)_4$ as a catalyst for the decomposition of this diazo compound in cyclopropanations of substituted styrenes.[179]

$$(3.4)$$

10 equiv Ph
5 mol% $Rh_2(OAc)_4$
DCM, rt

Y = IPh (**3.8c**)
Y = N_2 (**3.23c**)

3.24c
From **3.18c**, 100%
From **3.23c**, No reaction
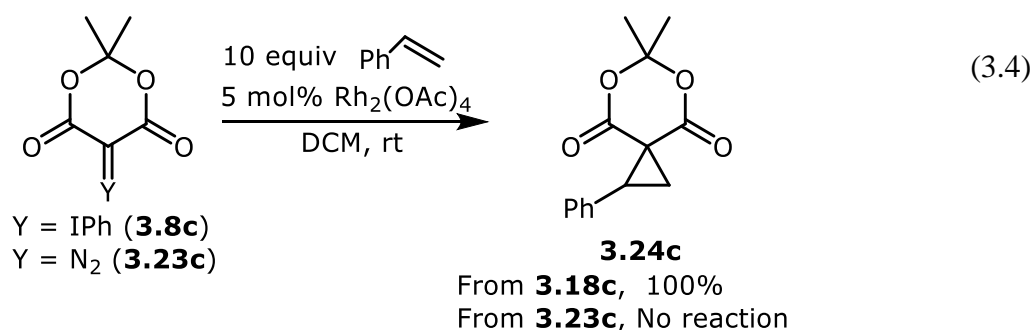
3.2. Geminal Dichlorination

The precedent of iodonium ylides acting as diazo surrogates in chemical reactions led us to suspect their potential as substrates for our geminal double ligand transfer reactions. As seen in

the proposed mechanism for the *gem*-dichlorination of diazo compounds using PhICl$_2$ (§2.2.5, Scheme 2-5), we postulated the leaving group ability of PhI to be sufficient for the transfer of one chloride ligand. The reaction of iodonium ylides and PhICl$_2$ could provide the reductive elimination of two equivalents of PhI and potentially afford a *gem*-dichlorination reaction. Therefore, these ylides could be potential substrates and help support our hypothesis that such an ylidic structure can allow for double ligand transfer (§1.3.3, Scheme 1-7). This led to the investigation of the *gem*-dichlorination of 1,3-iodonium ylides using PhICl$_2$.

As mentioned before, phenyliodonium ylides show limited thermal stability. For typical synthetic purposes, it can be advantageous for an ylide to be formed in situ and reacted immediately without isolation. However, the primary objective of this study was to determine whether double ligand transfer occurs from the reaction of PhICl$_2$ and iodonium ylides. Therefore, the amount of iodonium ylide reacting with PhICl$_2$ needed to be quantified. Also, typical conditions used to form iodonium ylides in situ would create unneeded complexity for studying the dichlorination reaction. Thus, we chose to use isolable iodonium ylides of 1,3-dicarbonyl compounds (**3.8**) for our studies. At the outset of this investigation, the *gem*-dichlorination of 2-diazo-1,3-dicarbonyl compound using PhICl$_2$ was concurrently being studied by another member of the Murphy group (K. Coffey). A secondary objective of this study was to determine the differences in reactivity between analogous diazonium- and iodonium ylides with PhICl$_2$.

3.2.1. Initial Studies and Reaction Optimization

For this study, PhICl$_2$ was synthesized in the same manner described in §2.2. The 1,3-dicarbonyl compounds were either obtained from commercial sources or synthesized, typically, via condensation reactions between a ketone and another carbonyl-containing compound (e.g., ketone, ester, carbonate, acid chloride, etc., eq 3.5). The resulting 1,3-dicarbonyl compounds

(**3.26**) were used to synthesize the iodonium ylides via a modified version of the protocol reported by Schank and Lick (eq 3.6).[153] The iodonium ylides used in this study were stored in a –20 °C freezer for, at most, 1 month before being discarded or purified.

$$(3.5)$$

$$(3.6)$$
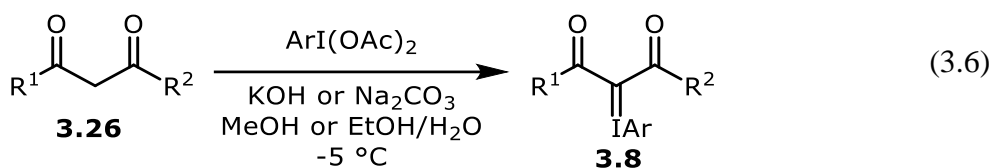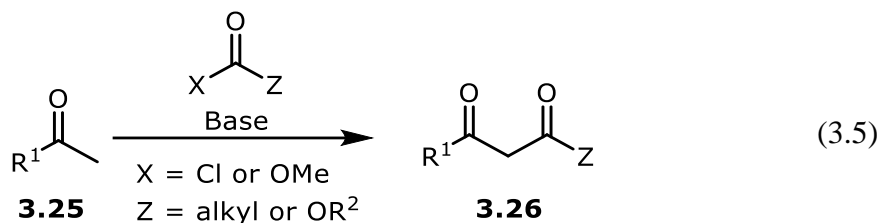
The phenyliodonium ylide of methyl benzoylacetate (**3.8e**) was chosen as the model substrate for reaction optimization studies. The optimization studies began by subjecting **3.8e** to the standard dichlorination condition developed for aryldiazoesters, which were determined to be the optimal conditions for the dichlorination of 2-diazo-1,3-dicarbonyl compounds as well.[103] These reactions were not monitored using TLC due to the iodonium ylide remaining at the baseline. Instead, the reactions were monitored by the colour change of the solution from yellow to near-colourless. After subsequent FCC, *gem*-dichloride **3.27e** was obtained in 52% yield (Table 3-1, entry 1). We found these reactions occurred very rapidly, typically within 5 minutes after the addition of PhICl$_2$. At this time, the ^{1}H NMR spectra of crude reaction mixtures indicated significant amounts of unreacted PhICl$_2$ (30–50%) remained despite complete consumption of the ylide. Using longer reactions times did not significantly affect the yield of **3.27e**. The short reaction time, 5 minutes, led us to believe the thermal stability of the ylide was not the main reason for the discrepancy between the conversion of ylide and the yield of the product. Therefore, we suspected that the reaction of **3.8e** and PhICl$_2$ generates a reactive intermediate which could be intercepted

by another molecule of **3.8e** leading to the formation of side products (e.g., products of a formal carbene dimerization reaction, see §3.2.3 for discussion) instead of the desired *gem*-dichloride. Therefore, to minimize side product formation, the reaction conditions were modified to reduce the relative concentration of **3.8e** versus PhICl$_2$ in the reaction mixture. This was accomplished by exploiting the difference in solubilities of these two reagents. To this end, a combination of reversing the order of addition (entry 2) and performing the reaction at 0 °C while diluting the reaction mixture allowed for **3.27e** to be obtained in higher yields (62% and 74%, entries 2 and 3, respectively). Interestingly, we found the dichlorination proceeded just as well when pyridine was not included in the reaction mixture (79% yield, entry 4). Apparently, the increased reactivity of **3.8e** enables its reaction with PhICl$_2$ without the need of pyridine-activation, unlike the diazo compounds. Equivalent amounts of *gem*-dichloride could be obtained when using MeCN

Table 3-1. Optimization of the Dichlorination of Iodonium Ylides
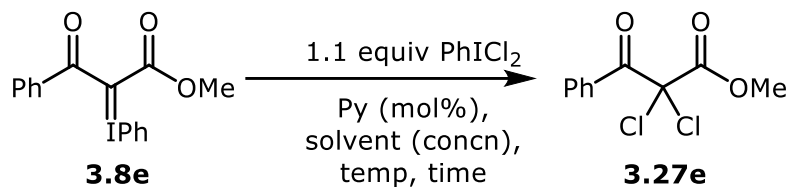
entry	solvent	concn (M)	temp (°C)	Py (mol%)	time (min)	yield (%)[a]
1	DCM	0.2	rt	5	5	52
2	DCM	0.2	rt	5	5	62[b]
3	DCM	0.1	0	5	5	74
4	DCM	0.1	0	0	5	79[b]
5	MeCN	0.1	0	0	5	79[b]
6	MeCN	0.1	0	0	5	66
7	MeCN	0.05	0	0	20	70[b]

[a]General conditions: **3.8e** (0.30 mmol, 1.0 equiv) dissolved in solvent and cooled (if necessary). Then, pyridine (0 or 5 mol%) added, followed by PhICl$_2$ (0.33 mmol, 1.1 equiv). Yields refer to isolated yield after column chromatography.[b]The ylide was added to a solution of the other reagents.

as the reaction solvent (79% yield, entry 5). When using MeCN as the reaction solvent, the difference between adding the ylide last or first was observed to follow the same trend (79% yield vs 66% yield, entry 5 vs 6) as when the reactions were conducted in DCM. As a final check, further dilution of the reaction mixture with MeCN proved detrimental to the reaction outcome (70% yield, entry 7). Therefore, the standard conditions for the dichlorination of iodonium ylides were considered to be the conditions shown in entry 5. The high yields of these reactions (~70% relative to $PhICl_2$) demonstrated that geminal double ligand transfer was occurring.

When choosing between DCM and MeCN as the preferred reaction solvent, we considered which solvent would likely provide the most robust reactions when applied to other iodonium ylides. In order to lower the amounts of the ylide undergoing formal carbene dimerization, we desired the solvent in which iodonium ylides and $PhICl_2$ had the larger difference in solubility. We chose MeCN as the preferred solvent because most iodonium ylides typically display lower solubility in MeCN than in DCM. Simply stirring $PhICl_2$ in MeCN at these concentrations (0.1 M) only allowed for the partial dissolution of this reagent. However, it should be noted that $PhICl_2$ synthesized while controlling the reaction parameters discussed in §2.2 could be completely dissolved with the assistance of sonication. Batches of $PhICl_2$ synthesized carelessly could not be completely dissolved in MeCN at this concentration, even with the assistance of sonication. Therefore, subsequent dichlorination reactions involved the dissolution of $PhICl_2$ in MeCN with the assistance of sonication to increase the availability of the chlorinating agent in solution.

3.2.2. Substrate Scope Studies

The standard dichlorination conditions were applied to a variety of phenyliodonium ylides of 1,3-dicarbonyl compounds. During this study, we found the reactions were all very rapid and were typically complete shortly after no remaining ylide was observed to be suspended in solution.

Generally, these dichlorination reactions were deemed to be complete between 5–100 minutes after the addition of the ylide to the reaction mixture. The *gem*-dichlorination of phenyliodonium ylides of other acyclic 1,3-dicarbonyl compounds (Table 3-2) was first investigated. Dichlorination of the phenyliodonium ylides of 1,3-ketoesters (**3.8e-i**) and dibenzyl malonate occurred (**3.8h**) in good yield (>75%). However, the phenyliodonium ylide of dibenzoylmethane (**3.8i**) was dichlorinated in low yield (28%). Other than this exception, the dichlorination of iodonium ylides using PhICl$_2$ can provide comparable yields of *gem*-dichlorinated products when compared to the dichlorination of the analogous diazo compounds. However, for the ylides of methyl (2-naphthoyl)acetate (**3.8g** and **3.23g**), the iodonium ylide was chlorinated in significantly higher

Table 3-2. Dichlorination of Diazonium- and Iodonium Ylides of Acyclic 1,3-Dicarbonyl Compounds
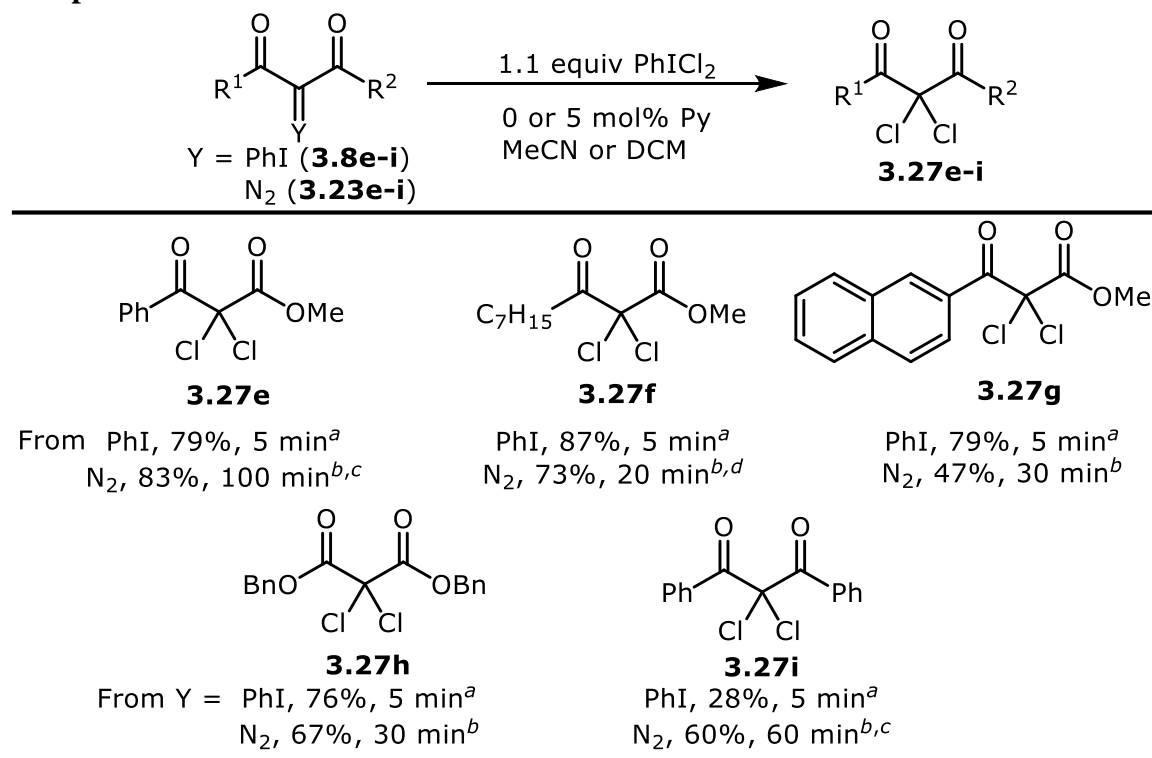
Y = PhI (**3.8e-i**)
N$_2$ (**3.23e-i**)

1.1 equiv PhICl$_2$

0 or 5 mol% Py
MeCN or DCM

3.27e-i

3.27e
From PhI, 79%, 5 min[a]
N$_2$, 83%, 100 min[b,c]

3.27f
PhI, 87%, 5 min[a]
N$_2$, 73%, 20 min[b,d]

3.27g
PhI, 79%, 5 min[a]
N$_2$, 47%, 30 min[b]

3.27h
From Y = PhI, 76%, 5 min[a]
N$_2$, 67%, 30 min[b]

3.27i
PhI, 28%, 5 min[a]
N$_2$, 60%, 60 min[b,c]

[a]General conditions: PhICl$_2$ (1.1 equiv), dissolved in MeCN (0.1 M), at 0 °C. Ylide (1.0 equiv) was added in one portion. Isolated yields after column chromatography.[b]General conditions: diazo compound (1.0 equiv), pyridine (0 or 5 mol%), and PhICl$_2$ (1.1 equiv), dissolved in DCM (0.2 M), at rt.[c]See Coffey and Murphy.[103] [d]Performed by T. Tuck.

yield than the diazo compound (79% vs 47%, respectively). In the case of ylides of dibenzoylmethane, the iodonium ylide (**3.8i**) provided significantly less product than **3.23i** (28% yield vs 60% yield, respectively).

Derivatives of ylide **3.8e** bearing substituted benzenes were synthesized and subjected to the standard dichlorination conditions to examine the steric and electronic effects of the substituents (Table 3-3). The presence of a methyl group on the benzene ring appeared to lower the yield of dichlorination when placed at the *para-* or *ortho-* position (**3.27e** vs **3.27j** and **3.27k**, 79% vs 70% and 72%, respectively). The minimal difference between the dichlor-

Table 3-3. Dichlorination of Analogs of the Phenyliodonium Ylide of Methyl Benzoylacetate

3.8e, 3.8j-o

PhICl$_2$ (1.1 equiv)
MeCN, 0 °C

3.27e, 3.27j-o[a]

3.27e
79%, 5 min

3.27j
70%, 5 min

3.27k
72%, 5 min

3.27l
70%, 10 min

3.27m
30%, 10 min

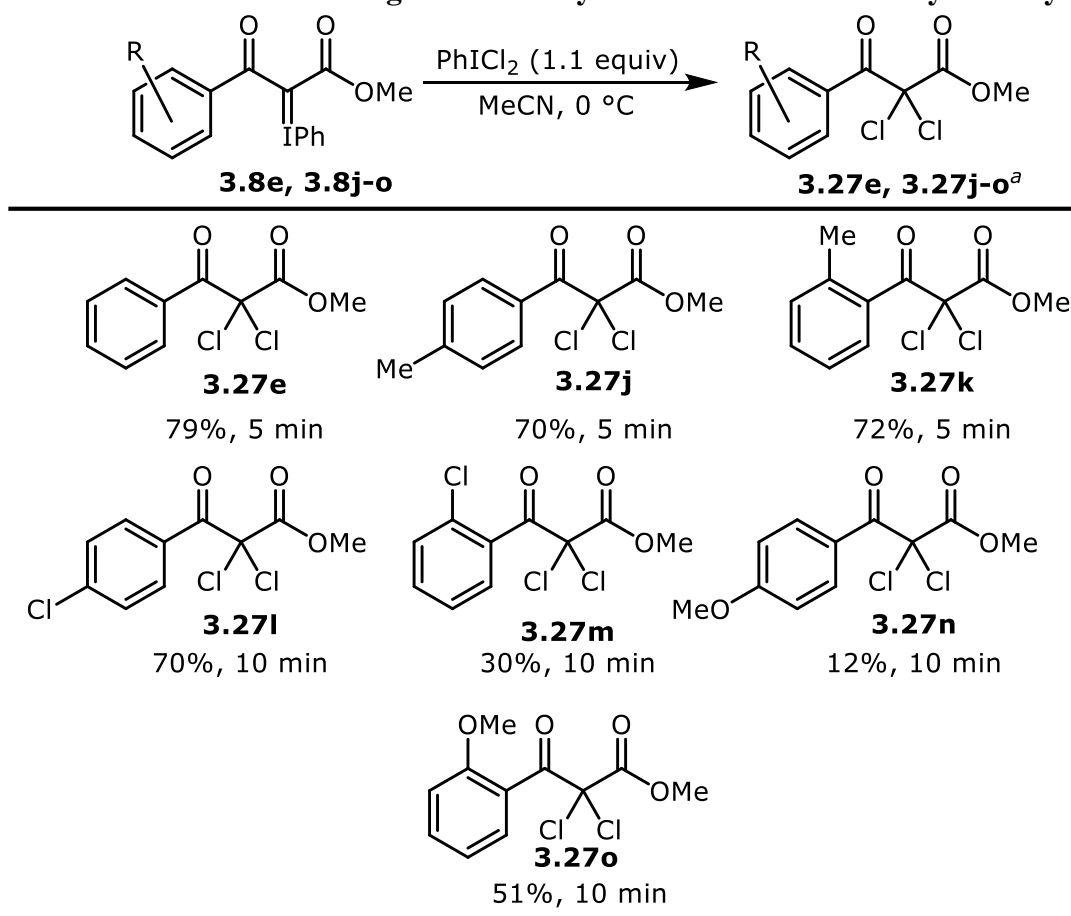**3.27n**
12%, 10 min

3.27o
51%, 10 min

[a]General conditions: PhICl$_2$ (1.1 equiv), dissolved in MeCN (0.1 M), at 0 °C. Ylide (1.0 equiv) was added in one portion. Isolated yields after column chromatography.

88

ination of **3.8j** and **3.8k** suggests a negligible steric effect of the methyl substituent. Using a chloro-or a methoxy- substituent as representatives of electron-withdrawing or electron-releasing groups, respectively, we found the positioning of these groups on the benzene ring played a significant contribution to the outcome of the reaction. The *para*-chlorinated isomer **3.8l**, was chlorinated in similar yield (70%) to **3.8j** and **3.8k**, but a dramatic decrease in yield was observed when using *ortho*-chlorinated isomer **3.8m** (30%). The opposite trend was found when using a methoxy-substituent, where the *para*- isomer provided very little dichlorination (**3.27n**, 12% yield), significantly lower than the *ortho*- isomer (**3.27o**, 51% yield). We noticed that two poorly-performing ylides, **3.8m** and **3.8n**, were isolated as beige or yellow solids which decomposed rapidly at room temperature. Ylide **3.8m** decomposed into a yellow liquid within 1 hour at room temperature while **3.8n** decomposed within a few minutes at room temperature. Synthesis and isolation of ylide **3.8n** involved precipitation in solvent cooled to $-78\ °C$ and the solid was handled using labware chilled with dry-ice and within glassware chilled in a dry-ice/acetone bath. We speculate the low thermal stability may be correlated to their low yields in their dichlorination reactions.

The dichlorination of phenyliodonium ylides of cyclic 1,3-dicarbonyl compounds revealed some differences in reactivity when compared to the acyclic 1,3-dicarbonyl compounds. This was not surprising as ylides of cyclic 1,3-dicarbonyl compounds are, typically, less reactive than their acyclic counterparts. This difference was most notable during the dichlorination of the diazo compounds derived from cyclic 1,3-dicarbonyls, which were found to proceed very sluggishly (i.e., requiring days to complete reaction).[103] When treated with $PhICl_2$, we noticed iodonium ylide **3.8p** reacted very slowly, even when the reaction was performed at room temperature (3 hours, Scheme 3-5). Purification of the crude reaction mixture via FCC led to the isolation of 2,2-

dichloro-2'-hydroxyacetophenone (**3.27p'**), presumably via the hydrolysis and subsequent decarboxylation of the dichlorinated 1,3-ketoester.

Scheme 3-5. Formation of 2,2-Dichloro-2'hydroxyacetophenone
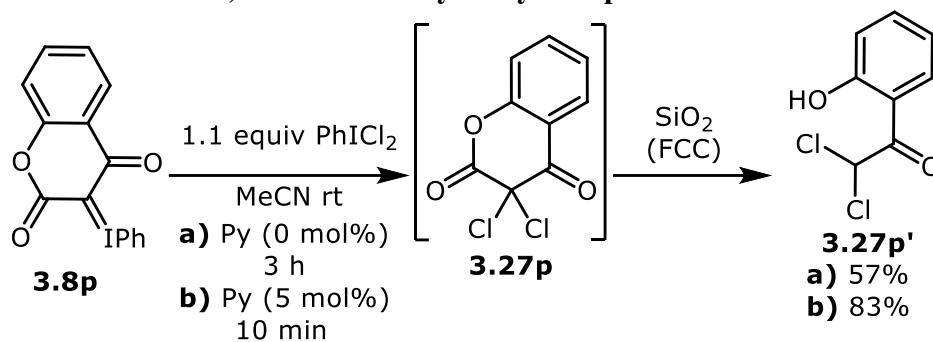
Only trace amounts of **3.27p'** were observed in the ^{1}H NMR spectra of the crude reaction mixtures over the course of our studies, leading us to believe the majority of the decomposition of **3.27p** into **3.27p'** occurs during FCC. The dichlorination of this ylide benefited from the inclusion of 5 mol% of pyridine into the reaction mixture. The presence of this catalytic amount of pyridine increased the reaction rate and led to improved yields of **3.27p'** (57% vs 83%, Scheme 3-5), similar to what was observed when the dichlorination of diazo compounds was studied (§2.2.1). We believe the rate of formation of **3.27p** benefits from the pyridine-activation of PhICl$_2$ because of the stabilization the 4-hydroxycoumarin backbone provides to the phenyliodonium ylide, rendering the ylide **3.8p** less nucleophilic than **3.8e–o**. Ylide **3.8p** shows exceptional thermal stability amongst phenyliodonium ylides and is also one of the few phenyliodonium ylides that can be crystallized and analyzed by single-crystal X-ray diffraction.[147] The X-ray structure of **3.8p** shows the zwitterionic form has significant contribution to the electronic structure.

The dichlorination reactions of phenyliodonium ylides of other cyclic 1,3-dicarbonyl compounds (**3.8a**, **3.8c**, **3.8d**, and **3.8q–r**) were met with varying levels of success (Table 3-4). The phenyliodonium ylide of 1,3-cyclohexandione (**3.8q**) was dichlorinated in excellent yield

90

(94%) while the *gem*-dimethylated analog (**3.8a**) provided the respective dichloride in low yield (**3.27a**, 32%). Low yields were also observed when chlorinating other phenyliodonium ylides bearing a transannular, fully-substituted, sp^3-hybridized carbon (**3.27r'** and **3.27c**, 32% and 44%, respectively). We suspect the steric hindrance provided by this fully-substituted centre impedes our desired reaction. Similar to chlorination of **3.8p**, the resulting product of

Table 3-4. Dichlorination of Diazonium and Phenyliodonium Ylides of Cyclic 1,3-Dicarbonyl Compounds

Y = PhI, **3.8**
Y = N$_2$, **3.23**

1.1 equiv PhICl$_2$
0 or 5 mol% Py
MeCN or DCM

3.27

3.27q
From Y = PhI, 94%, 5 min[a]
N$_2$, 39%, 60 min[b]

3.27a
PhI, 32%, 5 min[a]
N$_2$, 73%, 16 h[b]

3.27r
PhI, 32%, 5 min [a,c]
N$_2$, ND

3.27c
From Y = PhI, 44%, 20 min[a,d]
N$_2$, NR[b,d]

3.27d
PhI, 85%, 100 min[a,e]
N$_2$, 60%, 3 days[b]
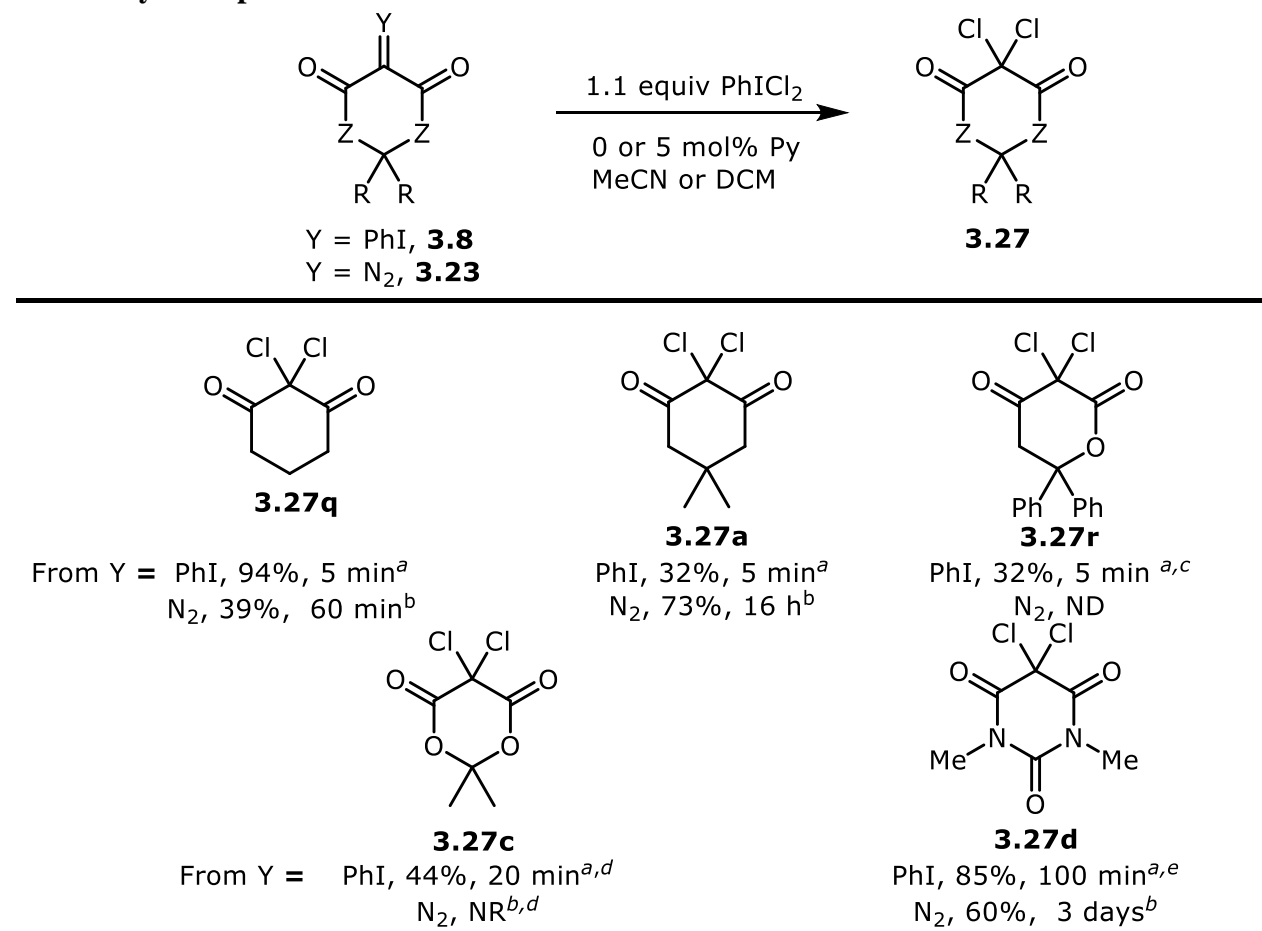
[a]General conditions: PhICl$_2$ (1.1 equiv), dissolved in MeCN (0.1 M), at 0 °C, then **3.8** (1.0 equiv) was added in one portion. Isolated yield after column chromatography.[b]General conditions: diazo compound (1.0 equiv), Py (5 mol%), and PhICl$_2$(1.1 equiv), dissolved in DCM (0.2 M), at rt. Isolated yield after column chromatography. See Coffey and Murphy.[103] [c]This product decarboxylated upon column chromatography to yield **3.27r'** (see text).[d]NR = no reaction.[e]Pyridine (5 mol%) was included in the reaction mixture, the cooling bath was allowed to warm naturally.

the dichlorination of **3.8r** underwent decomposition during purification yielding **3.27r'** in 32%

yield (eq Scheme 3-6). Finally, the phenyliodonium ylide of dimethylbarbituric acid (**3.8d**)

provided good yield of the respective dichloride (**3.27d**, 85%). In the presence of 5 mol% pyridine,

the dichlorination reactions of ylides **3.8c** and **3.8d** were observed to provide more favorable

product distributions (determined by ^{1}H NMR spectroscopy analysis of the crude reaction

mixtures). Also, performing these reactions within a flask submerged in a 0 °C water bath that was

allowed to warm naturally over the course of the reaction time was found to provide better results

than maintaining the reaction temperature at 0 °C. These modifications led to the yields described

for their chlorination in Table 3-4.

**Scheme 3-6. Formation of 1,1-Dichloro-4,4-diphenylbut-3-en-2-one**
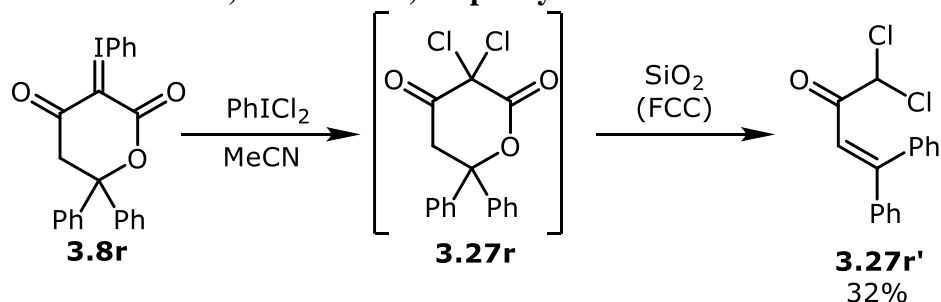
Subjecting iodonium phenolate **3.28** or cyclic iodonium ylide **3.11** to PhICl$_2$, failed to

generate the respective dichlorinated compounds (eqs 3.7 and 3.8). An iodonium phenolate (**3.28**)

failed to react while another student (T. Tuck) found attempting chlorination of **3.11** provided an

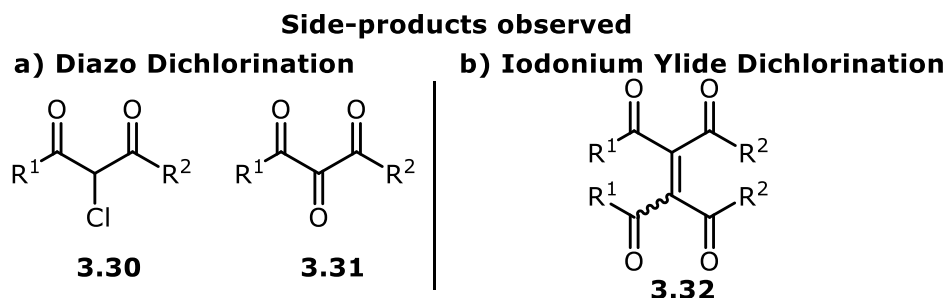intractable mixture of products.

(3.7)

$$(3.8)$$
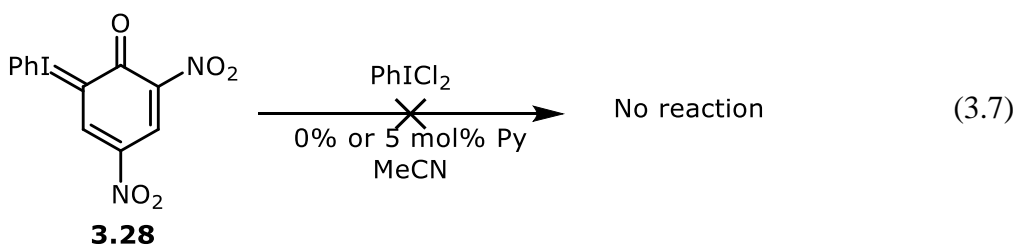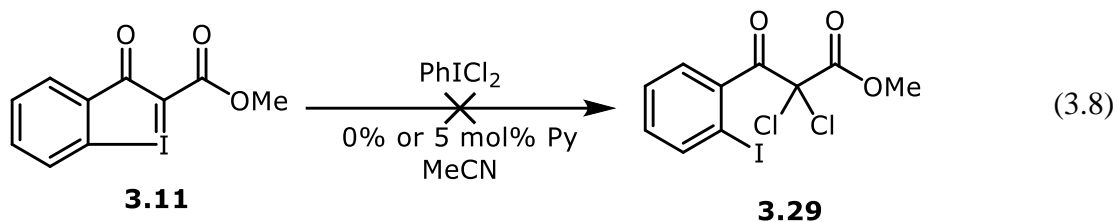
When comparing the dichlorination of iodonium ylides of cyclic 1,3-dicarbonyl compounds relative to the analogous diazo compounds, we found the iodonium ylides reacted faster, with typical reactions completing within less than one tenth of the reaction time. Yields of dichlorides obtained from iodonium ylides without an endocyclic fully-substituted sp^3-hybridized carbon were found to be higher than the resulting diazo compounds. It is notable that 5-diazo Meldrum's acid (**3.23c**) failed to react with $PhICl_2$ while the analogous phenyliodonium ylide (**3.8c**) was able to, even at lower temperature. This increase in reactivity is similar to what was discussed earlier with respect to relative reactivity of iodonium ylides and diazo compounds in metal-catalyzed decomposition to metal carbenes.

3.2.3. Side Product Analysis

Over the course of this study, the side products observed in the dichlorination of iodonium ylides using differed from those observed during the dichlorination of diazo compounds (Figure 3-4). Side products of the dichlorination of diazo compounds were found to be monochlorides (**3.30**) and tri-carbonyl compounds (**3.31**).[103] In contrast, the reaction of $PhICl_2$ and iodonium ylides provided inseparable mixtures of side products which did not contain **3.30** or **3.31**. Analyzing mixtures of side products formed in the reaction of **3.8m** with $PhICl_2$ by GC-MS revealed a component in which the nominal mass and isotopic ratio was consistent with alkene **3.32** ($R_1 = 2\text{-Cl-}C_6H_4$, $m/z = 420$, $[M]^+:[M+2]^+:[M+4]^+$, 9:6:1).

Side-products observed
a) Diazo Dichlorination   **b) Iodonium Ylide Dichlorination**

3.30   **3.31**   **3.32**

Figure 3-4. Side products observed in the dichlorination of diazonium- and phenyliodonium ylides of 1,3-dicarbonyl compounds.

These types of alkenes can be formed via dimerization reactions when these ylides are used in reactions as precursors to carbene or carbenoid intermediates. This led us to investigate if the reaction between iodonium ylides and PhICl$_2$ can provide other products of carbenoid reactivity. We attempted to trap potential carbenoid intermediates via an intramolecular cyclopropanation of the alkene present in ylide **3.8s**. Synthesis of this ylide led to the recovery of an unstable liquid which rapidly decomposed at room temperature. Forming the ylide in situ and treatment using PhICl$_2$ did not lead to the desired cyclopropane **3.33** (eq 3.9).

3.8s   **3.33**   (3.9)
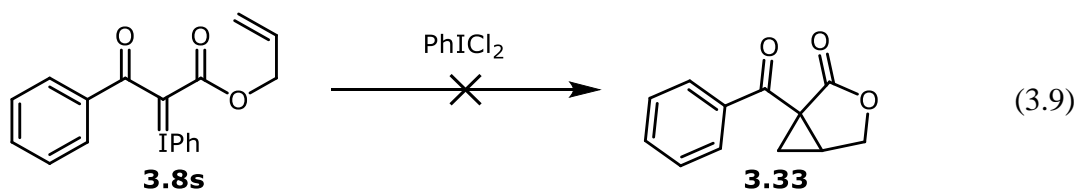
After observing this negative result, we decided to design a system which could potentially trap a carbene generated at the ylidic carbon based on a different type of reaction. Rhodium- and copper carbenoid species generated from ylides similar in structure to **3.8t** are known to react with rhodium- or copper catalysts to form the corresponding oxonium ylides and undergo subsequent [2,3]-rearrangement to yield furanones **3.34**.[170,180,181] However, subjecting **3.8t** to PhICl$_2$ did not yield such carbenoid reactivity (eq 3.10)

(3.10)
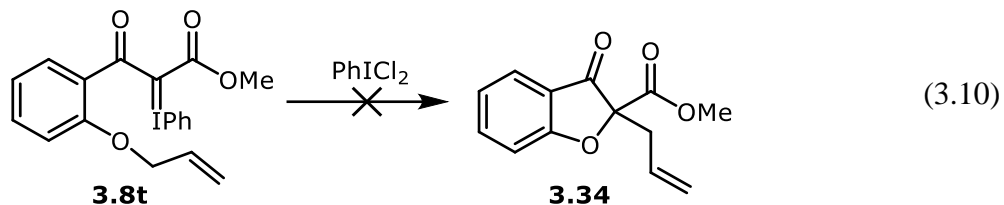
While attempts to trap potential carbenoid intermediates via intramolecular processes failed, an intermolecular cyclopropanation was found to occur through the mixture of ylide **3.8e**, PhICl$_2$, and excess styrene (eq 3.11). ^{1}H NMR analysis of the crude reaction mixture revealed the presence of cyclopropanes **3.24e** with an 8.4:1 diastereomeric ratio (46% combined yield), favoring the isomer containing a *trans*- stereochemical relationship between the carbomethoxy- and the phenyl group. An analytic sample of the major diastereomer was obtained in low isolated yield (19%) after purification via successive column chromatography. The signals of the minor diastereomer found in the ^{1}H NMR spectrum of the crude reaction mixture matched the data for the *cis*- isomer reported by Charette et al.[182] They found *cis*-**3.24e** as the major product when synthesizing the cyclopropane through the rhodium carbenoid (eq 3.12)[182] and have unambiguously determined the geometry of the stereocentres of this cyclopropane via X-ray crystallography.[183]

(3.11)

46% NMR yield (8.4:1 *trans*:*cis*)
19% isolated yield (*trans*)

$$(3.12)$$
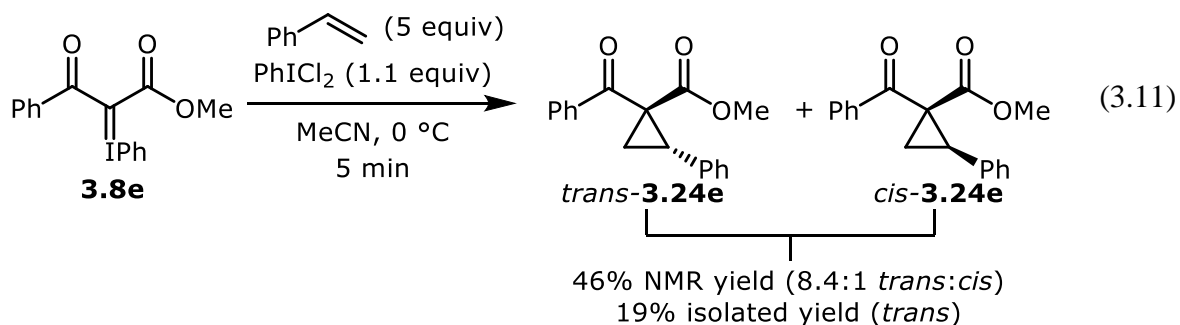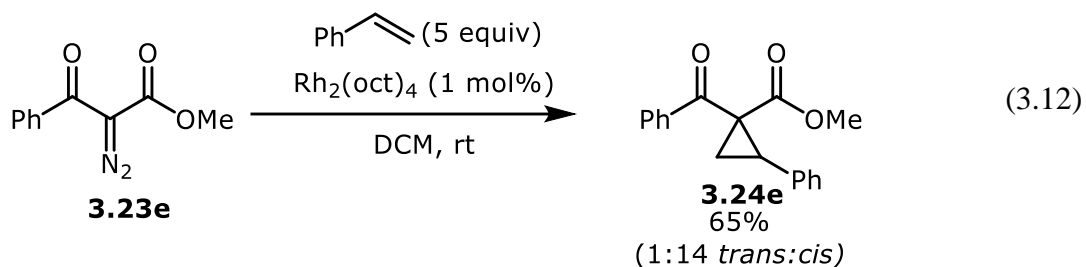
3.2.4. Mechanistic Discussion

Based on the general reactivity patterns of iodonium ylides and that the fact the side products of the dichlorination of iodonium ylides and diazo compounds differ, we currently presume the dichlorination of iodonium ylides using $PhICl_2$ does not occur through a mechanism analogous to our tentative mechanistic proposal for the reaction of diazo compounds and $PhICl_2$ (Scheme 2-5, §2.2.5). Despite the carbenoid reactivity observed during the reaction of $PhICl_2$ and iodonium ylides (i.e., formation of formal carbene dimer and cyclopropanation), due to the mild reaction conditions (0 °C), we do not believe free carbene intermediates are involved, which generally require high temperatures or photolysis to facilitate the α-elimination of PhI.[165]

For the dichlorination of iodonium ylides of 1,3-dicarbonyl compound we propose the following sequence of events (Scheme 3-7): First, the ylide (**3.35**) exchanges for one of the chlorides of $PhICl_2$. Due to the high zwitterionic character of iodonium ylides of 1,3-dicarbonyl, the oxygen could act as the nucleophilic site of the ylide. Association of the displaced chloride ligand onto the iodonium of **3.36** could lead to intermediate **3.37** and subsequent pseudorotation could place a chloride ligand in proximity for an intramolecular S_N2'-type reductive elimination via a 5-membered ring transition state (**3.38**) to yield iodane **3.39**, which can undergo another reductive elimination of a second equivalent of PhI to furnish dichloride **3.40**.

96

Scheme 3-7. Speculative Dichlorination Mechanism of Iodonium Ylides
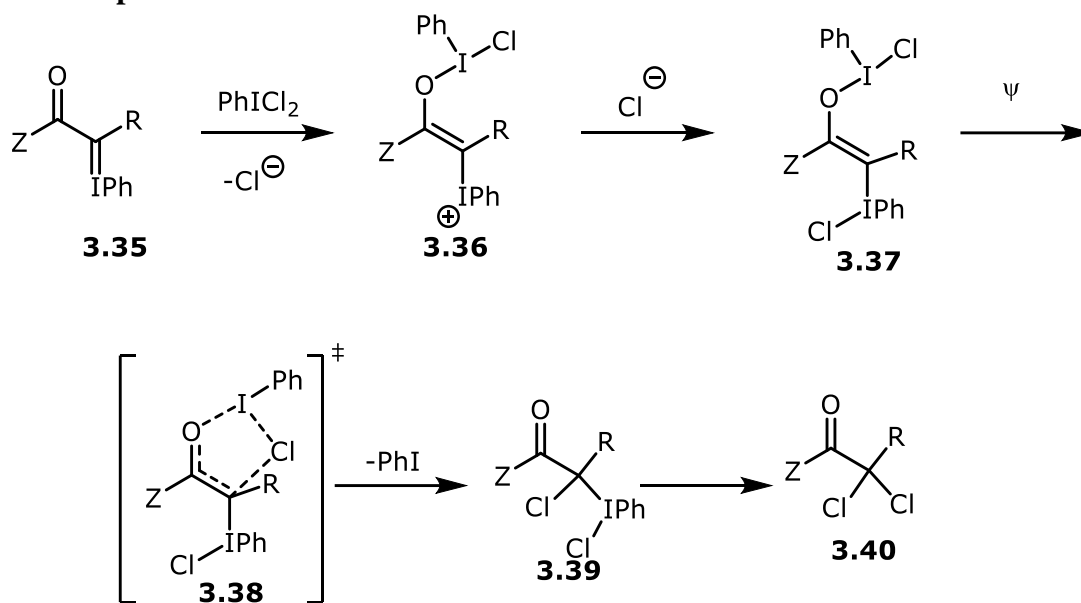
Intercepting intermediate **3.36** with ylide **3.35** or styrene could ultimately lead to the formal

carbene dimerization product or the cyclopropanation product, respectively. A similar S_N2'-type

reductive elimination has been previously proposed by Legault et al. for the α-oxytosylation of

acetophenone using HTIB, via iodoenolate **3.41**, and supported using DFT calculations (Scheme

3-8).[184]

Scheme 3-8. S_N2'-type Reductive Elimination
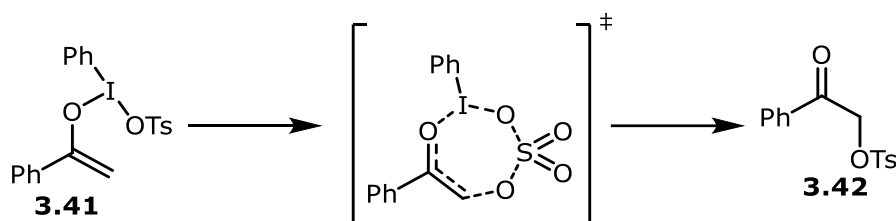
Our proposed reaction mechanism is quite speculative as there are, to our knowledge, no

literature examples of iodonium ylides of 1,3-dicarbonyl compound reacting with

(dihaloiodo)arenes. Nevertheless, the high reactivity between iodonium ylides of 1,3-dicarbonyl

compound and PhICl₂ provides dichlorination of a variety of ylides under very mild conditions and

97

presents an interesting introduction to the study between the reaction of these ylides and hypervalent iodine(III) reagents. The ability for cyclopropanes to be generated when styrene was added to our reaction mixtures caught our attention as the cyclopropane formed from a reaction whose diastereoselectivity is complementary to the selectivity obtained when proceeding through metallocarbenoid chemistry. This inspired a systematic study into metal-free cyclopropanation of iodonium ylides using hypervalent iodine reagents.

3.3. Concluding Remarks

In this chapter, the *gem*-dichlorination of iodonium ylides of acyclic and cyclic 1,3-dicarbonyl compounds using PhICl$_2$ was described. These reactions were found to proceed rapidly under mild conditions (i.e., 5–100 min). Dichlorination of the phenyliodonum ylides of acyclic 1,3-dicarbonyl compounds proceeded in good yields (typically >70%) unless the iodonium ylide was observed to be prone to decomposition at room temperature. When compared with the dichlorination of diazo compounds, the analgous iodonium ylides display higher reactivity towards PhICl$_2$ as the iodonium ylides react without the need pyridine to activate PhICl$_2$. The optimal conditions for the dichlorination of iodonium ylides allowed for faster reactions than the optimal conditions for the dichlorination of the analogous diazo compounds. Notably, when investigating the dichlorination of the exceptionally stable diazonium- and iodonium ylides of Meldrum's acid, only the iodonium ylide was found able to be chlorinated. Phenyliodonium ylides of both acyclic and cyclic 1,3-dicarbonyl compounds were found to readily react with PhICl$_2$. Some less reactive phenyliodonium ylides of cyclic 1,3-dicarbonyl compounds benefited from the addition of catalytic amounts of pyridine to the reaction. The formal carbene dimerization of the iodonium ylide was observed, and this led to the investigation of other carbenoid reactivity that could be provided by the mixture of an iodonium ylide with PhICl$_2$.

When the *gem*-dichlorination of the phenyliodonium ylide of methyl benzoylacetate was performed in the presence of styrene, modest amounts of cyclopropanation were observed. Attempts to optimize the cyclopropanation using PhICl$_2$ failed to provide increased amounts of cyclopropanation products. This led to a study focusing on the identification of reagents that could activate iodonium ylides towards metal-free intermolecular cyclopropanation of alkenes and is the subject of Chapter 4.

3.4. Experimental

All reactions were performed using oven-dried or flame-dried glassware under a positive pressure of nitrogen unless otherwise stated. PhICl$_2$ was synthesized as described in Chapter 2. Iodonium ylides **3.11**[185] and **3.28**.[186] were prepared using literature procedures. Dry DCM, THF, DCE, toluene, and Et$_2$O were obtained from a JC Meyer solvent purification system,[122] and were used without further purification. Anhydrous MeCN and DMSO were obtained by storing the solvents over activated 3 Å or 4 Å molecular sieves (respectively) overnight and were used without further purification. Molecular sieves were activated by heating the sieves to 150–300 °C under high vacuum (0.1–0.05 torr) overnight. All other solvents and reagents were obtained from commercial sources (e.g., Aldrich, Oakwood Chemicals) and were used without further purification unless otherwise stated. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm Kieselgel 60 F254 (Merck). Unless otherwise stated, flash chromatography columns were packed with 230–400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.0 ppm). Positive ion electrospray ionization (+ESI) and negative ion electrospray ionization (-ESI) were performed

with a Thermo Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. For ESI, samples were infused at 10 µL/min in either 1:1 CH_3OH/H_2O+0.1% formic acid or 1:1 CH_3OH/H_2O+0.2% NH_4OH. IR spectroscopy was perofmred using aPerkinElmer Spectrum Two FT-IR spectrometer.

General Procedure 3.1 (GP3.1) – Synthesis of the of β-Ketoesters

A dry two neck flask equipped with a reflux condenser, a rubber septum, and a magnetic stir bar was charged with NaH (60% wt in mineral oil, 4.0 g, 100 mmol). To this flask were added toluene (8 mL) and dimethyl carbonate (9.1 g, 100 mmol, 2.5 equiv), and the resulting mixture was heated to reflux and acetophenone (4.8 g, 40 mmol, 1.0 equiv) in toluene (20 mL) was added dropwise into the flask. The reaction mixture was stirred for 0.5 h, at which point hydrogen evolution had ceased. The suspension was cooled to 0 °C, diluted with EtOAc (150 mL), and carefully quenched with MeOH (10 mL), followed by H_2O, and then acidified to pH < 5 using 1 M HCl. The organic layer was separated, washed sequentially with H_2O (200 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting biphasic liquid was partitioned between MeCN (20 mL) and hexanes (10 mL) and washed with hexanes (25 mL × 2) and concentrated in vacuo to afford the β-ketoesters.

The following known 1,3-ketoesters were synthesized using this method and their spectral data matched those reported in the literature: methyl benzoylacetate (**3.26e**, 97% yield),[187] methyl (2-naphthoyl)acetate (**3.26g**, 89% yield),[187] methyl (2-toluoyl)acetate (**3.26j**, 91% yield),[187] methyl (4-chlorobenzoyl)acetate (**3.26l**, 83% yield),[188] and methyl (4-anisoyl)acetate (**3.26n**, 87% yield).[187]

General Procedure 3.3.1 (GP3.3.1) – Synthesis of Phenyliodonium Ylides of Acyclic 1,3-Dicarbonyl Compounds

The following procedure was based upon a protocol reported by Lick:[153] To a cooled (–5 °C) 50 mL round bottom flask containing a stirring solution of acyclic 1,3-dicarbonyl compound (5.0 mmol) in MeOH (3.5 mL) was added 30% (wt/v) KOH/MeOH (3.5 mL) solution over 1 minute. To this mixture, iodobenzene diacetate (5.0 mmol) in MeOH (8 mL) was added slowly to ensure the reaction temperature remained < 0 °C. After allowing the mixture to stir for 30–60 min, the resulting reaction mixture was poured onto ice (~100 mL), diluted with water (75 mL), and then transferred to a separatory funnel and extracted with DCM (30 mL × 3). The combined organic extracts were dried over MgSO$_4$, filtered, and then concentrated to ~20% of its original volume using a rotary evaporator. The resulting solution was treated with solvent (e.g., Et$_2$O and/or hexanes) and cooled to 0 °C to induce precipitation of the ylide. The solid was collected via suction filtration and dried in vacuo to yield the phenyliodonium ylides as typically white amorphous solids and were either used immediately or stored in a –20 °C freezer. Note: Iodonium ylides of acyclic 1,3-dicarbonyl compounds are typically thermally unstable. It is recommended that work-up/isolation be performed as quickly as possible, while keeping the organic extracts cooled in an ice-water bath whenever possible.

This method was used to prepare **3.8e**, **3.8i**. Their spectral data matched those reported in the literature.[153]

**General Procedure 3.3.2 (GP3.3.2) – Synthesis of Phenyliodonium Ylides of Cyclic β-Dicarbonyl Compounds**

The following procedure was based upon a protocol reported by Lick:[153] A solution of PhI(OAc)$_2$ (5.0 mmol, 1.0 equiv) in EtOH (15 mL) was added to a stirred solution of cyclic iodonium ylide (5.0 mmol, 1.0 equiv) dissolved in 10% aq Na$_2$CO$_3$ (15 mL) at room temperature. The resulting mixture was stirred for 30 min at room temperature after which it was poured onto ice (~100 mL), diluted with water (50 mL), transferred to a separatory funnel, and then extracted with DCM (30 mL × 3). The combined organic extracts were dried over MgSO$_4$ and filtered through a sintered glass funnel and concentrated to ~20% of its original volume using a rotary evaporator. The resulting solution was treated with solvent (e.g., Et$_2$O and/or hexanes) and cooled to 0 °C in order to induce precipitation of the ylide. The solid was collected via suction filtration and dried in vacuo to yield the phenyliodonium ylides as white amorphous solids and were either used immediately or stored in a –20 °C freezer.

This method was used to prepare **3.8a**, **3.8c**, and **3.8d**. Their spectral data matched those reported in the literature.[153]

General Procedure 3.4 (GP3.4) – Dichlorination of Phenyliodonium Ylides

In a 10 mL round bottom flask, PhICl$_2$ (0.66 mmol, 1.1 equiv) was dissolved in MeCN (6 mL) with the assistance of sonication. The flask containing the resulting yellow solution was cooled to 0 °C and then ylide **3.8** (0.60 mmol, 1.0 equiv) was added in one portion. The reaction mixture was allowed to stir at 0 °C until the insoluble ylide could not be visually observed (typically 5–10 min) after which time, it was concentrated in vacuo and purified by flash chromatography (silica gel).

Phenyliodonium ylide of methyl benzoylacetate (3.8e)
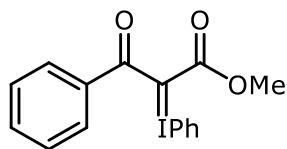
This iodonium ylide was formed via **GP3.3.1** using methyl benzoylacetate (1.78 g, 10.0 mmol). Following concentration of the organic extracts, the solution containing the crude iodonium ylide was diluted with CH_2Cl_2, $Et_2O$, and hexanes and concentrated in vacuo briefly to induce precipitation and the resulting suspension cooled to 0 °C. The solid was collected by vacuum filtration to yield the title compound as a white amorphous solid (2.07 g, 54% yield). mp 80–82 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.55–7.54 (m, 3H), 7.42–7.36 (m, 5H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.0, 165.0, 139.5, 133.1, 131.38, 131.21, 129.4, 128.1, 127.3, 112.9, 83.1, 51.6; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for $C_{16}H_{14}IO_3$, 380.9482; found 380.9481.

Phenyliodonium of methyl octanoylacetate (3.8f)
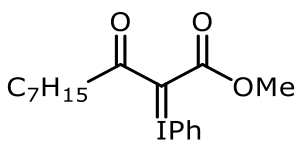
The title compound was synthesized via **GP3.3.1** using methyl octanoylacetate (**3.26f**)[189] (1.20 g, 6.0 mmol). Precipitation of the title compound from a mixture of DCM, Et_2O, and hexanes yielded a white amorphous solid (1.41 g, 58% yield). This compound decomposed slightly during acquisition of the NMR spectra. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (dd, *J* = 8.3, 0.9 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 3.66 (s, 3H), 2.99 (t, *J* = 7.7 Hz, 2H), 1.68–1.62 (m, 2H), 1.37–1.22 (m, 8 H), 0.89–0.84 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 190.3, 165.3, 132.9, 131.5, 131.3, 112.7, 51.8, 38.1, 31.9, 29.8, 29.3, 26.8, 22.8, 14.2 (the ylidic carbon was not observed).

## Phenyliodonium ylide of methyl (2-naphthoyl)acetate (3.8g)
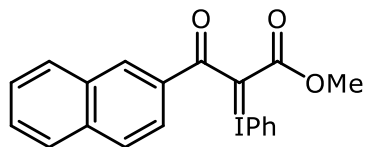
The title compound was synthesized via **GP3.3.1** using methyl (2-naphthoyl)acetate (**3.26g**) (1.37 g, 6.0 mmol). Precipitation of the title compound from a mixture of DCM and Et$_2$O was induced by adding hexanes to the solution and cooling the flask to 0 °C. Suction filtration afforded the title compound as a yellow amorphous solid (0.76 g, 29% yield). This compound decomposed slightly during acquisition of the NMR spectra. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.05 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 8.4, 1.4 Hz, 1H), 7.55 (dd, J = 7.0, 7.0 Hz, 1H), 7.49–7.45 (m, 2H), 7.41 (t, J = 7.8 Hz, 2H), 3.46 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.0, 165.2, 137.1, 134.2, 133.6, 132.8, 131.65, 131.55, 128.9, 128.1, 127.8, 126.77, 126.64, 126.3, 126.0, 113.0, 83.8, 51.9; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{20}$H$_{16}$IO$_3$, 431.0139; found 431.0138.

Phenyliodonium ylide of dibenzyl malonate (3.8h)[176]
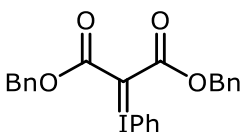
KOH (3.02 g, 169 mmol, 16.9 equiv) was stirred in MeCN (30 mL) and the the reaction vessel was placed in 0 °C ice-water bath. To this suspension, dibenzyl malonate (**3.26h**)[190] (2.84 g, 10.0 mmol, 1.0 equiv) was added dropwise, followed by PhI(OAc)$_2$ (3.22 g, 10.0 mmol, 1.0 equiv) in one portion and the resulting mixture was stirred for 2 h at 0 °C after which it was poured onto ice-water and filtered. The solid was washed with cold Et$_2$O, collected, and dried in vacuo to yield the title compound as a white amorphous solid (3.82 g, 87% yield). IR (ATR) 1618, 1583, 1387, 1303, 1318, 1213, 1068 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.64 (d, J = 7.8 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.37–7.25 (m, 12H), 5.20 (s, 4H); ^{13}C

NMR (125 MHz, CDCl$_3$) δ 165.6, 137.4, 132.1, 131.6, 131.4, 128.4, 127.9, 114.6, 66.7 (2 resonances were not resolved); HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{23}$H$_{20}$IO$_4$, 487.0401; found 487.0402.

Note: The procedure used to synthesize the title compound was based on the alternate (i.e., older) procedure reported by Charette et al.[176] for "bis(methoxycarbonyl)(phenyliodinio)methanide" (found in the main article), which gave ylide **3.8h** as a white solid. When using the authors' new general procedure for the synthesis of iodonium ylides of malonate esters (found in the supporting information), we obtained ylide **3.8h** as an impure brown liquid, as reported by the authors.

Phenyliodonium of methyl (4-toluoyl)acetate (3.8j)
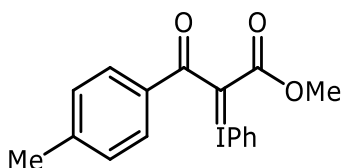
The title compound was synthesized via **GP3.3.1** using methyl (4-toluoyl)acetate (**3.26j**) (1.15 g, 6.0 mmol). A solution of the title compound dissolved in DCM was treated with Et$_2$O, cooled to 0 °C, and the resulting precipitate was collected using suction filtration to yield the title compound as a white amorphous solid (0.73 g, 31% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.85 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 3.49 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.1, 165.1, 139.8, 136.5, 133.3, 131.6, 131.4, 128.6, 128.1, 113.1, 51.8, 21.6 (C=I not observed).

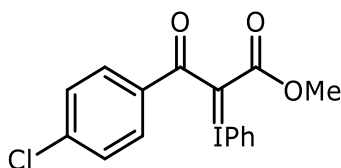**Phenyliodonium of methyl (2-toluoyl)acetate (3.8k)**
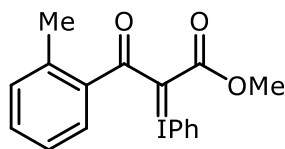
The title compound was synthesized via **GP3.3.1** using methyl (2-toluoyl)acetate (**3.26k**) (1.15 g, 6.0 mmol). A solution of the title compound dissolved in DCM was treated with Et$_2$O, cooled to 0 °C, and the resulting precipitate was collected using suction filtration to yield the title compound as a white

amorphous solid (1.58 g, 67% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.82 (d, J = 7.8 Hz, 2H), 7.49 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.7 Hz, 2H), 7.19–7.12 (m, 4H), 3.44 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.3, 164.7, 140.8, 134.0, 133.0, 131.4, 131.2, 129.7, 127.9, 126.3, 125.1, 113.2, 51.8, 19.2 (C=I carbon not observed).

Phenyliodonium of methyl (4-chlorobenzoyl)acetate (3.8l)

The title compound was synthesized via **GP3.3.1** using methyl (4-chlorobenzoyl)acetate (**3.26l**) (2.56 g, 12.0 mmol). A solution of the title compound dissolved in Et$_2$O was treated with hexanes, cooled to 0 °C, and the resulting precipitate was collected using suction filtration to yield the title compound as a white amorphous solid (2.39 g, 48% yield). This compound decomposed slightly during acquisition of the NMR spectra. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, J = 7.9 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.45 (s, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 8.3 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 184.8, 165.0, 137.9, 135.5, 133.4, 131.6, 131.5, 129.8, 127.6, 113.0, 83.0, 51.9.

Phenyliodonium of methyl (2-chlorobenzoyl)acetate (3.8m)

The title compound was synthesized via **GP3.3.1** using methyl (2-chlorobenzoyl)acetate (**3.26m**) (1.28 g, 6.0 mmol). A solution of the title compound dissolved in DCM was treated with Et$_2$O, cooled to 0 °C, and the resulting precipitate was collected 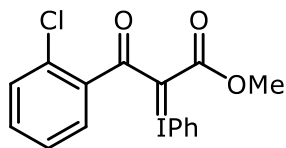using suction filtration to yield the title compound as an eggshell-white coloured amorphous solid (1.81 g, 73% yield). This compound decomposed slightly during acquisition of the NMR spectra. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.87 (d, J = 7.7 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.40 (t, J = 7.8 Hz, 2H), 7.35–7.31 (m, 1H), 7.25–7.21 (m, 3H), 3.46

(s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 182.9, 164.7, 140.2, 137.6, 133.0, 131.7, 131.5, 130.4, 129.14, 129.08, 127.9, 126.5, 112.9, 52.1.

Phenyliodonium of methyl (4-methoxybenzoyl)acetate (3.8n)
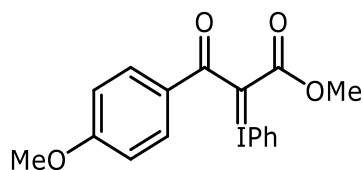
The title compound was synthesized via **GP3.3.1** using methyl (4-anisoyl)acetate (**3.26n**) (1.25 g, 6.0 mmol). A solution of the title compound dissolved in a mixture of CH$_2$Cl$_2$ and Et$_2$O was treated with hexanes, cooled to –78 °C, and the resulting precipitate was collected via suction filtration to yield the title compound as yellow solid (2.15 g, 87% yield). NOTE: All manipulations with this compound after its precipitation were performed using labware cooled by dry-ice or a dry ice/acetone bath. This compound decomposed slightly during acquisition of the NMR spectra. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.76 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 185.2, 165.1, 160.9, 137.3, 132.9, 131.2, 131.0, 130.6, 113.2, 112.5, 82.8, 55.2, 51.6.
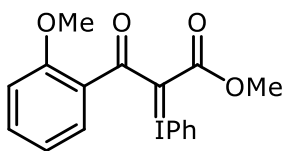
Phenyliodonium ylide of methyl (2-methoxybenzoyl)acetate (3.8o)

The title compound was synthesized via **GP3.3.1** using methyl (2-anisoyl)acetate (**3.26o**) (2.50 g, 12.0 mmol). A solution of the title compound dissolved in DCM was treated with hexanes, cooled to 0 °C, and the resulting precipitate was collected using suction filtration to yield the title compound as a light orange solid (1.39 g, 28% yield). This compound decomposed slightly during acquisition of the NMR spectra. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.79 (d, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.26 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.17 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.93 (dd, *J*

= 7.4, 7.4 Hz, 1H), 6.87 (d, J = 8.3 Hz, 1H), 3.77 (s, 3H), 3.41 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 183.8, 165.0, 156.0, 137.6, 132.2, 131.6, 131.1, 129.5, 127.9, 120.4, 113.0, 110.8, 55.8, 51.9 (C=I carbon not observed).

Phenyliodonium ylide of 6,6-diphenyldihydro-2*H*-pyran-2,4(3*H*)-dione (3.8r)
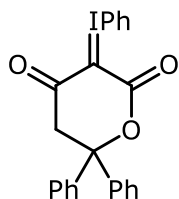
The title compound was synthesized via **GP3.3.2** using 6,6-diphenyldihydro-2H-pyran-2,4(3H)-dione (**3.26r**) (2.64 g, 10.0 mmol). Following the concentration of the organic extracts, the solution containing the iodonium ylide was treated with Et$_2$O and flask containing the mixture was cooled in an ice-water bath. The solid was isolated by suction filtration and dried in vacuo to yield the compound as a white amorphous solid (1.81 g, 39% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47–7.14 (m, 15H), 3.46 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 183.8, 165.5, 143.3, 132.9, 131.2, 131.1, 128.6, 127.8, 126.0, 112.7, 84.5, 74.9, 46.7; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{23}$H$_{18}$IO$_3$, 469.0295; found 469.0296.
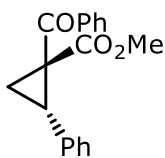
Methyl *trans*-1-benzoyl-2-phenylcyclopropanecarboxylate (*trans*-3.24e)

In a 10 mL round bottom flask, PhICl$_2$ (60 mg, 0.22 mmol, 1.1 equiv) was dissolved in MeCN (2 mL) with the assistance of sonication. The flask was then cooled to 0 °C in an ice-water bath. To the flask, styrene (86 mg, 5.0 equiv) and ylide **3.8e** (76 mg, 0.20 mmol, 1.0 equiv) were added in one portion and in rapid succession. The mixture was allowed to stir for 5 minutes and then the volatiles removed in vacuo. Hexamethyldisiloxane (16 μL, 0.075 mmol) was added (as an internal standard) to the residue before dissolving the mixture in CDCl$_3$. The NMR yield was obtained by comparison of the peak integrals for signals found at 1.81 ppm (*trans*-**3.24e**) and 1.76 ppm (*cis*-**3.24e**) relative to that of the internal standard. The NMR sample was concentrated in vacuo and subjected to flash column

chromatography (5% then 10% EtOAc/hexanes). Secondary silica gel (60Å 40–63 μm mesh purchased from Sorbtech) column chromatography (5% then 10% EtOAc/hexanes) allowed for partial separation of the title compound as a white solid (10 mg, 19% yield). R_f = 0.28 (10% EtOAc/hexanes, UV active); IR (ATR) 2952, 1716, 1667, 1432, 1331, 1278, 1143, 1013 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (dd, J = 8.2, 1.0 Hz, 2H), 7.40 (tt, J = 7.4, 1.5 Hz, 1H), 7.28 (t, J = 7.7 Hz, 2H), 7.12–7.08 (m, 4H), 7.05–7.02 (m, 1H), 3.64 (s, 3H), 3.52 (d, J = 0.8 Hz, 1H), 2.45 (d, J = 2.9 Hz, 1H), 1.81 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 192.5, 171.8, 137.1, 134.0, 132.8, 128.6, 128.28, 128.26, 128.0, 127.3, 52.7, 41.8, 34.0, 18.6; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{18}$H$_{17}$O$_3$, 281.1172; found 281.1172.

Methyl (2-toluoyl)acetate (3.26k)
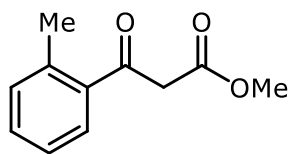
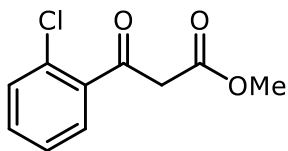Following **GP3.1** using 2'-acetophenone (5.36 g, 40 mmol), the title compound was obtained as a yellow liquid (6.60 g, 86% yield). This compound was observed to exist in a 4:1 mixture of keto:enol tautomers when dissolved in CDCl$_3$. R_f = 0.42 (20% EtOAc/hexanes, UV active); IR (ATR) 2953, 1743, 1698, 1626, 1434, 1245, 1201, 1037 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 12.46 (s, 0.2H, enol form), 7.73 (d, J = 7.7 Hz, 0.8H, keto form), 7.49–7.46 (m, 1H), 7.40–7.32 (m, 2H), 7.29 (d, J = 8.4 Hz, 0.4H, enol form), 5.36 (s, 0.2 H, enol form), 4.04 (s, 1.6H, keto form), 3.87 (s, 0.6H, enol form), 3.81 (s, 2.4H, keto form), 2.62 (s, 2.3H, keto form), 2.53 (s, 0.6H, enol form); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.2, 174.8, 172.9, 167.9, 139.2, 136.3, 135.8, 134.2, 132.07, 132.01, 130.8, 129.9, 129.1, 128.2, 125.66, 125.57, 91.1, 52.0, 51.1, 47.6, 21.4, 20.3; HRMS (+ESI) calcd for C$_{11}$H$_{13}$O$_3$, [M+H]$^+$ 193.0859; found 193.0860.

Methyl (2-chlorobenzoyl)acetate (3.26m)

Following **GP3.1** using 2'-chloroacetophenone (3.09 g, 20 mmol), the title compound obtained as a red liquid (2.02 g, 48% yield). This compound was observed to exist in a 2:1 ratio of keto:enol tautomers when dissolved in $CDCl_3$. $R_f = 0.45$ (20% EtOAc/hexanes, UV active) IR (ATR) 2953, 1743, 1698, 1626, 1589, 1471, 1434, 1245, 1201, 1038 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 12.41 (s, 0.3H, enol), 7.64 (d, $J = 7.7$ Hz, 0.7 H, keto), 7.60 (dd, $J = 7.4$, 1.7 Hz, 0.3H, enol), 7.48–7.46 (m, 1.7H, keto + enol), 7.41–7.33 (m, 1.4H, keto + enol), 5.60 (s, 0.3H, enol), 4.09 (s, 1.4H, keto), 3.84 (s, 1.0H, enol), 3.77 (s, 2.1H, keto); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.5, 173.0, 170.5, 167.4, 137.6, 133.5, 132.7, 132.1, 131.6, 131.2, 130.79, 130.63, 130.15, 130.05, 127.1, 126.9, 93.0, 52.4, 51.6, 48.9; HRMS (+ESI) m/z: [M+H]$^+$ calcd for $C_{10}H_{10}{}^{35}ClO_3$, 213.0313; found 213.0313.

Methyl (2-anisoyl)acetate (3.26o)
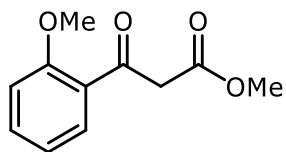
Following **GP3.1** using 2'methoxyacetophenone (6.01 g, 40 mmol), the title compound was obtained as a red liquid (8.16 g, 98% yield). $R_f = 0.18$ (20% EtOAc/hexanes, UV active); IR (ATR) 2950, 2842, 1738, 1669, 1597, 1485, 1463, 1485, 1242, 1161, 1019 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.88 (d, $J = 7.8$ Hz, 1H), 7.51 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.03 (dd, $J = 7.3$, 7.3 Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 3.98 (s, 2H), 3.90 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 192.9, 168.6, 152.9, 134.8, 131.0, 126.1, 120.8, 111.7, 55.4, 52.0, 50.4; HRMS (+ESI) m/z: [M+H]$^+$ calcd for $C_{11}H_{13}O_4$, 209.0808; found 209.0808.

6,6-Diphenyldihydro-2H-pyran-2,4(3H)-dione (3.26r)
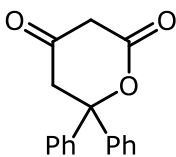
A solution of *n*-BuLi (2.5 M in hexanes) (18.5 mL, 46.25 mmol, 2.5 equiv) was added dropwise to a stirred −20 °C solution of *i*Pr$_2$NH (4.68 g, 46.25 mmol, 2.5 equiv) in THF (46.25 mL) and the resulting mixture was stirred for an additional 15 minutes after which it cooled to −78 °C. Methyl acetoacetate (2.15 g, 18.5 mmol, 1.0 equiv) was added dropwise into the flask and the mixture was allowed continue to stir for 40 minutes before benzophenone (4.05 g, 22.2 mmol, 1.2 equiv) in THF (5 mL) was added dropwise into the flask. After the reaction mixture was stirred for an additional hour, it was acidified to pH = 1 using 1 N HCl and allowed to warm to room temperature. The mixture was transferred to a separatory funnel and extracted with Et$_2$O (100 mL) and concentrated in vacuo. The crude mixture was treated with 1 M KOH (200 mL) and allowed to stir at room temperature for 16 h. The resulting suspension was filtered and the filtrate was cooled to 0 °C, acidified with concd aq. HCl to pH = 1, and then extracted with DCM (100 mL), and the organic layer was concentrated in vacuo. The resulting solid was triturated with Et$_2$O to yield the title compound as a white solid (2.83 g, 57% yield). mp 171–173 °C; R$_f$ = 0.50 (EtOAc, UV active); IR (ATR) 3028 (br), 1674, 1614, 1470, 1449, 1321, 1236, 1007 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37–7.31 (m, 10H), 3.39 (s, 2H), 3.18 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.8, 167.5, 141.8, 129.2, 128.8, 125.9, 84.8, 50.4, 46.1; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{17}$H$_{15}$O$_3$, 267.1016; found 267.1015.

2,2-Dichloro-5,5-dimethylcyclohexane-1,3-dione (3.27a)[103]
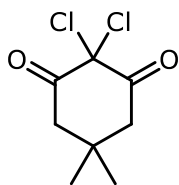
The title compound was synthesized via **GP3.4** using ylide **3.8a** (205 mg, 0.60 mmol) to afford the title compound as a white solid (40 mg, 32% yield) after flash column chromatography (10% EtOAc/hexanes then 20% EtOAc/hexanes). ^{1}H

NMR (300 MHz, CDCl$_3$) δ 2.95 (s, 4H), 1.04 (s, 6H). The spectral data are consistent with that reported in the literature.

5,5-Dichloro-Meldrum's acid (3.27c)
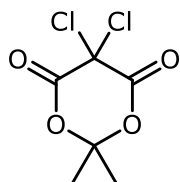
In a 10 mL round bottom flask, PhICl$_2$ (182 mg, 0.66 mmol, 1.1 equiv) was dissolved in anhydrous MeCN (6 mL) with the assistance of sonication. The reaction vessel was placed into a 0 °C water bath and pyridine (10% (v/v) DCM) (24 μL, 0.015 mmol, 5 mol%) was added. Ylide **3.8c**[153] (208 mg, 0.60 mmol, 1.0 equiv) was added to the flask in one portion and the mixture was stirred for 20 minutes as the bath was allowed to warm towards room temperature in ambient conditions. Following the reaction time, in which the colloidal suspension became a pale yellow solution, the mixture was concentrated in vacuo and the residue was subjected to purification by flash column chromatography (hexanes, followed by 5% then 10% EtOAc/hexanes) to yield the title compound as a colourless film (56 mg, 44% yield). R$_f$ = 0.0 (decomposed, 10% EtOAc/hexanes, visualized by bromophenol blue stain); mp 44–46 °C; IR (ATR) 1788, 1754, 1395, 1383, 1293, 1195, 1099 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.89 (s); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.4, 108.0, 67.5, 28.3; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_6$H$_7$Cl$_2$O$_4$, 212.9727; found 212.9718.

_N_,_N_-Dimethyl-5,5-dichlorobarbituric acid (3.27d)[103]
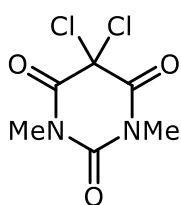
In a 10 mL round bottom flask, PhICl$_2$ (91 mg, 0.33 mmol, 1.1 equiv) was dissolved in anhydrous MeCN (3 mL) with the assistance of sonication. The reaction vessel was placed in a 0 °C water bath and pyridine (10% (v/v) in DCM) (12 μL, 0.015 mmol, 5 mol%) was added. Ylide **3.8d**[153] (107 mg, 0.30 mmol, 1.0 equiv) was added into the flask in one portion and the mixture was stirred for 100 minutes as the cooling bath was

allowed to warm towards room temperature in ambient conditions. Following the reaction time, in which the colloidal suspension became a pale yellow solution, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (hexanes, followed by 10% then 20% EtOAc/hexanes) to yield the title compound as a colourless film (57 mg, 85% yield). R_f = 0.40 (20% EtOAc/hexanes, UV active); ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.42 (s); ^{13}C NMR (125 MHz, CDCl$_3$) δ 161.4, 148.9, 71.9, 30.6. These data are consistent with literature values.

Methyl benzoyldichloroacetate (3.27e)[103]
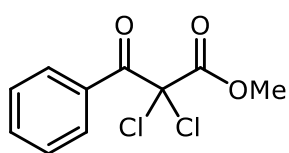
The title compound was synthesized via **GP3.4** using ylide **3.8e** (124 mg, 0.5 mmol). Purification via flash column chromatography (5% to 10% EtOAc/hexanes) afforded the title compound as a clear, colourless liquid (98 mg, 79% yield). R_f = 0.50 (20% EtOAc/hexanes, UV active); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.02 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.9 Hz, 2H), 3.84 (s, 3H). These data are consistent with literature values.

Methyl octanoyldichloroacetate (3.27f)
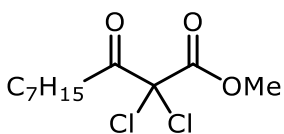
The title compound was synthesized via **GP3.4** using ylide **3.8f** (121 mg, 0.60 mmol). Purification via flash column chromatography (5% EtOAc/hexanes) afforded the title compound as a clear, colourless liquid (70 mg, 87% yield). R_f = 0.56, UV active); IR (ATR) 2956, 2927, 2857, 1770, 1747, 1244, 1006 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.89 (s, 3H), 2.80 (t, J = 7.3 Hz, 2H), 1.66 (tt, J = 7.2, 7.2 Hz, 2H), 1.30–1.26 (m, 8H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.4, 164.1, 81.8, 55.0, 35.8, 31.7, 29.0,

28.8, 24.3. 22.7, 14.1; HRMS (+ESI) *m/z*: [M+H]⁺ calcd for $C_{11}H_{19}^{35}Cl_2O_3$ 269.0705; found 269.0706.

Methyl (2-naphthoyl)dichloroacetate (3.27g)

The title compound was synthesized via **GP3.4** using ylide **3.8g** (129 mg, 0.30 mmol). Purification via flash column chromatography (5% then 10% EtOAc/hexanes), afforded the title compound as a colourless liquid (49 mg, 55% yield). R_f = 0.41 (10% EtOAc/hexanes, UV active); IR (ATR) 3060, 2956, 1765, 1705, 1435, 1240, 1009 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.64 (s, 1H), 8.03 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.89 (dd, *J* = 9.0, 9.0 Hz, 2H), 7.65 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.58 (dd, *J* = 7.5, 7.5 Hz, 1H), 3.87 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 183.4, 164.9, 135.9, 132.7, 132.2, 130.1, 129.6, 128.7, 128.03, 127.89, 127.3, 125.1, 82.0, 55.2; HRMS (+ESI) *m/z*: [M+H]⁺ calcd for $C_{14}H_{11}^{35}Cl_2O_3$, 297.0080; found 297.0080.

Dibenzyl dichloromalonate (3.27h)
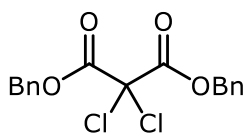
The title compound was synthesized via **GP3.4** using ylide **3.8h** (97 mg, 0.20 mmol). Purification via flash column chromatography (5% then 10% EtOAc/hexanes), afforded the title compound as a clear, colourless liquid (54 mg, 76% yield). R_f = 0.52 (20% EtOAc/hexanes, visualized by CAM stain); IR (ATR) 3035, 1762, 1456, 1233, 1000, 694 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.33 (m, 6H), 7.31–7.27 (m, 4H), 5.26 (s, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 162.7, 134.0, 129.0, 128.8, 128.4, 77.5, 70.0; HRMS (+ESI) *m/z*: [M+NH₄]⁺ calcd for $C_{17}H_{18}^{35}Cl_2NO_4$, 370.0607; found 370.0612.

Dibenzoyldichloromethane (3.27i)[103]

The title compound was synthesized via **GP3.4** using ylide **3.8i**[153] (85 mg, 0.20 mmol). Purification via flash column chromatography (5% then 10% EtOAc/hexanes) afforded the title compound as a faintly yellow film (16 mg, 28% yield). R_f = 0.43 (20% EtOAc/hexanes, UV active) ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (dd, J = 8.3 Hz, 0.9 Hz, 4H), 7.54 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.8 Hz, 4H). These data are consistent with previously reported in the literature.
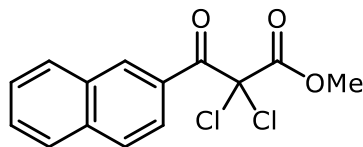
Methyl (4-toluoyl)dichloroacetate (3.27j)

The title compound was synthesized via **GP3.4** using ylide **3.8j** (118 mg, 0.30 mmol). Purification via flash column chromatography (5% then 10% EtOAc/hexanes) afforded the title compound as a faintly yellow liquid (55 mg, 70% yield). R_f = 0.44 (10% EtOAc/hexanes, UV active); IR (ATR) 2956, 1766, 1684, 1707, 1683, 1244, 1185, 1011, 860 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.7 Hz, 2H), 3.85 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 183.0, 164.9, 145.7, 130.4, 129.5, 128.1, 81.9, 55.1, 21.9; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{11}$H$_{11}$^{35}Cl$_2$O$_3$, 261.0080; found 261.0080.

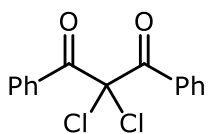**Methyl (2-toluoyl)dichloroacetate (3.27k)**

The title compound was synthesized via **GP3.4** using ylide **3.8k** (236 mg, 0.60 mmol). Purification via flash column chromatography (5% then 10% EtOAc/hexanes) afforded the title compound as a yellow liquid (113 mg, 72% yield). R_f = 0.62 (10% EtOAc/hexanes, UV active); IR (ATR) 2957, 1768, 1712, 1435, 1236, 1000 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.74 (d, J = 7.8 Hz, 1H), 7.41 (dd, J

= 7.5, 7.5 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.23 (dd, J = 7.6, 7.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR

(125 MHz, CDCl$_3$) δ 188.1, 164.6, 139.8, 132.34, 132.26, 132.10, 128.1, 125.3, 81.9, 55.0, 21.1;

HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{11}$H$_{11}$^{35}Cl$_2$O$_3$, 261.0080; found 261.0079.

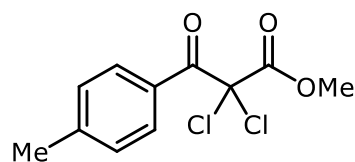**Methyl (4-chlorobenzoyl)dichloroacetate (3.27l)**

The title compound was synthesized via **GP3.4** using ylide **3.8l** (249 mg, 0.60 mmol). Purification via flash column chromatography (5% then 10% EtOAc/hexanes) afforded the title compound as a clear, colourless liquid (118 mg, 70% yield) after R$_f$ = 0.52 (10% EtOAc/hexanes, UV active); IR (ATR) 2957, 1766, 1587, 1247, 1092, 1008 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 182.4, 164.4, 141.1, 131.7, 129.2, 81.5, 55.2; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{10}$H$_8$^{35}Cl$_3$O$_3$, 280.9534; found 280.9522.
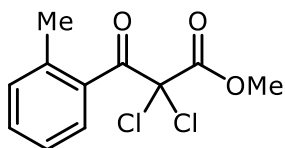
Methyl (2-chlorobenzoyl)dichloroacetate (3.27m)
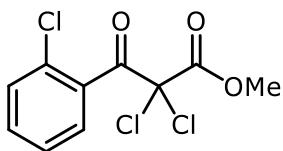
The title compound was synthesized via **GP3.4** using ylide **3.8m** (249 mg, 0.60 mmol). Purification via flash column chromatography (hexanes, followed by 5% then 10% EtOAc/hexanes) afforded the title compound as a clear, colourless liquid (51 mg, 30% yield). R$_f$ = 0.26 (10% EtOAc/hexanes, UV active); IR (ATR) 2958, 1769, 1769, 1744, 1589, 1434, 1235, 1000 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.65 (dd, J = 7.8, 1.2 Hz, 1H), 7.49 (dd, J = 8.1, 0.9 Hz, 1H), 7.45 (ddd, J = 7.7, 7.7, 1.5 Hz, 1H), 7.34 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 187.9, 164.0, 134.0, 132.5 (2C), 130.8, 128.6, 126.5, 81.3, 55.2; HRMS (+ESI) m/z: [M+Na]$^+$ calcd for C$_{10}$H$_7$Cl$_3$NaO$_3$, 302.9353; found 302.9353.

Methyl (2-anisoyl)dichloroacetate (3.27n)[191]
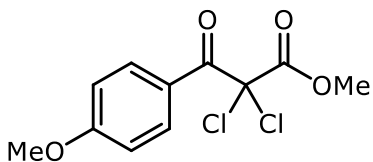
The title compound was synthesized via **GP3.4** using ylide **3.8n** (123 mg, 0.30 mmol). Purification via flash column chromatography (hexanes, followed by 10% then 20% EtOAc/hexanes) afforded the title compound as a clear, colourless film (9 mg, 12% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.1 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H). These data are consistent with what was previously reported in the literature.
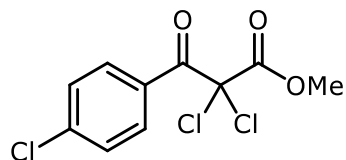
Methyl (2-anisoyl)dichloroacetate (3.27o)
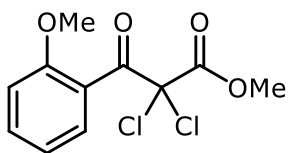
The title compound was synthesized via **GP3.4** using ylide **3.8o** (124 mg, 0.30 mmol). Purification via flash column chromatography (hexanes, followed by 5% then 10% EtOAc/hexanes) afforded the title compound as a clear, colourless liquid (42 mg, 51% yield). R_f = 0.30 (20% EtOAc/hexanes, UV active); IR (ATR) 2953, 1768, 1693, 1596, 1487, 1252, 1017 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.94 (dd, J = 7.8, 1.7 Hz, 1H), 7.61–7.58 (m, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 184.2, 163.9, 157.6, 135.5, 133.0, 122.4, 121.6, 111.8, 85.3, 55.0, 54.3; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{11}$H$_{11}$^{35}Cl$_2$O$_4$, 277.0029; found 277.0030.

2'-Hydroxy-2,2-dichloroacetophenone (3.27p')
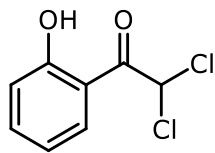
In a 10 mL round bottom flask, ylide **3.8p** (109 mg, 0.30 mmol, 1.0 equiv) was suspended in anhydrous MeCN (3 mL) at room temperature. To this flask, were added pyridine (1.2 μL, 0.015 mmol, 5 mol%) and PhICl$_2$ (91 mg, 0.33 mmol, 1.1 equiv) in one portion and the resulting mixture was allowed to stir for 10 minutes at ambient

temperature during which the reaction mixture became a clear, light-brown solution. The mixture was concentrated in vacuo and the residue was purified via flash column chromatography (5% then 10% EtOAc/hexanes) to yield the title compound as a yellow liquid (51 mg, 83% yield). $R_f =$ 0.49 (10% EtOAc/hexanes, UV active); IR (ATR) 3119, 2924, 1648, 1615, 1486, 1452, 1255, 1157 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 11.4 (s, 1H), 7.87 (dd, J = 8.2, 1.5 Hz, 1H), 7.57 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.07 (dd, J = 8.5, 0.7 Hz, 1H), 6.97 (ddd, J = 8.2, 7.2, 1.0 Hz, 1H) 6.75 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 190.9, 164.3, 138.3, 130.2, 119.5, 119.4, 114.6, 67.2; HRMS (-ESI) m/z: [M-H]$^-$ calcd for C$_8$H$_5{}^{35}$Cl$_2$O$_2$, 202.9672; found 202.9660.

2,2-Dichlorocyclohexane-1,3-dione (3.27q)[103]
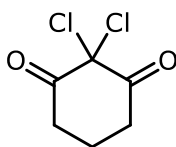
In a 10 mL round bottom flask, ylide **3.8q**[153] (125 mg, 0.40 mmol, 1.0 equiv) was suspended in MeCN (4 mL) at 0 °C. To this suspension, PhICl$_2$ (121 mg, 0.44 mmol, 1.1 eq.) was added in one portion and the mixture was stirred for 5 minutes. The solvent was removed by rotary evaporation, and the remaining volatiles were removed by heating the crude mixture to 30 °C under high vacuum (0.2 torr) to the yield the title compound as a yellow solid (68 mg, 94% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.04 (t, J = 6.9, 6.9 Hz, 4H), 1.99 (quintet, J = 7.0, 7.0 Hz, 2H). The spectral data are consistent what has been reported in the literature.

1,1-Dichloro-4,4-diphenylbut-3-en-2-one (3.27r')
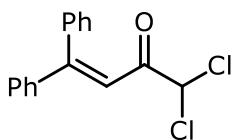
The title compound was synthesized via **GP3.4** using ylide **3.8r** (280 mg, 0.60 mmol). Purification via flash column chromatography (hexanes, followed by 5% then 10% EtOAc/hexanes) provided the title compound as a yellow liquid (59 mg, 34% yield). R_f = 0.56 (10% EtOAc/hexanes, UV active); IR (ATR) 3060,

1698, 1567, 1445, 1132, 906 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46–7.41 (m, 4H), 7.39–7.36 (m, 4H), 7.25–7.23 (m, 2H), 7.02 (s, 1H), 5.78 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 185.4, 161.1, 140.5, 138.1, 130.5, 129.20, 129.14, 128.9, 128.6, 128.3, 117.3, 70.5; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{16}$H$_{13}$^{35}Cl$_2$O, 291.0338; found 291.0337.

4. Metal-free Intermolecular Cyclopropanations of Iodonium Ylides

4.1.1. Background

Cyclopropanes are structural motifs that are important to medicinal and synthetic chemistry. Most cyclopropanation reactions using iodonium ylides employ the ylide as a precursor to either a free carbene or a metallocarbene. Metal catalysts, such as copper or rhodium complexes, can be used alongside iodonium ylides to perform intramolecular[168,192] or intermolecular[173,175–177] cyclopropanations of alkenes. As mentioned in §3.1.2, iodonium ylides have been viewed as safer carbene precursors when compared to the analogous diazo compounds. Another advantage to using iodonium ylides as carbene precursors is that the conditions used in their formation, and those used in their metal-catalyzed decomposition, often have a mutually benign relationship. As such, the convenient, one-pot cyclopropanation of alkenes (e.g., eq 4.1) from active methylene compounds (e.g., **4.1**) can be achieved through the intermediacy of an iodonium ylide (e.g., **4.2**).[193,194]
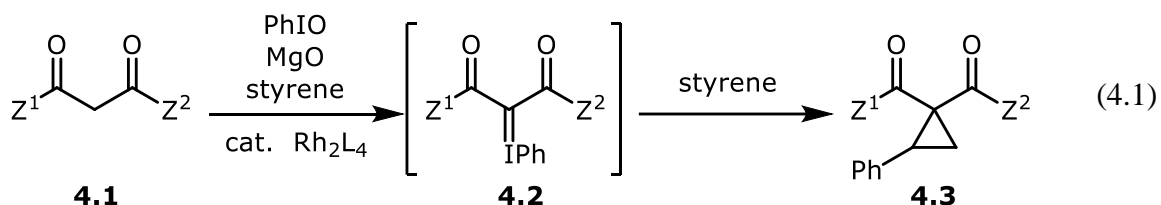
Isolated iodonium ylides can be used in cyclopropanation reactions which are capable of providing synthetically useful amounts of complex molecules. For example, Carreira et al. have recently used the phenyliodonium ylide of dimethyl malonate (**4.2a**) for the cyclopropanation of the terminal alkene of **4.4** to generate **4.5** (eq 4.2).[195] Reductive ring-opening of the cyclopropane would later play a key role in establishing the core of (+)-crotogoudin (Scheme 4-1) as the subsequent radical (**4.7**) was trapped via a 6-*exo-trig* cyclization.

$$(4.2)$$
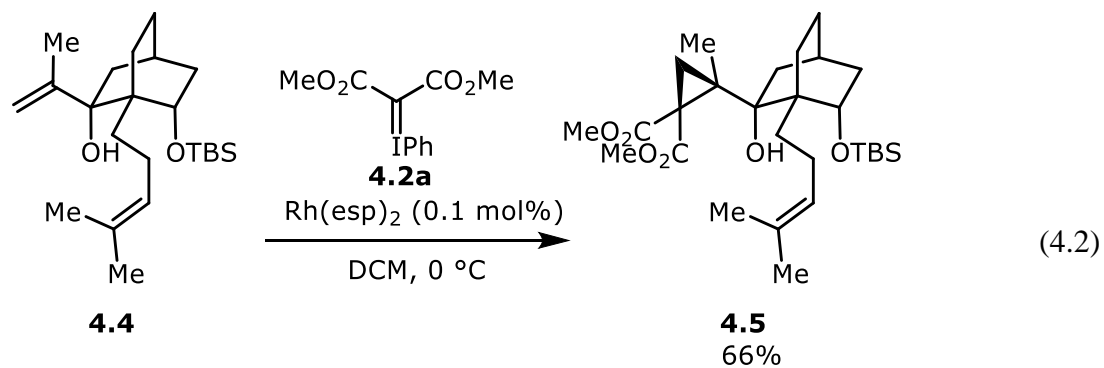
Scheme 4-1. Reductive Ring-opening for the Construction of the Core of (+)-Crotogoudin
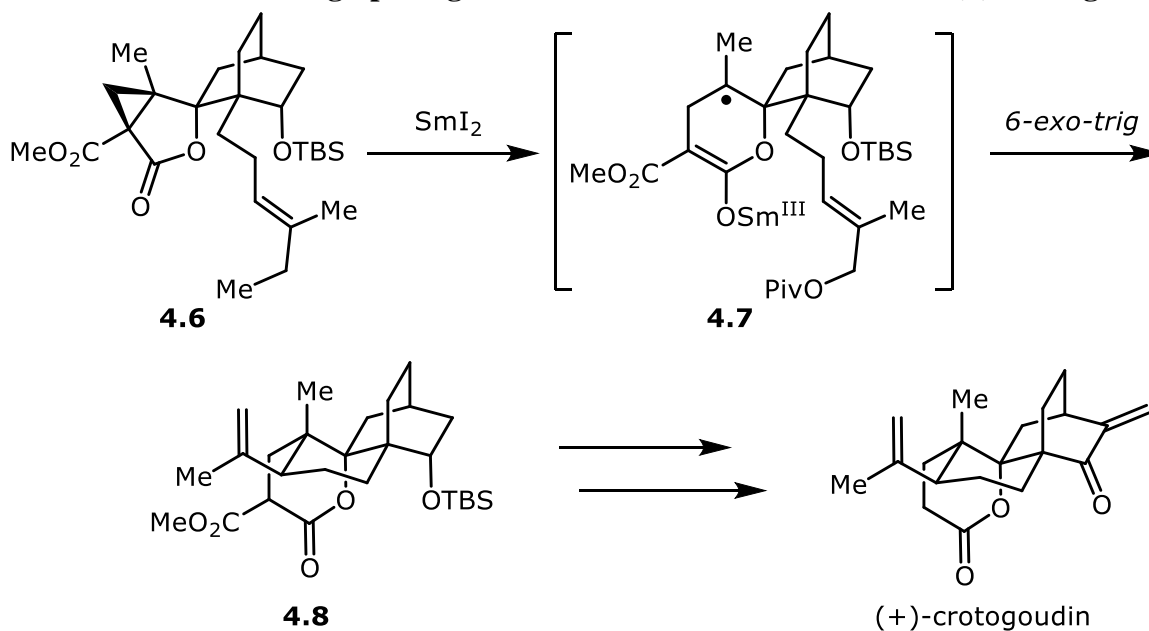
Metal-free methods for steering iodonium ylides towards cyclopropanation reactivity have been less studied relative to metal-catalyzed conditions. With respect to intramolecular metal-free cyclopropanations of iodonium ylides, Gallos et al.[196] and Moriarty et al.[168,197] have reported iodonium ylides of 1,3-dicarbonyl compounds, bearing an alkene four atoms away from the ylidic carbon, decompose readily to provide cyclopropanes when solvated in DCM. They report shorter or longer tethers failed to provide cyclopropanes. Moriarty et al.[197] suggested these cyclopropanations do not occur through an ionic mechanism (in which the alkene would perform a nucleophilic attack onto the iodonium, forming a carbocation) because the reactions were

121

insensitive to solvent polarity and rearrangement products were not observed in bicyclic systems such as **4.9**, which instead, afforded high amounts of cyclopropane **4.10** (eq 4.3).

$$(4.3)$$

4.9

4.10
95%
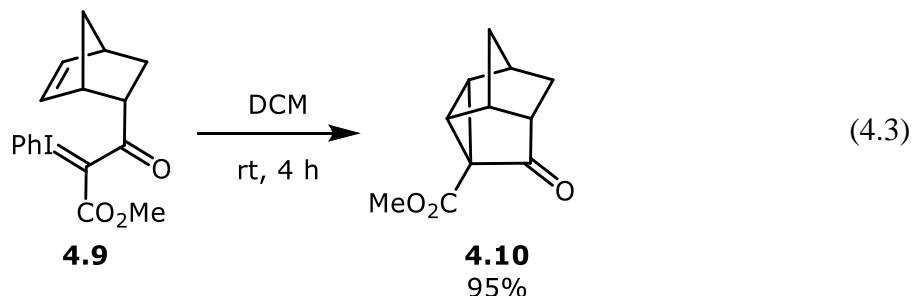
They also reasoned that a radical mechanism was not operative due to the absence of signals in the ESR spectrum of the mixture of the reagents.They proposed these cyclopropanations proceeded through a concerted [2+2] cycloaddition between the alkene and the ylide to yield 4-membered iodocycle **4.12**, which reductively eliminates iodobenzene to form the cyclopropane (eq 4.4).

$$(4.4)$$

4.11

4.12

4.13
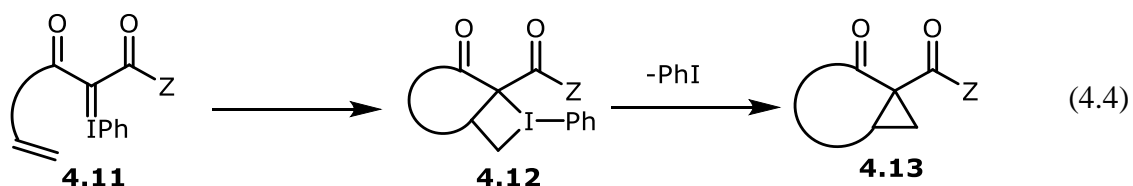
Using iodonium ylides for metal-free intermolecular cyclopropanation reactions often provide low yields of the desired cyclopropanes. Early examples utilized free carbenes generated via thermal- or photochemical processes. Thermal generation of free carbenes for the use in intermolecular cyclopropanations is of low synthetic utility. De Luca et al. reported that thermolysis and photolysis of the phenyliodonium ylide of diethyl malonate led to the cyclopropanation of *cis*- or *trans*-3-heptene (**4.14**) in unspecified "low yield", along with several other products arising from C–H insertion reactions.[165] Under thermal conditions, they observed the stereospecific generation of *cis*- and *trans*- isomers of cyclopropane **4.15** (eq 4.5), which served

as a basis for their proposal that the thermolysis of the ylide generated a singlet carbene that reacted faster than the conversion to the more stable triplet carbene. Photolysis of the ylide allowed *cis-***4.15** to be formed as the minor diastereomer regardless of the geometry of the parent alkene (eq 4.5), presumably through the direct generation of the triplet carbene from the photoexcited ylide.

$$(4.5)$$
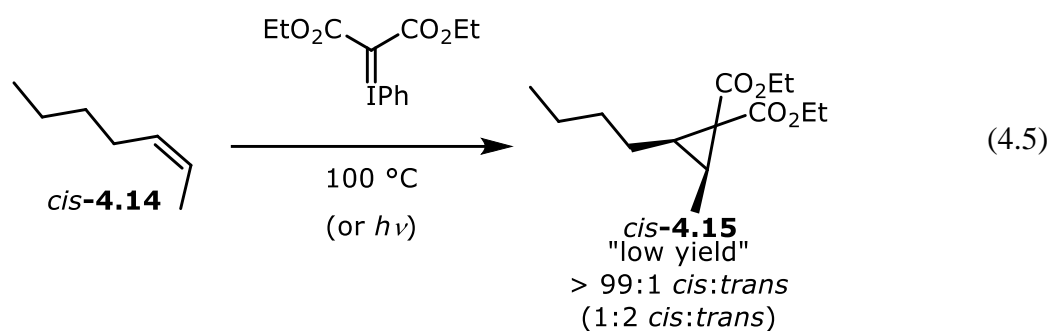
Hadjiarapoglou et al. have reported that the photolysis of the phenyliodonium ylide of bis(benzenesulfonyl)methane (**4.16**) provides low yields of intermolecular cyclopropanation (eq 4.6).[198] However, photochemical activation of iodonium ylides for the intermolecular cyclopropanation of alkenes is not a general method. For example, irradiation of the phenyliodonium ylide of cyclohexan-1,3-dione (**4.2b**), in the presence of styrene, generates dihydrofuran **4.18** with no trace of the isomeric cyclopropane (eq 4.7).[167] The cyclopropane could be obtained easily via the rhodium carbenoid[167] and when Hadjiarapoglou et al. subjected the cyclopropane to the same photochemical conditions which provided **4.18**, they found the cyclopropane isomerized to **4.18**. They proposed it is possible that the cyclopropane is a transient intermediate in the pathway towards the formation of **4.18**. They supported this proposal with the claim that photochemical reactions between ylide **4.2b** and *m*-nitrostyrene, a (unspecified amount of) cyclopropane was observed in the ^{1}H NMR spectra of the crude reaction mixtures.

$$(4.6)$$

31%

$$(4.7)$$

72%
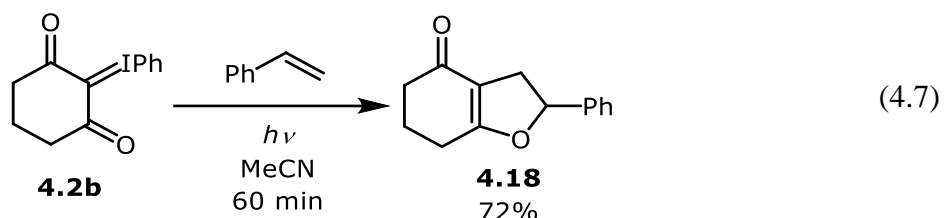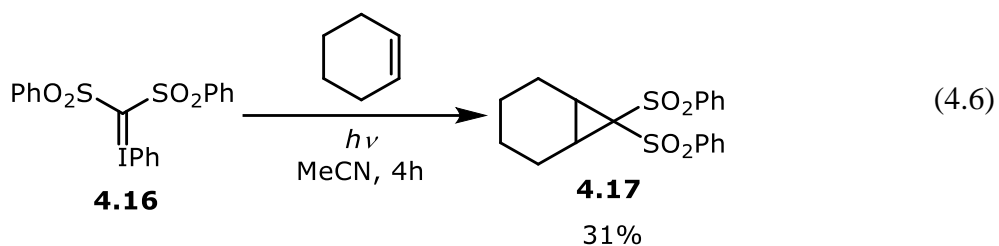
Recently, two examples of metal-free intermolecular cyclopropanation reactions have been reported. First, Guo et al., while investigating the Ni-catalyzed enantioselective cyclopropanations between 3-alkylidine-2-oxindoles (e.g., **4.19**) and **4.2a** (e.g., eq 4.8),[199]found a background reaction occurring in the absence of the metal and ligand (eq 4.9).

$$(4.8)$$

99% yield
99% ee

$$(4.9)$$

40% yield
0% ee
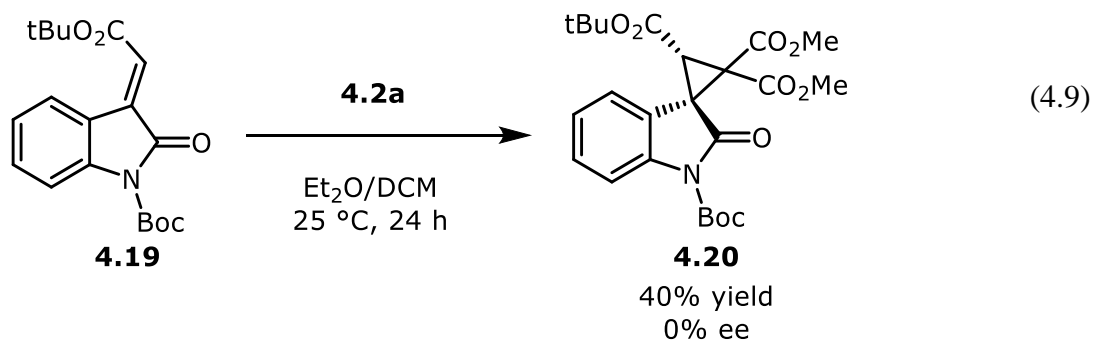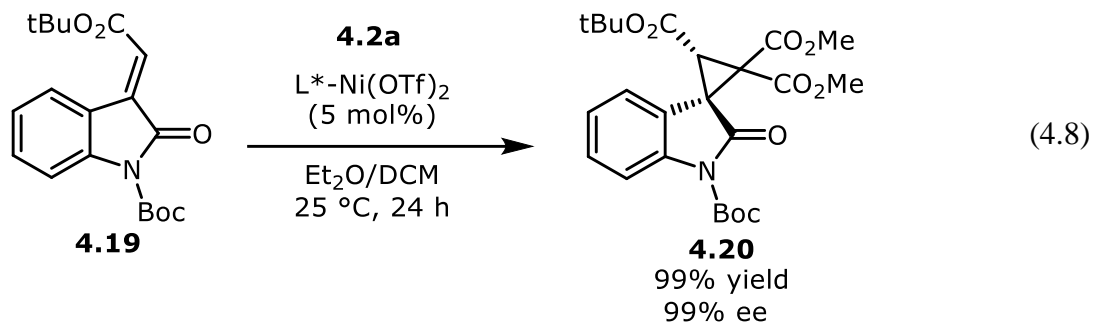
The authors suspected this reaction involved radical intermediates due to the observation of a signal in the ESR spectrum when analyzing a mixture of ylide **4.2a** and alkene **4.19**. They

proposed the decomposition of the ylide into a triplet carbene (**4.21**) and rationalized the high

diastereoselectivity of their reactions (>19:1 dr) was due to the ring closure of biradical **4.22** being

faster than bond rotation (eq 4.10).

$$\textbf{4.2a} \longrightarrow \underset{\textbf{4.21}}{\text{MeO}_2\text{C} \underset{\cdot\cdot}{\diagdown} \text{CO}_2\text{Me}} \longrightarrow \underset{\textbf{4.22}}{[\text{structure}]} \xrightarrow{\text{fast}} \textbf{4.20} \qquad (4.10)$$
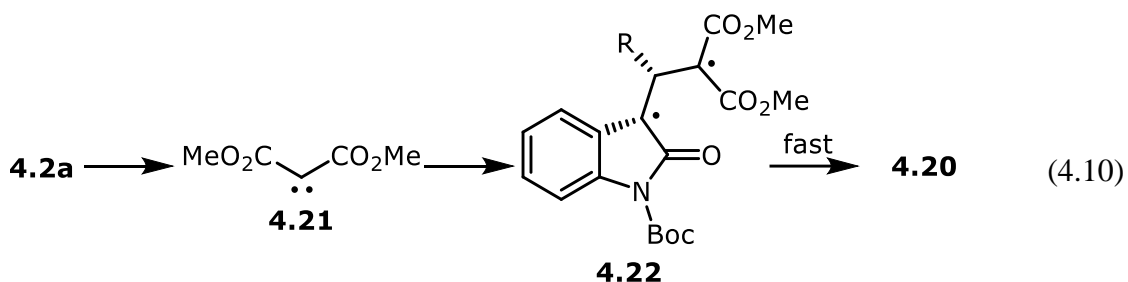
Another recent example of metal-free intermolecular cyclopropanation was found by Mayr

et al. during their study of the nucleophilicity of phenyliodonium ylides of cyclic 1,3-dicarbonyl

compounds (discussed in §3.1.2).[163] They rationalized the nucleophilicities of these ylides as

within the appropriate range to perform a Michael-initiated ring closure (MIRC)[200] when paired

with iminium ions derived from cinnamaldehyde. Their hypothesis was supported by the

demonstration of an asymmetric cyclopropanation reaction between ylide **4.2c** and

cinnamaldehyde via chiral iminium catalysis (eq 4.11).[163]

$$[\text{structure } \textbf{4.2c}] + \text{Ph}\diagup\diagdown\text{CHO} \xrightarrow[\text{rt, 24 h}]{[\text{catalyst}]} [\text{structure } \textbf{4.23}] \qquad (4.11)$$

4.23
up to 72% yield
up to 40% ee
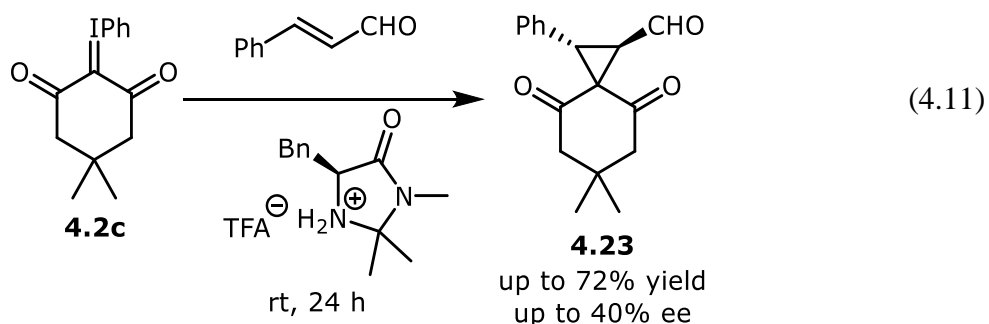
Given that metal-free intermolecular cyclopropanations using iodonium ylides have been

limited to sporadic, isolated reports, we decided to embark on a systematic study of the new metal-

free cyclopropanation reactions of iodonium ylides based upon the reaction of the phenyliodonium

ylide methyl benzoylacetate (**4.2d**), styrene, and PhICl$_2$ that is described in the previous section (§3.2.4, eq 3.11). We hoped to gain a deeper understanding about the reaction between iodonium ylides and various hypervalent iodine reagents that provide cyclopropanes.

4.1.2. Preliminary Studies – PhICl$_2$-Promoted Cyclopropanations

In a preliminary study, another member of the Murphy lab (C. Estrada) attempted to optimize the PhICl$_2$-mediated cyclopropanation reaction between the phenyliodonium ylide of methyl benzoylacetate (**4.2d**) and styrene (eq 4.12). Screening common reaction solvents, (e.g., DCM, DCE, EtOAc, hexanes, toluene, and methanol), including catalytic amounts of additives (i.e., pyridine or DMAP), or changing reaction temperature failed to provide higher amounts of the cyclopropane than what was obtained in the conditions shown in eq 3.11 (46% yield).

$$\text{(4.12)}$$
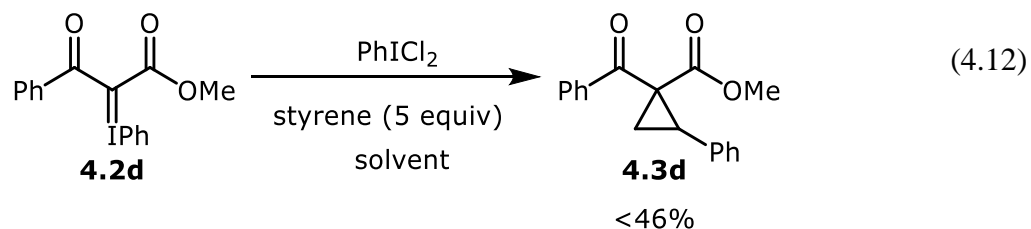
These low yields were not surprising because the dichlorination of iodonium ylides is extremely rapid as well, and is likely a significant competing process. Using a vast excess of styrene (>5 equiv) to out-compete opposing processes was deemed too impractical to be considered a potential solution. Therefore, we desired to substitute PhICl$_2$ with a reagent that would not participate in such competing side reactions. To assist with the rational identification of other reagents as potential candidates, we questioned the role of PhICl$_2$ in our reactions and hypothesized a mechanism in which the mixture of PhICl$_2$, styrene, and **4.2d** could provide the observed cyclopropane (Scheme 4-2). First, an oxygen of ylide **4.2d** displaces a chloride ligand of PhICl$_2$ to generate a more reactive iodonium species (**4.24**). Next, association of styrene onto the

iodonium of **4.24** generates complex **4.25**. The displaced chloride ligand could then perform a ligand exchange on the oxygen-bound iodanyl group to release zwitterion **4.25**, which cyclizes to form 4-membered iodocycle **4.26**, and subsequent reductive elimination of iodobenzene furnishes **4.3d**.

Scheme 4-2. Preliminary Mechanistic Hypothesis for PhICl₂-Promoted Cyclopropanation
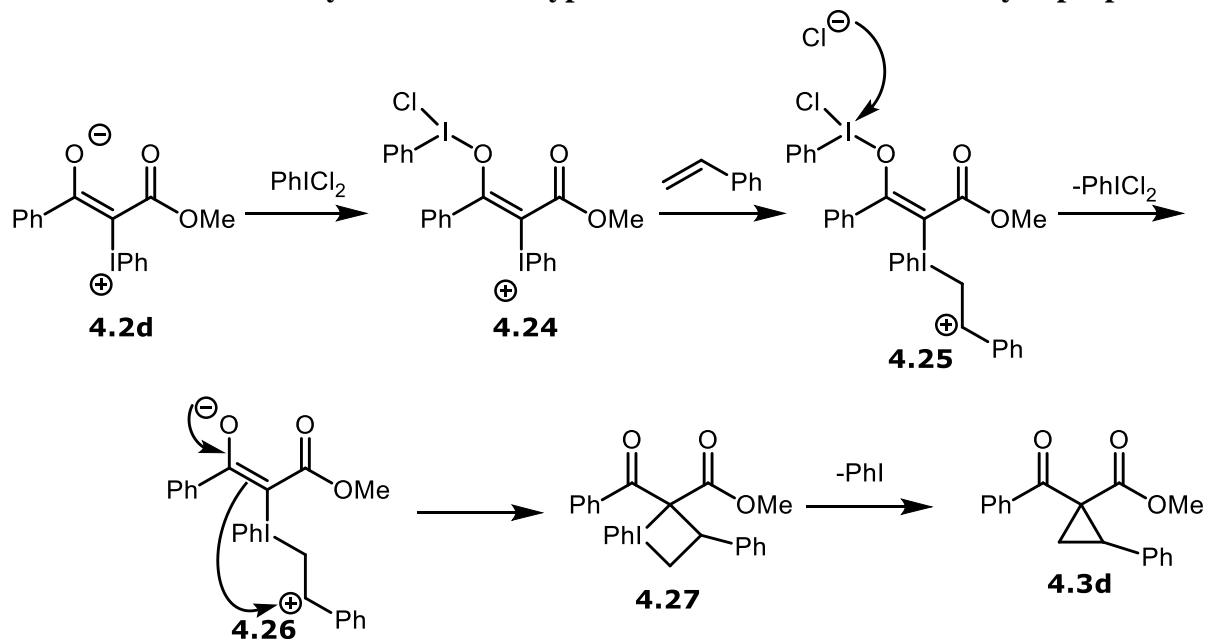
This hypothesis identifies the role of PhICl₂ as a Lewis acidic catalyst. These steps also rely on the leaving group ability and nucleophilicity of the ligand of the iodane (i.e., chloride) to be involved in ligand exchange processes that can enhance the electrophilicity of the iodine of the ylide (**4.2d** to **4.24**) and to regenerate PhICl₂ (**4.25** to **4.26**). The fact that PhICl₂ is not required to reductively eliminate to PhI is evident when analyzing the change in oxidation state of the ylidic carbon. This carbon takes the same oxidation state of the cyclopropane through the reductive elimination of one equivalent of PhI. The use of substoichiometric amounts of PhICl₂ could not provide conclusive results regarding its competency as a catalyst due to competing reactions which

would consume it in stoichiometric amounts (e.g., *gem*-dichlorination of ylide and *vic*-dichlorination of styrene).

Another feature of our mechanistic hypothesis is that the iodine of the ylide acts as an electrophilic site. The analogous diazo compound (**4.28d**), in which the internal nitrogen is unlikely to be attacked by styrene, was subjected to PhICl$_2$ in MeCN in both presence and absence of 5 mol% pyridine (eq 4.13). Unsurprisingly, no cyclopropanation was observed in these experiments.

$$(4.13)$$
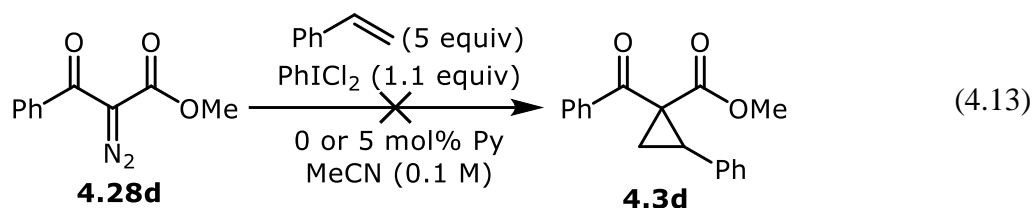
Using the preliminary mechanism (Scheme 4-2) as our working hypothesis, we screened various aryl-λ^3-iodanes such as TolIF$_2$, PhI(OAc)$_2$, PIFA, HTIB, and bis(3,5-dinitrobenzyloxy)iodobenzene. We hoped to find another iodane possessing appropriate electronic properties about the iodine and/or ligands that would allow for the cyclopropanation of styrene. When these iodanes were paired with **4.2d** in situ, there was either no reaction or the reagents reacted to provide intractable mixtures of products.

In light of these results, we considered two additional options (while being constrained to using metal-free reagents): first, the use of a non-HVI reagent as a Lewis acid or, second, the use of an additive to activate iodanes towards reactions with the ylide. When considering Lewis acids, we hypothesized that the ideal candidate needed to be able to associate with the oxygen of the ylide to generate a synthetic equivalent of **4.24**, and later, easily dissociate over the course of the reaction. When considering using an activated iodane, we desired an iodane that did not

decompose the ylide (or alkene) before the addition of the activator. Keeping these factors in mind allowed for the identification of two alternative conditions that allowed **4.2d** to engage in a cyclopropanation reaction with styrene. The first method employed TMSCl as a catalyst (§4.1.3), while the second method used TBAI-activated PhI(OAc)$_2$ (§4.1.4).

4.1.3. TMSCl-Catalyzed Cyclopropanations

Attempting optimization of TMSCl-catalyzed reactions did not lead to conditions providing the cyclopropane in higher yields than those shown in eq 4.14. Using 1 equivalent of TMSCl led to the decomposition of **4.2d** without the observation of **4.3d**. Other reagents were screened as potential Lewis acidic organocatalysts to facilitate the cyclopropanation, such as acyl halides, TMSOTf, and TMSBr (eq 4.15). These reagents led to the decomposition of the ylide, but no significant amounts of **4.3d** formed (<5% NMR yield).

$$(4.14)$$

17% NMR yield
6.5:1 *trans*:*cis*

$$(4.15)$$
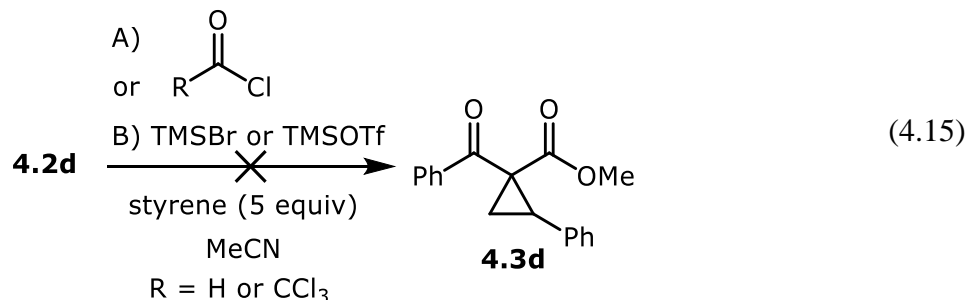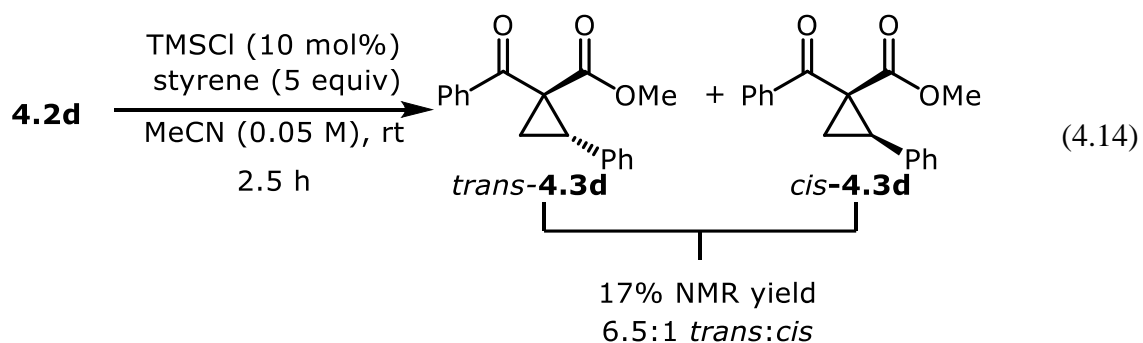
Mixture of TMSOTf and **4.2d**, at both room temperature and at 0 °C, led to the observation the rapid disappearance of the ylide. We hoped that the mixture of these two reagents would form

iodonium **4.29** and the low nucleophilicity of the triflate counter-ion would grant this potential intermediate an appreciable lifetime in situ, allowing for the electrophilic attack of the iodonium onto styrene (Scheme 4-3). Therefore, in an attempt to generate intermediate **4.30** for the use in a cyclopropanation reaction, a stoichiometric amount of TMSOTf was first added to ylide **4.2d** in the presence of styrene. Then, TBACl was added, in rapid succession, in an attempt to cleave the TMS–O bond. However, no cyclopropanation was observed.

Scheme 4-3. Attempted Cyclopropanation Using TMSOTf/TBAC
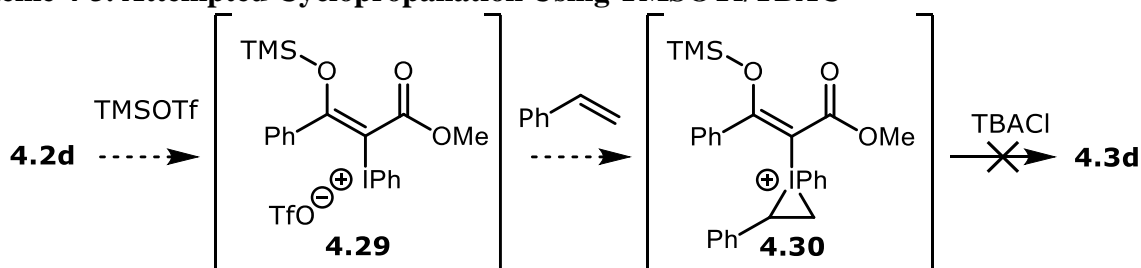
The conditions shown in eq 4.14 were used to briefly screen other phenyliodonium ylides of 1,3-dicarbonyl compounds for cyclopropanation reactivity, but little-to-no cyclopropanation was found. In light of the poor yields and potentially low substrate scope, research efforts were focused on developing the TBAI-promoted cyclopropanations, which, in preliminary studies, showed more promising results.

4.1.4. PhI(OAc)$_2$•TBAI Mediated Cyclopropanations

The cyclopropanation of **4.2d** using mixtures of PhI(OAc)$_2$ and TBAI led to the observation of complex mixtures of products in the ^{1}H NMR spectra of the crude reaction mixtures. Of these products, cyclopropane **4.3d** was identified in a 2:1 diastereomeric ratio with a 30% combined yield of the isomers (eq 4.16). Modification of the reaction solvent, reactant concentration, reaction temperature, and loading of PhI(OAc)$_2$ and TBAI were unable to provide increased yields of **4.3d**. Subjecting the crude reaction mixtures to purification via FCC in an

130

attempt to isolate side products led to the recovery and identification of ketone hydrate **4.31**.[153] This compound was not observed in the ^{1}H NMR spectra of crude reaction mixtures and it was possibly formed during column chromatography, by either the hydration of the parent tricarbonyl compound,[153] or by hydrolysis of the acylal (cf. eq., 1.13, §1.5),[105]

$$
\textbf{4.2d} \xrightarrow[\substack{\text{Ph}\diagup\!\!\!\diagdown \text{ (5 equiv)} \\ \text{MeCN (0.1 M)} \\ 1 \text{ h}}]{\substack{\text{PhI(OAc)}_2 \text{ (1 equiv)} \\ \text{TBAI (0.3 equiv)}}} \quad trans\text{-}\textbf{4.3d} \; + \; cis\text{-}\textbf{4.3d}
$$

(4.16)

30% NMR yield
2:1 *trans*:cis

$$
\textbf{4.2d} \xrightarrow[\substack{\text{styrene} \\ \text{MeCN} \\ \text{then SiO}_2}]{\substack{\text{TBAI} \\ \text{PhI(OAc)}_2}} \quad \textbf{4.31}
$$

(4.17)
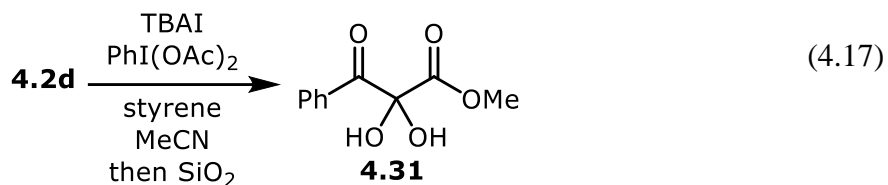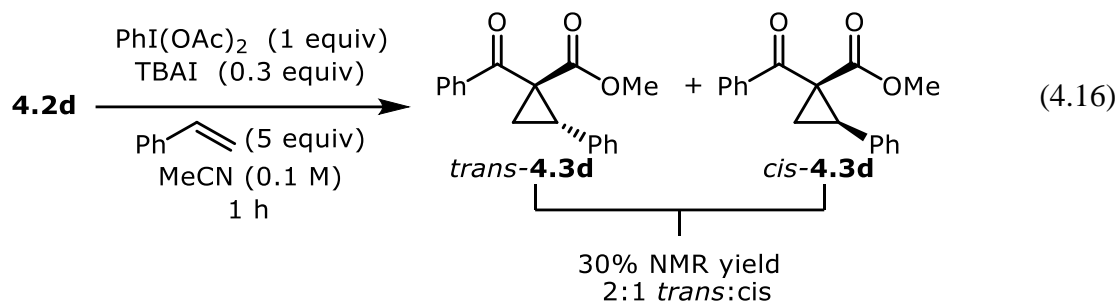
Although the yield of PhI(OAc)$_2$/TBAI promoted cyclopropanations between **4.2d** and styrene was lower than the PhICl$_2$-promoted conditions, we believed that reaction using the mixture of PhI(OAc)$_2$ and TBAI would have a larger substrate scope. We, therefore, used the conditions shown in eq 4.16 to investigate the scope of iodonium ylides applicable to the cyclopropanation of styrene (Table 4-1). Typical reaction mixtures became an intense red-orange colour upon adding PhI(OAc)$_2$ to a solution of the other reagents. The colour of the reaction mixtures faded slightly over 30 minutes (for phenyliodonium ylides of acyclic 1,3-dicarbonyl compounds) or over 60 minutes (for phenyliodonium ylides of cyclic 1,3-dicarbonyl compounds). After this time, the colour of the solutions was typically orange and further visible changes in colour were not observed. The mixtures were allowed to stir for an additional 30 or 60 minutes and, at this point, they were considered "complete" and the reactions were concentrated and

131

analyzed by ^{1}H NMR spectroscopy. Analogs of our model substrate (i.e., **4.2d**) bearing β-ketoesters with larger ester substituents (**4.2e–g**) also provided low yields of the respective cyclopropanes (17%, 29%, and 25%, **4.3e**, **4.3f**, and **4.3g**, respectively). Performing the reaction on a 0.30 mmol scale of **4.2g** led to a higher isolated yield of **4.3g** than the NMR yield

Table 4-1. Cyclopropanations of Phenyliodonium Ylides of 1,3-Dicarbonyl Compounds Using Styrene

4.3d
30%
2:1 dr

4.3e
17%
5:1 dr

4.3f
29%
4:1 dr

4.3g
25% (42%)[b]
2:1 dr

4.3h
56%
0.7:1 dr

4.3a
52%

4.3i
<5%

4.3b
58%

4.3c
89% (75%,[c] 82%[d])

4.3j
20%

4.3k
<5%
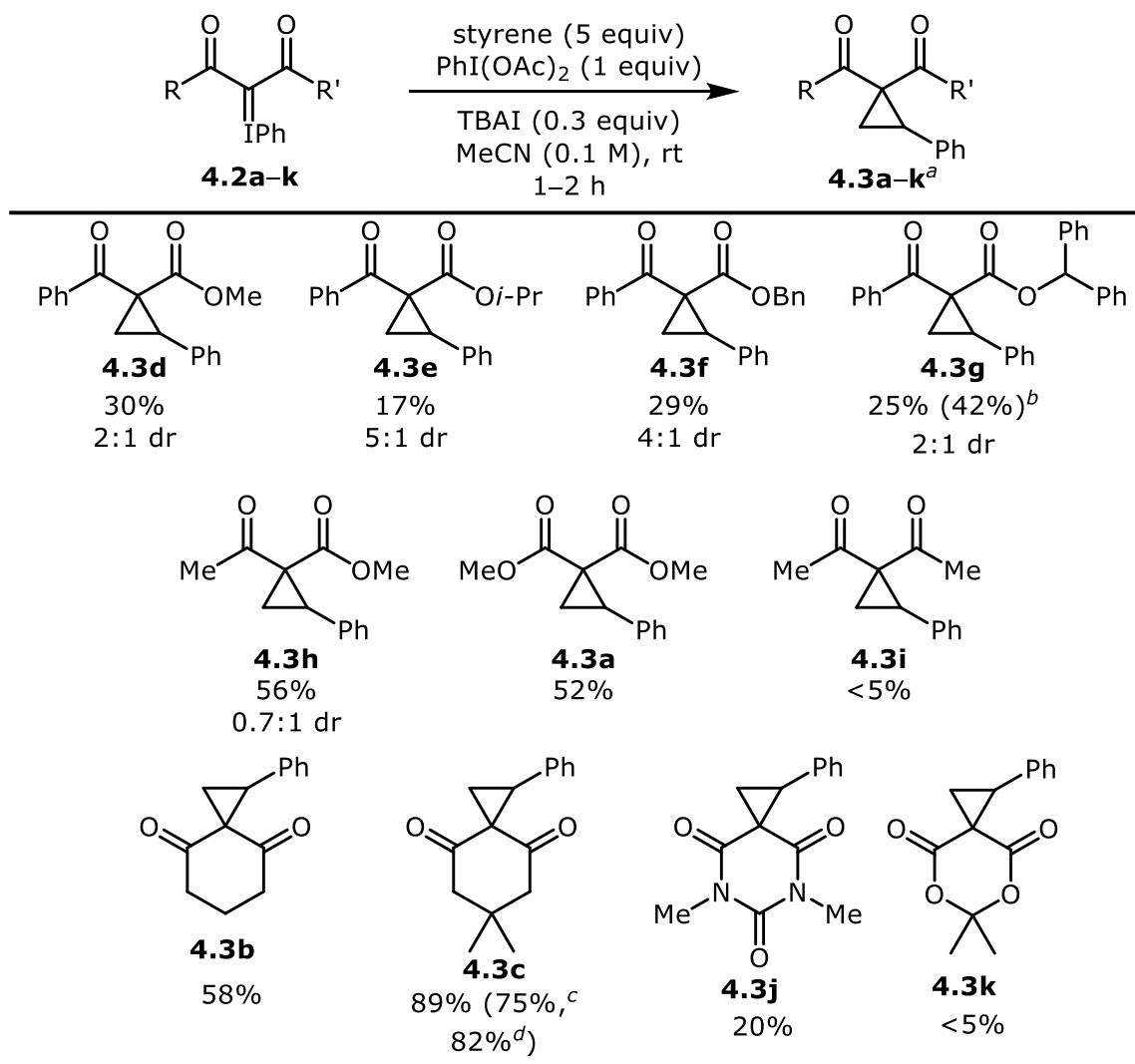
[a]General conditions: **4.2** (0.10 mmol), PhI(OAc)$_2$ (1.0 equiv), TBAI (0.30 equiv), styrene (5.0 equiv) in MeCN (1 mL), for 1 h (acyclic **4.2**) or 2 h (cyclic **4.2**) at rt. Yields were determined by ^{1}H NMR analysis using HMDSO as an internal standard. dr refers to the *trans*-:*cis*- ratio determined by analogy to *trans*- and *cis*-**4.3d**.[b]Performed on a 0.30 mmol scale, isolated yield after column chromatography.[c]Performed on a 0.20 mmol scale, isolated yield after column chromatography.[d]Performed on a 1.0 mmol scale, isolated yield after column chromatography.

obtained when the reaction was performed on a 0.10 mmol scale (42% isolated- vs 25% NMR yield). In the series of iodonium ylides of acyclic 1,3-dicarbonyls, the phenyliodonium ylides of methyl acetoacetate and dimethyl malonate provided the highest yields of cyclopropanes (56% and 52% yields, **4.3h** and **4.3a**, respectively), while the phenyliodonium ylide of acetylacetone was the only ylide that did not provide the respective cyclopropane (**4.3i**) in amounts detectable by ^{1}H NMR spectroscopy. The highest yields of cyclopropanation were found when using phenyliodonium ylides of cyclic 1,3-diketones, providing cyclopropanes **4.3b** and **4.4c** in 58% and 89% NMR yields, respectively. However, the ability to provide high yields of the respective cyclopropanes was not characteristic of phenyliodonium ylides of cyclic 1,3-dicarbonyl compounds, demonstrated as **4.2j** and **4.2k** were found to generate cyclopropanes in low (20% yield) or insignificant amounts (<5% yield).

Upon identification of a cyclopropane that was formed in excellent yield (i.e., **4.3c**, 89% NMR yield), its parent ylide (**4.2c**) was used as a model substrate for future investigative studies. When the reaction was performed on a larger scale (0.20 mmol), cyclopropane **4.3c** was isolated in 75% yield while a slightly higher isolated yield was obtained when performing the reaction on an even larger scale (1.0 mmol, 82%). We attempted to monitor the cyclopropanation of **4.2c** using ^{1}H NMR spectroscopy by performing the reaction in MeCN-d_3. This experiment found complete decomposition of **4.2c** occurred within 5 minutes and that **4.3c** had formed. A negligible change in the ^{1}H NMR spectrum was observed when reanalyzing this mixture after 30 minutes. However, a significantly lower isolated yield of **4.3c** was obtained when using a 5 minute reaction time versus a 120 minute reaction time (47% vs 75%, respectively). Therefore, the practice of using 1 or 2 h reaction times for iodonium ylides of acyclic or cyclic 1,3-dicarbonyl compounds, respectively, was kept for the remainder of these studies.

We next investigated the scope of styrenes that can undergo PhI(OAc)$_2$/TBAI promoted cyclopropanations with **4.2c** (Table 4-2). For this study, we lowered the loading of the alkene used in our cyclopropanation conditions from 5 equiv to 2 equiv and found that our model substrate (**4.2c**) furnished **4.3a** in 55% yield. Although pentafluorostyrene was found to be unable to provide the respective cyclopropane, styrenes bearing electron withdrawing groups (i.e., NO$_2$ or Cl) could be used to produce cyclopropanes in moderate yields (**4.3c.c** and **4.3c.d**, 60% and 64%, respectively). Moderately electron-rich *p*-methylstyrene generated slightly lower amounts of the desired product (**4.3c.e**, 44% yield). When 4-*tert*-butylstyrene was subjected to the cyclopropanation conditions, purification via FCC initially provided a solid which appeared mechanically sensitive as it liquefied upon being scratched by a metal spatula. The ^{1}H NMR spectrum of this material revealed a mixture of the cyclopropane and the dihydrofuran (**4.32f**). Allowing this mixture to stand at room temperature overnight led to the complete conversion into

Table 4-2. Cyclopropanation of Functionalized Styrenes

4.3c, Ar = Ph, 55%
4.3c.b, Ar = C$_6$F$_5$, <5%
4.3c.c, Ar = *m*-(NO$_2$)-C$_6$H$_4$, 60%
4.3c.d, Ar = *p*-C$_6$H$_4$Cl, 64%
4.3c.e, Ar = *p*-tolyl, 44%

4.32f, Ar = *p*-(*t*-Bu)-C$_6$H$_4$, 57%
4.32g, Ar = 3,4-(OMe)$_2$-C$_6$H$_3$, 82%
4.32h, Ar = *p*-anisyl, 93%
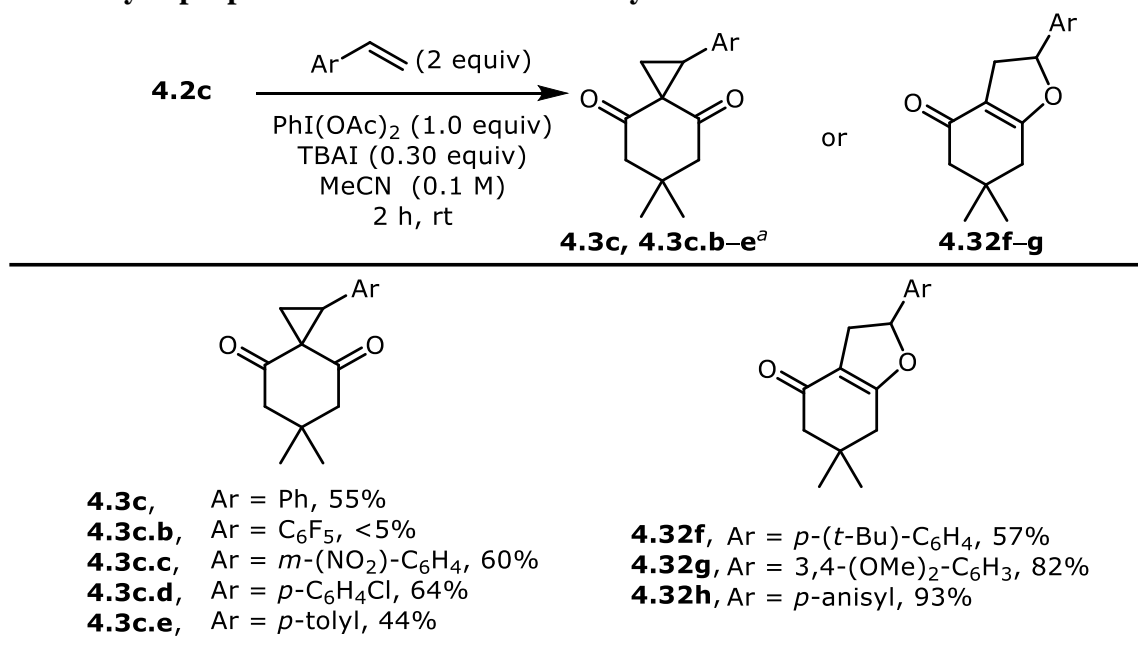
^{a}General conditions: **4.2c** (0.20 mmol or 0.30 mmol, 1.0 equiv), alkene (2.0 equiv), PhI(OAc)$_2$ (1.0 equiv), TBAI (0.30 equiv), in MeCN (0.1 M) at rt for 2 h. Isolated yields after column chromatography.

4.32f. It is presumed that the solid originally isolated via FCC was a cyclopropane, which then isomerized into the dihydrofuran (57% yield). When subjected to the cyclopropanation conditions, other styrenes bearing more electron-donating groups were found to directly provided dihydrofurans in excellent isolated yield (**4.32g** and **4.32h**, 82% and 93%, respectively) without the observation of the respective cyclopropanes.

Initial attempts to expand the alkene scope of the PhI(OAc)•TBAI mediated cyclopropanations revealed that many alkenes were unable to be converted to their respective cyclopropanes (Table 4-3). Even styrenes bearing a simple substitution (e.g., methyl or phenyl)

Table 4-3. Unsuitable Alkenes for PhI(OAc)$_2$•TBAI-Mediated Cyclopropanations
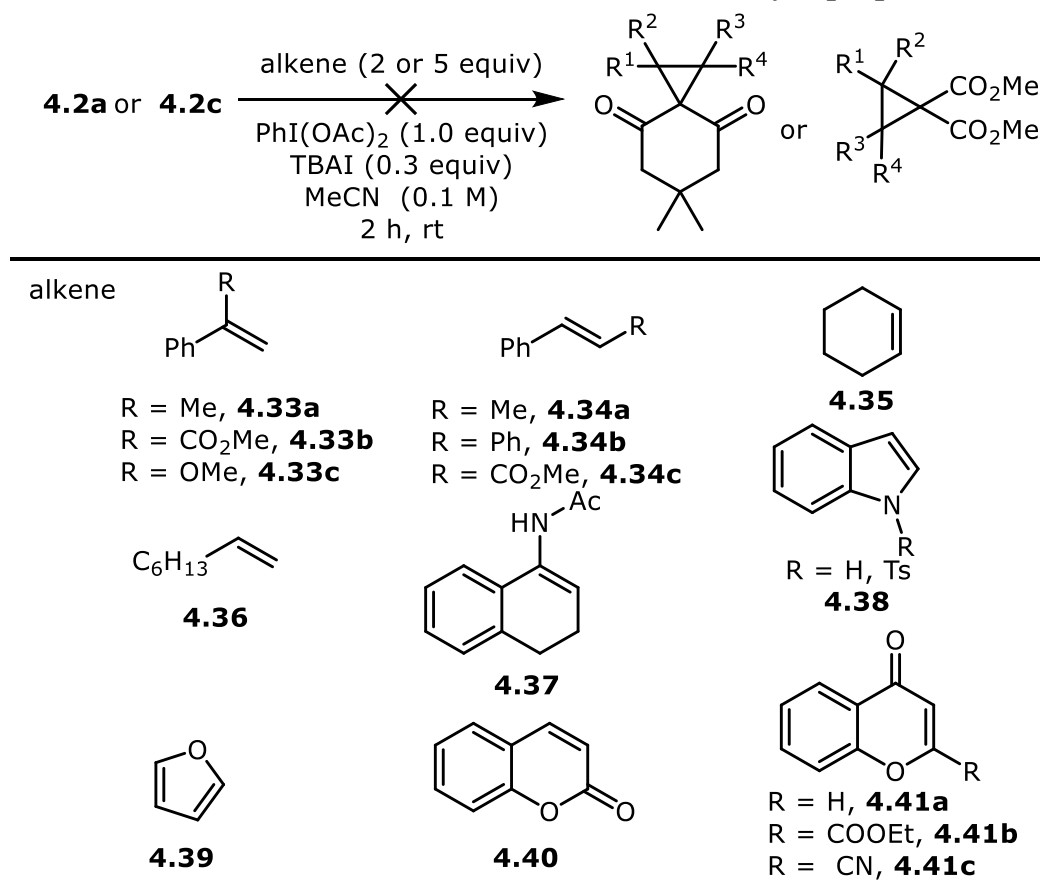
on the vinyl group completely prevented cyclopropanation from occuring. Other commercially available, or readily accessible, alkenes (**4.33–4.41**) were screened as potential cyclopropanation

substrates. However, ^{1}H NMR spectroscopic analysis of the crude reaction mixtures typically revealed little-to-no decomposition of the ylide. There was often partial decomposition of the alkene, but no cyclopropanes were observed. The mixture of iodide and PhI(OAc)$_2$ likely generates various reactive electrophilic iodine species. Therefore, it is not surprising that alkenes bearing electron donating groups were unsuccessful because electrophilic iodination of the alkene could lead to competing, non-productive pathways. For example, α-methylstyrene, in the presence of PhI(OAc)$_2$ and trimethylsulfonium iodide, has been reported to undergo iodoacetoxylation in 82% yield in less than 1 h.[201] The reaction of **4.2c** and α-methylstyrene led to the isolation of trace amounts of dihydrofuran **4.42**, bearing an iodomethyl group (eq. 4.18). Therefore, we focused our attempts in expanding the alkene scope of the PhI(OAc)$_2$•TBAI mediated cyclopropanations by screening endocyclic alkenes which do not possess allylic hydrogens such as courmarin (**4.40**) and chromen-4-ones **4.41a–c**. However, these efforts were also met with negative results.

$$(4.18)$$
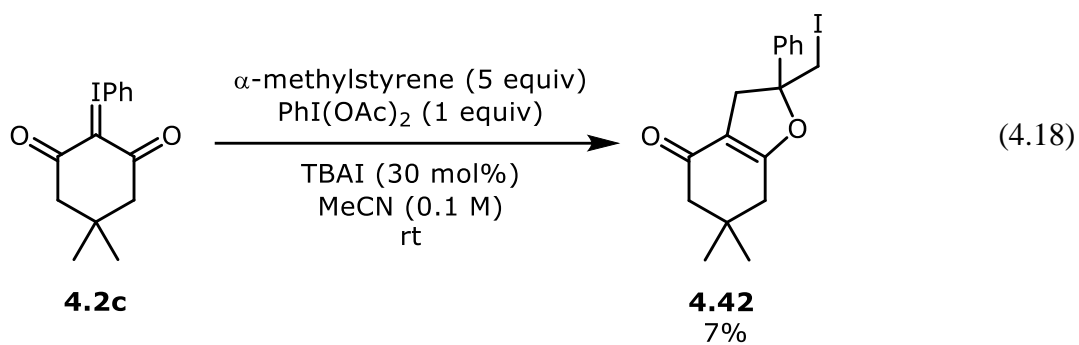
Next, we decided to use the 3-alkenylidene-2-oxindole as substrates for cyclopropanation, which possessed an exocyclic alkene. As previously shown in eqs 4.8 and 4.9, Guo et al. found that these alkenes are capable of engaging in reactions with **4.2a** to provide cyclopropanes. Under metal-catalyzed conditions, the authors report high yield and enantioselectivity (typically ≥90% yield, >92% ee) of the respective cyclopropanes while the uncatalyzed reaction was far from complete within the same timeframe (40% yield, 24 h). We suspected that the mechanism

operating in the uncatalyzed cyclopropanation was slow in comparison to both their metal-catalyzed cyclopropanation and to our PhI(OAc)$_2$•TBAI mediated conditions. When we attempted the cyclopropanation of a 3-alkylidene-2-oxindole (**4.43a**) with **4.2a** using a mixture of TBAI and PhI(OAc)$_2$, we found no traces of any cyclopropanes within this reagent mixture. Instead, we found near quantitative yield of dihydrofuran **4.44** (eq 4.19). Only one isomer of the dihydrofuran was observed. The ^{1}H NMR spectrum of **4.44** displayed the methine signal at δ = 4.33 ppm and appeared as an apparent triplet with J = 1.5 Hz. This coupling was interpreted as homoallylic coupling between the methine proton and the allylic methylene group. The other regioisomer would not be able to have this type of coupling. Another member of the Murphy group (B. Laevins) later obtained the X-ray crystal structure of this dihydrofuran, which confirmed the regiochemistry and determined the relative stereochemical relationship between the two stereocentres. Similar to the cyclopropanation product of **4.19** and ylide **4.2a**,[199] the product generated here was obtained through a *syn*-addition of the ylide to the alkene.

$$(4.19)$$
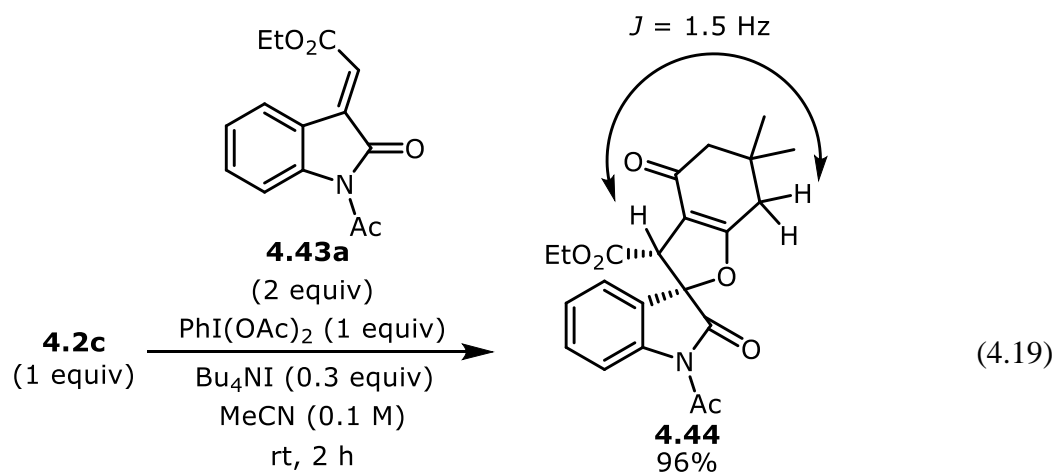
As previously mentioned, we (and other groups)[167] have found cyclopropanes originating from ylides of cyclic 1,3-dicarbonyl compounds, such as **4.2c**, have a tendency to form dihydrofurans either directly or through isomerization of the cyclopropane. On the other hand,

cyclopropanes arising from acyclic 1,3-dicarbonyl compounds appear to be more readily isolable. Therefore, we decided to use the phenyliodonium ylide of dimethyl malonate (**4.2a**) for further investigations into the alkene scope of our PhI(OAc)₂•TBAI mediated cyclopropanations. Subjecting this ylide to the same conditions as eq 4.20 allowed for the isolation of cyclopropane **4.45a** in 92% yield. The relative stereochemistry was determined by a comparison ^{1}H NMR spectrum of **4.45a** with a very similar cyclopropane of known stereochemistry (**4.20**).[199]

$$(4.20)$$
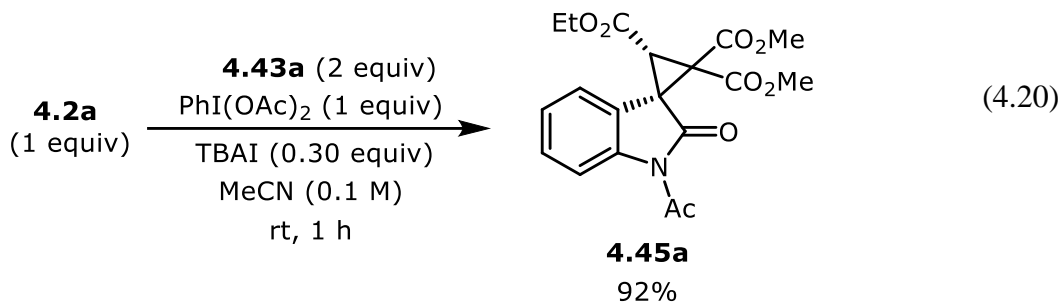
Due the observation that alkene **4.45a** provided excellent yield of the respective cyclopropane, we decided to investigate the cyclopropanation of various 3-alkylidene-2-oxindoles. The cyclopropanation of a 3-alkylidene-2-oxindole bearing a N–H bond (**4.46**) provided an intractable mixture (eq 4.21).

$$(4.21)$$

In systems where the nitrogen was substituted, we found cyclopropanations typically worked well and tolerated a variety of substitutions about the 3-alkylidene-2-oxindole core (**4.43a–l**, Table 4-4). These reactions used equimolar amounts of ylide **4.2a** and the alkene to demonstrate synthetic utility under practical conditions. 3-Alkylidine-2-oxindoles where R^3 is carbonyl derivative and R^1 = EWG typically provided products in the highest yields (**4.45a–d**, **4.45h**, **4.45j**),

usually >70%. However, **4.43i** (R^3 = Ph) provided significantly lower yield (28%) of its respective

cyclopropane. *N*-alkylated oxindoles generally provided moderate yields of the corresponding

cyclopropanes (**4.45e-g**, 48%, 75%, and 59%, respectively). It is interesting that **4.43g**, which bears

two alkenes, underwent cyclopropanation only at the tri-substituted alkene. The greater yield of

4.45e versus **4.45g** (i.e., **4.45**, R = Me vs R = allyl) suggests that the presence of a vinyl group may

not be deleterious to the cyclopropanation of **4.45g**. The preferential reaction of the trisubstituted

alkene versus the terminal alkene suggests that electronic factors play a larger role than steric

Table 4-4. Cyclopropanation of 3-Alkylidene-2-oxidoles
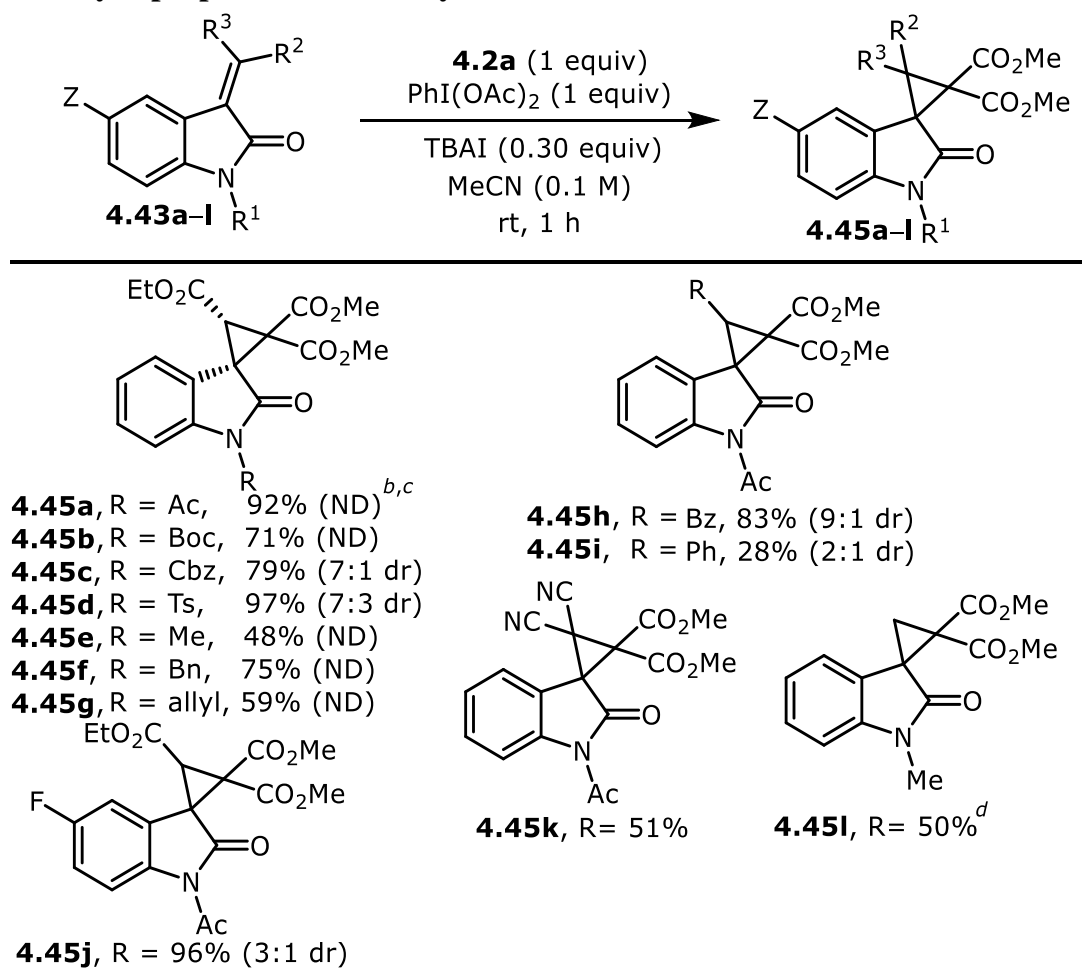
4.45a, R = Ac,   92% (ND)[b,c]
4.45b, R = Boc,   71% (ND)
4.45c, R = Cbz,   79% (7:1 dr)
4.45d, R = Ts,   97% (7:3 dr)
4.45e, R = Me,   48% (ND)
4.45f, R = Bn,   75% (ND)
4.45g, R = allyl, 59% (ND)

4.45h, R = Bz, 83% (9:1 dr)
4.45i, R = Ph, 28% (2:1 dr)

4.45k, R= 51%

4.45l, R= 50%[d]

4.45j, R = 96% (3:1 dr)

[a]General conditions: **4.2a** (0.30 mmol), alkene (1.0 equiv), PhI(OAc)$_2$ (1.0 equiv). TBAI (0.30 equiv), in MeCN (0.1 M) at rt for 1 h. Isolated yields after column chromatography. Diastereomeric ratio determined after purification via column chromatography.[b]ND = Not determined.[c]Used 2 equiv of alkene.[d]Two-step yield, see main text.

effects in the ability for an alkene to participate in cyclopropanation. This chemoselectivity is consistent with the fact that 1-octene (**4.36**) was unable to provide cyclopropanation products in our previous study. We desired to perform a cyclopropanation on a 3-methylene-2-oxindole, and therefore synthesized alkene **4.43l** from β-hydroxysilane (**4.47**) via a protocol described by Loreto et al.[202] Following elimination under acidic conditions, the resulting alkene is known to polymerize when concentrated to dryness.[202] Therefore, we synthesized alkene **4.43l** and subjected it to our cyclopropanation conditions without isolation. This was performed by first preparing **4.48**, and then treating it with $BF_3 \cdot Et_2O$. This reaction led to clean conversion to the alkene when analyzed by TLC. Once the reaction was complete, it was quickly purified via an aqueous work-up. The organic extracts were concentrated to near-dryness and were immediately subjected to the cyclopropanation conditions which provided the cyclopropane in 50% yield over two steps (Scheme 4-4).

Scheme 4-4. Two-step Elimination/Cyclopropanation
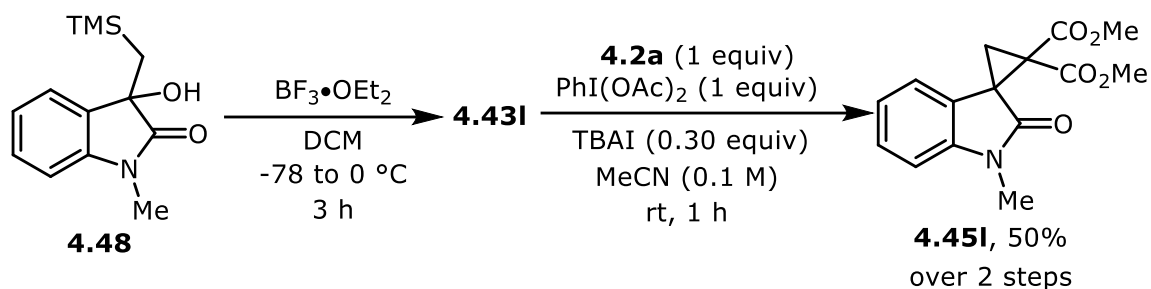
Attempts to obtain different analogs of **4.43l** by acylating the nitrogen of **4.49** led to the formation of white insoluble material (likely polymeric) upon addition of bases such as pyridine, DMAP, or *N*-methylimidazole (eq 4.22).

$$(4.22)$$
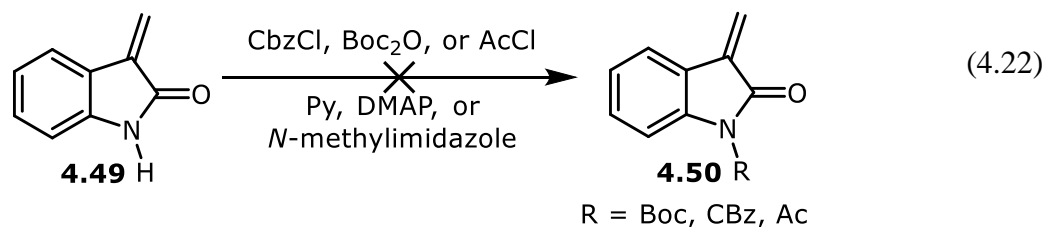
We continued to expand the alkene scope by screening other alkene-containing carboskeletons which could undergo cyclopropanation under our PhI(OAc)$_2$•TBAI mediated conditions. A direct analog to the 3-alkylidene-2-oxindoles, 3-alkylidene-benzofuran-2-one (**4.51**), was able to afford cyclopropane **4.52** in 83% yield (eq 4.23).

$$(4.23)$$
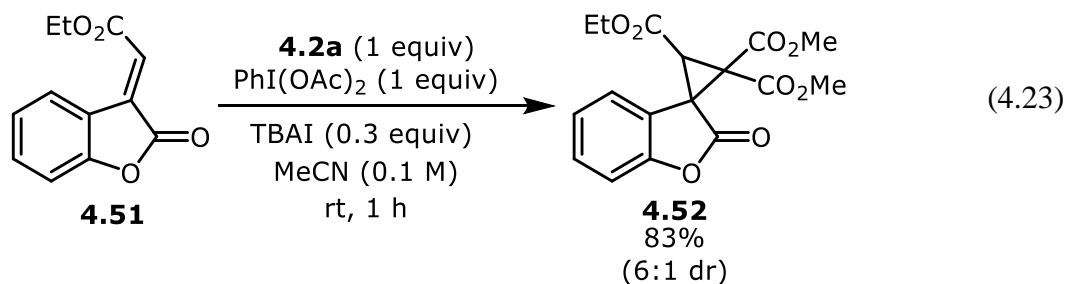
From all of the studies previously outlined in this section, we noticed that the common structural element shared between all of the alkenes that were successful in our cyclopropanation reactions were ones which contained alkenes conjugated to a benzene or functionalized-benzene. We, therefore, desired to diversify the alkene substrate scope to non-stryrenyl moieties. Our study of 3-alkylidene-2-oxindoles showed that the best yields were, typically, substrates in which the alkene was conjugated to two-carbonyl groups. Screening other enediones found that they also provided cyclopropanes in widely varying yields (24–79%, Table 4-5). We found exocyclic alkenes such as a Meldrum's acid alkylidene (**4.53a**) and the Knoevenagel condensation adduct between malononitrile and ninhydrin (**4.53b**), provided cyclopropanes **4.55a** and **4.55b** in 74% yield and 35% yield, respectively. Endocyclic alkenes found in *N*-phenylsuccinimide (**4.53a**) and 1,4-benzoquinone were found to provide low yields of cyclopropanation (27% and 24% yield for

Table 4-5. Cyclopropanations of 1,1- and 1,2-Enediones[a]

4.53   4.54   4.55   4.56

4.55a 74%   4.55b 35%   4.56a 27%   4.56b, Z'= H (24%)
4.56c, Z'= OAc (38%)
4.56d, Z'= OTs (79%)
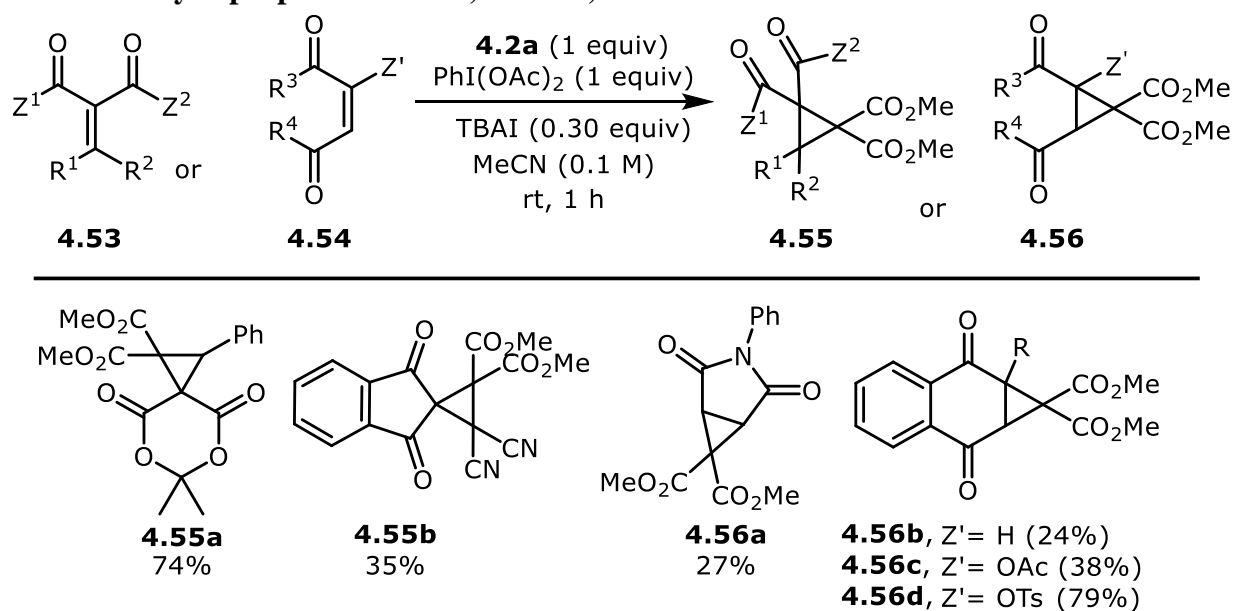
[a]General conditions: **4.2a** (0.30 mmol), alkene (1.0 equiv), PhI(OAc)$_2$ (1.0 equiv). TBAI (0.30 equiv), in MeCN ([alkene] = 0.1 M) at rt for 1 h. Isolated yields after column chromatography.

4.55a and **4.55b**, respectively). The substituent at the 2-position of 1,4-benzoquinone was found to have a large effect towards the outcome on the reaction as demonstrated by the parent compound (**4.54b**) providing cyclopropane **4.56b** in only 24% yield, while higher yields of the respective cyclopropanes were obtained when the 2-position of the benzoquinone was an acetoxy- or a tosyloxy group (**4.56c** and **4.56d**, 38% and 79%, respectively). While studying the cyclopropanations of the various alkenes using **4.2a** (discussed in the previous section), we observed the major side product to be tetramethyl ethene-1,1,2,2-tetracarboxylate (i.e., (CO$_2$Me)$_2$C=C(CO$_2$Me)$_2$), formed from a formal carbene dimerization of the iodonium ylide. Traces of other side products believed to arise from the decomposition of the ylide were observed by ^{1}H NMR spectroscopy, but could not be identified. Typically, the lower the yield of cyclopropanation, the larger the amount of the dimer that was formed.

In summary, initially, it appeared difficult to predict whether what factors determined whether a given alkene could undergo cyclopropanation. Ultimately, substrate scope studies outlined in this section identified alkenes contained within styrenes, 3-alkylidene-2-oxindoles, 3-benzofuran-2-ones and various enediones were capable of undergoing cyclopropanation reactions with the phenyliodonium ylides of dimedone or dimethyl malonate when treated with a mixture of PhI(OAc)$_2$ and TBAI. Many successfully cyclopropanated alkenyl groups were conjugated to electron-withdrawing groups and raised the question whether a MIRC mechanism was operative in these systems. However, such a mechanism is unlikely to occur in cyclopropanation reactions involving styrene. During the substrate scope study described in this study, a concurrant investigation aimed to reveal mechanistic details of the cyclopropanation reaction were performed, and is the subject of the next section.

4.1.5. Mechanistic Investigations

To further understand the PhI(OAc)$_2$/TBAI mediated cyclopropanation between **4.2c** and styrene, a series of probing experiments were conducted (Table 4-6). Control reactions performed on this system confirmed the combination of both PhI(OAc)$_2$ and iodide was needed to provide cyclopropanation (entry 1 vs entries 2 and 3). Other sources of inorganic iodide can be used, such as KI and *N*-methylpyridinium iodide (NMPI), but provided the cyclopropane in lower yields (entries 4 and 5, 82% and 50%, respectively) relative to TBAI. The iodide could not be replaced by other halides such as bromide or chloride (entries 6 and 7). Lowering the loading of PhI(OAc)$_2$ from 1 equiv to 0.1 equiv provided **4.3c** in 71% yield (entry 8), confirming our initial hypothesis that the activator can be used in catalytic quantities.

Table 4-6. Investigating the Effect of Iodide and PhI(OAc)$_2$

4.3c[a]
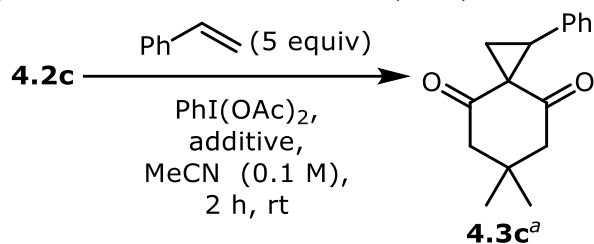
entry	PhI(OAc)$_2$ (equiv)	additive (equiv)	yield (%)[a]
1	1.0	TBAI (0.3)	89
2	1.0	None	<5
3	0	TBAI (0.3)	<5
4	1.0	KI (0.3)	82
5	1.0	NMPI (0.3)	50
6	1.0	TBAC (0.3)	<5
7	1.0	TBAB (0.3)	<5
8	0.10	TBAI (0.3)	71

[a]General conditions: **4.2c** (0.10 mmol, 1.0 equiv), styrene (5 equiv), additive (0 or 0.30 equiv). Yield determined by ^{1}H NMR analysis of the crude reaction mixture.

After establishing the fact that iodide played a critical role in our cyclopropanations, a set of experiments were performed to provide further insights into what role the PhI(OAc)$_2$•TBAI mixture was playing. When designing these experiments, we considered what was already known about the reaction between these two reagents. It is known that iodide is readily oxidized by various oxidants, such as PhI(OAc)$_2$, and this process has been used in many transformations of organic molecules.[203] The reactive iodine species in such reactions is often unclear as multiple reactive species such as diiodine (I$_2$), acyl hypoiodites (RCOI), or iodites (IO$^-$) can be generated.[203] Therefore, the term "electrophilic iodine species" ("I$^+$") is often used to encompass the possible reactive intermediates. Based on the general reactivity patterns of PhI(OAc)$_2$ and TBAI, these two reagents can react and provide various electrophilic iodine species shown in Scheme 4-5. First, iodide can exchange with one of the OAc ligands of PhI(OAc)$_2$, generating a more reactive iodane **4.57**. Ligand coupling would reductively eliminate PhI and provide acetylhypoiodite (AcOI).

Subsequently, an acetate anion and AcOI can combine to generate the diacetoxyiodate anion, $[(AcO)_2I]^-$.

Scheme 4-5. Possible Electrophilic Iodine Species Formed by Reaction of I⁻ and PhI(OAc)₂

4.57
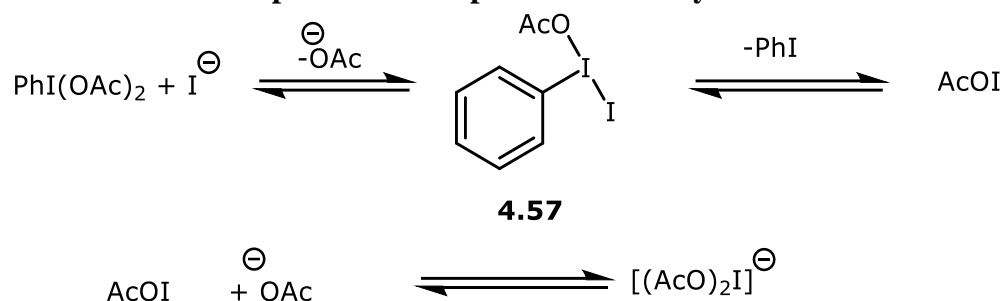
The reactive compounds potentially formed from the reaction of PhI(OAc)₂ and TBAI (i.e., **4.56**[204] or AcOI[205]) have been postulated to play key roles in the transformation of organic compounds. The formation of the diacetoxyiodate anion has been confirmed as Suárez et al. have shown that the mixture of PhI(OAc)₂ and TBAI can allow for the isolation of TBA[(AcO)₂I] (eq 4.24).[206] Recently, Muñiz et al. have reported this procedure is applicable for the synthesis of iodine(I) iodates bearing a variety of substituted benzoate ligands (eq 4.25).[207]

$$PhI(OAc)_2 \xrightarrow[\text{CHCl}_3]{\text{TBAI}} \underset{85\%}{TBA[(OAc)_2I]} \qquad (4.24)$$

$$PhI(O_2CAr)_2 \xrightarrow[\text{CHCl}_3]{\text{R}_4\text{NI}} \underset{\substack{\text{17 examples} \\ 71-99\%}}{R_4N[(O_2CAr)_2I]} \qquad (4.25)$$
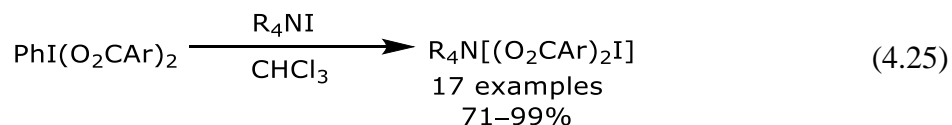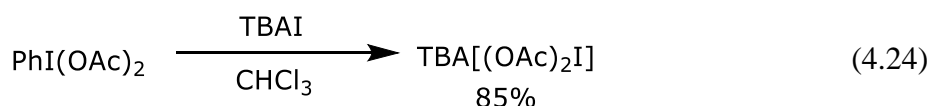
To test if the participation of an electrophilic iodine species in our cyclopropanation was possible, the cyclopropanation of styrene using **4.2c** was performed using another oxidant (i.e., Oxone), in place of PhI(OAc)₂, to oxidize the iodide. This reaction was found to form small amounts of the respective cyclopropane (27% yield, eq 4.26).

145

$$\text{4.2c} \xrightarrow[\substack{\text{Oxone (1.0 equiv)} \\ \text{TBAI (0.3 equiv)} \\ \text{MeCN (0.1 M)} \\ \text{2 h, rt}}]{\text{Ph} \diagdown \text{(5 equiv)}} \text{4.3c} \qquad (4.26)$$

4.3c
27% NMR yield
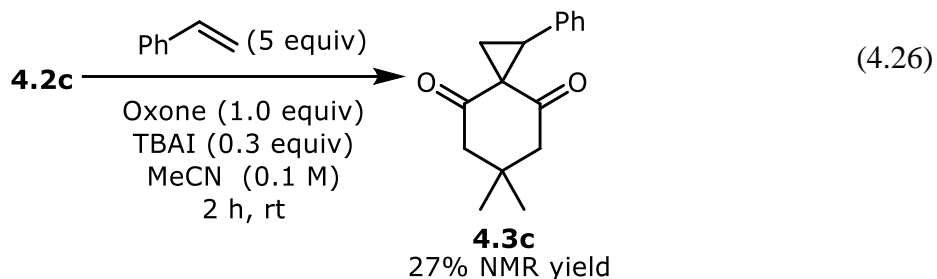
This observation led us to explore the effect of using different reagents bearing an iodine in different oxidation states upon the outcome of the cyclopropanation reaction in the presence and absence of PhI(OAc)$_2$ (Table 4-7). In the presence of PhI(OAc)$_2$, using I$_2$ in place of TBAI provided lower amounts of cyclopropane **4.3c** (55% yield vs 89% yield, entry 2 vs 1, respectively). Interestingly, reaction of styrene, **4.2c**, and I$_2$ in the absence of PhI(OAc)$_2$ provided dihydrofuran **4.31c** in 44% yield instead of the cyclopropane (entry 3). Two reagents containing a dicoordinate iodine anion, TBA[(OAc)$_2$I] and TBAI$_3$, were examined for reactivity and both were able to

Table 4-7. Investigating Different Iodine-containing Reagents

entry	PhI(OAc)$_2$ (equiv)	"Iodine"	%Yield 4.3c ^{a}
1	1.0	TBAI	89
2	1.0	I$_2$	55
3	0	I$_2$	0 (44)^b
4	0	TBA[(OAc)$_2$I]	50
5	1.0	TBA[(OAc)$_2$I]	86
6	0	TBAI$_3$	77
7	1.0	TBAI$_3$	88

^{a}General conditions: **4.2c** (0.10 mmol), PhI(OAc)$_2$ (0 or 1.0 equiv), "iodine" (0.30 equiv), MeCN (0.1 M). Yields refer to ones obtained using ^{1}H NMR. ^{b}Yield of dihydrofuran **4.32c**

provide cyclopropanation in the absence of PhI(OAc)$_2$ (50% and 77%, entry 4 and 6, respectively). In the presence of PhI(OAc)$_2$, both of these reagents provided **4.3c** in yields comparable to when using the PhI(OAc)$_2$•TBAI mixture (86% and 88% vs 89%, entries 5 and 7 vs entry 1, respectively).

In solution, the triiodide anion, I$_3^-$, can exist in equilibrium with diiodine and iodide. The fact that I$_3^-$-catalyzed reactions can provide cyclopropanation in the absence in of PhI(OAc)$_2$ while the other two iodine species do not, suggests that the dicoordinate iodine species is an active catalytic species. If this postulate is accepted, and considering the data presented in Table 4-7, it is possible to believe the mixture of TBAI and PhI(OAc)$_2$ generates TBA[(OAc)$_2$I] in situ, with the iodine(I) iodate being the active catalytic species. To test this hypothesis, we desired another iodine(I) iodate that could promote cyclopropanation between **4.2c** and styrene. We therefore attempted to generate TBA[IF$_2$] in situ via the reaction of TolIF$_2$ and TBAI for the use in cyclopropanation reactions. To our knowledge, the adduct(s) formed from the reaction of iodide and TolIF$_2$ have not been investigated. This mixture was found to provide slightly higher yields than using the mixture of PhI(OAc)$_2$ and TBAI (eq 4.27).

$$(4.27)$$

4.3c
94% NMR yield
85% isolated yield
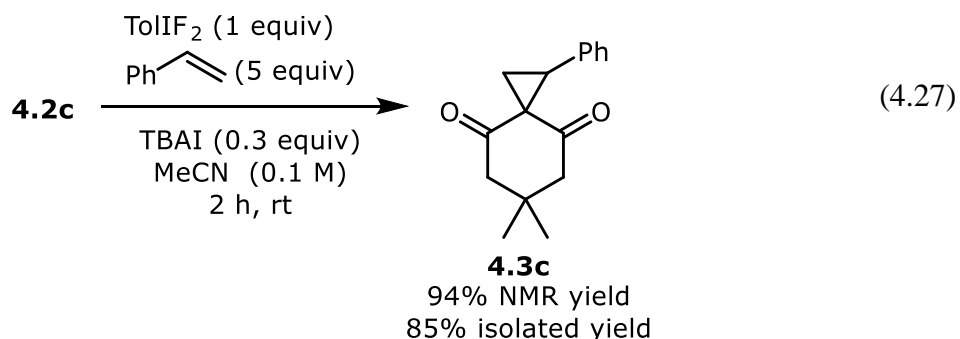
We hypothesize that if the difluoroiodate anion is generated from the mixture of TolIF$_2$ and I$^-$, the high yields obtained in the cyclopropanation reactions can be due to the iodate exhibiting a lower degree of dissociation (eq 4.28) than the diacetoxyiodate anion. This would

147

lower the amount of reactive intermediates (e.g., IF) that could be detrimental to the cyclopropanation reaction.

$$\left[F{-}I{-}F\right]^{\ominus} \;\rightleftharpoons\; I{-}F \;+\; F^{\ominus} \tag{4.28}$$
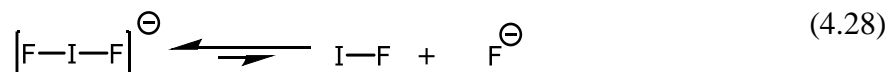
To examine the possibility of radical participation, we investigated the effect of the presence of radical inhibitors in the cyclopropanation of **4.2c** and styrene using PhI(OAc)$_2$ and TBAI. We found that when 1,4-benzoquinone was included in the reaction mixture, a significantly lower amount of **4.3c** was formed (47% yield, eq 4.29). In separate experiments, attempting cyclopropanations in the presence of BHT or TEMPO completely prevented the formation of the **4.3c** (eq 4.29). Performing the cyclopropanation of **4.2c** using PhI(OAc)$_2$•TBAI in the dark had little effect on the yield of the cyclopropane (80%). These experiments led us to suspect the existence of non-photogenerated radical intermediates in the cyclopropanation of styrene using **4.2c**.

$$\text{(4.29)}$$

Inhibitor	NMR Yield
1,4-benzoquinone	47%
BHT	<5%
TEMPO	<5%
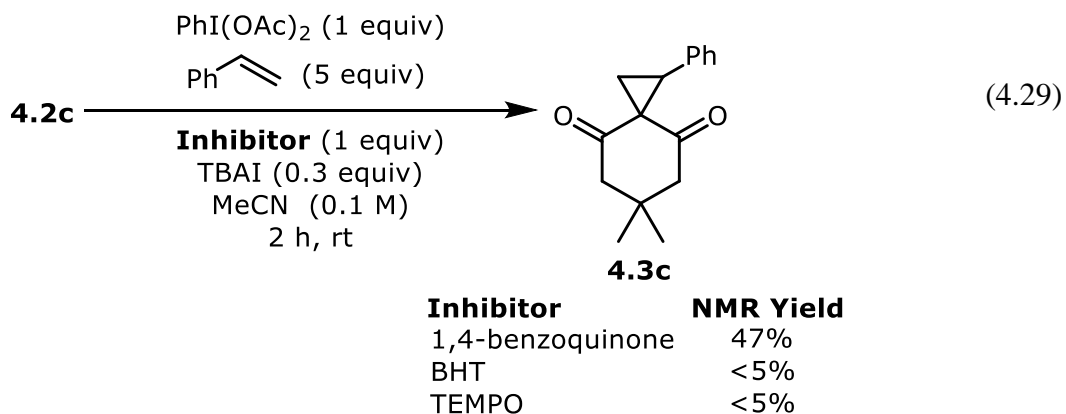
These observations, combined with our desire to find another hypervalent iodine(III) reagents that would activate iodonium ylides towards cyclopropanation, led us to investigate the use of peroxyiodane **4.58**[208,209] as a radical initiator. This reagent is a solid which can be stored indefinitely at room temperature (however, it has reported to decompose explosively when heated

to 140 °C).[208] Despite its stability in solid form, **4.58** slowly decomposes in solution at room

temperature ($t_{1/2}$ = 7.4 h at 30 °C in DCM).[209] It is believed the weak hypervalent I–OOtBu bond

homolyzes, generating *tert*-butylperoxy radical and iodanyl radical **4.59**, which is in equilibrium

with the benzoyloxyl radical **4.60** (eq 4.30).[209]

$$(4.30)$$
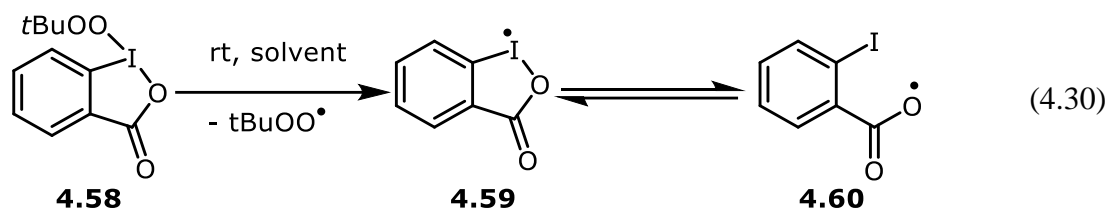
Ochiai et al. have used **4.58** to perform allylic-, benzylic-, and propargylic oxidations of

the respective allylic-, benzylic-, and propargylic ethers. For example, *n*-butyl benzyl ether (**4.61**)

was found to be oxidized in benzene in good yield (eq 4.31).[209]

$$(4.31)$$
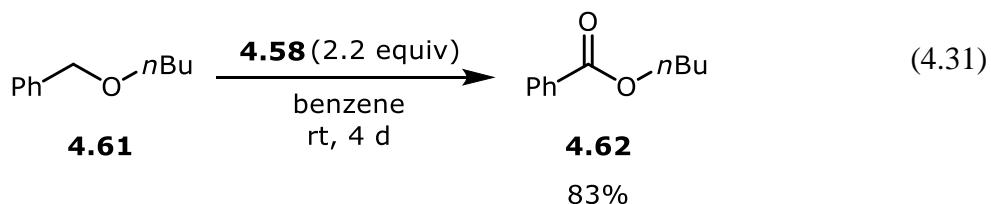
Given the low thermal stability of iodonium ylides, the room-temperature generation of an

iodanyl radical using **4.58** and its use to activate an iodonium ylide towards cyclopropanation was

thought to be an attractive feature. In un-optimized reaction conditions, we found the mixture of

ylide **4.2c**, **4.58**, and styrene in MeCN generates the respective cyclopropane in 35% NMR yield

(eq 4.32). For the oxidation of **4.61** using **4.58**, Ochiai et al. had found MeCN to be the *least*

efficient reaction solvent. Therefore, we tried using their optimal reaction solvent (i.e., benzene)

for our cyclopropanation reaction. However, upon addition of **4.58** to a mixture of the other

reagents, immediate polymerization of styrene was observed. While using **4.58** to activate

iodonium ylides towards cyclopropanation (or other) reactions provides an interesting opportunity for exploration, further studies were not pursued.

$$(4.32)$$

4.2c
35% NMR yield
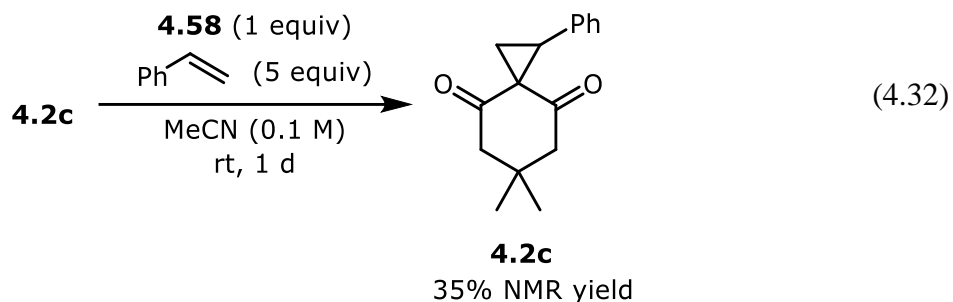
Over the course of the alkene substrate scope investigation using ylide **4.2a**, we noticed that, with the exception of styrene, other alkenes that were successful substrates for our PhI(OAc)$_2$•TBAI mediated cyclopropanations bore multiple electron-withdrawing groups. We wondered if a MIRC mechanism, similar to the one employed by Mayr et al. (eq 4.11), could be operative in our cyclopropanations. Under uncatalyzed conditions alkenes, **4.53a**, **4.53b**, and **4.43d** it was found that cyclopropanes still formed (**4.55a**, **4.55b**, and **4.45d**, 81%, 44%, and 87% yield, respectively, Table 4-8) in similar yields to when conducting the reaction in the presence of PhI(OAc)$_2$ and TBAI. It appears that the cyclopropanation of ylide **4.2a** and **4.43** benefits from the presence of PhI(OAc)$_2$•TBAI or TBA[(OAc)$_2$I] and allows for higher yield of the respective cyclopropane (**4.45d**, 97%). For *N*-phenylmaleimide and (2-tosyloxy)-1,4-benzoquinone (**4.54d**), no uncatalyzed reaction with the ylide was observed. The cyclopropanation of **4.2a** using **4.54d** revealed different results when compared to other systems. The use of TBA[(OAc$_2$)I] in place of TBAI did not provide any cyclopropane, while iodide, in the absence of PhI(OAc)$_2$, provided **4.56d** in 67% yield, and the presence of BHT did not prevent the PhI(OAc)$_2$•TBAI mediated

Table 4-8. Control Reactions for the Cyclopropanation of Various Alkenes[a]

4.2a (1 equiv) → alkene (1 equiv), additive (0 or 0.30 equiv), MeCN-d_3 (0.1 M), rt, 1 h → **4.45d, 4.55–4.56**

4.55a
81%

4.55b
44%

4.45d
87%
97%[b]

4.56a
<5%

4.56d
<5%, <5%[b]
67%[c], 75%[d]
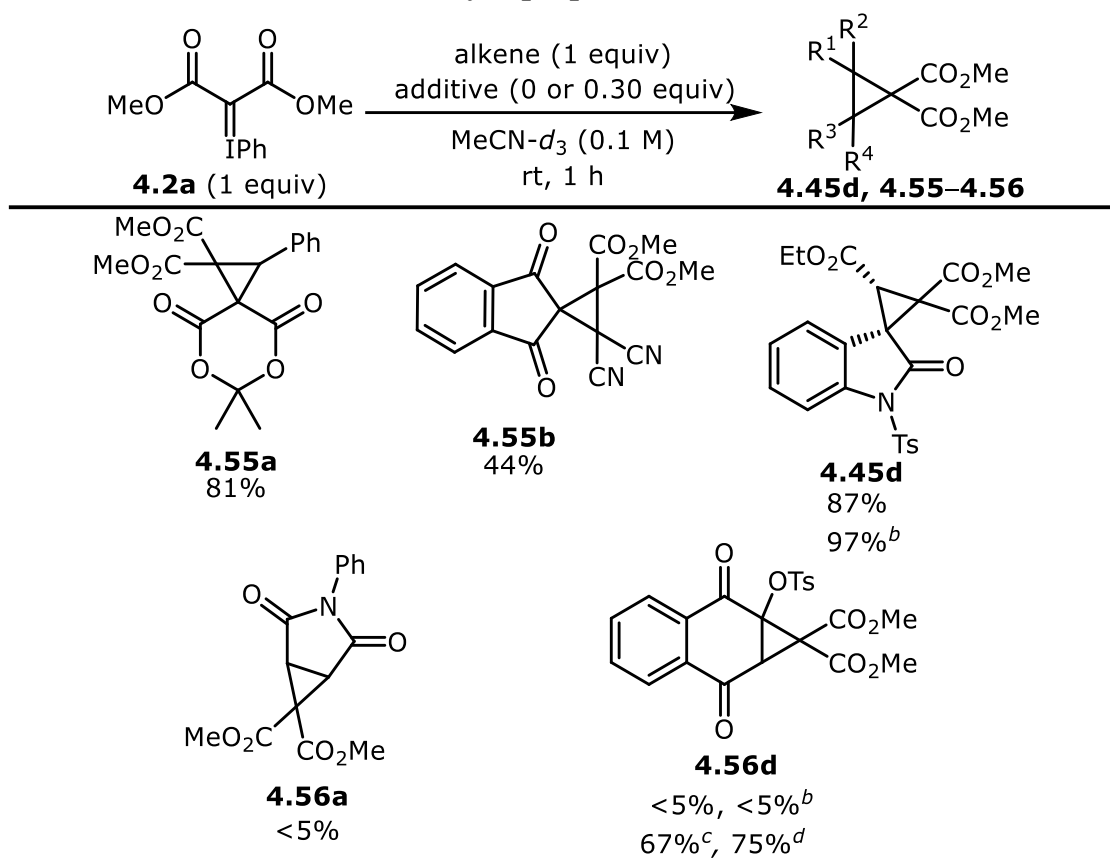
[a]General conditions: **4.2a** (0.10 mmol), alkene (1.0 equiv), and MeCN-d_3 (0.1 M) at rt. Yields obtained via ^{1}H NMR spectroscopy using HMDSO as an internal standard.[b]Reaction contained TBA[(OAc$_2$)I] (0.30 equiv) as an additive.[c]Reaction mixture contained TBAI (0.3 equiv) as an additive. [d]Reaction mixture contained PhI(OAc)$_2$ (1.0 equiv), TBAI (0.3 equiv), and BHT (1.0 equiv) as additives.

cyclopropanation (75% yield). These results suggest the mechanisms involved with the formation of cyclopropanes are highly system-dependent and in order for more details to be elucidated, more probing reactions would be necessary.

4.2. Concluding Remarks

In this chapter, the mixture of PhI(OAc)$_2$ and TBAI allowed for various phenyliodonium ylides derived from, for example, 1,3-ketoesters, 1,3-diketones, and malonate esters to engage in cyclopropanation reactions with styrene. The phenyliodonium ylides of dimedone and dimethyl malonate engaged in reactions which provided high yields (89% and 52%, respectively) among

the series of iodonium ylides derived from cyclic- and acyclic 1,3-dicarbonyl compounds, respectively. These two ylides were used in subsequent reactions as model substrates to represent iodonium ylides of cyclic- and acyclic 1,3-dicarbonyl compounds. Investigating the alkene substrate scope for these reactions revealed a tendency for alkenes conjugated to electron withdrawing groups to provide the desired cyclopropanes, while simple olefins and alkenes conjugated to electron rich functionalities failed to provide cyclopropanes.

A series of probing reactions were performed using the phenyliodonium ylide of dimedone and styrene. Investigative experiments revealed the active intermediate formed from the reaction of PhI(OAc)$_2$ and TBAI may be TBA[(OAc)$_2$I] and that radical intermediates may be involved. A mixture of the phenyliodonium ylide of dimedone, styrene, and a peroxyiodane (known to generate radicals in situ at room temperature) also provided cyclopropanation. It was found that TBAI$_3$ and TBA[(OAc)$_2$I] could be used, in catalytic amounts, promote the cyclopropanation reaction between the phenyliodonium ylide of dimedone and styrene. It may be worthwhile to investigate the applicability of different types of other iodine(I) reagents to this reagent. For example, bis(acyloxy)iodates(I) (**4.63**), in which the iodine appears within a heterocycle, could possibly be used to increased yields and/or functional group tolerance when used in cyclopropanation reactions. Additionally, the cationic iodate(I), **4.64**,[210] may allow for iodonium ylides to engage in cyclopropanation reactions with a different set of alkenes.
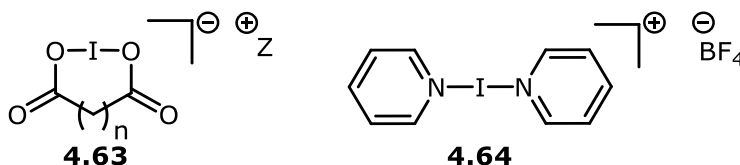
Figure 4-1. Iodine(I) reagents that can be investigated in future cyclopropanation reactions.

Preliminary control reactions performed on various alkenes suggest multiple mechanisms are possible for the formation of cyclopropanes. The mechanisms that are operative appear to be highly system-dependent. Different alkenes were found able to engage with iodonium ylides in cyclopropanations using one or more of the following reagents, reagent mixture, or conditions: 1) a mixture of PhI(OAc)$_2$ or TolIF$_2$ and TBAI, 2) TBAI, 3) TBAI$_3$, 4) TBA[(OAc)$_2$I], 5) a peroxyiodane, or 6) uncatalyzed conditions. Of the preceding reagent/reagent mixtures, the use of PhI(OAc)$_2$ and TBAI was the most studied and appears effect the cyclopropanation of phenyliodonium ylides with the widest range of alkenes (styrenes, 3-alkylidine-2-oxindoles, 1,1-enediones, and 1,2-enediones). In addition, this reagent mixture provided cyclopropanation in the highest yields (up to 97%). Currently, the details of what factors allow for cyclopropanations to occur in conditions 1–5 remain unclear, and are the subject of future investigations.

4.3. Experimental

All reactions were performed using oven-dried or flame-dried glassware under a positive pressure of nitrogen unless otherwise stated. PhICl$_2$ and TolIF$_2$ were synthesized as described in Chapter 2. The following were prepared using literature procedures: diazo compound **4.28d**;[211] alkenes **4.33b**,[212] **4.33c**,[213] **4.34c**,[214] **4.37**,[215] **4.38b**,[216] **4.41a**,[217] **4.41b**,[218] and **4.41c**;[219] and HVI reagents **4.58**[208] TBA[I(OAc)$_2$],[206] TBAI$_3$,[220] and (diacetoxy)iodoarenes.[221] Iodonium ylides were synthesized using procedures described in Chapter 3. The spectral data for known iodonium ylides matched those described in the literature. **4.53a** was obtained from the laboratory of Prof. E. Fillion. Dry DCM, THF, DCE, toluene, and Et$_2$O were obtained from a JC Meyer solvent purification system,[122] and were used without further purification. Anhydrous MeCN and DMSO were obtained by storing the solvents over activated 3 Å or 4 Å molecular sieves (respectively) overnight and were used without further purification. Molecular sieves were activated by heating

the sieves to 150–300 °C under high vacuum (0.1–0.05 torr) overnight. All other solvents and reagents were obtained from commercial sources (e.g., Aldrich, Oakwood Chemicals) and were used without further purification unless otherwise stated. Thin layer chromatography was performed on glass plates pre-coated with 0.25 mm Kieselgel 60 F254 (Merck). Unless otherwise stated, flash chromatography columns were packed with 230–400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-*d* (77.0 ppm). Positive ion electrospray ionization (+ESI) and negative ion electrospray ionization (-ESI) were performed with a Thermo Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. For ESI, samples were infused at 10 µL/min in either 1:1 CH_3OH/H_2O+0.1% formic acid or 1:1 CH_3OH/H_2O+0.2% NH_4OH. IR spectroscopy was perofmred using aPerkinElmer Spectrum Two FT-IR spectrometer.

General Procedure 4.1 (GP4.1) – Transesterification of Methyl Benzoylacetate

The following procedure was based upon a transesterification procedure reported by Doyle.[222] To a solution of methyl benzoylacetate (5.45 g, 30 mmol, 1.0 equiv) dissolved in toluene (15 mL) was added DMAP (183 mg, 1.5 mmol, 5 mol%) and alcohol (36 mmol, 1.2 equiv). The resultant mixture was heated to reflux and the condensate was allowed to pass through a column of activated 4Å molecular sieves. After 16 h, the reaction mixture was cooled to room temperature, concentrated via rotary evaporation, and the residue was subjected to flash chromatography (mobile phase: either varying concentrations of EtOAc/hexanes or 1% EtOAc/1:1 DCM:hexanes) to isolate the product away from the unreacted starting material.

Isopropyl benzoylacetate (**4.1e**, 50% yield)[223] and benzyl benzoylacetate (**4.1f**, 61% yield)[224] were synthesized using this procedure and their spectral data matched those reported in the literature.

General Procedure 4.2 (GP4.2) – PhI(OAc)$_2$•TBAI Promoted Cyclopropanation of Iodonium Ylides of 1,3-Dicarbonyl Compounds

In a 10 mL round bottom flask, alkene (0.60 mmol, 2 equiv) was stirred in anhydrous MeCN (3 mL) at room temperature and TBAI (11 mg, 0.09 mmol, 30 mol%) was added into the solution. In rapid succession, iodonium ylide (0.30 mmol, 1.0 equiv) and PhI(OAc)$_2$ (96 mg, 0.30 mmol, 1.0 equiv) were added into the flask and the mixture was stirred for either 1 hour (when using iodonium ylides of acyclic 1,3-dicarbonyl compounds) or 2 hours (when using iodonium ylides of cyclic 1,3-dicarbonyl compounds). The reaction mixture was then concentrated to dryness and if NMR yields were desired, HMDSO (1.5 μL/mmol of ylide) was added to the residue prior to ^{1}H NMR spectroscopic analysis. The concentrated reaction mixture was loaded onto a column of silica gel using a minimal amount of CHCl$_3$ and mixtures of EtOAc/hexanes were used to elute the cyclopropane.

Note: Characterization, diastereoselectivities (where appropriate), and NMR yields of cyclopropanes **4.3e–g** were obtained in analogy to **4.3d** (labeled as **3.24e** in Chapter 3) for which the spectral data of *cis*-**4.3d**[183] have been previously reported in the literature. The spectral data appearing in the literature was used identify and quantify cyclopropanes **4.3a**,[225] **4.3b**,[167] **4.3h**,[226] and **4.3j**.[227]

Benzhydryl benzoylacetate (4.1g)
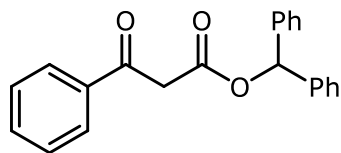
The title compound was synthesized via **GP4.1** using methyl benzoylacetate (30.0 mmol) and benzhydrol (36.0 mmol). Purification via flash chromatography (1% EtOAc/1:1 DCM:hexanes solution) afforded the title compound as an pink liquid (6.63 g, 20.1 mmol, 67% yield) which solidified after storage in a 4 °C refrigerator, yielding a pink solid. This compound was observed to exist in a 5:1 mixture of enol:keto tautomers when dissolved in CDCl$_3$. R$_f$ = 0.34 (1% EtOAc/1:1 hexanes:DCM, UV active); IR (ATR) 3058, 1747, 1682, 1636, 1250, 1194 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 12.45 (s, 1H, enol), 7.94 (d, J = 8.0 Hz, 0.4H, keto), 7.81 (d, J = 7.2 Hz, 2H, enol), 7.77 (d, J = 7.2 Hz, 0.2H, keto), 7.60 (t, J = 7.5 Hz, 0.4H, keto), 7.50–7.28 (m, 16H), 7.04 (s, 1H, enol), 6.96 (s, 0.2H, keto), 5.87 (s, 1H, enol), 4.10 (s, 0.4H, keto); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.34, 172.23, 166.6, 140.2, 139.7, 136.1, 133.8, 133.4, 131.5, 128.9, 128.70, 128.68, 128.60, 128.13, 128.12, 128.05, 127.25, 127.23, 126.2, 87.5, 78.2, 46.4. 2 carbon resonances were not resolved; HRMS (+ESI) *m/z*: [M+Na]$^+$ calcd for C$_{22}$H$_{18}$NaO$_3$, 353.1148; found 353.1129.

Phenyliodonium ylide of isopropyl benzoylacetate (4.2e)
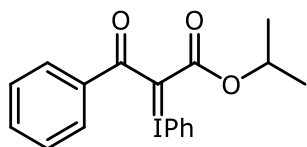
The title compound was synthesized via **GP3.3.1** using isopropyl benzoylacetate (**4.1e**) (2.06 g, 10.0 mmol). After concentrating the organic extracts, the solution containing the iodonium ylide was diluted with DCM, Et$_2$O, and hexanes, and then briefly concentrated in vacuo to induce precipitation of the ylide, and the resulting suspension was cooled to 0 °C. The solid was collected by vacuum filtration, washed with hexanes (20 mL), and dried in vacuo to yield the title compound as a white amorphous solid (802 mg, 20% yield). mp 59–61 °C; IR (ATR) 2977, 1627, 1469, 1260, 1105,

1010 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.89 (dd, J = 8.3, 1.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.51–7.49 (m, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.35–7.30 (m, 3H), 4.81 (sep, J = 6.3 Hz, 1H), 0.93 (d, J = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.2, 164.3, 140.0, 133.5, 131.62, 131.48, 129.4, 128.3, 127.4, 112.9, 85.6, 68.1, 21.9; HRMS (+ESI) m/z: [M+H]$^+$ calcd C$_{18}$H$_{18}$IO$_3$, 409.0295; found 409.0295.
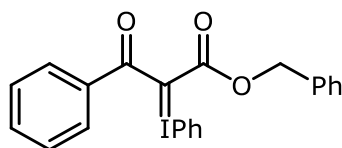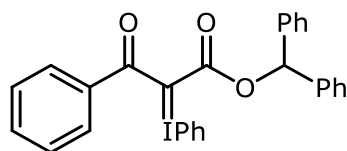
Phenyliodonium ylide of benzyl benzoylacetate (4.2f)

The title compound was synthesized via **GP3.3.1** using benzyl benzoylacetate (**4.1f**) (1.27 g, 5.0 mmol). After concentrating the organic extracts, the solution containing the iodonium ylide was treated with Et$_2$O and hexanes, and cooled to 0 °C to induce precipitation of the ylide. Vacuum filtration afforded the title compound as a white amorphous solid (724 mg, 32% yield). mp 61–63 °C; IR (ATR) 3057, 1677, 1646, 1469, 1262, 1040 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, J = 7.5 Hz, 2H), 7.55–7.53 (m, 3H), 7.36 (t, J = 7.7 Hz, 3H), 7.33–7.29 (m, 2H), 7.24–7.23 (m, 3H), 7.00–6.99 (m, 2H), 4.98 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.4, 164.5, 139.7, 136.6, 133.6, 131.58, 131.49, 129.6, 128.3, 127.88, 127.76, 127.60, 113.0, 84.0, 66.6. One resonance was not resolved; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{22}$H$_{18}$IO$_3$, 457.0295; found 457.0294.

Phenyliodonium ylide of benhydryl benzoylacetate (4.2g)

The title compound was synthesized via **GP3.3.1** using benhydrol benzoylacetate (**4.1g**) (1.27 g, 5.0 mmol). After concentrating the organic extracts, the solution containing the iodonium ylide was treated with Et$_2$O and hexanes to induce precipitation of the ylide. Vacuum filtration afforded the title compound as a white amorphous solid (724 mg, 32% yield). mp 120–122 °C; IR (ATR) 3053,

1650, 1529, 1325, 1252, 1016 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 7.1 Hz, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 7.37–7.32 (m, 4H), 7.24–7.21 (m, 6H), 7.07–7.03 (m, 4H), 6.80 (s, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.4, 163.6, 140.8, 139.8, 133.2, 131.37, 131.20, 129.5, 128.30, 128.14, 127.6, 127.3, 126.9, 112.7, 77.6 (C=I was not observed); HRMS (+ESI) m/z: [M+H]$^{+}$calcd for C$_{28}$H$_{22}$NO$_3$, 533.0608; found 533.0608.

6,6-Dimethyl-1-phenylspiro[2.5]octane-4,8-dione (4.3c)[228]
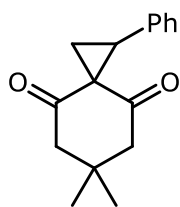
The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and styrene (104.2 mg, 0.60 mmol, 2.0 equiv). Purification via column chromatography (5% then 10% EtOAc/hexanes), led to the title compound to be isolated as a white solid (40 mg, 55% yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.49–7.23 (m, 5H), 3.30 (dd, J = 10.2, 10.2 Hz, 1H), 2.69–2.53 (m, 3H), 2.40–2.22 (m, 3H), 1.16 (s, 3H), 1.13 (s, 3H). These data match those that have been previously reported in the literature.

6,6-Dimethyl-1-(3-nitrophenyl)spiro[2.5]octane-4,8-dione (4.3c.c)
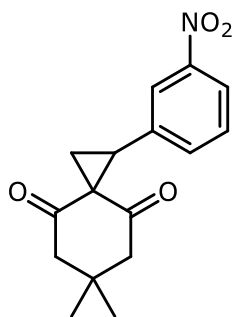
The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and 3-nitrostyrene (89.5 mg, 0.60 mmol, 2.0 equiv). Purification by column chromatography (5% to 30% EtOAc /hexanes), led to the title compound to be isolated as a white solid (51 mg, 60% yield). mp 102–104 °C; R$_f$ = 0.43 (20% EtOAc/hexanes, UV active); IR (ATR) 2961, 1699, 1673, 1527, 1347, 1334, 1217 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.10–8.08 (m, 2H), 7.54 (d, J = 7.8 Hz, 1H), 7.46 (dd, J = 7.8, 7.8 Hz, 1H), 3.33 (dd, J = 8.9, 8.9 Hz, 1H), 2.68–2.63 (m, 1H), 2.62–2.58 (m, 1H), 2.49 (dd, J = 8.8, 3.8 Hz, 1H), 2.39 (d, J = 16.5 Hz, 1H), 2.34 (dd, J = 9.1, 3.8 Hz, 1H), 2.26 (d, J = 16.5 Hz, 1H), 1.12, (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ

205.4, 202.2, 148.1, 135.76, 135.64, 129.0, 124.7, 123.0, 54.2, 53.3, 47.6, 45.7, 30.6, 29.3, 28.0, 23.7; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{16}$H$_{18}$NO$_4$, 288.1230; found 288.1230.

1-(4-Chlorophenyl)-6,6-dimethylspiro[2.5]octane-4,8-dione (4.3c.d)

The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and 4-chlorostyrene (0.60 mmol, 2.0 equiv). Purification by column chromatography (5% then 10% EtOAc/hexanes) led to the title compound to be isolated as a white solid (58 mg, 64% yield). mp 106–108 °C; R$_f$ = 0.24 (10% EtOAc/hexanes, UV active); IR (ATR) 2958, 1702, 1675, 1332, 1015 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 3.24 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.64 (d, *J* = 16.9 Hz, 1H), 2.60 (d, *J* = 16.9 Hz, 1H), 2.49 (dd, *J* = 8.9, 3.6 Hz, 1H), 2.39 (d, *J* = 16.6 Hz, 1H), 2.33 (dd, *J* = 9.1, 3.7 Hz, 1H), 2.25 (d, *J* = 16.7 Hz, 1H), 1.15 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.5, 201.7, 133.8, 131.7, 130.8, 128.2, 54.0, 53.2, 48.4, 47.3, 30.5, 29.2, 27.9, 22.5; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{16}$H$_{18}$^{35}ClO$_2$, 277.0990; found 277.0990.
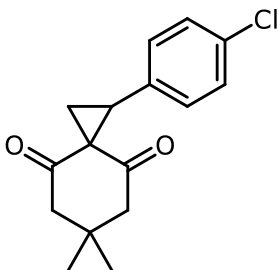
1-(4-Methylphenyl)-6,6-dimethylspiro[2.5]octane-4,8-dione (4.3c.e)
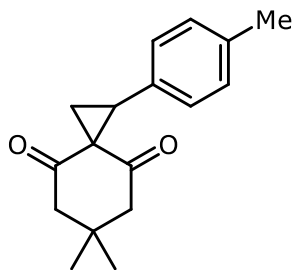
The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and 4-methylstyrene (71 mg, 0.60 mmol, 2.0 equiv). Purification by column chromatography (5% then 10% EtOAc/hexanes) led to the title compound to be isolated as thick yellow oil (34 mg, 44% yield). R$_f$ = 0.17 (10% EtOAc/hexanes, UV active); IR 2954, 1702, 1674, 1333, 1273 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.11 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 3.23 (t, *J* = 9.0 Hz, 1H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.56 (d, *J* = 16.7 Hz, 1H), 2.51 (dd, *J* = 9.0, 3.7 Hz,

159

1H), 2.36–2.30 (m, 5H), 2.21 (d, $J = 16.3$ Hz, 1H), 1.12 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.7, 201.7, 137.7, 130.1, 129.4, 128.7, 54.0, 53.2, 48.93 48.82, 30.5, 29.3, 27.9, 22.1, 21.2; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{17}$H$_{21}$O$_2$, 257.1542; found 257.1536.

**Benzhydryl 1-benzoyl-2-phenylcyclopropane-1-carboxylate (4.3g)**
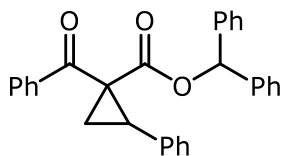
The title compound was synthesized via **GP4.2** using ylide **4.2g** (96 mg, 0.30 mmol, 1.0 equiv) and styrene (104.2 mg, 0.60 mmol, 2.0 equiv). Purification by column chromatography (5% then 10% EtOAc/hexanes), led to the isolated of the title compound as a yellow liquid (55 mg, 42% yield) with a 2:1.2 ratio of diastereomers. R$_f$ = 0.30 (10% EtOAc/hexanes, UV active); IR (ATR) 3031, 1725, 1677, 1258, 1147, 692 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (d, $J = 7.3$ Hz, 1.8H), 7.70 (d, $J = 7.3$ Hz, 3.3H), 7.53–7.00 (m, 46H), 6.84 (d, $J = 6.8$ Hz, 3.3H), 6.77 (d, $J = 7.6$ Hz, 3.3H), 6.58 (d, $J = 7.7$ Hz, 1.8H), 6.51 (s, 0.6H), 3.69 (dd, $J = 8.6, 8.6$ Hz, 1H), 3.58 (dd, $J = 8.6, 8.6$ Hz, 1.9H), 2.55–2.51 (m, 2.6H), 1.84 (dd, $J = 9.2$ Hz, 5.1 Hz, 1H), 1.74 (dd, $J = 9.0, 4.7$ Hz, 0.6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.6, 192.5, 170.2, 167.6, 139.7, 139.39, 139.32, 138.9, 137.44, 137.29, 134.5, 134.0, 133.0, 132.7, 129.2, 129.0, 128.79, 128.68, 128.60, 128.41, 128.35, 128.31, 128.28, 128.17, 128.03, 128.01, 127.80, 127.73, 127.52, 127.39, 127.33, 127.28, 127.18, 127.07, 126.97, 126.7, 78.5, 78.1, 42.7, 42.3, 34.3, 30.7, 20.3, 18.8; HRMS (+ESI) m/z: [M+Li]$^+$ calcd for C$_{30}$H$_{24}$LiO$_3$, 439.1880; found 439.1864.

**2-(4-(*tert*-Butyl)phenyl)-6,6-dimethyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (4.32.f)**
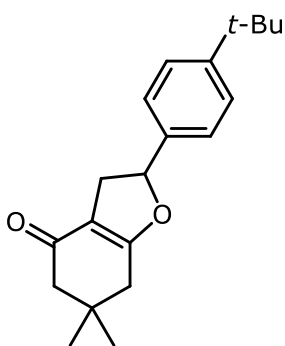
The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and 4-*tert*-butylstyrene (96.3 mg, 0.60 mmol, 2.0 equiv). Purification by column chromatography (5% to 40% EtOAc/hexanes) provided a white solid (51 mg, 57% yield) which partially decomposed to a yellow liquid at room temperature. ^{1}H NMR analysis of this material revealed a mixture of the dihydrofuran and isomeric cyclopropane in a 2:1 mol ratio. Allowing this mixture to stand overnight at room temperature furnished quantitative conversion of the cyclopropane to the title compound. $R_f = 0.23$ (10% EtOAc/hexanes, UV active); IR (ATR) 2957, 1739, 1632, 1399, 1217 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41 (d, $J = 8.5$ Hz, 2H), 7.26 (d, $J = 8.2$ Hz, 2H), 5.75 (dd, $J = 10.5, 7.9$ Hz, 1H), 3.26 (dddd, $J = 14.5, 10.6, 1.8, 1.8$ Hz, 1H), 2.91 (dddd, $J = 14.6, 7.9, 1.9, 1.9$ Hz, 1H), 2.36 (dd, $J = 1.6, 1.6$ Hz, 2H), 2.32 (d, $J = 15.9$ Hz, 1H), 2.29 (d, $J = 16.2$, 1H), 1.32 (s, 9H), 1.14 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.7, 176.0, 151.7, 137.5, 125.7, 111.5, 100.0, 86.6, 51.0, 37.8, 34.6, 34.1, 33.5, 31.3, 28.9, 28.5; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{20}$H$_{27}$O$_2$, 299.2006; found 299.2006.

1-(3,4-Dimethoxyphenyl)-6,6-dimethylspiro[2.5]octane-4,8-dione (4.32c.g)

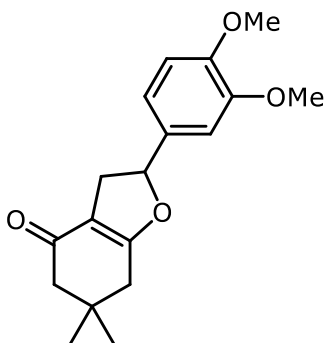The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and 3,4-dimethoxystyrene (99.7 mg, 0.60 mmol, 2 equiv). Purification by column chromatography (5% to 40% EtOAc/hexanes) led to the title compound to be isolated as a yellow liquid (74 mg, 82% yield). $R_f = 0.23$ (10% EtOAc/hexanes, UV active); IR (ATR) 2955, 1628, 1516, 1217, 1137 cm^{-1}; ^{1}H NMR

(500 MHz, CDCl$_3$) δ 6.89–6.82 (m, 3H), 5.71 (dd, J = 10.4, 8.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.25 (dd, J = 14.5, 10.5 Hz, 1H), 2.91 (dd, J = 14.6, 8.0 Hz, 1H), 2.36 (s, 2H), 2.29 (d, J = 16.2 Hz, 1H), 2.26 (d, J = 16.2 Hz, 1H), 1.14 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.7, 175.9, 149.32, 149.27, 132.9, 118.7, 111.5, 111.1, 109.1, 86.8, 55.95, 55.89, 51.0, 37.9, 34.2, 33.4, 29.0, 28.6; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{18}$H$_{23}$O$_4$, 303.1591; found 303.1590.

2-(4-Methoxyphenyl)-6,6-dimethyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (4.32c.h)
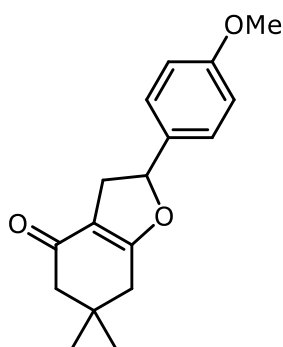
The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and 4-methoxystyrene (89.5 mg, 0.60 mmol, 2.0 equiv). Purification by column chromatography (5% to 40% EtOAc/hexanes) led to the isolation of the title compound as a viscous orange liquid (76 mg, 93% yield). An analytic sample was obtained by taking the above material and passing through another column of silica gel (5% to 20% EtOAc/benzene) to afford the title compound as a viscous yellow liquid. R$_f$ = 0.13 (20% EtOAc/hexanes, UV active); IR (ATR) 2957, 1626, 1514, 1400, 1217, 1003 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 5.74 (dd, J = 10.4, 7.9 Hz, 1H), 3.83 (s, 3H), 3.26 (dddd, J = 14.5, 10.6, 1.8, 1.8 Hz, 1H), 2.91 (dddd, J = 14.5, 7.9, 1.8, 1.8 Hz, 1H), 2.36 (dd, J = 1.8, 1.8 Hz, 2H), 2.29 (d, J = 16.4 Hz, 1H), 2.26 (d, J = 16.2 Hz, 1H), 1.16 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.6, 175.9, 159.8, 132.6, 127.5, 114.1, 111.5, 86.6, 55.3, 50.9, 37.8, 34.1, 33.5, 28.8, 28.5; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{17}$H$_{21}$O$_3$, 273.1485; found 273.1485.

2-(Iodomethyl)-6,6-dimethyl-2-phenyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (4.42)
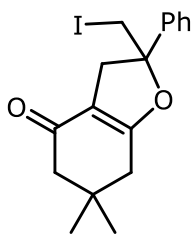
The title compound was synthesized via **GP4.2** using ylide **4.2c** (103 mg, 0.30 mmol, 1.0 equiv) and α-methylstyrene (71 mg, 0.60 mmol, 2.0 equiv). Column chromatography (10% to 40% EtOAc/hexanes) afforded the title compound as a colourless film (8 mg, 7% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45–7.35 (m, 5H), 3.65 (s, 2H), 3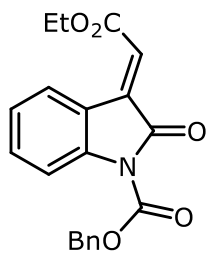.30 (d, J = 14.7 Hz, 1H), 3.24 (d, J = 14.8 Hz, 1H), 2.50–2.42 (m, 2H), 2.25 (s, 2H), 1.21 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.5, 174.4, 141.9, 128.7, 128.3, 124.8, 111.7, 91.7, 50.9, 39.2, 37.6, 34.2, 29.1, 28.4, 16.5. 0; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{17}$H$_{20}$IO$_2$, 383.0502; found 383.0502.

Benzyl (*E*)-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (4.43c)

In an 100 mL round bottom flask, benzyl 2,3-dioxoindoline-1-carboxylate (1.69 g, 6.0 mmol, 1.0 equiv) was dissolved in CHCl$_3$ (15 mL) with magnetic stirring and cooled in a brine-ice bath. (Carbethoxymethylene)triphenylphosphorane (2.08 g, 6.0 mmol, 1.0 equiv) was then added in one portion and the mixture was stirred overnight (16 h) while the cooling bath was allowed to expire naturally. The reaction mixture was concentrated using rotary evaporation and the residue was recrystallized using EtOH to yield the title compound as a yellow solid (1.34 g, 64% yield). mp 107–109 °C (EtOH); R$_f$ = 0.25 (10% EtOAc/hexanes, UV active); IR (ATR) 2975, 1757, 1732, 1707, 1596, 1305, 1198, 1029 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.72 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.48–7.34 (m, 5H), 7.24 (dd, J = 8.1, 8.1 Hz, 1H), 6.97 (s, 1H), 5.50 (s, 2H), 4.36 (d, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.6, 165.3,

150.4, 141.3, 136.0, 134.8, 132.9, 128.73, 128.59, 128.39, 128.17, 125.0, 123.7, 120.3, 115.1, 68.8, 61.4, 14.2; HRMS (+ESI) [M+H]$^+$ *m/z*: calcd for C$_{20}$H$_{18}$NO$_5$, 352.1179; found 352.1178.

Ethyl (*E*)-2-(2-oxo-1-tosylindolin-3-ylidene)acetate (4.43d)
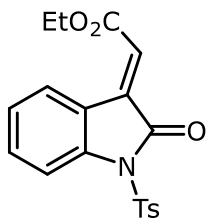
In an 100 mL round bottom flask, 1-tosylindoline-2,3-dione (1.51 g, 5.0 mmol, 1.0 equiv) was dissolved in CHCl$_3$ (25 mL) with magnetic stirring and cooled in a brine-ice bath. (Carbethoxymethylene)triphenylphosphorane (2.08 g, 6 mmol, 1.0 equiv) was then added in one portion and the mixture was stirred overnight (16 h) while the cooling bath was allowed to expire naturally. The reaction mixture was cooled to 0 °C to induce precipitation of a solid which was collected by vacuum filtration. The filter cake was washed with cold CHCl$_3$ (20 mL) and collected to yield the title compound (0.763 g, 41% yield). mp 117–119 °C; R$_f$ = 0.18 (10% EtOAc/hexanes, UV active); IR (ATR) 2982, 1756, 1713, 1596, 1377, 1310, 1201, 1194, 1176 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.63 (d, *J* = 7.8 Hz, 1H), 8.01–7.96 (m, 3H), 7.46 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.20 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.82 (s, 1H), 4.30 (q, *J* = 7.7 Hz, 2H), 2.42 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.9, 165.0, 146.0, 141.1, 135.4, 135.1, 133.2, 129.9, 128.8, 128.0, 125.0, 124.1, 120.3, 113.6, 61.5, 21.7, 14.1; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{19}$H$_{18}$NO$_5$S, 372.0900; found 372.0900.

Ethyl 1'-acetyl-6,6-dimethyl-2',4-dioxo-4,5,6,7-tetrahydro-3H-spiro[benzofuran-2,3'-indoline]-3-carboxylate (4.44)
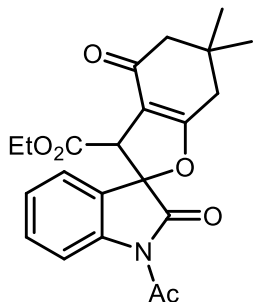
Synthesized via **GP4.2** using ylide **4.2c** (102 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43a**[229] (155.0 mg, 0.60 mmol, 1.0 equiv). Purification by column chromatography (5% to 40%, EtOAc/hexanes) led to the title compound to be isolated an orange red foam (115 mg, 96% yield). R_f = 0.40 (40% EtOAc/hexanes, UV active); IR (ATR) 2958, 1771, 1737, 1717, 1646, 1175, 1166 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.26 (d, J = 8.3 Hz, 1H), 7.45 (ddd, J = 8.0, 8.0, 1.4 Hz, 1H), 7.33 (dd, J = 7.6, 0.9 Hz, 1H), 7.21 (ddd, J = 7.7, 7.7, 1.0 Hz, 1H), 4.33 (dd, J = 1.5, 1.5 Hz, 1H), 3.92 (m, 2H), 2.71 (s, 3H), 2.52 (d, J = 17.7 Hz, 1H), 2.48 (d, J = 17.7 Hz, 1H), 2.39 (d, J = 16.3 Hz, 1H), 2.35 (d, J = 16.3 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 193.2, 176.9, 174.0, 170.2, 167.6, 140.5, 131.8, 125.6, 125.3, 122.9, 116.9, 111.5, 87.7, 61.5, 53.6, 50.9, 37.6, 34.7, 28.8, 28.1, 26.5, 13.6; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{22}$H$_{24}$NO$_6$, 398.1604; found 398.1599.

3-Ethyl 2,2-dimethyl 1'-acetyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2,3-tricarboxylate (4.45a)
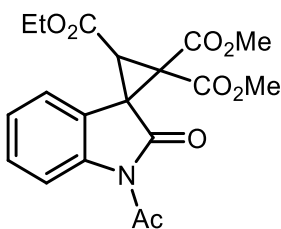
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43a**[229] (155 mg, 0.60 mmol, 2.0 equiv). Purification by column chromatography (pure hexanes followed by 5% to 30% EtOAc/hexanes) led to the title compound to be isolated as an orange liquid containing a mixture of diastereomers (107 mg, 92% yield). An analytic sample of the major diastereomer was obtained by dissolving the above material in minimal CHCl$_3$ and

passing through another column of silica gel (hexane followed by 10% EtOAc/hexanes then 20% EtOAc/hexanes) to yield the major diastereomer as a yellow solid. mp 84–86 °C; R_f = 0.22 (20% EtOAc/hexanes, UV active); IR (ATR) 2956, 1751, 1737, 1721, 1317, 1188, 1165 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.34 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.40 (ddd, J = 7.9, 7.9, 0.9 Hz, 1H), 7.21–7.18 (m, 1H), 4.28–4.18 (m, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 3.46 (s, 3H) 2.66 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.8, 170.2, 164.62, 164.42, 162.6, 141.2, 129.3, 126.3, 124.5, 119.7, 116.1, 62.1, 53.6, 53.4, 47.8, 40.6, 38.2, 26.8, 14.0; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{19}$H$_{20}$NO$_8$, 390.1183; found 390.1182.

1'-(*tert*-Butyl) 3-ethyl 2,2-dimethyl 2'-oxospiro[cyclopropane-1,3'-indoline]-1',2,2,3-tetracarboxylate (4.45b)[199]
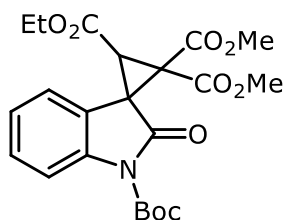
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43b**[199] (95 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (hexanes, followed by 10% then 20% EtOAc/hexanes) led to the isolation of the title compound as a viscous orange oil which partially foamed when placed under high vacuum (96 mg, 71% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.35 (ddd, J = 7.9, 7.9, 0.8 Hz, 1H), 7.12 (dd, J = 7.7, 7.7 Hz, 1H), 4.25–4.13 (m, 2H), 3.80 (s, 6H), 3.42 (s, 1H), 1.62 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H). These data match those previously reported in the literature.
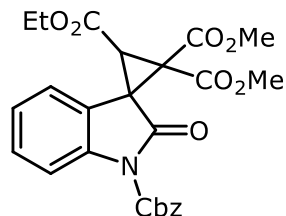
1'-Benzyl 3-ethyl 2,2-dimethyl 2'-oxospiro[cyclopropane-1,3'-indoline]-1',2,2,3-

tetracarboxylate (4.45c)

The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43c** (105 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (hexanes, followed by 10% to 40% EtOAc/hexanes) led to the title compound to be isolated as thick orange oil (117 mg, 81% yield) as a 7.1:1 mixture of the diastereomers. R_f = 0.50 (40% EtOAc/hexanes, UV active); IR (ATR) 2955, 1796, 1733, 1251, 1187 cm^{-1}; major diastereomer: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.99 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 7.0 Hz, 2H), 7.43 (d, J = 7.9 Hz, 1H), 7.38–7.32 (m, 4H), 7.15 (dd, J = 7.7, 7.7 Hz, 1H), 5.44 (s, 2H), 4.29–4.13 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.44 (s, 1H), 1.23 (t, J = 7.1 Hz, 3H); major diastereomer: ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.1, 164.8, 164.4, 162.8, 150.2, 140.5, 134.8, 129.3, 128.69, 128.61, 128.2, 126.6, 124.2, 119.7, 114.9, 68.9, 62.1, 53.7, 53.4, 47.8, 40.5, 38.4, 14.1; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{25}$H$_{24}$NO$_9$, 482.1446; found 482.1445.

3-Ethyl 2,2-dimethyl 2'-oxo-1'-tosylspiro[cyclopropane-1,3'-indoline]-2,2,3-tricarboxylate (4.45d)
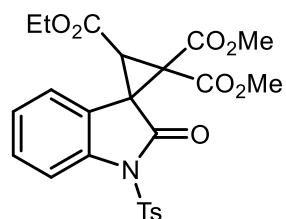
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43d** (111 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (hexanes, followed by 10% to 40% EtOAc/hexanes) led to the major isomer of the title compound to be isolated as a yellow oil (102 mg, 68% yield) and the minor isomer of the title compound to be isolated as a yellow-brown solid (44 mg, 29% yield). Major diastereomer R_f = 0.39 (40%

EtOAc/hexanes, UV active); IR (ATR) 2956, 1736, 1235, 1169, 1088 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.03 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.44 (dd, J = 7.9, 0.8 Hz, 1H), 7.41 (ddd, J = 8.0, 8.0, 1.3 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.16 (ddd, J = 7.8, 7.8, 1.0 Hz, 1H), 4.25–4.16 (m, 2H), 3.78 (s, 3H), 3.67 (s, 3H), 3.38 (s, 1H), 2.45 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.1, 164.5, 163.9, 162.7, 145.9, 140.3, 134.8, 129.7, 129.4, 128.1, 127.1, 124.1, 119.6, 113.2, 62.1, 53.46, 53.35, 47.7, 40.1, 37.7, 21.7, 13.9; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{24}$H$_{24}$NO$_9$S, 502.1166; found 502.1166.

Minor diastereomer: mp 176–178 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00 (d, J = 7.8 Hz, 2H), 7.97 (d, J = 8.2 Hz, 1H), 7.40–7.33 (m, 1H), 7.31 (d, J = 7.7 Hz, 2H), 7.14–7.12 (m, 2H), 4.25–4.13 (m, 2H), 3.72 (s, 3H), 3.68 (s, 3H), 3.56 (s, 1H), 2.41 (s, 3H), 1.15 (t, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 167.9, 164.3, 163.2, 162.2, 145.7, 140.1, 135.1, 129.7, 128.2, 124.5, 122.5, 122.3, 119.5, 113.6, 61.9, 53.9, 53.2, 49.6, 39.1, 37.3, 21.7, 13.8 (one C=$\underline{C}$ not resolved); HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{24}$H$_{24}$NO$_9$S, 502.1166; found 502.1165.

3-Ethyl 2,2-dimethyl 1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2,3-tricarboxylate (4.45e)

The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43e**[230] (69 mg, 0.30 mmol, 1.0 equiv). Purification was attempted via column chromatography (hexanes, followed by 10% to 40% EtOAc/hexanes) furnished a yellow oil (68 mg, 62% yield) containing an inseparable mixture of the title compound and tetramethyl ethene-1,1,2,2-tetracarboxylate in a 70:30 mol ratio (corrected yield of cyclopropane: 52 mg, 48% yield). R$_f$ = 0.32 (40% EtOAc/hexanes, UV active); IR (ATR) 2982, 1766, 1746, 1734, 1712, 1612, 1328, 1229, 1028 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41 (d, J = 7.8 Hz, 1H), 7.33 (dd, J = 7.8, 7.8

Hz, 1H), 7.04 (dd, J = 7.6, 7.6 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 4.19–4.13 (m, 2H), 3.80 (s, 6H), 3.39 (s, 1H), 3.24 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.3, 165.4, 164.8, 163.3, 144.7, 128.8, 126.9, 122.1, 120.6, 108.3, 61.8, 53.5, 53.2, 46.8, 40.1, 37.3, 26.8, 14.0;HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{18}$H$_{20}$NO$_7$, found 362.1234; found 362.1233.

3-Ethyl 2,2-dimethyl 1'-benzyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2,3-tricarboxylate (4.45f)
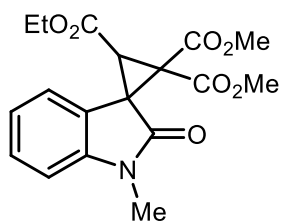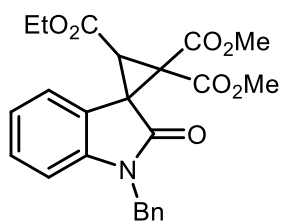

The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43f**[231] (92.2 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (hexanes, followed by 5% to 20% EtOAc/hexanes) led to the title compound to be isolated as an orange foam (99 mg, 75% yield). An analytic sample was obtained by recrystallizing this material in using chloroform/hexanes, resulting in an offwhite solid. mp 164–166 °C; R$_f$ = 0.50 (50% EtOAc/hexanes, UV active); IR (ATR) 2994, 1760, 1744, 1733, 1714, 1610, 1356, 1258, 1157 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (d, J = 7.8 Hz, 1H), 7.24–7.17 (m, 5H), 7.14–7.10 (m, 1H), 6.91 (dd, J = 7.7, 7.7 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 5.08 (d, J = 16.0 Hz), 4.95 (d, J = 15.6 Hz, 1H), 4.72 (d, J = 15.9 Hz, 1H), 4.16–4.06 (m, 2H), 3.71 (s, 3H), 3.70 (s, 2H), 3.38 (s, 1H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.6, 165.3, 164.8, 163.3, 143.9, 135.3, 128.75, 128.72, 127.7, 127.24, 127.08, 122.1, 120.6, 109.1, 61.8, 53.41, 53.23, 47.1, 44.3, 40.2, 37.3, 14.0; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{24}$H$_{24}$NO$_7$, 438.1547; found 438.1548.

3-Ethyl 2,2-dimethyl 1'-allyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2,3-tricarboxylate (4.45g)
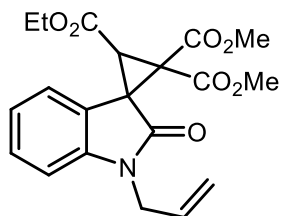
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43g** (77.8 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (10% to 40% EtOAc/hexanes) to recover the title compound as a thick orange oil (69 mg, 59% yield). An analytical sample was obtained by repeating the chromatography stated above to yield an off-white solid. mp 103–105 °C; R_f = 0.12 (20% EtOAc/hexanes, UV active) IR (ATR) 2950.0, 1747.4, 1737.3, 1706.5, 1613.2, 1366, 1192 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 (d, J = 7.9 Hz, 1H), 7.30 (ddd, J = 7.8, 7.8, 1.0 Hz, 1H), 7.03 (ddd, J = 7.7, 7.7, 0.8 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 5.84 (dddd, J = 16.8, 10.8, 5.6, 5.6 Hz, 1H), 5.30–5.22 (m, 2H), 4.40 (dddd, J = 16.2, 5.3, 1.6, 1.6 Hz, 1H), 4.32 (dddd, J = 16.5, 5.5, 1.6, 1.6 Hz, 1H), 4.26–4.14 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.43–3.41 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.2, 165.4, 164.8, 163.4, 144.0, 131.0, 128.8, 127.1, 122.1, 120.7, 117.9, 109.0, 61.9, 53.47, 53.28, 47.0, 43.0, 40.1, 37.4, 14.1; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{20}$H$_{22}$NO$_7$, 388.1391; found 388.1389.

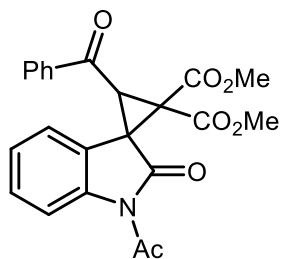**Dimethyl 1'-acetyl-3-benzoyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2-dicarboxylate (4.45h)**

The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43h**[229] (87 mg, 0.10 mmol, 1.0 equiv). Purification by column chromatography (0.5% MeOH/DCM). Fractions containing the product were collected and concentrated by rotary evaporation and the resulting material dissolved in minimal CHCl$_3$ and passed through another

column of silica (hexanes, followed by 10% then 20% EtOAc/hexanes) led to the title compound to be isolated as a pale orange liquid which became of light yellow foam (106 mg, 83% yield) when placed under high vacuum. ^{1}H NMR analysis of this material showed 88:12 ratio between major and minor diastereomers. R_f = 0.50 (40% EtOAc/hexanes, UV active); IR (ATR) 2945, 1742, 1720, 1689, 1252, 1164 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.33–8.31 (m, 1H), 8.15 (dd, J = 8.2, 1.1 Hz, 2H), 7.60 (dddd, J = 7.4, 7.4, 1.4, 1.4 Hz, 1H), 7.50 (dd, J = 7.8, 7.8 Hz, 2H), 7.36 (ddd, J = 7.9, 7.9, 1.3 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.15 (dd, J = 7.8, 7.8 Hz, 1H), 4.08 (s, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 189.4, 173.2, 170.2, 165.2, 163.2, 141.2, 136.4, 133.9, 129.2, 128.9, 128.4, 126.2, 124.6, 119.9, 116.1, 53.6, 53.4, 49.9, 41.6, 40.9, 26.8 (one C=$\underline{C}$ was not resolved); HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{23}$H$_{20}$NO$_7$, 422.1234; found 422.1233.

Dimethyl 1'-acetyl-3-benzoyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2-dicarboxylate (4.45i)
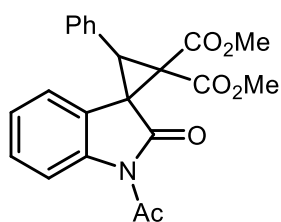
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43i**[232] (79.0 mg, 0.30 mmol, 1.0 equiv). Purification was attempted via column chromatography (10% then 20% EtOAc/hexanes) and afforded a thick yellow oil (34 mg) which partially foamed when placed under hi-vacuum. This material was a 94:6 mol ratio between the title compound (corrected yield 28%, 2:1 ratio of diastereomers) and tetraethyl ethene-1,1,2,2-tetracarboxylate. R_f = 0.13 (20% EtOAc/hexanes, UV active); IR (ATR) 2954, 1738, 1716, 1500.0, 1463, 1245, 1523, 1176 cm^{-1}; Major diastereomer: ^{1}H NMR (500 Hz, CDCl$_3$) δ 8.36 (d, J = 8.0 Hz, 1H), 7.42–7.25 (m, 6H), 7.21 (dd, J = 7.8, 7.8 Hz, 1H), 7.10 (d, J = 7.0 Hz, 1H), 4.28 (s, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.57 (s, 3H); Minor diastereomer: ^{1}H NMR (500 Hz, CDCl$_3$) δ 8.36 (d, J = 8.0 Hz, 1H), 7.42–7.25 (m,

6H), 6.99 (dd, J = 7.7, 7.7 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 4.08 (s, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 2.69 (s, 3H); mixture: ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.1, 171.1, 170.67, 170.49, 166.3, 165.5, 164.1, 163.9, 141.2, 140.8, 130.2, 130.0, 129.7, 129.5, 129.0, 128.7, 128.3, 128.04, 127.93, 127.77, 127.72, 125.0, 124.1, 123.8, 122.0, 120.7, 116.5, 116.0, 54.6, 53.9, 53.00, 52.88, 51.9, 50.3, 42.2, 41.8, 40.6, 40.1, 26.87, 26.72; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{22}$H$_{20}$NO$_6$, 394.1285; found 394.1285.

3-Ethyl 2,2-dimethyl 1'-acetyl-5'-fluoro-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2,3-tricarboxylate (4.45j)
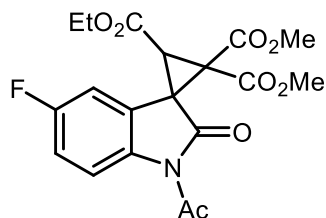
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43j**[233] (83.2 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (hexanes, followed by 5% to 20% EtOAc/hexanes) led to the title compound to be isolated as an orange liquid (117 mg, 96% yield) as a 3:1 mixture of diastereomers. R$_f$ = 0.22 (20% EtOAc/hexanes, UV active); IR (ATR) 2988, 1733, 1603, 1476, 1371, 1254, 1017 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.31–8.28 (m, 1.4H), 7.21 (dd, J = 9.4, 2.6 Hz, 1H), 7.12–7.03 (m, 1.5H), 6.89 (dd, J = 8.4, 2.4 Hz, 0.4H), 4.25–4.19 (m, 3H), 3.83 (s, 1H), 3.81 (s, 6H), 3.73 (s, 1H), 3.64 (s, 0.3), 3.43 (s, 1H), 2.65 (s, 1H), 2.61 (s, 3H), 1.31–1.22 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.5, 170.2, 169.97, 169.95, 164.4, 164.1, 164.0, 163.4, 162.50, 162.47, 159.8 (d, ^1J = 244.6 Hz), 159.4 (d, ^1J = 242.9), 137.3 (d, ^4J = 2.4 Hz), 137.0 (d, ^4J = 2.7 Hz), 124.3 (d, ^3J = 10.0 Hz), 121.8 (d, ^3J = 10.0 Hz), 117.9 (d, ^3J = 8.2 Hz), 117.2 (d, ^3J = 8.2 Hz), 116.0 (d, ^2J = 22.7 Hz), 115.8 (d, ^2J = 23.0 Hz), 114.2 (d, ^2J = 27.5 Hz), 109.3 (d, ^2J = 26.7 Hz), 62.3, 62.1, 54.1, 53.7, 53.6, 53.3, 49.9, 48.0, 40.4, 39.2, 38.4, 37.4, 26.7, 26.4, 14.0; ^{19}F NMR (470 MHz, CDCl$_3$) δ -115.9 (minor), -116.4 (major); HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{19}$H$_{19}$FNO$_8$, 408.1089; found 408.1089.
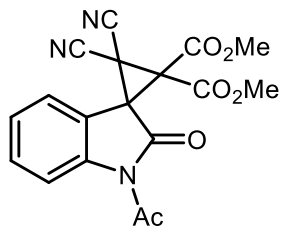
Dimethyl 1'-acetyl-3,3-dicyano-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2-dicarboxylate (4.45k)

The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.43k**[234] (71 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (hexanes, followed by 10% to 30%, EtOAc/hexanes) led to the title compound to be isolated as slightly pink solid (56 mg, 51% yield).

mp 188–191 °C; R_f = 0.32 (20% EtOAc/hexanes, UV active); IR (ATR) 2958, 2259, 1753, 1739, 1718, 1465, 1267, 1174 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.40 (d, J = 7.8 Hz, 1H), 7.56 (dd J = 7.6, 7.6 Hz, 1H), 7.40 (d, J = 7.0 Hz, 1H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.7, 167.1, 159.4, 141.8, 132.0, 125.8, 124.3, 117.3, 116.2, 108.5, 108.0, 55.1, 54.8, 50.2, 44.3, 26.8, 22.9; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{18}$H$_{14}$N$_3$O$_6$, 368.0877; found 368.0879.

Dimethyl 1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-2,2-dicarboxylate (4.45l)[235]
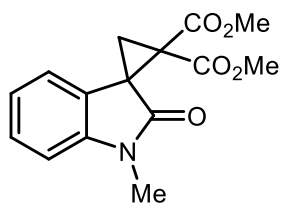
3-Hydroxy-1-methyl-3-((trimethylsilyl)methyl)indolin-2-one (**4.47**)[202] (235.4 mg, 1.0 mmol) was dissolved in DCM (30 mL) and cooled to –78 °C, and BF$_3$•OEt$_2$ (1.5 mL, 1.725 g, 12.2 mmol) was added dropwise to the resulting solution and the reaction mixture was allowed to stir for 2 h at –78° C, and then for 1 h at 0 °C. Then, a solution of sat. NaHCO$_3$ (20 mL) was added to the flask and diluted with DCM (80 mL). The layers were separated and the aqueous layer was extracted with DCM (40 mL × 2) and the combined organic layers were dried over MgSO$_4$, filtered, and concentrated to near dryness using a rotary evaporator.

The resulting orange liquid was immediately transferred to a flame-dried 50 mL round bottom flask using anhydrous MeCN (10 mL) to assist in the transfer. To this flask, TBAI (110 mg, 0.30 mmol, 30 mol%), ylide **4.2a** (334 mg, 10 mmol, 1.0 equiv), and PhI(OAc)$_2$ (322 mg, 10 mmol, 1.0 equiv) were sequentially added, and the resulting mixture was allowed to continue to stir for 1 hour at ambient temperature. The reaction with quenched with a solution of sat. Na$_2$S$_2$O$_3$ (5 mL) and diluted with H$_2$O (10 mL). The organic layer was concentrated to approximately half its original volume and the biphasic mixture was extracted with CH$_2$Cl$_2$ (25 mL × 3). The combined organic layers were washed with brine, dried using MgSO$_4$, filtered, and concentrated using a rotary evaporator. The crude material was loaded onto a column of silica gel using a minimal amount of CHCl$_3$. Column chromatography (hexanes, then 10% to 25% EtOAc/hexanes). Fractions containing the title compound were collected and concentrated to yield an orange solid (155 mg) containing a mixture of the title compound and tetramethyl ethene-1,1,2,2-tetracarboxylate in a 96:4 mol ratio. The corrected yield of the cyclopropane over the two steps is 145 mg (50% yield). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36–7.30 (m, 2H), 7.02 (dd, J = 7.6, 7.6 Hz, 1H), 6.89 (d, 7.8 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.26 (s, 3H), 2.49 (d, J = 5.2 Hz, 1H), 2.45 (d, J = 5.2 Hz, 1H). The spectral data matches those reported previously in the literature.

3'-Ethyl 2',2'-dimethyl 2-oxo-2H-spiro[benzofuran-3,1'-cyclopropane]-2',2',3'-tricarboxylate (4.52)
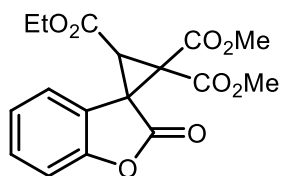
The title compound was synthesizied via **GP4.2** using ylide (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.51**[236] (65.5 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (hexanes, followed by 10% to 40% EtOAc/hexanes) led to the major isomer of the title compound to be isolated as a yellow oil (65 mg, 62% yield) and the minor isomer of the title compound as a yellow oil (22 mg, 21% yield).

$R_f = 0.25$ (20% EtOAc/hexanes, UV active); IR (ATR) 2956, 1803, 1757, 1728, 1431, 1256, 1159, 1071 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43 (d, J = 7.8 Hz, 1H), 7.37 (dd, J = 7.8, 7.8 Hz, 1H), 7.17–7.12 (m, 2H), 4.22–4.17 (m, 2H), 3.81 (s, 6H), 3.45 (s, 1H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 171.9, 164.5, 163.7, 162.5, 154.5, 129.8, 127.3, 123.9, 119.5, 110.7, 62.2, 53.8, 53.4, 47.2, 38.18, 38.12, 14.0; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{17}$H$_{17}$O$_8$, 349.0918; found 349.0918.

Minor Diastereomer

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (ddd, J = 7.82, 7.8, 1.2 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 7.11 (dd, J = 7.6, 7.6 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.65 (s, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.5, 164.3, 163.1, 162.2, 154.3, 130.0, 124.2, 122.6, 122.3, 111.0, 62.2, 53.9, 53.4, 48.9, 37.9, 37.1, 13.9.

Dimethyl 6,6-dimethyl-4,8-dioxo-2-phenyl-5,7-dioxaspiro[2.5]octane-1,1-dicarboxylate (4.55a)

The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.53a** (70 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (10% to 40% EtOAc/hexanes) led to the title compound to be isolated a white solid (80 mg, 74% yield). mp 135–137 °C; R_f = 0.48 (40% EtOAc/hexanes, UV active); IR (ATR) 2970, 1735, 1434, 1332.9, 1230.2, 1081.2 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40–7.34 (m, 5H), 4.41 (s, 1H), 3.88 (s, 3H), 3.80 (s, 3), 2.07 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 165.1, 164.1, 162.1, 161.4, 129.5, 129.3, 128.0 (2C), 105.9, 54.2, 53.7, 53.6, 43.9, 36.5, 27.63, 27.57; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{18}$H$_{19}$O$_8$, 363.1074; found 363.1075.

Dimethyl 3,3-dicyano-1',3'-dioxo-1',3'-dihydrospiro[cyclopropane-1,2'-indene]-2,2-dicarboxylate (4.55b)
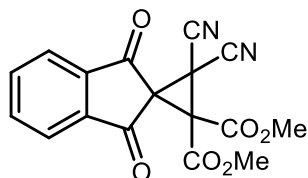
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.53b**[237] (62.4 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (10%, to 40% EtOAc/hexanes) led to the title compound to be isolated a thick orange liquid (36 mg, 35% yield). R_f = 0.22 (40% EtOAc/hexanes, UV active); IR (ATR) 2195.2, 2253, 1741, 1716, 1592, 1436, 1240 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13–8.00 (m, 4H), 3.93 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 185.9, 158.5, 141.6, 137.3, 124.5, 107.7, 55.0, 49.8, 44.4, 20.4; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{17}$H$_{11}$N$_2$O$_6$, 339.0623; found 339.0612.

Dimethyl 2,4-dioxo-3-phenyl-3-azabicyclo[3.1.0]hexane-6,6-dicarboxylate (4.56a)

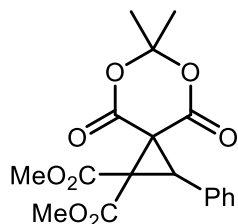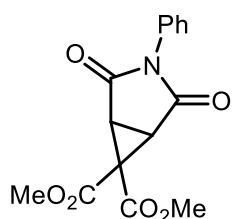The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30 mmol, 1.0 equiv) and alkene **4.54a** (52.0 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (10% to 40% EtOAc/hexanes) led to the title compound to be isolated a white solid (25 mg, 27% yield). An analytical sample of this material was obtained by triturating this material using Et$_2$O. mp 176–178 °C; R_f = 0.49 (40% EtOAc/hexanes, UV active); IR (ATR) 3078, 1724, 1256, 1160 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.39–7.36 (m, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 3.26 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 168.7, 165.5, 164.0, 130.9, 129.2, 128.8, 126.0, 54.09, 53.99, 44.3, 31.2; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{15}$H$_{14}$NO$_6$, 304.0816; found 304.0815.

Dimethyl 2,7-dioxo-1a,2,7,7a-tetrahydro-1H-cyclopropa[b]naphthalene-1,1-dicarboxylate (4.56b)
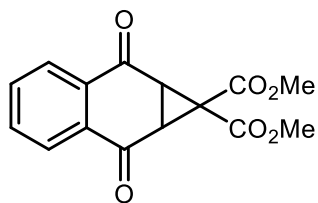
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30, 1.0 equiv) and 1,4-benzoquinone (47.4 mg, 0.30, 1.0 equiv). Attempted purification via column chromatography (10% to 40%, EtOAc/hexanes) provided a yellow film (22 mg) containing a mixture of the title compound and tetramethyl ethene-1,1,2,2-tetracarboxylate in a 96:4 mol ratio (21 mg, 24% corrected yield). R_f = 0.35 (40% EtOAc/hexanes, UV active; IR (ATR) 2956, 1737, 1686, 1596, 1436, 1293, 1241, 1161 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.92–7.88 (m, 2H), 7.65–7.56 (m, 2H), 3.72 (s, 3H), 3.19 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 188.0, 166.7, 163.5, 134.5, 132.8, 126.7, 54.0, 53.1, 43.7, 36.8; HRMS (+ESI) m/z: [M+H]$^+$ calcd for C$_{15}$H$_{13}$O$_6$, 289.0707; found 289.0706.

Dimethyl 1a-acetoxy-2,7-dioxo-1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1,1-dicarboxylate (4.56c)

Synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30, 1.0 equiv) and alkene **4.54c**[238] (64.9 mg, 0.30, 1.0 equiv). Purification was attempted via column chromatography (10% to 40% EtOAc/hexanes) provided a yellow film (42 mg) containing a mixture of the title compound and tetramethyl ethene-1,1,2,2-tetracarboxylate in a 89:11 mol ratio (38 mg, 37% corrected yield). R_f = 0.38 (40% EtOAc/hexanes, UV active); IR (ATR) 2958, 1742, 1693, 1596, 1436, 1291, 1247, 1204, 1091 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.15–8.10 (m, 2H), 7.82–7.75 (m, 2H), 3.86 (s, 3H), 3.73 (s, 1H), 3.25 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.6, 184.5, 169.2, 162.68, 134.70, 134.59, 132.5,

131.8, 127.2, 126.8, 66.1, 63.1, 54.2, 53.3, 47.9, 41.7, 20.2; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{17}$H$_{15}$O$_8$, 347.0761; found 347.0761.

**Dimethyl 2,7-dioxo-1a-(tosyloxy)-1a,2,7,7a-tetrahydro-1*H*-cyclopropa[*b*]naphthalene-1,1-dicarboxylate (4.56d)**
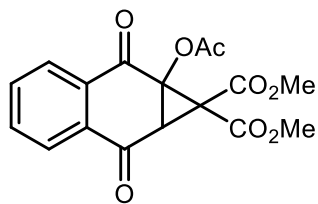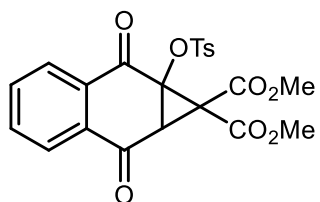
The title compound was synthesized via **GP4.2** using ylide **4.2a** (100 mg, 0.30, 1.0 equiv) and alkene **4.54d**[238] (98.5 mg, 0.30 mmol, 1.0 equiv). Purification by column chromatography (10% to 40% EtOAc/hexanes) led to the title compound to be isolated a yellow-orange foam (109 mg, 79% yield).R$_f$ = 0.30 (40% EtOAc/hexanes, UV active); IR (ATR) 2958, 1754, 1740, 1693, 1595, 1246.0, 1180, 1077 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 (d, *J* = 8.9 Hz, 1H), 8.03 (d, *J* = 6.6 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.78–7.76 (m, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 4.03 (s, 1H), 3.75 (s, 3H), 3.20 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 185.7, 183.9, 162.1, 161.5, 146.0, 134.83, 134.78, 133.0, 132.2, 131.5, 129.8, 128.5, 127.3, 126.9, 68.3, 54.2, 53.4, 47.9, 40.9, 21.8; HRMS (+ESI) *m/z*: [M+H]$^+$ calcd for C$_{22}$H$_{19}$O$_9$S, 459.0744; found 459.0743.

References

(1)   Swain, P. A. *Bull Hist Chem* **2005**, *30*, 103.

(2)   Kaiho, T. *Iodine chemistry and applications*; Wiley: Hoboken, New Jersey, 2015.

(3)   Larsen, P. R. *Metabolism* **1972**, *21*, 1073–1092.

(4)   Hetzel, B. *The Lancet* **1983**, *322*, 1126–1129.

(5)   Jackson, E. L.; Hudson, C. S. *J. Am. Chem. Soc.* **1937**, *59*, 994–1003.

(6)   Pauling, L. *J. Am. Chem. Soc.* **1932**, *54*, 3570–3582.

(7)   Allen, L. C. *J. Am. Chem. Soc.* **1989**, *111*, 9003–9014.

(8)   IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). https://goldbook.iupac.org/html/O/O04365.html (accessed Nov 28, 2017).

(9)   Lewis, G. N. *J. Am. Chem. Soc.* **1916**, *38*, 762–785.

(10) Musher, J. I. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 54–68.

(11) Minkin, V. I. *Pure Appl. Chem. //*, *71* (10), 1919–1981.

(12) Reed, A. E.; Schleyer, P. V. *J. Am. Chem. Soc.* **1990**, *112*, 1434–1445.

(13) Noury, S.; Silvi, B.; Gillespie, R. J. *Inorg. Chem.* **2002**, *41*, 2164–2172.

(14) Ivanov, A. S.; Popov, I. A.; Boldyrev, A. I.; Zhdankin, V. V. *Angew. Chem. Int. Ed.* **2014**, *53*, 9617–9621.

(15) Kutzelnigg, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 272–295.

(16) Magnusson, E. *J. Am. Chem. Soc.* **1990**, *112*, 7940–7951.

(17) *Chemistry of Hypervalent Compounds*, 1st ed.; Akiba, K., Ed.; Wiley-VCH: New York, 1999.

(18) Lee, D. Y.; Martin, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 5745–5746.

(19) Akiba, K.; Yamashita, M.; Yamamoto, Y.; Nagase, S. *J. Am. Chem. Soc.* **1999**, *121*, 10644–10645.

(20) Willgerodt, C. *J. Für Prakt. Chem.* **1886**, *33*, 154–160.

(21) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178.

(22) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358.

(23) Zhdankin, V. V. *Arkivoc* **2009**, *i*, 1–62.

(24) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328–3435.

(25) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishing: New York, 1992.

(26) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*, 1 ed.; Best Synthetic Methods; Academic Press: London, 1997.

(27) *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Topics in Current Chemistry; Springer Berlin Heidelberg: Berlin, 2003; Vol. 224.

(28) Zhdankin, V. V. *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, 1 ed.; John Wiley & Sons, Ltd.: New York, 2014.

(29) *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Topics in Current Chemistry; Springer International Publishing: Cham, 2016; Vol. 373.

(30) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579–2586.

(31) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 6547–6551.

(32) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192–5197.

(33) Shinomoto, Y.; Yoshimura, A.; Shimizu, H.; Yamazaki, M.; Zhdankin, V. V.; Saito, A. *Org. Lett.* **2015**, *17*, 5212–5215.

(34) Stridfeldt, E.; Seemann, A.; Bouma, M. J.; Dey, C.; Ertan, A.; Olofsson, B. *Chem. Eur. J.* **2016**, *22*, 16066–16070.

(35) Tóth, B. L.; Kovács, S.; Sályi, G.; Novák, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 1988–1992.

(36) Kovács, S.; Tóth, B. L.; Borsik, G.; Bihari, T.; May, N. V.; Stirling, A.; Novák, Z. *Adv. Synth. Catal.* **2017**, *359*, 527–532.

(37) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975–7978.

(38) Yoshimura, A.; Nguyen, K. C.; Klasen, S. C.; Saito, A.; Nemykin, V. N.; Zhdankin, V. V. *Chem. Commun.* **2015**, *51*, 7835–7838.

(39) Amey, R. L.; Martin, J. C. *J. Org. Chem.* **1979**, *44*, 1779–1784.

(40) Ochiai, M.; Masaki, Y.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 5511–5513.

(41) Ye, C.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2005**, *7*, 3961–3964.

(42) Hossain, M. D.; Kitamura, T. *Tetrahedron Lett.* **2006**, *47*, 7889–7891.

(43) Merritt, E. A.; Carneiro, V. M. T.; Silva, L. F.; Olofsson, B. *J. Org. Chem.* **2010**, *75*, 7416–7419.

(44) Beringer, F. M.; Falk, R. A.; Karniol, M.; Lillien, I.; Masullo, G.; Mausner, M.; Sommer, E. *J. Am. Chem. Soc.* **1959**, *81*, 342–351.

(45) Kraszkiewicz, L.; Skulski, L. *Synthesis* **2008**, No. 15, 2373–2380.

(46) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, No. 24, 2521–2523.

(47) Lucas, H. J.; Kennedy, E. R. *Org. Synth.* **1942**, *22*, 69.

(48) Zhang, C.; Zhao, X.-F. *Synthesis* **2007**, No. 04, 551–557.

(49) Sarie, J. C.; Thiehoff, C.; Mudd, R. J.; Daniliuc, C. G.; Kehr, G.; Gilmour, R. *J. Org. Chem.* **2017**, *82*, 11792–11798.

(50) Sharefkin, J. G.; Saltsman, H. *Org. Synth.* **1963**, *43*, 62.

(51) Sutherland, A.; Vederas, J. C. *Chem. Commun.* **2002**, No. 3, 224–225.

(52) Sheremetev, A. B.; Konkina, S. M. *Mendeleev Commun.* **2003**, *13*, 277–278.

(53) Koposov, A. Y.; Boyarskikh, V. V.; Zhdankin, V. V. *Org. Lett.* **2004**, *6*, 3613–3615.

(54) Das, J. P.; Roy, U. K.; Roy, S. *Organometallics* **2005**, *24*, 6136–6140.

(55) Archer, E. M.; van Schalkwyk, T. G. *Acta Crystallogr.* **1953**, *6*, 88–92.

(56) Alcock, N. W.; Countryman, R. M.; Esperås, S.; Sawyer, J. F. *J. Chem. Soc. Dalton Trans.* **1979**, 854–860.

(57) Carpenter, G. B.; Richards, S. M. *Acta Crystallogr.* **1962**, *15*, 360–364.

(58) Wang, X.; Studer, A. *Acc. Chem. Res.* **2017**, *50*, 1712–1724.

(59) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.

(60) Yevitz, M.; Stanko, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 1513–1516.

(61) Miyamoto, K.; Shiro, M.; Ochiai, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8931–8934.

(62) Stang, P. J.; Schwarz, A.; Blume, T.; Zhdankin, V. V. *Tetrahedron Lett.* **1992**, *33*, 6759–6762.

(63) Moriarty, R.; Hu, H.; Gupta, S. *Tetrahedron Lett.* **1**, *22*, 1283–1286.

(64) Greaney, M.; Motherwell, W. *Tetrahedron Lett.* **6**, *41*, 4463–4466.

(65) Prakash, O.; Saini, N.; Tanwar, M. P.; Moriarty, R. M. *Contemp. Org. Synth.* **1995**, *2*, 121–131.

(66) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, No. 04, 517–538.

(67) Yoshida, M.; Fujikawa, K.; Sato, S.; Hara, S. *Arkivoc* **2003**, *vi*, 36–42.

(68) Yu, J.; Tian, J.; Zhang, C. *Adv. Synth. Catal.* **2010**, *352*, 531–546.

(69) In *IUPAC Compendium of Chemical Terminology*; Nič, M., Jirát, J., Košata, B., Jenkins, A., McNaught, A., Eds.; IUPAC: Research Triangle Park, NC, 2009.

(70) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318–1330.

(71) Johnson, A. W. *Ylid Chemistry*; Academic Press: New York, 1966.

(72) Zbiral, E.; Rasberger, M. *Tetrahedron* **1969**, *25*, 1871–1874.

(73) Schlosser, M.; Chirstmann, K.-F. *Synthesis* **1969**, No. 01, 38–39.

(74) Moriarty, R. M.; Prakash, I.; Prakash, O.; Freeman, W. A. *J. Am. Chem. Soc.* **1984**, *106*, 6082–6084.

(75) Matveeva, E. D.; Podrugina, T. A.; Grishin, Y. K.; Tkachev, V. V.; Zhdankin, V. V.; Aldoshin, S. M.; Zefirov, N. S. *Russ. J. Org. Chem.* **2003**, *39*, 536–541.

(76) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981–10080.

(77) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, 1st ed.; Wiley-Interscience: New York, 1998.

(78) Roedig, A.; Aman, H.; Fahr, E. *Eur. J. Org. Chem.* **1964**, No. 1, 47–59.

(79) Bloomfield, G. F. *J. Chem. Soc. Resumed* **1944**, 114–120.

(80) Patnaik, P. *A Comprehensive Guide to the Hazardous Properties of Chemical Substances*, 3rd ed.; John Wiley: Hoboken, NJ, 2007.

(81) Ochiai, M.; Sueda, T.; Miyamoto, K.; Kiprof, P.; Zhdankin, V. V. *Angew. Chem.* **2006**, *118*, 8383–8386.

(82) Waser, J. Benziodoxoles Stability Data https://lcso.epfl.ch/BXStabilityData (accessed Jul 31, 2017).

(83) Plumb, J. B.; Harper, D. J. *Chem. Eng. News Arch.* **1990**, *68*, 3.

(84) Fiederling, N.; Haller, J.; Schramm, H. *Org. Process Res. Dev.* **2013**, *17*, 318–319.

(85) Buchner, E.; Curtius, T. *Berichte Dtsch. Chem. Ges.* **1885**, *18*, 2371–2377.

(86) Patrick, T. B.; Scheibel, J. J.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 3917–3918.

(87) Rappe, C.; Albrecht, B. *Acta Chem. Scand.* **1966**, *20*, 253–255.

(88) Krebs, A.; Born, W.; Kaletta, B.; Nickel, W.-U.; Rüger, W. *Tetrahedron Lett.* **1983**, *24*, 4821–4824.

(89) Sontakke, C. V.; Patil, S. P.; Unny, V. K. P.; Sivaprasad, N. *J. Label. Compd. Radiopharm.* **2005**, *48*, 597–604.

(90) Guziec, F. S. G.; Sanfilippo, L. J. *Synthesis* **1988**, No. 07, 547–549.

(91) Micetich, R. G.; Maiti, S. N.; Tanaka, M.; Yamazaki, T.; Ogawa, K. *J. Org. Chem.* **1986**, *51* (6), 853–858.

(92) Fujiwara, T.; Takeuchi, Y. *J. Fluorine Chem.* **2005**, *126*, 941–955.

(93) Tanner, D. D.; Van Bostelen, P. B. *J. Org. Chem.* **1967**, *32*, 1517–1521.

(94) Regitz, M. *Justus Liebigs Ann. Chem.* **1964**, *676*, 101–109.

(95) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070.

(96) Nicolaou, K. C.; Simmons, N. L.; Ying, Y.; Heretsch, P. M.; Chen, J. S. *J. Am. Chem. Soc.* **2011**, *133*, 8134–8137.

(97) Boni, M.; Ghelfi, F.; Pagnoni, U. M.; Zucchi, C. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1622–1626.

(98) Kelly, B. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 13930–13931.

(99) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052–13053.

(100) Wicha, J.; Zarecki, A.; Kocór, M. *Tetrahedron Lett.* **1973**, *14*, 3635–3638.

(101) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2002**, No. 02, 0323–0326.

(102) Smith, M. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001.

(103) Coffey, K. E.; Murphy, G. K. *Synlett* **2015**, *26*, 1003–1007.

(104) Murphy, G. K.; Abbas, F. Z.; Poulton, A. V. *Adv. Synth. Catal.* **2014**, *356*, 2919–2923.

(105) Axiotis, B.; Spyroudis, S.; Varvoglis, A. *Chim. Chron. New Ser.* **1981**, *10*, 185–191.

(106) Mao, H.; Tang, Z.; Hu, H.; Cheng, Y.; Zheng, W.-H.; Zhu, C. *Chem. Commun.* **2014**, *50*, 9773–9775.

(107) Hara, S.; Sekiguchi, M.; Ohmori, A.; Fukuhara, T.; Yoneda, N. *Chem. Commun.* **1996**, No. 16, 1899–1900.

(108) Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183–3185.

(109) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

(110) Yusubov, M. S.; Zagulyaeva, A. A.; Zhdankin, V. V. *Chem. Eur. J.* **2009**, *15*, 11091–11094.

(111) Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis* **1983**, No. 03, 197–199.

(112) Yuan, W.; Eriksson, L.; Szabó, K. J. *Angew. Chem. Int. Ed Engl.* **2016**, *55*, 8410–8415.

(113) Hari, D. P.; Waser, J. *J. Am. Chem. Soc.* **2016**, *138*, 2190–2193.

(114) Ramsden, C. A.; Smith, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 6842–6843.

(115) Constantinou, M.; Aigbirhio, F. I.; Smith, R. G.; Ramsden, C. A.; Pike, V. W. *J. Am. Chem. Soc.* **2001**, *123*, 1780–1781.

(116) Ramsden, C., A. *Arkivoc* **2014**, *i*, 109–126.

(117) Arrica, M. A.; Wirth, T. *Eur. J. Org. Chem.* **2005**, No. 2, 395–403.

(118) Emer, E.; Twilton, J.; Tredwell, M.; Calderwood, S.; Collier, T. L.; Liégault, B.; Taillefer, M.; Gouverneur, V. *Org. Lett.* **2014**, *16*, 6004–6007.

(119) Sinclair, G. S.; Tran, R.; Tao, J.; Hopkins, W. S.; Murphy, G. K. *Eur. J. Org. Chem.* **2016**, No. 27, 4603–4606.

(120) Sawaguchi, M.; Ayuba, S.; Hara, S. *Synthesis* **2002**, No. 13, 1802–1803.

(121) Hupp, J. T.; Nguyen, S. T. Chemical Safety: Synthesis Procedure https://cen.acs.org/articles/89/i2/Chemical-Safety-Synthesis-Procedure.html (accessed Oct 4, 2017).

(122) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(123) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443–12452.

(124) Bortolini, O.; Nino, A. D.; Garofalo, A.; Maiuolo, L.; Russo, B. *Synth. Commun.* **2010**, *40*, 2483–2487.

(125) Zhu, K.; Li, S.; Wang, F.; Huang, F. *J. Org. Chem.* **2009**, *74*, 1322–1328.

(126) Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 3195–3197.

(127) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709–1716.

(128) Curphey, T. J. *Org. Prep. Proced. Int.* **1981**, *13*, 112–115.

(129) Davies, H. M. L.; Cantrell, W. R.; Romines, K., R.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93.

(130) Bhawal, B. M.; Khanapure, S. P.; Biehl, E. R. *Synthesis* **2002**, No. 02, 112–114.

(131) Desage-El Murr, M.; Nowaczyk, S.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* **2006**, No. 6, 1489–1498.

(132) Meyer, M. D.; Hancock, A. A.; Tietje, K.; Sippy, K. B.; Prasad, R.; Stout, D. M.; Arendsen, D. L.; Donner, B. G.; Carroll, W. A. *J. Med. Chem.* **1997**, *40*, 1049–1062.

(133) Gu, P.; Su, Y.; Wu, X.-P.; Sun, J.; Liu, W.; Xue, P.; Li, R. *Org. Lett.* **2012**, *14*, 2246–2249.

(134) Doyle, M. P.; Hu, W. *Adv. Synth. Catal.* **2001**, *343*, 299–302.

(135) Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 604–607.

(136) Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. *J. Org. Chem.* **2007**, *72*, 2216–2219.

(137) Smith, I, Lee; Howard, K., L. *Org. Synth.* **1944**, *24*, 53.

(138) Trost, B. M.; Xie, J.; Sieber, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 20611–20622.

(139) Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 4975–4978.

(140) Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094–5102.

(141) Doyle, M. P.; Forbes, D. C.; Vasbinder, M. M.; Peterson, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 7653–7654.

(142) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253–9260.

(143) Xu, B.; Tambar, U. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 9868–9871.

(144) Xu, B.; Tambar, U. K. *J. Am. Chem. Soc.* **2016**, *138*, 12073–12076.

(145) Yusubov, M. S.; Yoshimur, A.; Zhdankin, V. V. *Arkivoc* **2016**, *i*, 342–374.

(146) Zhu, S.-Z.; Chen, Q.-Y. *J. Chem. Soc. Chem. Commun.* **1990**, No. 20, 1459–1460.

(147) Alcock, N. W.; Bozopoulos, A. P.; Hatzigrigoriou, E.; Varvoglis, A. *Acta Crystallogr. C* **1990**, *46*, 1300–1303.

(148) Zhu, C.; Yoshimura, A.; Ji, L.; Wei, Y.; Nemykin, V. N.; Zhdankin, V. V. *Org. Lett.* **2012**, *14*, 3170–3173.

(149) Zhu, C.; Yoshimura, A.; Solntsev, P.; Ji, L.; Wei, Y.; Nemykin, V. N.; Zhdankin, V. V. *Chem. Commun.* **2012**, *48*, 10108–10110.

(150) Schiering, D. W.; Katon, J. E. *Appl. Spectrosc.* **1986**, *40*, 1049–1054.

(151) Antos, A.; Elemes, Y.; Michaelides, A.; Nyxas, J., A.; Skoulika, S.; Hadjiarapoglou, L. P. *J. Org. Chem.* **2012**, *77*, 10949–10954.

(152) Gudriniece, E.; Neilands, O.; Vanag, G. *Zh. Obshch. Khim.* **1957**, *27*, 2737.

(153) Schank, K.; Lick, C. *Synthesis* **1983**, No. 05, 392–395.

(154) Zhdankin, V. V.; Protasiewicz, J. D. *Coord. Chem. Rev.* **2014**, *275*, 54–62.

(155) Macikenas, D.; Skrzypczak-Jankun, E.; Protasiewicz, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 7164–7165.

(156) Macikenas, D.; Skrzypczak-Jankun, E.; Protasiewicz, J. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 2007–2010.

(157) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264.

(158) Saito, M.; Kobayashi, Y.; Tsuzuki, S.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 7653–7657.

(159) Rotstein, B. H.; Stephenson, N. A.; Vasdev, N.; Liang, S. H. *Nat. Commun.* **2014**, *5*, 4365.

(160) Pongratz, E.; Kappe, T. *Monatshefte Für Chem. Chem. Mon.* **1984**, *115*, 231–242.

(161) Neilands, O.; Vanag, G. *Zh. Obshch. Khim.* **1960**, *30*, 510–518.

(162) Prikule, D. E.; Neilands, O. *Zh. Org. Khim.* **1981**, *17*, 2119–2122.

(163) Chelli, S.; Troshin, K.; Mayer, P.; Lakhdar, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2016**, *138*, 10304–10313.

(164) Mayr, H.; Patz, M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957.

(165) Camacho, M. B.; Clark, A. E.; Liebrecht, T. A.; DeLuca, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 5210–5211.

(166) Zhu, S.-Z. *Heteroat. Chem.* **1994**, *5*, 9–18.

(167) Bosnidou, A.-E.; Kalpogiannaki, D.; Karanestora, S.; Nixas, J. A.; Hadjiarapoglou, L. P. *J. Org. Chem.* **2015**, *80*, 1279–1283.

(168) Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. *J. Am. Chem. Soc.* **1989**, *111*, 6443–6444.

(169) Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947–958.

(170) Murphy, G. K.; West, F. G. *Org. Lett.* **2006**, *8*, 4359–4361.

(171) Müller, P.; Fernandez, D.; Nury, P.; Rossier, J.-C. *J. Phys. Org. Chem.* **1998**, *11*, 321–333.

(172) Müller, P. *Acc. Chem. Res.* **2004**, *37*, 243–251.

(173) Müller, P.; Allenbach, Y. F.; Chappellet, S.; Ghanem, A. *Synthesis* **2006**, No. 10, 1689–1696.

(174) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2002**, *85*, 483–494.

(175) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014–18015.

(176) Goudreau, S. R.; Marcoux, D.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 470–473.

(177) Moreau, B.; Alberico, D.; Lindsay, V. N. G.; Charette, A. B. *Tetrahedron* **2012**, *68*, 3487–3496.

(178) Hatzigrigoriou, E.; Spyroudis, S.; Varvoglis, A. *Eur. J. Org. Chem.* **1989**, No. 2, 167–170.

(179) Lee, Y.-R.; Choi, J.-H. *Bull. Korean Chem. Soc.* **2006**, *27*, 503–507.

(180) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983–5986.

(181) Pierson, N.; Fernández-García, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705–4708.

(182) Marcoux, D.; Charette, A. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 10155–10158.

(183) Marcoux, D.; Goudreau, S. R.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 8939–8955.

(184) Beaulieu, S.; Legault, C. Y. *Chem. Eur. J.* **2015**, *21*, 11206–11211.

(185) Padwa, A.; Sá, M. M. *Quím. Nova* **1999**, *22*, 815–820.

(186) Spyroudis, S.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 135–137.

(187) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176–4179.

(188) Borowiecki, P.; Bretner, M. *Tetrahedron Asymmetry* **2013**, *24*, 925–936.

(189) Kwan, E. E.; Scheerer, J. R.; Evans, D. A. *J. Org. Chem.* **2013**, *78*, 175–203.

(190) Wolfe, S.; Ro, S.; Kim, C.-K.; Shi, Z. *Can. J. Chem.* **2001**, *79*, 1238–1258.

(191) Duan, X.; Zhou, H.; Tian, X.; Liu, J.; Ma, J. *Synthesis* **2015**, *47*, 777–782.

(192) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2001**, *84*, 1093–1111.

(193) Müller, P.; Ghanem, A. *Org. Lett.* **2004**, *6*, 4347–4350.

(194) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327–2329.

(195) Breitler, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11168–11171.

(196) Gallos, J. K.; Koftis, T. V.; Massen, Z. S.; Dellios, C. C.; Mourtzinos, I. T.; Coutouli-Argyropoulou, E.; Koumbis, A. E. *Tetrahedron* **2002**, *58*, 8043–8053.

(197) Moriarty, R. M.; Tyagi, S.; Kinch, M. *Tetrahedron* **2010**, *66*, 5801–5810.

(198) Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A. *J. Am. Chem. Soc.* **1985**, *107*, 7178–7179.

(199) Guo, J.; Liu, Y.; Li, X.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2016**, *7*, 2717–2721.

(200) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609–2612.

(201) Rao, D. S.; Reddy, T. R.; Babachary, K.; Kashyap, S. *Org. Biomol. Chem.* **2016**, *14*, 7529–7543.

(202) Loreto, M. A.; Migliorini, A.; Tardella, P. A.; Gambacorta, A. *Eur. J. Org. Chem.* **2007**, No. 14, 2365–2371.

(203) Finkbeiner, P.; Nachtsheim, B. J. *Synthesis* **2013**, No. 08, 979–999.

(204) Fan, R.; Sun, Y.; Ye, Y. *Org. Lett.* **2009**, *11*, 5174–5177.

(205) Zaimoku, H.; Hatta, T.; Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2012**, *14*, 6088–6091.

(206) De Armas, P.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc. Perkin Trans. 1* **1989**, No. 3, 405–411.

(207) Muñiz, K.; García, B.; Martínez, C.; Piccinelli, A. *Chem. Eur. J.* **2017**, *23*, 1539–1545.

(208) Ochiai, M.; Ito, T.; Masaki, Y.; Shiro, M. *J. Am. Chem. Soc.* **1992**, *114*, 6269–6270.

(209) Ochiai, M.; Ito, T.; Takahashi, H.; Nakanishi, A.; Toyonari, M.; Sueda, T.; Goto, S.; Shiro, M. *J. Am. Chem. Soc.* **1996**, *118*, 7716–7730.

(210) Barluenga, J. *Angew. Chem. Int. Ed.* **1985**, *24*, 319–320.

(211) Sandridge, M. J.; France, S. *Org. Lett.* **2016**, *18*, 4218–4221.

(212) Huang, C.-Y. (Dennis); Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 5638–5641.

(213) Nishimoto, Y.; Kita, Y.; Ueda, H.; Imaoka, H.; Chiba, K.; Yasuda, M.; Baba, A. *Chem. Eur. J.* **2016**, *22*, 11837–11845.

(214) Agasti, S.; Dey, A.; Maiti, D. *Chem. Commun.* **2016**, *52*, 12191–12194.

(215) Frank, D. J.; Franzke, A.; Pfaltz, A. *Chem. Eur. J.* **2013**, *19*, 2405–2415.

(216) Williams, C. W.; Shenje, R.; France, S. *J. Org. Chem.* **2016**, *81*, 8253–8267.

(217) Stubbing, L. A.; Li, F. F.; Furkert, D. P.; Caprio, V. E.; Brimble, M. A. *Tetrahedron* **2012**, *68*, 6948–6956.

(218) Velema, W. A.; van der Toorn, M.; Szymanski, W.; Feringa, B. L. *J. Med. Chem.* **2013**, *56*, 4456–4464.

(219) Ellis, G. P.; Shaw, D. *J. Med. Chem.* **1972**, *15*, 865–867.

(220) Buckles, R. E.; Yuk, J. P. *J. Am. Chem. Soc.* **1953**, *75*, 5048–5052.

(221) McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299–3306.

(222) Xu, X.; Wang, X.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 790–793.

(223) McDonald, S. L.; Wang, Q. *Chem. Commun.* **2014**, *50*, 2535–2538.

(224) Yang, M.-H.; Hunt, J. R.; Sharifi, N.; Altman, R. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 9080–9083.

(225) Nishimura, T.; Maeda, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 7324–7327.

(226) Müller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Flack, H. D. *Org. Lett.* **2004**, *6*, 1725–1728.

(227) Qian, P.; Du, B.; Song, R.; Wu, X.; Mei, H.; Han, J.; Pan, Y. *J. Org. Chem.* **2016**, *81*, 6546–6553.

(228) Xia, L.; Lee, Y. R. *Adv. Synth. Catal.* **2013**, *355*, 2361–2374.

(229) Tan, B.; Candeias, N. R.; Iii, C. F. B. *Nat. Chem.* **2011**, *3*, 473–477.

(230) Liu, Y.-Y.; Duan, S.-W.; Zhang, R.; Liu, Y.-H.; Chen, J.-R.; Xiao, W.-J. *Org. Biomol. Chem.* **2016**, *14*, 5224–5228.

(231) Zhu, X.; Chiba, S. *Chem. Commun.* **2016**, *52*, 2473–2476.

(232) Gerten, A. L.; Slade, M. C.; Pugh, K. M.; Stanley, L. M. *Org. Biomol. Chem.* **2013**, *11*, 7834–7837.

(233) Tan, B.; Zeng, X.; Leong, W. W. Y.; Shi, Z.; Barbas, C. F.; Zhong, G. *Chem. Eur. J.* **2012**, *18*, 63–67.

(234)   Younes, M. I. *Liebigs Ann. Chem.* **1990**, *1990*, 703–704.

(235)   Wilson, E. E.; Rodriguez, K. X.; Ashfeld, B. L. *Tetrahedron* **2015**, *71*, 5765–5775.

(236)   Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 9124–9127.

(237)   Donckele, E. J.; Finke, A. D.; Ruhlmann, L.; Boudon, C.; Trapp, N.; Diederich, F. *Org. Lett.* **2015**, *17*, 3506–3509.

(238)   Smith, R. B.; Canton, C.; Lawrence, N. S.; Livingstone, C.; Davis, J. *New J. Chem.* **2006**, *30*, 1718–1724.