Innovative Studies for the Construction of Carbon-Carbon Bonds to Access Synthetically
Challenging Scaffolds and Novel Models for Halogen Bonding Studies

by

Siawash Ahmar

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Author's Declaration

I herby 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

The formation of carbon-carbon bonds to access sterically challenging all-carbon quaternary centers still remains a synthetic challenge. Conjugate addition reactions have proven to be a very effective strategy for transferring alkyl and alkenyl groups to the electrophilic site of α,β-unsaturated compounds for the formation of quaternary centers; however, prior to the research described in Chapter one, no general strategies had been reported. The objective of my research was to address this void and develop a general and versatile conjugate alkynylation protocol that gives rise to propargylic quaternary centers. Chapter 1 disclosed two complementary protocols that were developed for the conjugate alkynylation of alkylidene Meldrum's acids. The scope of both the nucleophilic acetylide and electrophile were examined.

Chapter 2 focused on the Ag(I)-catalysed lactonization of propargylic Meldrum's acid adducts, discussed in Chapter 1, that afforded complex γ-butyrolactones. Various other electrophilic reagents such as: halogens, PhSeBr, and transition metals were also screened for reactivity, but gave inferior results to Ag_2CO_3. Lactonization was sensitive to reaction conditions, particularly for internal alkynes, where E and Z isomers can be formed.

In Chapter 3, an intramolecular Rh-catalyzed conjugate alkylation protocol was explored by preparing models that possessed a highly electrophilic site that was proximal to a carbon-metal bond which can undergo transmetallation. Tricarbastannatrane derivatives were the main focus as analogous tributylstannane substrates displayed regioselective transmetallation problems, and carbon-boron bonds showed no reactivity. Efforts to prepare models possessing the carabstannatrane group were thwarted by protodestannylation of the C–Sn bond. Additionally, due to the cost of tricabastannatranes, an in situ procedure starting from inexpensive starting material was found, albeit in low yields.

Finally, in Chapter 4 solution and solid state studies of intramolecular halogen bonding interactions were investigated. A series of Meldrum's acid models were prepared that carefully placed halogen bond donors and acceptors to allow for interactions to take place based on the results obtained from previous models. Though none of the models prepared displayed any

intramolecular interactions, sufficient evidence for intermolecular interactions between halogen donor of one molecule and the acceptor on another molecule were observed.

To My Family and Late Grandmother

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List of Abbreviations

Ac acetyl
app apparent
aq aqueous
Ar aryl

BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn benzyl
Boc *tert*-butyloxycarbonyl
br broad
Bpin boron pinacol ester (pinacolato boron)
Bu butyl
Bz benzoyl

calcd calculated
CAN ceric ammonium nitrate (diammonium cerium(IV) nitrate)
cat catalytic
cod cycloocta-1,5-diene
COSY correlated spectroscopy
Cp cyclopentadienyl
Cy cyclohexyl

d doublet
DART direct analysis in real time
dba dibenzylideneacetone
DCE dichloroethane
DCM dichloromethane
DDQ 2,3-dichloro-5,6-dicyanobenzoquinone
DEPT distortionless enhancement by polarization transfer
DMAP 4-dimethylaminopyridine
DME 1,2-dimethoxyethane
DMF dimethylformamide
DMSO dimethylsulfoxide
dppf 1,1`-bis(diphenylphosphino)ferrocene
dppp 1,3-bis(diphenylphosphino)propane Cp cyclopentadiene
Cy cyclohexyl
d doublet
DART direct analysis in real time
dba dibenzylideneacetone
DCE dichloroethane
DCM dichloromethane
DEPT distortionless enhancement by polarization transfer
DMAP 4-dimethylaminopyridine
DME 1,2-dimethoxyethane
DMF dimethylformamide
DMSO dimethylsulfoxide
dppf 1,1`-bis(diphenylphosphino)ferrocene
dppp 1,3-bis(diphenylphosphino)propane xii

dr diastereomeric ratio

EDG electron donating group
ee enantiomeric excess
EI electron impact
Et ethyl
EtOAc ethyl acetate
equiv equivalents
er enantiomeric ratio
ESI electrospray ionization
EWG electron withdrawing group

GC-MS tandem gas chromatography-mass spectrometry

h hour
HB hydrogen bonding
HMBC heteronuclear multiple bond correlation
HMPA hexamethylphosphoramide
HMQC heteronuclear multiple quantum coherence
HPLC high performance liquid chromatography
HRMS high resolution mass spectrometry
Hz hertz

i-Pr isopropyl
IR infrared

J spin coupling constant

L ligand
L* chiral ligand
L. A. Lewis acid
LDA lithium diisopropylamide

m multiplet
m meta
M metal or molarity (moles/litre)
Me methyl
MeCN acetonitrile

NHC *N*-heterocyclic carbene
NMP *N*-methyl-2-pyrrolidone
NMR nuclear magnetic resonance
nOe nuclear Overhauser enhancement
NOESY nuclear Overhauser enhancement spectroscopy
Nu nucleophile

o ortho
OTf triflate (trifluoromethanesulfonate)

p para

PCC pyridinium chlorochromate
Ph phenyl
Piv pivaloyl (trimethylacetyl)
pK_a -log of acid dissociation constant
ppm parts per million
py pyridine

q quartet
quant quantitative

rac racemic
rt room temperature
s singlet
SM starting material

t triplet
t-Bu *tert*-butyl
temp temperature
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
TMS trimethylsilyl
Ts tosyl (*p*-toluenesulfonyl)

UV ultraviolet

XB halogen bonding

wt weight

Chapter 1. Conjugate Additions of Alkynyl Alanes and Grignards to Alkylidene Meldrum's Acid Derivatives for the Formation of All-Carbon Propargylic Quaternary Stereocenters

1.1. Introduction

1.1.1. Conjugate Addition Reactions for the Formation of All-Carbon Quaternary Stereocenters

The focus of this section is to give a brief overview of conjugate addition reactions of sp^3, sp^2 and sp nucleophiles to α,β-unsaturated electrophiles in the formation C–C bonds focusing on all-carbon quaternary products. Conjugate addition reactions makeup a class of reactions that involve the nucleophilic attack at β-position of an α,β-unsaturated carbonyl. The regioselectivity of the nucleophilic addition is governed by the "hardness" or "softness" of the nucleophile, and steric accessibility at the electrophilic positions (Figure 1.1).
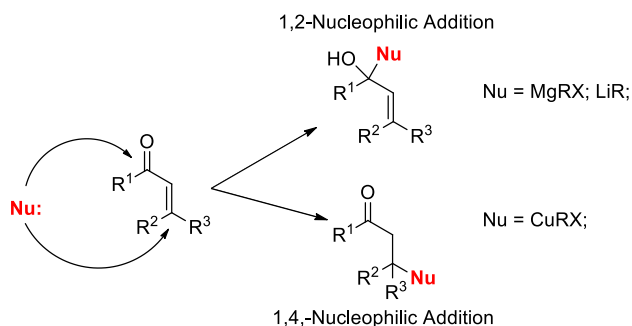
Figure 1.1. 1,2-Nucleophilic Addition versus 1,4-Nucleophilic Conjugate Addition

All-carbon quaternary centers are omnipresent throughout nature and therefore a great deal of attention has been placed on strategies to access these stereocenters.[1] Figure 1.2 illustrates selected examples of naturally occurring molecules that possess all-carbon quaternary centers; the highlighted centers have been formed through conjugate addition reactions in either the total synthesis of the molecule,[2] or en route to the total synthesis.[3]

Dehaloperophoramidine *Serotonin Receptor Inhibitor* *Briarein A*
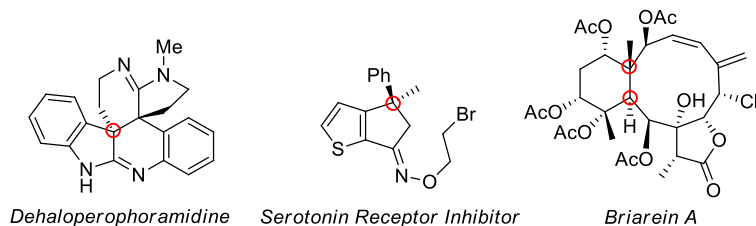
Figure 1.2. Selected Examples of Naturally Occurring Molecules That Have Had Their Structural Cores Prepared Through a Conjugate Addition Step

Significant progress has been made in the 1,4-addition of alkyl, aryl and alkenyl groups to tetra- or trisubstituted acceptors for the formation of quaternary stereocenters with recent examples of enantioselective methodologies. Despite these advances, one of the main challenges still facing synthetic chemists is the steric hindrance at the electrophilic β-carbon. To circumvent these obstacles, synthetic chemists have resorted to the use of strongly nucleophilic reagents such as Grignard reagents,[4] or Lewis acidic reagents such alanes and boranes. Alternatively, activated electrophiles such as doubly activated enones,[5] and/or the addition of catalysts that enhance the reactivity of the system while directing the regio- and/or stereoselectivity of the 1,4-addition have been successful.[6] Typically, a combination of two or more of the mentioned strategies are required to obtain highest yields and enantioselectivities as illustrated in Scheme 1.1.

Analogous strategies have been exploited for the conjugate alkenylation to form all-carbon quaternary centers bearing at least one sp^2 hybridized carbon atom. However, due to the availability of alkenyl nucleophiles, novel strategies were required to expand the nucleophilic scope of these reagents. Alkenylalanes can be accessed by the hydroalumination of desired alkyne, or Li halogen exchange using an alkyllithium followed by nucleophilic substitution with ZnCl$_2$, or AlR$_2$Cl (Scheme 1.2). A disadvantage to the latter approach involves a tedious isolation step to remove the Li$^+$ salts that further complicates their use.

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Scheme 1.1. Selected Examples of Conjugate Alkylation Methodologies for the Formation of Quaternary Centers

Reactive Nucleophiles
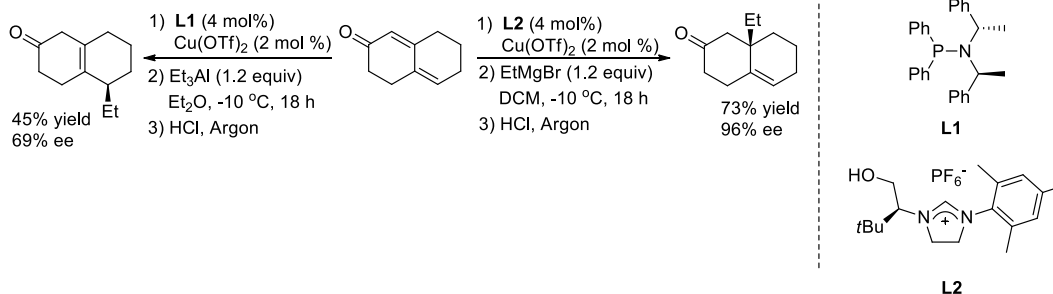
Activated Electrophiles
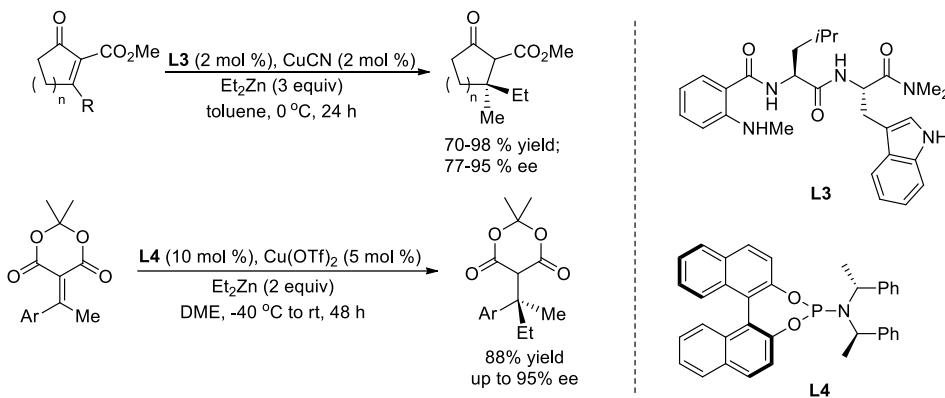
As already mentioned, all-carbon benzylic quaternary centers can be formed by the 1,4-conjugate addition of alkyl nucleophiles to α,β-unsaturated acceptors bearing an aryl moiety at the β-position; or in the reverse manner by the addition of aryl nucleophiles to electrophilc acceptors bearing an alkyl group at the β-position. Alexakis reported the first copper-catalyzed asymmetric conjugate addition of aryl and vinyl alanes to 3-methylcyclohex-2-enone (Scheme 1.3a).[7] This methodology expanded the scope of aryl groups, where previous approaches were limited to the addition of Ph groups, and overcame the poor reactivity of electron deficient arylzinc reagents.

Scheme 1.2. Preparation of a) Vinyl- and b) Arylalanes

a)

$$R\!\!-\!\!\!\equiv \xrightarrow[\substack{\text{heptane} \\ 50\ ^{\circ}\text{C, 2h}}]{\text{DIBAL-H}} \underset{R}{\diagup}\!\!\diagdown \text{Al}(i\text{-Bu})_2$$

b)

$$\underset{R}{\diagup}\!\!\diagdown^{X} \xrightarrow[\text{2) M}]{\text{1) R'Li}} \underset{R}{\diagup}\!\!\diagdown^{M}$$

$$\underset{R}{\diagup}\!\!\diagdown^{\text{AlR}_2} \qquad \left(\underset{R}{\diagup}\!\!\diagdown^{\text{Zn}}\right)_2 \qquad \text{R'}\!\!-\!\!\bigcirc\!\!-^{\text{AlR}_2} \qquad \left(\text{R'}\!\!-\!\!\bigcirc\!\!-^{\text{Zn}}\right)_2$$
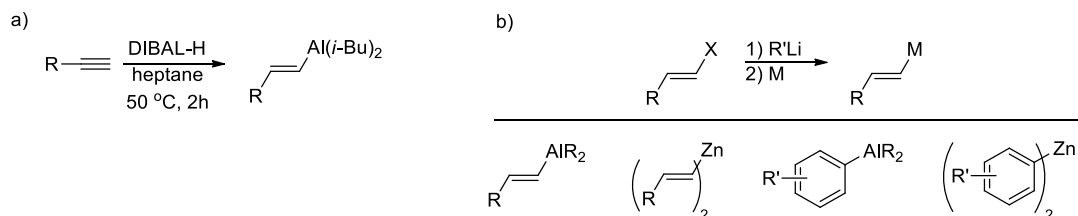
Rh-catalyzed conjugate addition of tetraarylborates, Ar$_4$BNa, to β,β-disubstituted α,β-unsaturated ketones has been reported by Hayashi (Scheme 1.3b).[8] Highest enantioselectivities were achieved using chiral diene **L6**, and various aryl groups were introduced to both cyclic and acyclic enones giving rise to benzylic all-carbon quaternary centers. Shortly after, a protocol using arylalanes in the Rh-catalyzed conjugate arylation of enones with commercially available BINAP was reported (Scheme 1.3c).[9] In comparison to Hayashi's protocol which requires 2–4 equivalents of the nucleophile that already bears four aryl groups and higher temperatures, the latter methodology disclosed by Alexakis uses 1.2 equivalents of the arylalane and lower temperatures to achieve comparable enantioselectivities but lower yields (Scheme 1.3c). This example highlights the great potential of organo-alanes as attractive nucleophilic reagents for conjugate addition reactions.

As an alternate approach, Stoltz reported the first protocol for the enantioselective Pd-catalyzed conjugate arylation of β-substituted enones with commercially available arylboronic acids (Scheme 1.3d).[10] A wide range aryl groups bearing electron-rich and -poor substituents were inserted to form enantioenriched benzylic all-carbon quaternary centers using pyridinooxazoline **L8** for asymmetric induction. One notable advantage is the reactions did not require purification of solvents or careful handling of reagents showing tolerance to both air and water compared to previously reported strategies using air and moisture sensitive organometallic reagents.

Scheme 1.3. Selected Examples of Conjugate Arylation Methodologies
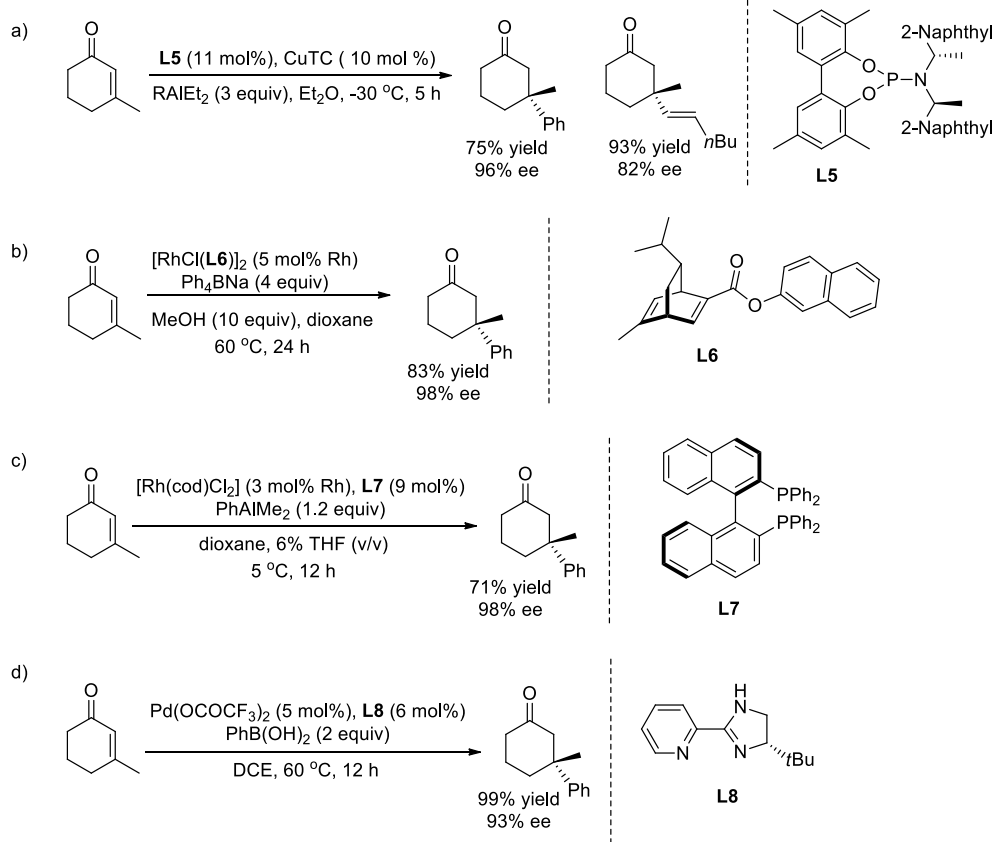
In spite of recent advances in the formation of all-carbon quaternary centers bearing alkyl and/or alkenyl groups, the number of analogous methods for the formation of propargylic all-carbon quaternary centers remains limited. Strategies employed to achieve 1,4-regioselectivity in the conjugate addition of alkyl or alkenyl groups to α,β-unsaturated carbonyl compounds, such as the use of Cu(I) salts, has been hindered by the inertness of the Cu−C(sp) bond (Scheme 1.4a).[11] In fact, mixed cuprates containing an acetylide and alkyl or alkenyl group were shown to selectively transfer the latter two groups to cyclohexenone, rendering the acetylides as nontransferable groups or "dummy ligands" (Scheme 1.4 b).[12] Even the sterically demanding t-Bu group was preferentially delivered, illustrating how tightly bound alkynyl groups are to Cu complexes. As result, synthetic chemists have developed alternate approaches to introduce alkynyl groups.

Scheme 1.4. Cu-acetylides as Nontransferable Groups
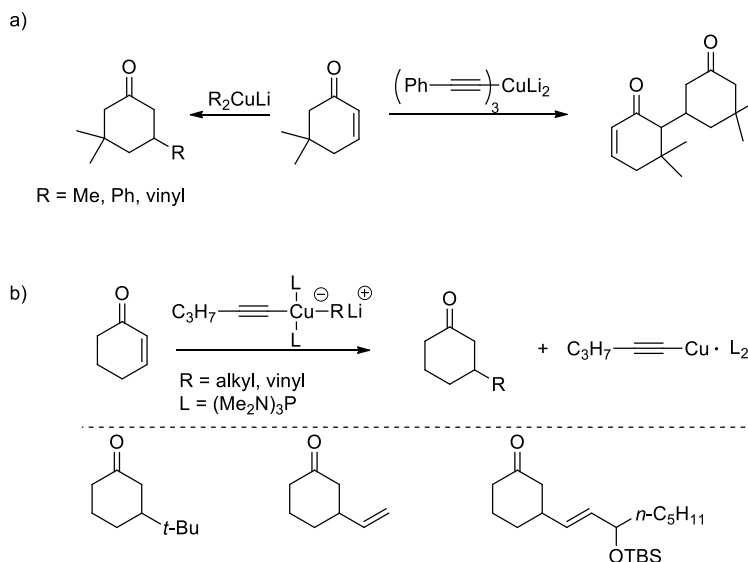
Nagata and Yoshioka discovered that alkylaluminum cyanides were exceptional reagents for the 1,4-conjugate addition of cyano groups (Scheme 1.5a).[13] This report illustrated that sp-hybridized carbons can undergo a 1,4-conjugate addition, and emphasized the impact of the reagent used where Na[Et$_3$AlCN], a non-Lewis acidic analogue of Et$_2$AlCN, resulted in trace amounts of the 1,4-adduct; whereas Lewis acidic Et$_2$AlCN afforded adducts in excellent yields. Noteworthy was the quaternary center formed using this approach (Scheme 1.5a). Based on these results, Hooz and Layton shortly thereafter reported the first example of conjugate alkynylation to α,β-unsaturated ketones using diethylalkynylalanes (Scheme 1.5b).[14] The significance of the enone geometry was shown where only those that can adopt an *s*-cis conformation afforded the 1,4-adduct through a postulated intramolecular delivery of the alkynyl group; in contrast to those locked in a *s*-trans conformation afforded the 1,2-adducts (Scheme 1.5c).

Scheme 1.5. Early Examples of Conjugate Alkynylation

a) Et$_2$AlCN (6 equiv), toluene, 0 °C, 0.5 h, 91% yield

b) R≡AlEt$_2$ (2 equiv), Et$_2$O:pet ether (3:1), rt, 4 h; *s*-cis intermediate possible

c) R≡AlEt$_2$ (2 equiv), Et$_2$O:pet ether (3:1), rt, 4 h
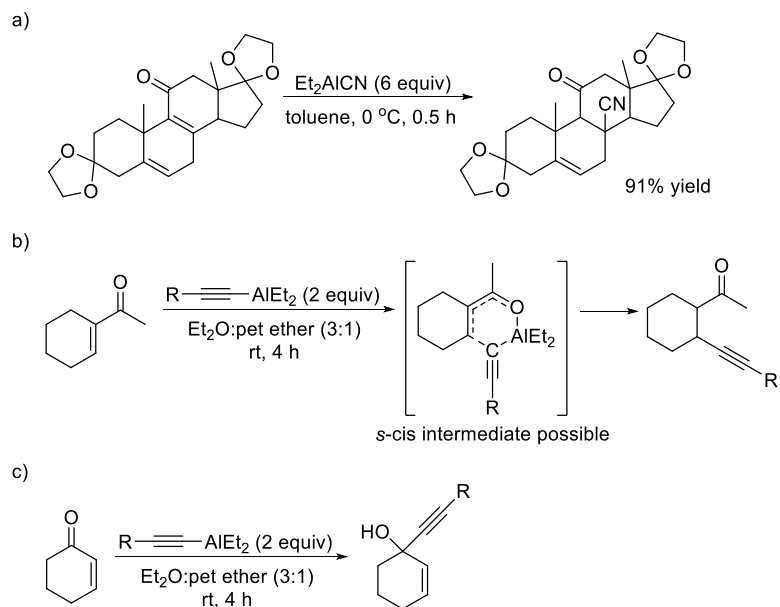
Pappo and Collins disclosed that 1,4-conjugate alkynylations to enones locked in an *s*-trans conformation can be overcome by a directing group adjacent to the site of attack (Scheme 1.6a).[15] Participation of the directing group was proven by the *cis* relationship between the hydroxyl group and alkyne, and moreover by the recovery of starting material when blocking the interaction with a tetrahydropyranyl group (Scheme 1.6a). As an alternate approach, Schwartz developed Ni(I) catalyzed conditions for the 1,4-conjugate alkynylation of *s*-trans enones.[16] DIBAL-H was necessary to have efficient catalytic activity, which was apparent by the lack of reactivity observed in the absence of the reducing agent, and the isolation of equimolar amounts (based on Ni) of coupled diacetylene. Furthermore, screening other metal actetylides, such as Li and Mg, did not afford the 1,4-adducts with their protocol.

Scheme 1.6. 1,4-Conjugate Alkynylation of *s*-Trans α,β-Enones

Alkynylboranes have also been shown to be suitable nucleophiles in 1,4-conjugate additions. Brown reported the 1,4-addition of 9-alkynyl-9-borabicyclo[3.3.1]nonanes **1.1** to *s*-cis enones, but they suffered the same limitation as alkynylalanes towards *s*-trans enones (Scheme 1.7).[17] Of personal interest was their sole example of an all-carbon quaternary centered adduct **1.2** that required long reaction times; this example showed the potential for the formation propargylic quaternary centers through conjugate addition reactions.

Scheme 1.7. 1,4-Conjugate Additions with Alkynylboranes

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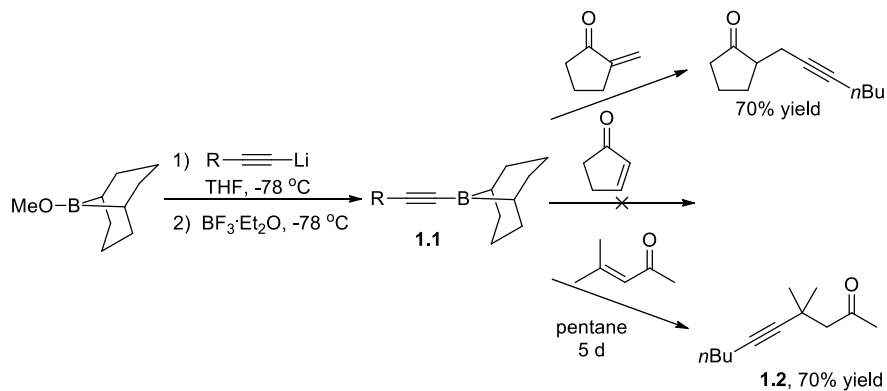
Asymmetric protocols for the conjugate alkynylation to *α,β*-unsaturated carbonyls have begun to appear. The Chong group here at the University of Waterloo reported the asymmetric conjugate alkynylation of enones using catalytic binaphthol ligands **L9** (Scheme 1.8).[18] What is conceptually impressive about this protocol is that the reactivity was dependent on the transesterification of the achiral boronate with **L9** generating a more reactive nucleophile that is also responsible for the asymmetric induction and delivery of the acetylide to the enone. As was previously observed with racemic protocols, only *s*-cis enones underwent the conjugate addition, where high yields and enantioselectivities were obtained.

Scheme 1.8. Asymmetric Alkynylboration of Enones
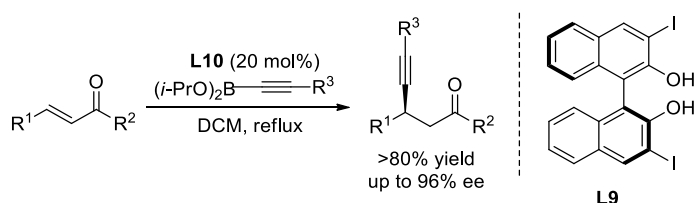
Corey reported the Ni(II) catalyzed asymmetric conjugate addition of alkynylalanes to *α,β*-enones using either chiral ligands **L10** or **L11** (Scheme 1.9).[19] The overall success of the reaction was sensitive to solvents, counterions and temperature in order to attain optimum results. Modest to good yields and enantioselectivities were obtained, but ultimately inferior to other asymmetric protocols. In contrast to previously reported Ni(I) catalyzed additions of alkynylalanes by Schwartz requiring equimolar amounts of DIBAL-H, this approach uses strongly coordinating chiral ligands that prevent the reductive elimination of two acetylides, thereby allowing the use of Ni(II) salts.

Scheme 1.9. Enantioselective Conjugate Alkynylation
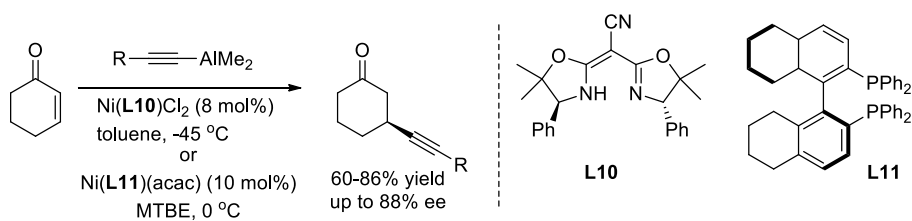
Alkynylzinc reagents do not react with α,β-enones and require special conditions such as the addition of strong Lewis acids to activate the β-position,[20] or activated acceptors such as nitroolefins[21] and doubly activated Michael acceptors.[22-22] Trialkylsilyl triflates (R_3SiOTf) have been employed in the Lewis acid activation of α,β-enones for the 1,4-addition of alkynylzinc reagents at very low temperatures (Scheme 1.20a). Unlike alkynylaluminum and boron reagents, alkynylzincs add to both *s*-cis and *s*-trans α,β-enones to form γ,δ-acetylenic silyl enol ethers, but require excess of both TBSOTf and alkynylzinc reagents (1.3 equivalents of both) to obtain high yields. In the absence of Lewis acids, alkynylzincs have been added to nitrooelfins in presence of chiral amino alcohol **L12**, which was essential to obtain reactivity (Scheme 1.20b). As was required with the previous report, excess of the alkyne, alkylzinc and chiral ligand (3 equivalents of each) were necessary to obtain optimum results. Furthermore, the nucleophilic scope of alkyne was limited to aryl-substituted terminal alkynes.

Carreira reported the conjugate alkynylation of in situ generated alkynylzinc reagents to chiral oxazepanedione acceptors **1.3** (Scheme 1.20c). [23] Mild reaction conditions and substoichiometric amounts of Zn(II) salts afforded 1,4-adducts that were readily hydrolyzed to β-alkynyl acids over two steps in good to excellent yields and enantioselectivities.

Scheme 1.20. Conjugate Alkynylation
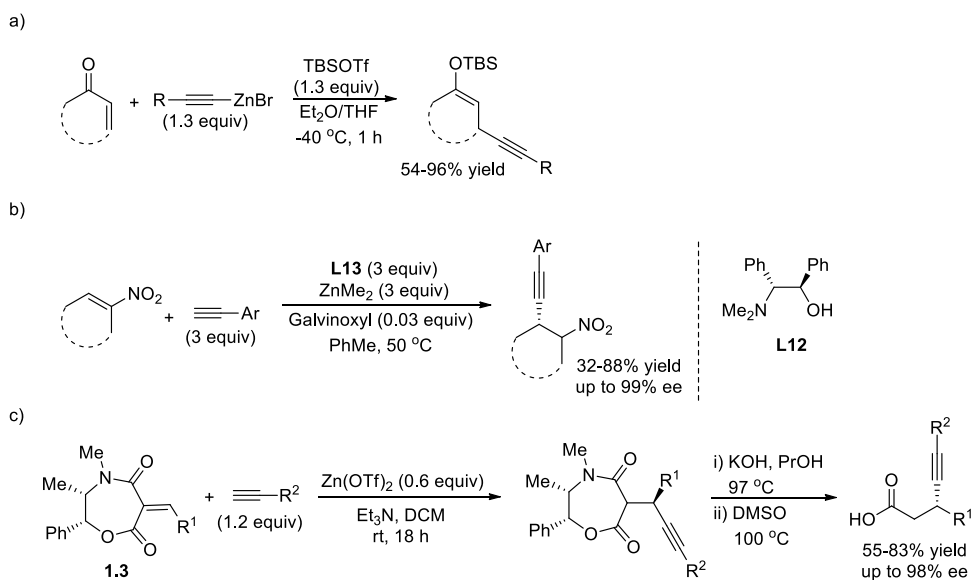
Early reports claimed that Cu-acetylides do not partake in 1,4-conjugate addition reactions due the strength of the Cu–C(sp) bond (vide supra). However, more recently it has been shown that the same strategy used for the alkynylzinc reagents could be applied to Cu-acetylides, where either TBSOTf[24] or TMSI[25] act as strong activators of α,β-unsaturated carbonyls (Scheme 1.21). Alkynyl copper(I)·LiI–TMSI complexes showed preference for *s*-trans enones, such as cyclic enones, and failed to give appreciable yields to acyclic enones (Scheme 1.21a). TMSI was superior to other trialkylsilyl halides and triflates; LiI was shown to be vital to obtain high yields. According to their proposed mechanism,[25] coordination of the silyl group to the oxygen of the carbonyl not only activates the β-position, but also allows for an interaction between the I and Cu to form a tighter π-complex with the alkene (Scheme 1.21a). This Si–I–Cu interaction is important because the strength of the Cu-acetylide bond does not allow for a tight complexation to the olefin, and therefore TMSI functions as both a Lewis acid and coordinator to direct the conjugate addition. This also accounts for the poor reactivity observed with *s*-cis enones, where steric interactions that would result from the Si–I–Cu complexation would not allow for its formation; and, the superiority of the TMSI over other halides as I is the most nucleophilic in that group allowing for the greatest orbital overlap. Interestingly, TBSOTf mediated 1,4-addition of Cu-acetylides were reported to add to both *s*-cis and -trans enones in good yields (Scheme 1.21b).[24] This is somewhat contradictory to the TMSI protocol which only differs in counter ion, I⁻ for ⁻CN, and solvent, suggesting that an alternate silyl activated species may be formed prior to delivery of the acetylide. Both strategies afford silyl enol ethers that are hydrolyzed in the workup (Scheme 1.21a), or can be hydrolyzed in subsequent steps (Scheme 1.21b).

Scheme 1.21. Cu-catalyzed Conjugate Alkynylations
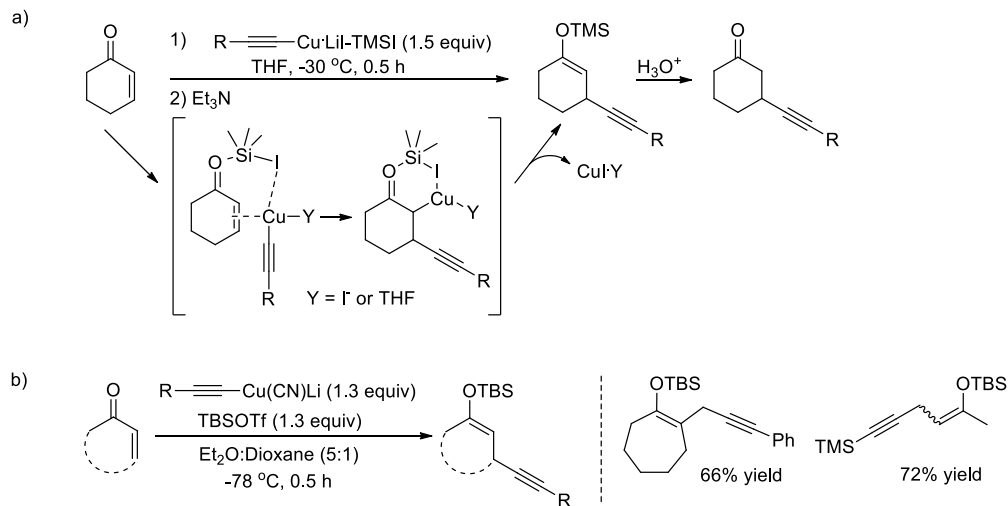
Catalytic enantioselective Cu(II) catalyzed conjugate alkynylations to Meldrum's acid alkylidene derivatives have been reported the Carreira group (Scheme 1.22).[26] Alkynylcopper reagents were generated in situ under aqueous conditions using phenylacetylene, catalytic amounts of $Cu(OAc)_2$ and sodium ascorbate, which proceed to add to Meldrum's acid alkylidenes at low temperatures. Enantioenriched tertiary propargyl centers were formed using **L13** in good to excellent yields and selectivities. Due the heterogeneous nature of the reaction, a large excess of phenylacetylene was required to form the organic phase where the conjugate addition is believed to take place. Although limited to phenylacetylenes, this procedure showcased mild enantioselective conditions for the addition of Cu-acetylides in the absence of strong activating agents.

Scheme 1.22. Enantioselective Conjugate Addition of Cu-acetylides
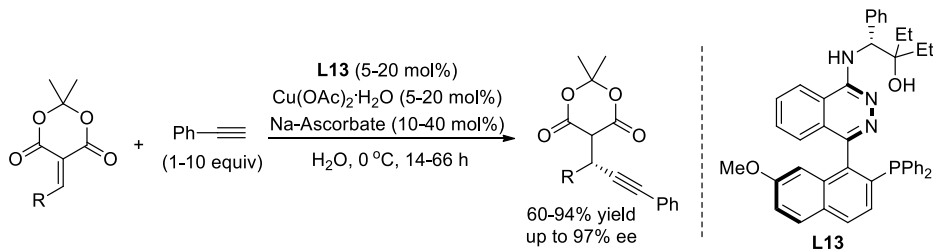
Hayashi has reported the Rh(I)-catalyzed enantioselective conjugate alkynylation to *α,β*-unsaturated enones (Scheme 1.23a).[27] Sterically demanding (triisopropylsilyl)acetylene in combination with the bulky chiral ligand **L14** were essential in order to suppress the favourable Rh-catalyzed alkyne dimerization and allow for the conjugate addition to take place in high yields and enantioselectivities. As an alternate approach to commissioning sterically bulky ligands interacting with sterically bulky alkynyl reagents, our group has reported the Rh-catalyzed conjugate addition of TMS-acetylene to Meldrum's acid alkylidenes (Scheme 1.23b).[28] Enantioenriched propargyl centers were obtained using commercially available ligand **L15** under mild reaction conditions that afforded adducts in good to excellent yields and selectivities. Unlike other acceptors, such as cyclic and acyclic carbonyls that typically do not allow for a wide range of transformations, propargylic Meldrum's acid derivatives can be readily transformed to a variety of different chiral compounds (Scheme 1.23b). Additionally, the removal of the TMS group gives rise to terminal alkynes that can undergo Sonogashira coupling reactions expanding the scope of the acetylide.

Scheme 1.23. Enantioselective Rh(I)-catalyzed Conjugate Alkynylations
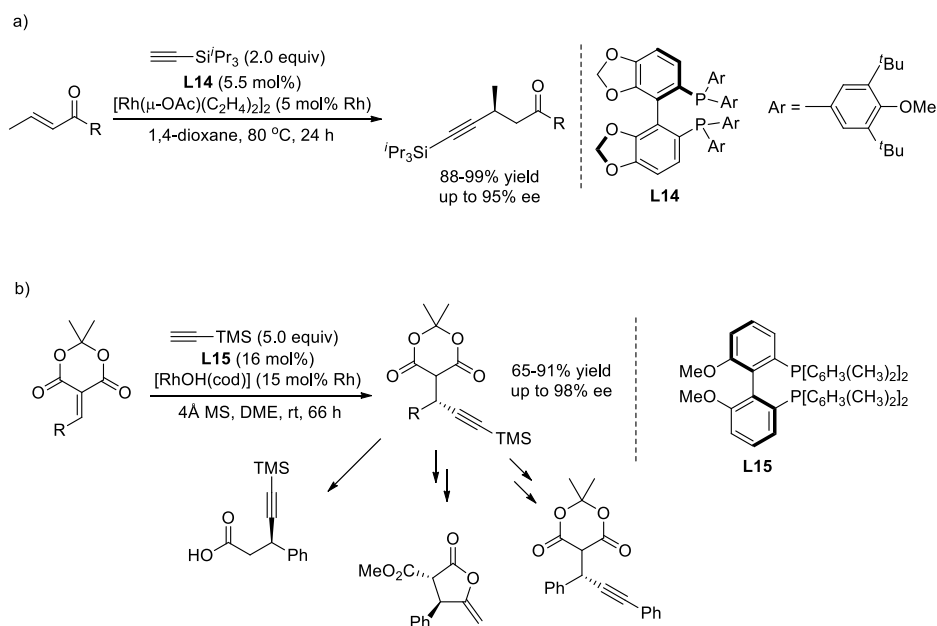
Although significant progress has been made in the conjugate addition of alkynyl groups to *α,β*-unsaturated acceptors to access tertiary propargyl centers, no general strategy to

prepare propargylic all-carbon quaternary centers had been reported prior to the research described in the this chapter. It is should be noted that propargylic all-carbon quaternary centers have been prepared by Alexakis' group via the copper-catalyzed 1,4-addition of alkyl Grignards to cyclic enynones.[29] As well, S_N2' addition of alkynylalanes to allylic phosphates resulting in enantiopure 1,4-enynes adducts has been reported by Hoveyda.[30]

Scheme 1.24. a) Cu-Catalyzed Conjugate Addition to Enynones; b) Cu-Catalyzed Allylic Substitutions Reactions to Allylic Phosphates with Alkynylalanes
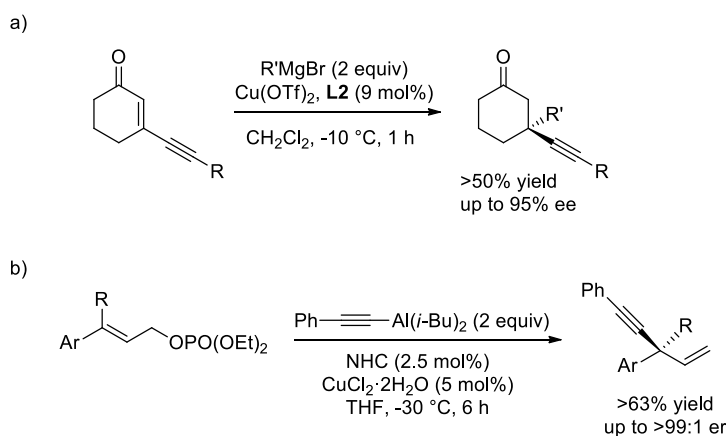
1.2. Proposal

At the outset of our research, no general methodology for the addition of alkynyl groups in the formation propargyl quaternary centers had been reported. This was somewhat surprising given the synthetic potential of a carbon based handle at a synthetically challenging center that can be readily manipulated and allow for further transformations. To address this void, we sought the opportunity to develop conditions to access all-carbon quaternary propargyl centers, as well as expand on conjugate arylation methodologies to Meldrum's acid alkylidenes in the formation of benzylic all-carbon quaternary centers.

The convenience with which benzylidene Meldrum's acids can be prepared from inexpensive starting materials makes them an attractive acceptor for developing methodologies for conjugate arylation and alkynylation protocols. Moreover, given our

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group's success in developing enantioselective protocols for the conjugate addition of alkyl groups affording quaternary centers, and alkenyl[31] and alkynyl[28] groups for the formation of tertiary centers, it was a logical extension to investigate the addition of aryl and alkynyl groups to access sterically crowded all-carbon centers that would otherwise be inaccessible. These Meldrum's acid derivatives can serve as building blocks for further transformations (Scheme 1.25).

Scheme 1.25. General Scheme for the Conjugate Addition of Aryl and Alkynyl Nucleophiles to Alkylidene Meldrum's Acid Derivatives
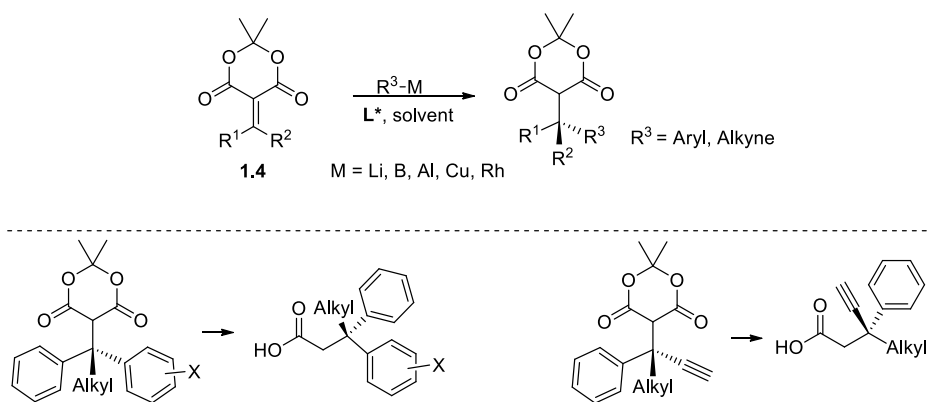
1.3. Results and Discussion

In determining suitable reagents for the conjugate addition of aryl and alkynyl groups to alkylidene Meldrum's acids **1.4**, aluminum based reagents were an attractive starting point due to their Lewis acidic nature and ability to functionalize with the desired nucleophiles. PhAlMe$_2$ was easily prepared by the addition of PhLi to Me$_2$AlCl at low temperatures. LiCl salts can be separated by letting them settle and carefully cannulating the supernatant into another vessel. Alexakis reported that Li$^+$ salts did not affect the overall yield and enantioselectivity of their conjugate arylation protocol,[7] but as a starting point reactions were run void of them. Briefly screening solvents quickly revealed preferential delivery of the sterically less demanding Me group over the Ph group, with an overall conversion of less than 50% and recovery of starting material in THF (Table 1.1 entries 1–3)[32] Problems of alkyl transfer with ArAlMe$_2$ onto β-substituted enones has been documented at elevated

temperatures.[7] Transition metals have been shown to alter the regio- and chemoselectivity of conjugate addition reactions;[33] with this in mind substoichiometric amounts of Cu(I/II) salts were tested (Table 1.1 entries 1–2). Gratifyingly, a reversal in selectivity with preferential delivery of the Ph was observed, and an increase in the overall conversion (>75%) after 48 hours was obtained. Although both Cu(I) and Cu(II) salts afforded all-carbon dibenzylic quaternary adducts **1.5a**, significant amounts of the Me transfer adduct **1.6a** was still observed in the crude ^{1}H-NMR.

Phosphorus ligands are the most widely used ligands in Cu-catalyzed conjugate addition reactions and have been shown to improve the efficiency of the overall reaction.[34] Encouraged by the improved transfer of the Ph moiety and overall reactivity with Cu-salts, phosphoramidite ligands were added to test for asymmetric induction and further chemoselectivity. In particular, phosphoramidite ligands **L4-5** have been successfully employed in the enantioselective addition of alkyl and aryl alanes to less reactive cyclic enones. In our hands the addition of **L4** resulted in the complete consumption of **1.4a** (entry 6–7); however no 1,4-adducts were isolated and a complex mixture was observed in the crude ^{1}HNMR. It is worth mentioning that the only distinguishable compounds isolated after column chromatography were trace amounts of Meldrum's acid and **L4**. As an alternate transition metal catalyst, [Rh(cod)Cl]$_2$ salts have also been reported in conjugate addition of alkyl and aryl groups, and were therefore tested with our system. Unfortunately, reactions using Rh(I) salts proved to be ineffective showing poor reactivity and affording trace amounts of reduced **1.4a** to **1.7**.

In order to avoid competing conjugate alkylation, organometallic reagents that do not possess transferable groups such Grignards, organolithium and boron reagents were also examined (Table 1.2). Both strongly nucleophilic PhMgCl and PhLi resulted in the isolation of starting material after 12 h (entries 1 and 2). The strong basicity of these reagents may result in γ-deprotonation of alkyl moiety that gets reprotonated after aqueous workup.[35] Further evidence for the deprotonation comes from the reactivity observed when catalytic amount of CuCl is added and >75% conversion is observed. It is also worth mentioning that trace amounts of biphenyl and 4'-haloacetophenone are observed in the crude ^{1}HNMR spectrum.[36]

Table 1.1. Conjugate Addition of Arylalanes to Alkylidene Meldrum's Acid Derivatives
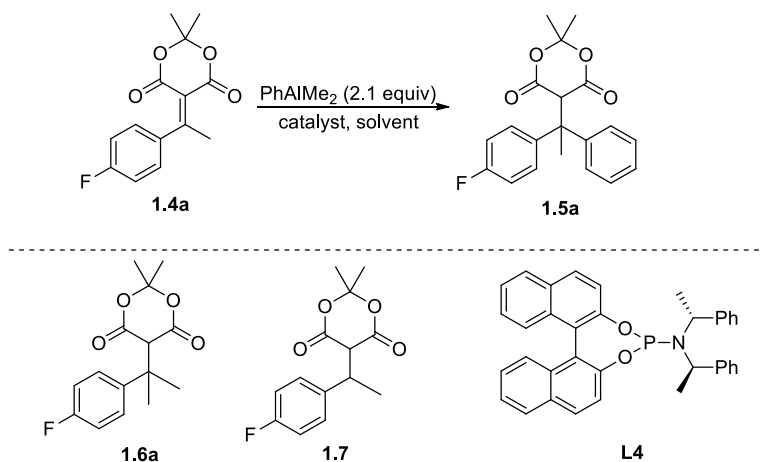
Entry	Catalyst	Solvent	Temp (°C) / t (h)	conv (%)[a]
1	-	DME	-78 to rt / 8	**1.5a** (9) : **1.6a** (38)
2	-	THF	-78 to rt / 8	no reaction
3	-	DCE	-78 to rt / 8	**1.5a** (11) : **1.6a** (30)
4	CuTC (0.5 equiv)	DME	-40 to rt / 48	**1.5a** (51) : **1.6a** (36)
5	Cu(OTf)$_2$ (0.5 equiv)	DME	-40 to rt / 48	**1.5a** (55) : **1.6a** (21)
6	Cu(OTf)$_2$ (20 mol%) + **L4** (40 mol%)	DME	-40 to rt / 48	complex mixture
7	CuTC (20 mol%) + **L4** (40 mol%)	DME	-40 to rt / 48	complex mixture
8	[Rh(cod)Cl]$_2$ (30 mol% Rh)	DME	-40 to rt / 48	Trace of **1.7**

[a] Conversion based on analysis of ^{1}HNMR[32]

9-Aryl-9-borabicyclo[3.3.1]nonanes (*B*-Ar-9BBN) have been used as a nucleophilic source of aryl groups in the Rh-catalyzed conjugate arylation of cyclic enones.[37] These borabicyclo reagents only possess one nucleophilic group, and therefore *B*-Ph-BBN was prepared and its reactivity was tested with **1.4** (Table 1.2, entries 5–9). No addition adducts were observed when 2.1 equivalents of the reagent was used (entry 5), but in the presence of CuCl and excess reagent, resulted in complete degradation of the starting material where Meldrum's acid was the only distinguishable compound (entry 6). Similar reactivity was observed with catalytic amounts [Rh(cod)Cl]$_2$ (entry 7). The isolation of Meldrum's acid may be explained by the hydrolysis of the alkylidene during the reaction by trace amounts of water, or more likely upon

aqueous workup. Additionally, the quaternary adducts formed by the arylation would be doubly benzylic and unstable when a Lewis acid is present, where the Meldrum's acid moiety acts as a leaving group resulting in C–C bond cleavage.[38] At the outset of this project, we had not reported the conditions necessary for Meldrum's acid to act as a leaving group and therefore did not account for it when developing arylation conditions.

Table 1.2. Screening Nucleophilic Aryl Reagents
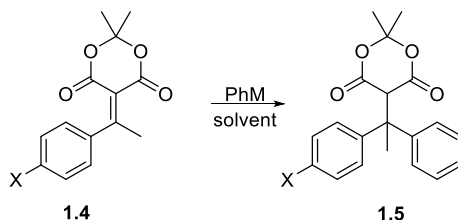
Entry	X	M^b	catalyst	Solvent /Temp / t (h)	% conv^a
1	F	Li	-	Et$_2$O / 0 to rt / 12 h	0
2	F	MgCl	-	Et$_2$O / 0 to rt / 12 h	0
3	F	MgCl	CuCl (10 mol%)	THF / 0 to rt / 6 h	**1.5a** (77)^d
4	Cl	MgCl	CuCl (10 mol%)	THF / 0 to rt / 6 h	**1.5b** (80)^d
5	F	9-BBN	-	Et$_2$O / 0 to rt / 12 h	0
6	F	9-BBN^c	CuCl (10 mol%)	DME / 0 to rt / 12 h	- ^{d}
7	F	9-BBN^c	[Rh(cod)Cl]$_2$ (20 mol% Rh)	DME / 0 to rt / 48 h	- ^{d}
8	F	9-BBN^c	[Rh(cod)Cl]$_2$ (20 mol% Rh) MeOH (20 mol%)	DME / 0 to rt / 48 h	-
9	F	9-BBN^c	[Rh(cod)Cl]$_2$ (20 mol% Rh) t-BuOK (20 mol%)	DME / 0 to rt / 48 h	-

^{a} Based on analysis of crude ^{1}HNMR; ^{b} 2.1 equivalents used; ^{c} 4.0 equivalents used; ^{d} Trace amounts of Meldrum`s acid was isolated

In parallel to the conjugate arylation studies, conditions for the conjugate addition of alkynylalanes to alkylidene Meldrum's Acids were also being explored. A mild synthetic route to prepare alkynylalanes that eschews the deprotonation of terminal alkynes with strong organolithium or sodium reagents was sought after. To that end we turned to a report by Binger that demonstrated trialkylaluminates **1.8** can react with terminal alkynes to lose H$_2$ and form the corresponding dialkylalkynylaluminum compounds **1.9** (Scheme 1.26a).[39] A catalytic

protocol appeared nearly 40 years later that showed alkynylalanes can be prepared with catalytic amount of Et₃N at lower temperatures, and be subsequently added to various electrophiles (Sceheme 1.26b).[40]

Scheme 1.26. Preparation of Alkynylalanes From Trialkylaminates
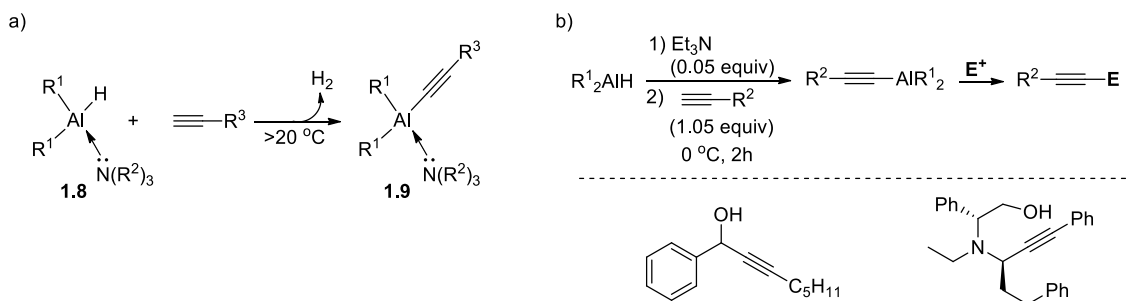
Attempts to prepare alkynylalanes with the above protocol resulted in incomplete formation of the alkynylalane reagent giving inconsistent results. Longer reaction times and elevated temperatures gave more consistent results and complete consumption of DIBAL-H (Table 1.3). High conversions were obtained in less Lewis basic solvents such as DME, DCE and toluene, Table 1.3 entries 1–4, where THF completely shut down reactivity (entry 2). Toluene proved to be the optimal solvent resulting in complete consumption of **1.4** after 24 h, and the isolation of product **1.10a** in good yield (entry 3). With this promising lead the scope of the nucleophile was investigated by subjecting 1-hexyne and TMS-acteylene to the same conditions. Though 1-hexyne underwent a 1,4-conjugate addition to afford the propargyl adduct **1.10b**, albeit in low yields, significant amounts of the vinyladduct **1.11** was also formed (entry 5–6). The isolation of **1.11** suggests that hydroalumination and conjugate alkenylation was favoured over deprotonation. Furthermore, varying amounts of **1.10b** and **1.11** are formed resulting in inconsistent results. More troublesome was TMS-acetylene which afforded complex mixtures with no propargyl adducts isolated (entry 7). These results suggested that a more predictable and widely applicable method was required to prepare alkynylalane reagents.

Efforts were also taken to probe the effects of transition metals on the conjugate addition of alkynylalanes to improve reactivity and induce enantioselectivity (Table 1.4). Cu(II) and Rh(I) salts with chiral ligands **L6**, **L7** and **L16** that offer different coordination modes,

were briefly examined. Using optimized conditions described above, a decrease or complete loss in reactivity was observed for both Cu(II) and Rh(I) salts with ligands **L7** and **L16** (entries 1–6). It should be noted that even low yielding reactions (entries 1–3, 6) afforded racemic mixtures of enantiomers suggesting a background reaction had taken place in the absence of the chiral-metal complex. Attempts to impede the background reaction to allow for

Table 1.3. Conjugate Alkynylation

1.4b, (1.0 equiv)

1.10a, R = Ph
1.10b, R = *n*-Bu

Entry	R	Solvent / t (h)	% Conv (% yield)[a]
1	Ph	DME / 36	**1.10a**, 94% (-)
2	Ph	THF / 48	no reaction, 0 (-)
3	Ph	Toluene / 24	**1.10a**, 100% (75%)
4	Ph	DCE / 36	**1.10a**, 88 (-)
5	*n*-Bu	Toluene / 48	**1.10b**, 50 (22%)
6	*n*-Bu	Toluene / 18	**1.11,** 89 (53%)
7	TMS	Toluene / 36	complex mixture

[a]Isolated yield.

transmetallation by running reactions at lower temperatures still resulted in racemic mixtures and slightly lower yields (entry 3). Reactions run with chiral diene **L6** afforded the highest yield but no enantioenrichment of the chiral center was observed.

It was determined that the focus will be to improve the scope of alkynylations by preparing the reagents from the corresponding lithiated alkyne. Additionally, the conjugate addition of alkynyl Grignards to alkylidene Meldrum's acid derivatives had not been reported and therefore offered another alkyne source to be investigated. Gratifyingly, high yields were obtained for aryl, alkyl and TMS substituted acetylides using both Al and Grignard protocols (Table 1.5, entries 1–4). Ethyne was directly inserted using the corresponding commercially available Grignard affording propargylic all-carbon adduct **1.10g** in excellent yield (86%, entry 5); **1.10g** has the added advantage of having a terminal alkyne that can readily undergo further transformations. Propargyl and homopropargyl alcohols were also added in moderate to good yields without the need for protection and deprotection (entries 6–7). Adducts **1.10h** and **1.10i** have an alcohol moiety that gives access to further synthetic manipulations.

Due to the synthetic utility of TMS-acetylene over Ph-acetylene, where subsequent transformations are possible, the electronic nature of the aromatic moiety of benzylidene Meldrum's acid derivatives and the steric effects at the electrophilic β-position were examined using TMS-acetylene (Table 1.5, entries 8–24). The electronic character of the aromatic group did not have a significant effect on the overall reactivity where both electron donating and withdrawing substituents at either the *ortho* or *para*-positions resulted in high yields (entries 8–14). Detrimental effects were observed for *ortho* substituted derivatives (entries 15−18, 12). Poor reactivity had previously been observed for *ortho*-substituted 5-(1-arylalkylidene) Meldrum's acids in our enantioselective conjugate alkylation protocol.[5a,b] It is worth mentioning that *ortho* substitution with the smaller fluorine atom **1.4k** yielded the desired adduct **1.10s** (entry 17), albeit in modest yields, suggesting that steric properties governed the overall efficiency of the reaction. Expanding to other aromatic and heteroaromatic groups, such as naphthyl and furyl respectively, were also well tolerated (entries 18−20); again steric effects directed reactivity where the sterically crowded 1-naphthyl derivative **1.4l** did not afford any 1,4-adducts, whereas the 2-naphthyl derivative **1.4m** afforded adducts in excellent yields for both protocols (entries 18 and 19 respectively).

Table 1.4. Probing Effects of Cu^{II} and Rh^{I} Salts in the Conjugate Addition of Alkynylalanes to Alkylidene Meldrum's Acids
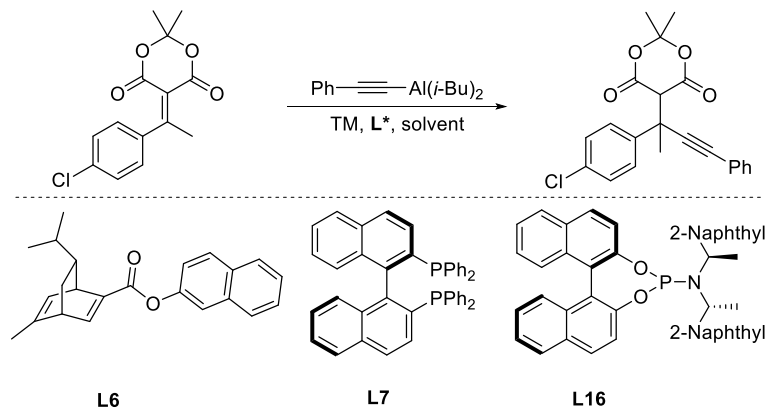
Entry	TM	L*	Solvent / Temp (°C) / Time (h)	% Yield^{a,b}
1	Cu(OTf)$_2$ (10 mol %)	**L16** (20 mol%)	Toluene / 0 °C to rt / 48 h	34
2	Cu(OTf)$_2$ (10 mol %)	**L16** (20 mol%)	DME / 0 °C to rt / 48 h	30
3	Cu(OTf)$_2$ (10 mol %)	**L16** (20 mol%)	DME / -60 to -45 °C / 48 h	28
4	[Rh(cod)Cl]$_2$ (10 mol% Rh)	**L7** (11 mol%)	Toluene / 0 °C to rt / 48 h	trace
5	[Rh(cod)Cl]$_2$ (10 mol% Rh)	**L7** (11 mol%)	DME / 0 °C to rt / 48 h	trace
6	[Rh(C$_2$H$_4$)$_2$Cl]$_2$ (10 mol% Rh) AgSbF$_6$ (10 mol%)	**L7** (11 mol%)	Toluene / 0 °C / 48 h	30
7	[Rh(C$_2$H$_4$)$_2$Cl]$_2$ (5 mol% Rh) AgSbF$_6$ (5 mol%)	**L6** (7 mol %)	Toluene / 0 °C / 48 h	89

^{a}Isolated yield. ^{b}Racemic mixtures determined by HPLC using a chiral Chiralcel AD-H column (250 x 4.6 mm) with iPrOH:hexane solvent mixtures as eluent.

Increasing the steric bulk of the alkyl moiety of the electrophilic acceptor from Me to the *i*-Pr and *c*-Hex group resulted in lower yields for alkynylalanes than for alkynyl Grignards (Table 1.5, entries 21−23). The extra steric bulk around the Al from Me groups likely interacts by steric repulsion with the larger groups at the electrophilic site resulting in the decreased reactivity. Greatest yields were achieved with an aryl-ester group at the electrophilic center (Table 1.5, entry 24). It is noteworthy that with respect to alkynylalanes, the alkynyl moiety was exclusively delivered where no Me transfer was observed for all cases.

Table 1.5. Optimized Conditions for Conjugate Alkynylation

R³≡M, Toluene, 0 °C to rt, 16h, M = AlMe₂, MgCl; **1.4** → **1.10**
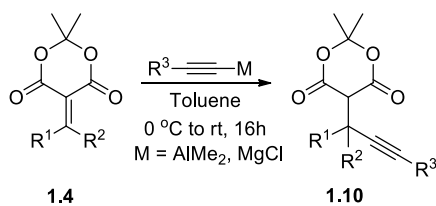
Entry	Alkylidene (R¹/R²)	Product (R³)	yield (%)[a] (M = AlMe₂)	yield (%)[a,b] (M = MgCl)
1	Ph / Me (**1.4c**)	Ph (**1.10c**)	77	81
2	Ph / Me (**1.4c**)	n-Bu (**1.10d**)	75	85
3	Ph / Me (**1.4c**)	TMS (**1.10e**)	83	85
4	Ph / Me (**1.4c**)	c-Hex (**1.10f**)	87	85
5	Ph / Me (**1.4c**)	H (**1.10g**)	N/A	86
6	Ph / Me (**1.4c**)	CH_2OH (**1.10h**)	72[c]	54[c]
7	Ph / Me (**1.4c**)	CH_2CH_2OH (**1.10i**)	69[c]	50[c]
8	4-MeC₆H₄ / Me (**1.4d**)	TMS (**1.10j**)	77	82
9	4-(MeO)C₆H₄ / Me (**1.4e**)	TMS (**1.10k**)	91	92
10	4-FC₆H₄ / Me (**1.4a**)	TMS (**1.10l**)	75	84
11	4-ClC₆H₄ / Me (**1.4b**)	TMS (**1.10m**)	85	83
12	4-(F₃C)C₆H₄ / Me (**1.4f**)	TMS (**1.10n**)	88	89
13	3-MeC₆H₄ / Me (**1.4ig**)	TMS (**1.10o**)	82	85
14	3-(MeO)C₆H₄ / Me (**1.4h**)	TMS (**1.10p**)	84	76
15	2-ClC₆H₄ / Me (**1.4i**)	TMS (**1.10q**)	NR	NR
16	2-(BnO)C₆H₄ / Me (**1.4j**)	TMS (**1.10r**)	NR	NR
17	2-FC₆H₄ / Me (**1.4k**)	TMS (**1.10s**)	39	27
18	1-naphthyl / Me (**1.4l**)	TMS (**1.10t**)	NR	NR
19	2-naphthyl / Me (**1.4m**)	TMS (**1.10u**)	76	84
20	2-furyl / Me (**1.4n**)	TMS (**1.10v**)	72	74
21	Ph / i-Pr (**1.4o**)	TMS (**1.10w**)	66	83
22	Ph / c-Hex (**1.4p**)	TMS (**1.10x**)	64	77
23	Ph / cyclopropyl (**1.4q**)	TMS (**1.10y**)	69	81
24	Ph / CO_2Me (**1.4r**)	TMS (**1.10z**)	94	92

[a]Isolated yield. [b]THF as the solvent furnished comparable results. [c]4 equiv were used.

Indenylidene Meldrum's acids **1.12** have been shown to be excellent electrophilic acceptors in conjugate alkylation reactions affording all-carbon quaternary centers.[5a-d] The

conjugate alkynylation protocols were applied to indenylidene Meldrum's acid **1.12** and adducts **1.13** were isolated good yields for both methods, Scheme 1.27.

Scheme 1.27. Conjugate Alkynylation of Indenylidene Meldrum's Acid **1.12**
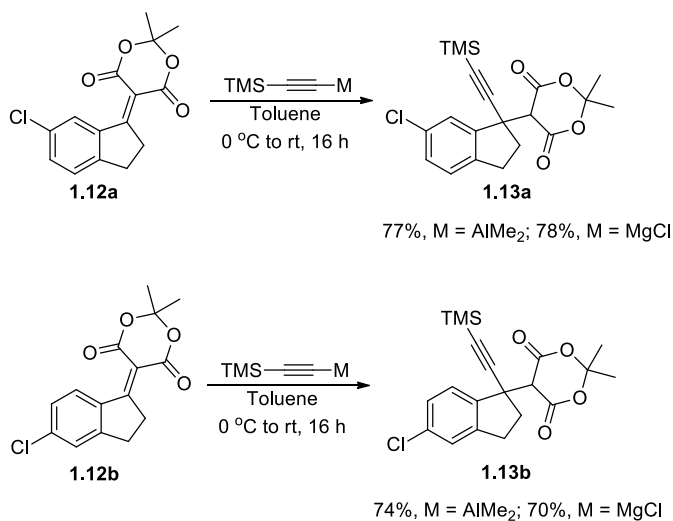
Single crystals of Meldrum's acid adduct **1.10aa** were obtained and the X-ray structure is shown in Figure 1.3. The Meldrum's acid moiety adopts a chair-like conformation with the larger quaternary center at the pseudo-axial position. Pertinent bond lengths are also listed in Figure 3, where an elongated $C(sp^3)$–$C(sp^3)$ bond length is observed between the Meldrum's acid moiety and the benzylic carbon (C5–C11, Figure 1.3); whereas typical $C(sp^3)$–$C(sp^3)$ and $C(sp)$–$C(sp)$ bond lengths are observed throughout the rest of the molecule.

Interestingly, a comparison between Meldrum's acid derivatives possessing a secondary, tertiary and quaternary benzylic centers show an increase in bond length with increasing substitution between C–C atoms of Meldrum's acid and the benzylic center (Figure 1.4). [41] This trend coincides with the reactivity observed for the Lewis acid catalyzed nucleophilic substitution of Meldrum's acid derivatives methodology developed in our group.[38] In order to initiate C–C bond cleavage between the benzylic center and Meldrum's acid moiety, a quaternary benzylic center or dibenzylic tertiary center was required.[38] An increase in bond length with an increase in substitution would allow for a more facile bond cleavage; since propargylic adduct **1.10aa** displays a longer bond length than the alkyl substituted quaternary

24

centered analogous, these compounds may be interesting substrates for unactivated C–C bond cleavage investigations.

Bond Length (Å)
C5-C11 (1.60)
C11-C19 (1.54)
C20-C21 (1.19)
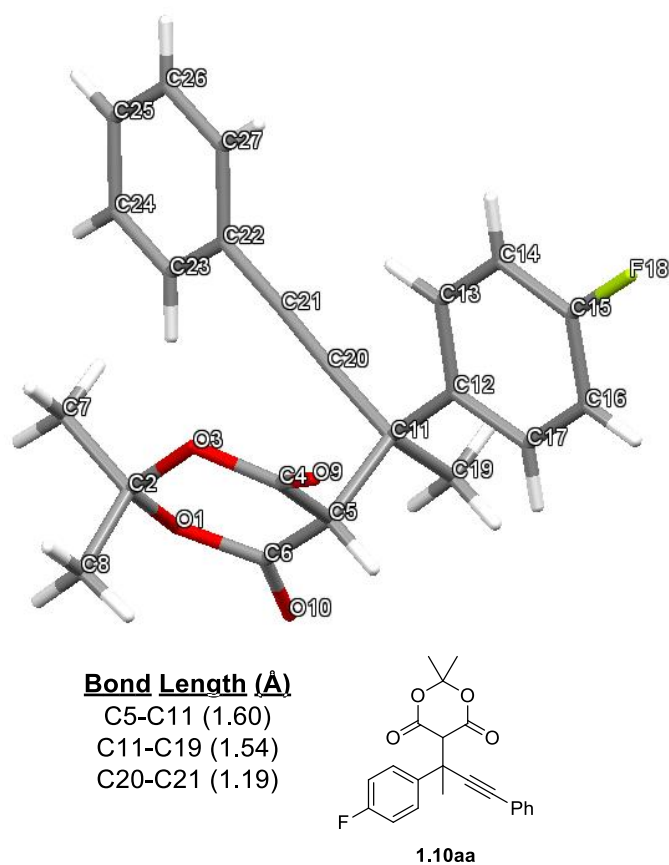
1.10aa

Figure 1.3. X-Ray Structure of Meldrum's Acid **1.10aa**

1.54 Å   1.55 Å   1.56 Å   1.56-1.68 Å
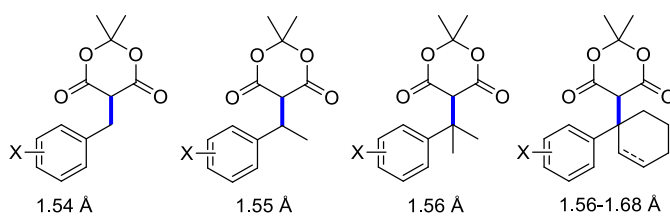
Figure 1.4. Comparison of Average C–C Bond Lengths of Meldrum's Acid Derivatives[41]

Propargylic Meldrum's acid adducts can serve as convenient building blocks. For example, **1.10g** can be hydrolyzed to the corresponding acid **1.14** that is not accessible through other methodologies. In combination with the described conjugate alkynylation protocols, up

to 5 different sites can undergo derivatization or subsequent transformations as shown in Scheme 1.28. Furthermore, in the following chapter the transformation of propargylic Meldrum's acid derivatives **1.10** to complex *γ*-butyrolactones will be discussed.

Scheme 1.28. Hydrolysis of Meldrum's Acid **1.10g** to Acid **1.14**
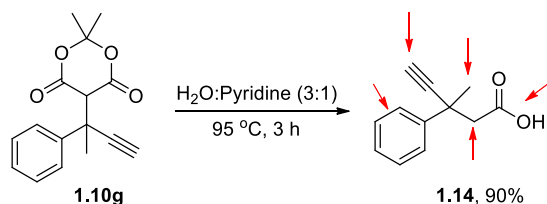
1.4. Summary
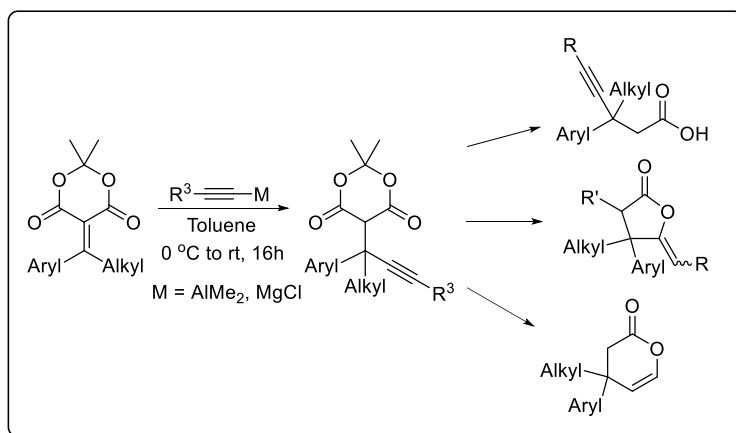
Figure 1.5. Developed Conditions for Conjugate Alkynylation

     In summary, the first general strategy for the formation of propargylic all-carbon quaternary centers has been described. Alkynylalanes and Grignards were used as nucleophilic sources, and the versatility of alkylidene Meldrum's acid derivatives as Michael acceptors has been expanded to access quaternary centers under mild reaction condition. Benzylic centers with electron rich and poor substituents are well tolerated while a wide range of substituted terminal alkynes can be inserted to access these all-carbon quaternary centers. Enantioselective conditions using Cu(II) and Rh(I) catalyst were attempted but resulted in sluggish reactivity.

Although analogous strategies using arylalanes and Grignards did afford the desired 1,4-adducts, these protocols suffer from significant Me transfer and low yields. Further investigations into transition metal, ligands and reaction conditions are required to develop a practical protocol.

1.5. Future Work

Developing catalytic enantioselective conditions for the conjugate alkynylation of alkylidene Meldrum's acid derivatives will address the absence of methodologies available to access enantioenriched propargylic all-carbon centers. The utility of such a methodology would undoubtedly be of great value to synthetic chemists expanding on an already diverse synthetic tool box. A more rigorous screening of transition metals and ligands is necessary to obtain enantioenriched propargylic quaternary centers. Based on the success of preparing tertiary propargylic centers, Ni(II), Cu(I/II), Rh(I) or Pd(II) catalyst would be a practical starting point. Additionally, while the use of alkynylalanes and Grignards were an effective nucleophilic source, even at very low temperatures; alkynylzinc or boranes may offer less reactive and therefore more controllable delivery of the alkynyl group.

1.6. Experimental
General Considerations
Reactions

All reactions were performed in flame-dried glassware under an argon atmosphere unless otherwise stated. Commercial grade reagents were used without further purification except as indicated below. Toluene, DMF and pyridine were dried by distilling over CaH_2 and stored in a Schlenk flask under argon. Et_2O, CH_2Cl_2, THF were obtained from a solvent purification system based on the published procedure.[42] MeOH was heated to reflux over Mg powder overnight and then distilled, and stored over 3 Å molecular sieves in a Schlenk flask. Phenylacetylene, 1-hexyne, cyclohexylacetylene, and trimethylsilylacetylene were purchased

and distilled over CaH$_2$ prior to use. CuCl was purified by reprecipitation from a conc. HCl aqueous solution and dried under vacuum, and stored in a nitrogen filled glovebox. Known alkylidene Meldrum's acids **1.4a–j, l-o,** and **1.4r** were prepared by Knoevenagel condensation of the corresponding ketone with Meldrum's acid.[5]

Reactions were monitored by thin-layer chromatography and visualized by UV quenching and/or staining with cerium ammonium molybdate. Flash chromatography was performed using 230-400 mesh silica gel.

Characterization:

^{1}H and ^{13}C NMR spectra for all compounds were obtained in CDCl$_3$ at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual CHCl$_3$ (7.24 ppm) and carbon spectra were calibrated to CDCl$_3$ (77.0 ppm). Carbon multiplicities (C, CH, CH$_2$, CH$_3$) were determined by combined DEPT 90/135 experiments. ^{19}F NMR spectra were recorded with ^{1}H decoupling in CDCl$_3$ referenced to TFA (-76.5 ppm). Chiral HPLC analyses were performed using a Chiralcel AD-H column (250 x 4.6 mm) with iPrOH:hexane solvent mixtures as eluent. High resolution mass spectrometry was performed at the University of Waterloo and the University of Toronto Mass Spectrometry facilities. Melting points are uncorrected.

General Procedure A: Preparation of Alkylidene Meldrum's Acids 1.4a-r

All alkylidene Meldrum's acids were prepared by the Knoevenagel condensation of Meldrum's acid with the corresponding ketones using the method reported by Brown and coworkers.[43] In general, a solution of TiCl$_4$ (2.1 equiv) in CH$_2$Cl$_2$ (3 M relative to ketone) was added dropwise to dry THF at 0 °C under nitrogen resulting in a yellow suspension. A solution containing both the ketone (1.1 equiv) and Meldrum's acid (1.0 equiv) in dry THF (0.7 M relative to ketone) was added slowly to the TiCl$_4$•THF complex. Subsequent rinses with THF (2×) of the flask containing the solution of ketone and Meldrum's acid was added to the reaction mixture. Pyridine (5.0 equiv) was then slowly added to the reaction mixture at 0 °C. The reaction was then allowed to warm up slowly to room temperature and stirred for 18 h.

The reaction mixture was cooled back down to 0 °C and quenched upon the addition of water, followed by dilution with ethyl acetate. The mixture was allowed to stir at room temperature until the solid had fully dissolved. The layers were partitioned, and the aqueous layer was extracted was ethyl acetate (2×). Combined organic fractions were washed with NaHCO$_3$ (2×), brine (1×), dried over MgSO$_4$, filtered and concentrated. Recrystallization from a saturated solution in MeOH afforded the pure alkylidene Meldrum's acids.

Characterization data for known compounds not fully described in the literature are provided.

5-(1-(2-Fluorophenyl)-3-(trimethylsilyl)prop-2-ynylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.4k)
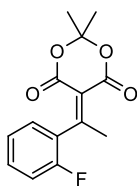
Prepared according to General Procedure A by the Knoevenagel condensation of 2-fluoroacetophenone (8.00 mL, 65.8 mmol, 1.1 equiv) and Meldrum's acid (10.8 g, 59.9 mmol, 1.0 equiv). Recrystallization from MeOH afforded **1.4k** (10.9 g, 69% yield) as beige crystals. M.p. 113-115 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.38-7.34 (m, 1H), 7.23-7.20 (m, 2H), 7.09-7.02 (m, 1H), 2.69 (s, 3H), 1.79 (broad s, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) 165.3 (C), 160.8 (C), 160.2 (C), 156.8 (d, J = 244.6 Hz, C), 130.9 (d, J = 8.4 Hz, CH), 129.2 (d, J = 15.2 Hz, C), 127.9 (d, J = 2.6 Hz, CH), 124.5 (d, J = 3.2 Hz, CH), 118.8 (C), 115.8 (d, J = 21.9 Hz, CH), 104.2 (C), 27.3 (m, CH$_3$), 25.6 (CH$_3$); HRMS (DART) m/z calcd for C$_{14}$H$_{12}$O$_4$F (M)$^-$: 263.07251 Found: 263.07255 .

5-(Cyclohexyl(phenyl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.4p)
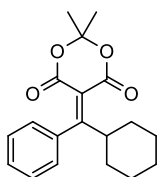
Prepared according to General Procedure A by the Knoevenagel condensation of Meldrum's acid with benzoylcyclohexane (4.71 g, 25.0 mmol, 1.1 equiv) and Meldrum's acid (3.27 g, 22.7 mmol, 1.0 equiv). Recrystallization from MeOH afforded **1.4p** (3.49 g, 49% yield) as needle-shaped colourless crystals. M.p. 152-154 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.37–7.35 (m, 3H), 7.00–6.97 (m, 2H), 3.66 (app t, J = 12.0 Hz, 1H), 1.78 (s, 6H), 1.74–1.64 (m, 5H), 1.44–1.31 (m, 2H), 1.18–0.97 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 179.2 (C), 160.8 (C), 160.2 (C), 137.6 (C), 127.9 (CH$_3$), 127.8 (CH$_3$), 125.4

(CH$_3$), 118.0 (C), 103.8 (C), 43.6 (CH), 30.7 (CH$_2$), 27.3 (CH$_3$), 25.7 (CH$_2$), 25.5 (CH$_2$); HRMS (DART) m/z calcd for C$_{19}$H$_{26}$NO$_4$ (M + NH$_4$)$^+$: 332.18563 Found: 332.18560.

5-(Cyclopropyl(phenyl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.4q)
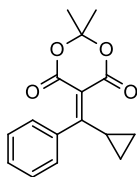
Prepared according to General Procedure A by the Knoevenagel condensation of Meldrum's acid with benzoylcyclopropane (3.38 mL, 24.5 mmol, 1.1 equiv) and Meldrum's acid (3.21 g, 22.3 mmol, 1.0 equiv). Recrystallization from MeOH afforded **1.4q** (4.79 g, 79% yield) as needle-shaped colourless crystals. M.p. 166-168 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.35–7.33 (m, 3H), 6.95–6.92 (m, 2H), 3.45–3.40 (m, 1H), 1.77 (s, 6H), 1.14–1.08 (m, 2H), 0.78–0.73 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) 179.5 (C), 162.0 (C), 159.9 (C), 134.6 (C), 128.2 (CH), 127.8 (CH), 126.5 (CH), 116.8 (C), 103.6 (C), 27.2 (CH$_3$), 17.8 (CH), 10.2 (CH$_2$); HRMS (DART) m/z calcd for C$_{16}$H$_{20}$NO$_4$ (M + NH$_4$)$^+$: 290.13868 Found: 290.13854.

Preparation of Arylalanes: (PhAlMe$_2$)

To a solution of PhLi (1.0 mmol, 1.9M in n-Bu$_2$O) at 0 °C was added a solution of Me$_2$AlCl (1.0 mmol, 1.0M in hexanes) dropwise and stirred for 30 min at this temperature. When supernatant was used, salts were allowed to precipitate over a 30 min period at 0 °C, after which time the supernatant can be cannulated/syringed as needed.

Note: PhMgCl can be used in the same manner as PhLi and identical results were obtained.

Conjugate Arylation of Alkylidene Meldrum's Acids with PhAlMe$_2$

A flame-dried flask flushed with argon, equipped with a magnetic stirrer and a septum, was charged with the copper salt (0.2 equiv) and DME (1.0 mL) and the resulting mixture was stirred at rt for 30 min. The mixture was then cooled to -40 °C and a solution of PhAlMe$_2$ (2.1 equiv) was added and stirred at this temperature for 10 min. A premixed solution of alkylidene Meldrum's acid (0.50 mmol, 1.0 equiv) in DME (5.0 mL) was then added dropwise to the copper-alane solution. The mixture was gradually warmed to rt. After the indicated time, the reaction was cooled back down in an ice-bath and quenched with 5% HCl (5 mL). The solution

was then transferred into a separatory funnel, and the flask was rinsed with EtOAc (2× 5 mL) and 5% HCl (5 mL). The layers were partitioned and the aqueous layer was extracted with EtOAc (3×) and combined organic layers were washed with brine (2×), dried over anhydrous MgSO₄, filtered and concentrated. After analysis of the crude reaction mixture by ^{1}H NMR the overall conversion was determined based on the ratio of **1.4**:**1.5**:acetophenone.

General Procedure B – Copper Catalyzed Conjugate Addition of Aryl Grignards to Alkylidene Meldrum`s Acid Derivatives

Procedure is based on a method reported by Hung et al.;[44] A flame-dried flask flushed with argon, equipped with a magnetic stirrer and a septum, was charged with a solution of PhMgCl (2.1 equiv, 2.0M in THF) at -5 °C, followed by the addition CuCl (0.1 equiv). A solution of the alkylidene Meldrum's acid **1.4** (1.0 mmol, 1.0 equiv) in THF (10 mL) was subsequently added dropwise. The resulting mixture was allowed to gradually warm to rt and stirred for 6 h. The reaction was quenched by cooling back down over an ice-salt bath, and slowly adding 5% HCl and EtOAc. The layers were partitioned and the aqueous layer was extracted with EtOAc (3×). Combined organic fractions were washed with brine, dried over MgSO₄ and concentrated. The crude residue was purified by flash chromatography on silica gel using a gradient of hexanes and EtOAc to isolated the desired product.

5-(1-(4-Fluorophenyl)-1-phenylethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.5a)
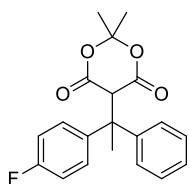
Prepared according to General Procedure B. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.5a** (61 mg, 18% yield) as a waxy beige solid. ^{1}H NMR (300 MHz, CDCl₃) 7.32-7.15 (m, 9H), 4.54 (s, 1H), 2.03 (s, 3H), 1.64 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, CDCl₃) 162.7 (C), 162.4 (C), 159.9 (d, J = 243.9 Hz, C), 140.0 (C), 137.1 (C), 129.1 (CH), 128.6 (CH), 128.4 (CH), 127.1(CH), 115.3 (d, J = 20.7 Hz, CH), 105.1 (C), 55.1 (CH), 49.6 (C), 31.3 (CH₃), 28.1 (CH₃), 27.5 (CH₃). MS data could not be collected on these samples.

5-(1-(4-Chlorophenyl)-1-phenylethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.5b)
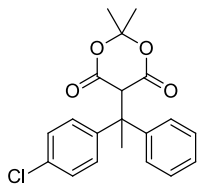
Prepared according to General Procedure B. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.5b** (54 mg, 15% yield) as a white solid. ^{1}H NMR (300 MHz, CDCl3) 7.32-7.15 (m, 9H), 4.54 (s, 1H), 2.03 (s, 3H), 1.64 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, CDCl3). 164.2 (C), 164.0 (C), 140.3 (C), 138.4 (C), 132.7 (C), 130.6 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 127.3 (CH), 105.2 (C), 53.4 (CH), 49.7 (C), 29.3 (CH$_3$), 28.1 (CH$_3$), 27.4 (CH$_3$). MS data could not be collected on these samples.

General Procedure C – Conjugate Alkynylation of Alkylidene Meldrum's Acids 1.4b with Alkynylalane: (*i*-Bu)$_2$Al–CCR

To a flame-dried round bottom flask equipped with a stir bar and septum, was added *i*-Bu$_2$AlH (3.0 equiv, 1.0M in hexanes) and triethylamine (0.15 equiv), and the resulting mixture was cooled to 0 °C. To this solution was added the alkyne (4.5 equiv) dropwise and stirred at this temperature for 3 h before letting it warm up to rt over 9 h. The resulting alkynylalane reagent was used without further purification.

A solution of the alkynylalane was cooled to 0 °C and a solution of **1.4b** (0.40 mmol, 1.0 equiv) in toluene (4.0 mL) was added dropwise over ~30 min, and the mixture was allowed to gradually warm to rt. Reaction progress was monitored by working up aliquots every 6 h, where reaction was typically complete within 24 h. The reaction was quenched upon the slow addition of a saturated solution of sodium potassium tartrate (5.0 mL) and stirred for 10 min. The solution was poured into a separatory funnel, and the flask was rinsed with EtOAc (2 × 5 mL) and 5% HCl (5 mL). The layers were partitioned and the aqueous layer was extracted with EtOAc (3×) and combined organic layers were washed with brine (2×), dried over anhydrous MgSO$_4$, filtered and concentrated. After analysis of the crude reaction mixture by ^{1}H NMR, the residue was dissolved in CH$_2$Cl$_2$ and concentrated onto a small amount of silica gel. The silica gel dried with the crude product was then loaded to the top of a packed silica gel column, and the products were isolated by flash column chromatography using the indicated solvent gradient.

General Procedure D – Preparation of Alkynylalane Reagents: Me₂Al–CCR

A procedure reported by Corey and coworkers was adapted:[19] A flame-dried round bottom flask flushed with argon and equipped with a magnetic stirrer was charged with the alkyne (1.4 mmol, 1 equiv) and THF (1.0 M relative to alkyne), and cooled to -60 °C. To this solution, 2.5 M *n*-BuLi in hexanes (1.4 mmol, 1 equiv) was added dropwise and stirred for 30 min followed by the dropwise addition of 1.0 M Me₂AlCl in hexanes (1.4 mmol, 1 equiv). The reaction mixture was gradually allowed to warm to 0 °C and then stirred for 4 h at this temperature. The solvent was then removed in vacuo and the residue was redissolved in a toluene-Et₂O mixture (6:1, 1.3 M relative to alkyne) resulting in a suspension. The supernatant was carefully cannulated leaving the precipitate behind and used in further reactions below. It should be noted that identical results are obtained in the presence and absence of the LiCl salts generated. Thus, an alternate approach preparing the alkynylaluminum reagents directly in Et₂O and then diluting with toluene (6X relative to Et₂O) gave identical results to the method given above.

General Procedure E – Preparation of Alkynyl Grignard Reagents:

A flame-dried round bottom flask flushed with argon, equipped with a magnetic stirrer and a septum, was charged with the alkyne (1.4 mmol, 1 equiv) and THF (0.5 M relative to alkyne). This solution was cooled to 0 °C followed by the dropwise addition of 2.0 M *i*-PrMgCl in THF (1.4 mmol, 1 equiv) and stirred at this temperature for 15 min. The reaction mixture was then removed from the ice bath and stirred for an additional 2 h to form the alkynyl Grignard that was used in further reactions.

General Procedure F – Alkynylation of Alkylidene Meldrum's Acids with AlkynylAlMe₂:
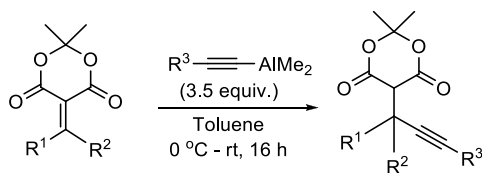
A flame-dried round bottom flask flushed with argon, equipped with a magnetic stirrer and a septum, was charged with alkylidene Meldrum's acid (0.40 mmol, 1.0 equiv) and toluene (2.0 mL). The mixture was stirred at ambient temperature for 10 min. The solution was then cooled to 0 °C followed by the dropwise addition of the alkynylalane solution (1.4 mmol, 3.5 equiv, prepared by General Procedure D). The reaction was gradually warmed to room temperature and stirred for 16 h. The reaction was quenched upon the slow addition of a saturated solution of sodium potassium tartrate (5.0 mL) and stirred for 10 min. The solution was poured into a separatory funnel, and the flask was rinsed with EtOAc (2× 5 mL) and 5% HCl (5 mL). The layers were partitioned and the aqueous layer was extracted with EtOAc (3×) and combined organic layers were washed with brine (2×), dried over anhydrous MgSO₄, filtered and concentrated. After analysis of the crude reaction mixture by ^{1}H NMR, the residue was dissolved in CH₂Cl₂ and concentrated onto a small amount of silica gel. The silica gel dried with the crude product was then loaded to the top of a packed silica gel column, and the products were isolated by flash column chromatography using the indicated solvent gradient.

General Procedure G - Alkynylation of Alkylidene Meldrum's Acids with Alkynyl Grignards
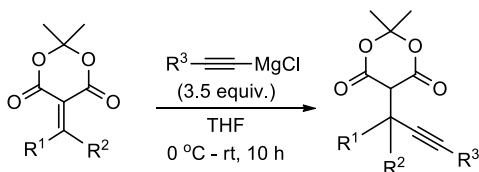
A flame-dried flask, purged with argon and equipped with a magnetic stirrer and septum, charged with alkylidene Meldrum's acid (0.40 mmol, 1.0 equiv) and THF (0.4 M) was cooled using an ice bath followed by the dropwise addition of the alkynyl Grignard. The reaction mixture was gradually warmed to room temperature and stirred for 10 h. The reaction was quenched upon the addition of deionized water and stirred for 10 min. The contents were poured into a separatory funnel, and the flask was rinsed with EtOAc (2 × 5 mL) and 5% HCl (5 mL). The aqueous layer was extracted with EtOAc (3×), and combined organic layers were washed with brine (2×), dried over anhydrous MgSO₄, filtered and concentrated. After analysis of the crude reaction mixture by ^{1}H NMR, the residue was dissolved in CH₂Cl₂ and concentrated onto a small amount of silica gel. The silica gel dried with the crude product was

then loaded to the top of a packed silica gel column and the products were isolated by flash column chromatography using the indicated solvent gradient.

5-(2-(4-Chlorophenyl)-4-phenylbut-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10a)
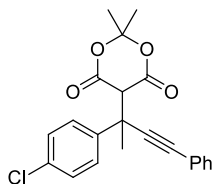
Prepared according General Procedure C. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10a** (114 mg, 75%) as a waxy white solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.57 (d, J = 8.5 Hz, 2H), 7.49-7.46 (dd, J = 7.6, 6.6 Hz, 2H), 7.34-7.30 (m, 5H), 3.91 (s, 1H), 2.01 (s, 3H), 1.70 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 162.7 (C), 162.5 (C), 140.8 (C), 133.3 (C), 131.7 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 122.3 (C), 105.2 (C), 89.9 (C), 87.8 (C), 56.8 (CH), 42.9 (C), 29.0 (CH$_3$), 28.5 (CH$_3$), 27. 9 (CH$_3$); HRMS (DART) m/z calcd for C$_{22}$H$_{23}$ClNO$_4$ (M + NH$_4$)$^+$: 400.13156. Found: 400.13167.

5-(2-(4-Chlorophenyl)oct-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10b)
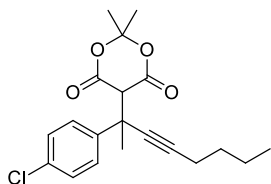
Prepared according General Procedure C. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10b** (31 mg, 22%) as a waxy beige solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.53 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 3.81 (s, 1H), 2.25 (t, J = 6.7 Hz, 2H), 1.91 (s, 3H), 1.66 (s, 3H), 1.56-1.38 (m, 7H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.1 (C), 162.8 (C), 141.0 (C), 132.8 (C), 128.3 (CH), 127.9 (CH), 105.1 (C), 86.9 (C), 80.9 (C), 56.9 (CH), 43.1 (C), 30.1 (CH$_2$), 30.0 (CH$_3$), 29.1 (CH$_3$), 27.8 (CH$_3$), 21.9 (CH$_2$), 18.4 (CH$_2$), 13.5 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{27}$^{35}ClNO$_4$ (M + NH$_4$)$^+$: 380.16286. Found: 380.16297.

5-(2,4-Diphenylbut-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10c)

Prepared according to general procedure F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10c** (107 mg, 77% yield by procedure F; 113 mg, 81% yield by procedure G) as an off white solid. M.p. 61-63 °C; ^{1}H NMR (300

MHz, CDCl$_3$) 7.61 (d, J = 7.6 Hz, 2H), 7.50-7.47 (m, 2H), 7.37-7.28 (m, 6H), 3.91 (s, 1H), 2.04 (s, 3H), 1.68 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.1 (C), 162.8 (C), 141.9 (C), 131.8 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 126.5 (CH), 122.6 (C), 105.3 (C), 90.4 (C), 86.8 (C), 57.1 (CH), 43.7 (C), 29.1 (CH$_3$), 29.0 (CH$_3$), 27.8 (CH$_3$); HRMS (DART) m/z calcd for C$_{22}$H$_{19}$O$_4$ (M)$^-$: 347.12888. Found: 347.12890.

2,2-Dimethyl-5-(2-phenyloct-3-yn-2-yl)-1,3-dioxane-4,6-dione (1.10d)

Prepared according to General Procedure F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10d** (99 mg, 75% yield by procedure F; 111 mg, 85% by procedure G) as a white solid. M.p. 77-79 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.53 (d, J = 7.5 Hz, 2H), 7.36-7.24 (m, 3H), 3.79 (s, 1H), 2.27 (t, J = 6.9 Hz, 2H), 1.90 (s, 3H), 1.66 (s, 3H), 1.56-1.38 (m, 7H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.4 (C), 162.9 (C), 142.7 (C), 128.3 (CH), 127.3 (CH), 126.4 (CH), 105.1 (C), 87.5 (C), 80.9 (C), 57.2 (CH), 43.4 (C), 30.7 (CH$_2$), 29.9 (CH$_3$), 29.1 (CH$_3$), 27.9 (CH$_3$), 21.9 (CH$_2$), 18.6 (CH$_2$), 13.6 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{28}$N$_1$O$_4$ (M + NH$_4$)$^+$: 346.20183. Found: 346.20249.

2,2-Dimethyl-5-(2-phenyl-4-(trimethylsilyl)but-3-yn-2-yl)-1,3-dioxane-4,6-dione (1.10e)
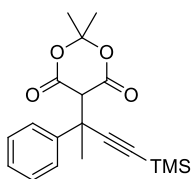
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10e** (114 mg, 83% yield by procedure D; 117 mg, 85% yield by procedure E) as an off white solid. M.p. 87-89 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.55 (d, J = 7.2 Hz, 2H), 7.37–7.24 (m, 3H), 3.82 (s, 1H), 1.94 (s, 3H), 1.66 (s, 3H), 1.54 (s, 3H), 0.21 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.0 (C), 162.7 (C), 141.8 (C), 128.3 (CH), 127.4 (CH), 126.4 (CH), 106.6 (C), 105.1 (C), 91.5 (C), 56.9 (CH), 43.8 (C), 29.4 (CH$_3$), 29.0 (CH$_3$), 27.9 (CH$_3$), -0.14 (CH$_3$); HRMS (DART) m/z calcd for C$_{19}$H$_{23}$O$_4$Si (M)$^-$: 343.13711 Found: 343.13734.

5-(4-Cyclohexyl-2-phenylbut-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10f)

Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10f** (123 mg, 87% yield by procedure D; 120 mg, 85% yield by procedure E) as a white solid. M.p. 69-72 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.55 (d, J = 7.4 Hz, 2H), 7.35–7.22 (m, 3H), 3.78 (s, 1H), 2.50–2.44 (m, 1H), 1.91 (s, 3H), 1.81–1.78 (broad m, 2H), 1.72–1.70 (broad m, 2H), 1.65 (s, 3H), 1.51–1.49 (m, 6H), 1.36–1.28 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.4 (C), 163.0 (C), 142.7 (C), 128.2 (CH), 127.3 (CH), 126.5 (CH), 105.1 (C), 91.6 (C), 81.0 (C), 57.3 (CH), 43.4 (CH), 32.5 (CH$_2$), 30.0 (CH$_3$), 29.1 (CH), 29.0 (CH$_3$), 27.8 (CH$_3$), 25.9 (CH$_2$), 24.7 (CH$_2$); HRMS (DART) m/z calcd for C$_{22}$H$_{25}$O$_4$ (M)$^-$: 353.17583. Found: 353.17606.

2,2-Dimethyl-5-(2-phenylbut-3-yn-2-yl)-1,3-dioxane-4,6-dione (1.10g)
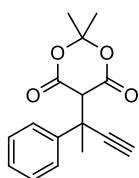
A flame-dried round-bottom flask flushed with argon and equipped with a stirbar was loaded with **1.4c** (98 mg, 0.40 mmol, 1.0 equiv) and THF (2.0 mL) and cooled to 0 °C. Then, a solution of 0.5 M ethynylmagnesium bromide (2.4 mL, 1.2 mmol, 3.0 equiv) in THF was added dropwise, and the solution was gradually warmed to rt. The reaction mixture was allowed to stir for 10 h at ambient temperature, and was quenched upon the addition of deionized water and stirred for 10 min. The solution was poured into a separatory funnel, and the flask was rinsed with EtOAc (2 × 5 mL) and 5% HCl (5 mL). The aqueous layer was extracted with EtOAc (3×), and combined organic layers were washed with brine (2×), dried over anhydrous MgSO$_4$, filtered and concentrated. After analysis of the crude reaction mixture by ^{1}H NMR, the residue was dissolved in CH$_2$Cl$_2$ and concentrated onto a small amount of silica gel. The silica gel dried with the crude product was loaded to the top of a packed silica gel column and the products were isolated by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10g** as an off white solid (91 mg, 86% yield).

Alternatively, **1.10g** was also prepared by the following procedure: A flame-dried round-bottom flask equipped with a magnetic stirbar was loaded with **1.10e** (0.6 mmol, 1.0

equiv) and THF (100 mL, 0.006 M) and cooled in an ice bath. A 1.0 M tetra-*n*-butylammonium fluoride solution (3.0 mL, 3.0 mmol, 5 equiv) was subsequently added to the solution of **1.10e**. The mixture was allowed to warm to room temperature and continued to stir for 2 h. The crude mixture was diluted with Et_2O, and the organic phase was washed with saturated aqueous NH_4Cl (20 mL), followed by water (3 X 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo resulting in yellow oil. Purification by flash chromatography on silica gel eluting with a gradient from 1:3 EtOAc:hexanes afforded **1.10g** (132 mg, 81% yield) as an off white solid. M.p. 66-70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.55 (d, *J* = 7.5 Hz, 2H), 7.36-7.26 (m, 3H), 3.95 (s, 1H), 2.59 (s, 1H), 1.97 (s, 3H), 1.70 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 162.5 (C), 162.2 (C), 141.6 (C), 128.4 (CH), 127.4 (CH), 126.2 (CH), 105.1 (C), 85.2 (C), 74.3 (CH), 56.6 (CH), 42.2 (C), 28.9 (CH_3), 28.1 (CH_3), 28.0 (CH_3); HRMS (DART) *m/z* calcd for $C_{16}H_{20}N_1O_4$ $(M + NH_4)^+$: 290.13923. Found: 290.13979.

5-(5-Hydroxy-2-phenylpent-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10h)
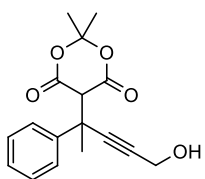
Prepared according to modified General Procedure F: A flame-dried round bottom flask flushed with argon and equipped with a magnetic stirrer was charged with propargyl alcohol (0.10 mL, 1.72 mmol, 4.0 equiv) in Et_2O (1.7 mL, 1.0 M) and cooled to -60 °C. To this solution, 2.5 M *n*BuLi in hexanes (1.37 mL, 3.44 mmol, 8.0 equiv) was added dropwise and stirred for 30 min followed by the dropwise addition of 1.0 M Me_2AlCl in hexanes (3.44 mL, 3.44 mmol, 8.0 equiv). The reaction mixture was gradually allowed to warm to 0 °C over 30 min and then stirred for 4 h at this temperature. The solution was diluted with toluene (10 mL) and subsequently added dropwise to a solution of **1.4c** (106 mg, 0.43 mmol, 1.0 equiv) in toluene (2.0 mL) at 0 °C. The reaction mixture was gradually warmed to rt and allowed to stir for 16 h. The reaction was quenched upon the addition of a saturated solution of sodium potassium tartrate (5.0 mL) and stirred for 10 min. The mixture was poured into a separatory funnel, and the flask was rinsed with EtOAc (2 × 5 mL) and 5% HCl. The layers were partitioned and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine (2×), dried over anhydrous $MgSO_4$, filtered and concentrated. After analysis of the crude reaction mixture by ^{1}H NMR, the residue was dissolved in CH_2Cl_2 and concentrated onto a small amount of

silica gel. The silica gel dried with the crude product was then loaded to the top of a packed silica gel column and the products were isolated by flash column chromatography eluting with 1:2 EtOAc:hexanes that afforded **1.10h** (93 mg, 72% yield) as an off white solid.

Similarly, a modified General Procedure of G: A flame-dried round-bottom flask flushed with argon, equipped with a magnetic stirrer and a septum, was charged with propargyl alcohol (0.10 mL, 1.72 mmol, 4.0 equiv) and THF (3.4 mL, 0.5 M) and cooled to 0 °C. Then, 2.0 M *i*-PrMgCl in THF (1.72 mL, 3.44 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred and gradually warmed up to rt over 2 h. The addition of the Grignard alkynylide was done according to General Procedure G. Purification by flash column chromatography on silica gel eluting with 1:2 EtOAc:hexanes afforded **1.10h** (70 mg, 54% yield) as an off white solid. M.p. 89-95 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.52 (d, J = 7.5 Hz, 2H), 7.34 (app t, J = 7.4 Hz, 2H), 7.27 (d, J = 7.1 Hz, 1H), 4.34 (s, 2H), 3.90 (s, 1H), 1.98 (broad s, 1H), 1.95 (s, 3H), 1.69 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 162.8 (C), 162.5 (C), 141.6 (C), 128.4 (CH), 127.6 (CH), 126.4 (CH), 105.2 (C), 87.2 (C), 84.5 (C), 56.8 (CH), 51.2 (CH$_2$), 42.6 (C), 28.6 (CH$_3$), 28.4 (CH$_3$), 27.9 (CH$_3$); HRMS (DART) m/z calcd for C$_{17}$H$_{22}$N$_1$O$_5$ (M + NH$_4$)$^+$: 320.14980. Found: 320.15064.

5-(6-Hydroxy-2-phenylhex-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10i)
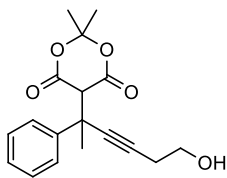
Prepared according to same procedure used for the preparation of **1.10h** using 3-butyn-1-ol. Purification by flash column chromatography on silica gel eluting with 1:2 EtOAc:hexanes afforded **1.10i** (79 mg, 69% yield by procedure D; 57 mg, 50% by procedure E) as a white solid. M.p. 91-95 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.51 (d, J = 7.4 Hz, 2H), 7.36–7.26 (m, 3H), 3.81 (s, 1H), 3.76 (t, J = 5.8 Hz, 2H), 2.51 (broad t, J = 5.9 Hz, 3H), 1.96 (s, 3H), 1.63 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.5 (C), 162.9 (C), 141.1 (C), 128.5 (CH), 127.7 (CH), 126.7 (CH), 105.5 (C), 84.2 (C), 83.9 (C), 61.1 (CH$_2$) 57.3 (CH), 43.3 (C), 29.0 (CH$_3$), 28.4 (CH$_3$), 27.5 (CH$_3$), 23.5 (CH$_2$); HRMS (DART) m/z calcd for C$_{18}$H$_{24}$N$_1$O$_5$ (M + NH$_4$)$^+$: 334.16545. Found: 334.16585.

2,2-Dimethyl-5-(2-(p-tolyl)-4-(trimethylsilyl)but-3-yn-2-yl)-1,3-dioxane-4,6-dione (1.10j)
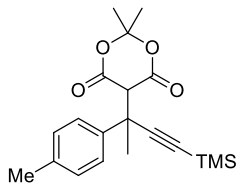
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10j** (110 mg, 77% yield by procedure D; 117 mg, 82% yield by procedure E) as an off white solid. M.p. 96-97 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.42 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 3.77 (s, 1H), 2.32 (s, 3H), 1.91 (s, 3H), 1.66 (s, 3H), 1.55 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.1 (C), 162.8 (C), 138.8 (C), 137.1 (C), 129.0 (CH), 126.4 (CH), 106.8 (C), 105.2 (C), 91.3 (C), 57.0 (CH), 43.6 (C), 29.4 (CH$_3$), 29.1 (CH$_3$), 28.0 (CH$_3$), 20.9 (CH$_3$), -0.1 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{30}$NO$_4$Si (M + NH$_4$)$^+$: 376.19441. Found: 376.19427.

5-(2-(4-Methoxyphenyl)-4-(trimethylsilyl)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10k)
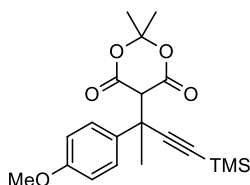
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10k** (136 mg, 91% yield by procedure D; 138 mg, 92% yield by procedure E) as a pale yellow solid. M.p. 80-82 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.45 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 3.73 (s, 1H), 1.91 (s, 3H), 1.64 (s, 3H), 1.53 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.1 (C), 162.9 (C), 158.8 (C), 133.5 (C), 127.8 (CH), 113.5 (CH), 107.0 (C), 105.2 (C), 91.2 (C), 57.1 (CH), 55.2 (CH$_3$), 43.4 (C), 29.4 (CH$_3$), 29.1 (CH$_3$), 27.9 (CH$_3$), -0.13 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{30}$NO$_5$Si (M + NH$_4$)$^+$: 392.18932. Found: 392.18948.

5-(2-(4-Fluorophenyl)-4-(trimethylsilyl)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10l)
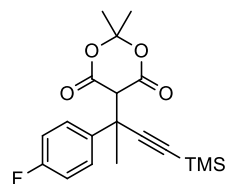
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10l** (108 mg, 75% yield by procedure D; 122 mg, 84% yield by procedure E) as a white solid. M.p. 77-80 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.54–7.49 (m, 2H), 7.01 (t, J = 8.6 Hz, 2H), 3.75 (s, 1H), 1.92 (s,

3H), 1.67 (s, 3H), 1.59 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 162.9 (C), 162.7 (C), 161.9 (d, J = 245.2 Hz, C), 137.5 (d, J = 3.2 Hz, C), 128.4 (d, J = 8.1 Hz, CH), 115.0 (d, J = 21.4 Hz, CH), 106.4 (C), 105.2 (C), 91.7 (C), 56.9 (CH), 43.2 (C), 29.5 (CH$_3$), 28.9 (CH$_3$), 28.0 (CH$_3$), -0.15 (CH$_3$); HRMS (DART) m/z calcd for C$_{19}$H$_{27}$FNO$_4$Si (M + NH$_4$)$^+$: 380.16934. Found: 380.17003.

5-(2-(4-Chlorophenyl)-4-(trimethylsilyl)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10m)
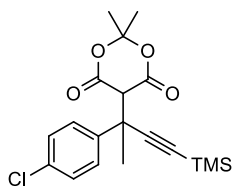
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10m** (131 mg, 85% yield by procedure D; 125 mg, 83% yield by procedure E) as a waxy white solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.48 (d, J = 8.6 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 3.78 (s, 1H), 1.90 (s, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 162.7 (C), 162.5 (C), 140.6 (C), 133.2 (C), 128.4 (CH), 128.0 (CH), 106.1 (C), 105.1 (C), 91.8 (C), 56.6 (CH), 43.2 (C), 29.4 (CH$_3$), 28.7 (CH$_3$), 28.1 (CH$_3$), -0.15 (CH$_3$); HRMS (DART) m/z calcd for C$_{19}$H$_{27}$ClNO$_4$Si (M + NH$_4$)$^+$: 396.13979. Found: 396.13989.

2,2-Dimethyl-5-(2-(4-(trifluoromethyl)phenyl)-4-(trimethylsilyl)but-3-yn-2-yl)-1,3-dioxane-4,6-dione (1.10n)
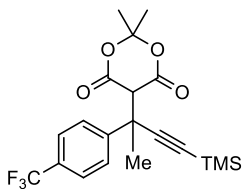
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10n** (146 mg, 88% yield by procedure D; 147 mg, 89% yield by procedure E) as white solid. M.p. 71-73 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.68 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 3.87 (s, 1H), 1.93 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 162.6 (C), 162.4 (C), 146.4 (C), 129.4 (q, J = 32.4 Hz, C), 126.8 (CH), 125.3 (q, J = 3.6 Hz, CH), 124.0 (q, J = 270.4 Hz, CF$_3$), 105.7 (C), 105.0 (C), 92.0 (C), 56.3 (CH), 43.2 (C), 29.4 (CH$_3$), 28.3 (CH$_3$), 28.1 (CH$_3$), -0.27 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{27}$F$_3$NO$_4$Si (M + NH$_4$)$^+$: 430.16614. Found: 430.16574.

2,2-Dimethyl-5-(2-m-tolyl-4-(trimethylsilyl)but-3-yn-2-yl)-1,3-dioxane-4,6-dione (1.10o)
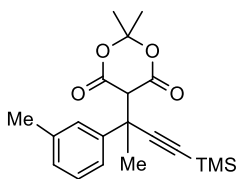
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10o**. (117 mg, 82% yield by procedure D; 122 mg, 85% yield by procedure E) as a white solid. M.p. 97-99 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.34–7.32 (m, 2H), 7.22 (dd, J = 7.5 Hz, 6.6 Hz, 2H), 7.07 (d, J = 7.3 Hz, 1H), 3.79 (s, 1H), 2.35 (s, 3H), 1.91 (s, 3H), 1.66 (s, 3H), 1.53 (s, 3H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.1 (C), 162.8 (C), 141.7 (C), 137.9 (C), 128.2 (CH), 127.2 (CH), 123.5 (CH) 106.8 (C), 105.2 (C), 91.5 (C), 56.8 (CH), 43.9 (C), 29.5 (CH$_3$), 29.1 (CH$_3$), 27.9 (CH$_3$), 21.6 (CH$_3$), -0.12 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{30}$NO$_4$Si (M + NH$_4$)$^+$: 376.19441. Found: 376.19411.

5-(2-(3-Methoxyphenyl)-4-(trimethylsilyl)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10p)
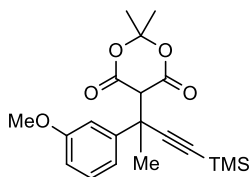
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10p** (126 mg, 84% yield by procedure D; 114 mg, 76% yield by procedure E) as a white solid. M.p. 116-118 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.24 (t, J = 8.0 Hz, 1H), 7.14 (dd, J = 2.1 Hz, 1.8 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.79 (dd, J = 7.9 Hz, 2.3 Hz, 1H), 3.82 (s, 1H), 3.79 (s, 3H), 1.91 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.0 (C), 162.6 (C), 159.4 (C), 143.6 (C), 129.2 (CH), 118.4 (CH), 112.8 (CH), 112.6 (CH), 106.5 (C), 105.1 (C), 91.5 (C), 56.7 (CH), 55.1 (CH$_3$), 43.8 (C), 29.6 (CH$_3$), 28.9 (CH$_3$), 28.0 (CH$_3$), -0.14 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{30}$NO$_5$Si (M + NH$_4$)$^+$: 392.18932. Found: 392.18972.

5-(2-(2-Fluorophenyl)-4-(trimethylsilyl)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10s)
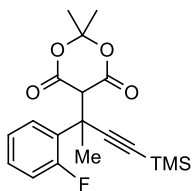
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10s** (56 mg, 39% yield by procedure D; 39 mg, 27% yield by procedure E) as a clear oil. ^{1}H NMR (300 MHz, CDCl$_3$) 7.82

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(dt, J = 8.1 Hz, 1.5 Hz, 1H), 7.27–7.23 (m,1H), 7.15 (t, J = 7.3 Hz, 1H), 7.02–6.95 (m, 1H), 4.45 (d, J = 5.7 Hz, 1H), 1.97 (s, 3H), 1.75 (s, 6H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) 162.9 (C), 162.5 (C), 159.9 (d, J = 242.2 Hz, C), 129.9 (d, J = 10.2 Hz, C), 129.7 (d, J = 4.0 Hz, CH), 129.1 (d, J = 8.9 Hz, CH), 124.4 (d, J = 2.9 Hz, CH), 115.9 (d, J = 23.5 Hz, CH), 105.3 (C), 104.6 (C), 91.9 (C), 53.8 (d, J = 7.1 Hz, CH), 42.1 (d, J = 3.4 Hz, C), 28.5 (CH3), 28.2 (d, J = 2.6 Hz, CH3), 27.7 (CH3), -0.10 (CH3); HRMS (DART) m/z calcd for $C_{19}H_{27}FNO_4Si$ (M + NH4)[+]: 380.16934. Found: 380.17018.

2,2-Dimethyl-5-(2-(naphthalen-2-yl)-4-(trimethylsilyl)but-3-yn-2-yl)-1,3-dioxane-4,6-dione (1.10u)
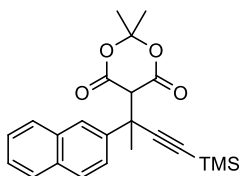
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10u** (120 mg, 76% yield by procedure D; 132 mg, 84% yield by procedure E) as beige solid. M.p. 107-110 °C; ^{1}H NMR (300 MHz, CDCl3) 8.04 (s, 1H), 7.84–7.81 (m, 3H), 7.63 (d, J = 8.7 Hz, 1H), 7.47–7.44 (m, 2H), 3.93 (s, 1H), 2.01 (s, 3H), 1.67 (s, 3H), 1.57 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) 163.2 (C), 162.7 (C), 139.2 (C), 133.0 (C), 132.5 (C) 128.3 (CH), 128.0 (CH), 127.5 (CH), 126.2 (CH), 125.8 (CH), 124.1 (CH), 106.7 (C), 105.2 (C), 92.0 (C), 56.6 (CH), 44.0(C), 29.5 (CH3), 29.0 (CH3), 28.1 (CH3), -0.069 (CH3); HRMS (DART) m/z calcd for $C_{23}H_{30}NO_4Si$ (M + NH4)[+]: 412.19441. Found: 412.19541.

5-(2-(Furan-2-yl)-4-(trimethylsilyl)but-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10v)
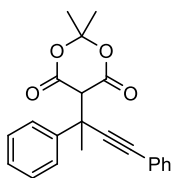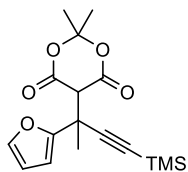

Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10v** (96 mg, 72% yield by procedure D; 99 mg, 74% yield by procedure E) as a yellow oil. ^{1}H NMR (300 MHz, CDCl3) 7.33 (s, 1H), 6.31 (s, 2H), 4.00 (s, 1H), 1.88 (s, 3H), 1.74 (s, 3H), 1.72 (s, 3H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) 162.6 (C), 162.1 (C), 154.5 (C), 141.8 (CH), 110.7 (CH), 106.7 (CH), 105.1 (C), 104.4 (C), 89.7 (C), 54.1 (CH), 39.2 (C), 28.4 (CH3), 26.7 (CH3), -0.18 (CH3); HRMS (DART) m/z calcd for $C_{17}H_{26}NO_5Si$ (M + NH4)[+]: 352.15802. Found: 352.15846.

2,2-Dimethyl-5-(4-methyl-3-phenyl-1-(trimethylsilyl)pent-1-yn-3-yl)-1,3-dioxane-4,6-dione (1.10w)
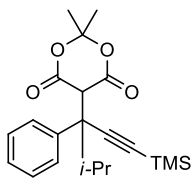
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10w** (98 mg, 66% yield by procedure D; 124 mg, 84% yield by procedure E) as a waxy white solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.53 (d, J = 7.2 Hz, 2H), 7.32–7.26 (m, 3H), 3.94 (s, 1H), 3.10 (app septet, J = 6.5 Hz, 1H), 1.55 (s, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.00 (s, 3H), 0.77 (d, J = 6.6 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.3 (C), 162.8 (C), 138.1 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 105.0 (C), 103.7 (C), 93.6 (C), 54.8 (C), 53.7 (CH), 33.1 (CH), 29.3 (CH$_3$), 27.0 (CH$_3$), 18.7 (CH$_3$), 18.5 (CH$_3$), -0.11 (CH$_3$); HRMS (DART) m/z calcd for C$_{21}$H$_{32}$NO$_4$Si (M + NH$_4$)$^+$: 390.21006. Found: 390.21013.

5-(1-Cyclohexyl-1-phenyl-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10x)
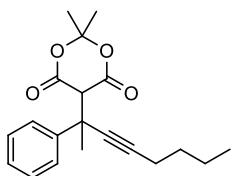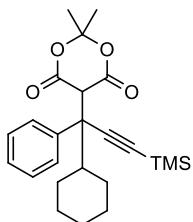
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10x** (114 mg, 69% yield by procedure D; 161 mg, 98% yield by procedure E) as a white solid. M.p. 125-127 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.52 (d, J = 7.3 Hz, 2H), 7.32–7.23 (m, 3H), 4.03 (s, 1H), 2.69 (broad s, 1H), 2.03 (broad s, 1H), 1.84–1.83 (broad m, 1H), 1.68–1.63 (broad m, 2H), 1.57 (s, 3H), 1.47–1.41 (m, 2H), 1.23–1.16 (m, 4H), 1.07 (s, 3H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.2 (C), 162.9 (C), 138.1 (C), 128.2 (CH), 128.0 (CH), 127.6 (CH), 104.9 (C), 104.7 (C), 93.5 (C), 54.2 (C), 53.1 (CH), 43.1 (CH), 29.2 (CH$_3$), 28.8 (CH$_2$), 28.3 (CH$_2$), 27.1 (CH$_3$), 26.4 (CH$_2$), 26.3 (CH$_2$), -0.1 (CH$_3$); HRMS (DART) m/z calcd for C$_{24}$H$_{36}$NO$_4$Si (M + NH$_4$)$^+$: 430.24136. Found: 430.24158.

5-(1-Cyclopropyl-1-phenyl-3-(trimethylsilyl)prop-2-ynyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10y)
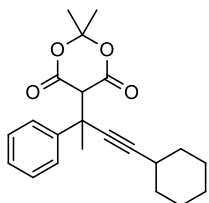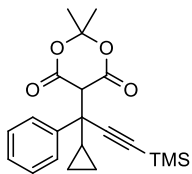
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10y** (102 mg, 69% yield by procedure D; 119 mg, 81% yield by procedure E) as an off white solid. M.p. 90-93 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.58 (appt d, J = 7.2 Hz, 2H), 7.36-7.26 (m, 3H), 3.89 (s, 1H), 1.92-1.89 (m, 1H), 1.62 (s, 3H), 1.48 (s, 3H), 0.85-0.81 (m, 1H), 0.67-0.64 (m, 1H), 0.44-0.39 (m, 2H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.2 (C), 163.2 (C), 141.1 (C), 128.2 (CH), 127.6 (CH), 127.1 (CH), 105.5 (C), 101.1 (C), 94.1 (C), 57.5 (CH), 51.5 (C), 29.7 (CH$_3$), 27.6 (CH$_3$), 17.9 (CH), 4.8 (CH$_2$), 2.9 (CH$_2$), -0.2 (CH$_3$); HRMS (DART) m/z calcd for C$_{21}$H$_{25}$O$_4$Si (M)$^-$: 369.15276. Found: 369.15292.

## Methyl 2-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-yl)-2-phenyl-4-(trimethylsilyl)but-3-ynoate (1.10z)
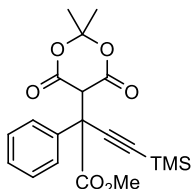
Prepared according to General Procedures F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10z** (146 mg, 94% yield by procedure D; 142 mg, 92% yield by procedure E) as an off white solid. M.p. 141-143 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.71 (d, J = 7.2 Hz, 2H), 7.37–7.29 (m, 3H), 4.92 (s, 1H), 3.72 (s, 3H), 1.85 (s, 3H), 1.73 (s, 3H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 170.4 (C), 162.7 (C), 160.5 (C), 135.5 (C), 128.5 (CH), 128.1 (CH), 126.7 (CH), 104.8 (C), 100.2 (C), 93.4 (C), 55.5 (CH), 53.9 (CH$_3$), 52.6 (C), 28.6 (CH$_3$), 26.6 (CH$_3$), -0.27 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{28}$NO$_6$Si (M + NH$_4$)$^+$: 406.16859. Found: 406.16927.

5-(2-(4-Fluorophenyl)-4-phenylbut-3-yn-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.10aa)
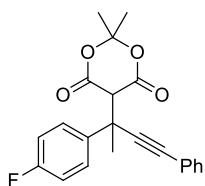
Prepared according to General Procedures C. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.10aa** (146 mg, 68% yield) as an off white solid. M.p. 81-84 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.62-7.57 (m, 2H), 7.50-7.46 (m, 2H), 7.32-7.30 (m, 3H), 7.04 (t, J = 8.9 Hz, 2H), 3.88 (s, 1H), 2.03 (s, 3H), 1.69 (s, 3H),

1.55 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 162.4 (C), 162.2 (C), 161.6 (d, J = 244.8 Hz, C), 141.1 (C), 139.1 (C), 137.1 (C), 131.8 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 115.2 (d, J = 21.4 Hz, CH), 105.4 (C), 90.3 (C), 86.8 (C), 57.6 (CH), 43.5 (C), 29.3 (CH$_3$), 28.9 (CH$_3$), 27.9 (CH$_3$).

(*E*)-5-(2-(4-Chlorophenyl)oct-3-en-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.11)
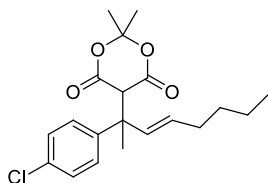
Prepared according to General Procedures C. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.11** (77 mg, 53% yield) as a beige solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.28-7.20 (m, 4H), 5.94 (d, J = 15.0 Hz, 1H), 5.52-5.47 (dt, J = 15.0 HZ, 9.0 HZ, 1H), 3.89 (s, 1H), 2.12-2.05 (dt, J = 9 Hz, 6 Hz, 2H), 1.72 (s, 3H), 1.68 (s, 3H), 1.59 (s, 3H), 1.37-1.28 (m, 4H), 0.87 (t, J = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.0 (C), 162.8 (C), 139.6 (C), 132. 7 (CH), 131.8 (C), 128.7 (CH), 128.2 (CH), 127.8 (CH), 105.4 (C), 56.1 (CH), 44.4 (C), 32.5 (CH$_2$), 29.9 (CH$_3$), 28.3 (CH$_3$), 22.5 (CH$_2$), 22.1 (CH$_2$), 13.6 (CH$_3$).

5-(6-Chloro-1-((trimethylsilyl)ethynyl)-2,3-dihydro-1H-inden-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.13a)
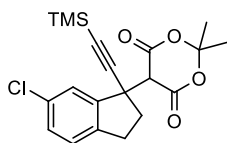
Prepared according to General Procedure F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.13a** (120 mg, 77% yield by procedure F; 116 mg, 74% by procedure G) as an off white solid. M.p. 125-127 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.32 (d, J = 1.5 Hz, 1H), 7.21 (dd, J = 8.0, 1.8 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H) 3.74 (s, 1H), 2.98–2.93 (m, 2H), 2.87–2.79 (m, 1H), 2.60–2.53 (m, 1H), 1.75 (s, 6H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 162.7 (C), 162.5 (C), 145.8 (C), 141.4 (C), 132.2 (C), 128.4 (CH), 125.7 (CH), 125.4 (CH), 106.3 (C), 105.4 (C), 89.7 (C), 53.5 (CH), 49.0 (C), 39.8 (CH$_2$) 29.6 (CH$_2$), 28.6 (CH$_3$), 28.2 (CH$_3$), -0.10 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{27}$Cl$_1$N$_1$O$_5$ (M + NH$_4$)$^+$: 408.13979. Found: 408.14031.

5-(5-Chloro-1-((trimethylsilyl)ethynyl)-2,3-dihydro-1H-inden-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1.13b)
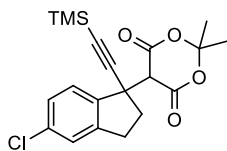
Prepared according to General Procedure F and G. Purification by flash column chromatography on silica gel eluting with a gradient from 1:4 to 1:2 EtOAc:hexanes afforded **1.13b** (122 mg, 78% yield by procedure F; 109 mg, 70% by procedure G) as an off white solid. M.p. 112-114 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 7.29 (d, J = 8.0 Hz, 1H), 7.19–7.16 (m, 2H), 3.67 (s, 1H), 3.00–2.85 (m, 3H), 2.58–2.51 (m, 1H), 1.75 (s, 3H), 1.73 (s, 3H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.0 (C), 162.7 (C), 144.8 (C), 142.5 (C), 134.1 (C), 126.8 (CH), 126.6 (CH), 124.8 (CH), 106.4 (C), 105.5 (C), 89.5 (C), 53.3 (CH), 48.9 (C), 39.9 (CH$_2$) 29.9 (CH$_2$), 28.5 (CH$_3$), 28.4 (CH$_3$), -0.14 (CH$_3$); HRMS (DART) m/z calcd for C$_{20}$H$_{27}$Cl$_1$N$_1$O$_5$ (M + NH$_4$)$^+$: 408.13979. Found: 408.14154.

Preparation of 3-Methyl-3-phenylpent-4-ynoic acid (1.14)
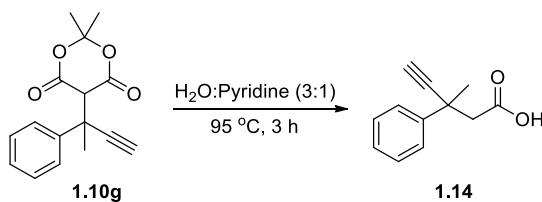
Procedure based on a procedure reported by DeWolf.[45] Meldrum's acid derivative **1.10g** was stirred in 3:1 pyridine:water (0.25 M) at 95 °C for 3 h. The solution was removed from heat and cooled to 0 °C followed by the acidification with 12N HCl to pH 2 and extracted with ethyl acetate. The organic extracts were washed with sat NH$_4$Cl, dried over MgSO4 and concentrated to afford **1.14** (90% yield) as a white solid. M.p. 83-86 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 8.78 (broad s, 1H), 7.54 (d, J = 6.5 Hz, 2H), 7.35-7.21 (m, 3H), 2.89 (AB, d, J = 14.9 Hz, 1H), 2.83 (AB, d, J = 14.9 Hz, 1H), 2.45 (s, 1H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 175.5 (C), 143.5 (C), 128.4 (CH), 127.0 (CH), 125.7 (CH), 87.5 (C), 72.2 (CH), 47.5 (CH$_2$), 37.9 (C), 29.6 (CH$_3$).

Chapter 2. Formation of Complex γ-Butyrolactones – Studies on Electrophilic Cyclization of Propargylic Meldrum's Acid Derivatives

2.1. Introduction

2.1.1. γ-Butyrolactone: A Ubiquitous Scaffold in Nature

Virtually all-living organisms produce lactones,[46] but their function varies greatly from organism to organism. For example, several species of marine organisms produce metabolites that have antimicrobial and antifungal activity such as **2.1**[47] and **2.2**[48] (Figure 2.1). Cyanobacteria (*Scytonema hofmanni*) eliminate competition and ensure their survival by excreting cyanobacterin **2.3**, which is toxic to other marine organisms and higher plants.[49] The African sugar-cane borer (*Eldana saccharina*) also secrets **2.4**, a male sex pheromone from its wing glands and abdomen.[50] γ-Butyrolactones have potential as pharmaceutical agents where **2.5** and its isomers have shown promising results in the treatment of HIV.[51]
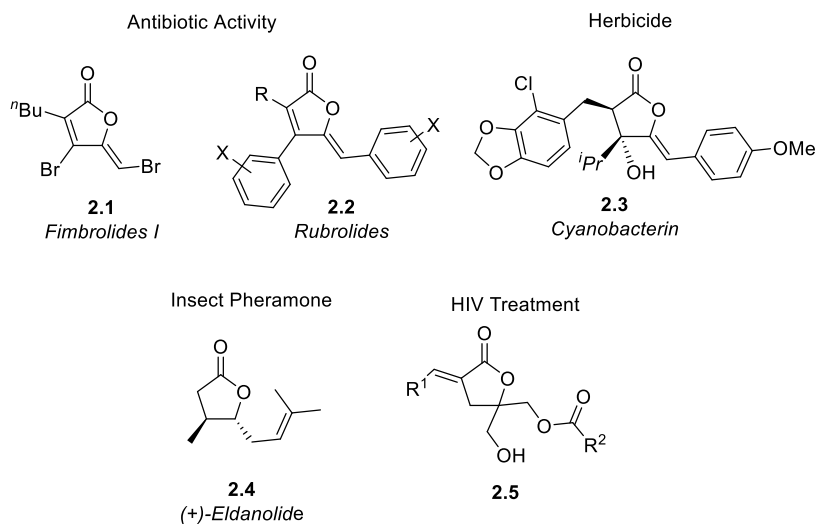
Figure 2.1. Selected Examples of Biologically Active γ-Butyrolactones

γ-Alkylidene butyrolactones are unique compared to other γ-butyrolactones in that they possess an enol lactone group which can function as a suicide substrate inhibiting

enzymes with specific nucleophilic groups at their active site.[52] According to the postulated mechanism,[53] acylation catalyzed by the target enzyme results in a stable acyl-enzyme complex, or can undergo further irreversible reactions at proximal sites to the reactive site, thereby inhibiting enzyme activity (Figure 2.2). The potential for generating reactive species exclusively within the active site allows for a higher degree of selectivity of these inactivators than that exhibited by conventional affinity reagents.
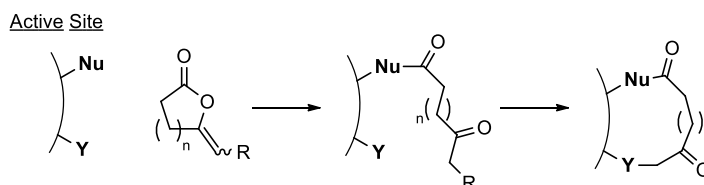
Figure 2.2. Proposed Mechanism of Enol Lactones as Suicide Inhibitors

Due to their biological and pharmacological importance, several synthetic approaches have been developed to access γ-alkylidene butyrolactones.[54] In the following section, an overview of methodologies that give rise γ-alkylidene butyrolactones will be discussed.

2.1.2 Synthetic Routes to γ-Alkylidene Butyrolactones

Several general strategies have been reported, their merits and shortcomings will be discussed in the following sections.

Transformation of five-membered heterocycles such 2-oxyfurans,[55] preformed γ-lactones[56] and maleic anhydrides[57] have all been used to prepare to γ-alkylidene butyrolactones (Scheme 2.1). 2-Trimethylsiloxyfurans and γ-ylidene butyrolactone have been used as nucleophilic synthons, whereas maleic anhydrides serve as electrophilic synthons. Although these transformations have been employed in the synthesis of natural products such as nostoclide 1 (Scheme 2.1),[58] the intrinsic nonstereoselective nature of these reactions result in mixtures of E and Z isomers in the absence of any overriding factors. These mixtures considerably reduce the overall yield of a desired product, and result in tedious and difficult separations.

Scheme 2.1. Transformation of Five-membered Heterocycles

Nostoclide I
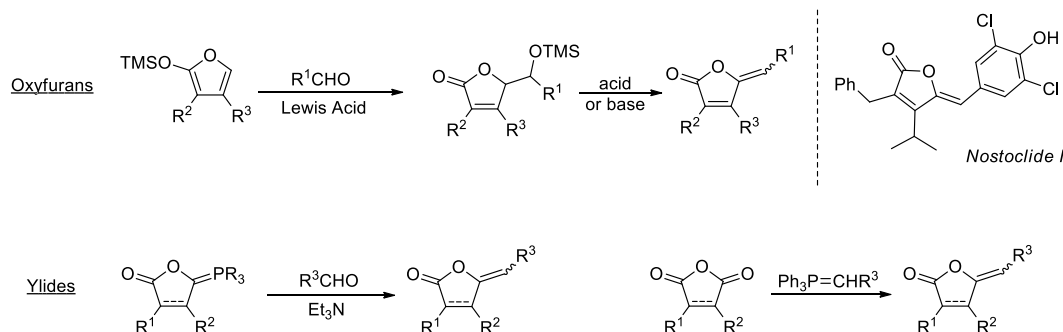
Langer initially reported the condensation of dianionic 1,3-dicarbonyls onto the Weinreb amide N,N′-dimethoxy-N,N′-dimethylethanediamide, [59] followed by a complementary methodology using 1,3-bis(trimethylsiloxy)-1,3-dienes onto oxalyl chloride (Scheme 2.2).[60] The latter approach proved to be superior to access γ-alkylidene butyrolactone **2.6** where improved yields and stereoselectivities were achieved (up to 88% isolated yields and *E:Z* ratios >98:2). A drawback to this approach is that 1,3-bis(trimethylsiloxy)-1,3-dienes are not stable and can be difficult to handle at temperatures above 0 °C because of decomposition, and thus required storage at temperatures below –20 °C under an inert atmosphere.

Scheme 2.2. Condensation of 1,3-Dicarbonyls Onto N,N′-Dimethoxy-N,N′-Dimethylethanediamide and Oxalyl Chloride
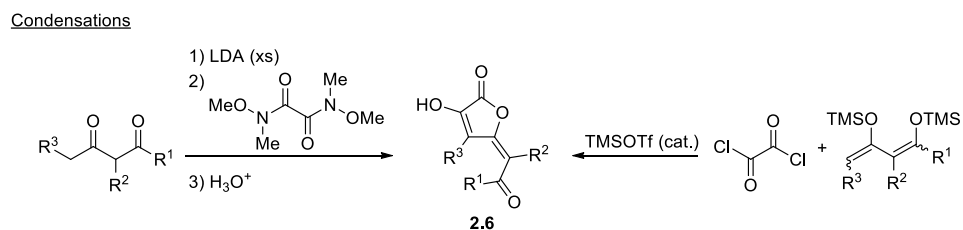
Negishi and coworkers reported a conceptually different strategy by utilizing Pd salts to catalyze the carbonylation of (*Z*)-*β*-halo-*α,β*-unsaturated ketones that can be trapped by intramolecular enols to form γ-alkylidene butyrolactone (Scheme 2.3). [61] Alternatively, acylpalladation[62] of internal alkynes followed by carbonylation results in the same intermediate

as the above strategy, which can undergo cyclization to the γ-alkylidene butyrolactone. The latter approach, although very attractive, suffers from poor regioselectivity and stereoselectivity problems with unsymmetrically substituted alkynes. With respect to the former intramolecular strategy, (Z)-β-halo-α,β-unsaturated ketones may be tedious to prepare and require several low yielding steps.

Scheme 2.3. Pd-catalyzed Carbonylations
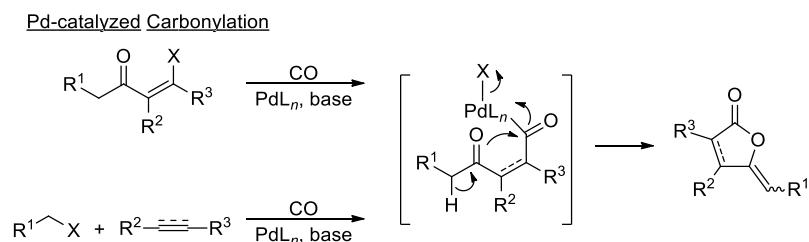
Finally, the electrophilic lactonization of alkynoic acids offers the most propitious route. Acid-catalyzed lactonization of 4-alkynoic acids generally offer excellent stereoselectivity,[63] but strategies that employ N-halosuccinimides (NXS)[64] or transition metals (Hg,[65] Pd,[66] Rh,[67] Ag,[68] Au[69]) to catalyze the cyclization are more attractive due to mild reaction conditions and shorter reaction times (Scheme 2.4). Halolactonization of alkynoic acids can be achieved with NXS (X = I, Br, Cl), $KHCO_3$ as the base and Bu_4NOH as a phase-transfer catalyst to exclusively form the E-olefin (Scheme 2.4). Halo enol lactones are versatile building blocks that can undergo subsequent transformations, and are themselves potential candidates for suicide inhibitors.
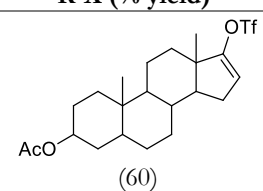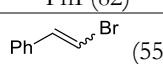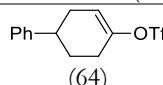
Mercury-mediated lactonization have also been reported, but are only synthetically useful for terminal alkynoic acids, where substitution at the terminus significantly reduces the yield of the desired γ-alkylidene butyrolactone. Furthermore, isomerization can be an issue with Hg^{2+} salts, presumably due to the readdition of Hg^{2+} to the olefin, and poor regioselectivity can result in the corresponding pyranone.

Scheme 2.4. Electrophilic Lactonization
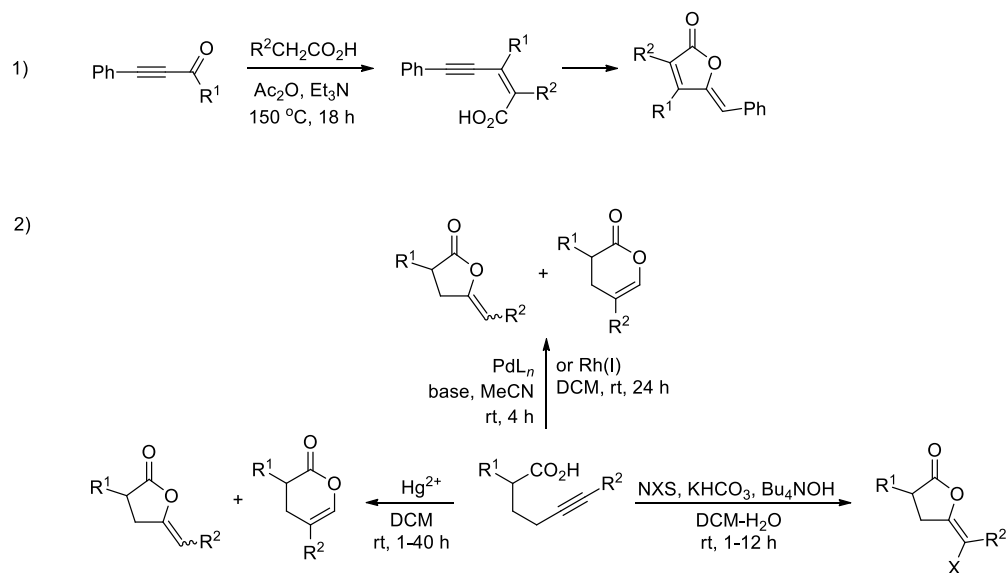
Pd and Rh catalyzed lactonizations have also been reported. These transition metals suffer from the same limitations as Hg^{2+} catalyzed reactions mentioned above, but with better stereo- and regioselectivities where optimum results are obtained for bulky terminal alkynes. Noteworthy is a tandem Pd-catalyzed lactonization -cross coupling reaction of alkenyl halides and triflates (Table 2.1),[70] which offers an attractive one pot approach to γ-alkylidene butyrolactones that would be inaccessible with other electrophiles.

Table 2.1. Tandem Pd-Catalyzed Lactonization-Cross Coupling Reactions

R^1 / R^2	R^3X (% yield)[a]
H / H	OTf (60)
H / H	PhI (82)
H / H	Ph~~~Br (55)
CO_2Me / Me	Ph—◯—OTf (64)

[a] Isolated yield.

52

The potential of Ag salts for lactonization reactions was first shown by Castañer and Pascual[71] back in 1958, where malonic acid **2.7** was converted to γ-alkylidene butyrolactone **2.8a** by either thermal isomerization, or more smoothly in an alcoholic solution of AgNO$_3$ at rt (Scheme 2.5). Shortly thereafter, catalytic protocols followed and revealed the importance of substitution at the terminal end of the alkyne, where alkyl groups result in mixtures of 5-*exo dig* and 6-*endo dig* cycloadducts, **2.8b** and **2.9b** respectively.[72]

Scheme 2.5. Early Examples of Ag^I Catalyzed Lactonization of Alkynoic Acids
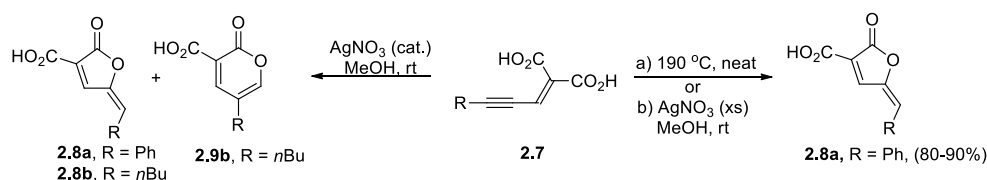
With respect to transition metal catalyzed lactonization methodologies, they all start from an alkynoic acid precursor that typically require several synthetic steps (Scheme 2.6a).[73] As an alternative precursor, Meldrum's acid derivatives **2.10a–d** have been efficiently transformed to the corresponding γ- butyrolactones **2.11–2.13**;[74] adducts **2.10** are easily prepared in 2 steps from inexpensive starting materials and allow for a wide range of derivatization at the benzylic position (Scheme 2.6b).[75] These compounds also possess an enolizable Meldrum's acid moiety that can trap either a π-allylpalladium complex or a Ag-activated alkyne complex, affording γ-butyrolactones **2.11** and **2.12–2.13** respectively. Both Ag(I) and Pd catalyzed reactions showed excellent regioselectivity affording γ-butyrolactones in moderate to excellent yields. Moreover, precursors **2.10a–d** allow for functionalization at both *α* and *β* positions of the γ-butyrolactone. It is worth mentioning that reports using Meldrum's acid derivatives as precursors to γ-alkylidene butyrolactone **2.12** and **2.13** were limited to terminal and aryl substituted alkynes and therefore require further investigation into substitution effects for internal alkynes.

Scheme 2.6. a) Synthetic Step Comparison of γ-Butyrolactones Precursors; b) Transition Metal Catalyzed Lactonization of Meldrum's Acid Derivatives

a)

7 steps

5 steps

3 steps

2.10
2 steps

b)

2.10a, R = Ac
2.10b, R = CO₂Et

Pd catalyst
THF/R'OH
40-60 °C

2.11
R' = H, Me, Et

2.10c

Agᴵ (cat.)
PhH/MeOH
85 °C

2.12

2.10d

Agᴵ (cat.)
DMF/H₂O
100 °C

2.13

2.2 Proposal

Lewis Acid
solvent:R⁴OH

2.14

2.15

+

6-*endo dig* products have not been reported from Meldrum's acid precursors but are possible

2.16
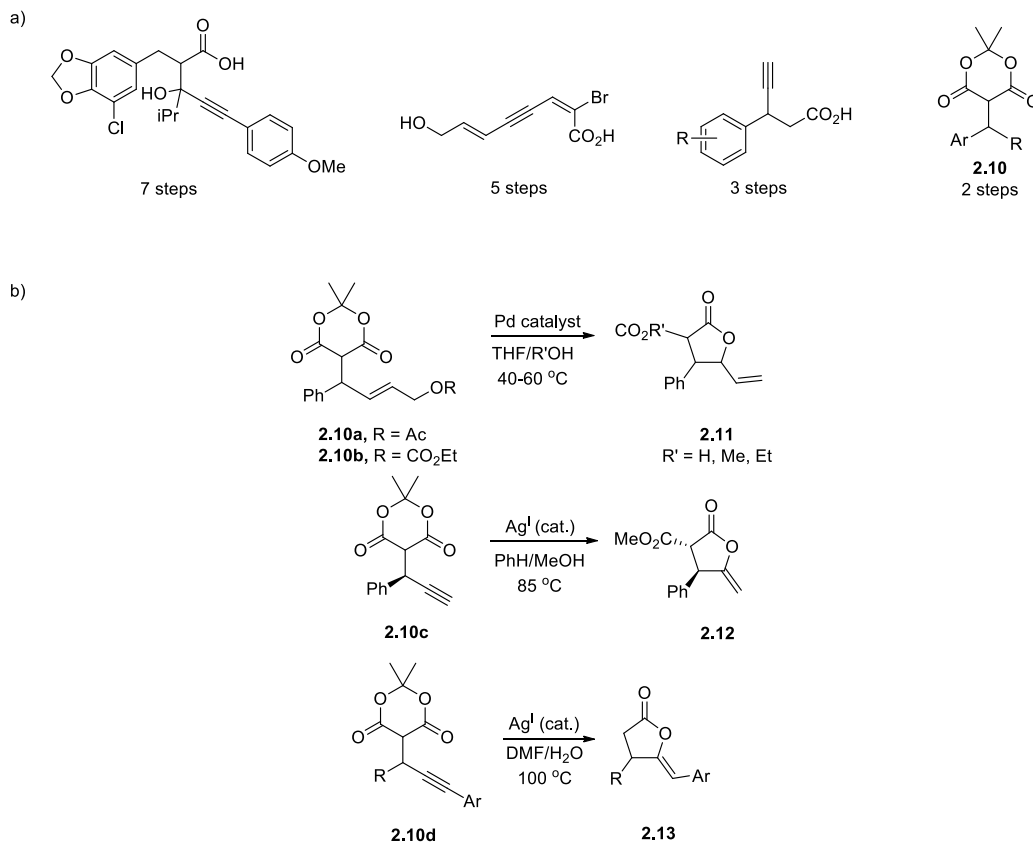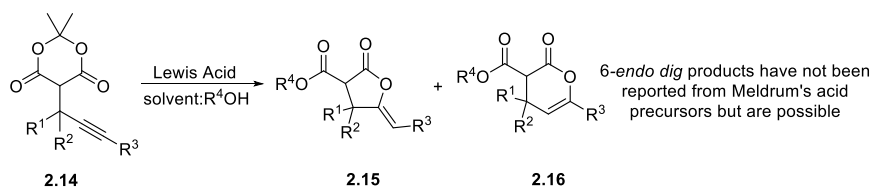
Figure 2.3. Proposal for Lewis Acid Catalyzed Lactonization of Propargylic Meldrum's Acids **2.14**

The motivation was to investigate transition metal catalyzed lactonization of propargylic Meldrum's acid derivatives **2.14**, discussed in the previous chapter, as outlined in Figure 2.3. Various Lewis acids from transition metals to halogens were screened to test the reactivity of **2.14** towards electrophilic activation. Furthermore, previous studies using tertiary propargylic Meldrum's acid derivatives investigated terminal alkynes and aryl substituted alkynes; the following investigations will include substituted alkynes with the aim to develop methodologies that utilize **2.14** as precursor to afford regioisomers **2.15** and/or **2.16**. This strategy would allow for the functionalization of both α and β positions that would otherwise be inaccessible or require multiple steps, particularly the quaternary stereocenter at the β position.

2.3. Results and Discussion

2.3.1 Development of Reaction and Exploration of Scope

Initial efforts to promote halolactonization of propargylic Meldrum's acid derivatives **2.14** with either Br_2 or I_2 resulted in formation of complex mixtures. Precautions to minimize side reactions such as running reactions in the dark, lower temperatures and high dilutions did not favour the formation of a sole product. *N*-halosuccinimides proved to be a more promising source of the electrophilic halide (Table 2.2). Halolactonization of alkynoic acids are sensitive to reaction conditions and therefore investigations were done with that in mind. The importance for a nucleophilic co-solvent was previously shown by our group, and was again vital to Ag-catalyzed lactonizations, which will be discussed in more detail in the following section. Greater than one equivalent of the halosuccinimide was required to observe any reactivity, entries 1 and 2, where only K_3PO_4 and $NaHCO_3$ showed depletion of **2.14** based on the crude ^{1}H-NMR spectrum. No combination of halosuccinimide, base and reaction conditions screened afforded a single product, but rather complicated mixtures containing either **2.14a** or **2.14b**. Entries 3–5 show that halo- and seleno-mediated lactonization is possible, albeit in poor selectivity, and the structures are solely based on impure compounds isolated after chromatography. Furthermore, difficulties with the reproducibility of halolactonization of alkynoic products have been reported, and analogous reproducibility

problems with **2.15a-b** were also observed. This may be due to instability of products formed. For example, neither **2.15b** nor **2.15c** were observed in the crude ^{1}H-NMR spectra, which suggests that either further reactivity, such as decarboxylation for **2.15b**, takes place upon isolation of crude products on silica gel (Figure 2.4).

Table 2.2. Halolactonization of Propargylic Meldrum's Acid Derivatives **2.14**

Entry	R^1	Lewis Acid	Base	Solvent	Temp (°C) / T (h)	Product (% yield)
1	H	NBS or NIS (1.1 equiv)	K$_3$PO$_4$ or K$_2$CO$_3$ or NaHCO$_3$ (3 equiv)	DCM:H$_2$O or DCM:MeOH (10:1)	rt / 24	no reaction
2	H	NBS (2.5 equiv)	K$_3$PO$_4$ or NaHCO$_3$	DCM:H$_2$O or DCM:MeOH (10:1)	rt / 24	mixture
3	H	NIS (2.5 equiv)	NaHCO$_3$ (3 equiv)	DCE:MeOH (4:1)	65 / 4	**2.15a** mixture
4	nBu	NBS (2.5 equiv)	K$_3$PO$_4$ or NaHCO$_3$ (3 equiv)	DCM:H$_2$O (4:1)	rt / 16	**2.15b** mixture
5	nBu	PhSeBr (1.1 equiv)	Et$_3$N (2 equiv)	THF:MeOH (10:1)	0 to rt / 4	**2.15c** mixture

A tandem Pd-catalyzed lactonization cross-coupling reaction was explored (Table 2.3). Screening Pd catalyst, it was determined that PdCl$_2$(PhCN)$_2$ resulted in the desired adduct, but was dependent on reaction conditions. In the absence of base and at elevated temperatures, decomposition of **2.14a** takes place, where ring opening products such as **2.17** were observed, entry 2. Compound **2.15d** was isolated in modest yields and under mild conditions by the sequential addition of the Pd catalyst to the preformed enolate and trapping the Pd-complex with allyl bromide, entry 4. Attempts to prepare **2.18b** in a one-step protocol by generating the enolate with K$_2$CO$_3$ in the presence of the Pd catalyst and allyl bromide, entry 7, furnishes a 1:1 mixture of uncoupled adduct **2.15d** and coupled adduct **2.18b**. Moreover, it was apparent that the scope of coupling partners was limited to allyl bromide where aryl halides resulted in the isolation of starting material **2.14a**, entry 9.
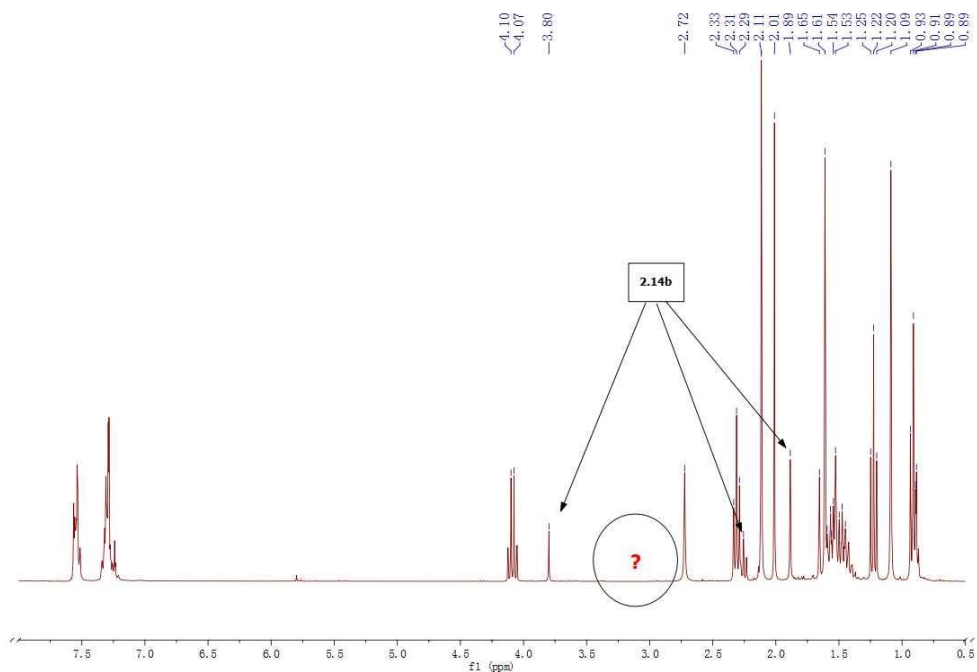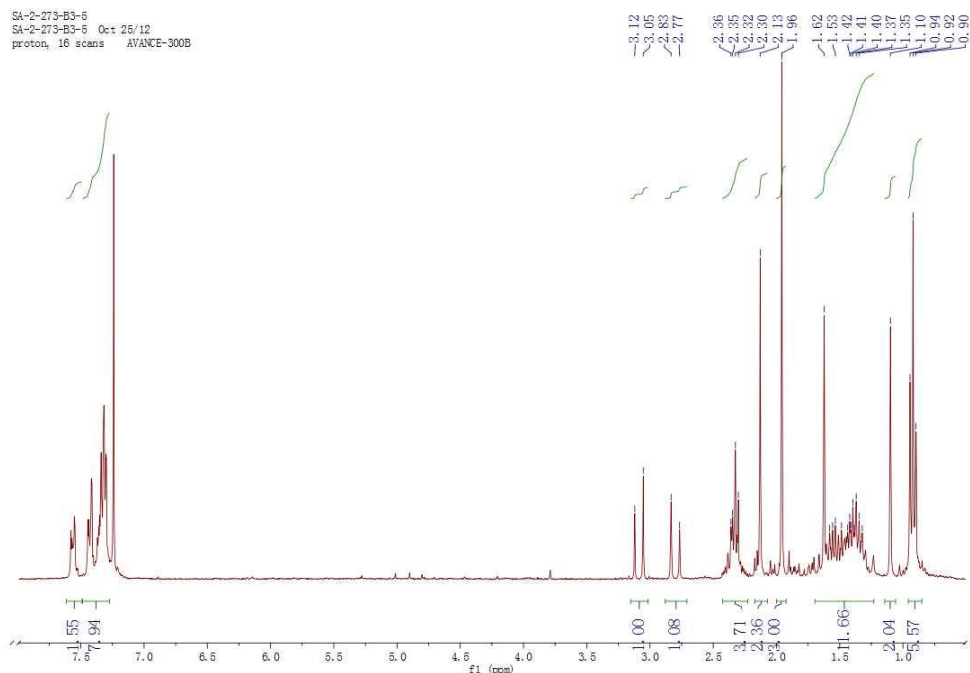
Figure 2.4. Comparison of ^{1}H-NMR Spectra of **2.15b**, crude (above) and Isolated (below)

After establishing that a tandem lactonization cross-coupling reaction is viable, a one-pot sequential conjugate alkynylation procedure was envisaged, scheme 2.7. The conjugate alkynylation protocol developed in the previous chapter presumably produces a magnesium halide enolate that can be trapped by a Pd salt and promote the tandem process discussed above. Encouragingly, a 1:1 mixture of γ-alkylidene butyrolactone **2.15f** was isolated. The mixture of both E and Z isomers suggests that two different modes of lactonization are taking place: an oxypalladation across the triple bond that would afford the Z isomer; and anti nucleophililc attack of the enolate to the Pd coordinated alkyne would afford the E isomer. Efforts to improve the selectivity by running the reaction in toluene, acetonitrile or quenching with water were unsuccessful.

Scheme 2.7. One Pot Tandem Conjugate Alkynylation Pd-Catalyzed Lactonization Cross-Coupling
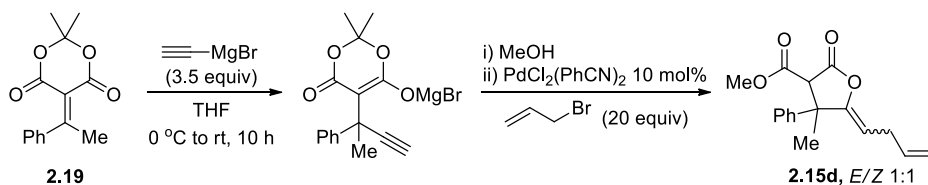
Table 2.3. Pd-Catalyzed Tandem Lactonization Cross-Coupling Reactions
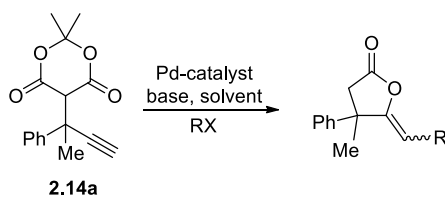
Entry	Catalyst	RX	Solvent	Base	Product (% yield)
1	Pd(OAc)₂(PPh₃)₂ or PdCl₂(PhCN)₂	Br	THF or DMF	-	no reaction
2	Pd(OAc)₂(PPh₃)₂	Br	DMF:H₂O 85 °C	-	**2.17**
3	Pd(OAc)₂(PPh₃)₂	Br	THF or MeCN or DMF	NaH	complex mixtures
4	PdCl₂(PhCN)₂	Br	THF	NaH	**2.15d**, 38%
5	PdCl₂(PhCN)₂	Br	MeCN or DMF	NaH	complex mixtures
6	PdCl₂(PhCN)₂	Br	THF	K₂CO₃ or NaHCO₃	complex mixture
7	PdCl₂(PhCN)₂	Br	THF:H₂O	K₂CO₃	**2.15e** : **2.15d** (1:1)
8	PdCl₂(PhCN)₂	Br	THF:MeOH	K₂CO₃	complex mixtures
9	PdCl₂(PhCN)₂	PhBr	THF	NaH	**2.14a** recovered

As already alluded to, Ag(I) salts were shown to catalyze the lactonization of propargyl Meldrum's acid derivatives. Expanding to quaternary propargylic derivatives **2.14**, various Ag(I) and Au(I/III) salts were screened to study the regio- and stereoselectivities. The formation of product was dependent on both transition metal and reaction conditions. Ag₂CO₃ was superior to other Ag(I) and Au(I/III) salts, Table 2.4 entries 1–5. Near quantitative yield of **2.15e** was obtained in 10:1 mixture of PhH:H₂O. In contrast, AuCl requires the addition of base to avoid competing side reactions to form **2.15e**, entries 4 and 5.

59
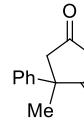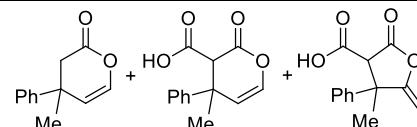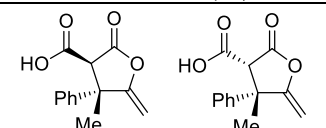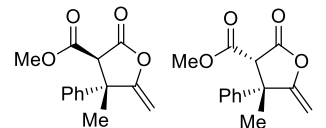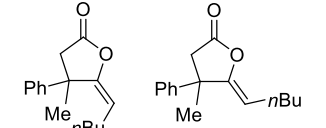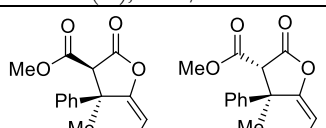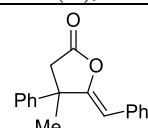
Interestingly, by repeating AuCl catalyzed reactions at rt, mixtures of **2.15f**, **2.16a** and **2.16b** were observed (entry 6). This result shows that in the absence of a nucleophilic enolate and at lower temperatures, AuCl catalyzes the formation of both the *5-exo-dig* and *6-endo-dig* products over an extended period of time. Efforts to selectively form one regioisomer over the other, preferably **2.16**, by modifying reaction conditions including using AuCl$_3$ salts, were not successful. At best, a 3:2 ratio of **2.16a** to **2.15e** was obtained (entry 7). It should be noted that all reactions ran with AuCl$_3$ resulted in complete consumption of Meldrum's acid derivatives **2.14** without affording a single distinct compound, and thus was abandoned from further screening.

In contrast to Au-catalyzed reactions, Ag$_2$CO$_3$ inherently possesses a basic counterion which can account for the higher yields observed. Altering temperature or nucleophilic cosolvent results in γ-alkylidene butyrolactones containing a carboxylic acid or ester moiety adjacent to the stereogenic center, **2.15f** and **2.15g** respectively (entries 8 and 9). Alkyl- and aryl-substituted propargyl Medrum's acids were more sensitive to cyclization conditions (entries 10−15). Regio- and stereoselective *E*-**2.15h** and *E*-**2.15i** isomers were isolated in a more polar and Lewis basic solvent such as THF (entries 10 and 12). In a less polar solvent such as benzene, mixtures of *E/Z* isomers were isolated (entries 11 and 13). Lactone *Z*-**2.15j** was exclusively formed in a mixture of benzene and water (entry 14).

Transition-metal-catalyzed cyclization of terminally substituted alkynoic acids have been reported to give mixtures of *E/Z* isomers,[68, 24] and was rationalized by the authors to be a result of isomerization of the *Z* isomer. To test this hypothesis, efforts to isomerize either *E*-**2.15h** or *Z*-**2.15j** by subjecting these products to Ag-salts in their respective reaction conditions over 24 h did not show any isomerization. Similarly, subjecting a mixture of E/Z isomers to the same reaction conditions did not change the relative ratio of the isomers formed.[76] These results suggest the possibility of competing paths of cyclization as illustrated in Figure 2.5. Path **I** gives rise to the *Z* isomer, where anti- attack of the carbonyl-O onto the alkyne-coordinated Ag(I) complex gives rise to the 5-*exo-dig* intermediate **Ia**. The *E*-isomer can be accounted for by a syn-oxymetalation of the carbonyl-O and Ag(I) ion across the triple bond giving rise to the 5-exo-dig intermediate **IIa**. Thermally induced cycloreversion of **Ia** and **IIa** resulted in the formation of acylketene intermediates **Ib** and **IIb** respectively,[77]

Table. 2.4. Ag^I and $Au^{I/III}$ Lactonization of Propargylic Meldrum's Acid Derivatives **2.14**
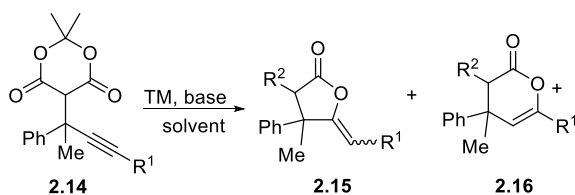
Entry	R	TM	Solvent	Temp (°C) / time (h)	Product (% yield)[a]
1	H	Ag$_2$CO$_3$	PhH:H$_2$O[b]	85 / 2	**2.15e**, (98)
2	H	Ag$_2$CO$_3$	THF:H$_2$O[b]	85 / 2	**2.15e** (88)
3	H	AgNO$_3$	PhH:H$_2$O[b]	85 / 2	**2.15e** (74)
4	H	AuCl + K$_2$CO$_3$	THF:H$_2$O[c]	85 / 2	**2.15e** (77)
5	H	AuCl	THF:H$_2$O[c]	85 / 2	complex mixtures
6	H	AuCl	THF:H$_2$O[c]	rt / 20	**2.16a**, **2.16b**, **2.15f**
7	H	AuCl + K$_2$CO$_3$	THF:H$_2$O[c]	rt / 20	**2.16a** + **2.15e** (3:2)
8	H	Ag$_2$CO$_3$	PhH:H$_2$O[d]	rt / 18	**2.15f** (88), 3:1 dr
9	H	Ag$_2$CO$_3$	PhH:MeOH[d]	85 / 2	**2.15g** (93), 3:1 dr
10	nBu	Ag$_2$CO$_3$	THF:H$_2$O[b]	85 / 2	**2.15h** (86), 29:1 E/Z mixture
11	nBu	Ag$_2$CO$_3$	PhH:H$_2$O[b]	85 / 2	**2.15h** (89), 2:3 E/Z mixture
12	nBu	Ag$_2$CO$_3$	THF:MeOH[d]	85 / 2	**2.15i** (81), 3:1 dr
13	nBu	Ag$_2$CO$_3$	PhH:MeOH[b]	85 / 2	**2.15i** (79), 2:1 E/Z mixture
14	Ph	Ag$_2$CO$_3$	PhH:H$_2$O[b]	85 / 2	**2.15j** (92)
15	nBu	Ag$_2$CO$_3$	THF:H$_2$O[b]	85 / 2	**2.15j** (88), 2:5 E/Z mixture

[a]Isolated yields. [b]10:1 ratio. [c]30:1 ratio. [d]4:1 ratio.

followed by nucleophilic attack of the corresponding solvent affording the γ-alkylidene butyrolactone.
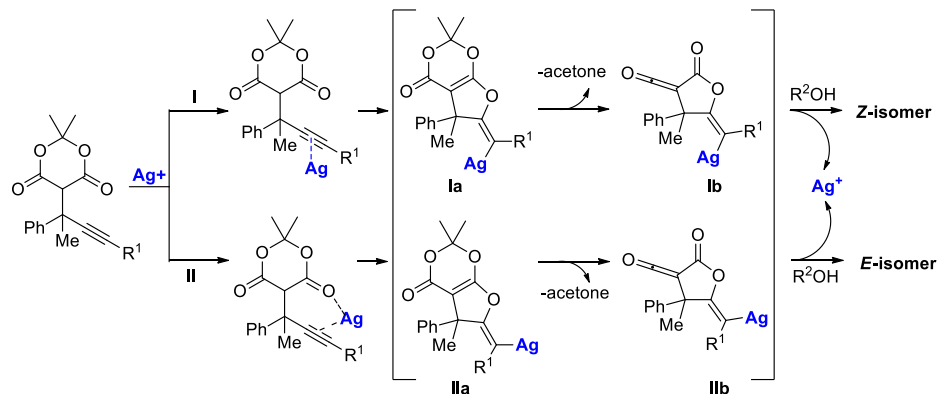
Figure 2.5. Proposed γ-Alkylidene Butyrolactone Mechanism

Alkyl- and aryl-substituted derivatives of **2.14** (R^1 = *n*Bu or Ph) subjected to identical reaction conditions for **2.15f**, gave mixtures of carboxylated and decarboxylated butyrolactones. However, upon gentle heating to 85 °C decarboxylated γ-alkylidene butyrolactones were exclusively formed (Table 2.5, entries 10, and 14). Further evidence for the acylketene intermediate was observed when cyclization reactions were run in the absence of a nucleophilic solvent. No cyclized products were observed as a result of rapid decomposition of the unstable acylketene intermediate.[74a]

2.4. Summary

Propargyl Meldrum's acid derivatives have been shown to be attractive precursors to prepare functionalized γ-alkylidene butyrolactones. *N*-halosuccinimides were shown to transform these Meldrum's acid derivatives to halo enol lactones. The vinylic halogen moiety offers a synthetic handle for further manipulations. Pd-catalyst opened the possibility of a tandem lactonization coupling methodology, but is currently limited to allyl bromide as a coupling partner. Optimum results were obtained using group 11 transition metals, where Ag_2CO_3 offered the highest yields and stereoselectivities. The γ-alkylidene butyrolactones

prepared using these Lewis acids display a stereogenic all-carbon quaternary center at the β or C-4 position and the potential for additional functionalization at the α or C-3 position. Ultimately, the developed methodology gives access to highly functionalized γ-alkylidene butyrolactones after three steps. Furthermore, NMR studies gave insight into the effects of alkyl substitution where E and Z isomer can be selectively formed by careful selection of reaction conditions.

2.5. Future Work

Silver (I) salts were shown to be reliable catalyst for the lactonization of propargyl Meldrum's acid derivatives but there is significant room for improvement for both halo- and Pd-catalyzed lactonization. Halo enol lactones are attractive scaffolds and conditions used to access these frameworks such as phase transfer catalyst may improve the selectivity of the lactonization as was the case for alkynoic acids. Applying this strategy directly to propargyl Meldrum's acid derivatives or converting propargyl Meldrum's acid derivatives to alkynoic acids, which proceeds in near quantitative yields, may offer access to halo enol lactones (Scheme 2.8).

Scheme 2.8. Halolactonization in the Presence of a Phase Transfer Catalyst
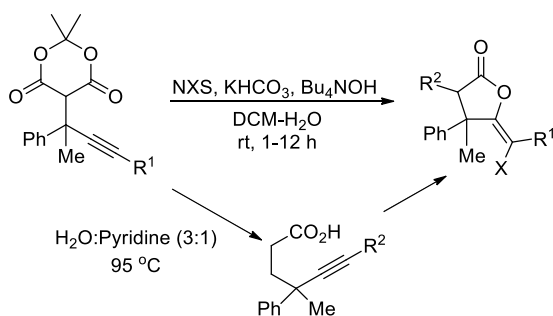
Optimization of the tandem Pd-catalyzed lactonization cross-coupling protocol developed will offer an efficient approach to accessing highly diverse γ-alkylidene butyrolactones. Alkenyl triflates may offer an extension to allyl bromides as coupling partners. Also, Rh[I] salts were neglected in transition metal catalyzed lactonization of propargyl

Meldrum`s acid derivatives, and have the potential for novel reactivity than previously observed.

2.6. Experimental
General Considerations
Reactions

All reactions were performed in flame-dried glassware under an argon atmosphere unless otherwise stated. THF and benzene were distilled over sodium/benzophenone ketyl before use. Et_3N was dried by distilling over CaH_2 and used immediately. Dichloromethane, 1,2-dichloroethane and MeCN were obtained from a solvent purification system based on the published procedure.[42] MeOH was heated to reflux over Mg powder overnight and then distilled, and stored over 3 Å molecular sieves in a Schlenk flask. Ethynylmagnesium bromide (0.5 M in THF) was purchased from Sigma-Aldrich and used without further purification. NaH (60% dispersion in mineral oil) was purchased from Sigma-Aldrich. All other reagents were purchased from commercial sources and used without further purification. Proparygl Meldrum's acid derivatives **2.14** were prepared according to procedures reported in Chapter 1. Reactions were monitored by thin-layer chromatography and visualized by UV quenching and/or staining with cerium ammonium molybdate. Flash chromatography was performed using 230-400 mesh silica gel.

Characterization

^1H and ^{13}C NMR spectra for all compounds were obtained in $CDCl_3$ or C_6D_6 at 300 MHz and 75 MHz, respectively unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual $CHCl_3$ (7.24 ppm) or C_6D_5H (7.15 ppm), and carbon spectra were calibrated to $CDCl_3$ (77.0 ppm). Carbon multiplicities (C, CH, CH_2, CH_3) were determined by combined DEPT 90/135 experiments. Melting points are uncorrected. High resolution mass spectra were run at either the University of Waterloo Mass Spectrometry facility and the AIMS facility at the University of Toronto. Melting points are uncorrected.

General Procedure A – Lewis Acid Activated Cyclization of Propargyl Meldrum's Acid Derivatives 2.14

2.14a, R^1 = H
2.14b, R^1 = nBu
2.14c, R^1 = Ph
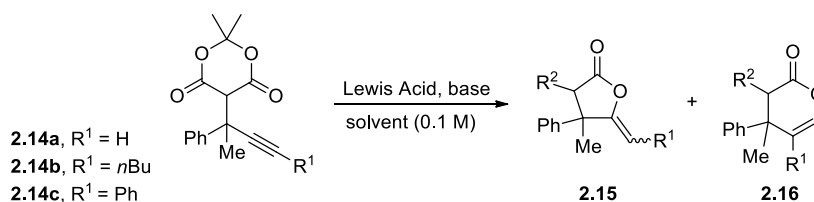
A flame dried resealable Schlenk tube equipped with magnetic stir bar and back filled with N$_2$, was loaded with propargylic Meldrum`s Acid adduct **2.14**, electrophile (NIS, NBS, PhSeBr, Ag(I) salts, AuCl) and base (NaHCO$_3$, K$_3$PO$_4$, Et$_3$N) in the corresponding solvent/s. The tube was sealed and stirred at the indicated temperature and time. The reaction was monitored using TLC and was brought to ambient temperature on complete consumption of the starting material. Reactions using NIS and NBS were halted by cooling reaction mixture in an ice bath and adding Na$_2$S$_2$O$_3$ (aq), followed by NH$_4$Cl (aq). Layers were partitioned and aqueous layer was extracted with CH$_2$Cl$_2$ (3×). Combined organic fractions were then washed with brine (1×), dried over MgSO$_4$ and concentrated. Purification by flash column chromatography on silica gel eluting with 1:2 EtOAc:hexanes afford the γ-alkylidene butyrolactones **2.15a-c**; reactions using Ag(I) salts and AuCl were halted by diluting with Et$_2$O, and then passing over a pad of silica to remove the transition metal salts. The homogeneous solution was concentrated onto a small amount silca gel that was loaded to the top of a silica gel column for purification by flash column chromatography. Eluting with 1:2 EtOAc:hexanes affords **2.15e-j** and **2.16a-b**.

(*E*)-Methyl 5-(iodomethylene)-4-methyl-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (2.15a)
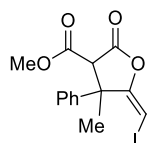
Prepared according to General Procedure A using: **2.14a** (100 mg, 0.367 mmol), NIS (210 mg, 0.917 mmol) and NaHCO$_3$ (78 mg, 0.917 mmol) in a 4:1 DCE:MeOH (0.1M) mixture at 65 °C for 3 h. **2.15a** was isolated as an impure yellow film (59 mg, 43%).[78] ^{1}H NMR (300 MHz, CDCl$_3$) 7.35–7.31 (m, 5H), 5.45 (s, 1H), 4.42 (s, 1H), 3.74 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 168.7 (C), 167.7 (C), 167.6 (C), 136.5 (C), 129.0 (CH), 128.7 (CH), 127.3 (CH), 58.4 (CH), 52.7 (CH$_3$), 52.1 (C), 17.9 (CH$_3$).

(*E*)-5-(1-Bromopentylidene)-4-methyl-4-phenyldihydrofuran-2(3H)-one (2.15 b)
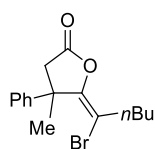
Prepared according to General Procedure A using: **2.14b** (120 mg, 0.367 mmol), NBS (330 mg, 1.85 mmol) and K_3PO_4 (390 mg, 1.85 mmol) in a 30:1 DCM:H_2O (0.1M) mixture at rt for 10 h. **2.15b** was isolated as an impure yellow film (31 mg, 26%). ^1H NMR (300 MHz, CDCl$_3$) 7.44–7.42 (m, 2H), 7.34–7.32 (m, 3H), 3.08 (d, J = 20.1 Hz, 1H), 2.80 (d, J = 20.1 Hz, 1H), 2.38–2.28 (m, 2H), 1.96 (s, 3H), 1.37 (m, 5H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 169.0 (C), 155.1 (C), 141.5 (C), 128.8 (CH), 127.0 (CH), 125.3 (CH), 88.2 (C), 44.1 (CH$_2$), 38.6 (C), 32.3 (CH$_2$), 28.6 (CH$_2$), 28.0 (CH$_3$), 22.0 (CH$_2$), 15.0 (CH$_3$). MS (EI) 322 (M$^+$).

4-Methyl-5-methylene-4-phenyldihydrofuran-2(3H)-one (2.15e)
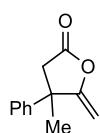
Prepared according to General Procedure A using: **2.14a** (100 mg, 0.367 mmol), Ag$_2$CO$_3$ (10 mg, 0.0367 mmol) and PhH/H$_2$O (10:1) as the solvent. The mixture was stirred at 85 °C for 2 h affording **2.15e** as a colorless oil (60 mg, 88% in THF/H$_2$O; 68 mg, 98% in PhH/H$_2$O) after purification. ^1H NMR (300 MHz, CDCl$_3$) 7.41–7.26 (m, 5H), 4.89 (d, J = 2.8 Hz, 1H), 4.30 (d, J = 2.9 Hz, 1H), 2.99 (d, J = 17.6 Hz, 1H), 2.79 (d, J = 17.6 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 172.4 (C), 164.0 (C), 143.7 (C), 128.8 (CH), 127.3 (CH), 125.7 (CH), 89.8 (CH$_2$), 47.2 (C), 45.0 (CH$_2$), 27.1 (CH$_3$); HRMS (DART) m/z calcd for C$_{12}$H$_{13}$O$_2$ (M + H)$^+$: 189.09101. Found: 189.09100.

(3*S**,4*S**)- and (3*S**,4*R**)-4-Methyl-5-methylene-2-oxo-4-phenyltetrahydrofuran-3-carboxylic acid (2.15f)
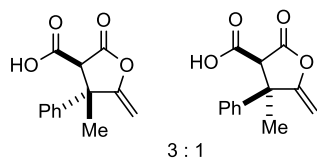
Prepared according to General Procedures A using: **2.14a** (100 mg, 0.367 mmol), Ag$_2$CO$_3$ (10 mg, 0.0367 mmol) and PhH/H$_2$O (4:1) as the solvent. The mixture was stirred at rt for 18 h affording **2.15f** as a colorless oil (75 mg, 88%) after purification. A mixture of diastereoisomers was obtained in a 3:1 ratio of major (3*S*,4*S* and 3*R*,4*R*) and minor (3*S*,4*R* and 3*R*,4*S*). ^1H NMR (300 MHz, CDCl$_3$) 7.40–7.34 (m, 5H, mixture), 5.07 (d, J = 3.2 Hz, 1H, major), 5.01 (d, J = 3.3 Hz, 1H, minor), 4.47–4.45 (m, 1H, mixture), 3.89 (s, 1H, major), 3.71 (s, 1H, minor), 1.95 (s, 3H, minor), 1.70 (s, 3H, major); ^{13}C NMR (75 MHz, CDCl$_3$) 170.1 (C),

168.0 (C), 162.1 (C, minor), 161.2 (C, major), 142.4 (C), 129.1 (CH, major), 128.7 (CH, minor), 128.3 (CH, major), 128.0 (CH, minor), 126.49 (CH, minor), 125.99 (CH, major), 91.8 (CH$_2$, major), 90.8 (CH$_2$, minor), 59.5 (CH, major), 58.4 (CH, minor), 51.2 (C, major), 50.1 (C, minor), 26.5 (CH$_3$, minor), 23.0 (CH$_3$, major). HRMS (DART) m/z calcd for C$_{13}$H$_{11}$O$_4$ (M)$^-$: 231.06628. Found: 231.06594.

(3*S**,4*S**)- and (3*S**,4*R**)-Methyl 4-methyl-5-methylene-2-oxo-4-phenyltetrahydrofuran-3-carboxylate (2.15g)
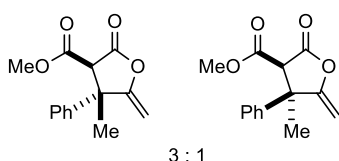
Prepared according to General Procedure A using: **2.14a** (100 mg, 0.367 mmol), Ag$_2$CO$_3$ (10 mg, 0.0367 mmol) and PhH/MeOH (10:1) as the solvent. The mixture was stirred at 85 °C for 2 h affording **2.15g** as a colorless oil (84 mg, 93%) after purification. NOE experiments showed a mixture of diastereoisomers was obtained, a 3:1 ratio of major (3*S*,4*S* and 3*R*,4*R*) and minor (3*S*,4*R* and 3*R*,4*S*). ^{1}H NMR (300 MHz, CDCl$_3$) 7.42–7.27 (m, 5H, mixture), 5.07 (d, J = 3.1 Hz, 1H, major), 4.98 (d, J = 3.1 Hz, 1H, minor), 4.46 (d, J = 3.1 Hz, 1H, major), 4.39 (d, J = 3.1 Hz, 1H, minor), 3.85 (s, 1H, major), 3.78 (s, 3H, major), 3.67 (s, 1H, minor), 3.26 (s, 3H, minor), 1.89 (s, 3H, minor), 1.61 (s, 3H, major); ^{13}C NMR (75 MHz, CDCl$_3$) 168.2 (C, major), 167.9 (C, minor), 166.2 (C, major), 165.7 (C, minor), 162.4 (C, minor), 161.2 (C, major), 143.0 (C, major), 139.4 (C, minor), 129.0 (CH, major), 128.3 (CH, minor), 127.9 (CH, minor), 127.8 (CH, major), 126.6 (CH, minor), 125.7 (CH, major), 91.3 (CH$_2$, major), 90.3 (CH$_2$, minor), 60.0 (CH, major), 59.7 (CH, minor), 52.8 (CH$_3$, major), 52.2 (CH$_3$, minor), 51.2 (C, major), 50.9 (C, minor), 27.3 (CH$_3$, minor), 23.0 (CH$_3$, major); HRMS (DART) m/z calcd for C$_{14}$H$_{13}$O$_4$ (M)$^-$: 245.08193. Found: 245.08181.

(*E*)-4-Methyl-5-pentylidene-4-phenyldihydrofuran-2(3H)-one (*E*-2.15h)
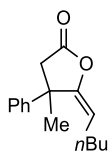
Prepared according to General Procedure A using: **2.14b** (100 mg, 0.367 mmol), Ag$_2$CO$_3$ (10 mg, 0.0367 mmol) and THF/H$_2$O (10:1) as the solvent. The mixture was stirred at 85 °C for 2 h affording **E-2.15h** as a colorless oil (77 mg, 86%) after purification. ^{1}H NMR (300 MHz, CDCl$_3$) 7.34–7.29 (m, 4H), 7.23–7.20 (m, 1H), 5.19 (s, 1H), 2.88 (d, J = 15.4 Hz, 1H), 2.64 (d, J = 15.4 Hz, 1H), 2.22 (app t, J = 7.3, 7.6 Hz, 2H), 1.59–

1.49 (m, 2H), 1.46 (s, 3H), 1.37 (sextet, J = 7.2, 7.5, 7.7, 7.1, 2H), 0.91 (t, 7.3, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 168.4 (C), 152.1 (C), 145.4 (C), 128.7 (CH), 126.9 (CH), 125.3 (CH), 109.8 (CH), 43.8 (CH$_2$), 38.2 (C), 32.3 (CH$_2$), 28.4 (CH$_2$), 28.2 (CH$_3$), 22.0 (CH$_2$), 13.8 (CH$_3$); HRMS (DART) m/z calcd for C$_{16}$H$_{24}$O$_2$N (M + NH$_4$)$^+$: 262.18016. Found: 262.18008.

(3S*,4R*,E)- and (3S*,4S*,E)-Methyl 4-methyl-2-oxo-5-pentylidene-4-phenyltetrahydrofuran-3-carboxylate (E-2.15i)
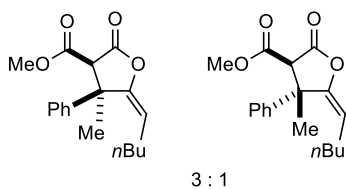
Prepared according to General Procedure A using: **2.14b** (100 mg, 0.367 mmol), Ag$_2$CO$_3$ (10 mg, 0.0367 mmol) and THF/MeOH (4:1) as the solvent. The mixture was stirred at 85 °C for 2 h affording **E-2.15i** as a colorless oil (90 mg, 81%) after purification. NOE experiments showed a mixture of diastereoisomers was obtained, a 3:1 ratio of major (3S,4R and 3R,4S) and minor (3S,4S and 3R,4R). ^{1}H NMR (300 MHz, CDCl$_3$) 7.33–7.26 (m, 5H, mixture), 5.26 (s, 1H, minor), 5.14 (s, 1H, major), 3.81 (s, 1H, major), 3.66 (s, 1H, minor), 3.61 (s, 3H, major), 3.30 (s, 3H, minor), 2.28–2.23 (m, 2H, mixture), 1.60–1.52 (m, 5H, mixture), 1.42–1.34 (m, 2H, mixture), 0.93 (t, J = 7.2 Hz, 3H, mixture); ^{13}C NMR (75 MHz, CDCl$_3$) 166.9 (C, major), 166.4 (C, minor), 164.8 (C, major), 164.4 (C, minor), 152.6 (C, major), 152.3 (C, minor), 143.8 (C, major), 141.7 (C, minor), 128.8 (CH, major), 128.4 (CH, minor), 127.4 (CH, minor), 127.4 (CH, major), 126.2 (CH, minor), 125.7 (CH, major), 109.7 (CH, major), 107.6 (CH, minor), 58.8 (CH, minor), 58.0 (CH, major), 52.3 (CH$_3$, major), 52.0 (CH$_3$, minor), 41.9 (C, minor), 41.5 (C, major), 32.3 (CH$_2$, minor), 32.0 (CH$_2$, major), 28.3 (CH$_2$), 27.7 (CH$_3$, minor), 23.0 (CH$_3$, major), 22.0 (CH$_2$), 13.8 (CH$_3$). HRMS (DART) m/z calcd for C$_{18}$H$_{26}$O$_4$N (M + NH$_4$)$^+$: 320.18563. Found: 320.18555.

(Z)-5-Benzylidene-4-methyl-4-phenyldihydrofuran-2(3H)-one (Z-2.15j)
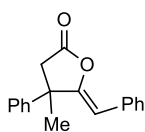
Prepared according to General Procedure A using: **2.14c** (100 mg, 0.367 mmol), Ag$_2$CO$_3$ (10 mg, 0.0367 mmol) and PhH/H$_2$O (10:1) as the solvent. The mixture was stirred at 85 °C for 2 h affording **Z-2.15j** as a colorless oil (89 mg, 92%) after purification. ^{1}H NMR (300 MHz, CDCl$_3$) 7.58 (d, J = 8.5 Hz, 2H), 7.44–7.21 (m, 8H), 5.47 (s, 1H), 3.04 (d, J = 17.7 Hz, 1H), 2.83 (d, J = 17.7 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (75

MHz, CDCl₃) 172.4 (C), 156.7 (C), 144.1 (C), 133.6 (C), 128.8 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 127.0 (CH), 125.9 (CH), 105.5 (CH), 47.9 (C), 44.5 (CH₂), 27.0 (CH₃); HRMS (DART) m/z calcd for $C_{18}H_{17}O_2$ (M + H)⁺: 265.12231. Found: 265.12156.

4-Methyl-4-phenyl-3,4-dihydro-2*H*-pyran-2-one (2.16a)
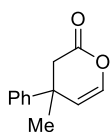
Prepared according to General Procedures A using: **2.14a** (100 mg, 0.367 mmol), AuCl (9 mg, 0.0367 mmol), K₂CO₃ (51 mg, 0.367 mmol) and THF (wet) as the solvent. The mixture was refluxed for 2 h affording **2.16a** as an impure yellow film (23 mg, 33%) after flash chromatography. ¹H NMR (300 MHz, CDCl₃) 7.38–7.32 (m, 5H), 6.60 (d, J = 6.0 Hz, 1H), 5.48 (d, J = 6.0 Hz, 1H), 2.95 (d, J = 15.6 Hz, 1H), 2.73 (d, J = 15.6 Hz, 1H), 1.51 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 168.7 (C), 146.4 (C), 129.0 (CH), 128.8 (CH), 127.8 (CH), 126.0 (CH), 116.0 (CH), 41.7 (CH₂), 33.0 (C), 26.8 (CH₃). MS (EI) 188 (M⁺).

Pd-Catalyzed Tandem Lactonization Cross-Coupling Reactions
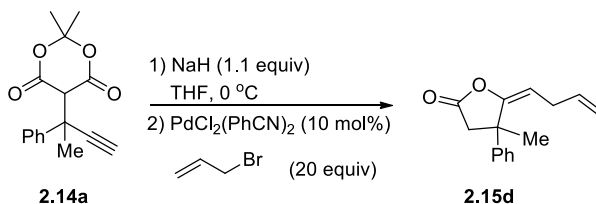
This modified procedure is based on Pd-catalyzed cyclized coupling of alkynoic acids with alkyl halides reported by Utimoto.[79] A flame-dried round bottom flask charged with argon and NaH (0.016 g, 0.646 mmol) in THF (0.74 mL) was cooled in an ice bath. A solution of **2.14a** (0.16 g, 0.518 mmol) in THF (0.74 mL) was then added dropwise and mixture was stirred for 30 min. PdCl₂(PhCN)₂ (20 mg, 0.0518 mmol) was then added followed by allyl bromide (0.90 mL, 10.36 mmol). The resulting mixture was stirred for 14 h at rt. The reaction was ceased by concentrating down on the reaction mixture onto a small amount of silica gel, and purified by loading it to the top of a column packed with silica gel and eluting with 1:6 EtOAc:hexanes. **2.15d** was isolated as a pale yellow oil (48 mg, 38%).

¹H NMR (300 MHz, CDCl₃) 7.39–7.32 (m, 5H), 5.58–5.45 (m, 1H), 5.25 (t, J = 8.1 Hz, 1H), 4.87–4.76 (m, 2H), 2.94 (d, J = 18.3 Hz, 1H), 2.77 (d, J = 18.6 Hz, 1H), 2.31–2.23 (m, 2H), 1.75 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) 172.7 (C), 157.3 (C), 144.1 (C), 135.4 (CH), 128.9

(CH), 127.2 (CH), 125.8 (CH), 115.2 (CH$_2$), 103.6 (CH), 48.0 (CH$_2$), 45.6 (C), 29.2 (CH$_2$), 25.7 (CH$_3$). HRMS (DART) *m/z* calcd for C$_{15}$H$_{20}$NO$_2$ (M + NH$_4$)$^+$: 246.14940. Found: 246.14662.

Chapter 3: Intramolecular Conjugate Addition

3.1. Introduction

3.1.1. Indolines: Background and Preparation

Indolines are common structural motifs with a broad range of applicability, from natural products that possess therapeutic activity,[80] to organocatalysts in stereoselective reactions (Figure 1).[81] For example, the antitumor antibiotic (+)-duocarmycin A was prepared by the key indoline synthon **3.1** (Figure 1). Therefore synthetic strategies that furnish substituted indolines, particularly consisting of enantioenriched centers, would be of great utility. Several approaches have been developed where those forming racemic compounds involving the reduction of indoles and radical cyclizations will not be discussed.[82] Rather, the focus of this section will be on enantioselective protocols for the formation of 3-substituted indolines.
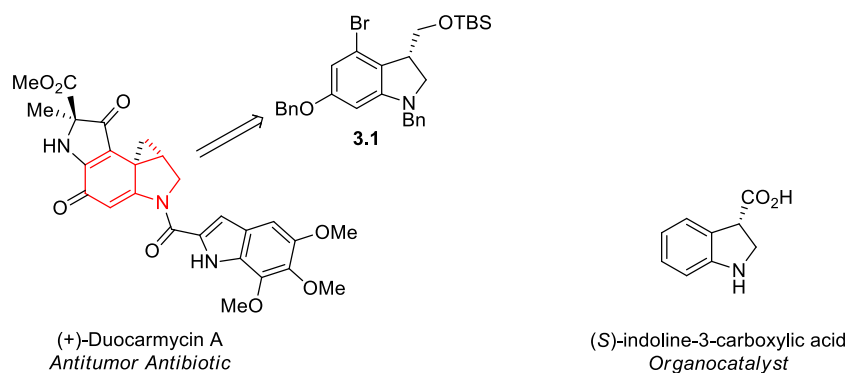
Figure 3.1. Selected Examples of Indolines Scaffolds

Independently, both Bailey and Groth reported (–)-sparteine-mediated carbolithiation of *N*-allyl-*N*-benzyl-2-bromoaniline in the synthesis of 3-substituted indolines (Scheme 3.1).[83,84] Lithium-halogen exchange in the presence of **L1** affords a chiral carbanion that can undergo intramolecular carbocyclization in good to excellent yields and enantioselectivities. However, this approach has limited substrate scope due to the harsh reaction conditions.

Scheme 3.1. Intramolecular Carbolithiation in the Formation of 3-Substituted Indolines

>65% yield, up to 90% ee
R^1 = 4/5-OBn, 4-Me; R^2 = Me, Bn, allyl
E = H, Br, CHO

L1, (-)-Sparteine
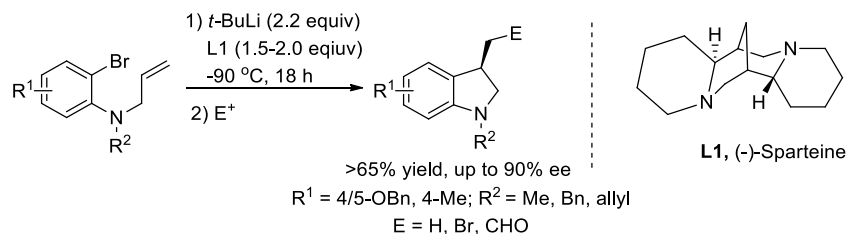
Another common strategy takes advantage of preexisting indoline backbones by using 3-substituted indoles as precursors. The Reisman group recently reported the formal [3+2] cycloaddition between 3-substituted indoles and 2-amidoacrylates to prepare various pyrroloindolines in high enantioselectivities (Scheme 3.2a).[85] It was postulated that the reaction proceeds through a stepwise mechanism in which (R)-BINOL·SnCl$_4$ complex activates the 2-amidoacrylate, promoting the conjugate addition by the indole resulting in an iminium ion that subsequently undergoes an intramolecular attack. Most notable derivative was **3.2** that possess an all-carbon quaternary center at 3-position of the indoline (Scheme 3.2a).

Alternatively, the asymmetric hydrogenation of indoles has been accomplished with Rh-**L2** complex, but only 2-substituted indoles afforded indoline adducts in high yields and selectivities; 3-substituted indoles resulted in predominately the hydrolysis of the amide (Scheme 3.2b).[86] The protecting group on the nitrogen atom of the indole was important, as it was believed to act as a secondary coordinating group. The poor reactivity of 3-substituted indoles was remedied by preparing the N-tosylated indole, affording the corresponding indolines in high yields and selectivities.[87] More recently, conditions for the asymmetric hydrogentation of unprotected indoles using Pd(II)/**L3** catalyst and a Brønsted acid as an activator have been described (Scheme 3.2c).[88] This strategy relies on the activation of unprotected indoles by protonation at the C-3 position forming an iminium ion that is prone to hydrogenation. Interestingly, for 2-substituted indoles the enatioselective-controlled step is the hydrogenation step, whereas for 2,3-disubstituted indoles it is the protonation step. Due to the significantly faster rate of protonation versus hydrogenation ($k_1 >> k_2$) a dynamic kinetic resolution is responsible for the high enantioselectivities observed.

Scheme 3.2. Enantioselective Approaches to 3-Substituted Indolines from Indole Precursors

a)

3:1 d.r
92% ee

5:1 dr
94% ee

3.2, 18:1 dr
86% ee

b)

R[1] = H, R[2] = *n*-Bu, R[3] = Ac, 94% yield, 94% ee
R[1] = Me, R[2] = H, R[3] = Ac, 37% yield, 86% ee
R[1] = *i*-Pr, R[2] = H, R[3] = Ts, 94% yield, 97% ee

L2

c)

82% yield, 92% ee

L3

Dynamic Kinetic Resolution
$k_1 \gg k_2$
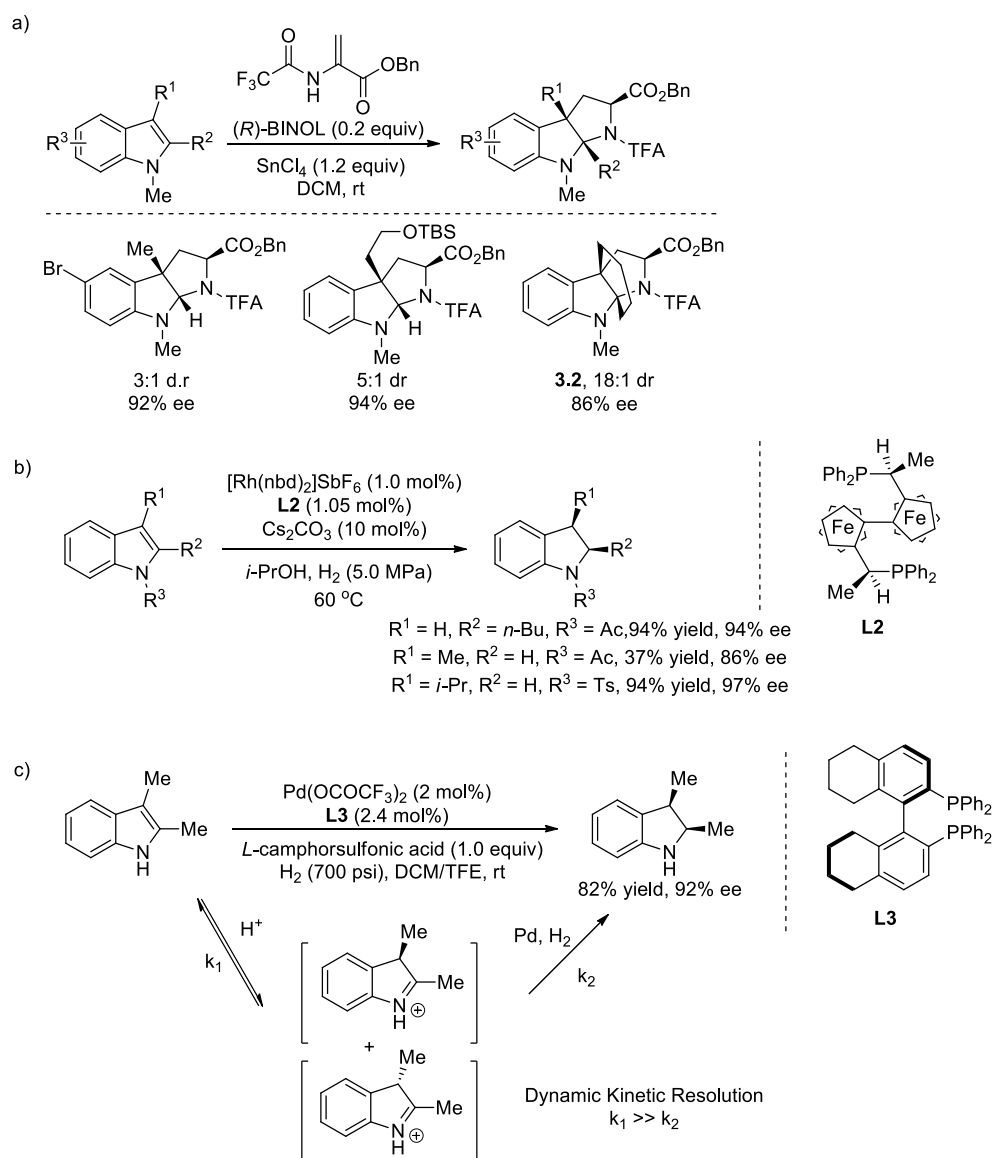
3.1.2. Intramolecular Cyclizations: Conjugate Addition Methodologies

A more practical and general approach that does not require the pre-existing indole to prepare 3-substituted indolines is required. One approach may be to use a latent C–M bond that can react at the designated time. Macdonald has reported a method for the intramolecular conjugate addition to 2-cyclohexenones that proceeded by the Lewis acid activation of the enone, followed by the nucleophilic attack of a weakly polarized $C(sp^3)$–Sn bond that resulted

in mixture of *cis-* and *trans-*2-decalones **3.3** in high yields (Scheme 3.3a).[89] For 3-methyl-2-cyclohexenone derivatives, where the alkylstannyl side chain is in the pseudoaxial position, the reaction does not undergo a conjugate addition but rather a hydride transfer from the β-position to the Me$_3$Sn group to the electrophilic position of the enone generating a single isomer ($\pm$)-**3.4** (Scheme 3.3b). It was postulated that the steric effects between the Me group at the disubstituted β-enone and the Me$_3$Sn bound to the nucleophilic carbon does not allow for the 6-membered transition state for the conjugate addition to take place. Interestingly, all carbon quaternary centers were accessible using shorter alkyl tether (n = 3) which preferentially undergoes the conjugate addition affording **3.5** in good yield. This example highlights the preference for conjugate addition over a hydride shift even for sterically demanding centers. Additionally, spiro-cycloadduct **3.6** were prepared using β-substituted cyclohexenones (Scheme 3.3d). Feldman employed this strategy in the preparation of the tricyclic core of ($\pm$)-halichlorine by refluxing intermediate **3.7** in toluene and MgBr$_2$ as the Lewis acid activator to access **3.8** (Scheme 3.3e).[90] In their hands, MgBr$_2$ proved to be a superior Lewis acid catalyst giving better yields and cleaner reactions than the TiCl$_4$ or SnCl$_4$ reported by Macdonald.

Scheme 3.3. Intramolecular Conjugate Addition of Tetraalkylstannanes to Cyclohexenone Derivatives
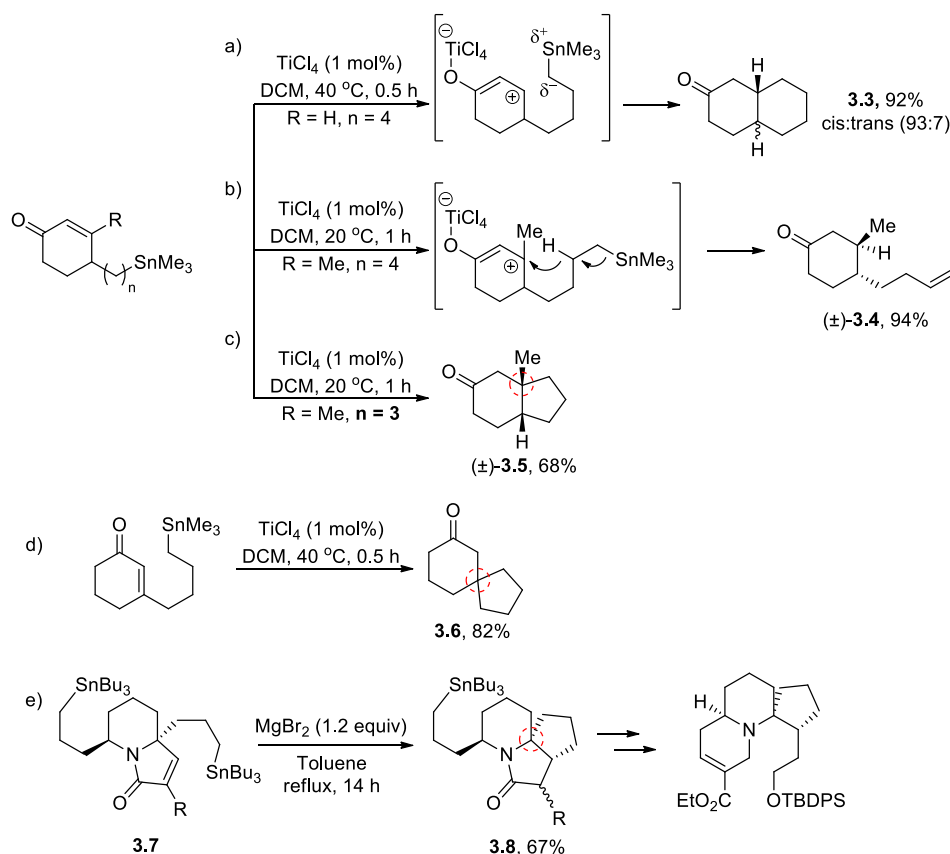
In order to achieve enantioselectivity, transmetallation with a chiral transition metal complex offers an attractive approach. Particularly, intramolecular methodologies as they do not suffer from the same limitations and are generally entropically more favoured than intermolecular reactions. Moreover, intramolecular conjugate addition of stabilized carbanionic centers to Michael acceptors is a well established process that has exhibited a great deal of synthetic utility.[91] In contrast, reports of methods that entail intramolecular Michael additions of nonstabilized carbanionic centers (e.g., organometallic species) to activated C–C double bonds are relatively rare. Focusing on the latter protocols, Piers has prepared various bicyclo-compounds by the copper mediated intramolecular conjugate addition of alkenyltrimethylstannes to α,β-enones (Table 3.1).[92] *Cis*-fused bicyclo[4.3.0]nonanes possessing quaternary centers were prepared (Table 3.1, entries 1–3), which would be challenging substrates to prepare using alternate approaches. These examples illustrate one of

the points made earlier, where the poor reactivity of monoalkenylcopper(I) species in intermolecular conjugate additions to enones is overcome by intramolecular nature of this protocol.[93] However, a drawback to this strategy is the need for excess (2.5 equiv) of Cu(I) salts.

Table 3.1. Cu-Mediated Intramolecular Conjugate Addition
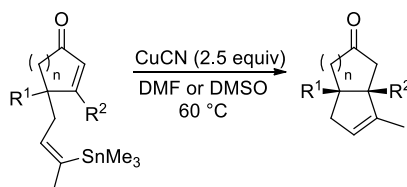
Entry	R^1	R^2	n	Yield (%)^a
1	H	Me	2	92
2	H	i-Pr	2	73
3	Me	Me	2	85^b
4	H	H	1	76^b
5	Me	H	1	77^b

^{a}Isolated yield. ^{b}Reaction run with CuCl at rt.

In contrast to copper-mediated conjugate additions, a catalytic protocol reported by Furman describes the intramolecular conjugate addition of vinylstannanes to 2,3-dihydro-4-pyridones catalyzed by [RhCl(cod)]$_2$ under mild conditions (Scheme 3.4).[94] Excellent yields of cycloadducts (±)-**3.9** were obtained as single diastereomers.

Scheme 3.4. Rh(I)-Catalyzed Intramolecular Conjugate Addition of Vinylstannanes
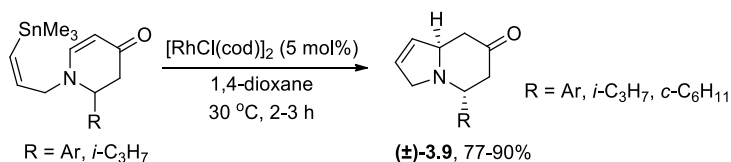
It is worth noting that majority of inter- and intramolecular procedures for the formation of C–C bonds utilize sp and sp^2 hybridized organometallic precursors, which can be ascribed to the relative stability of these C–M bonds (M = B, Si, Zn, Sn,) versus the strongly polar C–M bonds (M = Li, Na, MgX). Thus, notably absent are metal catalyzed intramolecular

conjugate additions that transfer sp^3-hybridized carbons, particularly in the formation of quaternary centers. With respect to the former, difficulty of transferring sp^3-hybridized carbons is likely due to poor reactivity and selectivity of the organometallic bond, alkyltin reagents for example, and competing side reactions such β-hydride eliminations for reagents bearing a β-hydrogen (Figure 3.2).[95] As a result, reagents that selectively transmetallate and are
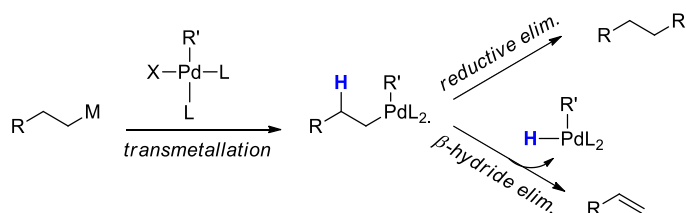
Figure 3.2. Schematic Example of β-Hydride Elimination versus Reductive Elimination

tolerant to majority of transformations offer an attractive solution. To this end, a report by Vedejs showed a convenient protocol to prepare 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane **3.10** that showed a significant advantage over other alkylstannanes in Stille coupling reactions (Scheme 3.5).[96] The atrane framework results in unique bonding and intramolecular interactions that are not observed for other stannanes.[97] For example, the apical Sn–C bond (2.21 Å) in **3.10b**, to the best of the authors' knowledge, is the longest bond length known for a tetraorganotin compound and is approximately 0.06 Å longer than the internal methylene Sn–C bonds (2.15-2.17 Å).[98] This abnormally long Sn–C bond is credited for the increased reactivity observed for these reagents where metal-alkyl exchange occurs exclusively at the exocyclic Sn–C bond circumventing unwanted alkyl transfers that have been reported for other alkylstannanes. Tricarbastannatranes **3.10** are crystalline in nature and less toxic than volatile trimethylstannanes,[99] and avoid tedious workups typically accompanied with greasy alkylstannanes. Furthermore, they are not air or moisture sensitive and can even be recycled.

Scheme 3.5. Stille Coupling of Carbastannatranes **3.10** versus Tetramethylstannane
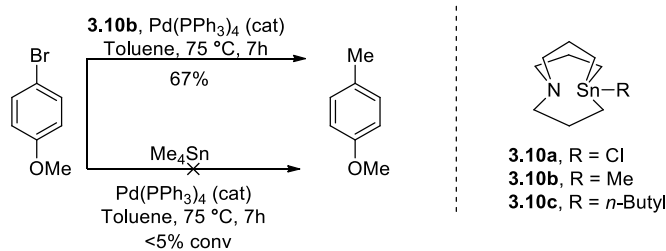
Tricarbastannatranes **3.10** have been mainly utilized in Stille coupling reactions. Their advantage over other nucleophilic coupling partners, particularly other stannanes, is exemplified by challenging reactions that afforded products which could not be accessed by other means. As an illustrative example, Hegedus reported that alkylation, via transmetalation, of **3.11** was only observed with carbastannatranes **3.10d** and **3.10e** (Scheme 3.6);[100] where any other combination of metal catalysts (Ni, W, Ir, Mo, Rh) and organometallic reagents (NaBPh₄, PhZnBr, H₂C=CHSnBu₃, PhSnMe₃) failed to afford any substituted products.

Scheme 3.6. Pd-Catalyzed Allylic Substitution With Carbastannatranes
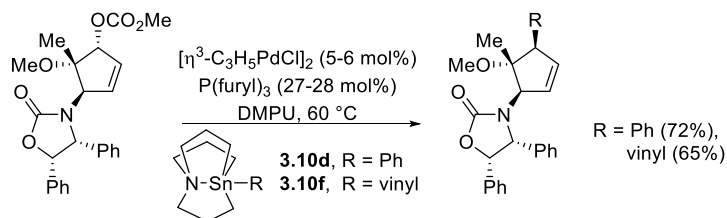
Furthermore, Fillion reported the enhanced reactivity of carbastannatrane **3.10f** compared to Me₃SnCH₂I and Bu₃SnCH₂I in the formation of sp³-*gem*-dimetallic species and evidence for a carbenoid intermediate in *cine*-substitution studies of Stille coupling reactions (Scheme 3.7).[101] NMR studies revealed carbenoid reactivity in the decomposition of **3.10f** with Pd-catalyst resulting in: cyclopropanation with excess norbornene, dimerization to ethene, O₂ trapping to form formaldehyde and iodostannatrane **3.10g** byproduct (Scheme 3.7). Observation of these adducts supported the Busacca-Farina *cine*-substitution mechanism in the Stille Coupling of sterically demanding vinyl stannanes.

Scheme 3.7. Carbastannatranes in *Cine*-Substitution Studies of Stille Coupling Reactions

3.10f
3.10g
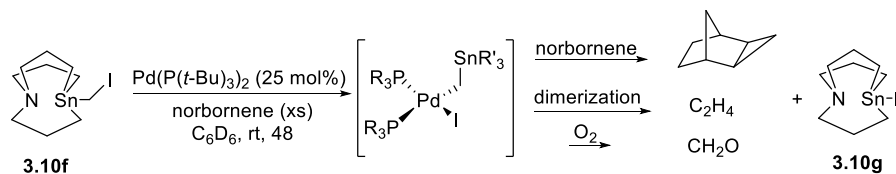
More recently, a stereoretentive protocol using secondary alkylcarbastannatranes **3.10h** as nucleophilic coupling partners in Stille coupling reactions has been reported by Biscoe (Scheme 3.8).[102] Chiral secondary alkyl groups were transferred with minimal erosion of enantiomeric excess or the formation of β-hydride elimination side products, further emphasizing the selective nature of alkylcarbastannatranes as nucleophilic sources of sp^3-hybridized carbons.

Scheme 3.8. Selected Example of Pd-Catalyzed Stereoretentive Cross-Coupling of Secondary Alkylcarbastannatrane with 2-Bromopyridine

3.10h, 94% e.e.
65%, 91% e.e.
L4
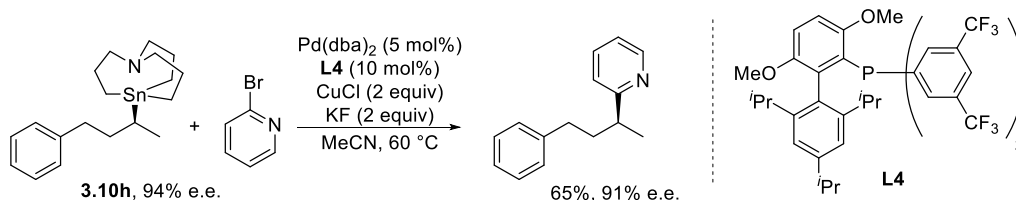
In order to address the challenges of accessing all-carbon stereogenic centers by an intramolecular protocol, highly electrophilic acceptors may be necessary. Our group's success in employing Meldrum's acid alkylidenes as activated acceptors for the preparation of adducts bearing enantioenriched all-carbon tertiary and quaternary centers offers an attractive strategy to develop an intramolecular protocol. The ease as to which unactivated nucleophiles can be inserted in a 1,4-fashion was shown by the Sc(OTf)$_3$-catalyzed conjugate addition of allylstannanes to alkylidene Meldrum's acid derivatives under mild reaction conditions developed in our group (Scheme 3.9).[103] High yields of tertiary and quaternary benzylic adducts were obtained.

Scheme 3.9. Lewis Acid Catalyzed Conjugate Allylation of Alkylidene Meldrum's Acid
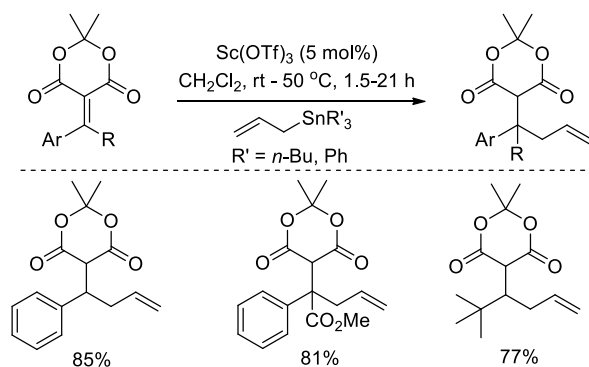
Furthermore, Rh-catalyzed inter- and intramolecular conjugate addition of vinylstannanes has also been developed in our laboratory (Scheme 3.10).[104] Optimal yields and enantiomeric ratios (er) were obtained using a cationic chiral Rh(I)-complex that was prepared by the addition of $AgSbF_6$ and chiral diene **L5**. Mild reaction conditions showed great functional group tolerance where aryl halides and boronic esters were unaffected, offering synthetic handles for further transformations (Scheme 3.10a). The allyl acetate or carbonate group was essential to obtain any reactivity, where vinyl stannanes did not add in appreciable amounts. Noteworthy was the intramolecular conjugate addition of **3.12** which afforded the cyclized Meldrum's acid **3.13** in modest yield and er (Scheme 3.10b). The superiority of the intramolecular addition of **3.12** was shown when the intermolecular conjugate addition with the analogous geminal stannane failed to show any reactivity under identical conditions used for **3.12** (Scheme 3.10a).

Scheme 3.10. Rh-Catalyzed Asymmetric a) Inter- and b) Intramolecular Conjugate Addition of Alkenylstannanes to Meldrum's Acid Benzylidenes
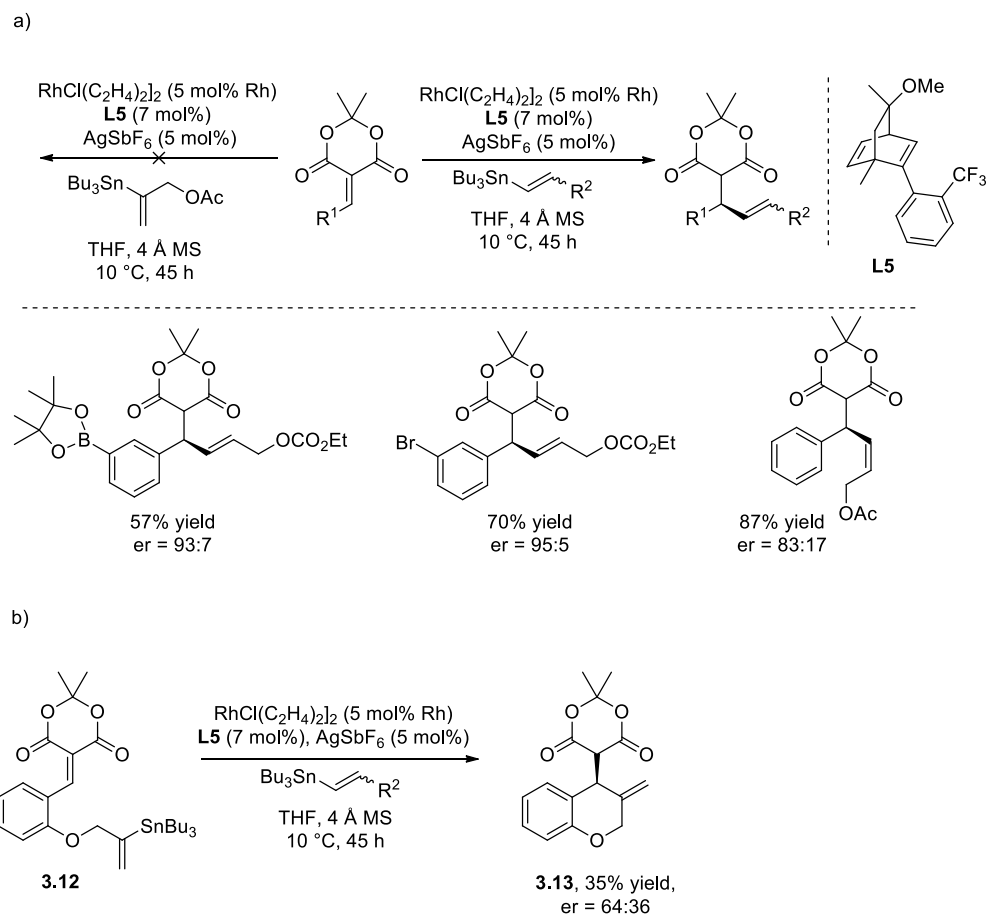
Prior to the outset of this project and to the best of our knowledge, no reports of conjugate addition reactions using alkyl carbastannatranes **3.10** had been reported until earlier this year when the Fillion group published such a procedure.[105] The 1,4-conjugate alkylation of benzylidene Meldrum's acid was achieved using 2 equivalents of alkyl carbastannatranes **3.10** and 1 equivalent of $B(C_6F_5)_3$ as strong bulky Lewis acid that dealkylates 1 equivalent of **3.10**, generating a cationic carbastannatranes that is responsible for activation of the alkylidene, while the second equivalent subsequently alkylates the β-position (Scheme 3.10). ^{119}Sn NMR in conjunction with HRMS studies showed evidence for tin-enolate intermediates, and adroit ^{13}C-NMR studies using CD_3-carbastannatranes helped establish that it was indeed the second equivalent of **3.10** that was responsible for the alkylation.

Scheme 3.11. First Report of Conjugate Addition Reactions Using Carbastannatranes
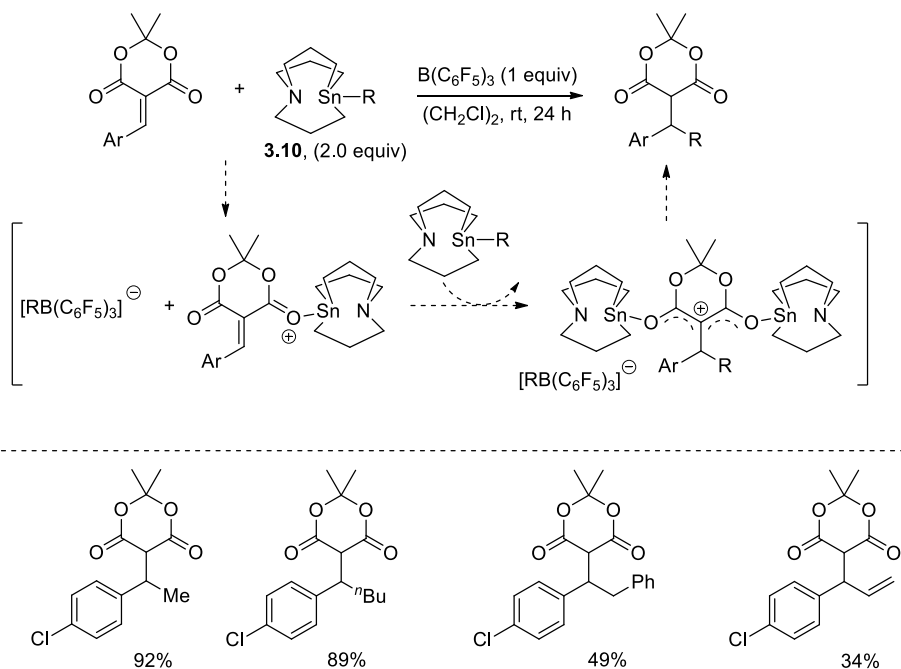
Previous attempts have been made in our group to study intramolecular conjugate additions using **3.14** as potential models (Table 3.2).[106] However, these compounds do not transmetallate with Rh-catalysts; intramolecular conjugate addition did take place upon formation of the more nucleophilic stannate complex by the addition of TBAB (entries 3 and 4).

Table 3.2. Results from Intramolecular Reactions of Meldrum's Acid Alkylidene **3.14**

Entry	TM (mol%)	Additive	Solvent	Temp (°C)	% Yield
1	[Rh(cod)Cl]$_2$ (0.1)	-	THF	rt	0
2	[Rh(cod)(MeCN)$_2$]BF$_4$ (0.05)	-	THF	rt	0
3	[Rh(cod)(MeCN)$_2$]BF$_4$ (0.05)	H$_2$O:TBAB	THF	50	23
4	-	H$_2$O:TBAB	THF	50	29

Efforts to examine alternative organometallic $C(sp^3)$-M sources, such as boron derivatives **3.15,** were prepared but did not show any reactivity towards Rh-catalysts and decomposition of starting material was observed at elevated temperatures (Scheme 3.12). Additionally, these compounds failed to condense with Meldrum's acid and therefore lacked an activated electrophilic site. Interestingly, these two examples show the potential for transferring sp^3-hybridized carbon atoms intramolecularly via conjugate addition, and draws attention to the need for a model system that possesses both an organometallic group that can transmetallate and an activated site for conjugate addition.

Scheme 3.12. Intramolecular Conjugate Addition Attempts with Boron Derivatives **3.15**

3.15, BR_n = B(pin), BF_3K
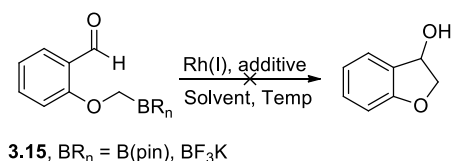
3.2. Proposal

The aim of this project was to develop a methodology for the enantioselective intramolecular formation of $C(sp^3)$–$C(sp^3)$ bonds (Figure 3.3). A model that possesses elements of previously successful conjugate addition reactions was envisaged, where an organometallic appendage proven to transmetallate can subsequently undergo a 1,4-conjugate addition at an activated site to afford enantioenriched 3-substituted indolines (Figure 3.3). Two potential routes will be explored where either an α-aminoorganometallic synthon will undergo a Knoevenagel condensation resulting in the model substrate **3.16** (Figure 3.3a); or *N*-alkylation of the Meldrum's acid derivative to access **3.16**. Models bearing the carbastannatrane group will be focused on as they have been shown to be ideal reagents for the selective transfer of sp^3-hybridized carbons.

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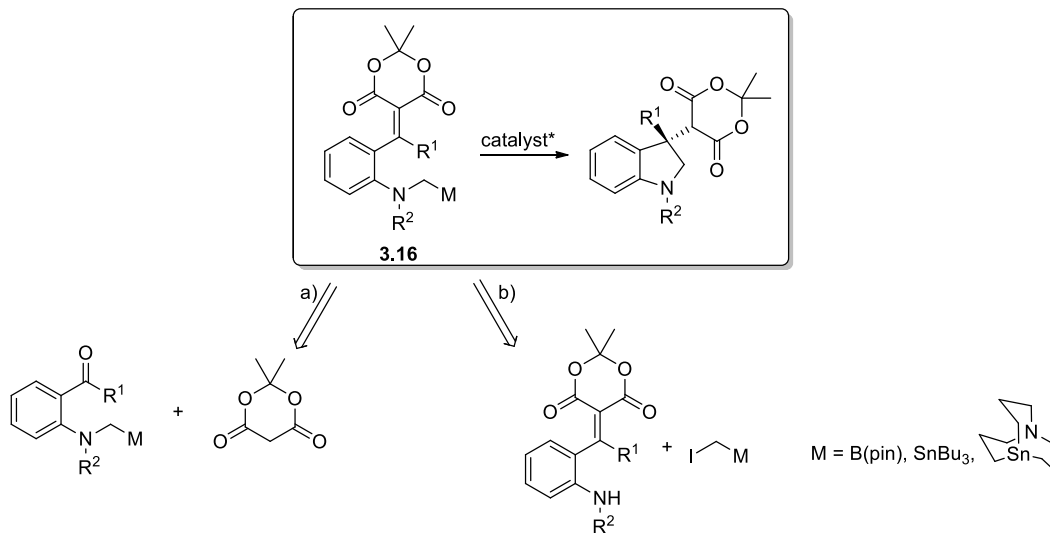
Figure 3.3. Proposed Model for Intramolecular Studies

3.3. Results and Discussion

3.3.1 Preparation of Iodomethyl Tricarbastannatrane and a Novel Approach to *In Situ* Formation of Chlorostannatrane

The selective insertion of transition metals into a C–M bond is essential for developing conditions for the intramolecular conjugate additions and in this regard carbastannatranes fulfill that requirement.

A procedure reported by Merck claimed to be "simple and scalable" method to access chlorostannatrane **3.10a**,[107] and therefore offered an ideal starting point. Hydrostannylation of triallylamine catalyzed by $Pd(OH)_2/C$ gave **3.17** in comparable yield to that reported. However, disproportionation with $SnCl_4$ resulted in varying amounts of **3.10a** with a maximum yield of 31% being obtained (Scheme 3.13). The authors did note the amount of alcohol or water was critical to obtaining high yields, and therefore required a Karl Fischer titration to determine the exact amount of water present. Due to inconsistency of results, and in order to avoid a tedious aqueous workup, an alternate approach to prepare **3.10a** was sought after.

Scheme 3.13. Thermal Disproportionation Preparation of **3.10a**

3.17, 56% (15.5 g)   **3.10a**, 9-31% (<1.6 g)
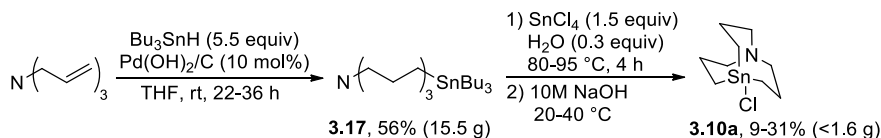
Although several approaches to prepare **3.10a** have been reported,[108] Vedejs' method proved to be efficient and reproducible, but requires the use of relatively expensive Schwartz' reagent, and as a result warranted a search for alternative approaches. It is worth noting that Buchwald has reported a very efficient procedure for the large scale preparation of Schwartz's reagent from the inexpensive zirconocene dichloride.[109] This procedure remedies the over reduction of previous strategies by the introduction of a CH_2Cl_2 wash that converts the zirconocene dihydride back to the monohydride. The overall success of this procedure is highly dependent on the removal of the insoluble Al contaminates by filtration using a modified cannula fitted with a piece of glass fiber filter paper, and the amount of time CH_2Cl_2 is in contact with the Schwartz' reagent; where a sufficient amount of time is required to convert dihydride to monohydride but prolonged exposure leads to complete decomposition to zirconocene dichloride (>10 min). As an alternate approach an *in situ* method was envisaged that would allow for the direct hydrozirconation of the olefin without the need to isolate the moisture, air and light sensitive Schwartz reagent from inexpensive starting reagents.

Previously reported in situ procedures for the generation of Schwartz' reagent for the reduction of olefins have used various hydride sources such as LiAlH,[110c] Red-Al, *t*-BuMgCl, and LiEt$_3$BH. However, they result in the formation of a heterogeneous reagent that is typically contaminated with varying amounts of reductant and other salts which can interact with substrates and intermediates. Therefore, the success of the hydrozirconation was dependent on the substrate (where rate of hydrozirconation appears to decrease in the order of: terminal alkyne > terminal monosubstituted alkene ≈ internal alkyne > 1,2-disubstituted alkene > 2,2-disubstituted alkene > trisustituted alkene),[111] solvent and source of the hydride.

Table 3.3 In Situ Hydrozirconation of Triallylamine in the Formation of **3.10a**
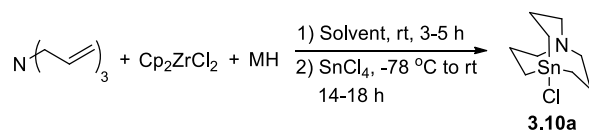
Entry	MH	Solvent	Yield (%)[a]
1	LiAlH(O*t*Bu)₃ (4.0 equiv)[b]	THF	11
2	LiAlH(O*t*Bu)₃ (3.5 equiv)[b]	THF	24
3	LiAlH(O*t*Bu)₃ (3.0 equiv)[b]	THF	17
4	LiAlH(O*t*Bu)₃ (3.2 equiv)[b]	DCM	-
5	LiAlH(O*t*Bu)₃ (3.2 equiv)[b]	Toluene	trace
6	LiAlH(O*t*Bu)₃ (3.2 equiv)[b]	DME	-
7	LiAlH(O*t*Bu)₃ (3.2 equiv)[c]	THF	37
8	LiEt₃BH (3.2 equiv)[b]	THF	-
9	LiEt₃BH (3.2 equiv)[c]	THF	-

[a]Isolated yield. [b] Order of addition: MH to a mixture of triallylamine and Cp₂ZrCl₂. [c] Cp₂ZrCl₂ and MH were premixed for 1 h then triallylamine was added

The problematic transfer of multiple hydrides with LiAlH₄ to zirconocene dichloride was not screened. Rather, LiAlH(O*t*Bu)₃ showed immediate promising results, albeit in low yields, where **3.10a** was obtained in THF (Table 3.3, entry 1). Reducing the number of equivalents from 4.0 to 3.5 improved the yield; moreover, it was determined that a slight excess of 3 equivalents gave best results, where a minimum of 3 equivalents of hydride are required for each molecule of triallylamine. Screening solvents that have been used in either the preparation of Schwartz' reagent or in the hydrozirconation of an olefin did not improve the formation of **3.10a** (entry 4–6). Further improvements were made by changing the order of addition, where slow addition of triallylamine to a premixed solution of Cp₂ZrCl₂ and LiAlH(O*t*Bu)₃ afforded **3.10a** in modest yields (entry 7). Using alternate hydride sources such as "Super hydride" (LiEt₃BH) proved to be inferior and did not afford any **3.10a**. It is important to note that the quality of LiAlH(O*t*Bu)₃ is essential to the overall success of the reaction, where aged LiAlH(O*t*Bu)₃ showed poor to no reactivity. On the other hand, freshly prepared LiAlH(O*t*Bu)₃ restored reactivity and gave optimum results.

In order to keep the project progressing, Schwartz' reagent was purchased in larger quantities and **3.10a** was prepared using Vedejs' protocol, while the in situ protocol was being developed.

3.3.2. Preparation of Alkylidene Meldrum's Acid Derivatives 3.16

Scheme 3.14. Addition–Elimination Approach to **3.16**
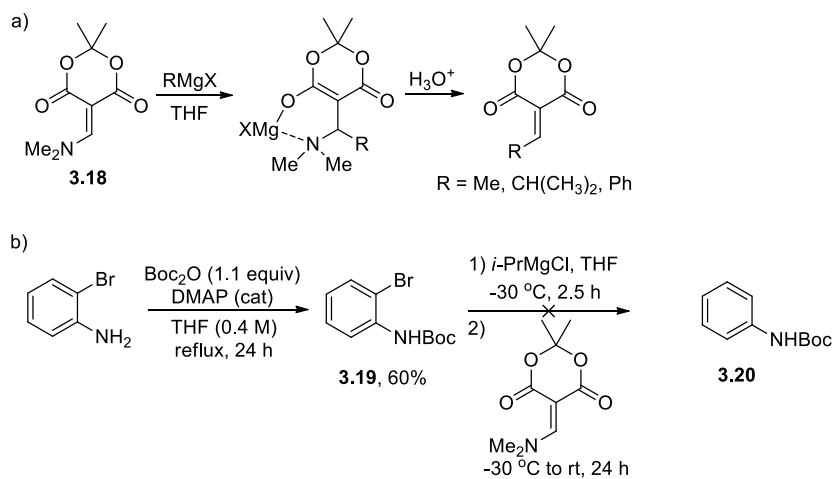
Based on a procedure by Ziegler[112] that showed various alkyl and aryl Grignards can be added to **3.18** via an addition-elimination reaction to access the corresponding alkylidene Meldrum's acid derivatives (Scheme 3.14a); an analogous strategy was envisaged using carbamate **3.19** as a pronucleophile that can undergo a halogen magnesium exchange and then participate in the nucleophilic attack of **3.18** (Scheme 3.14b). Protection of commercially available 2-bromoanaline with di-*t*-butyl dicarbonate gave the carbamate in good yields. However, treatment with *i*-PrMgCl failed to result in the desired alkylidene Meldrum's acid derivative, but rather gave varying amounts of starting material **3.19** as the major component and protonated **3.20** as the minor component in the reaction as determined by analysis of the crude ^{1}H NMR. The fact that **3.20** is seen as the major component suggests that the halogen magnesium exchange did take place, and efforts to achieve reactivity with **3.18** such as longer reaction times or higher temperatures did not result in the desired conjugate addition.[113] Attempts to generate the lithiated carbamate through lithium-halogen exchange with *n*BuLi and then trap the nucleophile with DMF to install the carbonyl at the 2-position also failed.

Though the above approach would have given rise to the model substrate in the fewest steps, commercially available 2-aminobenzyl alcohol proved to be a better starting point where carbamate **3.21** was prepared in ~80% yield after 2 steps (Scheme 3.15). Reported strategies for the Knoevenagel condensation of Meldrum's acid with aldehydes were not successful with **3.21**.[114] However, using stronger Lewis acidic conditions that have been successful for acetophenones afforded **3.22** in approximately 50% yield (Scheme 3.15). Disappointingly, efforts to alkylate **3.22** with **3.10j**, **3.23**, or **3.34** did not result in the model compound after extensive screening of bases, solvents and additives.[115] Most reactions gave either starting material **3.22**, or the hydrolyzed product of **3.21**. Based on these results it was determined that the ICH₂M moiety should be installed prior to the Knoevenagel condensation.

Scheme 3.15. Results for *N*-Alkylation of **3.22**
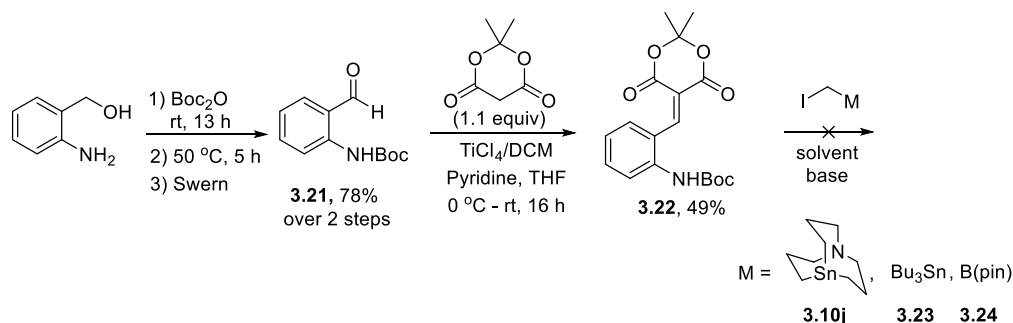
In addition to carbamate **3.21**, sulfonamide **3.27** was also prepared and reported conditions for *N*-alkylations were tested (Scheme 3.16).[116,117] Due the cost and number of synthetic steps to prepare the organometallic reagents **3.10j**, **3.23** and **3.24**, screening for optimal conditions for *N*-alkylation of **3.21** was done using benzyl bromide (Scheme 3.16a). It was found that *N*-alkylation can be achieved affording **3.26** in good yields using K₂CO₃ in DMF at rt, but these conditions failed to give alkylated products when **3.10j**, **3.23**, and **3.24** were used as electrophiles and resulted quantitative recovery of **3.21** and **3.27** (Schemes 3.16a and b respectively). Under more forcing condition, temperatures above 80 °C, decomposition of both reagents was observed. It is plausible the lack of reactivity observed with the organometallic electrophiles could be due to a stable "ate" complex formed between the Lewis acidic metal (B, Sn) and the enolate formed upon deprotonation (Scheme 3.16c). These

intermediates would impede *N*-alkylation and afford the corresponding starting material upon aqueous workup. The successful alkylation with benzyl bromide can be attributed to the absence of a Lewis acidic site.

Scheme 3.16. Results for *N*-Alkylations of Carbamate **3.21** and Sulfonamide **3.27**
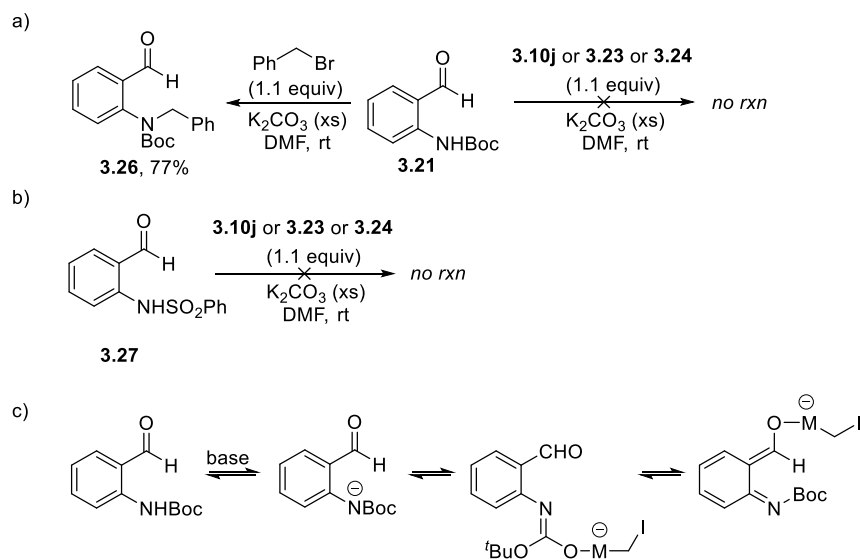
In order to avoid the postulated enolate interference for *N*-alkylation, amino alcohol **3.28** and **3.23** were chosen, based on cost and ease of preparation, to test for reactivity (Table 3.4). It was believed that based on the difference in pKa between the carbamate (~21 in DMSO)[118] and alcohol (~29 in DMSO),[119] alkylation could be achieved under the same conditions used to prepare **3.26**. However, complex mixtures and incomplete reactivity was observed (entry 1). Stronger bases such NaH or *n*BuLi did not improve selectivity and gave mixtures of products, where **3.29** was the only compound that could be isolated and characterized from the mixtures, entry 3. Noteworthy is that **3.29** does possess the desired *N*-alkylated moiety.

Table 3.4. Results for *N*-Alkylation of **3.28**

3.28
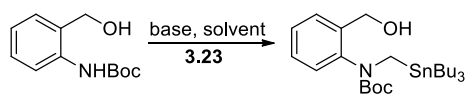
Entry	Reaction Conditions	Product (%yield)[a]
1	K$_2$CO$_3$ (1.5 equiv), DMF, rt, 10 h	mixture
2	1) NaH (1.1 equiv), DMF, rt, 4 h 2) **3.23** (1.5 equiv)	mixture
3	1) *n*-BuLi, THF, -78 °C 2) **3.23** (1.5 equiv)	 **3.29** (22)

[a]Isolated yields.

To mitigate competing *O*-alkylation, THP-protected **3.30** was prepared. *N*-alkylation of **3.30** to **3.31** was achieved smoothly in modest yields by complete deprotonation with KH followed by the addition of **3.23** (Scheme 3.17). Deprotection followed by Swern oxidation gave **3.32** in excellent yield over 2 steps. Finally, Knoevenagel condensation under strongly Lewis acidic conditions afforded model substrate **3.16a**. Though **3.16a** possesses a more stable C–Sn bond compared to the tricarbastannatrane C–Sn, the potential for intramolecular conjugate addition was still examined using Rh(I)-catalysts (Table 3.5).

Scheme 3.17. Preparation of Meldrum's Acid Alkylidene **3.16a**
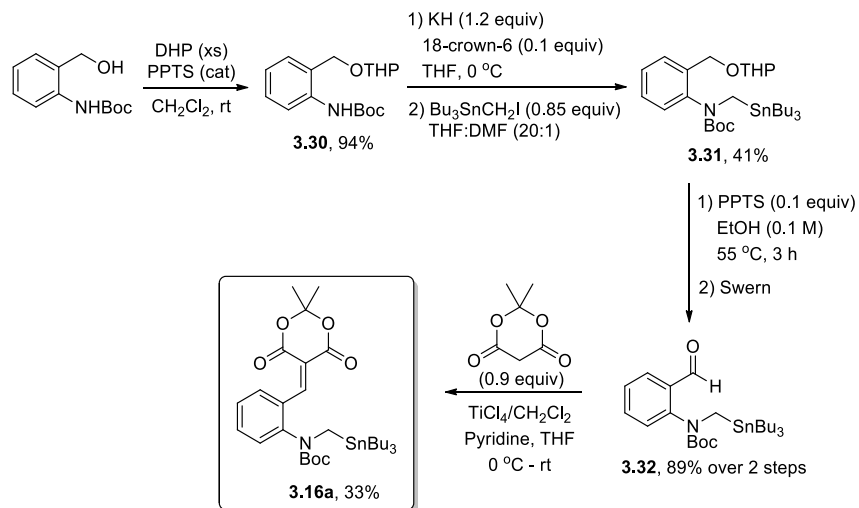
In the absence of any Rh-catalysts and using TBAF as an activator to form a hypervalent organotin complex,[120] no 1,4-conjugate addition adducts were observed and a 1:1 mixture of starting material **3.16a** and **3.32** was observed in the crude ^{1}H-NMR spectrum (Table 3.5, entry 1). Repeating the reactions at higher temperatures resulted in decomposition of starting material (entry 2). Rh-salts were then screened and displayed varying levels of reactivity. Reactions using [RhCl(C$_2$H$_4$)$_2$]$_2$ did not show any reactivity after 72 h at rt and decomposition after 16 h at elevated temperatures, entries 3–4. The addition of phosphine ligands (entry 5) or using a cationic Rh-catalyst that was very effective in conjugate addition reactions (vide supra)[104a] (entry 6) both failed to give any isolatable adducts. Interestingly both [Rh(cod)Cl]$_2$ and [Rh(OH)(cod)]$_2$ afforded spiro compound **3.33**. The structure of **3.33** was proposed based on ^{1}H, ^{13}C, DEPT 135/90, COSY, HMQC and HMBC data collected which match the structure of **3.33**. The formation of **3.33** can be explained by transmetallation taking place between the sterically less challenging Sn–C bond giving rise to intermediate **3.34** (Figure 3.4). The intramolecular participation of nitrogen lone-pairs has been shown to enhance reactivity in Stille reactions;[121] in **3.16a** the lone pair of electrons on the oxygen of the carbonyl group may have directed the transmetallation of the *n*Bu groups, as well as stabilize the formation of **3.34**. Successive *β*-hydride elimination of the corresponding Rh-*n*Bu followed by the reduction of alkylidene moiety gives rise to the Rh-η_3-intermediate **3.35**. Nucleophilic attack of enolate onto the Sn liberates the Rh-catalyst and gives rise to **3.33**. Alternatively,

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Table 3.5. Results for the Rh-Catalyzed Intramolecular Conjugate Addition of Meldrum's Acid Benzylidene **3.16a**
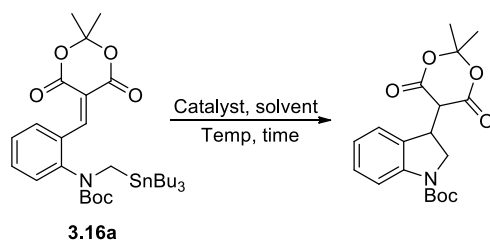
Entry	Catalyst[a]	Solvent	Temp (°C) / Time (h)	Pdt
1	TBAF (1.3 equiv)	THF	rt / 72	**3.16a:3.32** (1:1)
2	TBAF (1.3 equiv)	THF	55 / 24	decomp
3	[RhCl(C$_2$H$_4$)$_2$]$_2$	THF	rt / 72	**3.16a**
4	[RhCl(C$_2$H$_4$)$_2$]$_2$	THF	55 / 16	complex mixtures[b]
5	[RhCl(C$_2$H$_4$)$_2$]$_2$ PPh$_3$ (20 mol%)	THF	rt / 72	**3.16a**
6	[RhCl(C$_2$H$_4$)$_2$]$_2$ AgSbF$_6$ (20 mol%) PPh$_3$ (20 mol%)	THF	rt / 72	**3.16a** (major)
7	[RhCl(C$_2$H$_4$)$_2$]$_2$ AgSbF$_6$ (20 mol%) PPh$_3$ (20 mol%)	THF	55 / 8	decomp
8	[Rh(cod)Cl]$_2$	THF	rt / 72	**3.33**
9	[Rh(cod)Cl]$_2$ PPh$_3$ (20 mol%)	THF	rt / 72	**3.16a**
10	[Rh(cod)Cl]$_2$ AgSbF$_6$ (20 mol%) PPh$_3$ (20 mol%)	THF	rt / 72	**3.16a** (major)
11	[Rh(cod)(MeCN)$_2$]BF$_4$	THF	rt / 72	**3.16a** (major)
12	[Rh(cod)(MeCN)$_2$]BF$_4$ PPh$_3$ (20 mol%)	THF	rt / 72	**3.16a**
13	[Rh(cod)(MeCN)$_2$]BF$_4$	THF	55 / 22	inseparable mixture
14	[Rh(OH)(cod)]$_2$	THF	rt / 120	**3.33**[b]
15	[Rh(OH)(cod)]$_2$	THF	55 / 18	complex mixture[b]

[a]10 mol% Rh was used. [b]Complete consumption of starting material.

oxidative insertion of the Rh(I) catalyst affording intermediate **3.36**, can then undergo a β-hydride elimination resulting in intermediate **3.37** and 1-butene (Figure 3.4). Intramolecular coordination by the oxygen of the carbamate can direct hydrorhodiation of the olefin resulting in intermediate **3.35**, which can proceed through the same sequence to **3.33**. Efforts to obtain single crystals of **3.33** failed to give a solid and a yellow waxy oil was isolated. The undesired

regioselectivity of transmetallation further underscores the need for an organometallic moiety that will selectively transmetallate.
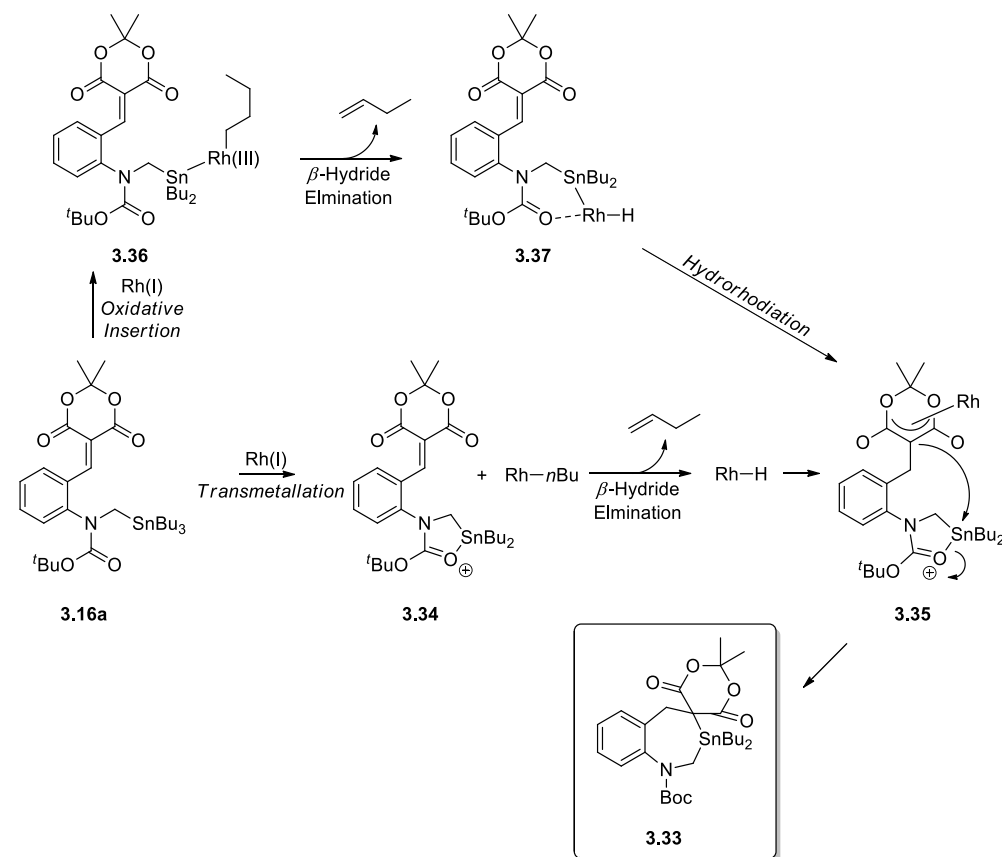
Figure 3.4. Proposed Mechanism for the Formation of **3.33**

Efforts to prepare the analogous models of **3.16** with organometallic electrophiles **3.10j** or **3.24** proved to be more problematic than with **3.23**. Using the same conditions for the preparation of **3.16a**, *N*-alkylation with **3.10j** smoothly formed the desired adduct **3.36**; however, alkylation with **3.24** was not as clean (Scheme 3.18). Moreover, efforts to purify crude material of either reaction with **3.10j** or **3.24** were unsuccessful and resulted in decomposition on silica gel. As result, crude material of both reactions were subjected to deprotection with catalytic amounts of PPTS that resulted in complete decomposition of crude material drawing attention to the limitation of this approach. For crude **3.36**, evidence for

protodestannylation of the C–Sn bond was obtained by the isolation of carbamate **3.37**, and the isolation of **3.10a** by treating the aqueous layer with excess HCl and extraction with DCM.

Scheme 3.18. Results for the *N*-Alkylation of **3.30** With **3.10j** and **3.24**
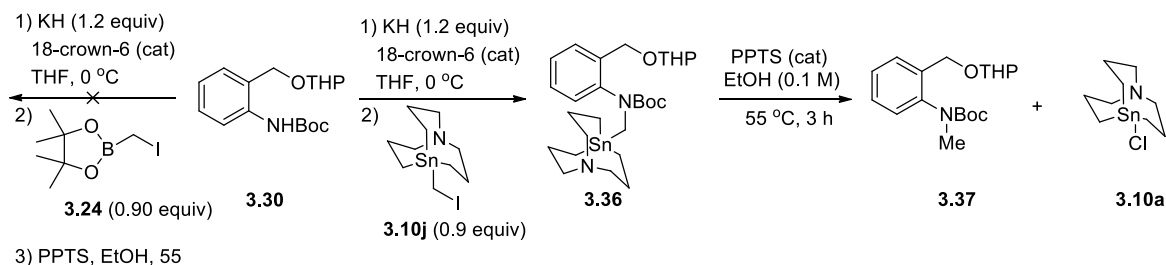
As an alternate approach, a TMS-protected derivative **3.38** possessing a labile C–Si compared to other silyl based protecting groups was prepared in good yield (Scheme 3.19). Subjecting **3.38** to previously successful *N*-alkylation conditions with **3.10j** afforded the alkylated cyclic carbamate **3.39**. Intramolecular ring-closure reactions of carbamate esters to form 1,3-benzoxazin-2-ones have been studied by Fife and believed to proceed through a isocyanate intermediate.[122] The formation of **3.39** may also proceed through an isocyanate intermediate that is trapped by the migration of labile TMS group followed by intramolecular nucleophilic attack.

Scheme 3.19. Results for the *N*-Alkylation of Carbamate **3.38** with **3.10j**
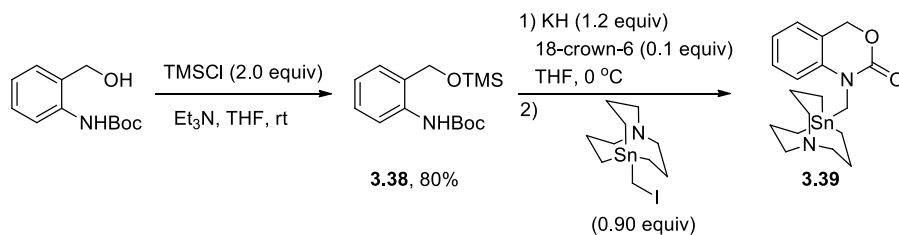
In order to avoid cyclization via the proposed isocyanate intermediate in the formation of **3.39**, amide **3.40** was prepared (Scheme 3.20). Subjecting **3.40** to *N*-alkylation conditions with **3.10j** resulted in consumption of starting material as indicated by TLC and analysis of the

crude ^{1}H NMR spectrum (Scheme 3.20); however, due to the lack of the TMS group it was determined that the desired adduct was not formed. Efforts to isolate the product were fruitless as novel peaks and spots were observed after flash column chromatography suggesting decomposition by the silica gel.

Scheme 3.20. Results for the *N*-Alkylation of Amide **3.40** with **3.10j**
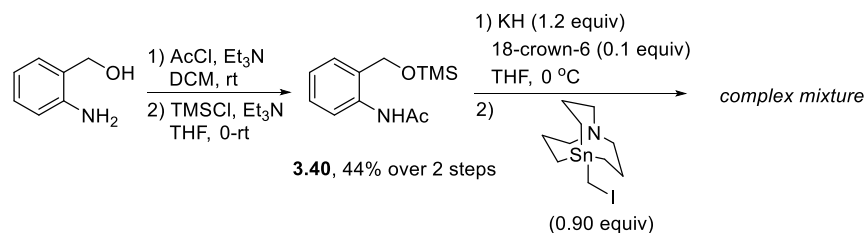
The final strategy that was explored was starting from commercially available 2-nitrobenzaldehyde where acetalization followed by nitro reduction with Na$_2$S·9H$_2$O cleanly afforded the aniline derivative that was directly protected with Boc anhydride to give **3.41** (Scheme 3.21). *N*-Alkylation with **3.23** was successful affording the **3.42** in modest yield of 43%, but alkylation with carbastannatrane **3.10j** failed to afford the desired adduct. Efforts to purify under neutral or basic conditions by deactivating silica gel with the addition of 1% Et$_3$N, or using alumina (Al$_2$O$_3$) based columns were unsuccessful.

Scheme 3.21. Synthesis of Acetal **3.42**
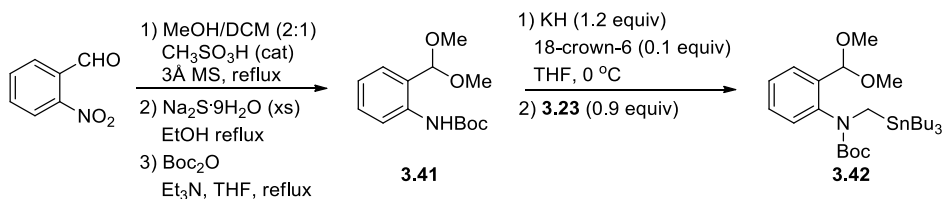
3.4. Summary

Due to the synthetic utility of tricarbastannatranes, particularly in enhanced and selective transfer of alkyl groups, a novel in situ procedure for the preparation of chloro carbastannatranes **3.10a** starting from inexpensive starting reagents has shown some promise. This lead requires optimization but may offer the most inexpensive and direct approach to **3.10a**.

Meldrum's acid benzylidene **3.16a** was successfully prepared but failed to transmetallate at the *α*-amino C–Sn bond; instead transmetallation took place at one of the *n*Bu groups. Efforts to install an organometallic appendage that does not suffer from selectivity issues was problematic. The desired enhanced reactivity of alkyl tricarabastannatranes proved to also be responsible for the inability to prepare and isolate carbastannatrane derivatives of **3.16**. It was decided that due to inherent instability and ease of protodestannylation of the C–Sn bond, novel models or strategies must be explored.

3.5. Future Work

Improving the in situ hydrozirconation of triallylamine protocol may be achieved by the addition of Lewis acids. Negishi reported the hydrozirconation of monosubstituted alkenes, which are typically sluggish, can be accelerated with improved yields by the catalytic addition of various Lewis acids (AlCl$_3$, AgBF$_4$, PdCl$_2$(PPh$_3$)$_2$), where an increase of up to 70% yield was obtained. [123] Additionally, alternate zirconocene hydride sources, such as *i*-BuZrCp$_2$Cl, will need to be tested to determine the optimum conditions.

With respect to the development of an intramolecular asymmetric conjugate addition protocol, rather than utilizing an organometallic group for transmetallation, direct C(sp^3)–H activation would avoid the instability or selectivity of the C–M bond. Daugulis has used pyridine and 8-aminoquinoline groups as auxiliary groups in the direct alkylation of unactivated sp^2 and sp^3 C–H bonds, where careful substrate design allows complete control of which C–H bond is activated (Figure 3.5a).[124] A similar strategy can be employed where **3.43**

(Figure 3.5b) possess a strategically placed directing group which activates the desired C–H bond that can undergo an intramolecular cyclization with an electrophilic site resulting in a 3-substituted indoline. It should be noted that efforts towards the preparation of **3.43** and analogous with different directing groups have already begun but insufficient results were obtained to be included.
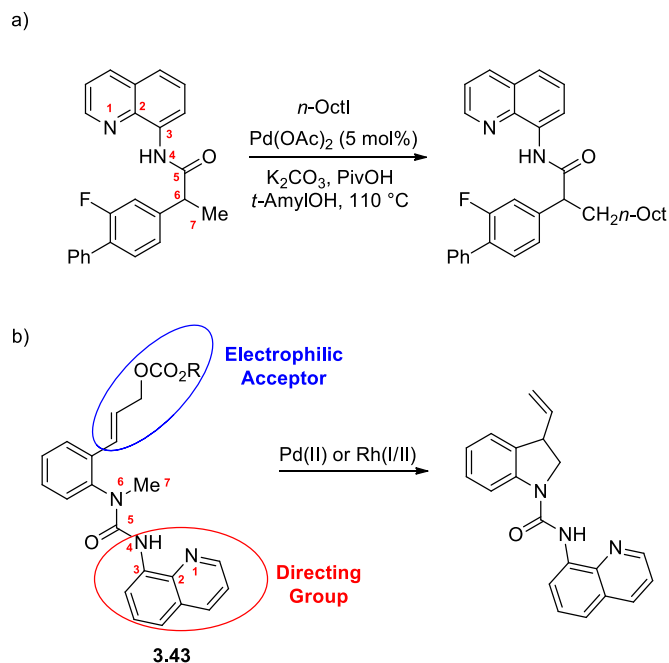
Figure 3.5. Pd-Catalyzed 8-Aminoquinoline Directed Alkylation of sp^3 C–H Bonds; b) Proposed Future Work – Auxiliary Assisted Tandem C(sp^3)–H Bond Activation Intramolecular Allylation Methodology

3.6. Experimental

General Considerations

Reactions

All reactions were carried out in oven or flame-dried glassware under dry nitrogen or argon atmosphere. CH_2Cl_2, DCE and Et_2O were obtained from a solvent purification system based on the published procedure;[42] THF was distilled from sodium-benzophenone ketyl under nitrogen. DMF, DMSO and Et_3N were dried by distilling over CaH_2 and stored in a

Schlenk flask under argon. EtOH was distilled over Mg powder under argon and stored over 3Å molecular sieves. Reactions were monitored by thin-layer chromatography and visualized by UV quenching and/or staining with cerium ammonium molybdate. Flash chromatography was performed using 230-400 mesh silica gel.

Characterization

Unless otherwise stated, ^{1}H and ^{13}C NMR spectra for all compounds were obtained in CDCl$_3$ at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual CHCl$_3$ (7.24 ppm) and carbon spectra were calibrated to CDCl$_3$ (77.0 ppm). Carbon multiplicities (C, CH, CH$_2$, CH$_3$) were determined by combined DEPT 90/135 experiments. High resolution mass spectrometry was performed at the University of Waterloo and the University of Toronto Mass Spectrometry facilities. Melting points are uncorrected.

Hydrostannylation-Thermal Disproportionation Approach to Chloro Tricarbastannatrane 3.10a

N$\langle\!\!\!\diagdown\!\!\!\rangle_3$
$\xrightarrow[\text{THF, rt, 22-36 h}]{\substack{\text{Bu}_3\text{SnH (5.5 equiv)} \\ \text{Pd(OH)}_2\text{/C (10 mol\%)}}}$
N$\langle\!\!\!\diagdown\!\!\!\rangle_3$SnBu$_3$
3.17, 56% (15.5 g)
$\xrightarrow[\substack{\text{2) 10M NaOH} \\ \text{20-40 °C}}]{\substack{\text{1) SnCl}_4\text{ (1.5 equiv)} \\ \text{H}_2\text{O (0.3 equiv)} \\ \text{80-95 °C, 4 h}}}$
3.10a, 9-31% (<1.6 g)
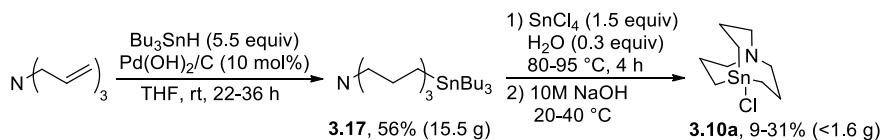
The procedure is based on a report by Yang et al. at Merck research laboratories. Freshly prepared Bu$_3$SnH[125] (221 mmol, 5.5 equiv) in THF (138 mL) was deoxygenated by bubbling argon and was slowly added by syringe pump (10 mL/h) to a deoxygenated mixture of triallylamine (40.3 mmol, 1.0 equiv) and Pd(OH)$_2$/C (4.03 mmol, 0.10 equiv) in THF (40 mL) at rt. After complete addition, the reaction mixture was filtered over a pad of Celite to remove the heterogenous catalyst and concentrated. Purification by flash chromatography on silica gel was achieved by initially eluting with hexanes to remove (Bu$_3$Sn)$_2$ byproduct, and then a 9:1 mixture of hexanes/EtOAc. Compound **3.17** was isolated as clear colourless oil (22.7 g, 57%). NMR data matched that of reported procedures. ^{1}H NMR (CDCl$_3$, 300 MHz) 2.36 (t, J = 7.5 Hz, 6H), 1.61 (m, 6H), 1.50–1.40 (m, 18H), 1.33–1.21 (m, 18H), 0.89–0.77 (m, 45H),

0.69 (t, J = 8.5 Hz, 6H). ^{13}C NMR (CDCl$_3$, 75 MHz) 28.7 (J_{Sn-C} = 19.5 Hz), 27.1 (J_{Sn-C} = 52.0 Hz), 24.4 (J_{Sn-C} = 17.1 Hz), 14.2 (CH$_2$), 8.8 (J_{Sn-C} = 308.0 Hz), 6.3 (J_{Sn-C} = 299.1 Hz).

Water (36 μL) was added to a pure[126] **3.17** (7.35 mmol) and heated to 80 °C, followed by the slow addition of SnCl$_4$ (11.7 mmol). The resulting mixture was then stirred at 95 °C for 4 h. The reaction was cooled back down to rt and stirred at this temperature for 30 min. The temperature was then raised to 50 °C and aqueous NaOH (30 mL, 10 M) was slowly added dropwise and continued to stir for an additional 40 min. The reaction was cooled back down to rt, the layers were partitioned and the aqueous layer was washed with MTBE. The aqueous layer was cooled in an ice bath and acidified with conc. HCl (pH 2.5). The mixture was extracted with CH$_2$Cl$_2$ (50 mL) and organic fractions were dried over MgSO$_4$ and filtered. Removal of solvent afforded **3.10a** as beige solid that can be recrystallized from MeOH (0.67 g, 31%). The NMR data matched that of reported procedures.[127] ^{1}H NMR (CDCl$_3$, 300 MHz) 2.47 (t, J = 6.5 Hz, 6H), 1.83 (m, J_{Sn-H} = 107 Hz, 6H), 1.21 (m, J_{Sn-H} = 69 Hz, 6H). ^{13}C NMR (CDCl$_3$, 75 MHz) 53.6 (CH$_2$, J_{Sn-C} = 38.5 Hz), 23.1 (CH$_2$, J_{Sn-C} = 28.9 Hz), 14.2 (CH$_2$, J_{Sn-C} = 476.6 Hz).

In Situ Preparation of Chloro Tricarbastannatrane 3.10a
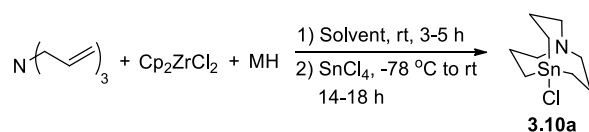
To a premixed solution of the metal hydride (5.53 mmol, 3.2 equiv) in THF (17 mL) was added a solution of Cp$_2$ZrCl$_2$ (5.53 mmol, 3.2 equiv) in THF (5.5 mL) at rt resulting in a light grey mixture. The flask was wrapped in aluminum foil and stirred for 30 min, followed by the addition of triallylamine (1.73 mmol, 1.0 equiv) which was then allowed to stir for an additional 5 h. The turbid greenish brown solution was cooled to -78 °C and SnCl$_4$ was added dropwise and allowed to gradually warmup to rt overnight. The reaction was quenched upon the addition of ice and 10% HCl to help dissolve aluminum oxide byproducts. The layers were partitioned and the aqueous layer was extracted with CH$_2$Cl$_2$ (3×). The organic layer was

washed with H₂O, dried over MgSO₄, filtered and concentrated. Compound **3.10a** can be further purified by recrystallization from MeOH as a beige solid (0.18 g, 37%).

Preparation of tert-butyl (2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)phenyl)carbamate (3.22)
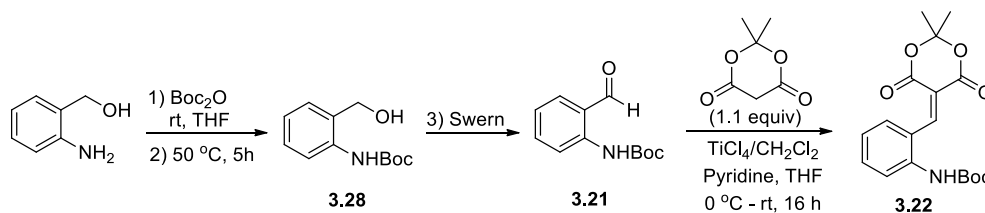
Boc-protection of 2-aminobenzyl alcohol was achieved using reported procedure:[128] to a solution of 2-aminobenzyl alcohol (41.0 mmol) in THF (21 mL) was added Boc anhydride (43.0 mmol) in one portion and the solution was stirred at rt overnight. The resulting bright orange solution was stirred at 50 °C and the progress of the reaction was monitored by TLC. The solvent was removed in vacuo and crude mixture was purified by flash column chromatography on silica gel eluting with a gradient from 9:1 to 1:1 hexanes:EtOAc. Carbamate **3.28** was isolated as an yellow-orange oil (7.68 g, 84%) and characterization matched that reported.

To a solution of oxalyl chloride (40.8 mmol) in CH₂Cl₂ (26 mL) at -78 °C was added DMSO (121.1 mmol) dropwise and stirred for 45 min. A solution of **3.28** (40.4 mmol) in CH₂Cl₂ (40 mL) was then slowly added at -78 °C and stirred for 30 min, followed by the slow addition of Et₃N (242.3 mmol) and additional stirring at -78 °C for 45 min and at -20 °C for 30 min. The reaction was quenched by the addition of water and extracted with CH₂Cl₂ (3×). The organic layer was then washed with 5% HCl, dried over MgSO₄, filtered and concentrated. Analyses of the crude ¹H NMR matched that reported for **3.21** and was sufficiently pure to proceed to the next step.

Alkylidene Meldrum's acid **3.22** was prepared by the Knoevenagel condensation of Meldrum's acid with **3.21** using the method reported by Brown and coworkers.[129] A solution

of TiCl$_4$ (52.4 mmol, 2.1 equiv) in CH$_2$Cl$_2$ (9 mL) was added dropwise to dry THF (91 mL) at 0 °C under nitrogen resulting in a yellow suspension. A premixed solution of **3.22** (27.4 mmol, 1.1 equiv) and Meldrum's acid (24.9 mmol, 1.0 equiv) in dry THF (39 mL) was added slowly to the TiCl$_4$·THF complex. Subsequent rinses with THF (2×) of the flask containing the solution of **3.21** and Meldrum's acid was added to the reaction mixture. Pyridine (125 mmol, 5.0 equiv) was then slowly added to the reaction mixture at 0 °C. The reaction was then allowed to warm up slowly to room temperature and stirred for 18 h. The reaction mixture was cooled back down to 0 °C and quenched upon the addition of water, followed by dilution with ethyl acetate. The mixture was allowed to stir at room temperature until the solid had fully dissolved. The layers were partitioned, and the aqueous layer was extracted was EtOAc (2×). Combined organic fractions were washed with NaHCO$_3$ (2×), brine (1×), dried over MgSO$_4$, filtered and concentrated. Recrystallization from a saturated solution of MeOH afforded the pure alkylidene Meldrum's acids **3.22** (4.24 g, 49%) as a beige crystals. Mp 166-168 °C; ^{1}H NMR (300 MHz, CDCl$_3$) 8.45 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.46 (dt, J = 8.4, 1.3 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 6.57 (br s, 1H), 1.80 (s, 6H), 1.46 (s, 9H). ^{13}C NMR (CDCl$_3$, 75 MHz) 159.5 (C), 154.5 (C), 152.9 (CH), 138.2 (C), 133.3 (CH), 131.1 (CH), 125.3 (C), 124.3 (CH), 123.0 (CH), 116.0 (C), 104.8 (C), 81.6 (C), 28.2 (CH$_3$), 27.7 (CH$_3$). MS (EI) 452 (M$^+$).

Synthesis of 1-((tributylstannyl)methyl)-1H-benzo[d][1,3]oxazin-2(4H)-one (3.29)

To a solution of **3.28** (1.05 mmol, 1.0 equiv) in THF (10 mL) at -78 °C was slowly added nBuLi (2.10 mmol, 2.0 equiv, 2.5M in hexanes) and the resulting mixture was stirred for 1 h. A solution of Bu$_3$SnCH$_2$I (**3.23**, 1.50 mmol, 1.0 equiv)[101] in 1 mL of THF:DMF (20:1) was then slowly added and the mixture was gradually warmed to rt. Monitoring the consumption of **3.28** by TLC, the reaction was quenched upon the addition of water. The aqueous layer was extracted with EtOAc (3×); combined organic fractions were washed with brine (1×) and dried over MgSO$_4$. The filtrate was concentrated onto a small amount of silica gel and loaded

to the top of a silica gel column. Flash column chromatography eluting with 9:1 EtOAc:hexanes afforded **3.29** (104 mg, 22%) as a pale yellow film. ^{1}H NMR (300 MHz, CDCl$_3$) 7.33 (t, J = 8.0 Hz, 1H), 7.10–6.96 (m, 3H), 5.11 (s, 2H), 3.35 (d, 12.4 Hz, 1H), 3.31 (d, 12.4 Hz, 1H), 1.51–1.32 (m, 6H), 1.29–1.20 (m, 6H), 0.91–0.82 (m, 15H). ^{13}C NMR (CDCl$_3$, 75 MHz) 153.5 (C), 139.0 (C), 128.9 (CH), 124.0 (CH), 122.5 (CH), 120.8 (C), 113.2 (CH), 67.0 (CH$_2$), 30.4 (CH$_2$), 28.9 (CH$_2$, J_{Sn-C} = 10.5 Hz), 27.3 (CH$_2$, J_{Sn-C} = 40.0 Hz), 13.6 (CH$_3$), 10.4 (CH$_2$, J_{Sn-C} = 166.7 Hz). MS (EI) m/z 396 (M$^+$ − C$_4$H$_9$).

Preparation of tert-butyl (2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl)phenyl)((tributylstannyl)methyl)carbamate 3.16a
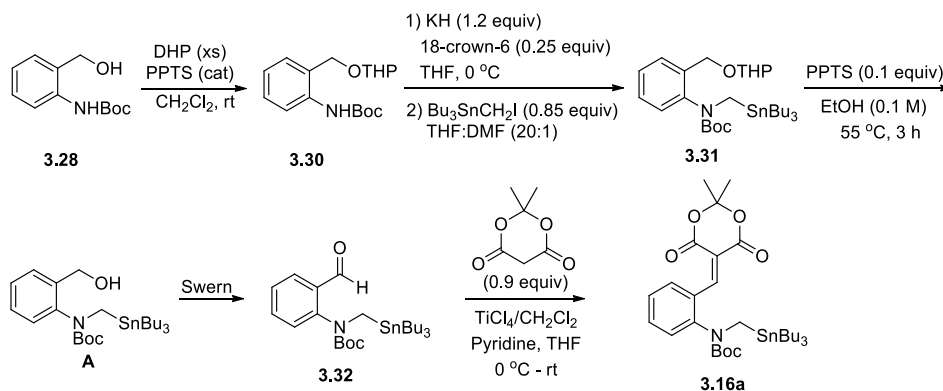
Carbamate **3.30** was prepared based on a procedure reported by Yoshikoshi:[130] To a solution of **3.28** (8.53 g, 38.20 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (255 mL) was added dihydropyran (4.82 g, 57.31 mmol, 1.5 equiv) and PPTS (0.96 g, 3.82 mmol, 0.1 equiv) at rt and was stirred for 5 h. The mixture was then diluted with Et$_2$O and washed with brine. Removal of solvent in vacuo afforded **3.30** (11.02 g, 94%) as colourless oil and was sufficiently pure to proceed to the next step. ^{1}H NMR (300 MHz, CDCl$_3$) 8.00 (br s, 1H), 7.97 (s, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.15 (d, J = 6.6 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 4.81 (d, J = 11.6 Hz, 1H), 4.67 (m, 1H), 4.47 (d, J = 11.6 Hz, 1H), 3.97–3.92 (m, 1H), 3.60–3.56 (m, 1H), 1.86–1.72 (m, 2H), 1.64–1.56 (m, 4H), 1.50 (s, 9H). ^{13}C NMR (CDCl$_3$, 75 MHz) 153.1 (C), 138.3 (C), 129.7 (CH), 129.1 (CH), 125.5 (C), 122.5 (CH), 120.2 (CH), 98.1 (CH), 79.9 (C), 67.9 (CH$_2$), 63.0 (CH$_2$), 30.5 (CH$_2$), 28.3 (CH$_3$), 25.2 (CH$_2$), 19.6 (CH$_2$). MS (EI) m/z 308 (M+H).

Carbamate **3.31** was prepared according to the following procedure: Compound **3.30** (3.68 g, 12.00 mmol, 1.0 equiv) was dissolved in THF (40 mL) and cooled in an ice bath, followed by the addition of KH (30% by wt, 14.15 mmol, 1.2 equiv)[131] in two equal portions and stirred for 2.5 h. 18-Crown-6 (0.80 g, 3.02 mmol, 0.25 equiv) was added to the mixture, followed by the dropwise addition of **3.23** (10.20 mmol, 0.85 equiv). The solution was gradually warmed to rt and continuously stirred for 16 h. The reaction was diluted with Et_2O and then quenched by the addition of H_2O. The layers were partitioned and the aqueous layer was extracted with Et_2O (2×). Combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude compound was purified by flash column chromatography on silica gel eluting with 5:1 hexanes:EtOAc. Compound **3.31** (2.55 g, 41%) was isolated as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) 7.51–7.48 (m, 1H), 7.22–7.20 (m, 2H), 7.02 (m, 1H), 4.75–4.67 (m, 2H), 4.51–4.46 (m, 1H), 3.92 (m, 1H), 3.57–3.53 (m, 1H), 3.21–3.17 (m, 1H), 2.94–2.84 (m, 1H), 1.80–1.32 (m, 30H), 0.89 (m, 16H). ^{13}C NMR ($CDCl_3$, 75 MHz) 155.0 (C), 143.0 (C), 135.3 (C), 128.1 (CH), 127.8 (CH), 126.9 (CH), 126.6 (CH), 98.0 (CH), 79.3 (C), 64.7 (CH_2), 61.9 (CH_2), 36.9 (CH_2), 30.5 (CH_2), 29.0 (CH_2), 28.2 (CH_3), 27.5 (CH_2), 25.5 (CH_2), 19.4 (CH_2), 13.7 (CH_3), 10.8 (CH_2).

Compound **3.32** was prepared according to following procedure: Compound **3.31** (8.46 g, 13.86 mmol) and PPTS (0.35 g, 1.38 mmol) were weighed into a flask and diluted with EtOH (140 mL). The mixture was stirred at 55 °C while monitoring the progress of the reaction by TLC. The reaction was cooled back to rt and solvent was removed in vacuo. Purification by flash column chromatography on silica gel eluting with a gradient from 1:12 to 1:9 EtOAc:hexanes afforded **A** (6.72 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.48–7.46 (m, 2H), 7.25 (br s, 2H), 7.03 (br s, 1H), 4.57 (br s, 2H), 3.12–2.90 (br m, 2H), 1.51 (br s, 9H), 1.46 (br s, 12H), 1.28 (br s, 21H), 0.85 (br m, 25H). ^{13}C NMR ($CDCl_3$, 75 MHz) 155.1 (C), 142.9 (C), 137.5 (C), 129.0 (CH), 128.5 (CH), 127.2 (CH), 126.9 (CH), 79.9 (C), 61.3 (CH_2), 37.3 (CH_2), 29.0 (CH_2), 28.2 (CH_3), 27.3 (CH_2), 13.6 (CH_2), 12.9 (CH_3).

Subjecting compound **A** (6.70 g, 12.75 mmol) to Swern conditions (see procedure used to prepare aldehyde **3.21** vide supra for details) afforded compound **3.32** (5.75 g, 86%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) 10.06 (s, 1H), 7.84 (d, J = 6.9 Hz, 1H), 7.56 (dt, J = 7.5, 1.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.9 Hz), 3.20–3.14 (br m, 2H), 1.47–

1.39 (m, 8H), 1.25 (m, 16H), 0.83 (m, 17H). ^{13}C NMR (CDCl$_3$, 75 MHz) 189.9 (CHO), 154.8 (C), 147.8 (C), 134.5 (CH), 131.8 (C), 127.8 (CH), 126.9 (CH), 126.6 (CH), 80.7 (C), 38.1 (CH$_2$), 28.9 (CH$_2$, J_{Sn-C} = 10.5 Hz), 27.9 (CH$_3$), 27.3 (CH$_2$, J_{Sn-C} = 28.3 Hz), 13.6 (CH$_3$), 10.7 (CH$_2$).

Compound **3.16a** was prepared by the Knoevenagel condensation of **3.32** with Meldrum's acid according to the same procedure used to prepare **3.22** (vide supra). Purification by flash column chromatography on silica gel eluting with 1:5 EtOAc:hexanes afforded **3.16a** (2.92 g, 33%) as a yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$) 8.41 (s, 1H), 7.85 (br s, 1H), 7.48 (t, J = 10.5 Hz, 1H), 7.27–7.19 (m, 2H), 3.11 (br s, 2H), 1.80 (s, 6H), 1.48–1.40 (m, 6H), 1.33–1.23 (m, 20H), 0.92–0.83 (m, 17H). ^{13}C NMR (CDCl$_3$, 75 MHz) 159.3 (C), 155.4 (C), 154.5 (CH), 137.2 (C), 133.1 (CH), 130.8 (CH), 129.3 (C), 126.5 (CH), 125.8 (CH), 115.6 (C), 104.5 (C), 80.7 (C), 38.3 (CH$_2$), 28.9 (CH$_2$, J_{Sn-C} = 10.5 Hz), 28.0 (CH$_3$), 27.6 (CH$_3$), 27.3 (CH$_2$), 17.5 (CH$_2$), 13.5 (CH$_3$), 10.5 (CH$_3$). HRMS (ESI) m/z calcd for C$_{31}$H$_{49}$NO$_6$Sn (M$^+$– C$_4$H$_9$) 593.17993. Found 593.17979.

Preparation of tert-butyl 3,3-dibutyl-2',2'-dimethyl-4',6'-dioxo-2,3-dihydrospiro[benzo[f][1,3]azastannepine-4,5'-[1,3]dioxane]-1(5H)-carboxylate 3.33.

3.16a   [RhCl(cod)]$_2$ (10 mol% Rh)   **3.33**
                    THF, rt, 48 h
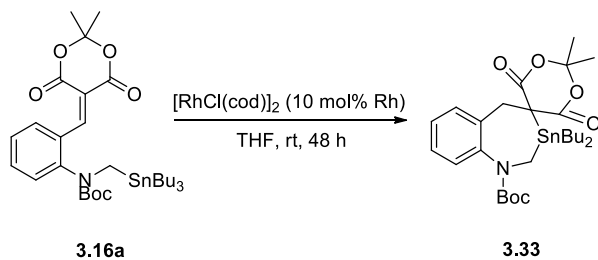
A flame-dried Schlenk tube purged with argon and equipped with a magnetic stirrer was charged with **3.16a** (110 mg, 0.17 mmol) and [RhCl(cod)]$_2$ (0.085 mmol). The walls of the Schlenk tube were washed with THF (1.7 mL) to ensure complete transfer of reagents. The Schlenk tube was sealed and the resulting bright yellow solution was stirred for 48 h at rt. The mixture was then passed over a pad of silica and concentrated onto a small amount of silica gel. The silica gel dried with the crude product was loaded to the top of a packed silica gel column eluting with a gradient from 1:11 to 1:1 EtOAc/hexanes affording **3.16a** (28 mg, 27% not completely pure) as a thin film. ^{1}H NMR (500 MHz, CDCl$_3$) 7.26 (d, J = 7.8 Hz, 1H), 7.15

(m, 1H), 7.06 (m, 1H), 6.75 (d, 7.7 Hz, 1H), 3.48 (d, J = 16.0Hz, 1H), 3.21 (d, J = 12.5 Hz, 1H), 2.96 (d, J = 15.9 Hz, 1H), 2.41 (d, J = 12.5 Hz, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.36–1.28 (m, 17H), 1.25 (s, 9H), 1.22–1.17 (m, 7H), 0.81 (m, 3H). ^{13}C NMR (CDCl$_3$, 125 MHz) 167.5 (C), 167.0 (C), 161.3 (C), 140.0 (C), 139.4 (C), 129.1 (CH), 127.9 (CH) 126.1 (CH), 125.2 (CH), 103.0 (C), 83.8 (C), 77.2 (C), 38.1 (CH$_2$), 28.1 (CH$_3$), 27.8 (CH$_2$), 27.3 (CH$_2$), 26.5 (CH$_2$), 26.3 (CH$_3$), 26.1 (CH$_2$), 24.9 (CH$_3$), 23.2 (CH$_2$), 19.4 (CH$_2$), 18.9 (CH$_2$), 13.7 (CH$_3$), 13.6 (CH$_3$).
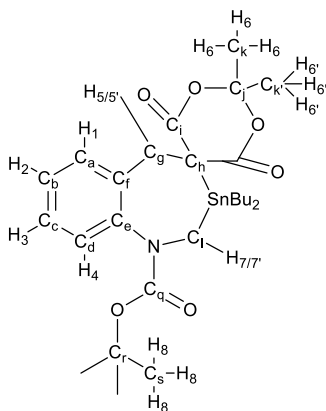
HMQC NMR DATA (CDCl$_3$, 300 MHz)	
Proton(s) (δ ppm)	Exhibited Coupling With (δ ppm)
6.75 (H$_1$)	125.2 (C$_a$)
7.15 (H$_2$)	128.0 (C$_b$)
7.06 (H$_3$)	126.0 (C$_c$)
7.26 (H$_4$)	129.1 (C$_d$)
3.49, 2.96 (H$_{5/5'}$)	23.2 (C$_g$)
1.72, 1.68 (H$_{6/6'}$)	28.1, 26.0 (C$_{k/k'}$)
3.21, 2.41 (H$_{7/7'}$)	38.1 (C$_l$)
1.25 (H$_8$)	24.5 (C$_5$)

Note: HMQC data for stannyl butyl groups were omitted because they could not be unambiguously assigned.

HMBC NMR DATA (CDCl$_3$, 300 MHz)	
Proton(s) (δ ppm)	Exhibited Coupling With (δ ppm)
6.75 (H$_1$)	128.0 (C$_b$), 139.4 (C$_f$)
7.15 (H$_2$)	125.2 (C$_a$), 139.4 (C$_f$)
7.06 (H$_3$)	129.1 (C$_d$), 140.0 (C$_e$)
7.26 (H$_4$)	140.0 (C$_e$)
3.49, 2.96 (H$_{5/5'}$)	125.2 (C$_a$), 139.4 (C$_f$), 77.2 (C$_h$), 167.5 (C$_i$)
1.72, 1.68 (H$_{6/6'}$)	103.0 (C$_j$)
3.21, 2.41 (H$_{7/7'}$)	161.3 (C$_n$)
1.25 (H$_8$)	83.8 (C$_r$)

Preparation of tert-butyl (1-aza-5-stannabicyclo[3.3.3]undecan-5-ylmethyl)(2-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenyl)carbamate 3.36.
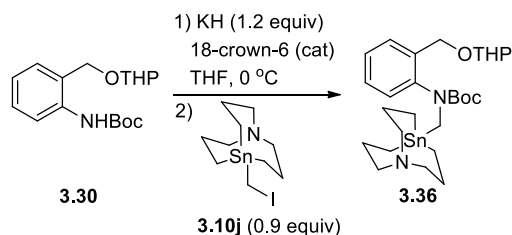
Carbamate **3.36** was prepared according to the same procedure as **3.31** (vide supra) using **3.30** (0.40 g, 1.30 mmol) and **3.10j** (0.47 g, 1.17 mmol) as the alkylating group. Purification by flash column chromatography on silica gel eluting with 1:10 EtOAc:hexanes afforded **3.36** (0.39 g, 52%) as waxy solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.48 (br m, 1H), 7.19 (br m, 2H), 7.00 (br s, 1H), 4.74–4.56 (m, 2H), 4.49–4.42 (m, 1H), 3.89 (br m, 1H), 3.52 (br m, 1H), 2.57–2.48 (m, 1H), 2.34 (t, J = 5.4 Hz, 6H), 1.89–1.76 (m, 2H), 1.68–1.49 (m, 13H), 1.27 (br s, 7H), 0.68 (m, 6H). ^{13}C NMR (CDCl$_3$, 75 MHz) 154.8 (C), 143.6 (C), 127.6 (CH), 127.3 (CH), 126.9 (CH), 126.2 (CH), 98.1 (CH), 78.7 (C), 64.9 (CH$_2$), 63.0 (CH$_2$), 62.2 (CH$_2$), 54.9 (CH$_2$), 30.6 (CH$_2$), 28.4 (CH$_3$), 25.5 (CH$_2$), 23.4 (CH$_2$), 19.4 (CH$_2$), 8.0 (CH$_2$).

Synthesis of 1-(1-aza-5-stannabicyclo[3.3.3]undecan-5-ylmethyl)-1H-benzo[d][1,3]oxazin-2(4H)-one 3.39
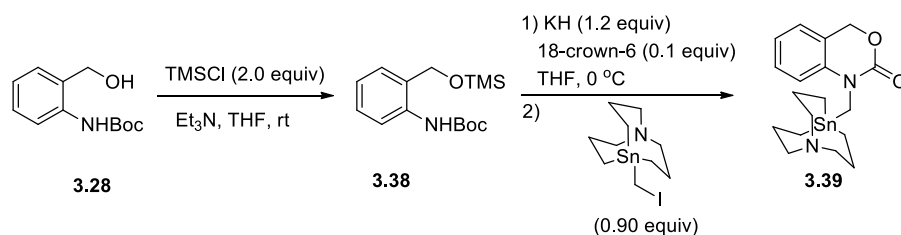
Compound **3.38** was prepared based on a reported procedure:[132] To a mixture of **3.28** (0.46 g, 2.05 mmol, 1.0 equiv) and Et$_3$N (4.10 mmol, 2.0 equiv) in THF (2.1 mL) at 0 °C was added TMSCl (4.10 mmol, 2.0 equiv) dropwise. While stirring, the reaction was gradually warmed to rt and the progress of the reaction was monitored by TLC. Excess reagents and solvent were removed under highvac, and crude was redissolved in Et$_2$O. Filtering through a pad of silica gel eluting with EtOAC afforded **3.38** (0.48 g, 80%) as yellow oil that was

sufficiently pure to proceed to the next step. ^{1}H NMR (300 MHz, CDCl$_3$) 7.98–7.93 (br m, 2H), 7.26 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 4.67 (s, 2H), 1.51 (s, 9H), 0.14 (s, 9H). ^{13}C NMR (CDCl$_3$, 75 MHz) 153.0 (C), 138.4 (C), 128.7 (CH), 128.1 (CH), 127.8 (C), 122.4 (CH), 120.1 (CH), 79.9 (C), 64.6 (CH$_2$), 28.3 (CH$_3$), 0.51 (CH$_3$).

Compound **3.39** was isolated as the major product in the *N*-alkylation of **3.38** (64 mg, 0.22 mmol) using the same conditions outlined for the preparation **3.31** with **3.10j** (78 mg, 0.19 mmol) as the alkylating group. Purification by flash column chromatography on silica gel eluting with 1:4 EtOAc:hexanes afforded **3.39** (44 mg, 48%) as a thin film. ^{1}H NMR (300 MHz, CDCl$_3$) 7.28 (m, 1H), 7.06–6.95 (m, 2H), 6.87 (d, J = 8.1 Hz, 1H), 5.08 (s, 2H), 3.06 (m, 2H), 2.32 (t, J = 5.4 Hz, 6H), 1.61 (quint, J = 6.0 Hz, 6H), 0.70 (t, J = 6.6 Hz). ^{13}C NMR (CDCl$_3$, 75 MHz) 153.0 (C), 139.3 (C), 128.7 (CH), 123.8 (CH), 121.9 (CH), 120.9 (C), 113.4 (CH), 66.9 (CH$_2$), 54.5 (CH$_2$, J_{Sn-C} = 14.2 Hz), 37.4 (CH$_2$), 23.1 (CH$_2$, J_{Sn-C} = 12.4 Hz), 7.51 (CH$_2$, J_{Sn-C} = 207.1 Hz). HRMS (ESI) m/z calcd for C$_{18}$H$_{26}$N$_2$O$_2$^{116}Sn (M+H) 418.10117. Found 418.10103.

Preparation of tert-butyl (2-(dimethoxymethyl)phenyl)((tributylstannyl)methyl)carbamate 3.42.
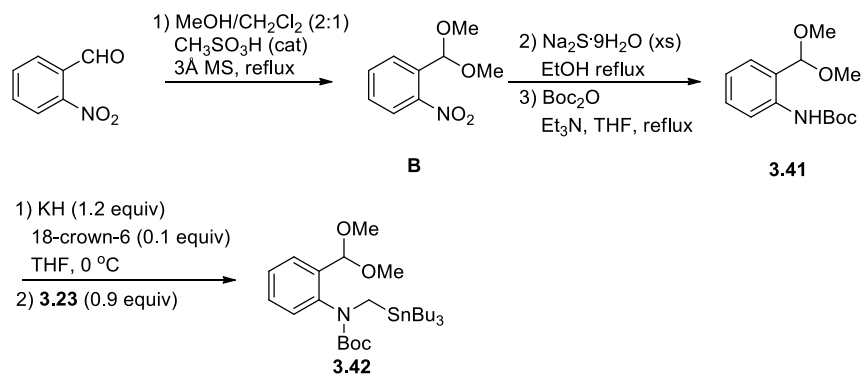
Acetal **B** was prepared according to literature procedure:[133] To a solution of 2-nitrobenzaldehyde (9.50 g, 62.86 mmol) in MeOH:CHCl$_3$ (2:1, 150 mL) was added methanesulfonic acid (1.88 mmol). The mixture was refluxed in a flask fitted with a soxhlet apparatus containing 3 Å MS (15g) for 24 h. The reaction was cooled back to rt, Et$_3$N (1 mL)

was added and the solvent was evaporated *in vacuo*. Crude sample was purified by flash column chromatography over silica gel eluting with 1:5 EtOAc:hexanes affording **B** (11.64 g, 94%) as yellow solid. Characterization data matched that reported.[133]

Compound **3.41** was prepared by the following procedure:[133] To a solution of **B** (2.72 g, 13.80 mmol) in EtOH (27 mL) was added $Na_2S \cdot 9H_2O$ (8.29 g, 34.50 mmol) and the mixture was refluxed for 1.5 h. After cooling to rt, Et_3N (1 mL) was added and solvent was removed *in vacuo*. The crude oil was dissolved in Et_2O (20 mL), Et_3N (1 mL) and H_2O (20 mL). The layers were partitioned and the aqueous layer was extracted with EtOAc (3×). Combined organic fractions were washed with brine, dried over $MgSO_4$, filtered and concentrated. Characterization data for **3.41** (2.43 g, 66%) matched that reported, and was isolated as a yellow oil sufficiently pure to proceed to the next step.

Compound **3.42** was prepared by the same procedure described for **3.31 (**vide supra) using **3.41** (337 mg, 1.26 mmol) and **3.23** (488 mg, 1.13 mmol). Purification by flash column chromatography on silica gel eluting with 1:19 EtOAc:hexanes afforded **3.42** (310 mg, 43%) as a thin film. ^1H NMR (300 MHz, $CDCl_3$) 7.58–7.55 (m, 1H), 7.28–7.26 (m, 2H), 7.01–6.98 (s, 1H), 5.33 (s, 1H), 3.36 (s, 3H), 3.26 (s, 3H), 3.15 (d, J = 12.7 Hz, 1H), 2.79 (d, J = 12.7 Hz, 1H), 1.53–1.43 (m, 7H), 1.27 (m, 15H), 0.86 (m, 16H). ^{13}C NMR ($CDCl_3$, 75 MHz) 155.1 (C), 143.5 (C), 134.9 (C), 129.2 (CH), 127.6 (CH), 127.1 (CH), 126.8 (CH), 100.5 (CH), 79.2 (C), 53.8 (CH_3), 53.5 (CH_3), 37.5 (CH_2), 29.1 (CH_2), 28.1 (CH_3), 27.3 (CH_2), 13.5 (CH_3), 10.8 (CH_2).

Chapter 4. Halogen Bonding: σ-Hole Interactions Studies using Benzyl Meldrum's Acid Derivatives and Halogen Bond Directed Diels-Alder Reactions

4.1. Introduction

Schneider recently stated, "with courageous simplification, one might assert that the chemistry of the last century was largely the chemistry of covalent bonding, whereas that of the present century is more likely to be the chemistry of noncovalent binding".[134] This statement draws attention to the relatively understudied area of noncovalent interactions. Particularly halogen bonding (XB), which can be regarded as the poorly recognized counterpart of hydrogen bonding (HB). XB is not a new phenomenon, in fact, "iodide of iodammonium" complexes, $NH_3 \cdot I_2$, were described two centuries ago.[135] More recently, complexes of dihalogens with different oxygen/nitrogen Lewis bases as interaction partners have been characterized crystallographically.[136,137] However, these complexes were frequently referred to as charge-transfer complexes.[137]

The concept of XB has been broadened further than strictly for complexes of dihalogens with various Lewis bases, and now follows closely to that of HB. The IUPAC definition for XB is, "a halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity".[138] Halogen bonds are represented by three dots, R–X···Y, where R–X is the halogen bond donor and X is any halogen atom with an electrophilic (electron-poor) region, and R is an electron-withdrawing group ranging from another halogen atom to organic or inorganic atom (e.g., haloalkanes, haloarenes, dihalogens, halonium ions). Y is the halogen bond acceptor possessing at least one nucleophilic (electron-rich) region (e.g., atom with lone pair of electrons, π system, anions). Evidence for the presence of a halogen bond may be experimental and or theoretical. A non-exhaustive list of some of the key features for a halogen-bonded complex, R–X···Y, are: (1) the interatomic distance between X and Y is less than the sum of the van der Waals radii; (2) elongation of the R–X bond length compared to free R–X; (3) The R–X···Y bond angle tends to be close to 180°; (4) forces involved are primarily electrostatic, but polarization, charge transfer, and dispersion contributions all play an important role; (5) observable differences

with respect to the NMR chemical shifts for both the R–X and Y nuclei.[138] These features and the extent to which they are observed may vary based on the system, but the greater the number of features present, the more reliable the characterization of an interaction as a halogen bond is.
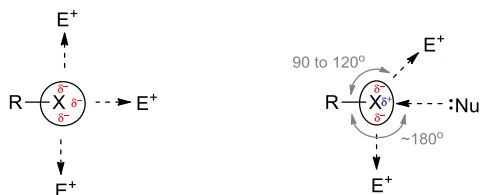
Figure 4.1. Traditional View of Halogens Uniformly Negative Surface Interacting with Electrophiles (left); Halogen Interactions with Both Electrophiles and Nucleophiles Based on the Anisotropic Distribution of Electrons at the Surface.

XB appears to contradict the traditional view of unfavourable repulsive interactions between species with similar electronic character, where halogens are viewed as being negative in character, Figure 4.1. The question then arises why and how do these inherently negative entities interact favourably with other negative sites? The contradiction lies in the idea that an atom in a given molecule can be treated as entirely negative or positive. Surveys of crystallographic database have revealed characteristic patterns of R–X···Y systems that were interpreted as attractive noncovalent interactions.[139,140] These noncovalent interactions are mainly electrostatically driven,[141] and therefore suggest that these atoms possess positively and negatively charged regions that can interact favorably with both nucleophilic and electrophilic sites respectively (Figure 4.1. right). This has been comprehensively confirmed computationally in terms of the atoms' electrostatic potentials, and will be discussed in more detail in the next section.

The occurrence of a region with positive electrostatic potential on the halogen's surface that extends along the R–X bond axis is the basis of XB. This region has been referred to as the "σ-hole",[142] or the σ* orbital, and is attributed to the anisotropic charge distribution of a covalently-bonded halogen atom.[142,143] Both hydrogen and halogen bonding are directional and strong, and these noncovalent interactions originate from the σ-hole that arises at the

110

surface of the atom from which electrons are being pulled away by an electron withdrawing substituent. The σ-hole concept has been extended to also describe noncovalent interactions between a covalently-bonded atom of Groups IV–VII and a Lewis basic site.[143] For example, sulfur atoms have been observed to interact with both nucleophilic and electrophilic sites within the crystal lattice of a XB complex.[139,144] If noncovalent interactions are considered to be mainly electrostatically driven,[141] then atoms that are traditionally viewed solely as electron rich, such as sulfur and halogens, are still able interact favorably with both nucleophilic and electrophilic sites strongly would indicate that these atoms must comprise of both positively and negatively charged regions. These observations have been studied and confirmed computationally in terms of the atoms' electrostatic potentials.[145] An important feature of the electrostatic potential is that it is not just computationally determined but is a physical property that can be determined experimentally by diffraction techniques.[146] Computed molecular electrostatic potentials (MEP) show a maximal positive region along the extension of the R–X bond, the σ-hole, which can interact attractively with nucleophilic sites (Figure 4.2.). The main factors that affect the magnitude of the σ-hole making it more positive are the electron-withdrawing power of R, and the polarizability of X, where I > Br > Cl > F.[143] Compounds with multiple (R–X)$_n$ bonds are able to have n number of XB interactions. Additionally, MEP calculations show negative regions found along the lateral sides of the molecule that can interact favorably with electrophilic sites (Figure 4.2.).[143]
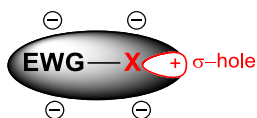
Figure 4.2. Schematic Diagram Illustrating Computed MEP.

Another way to view XB is to consider the atomic orbitals (AOs) involved. Kutzelnigg pointed out that qualitative descriptions of chemical bonding, such as hybridization, only apply to first row elements and should not be generalized to higher main group elements.[147] It should be noted that the calculations used to draw the following conclusions are beyond the level of understanding of this author and therefore will be omitted from discussion; however, the conclusions drawn from them allow for a greater understanding of the σ-hole concept and will

be discussed. The main difference between the atoms of the first row versus that of the higher rows are their cores. The s and p valence AOs of the first row atoms are localized in approximately the same region of space, whereas the p valence AOs of higher row atoms are extended further in space.[147] As a result, for first row atoms both lone-pair repulsion and isovalent hybridization play a more significant role than for the heavy main group elements. For example, the lone pair of electrons on N in a NR_3 molecule are essentially sp^3-hybridized, whereas the corresponding electrons for P and heavier atoms within the same group are found in s-orbitals.[145] With respect to halogen bonding, for halogens other than F, 4 out of the 7 valence electrons are assigned to 2 p-orbitals that are perpendicular to each other and can explain the negative belt along the lateral side of the halogen. The remaining 3 electrons are then allocated to 2 orbitals, the s-orbital and the remaining p-orbital that will be in the orientation of the bond (Figure 4.3.). Compared to the 2 filled p-orbitals, the singly occupied p-orbital participates in the R–X bond and is depleted in electronic density in the outer lobe of the orbital.[143] This outer portion of the half-filled bonding orbital is along the extension of R–X bond and is referred to as the σ-hole.

Fluorine   Chlorine and Higher
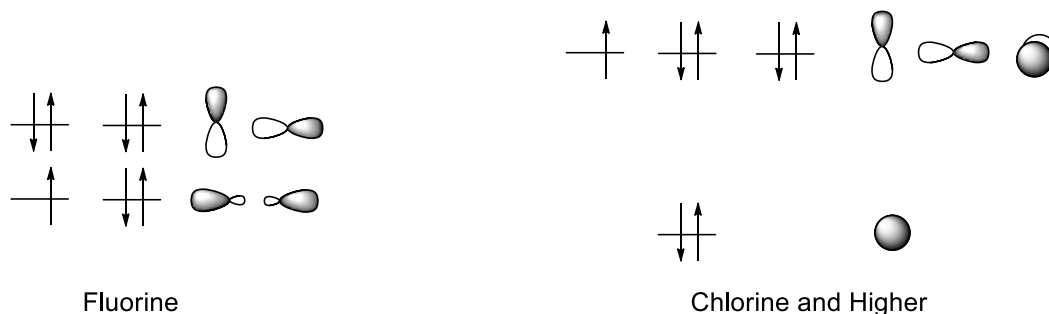
Figure 4.3. Schematic View of the Valence States of F versus Higher Halogens.

HB has been extensively studied in gas phase, solution and solid states. Our group has recently extended studies on non-classical persistent intramolecular C–H⋯X (where X = O, S, Br, Cl, and F) bonding in solution, using ^{1}H NMR spectroscopy for various benzyl Meldrum's acids.[148] Further evidence for the noncovalent interactions was gained by solid-state X-ray analysis that revealed hydrogen bonding occurred through a six-membered ring (Figure 4.4).[148] The ease of preparation of 5-benzyl Meldrum's acid derivatives permitted structural modifications of both the aromatic moiety and the benzylic tether that were shown to affect

the C–H⋯X interaction.[148] Three derivatives in particular were further studied in gas phase using infrared multiple dissociation (IRMPD) spectroscopy (Figure 4.4.), and in conjunction with combined NMR and computational studies, to quantify the C–H⋯X interactions.[149] It was computed that the C−H⋯X hydrogen bonding interaction, where X is an oxygen atom, was comparable in magnitude to that of the HF⋯HCl dimer; and when X is a sulfur atom, C−H⋯S interaction was found to be approximately 50% stronger than that observed for water dimer.[149] Furthermore, the removal of the acidic hydrogen results in a geometric conformational change where the phenyl ring is orientated away from the α-carbon. The absence of the acidic hydrogen does not allow for hydrogen bonding that would occur in the neutral molecule, illustrating the importance that hydrogen bonding plays in the stabilization of the overall molecule.[149] Based on these experimental and computational results, it is evident that benzyl Meldrum's acids derivatives served as valuable models to study noncovalent interactions in solution, solid and gas phase.
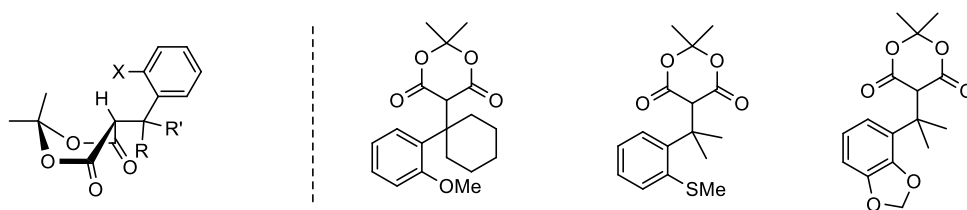
Figure 4.4. Meldrum's Acid Derivatives Show HB Interactions by Six-Membered Ring (left). Models Used for IRMPD Studies (right).

As already discussed, XB occurs at the surface of the molecule and is believed to be involved in molecular recognition processes throughout nature.[150] Almost all living organisms from simple organisms such as fungi to more advanced species such as humans, have been shown to either produce or use organohalogen compounds. Figure 4.5. illustrates an example of some naturally occurring compounds; where compound **4.1** is a insecticide produced by the Thai plant *Arundo donax*; **4.2** is produced by the marine organism *Lissoclinum voeltzkowi* and has been shown to have anticancer activity at the nanograms per milliliter level; **4.3** is a sex hormone in several species of ticks and is also produced by grasshoppers as an ant repellent; **4.4** was isolated from the cerebrospinal fluid of humans, cats and rodents and plays an important role in inducing sleep.[151]
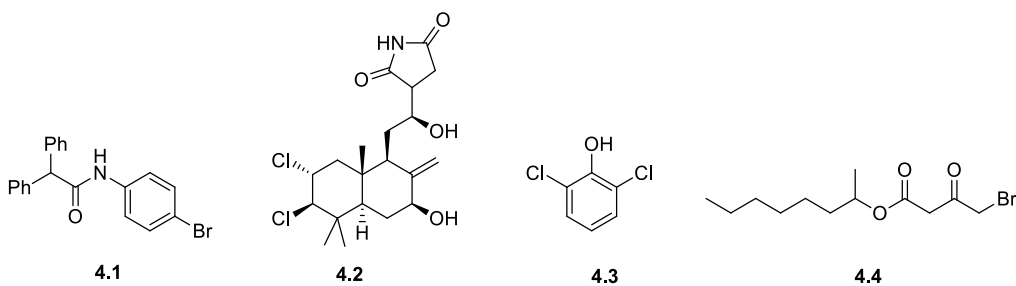
Figure 4.5. Selected Examples of Naturally Occurring Organohalogened Compounds

In contrast to HB, XB interactions outside gas phase and computational studies are not as well understood. Although some very fundamental studies of XB in solution have recently appeared,[152] they are typically limited to perfluorinated species and therefore are limited in scope. Novel models that would allow for a wider range of interactions would be of great value, particularly since XB is expected to play an essential role in biological processes which ultimately take place in solution.

4.2. Proposal

Based on our group's experience with Meldrum's acid derivatives and their use in intramolecular HB, an obvious extension, that being the parallelism of hydrogen and halogen bonding, would be to prepare Meldrum's acid derivatives with both XB donating and accepting groups to study R–X···Y type interactions. As a starting point it was believed that having as many of the structural features that promoted HB would be advantageous. With respect to these studies, it was found that gem-dimethyl substituents at the benzylic position, and SMe > Br > Cl, OMe groups at the *ortho*-position of aromatic group had the maximum interaction based on the difference in chemical shift in ^{1}H-NMR for HB models compared to analogous blank models that did not possess an electronegative atom.[148] It was envisaged that models bearing a halogen at the 5-position of Meldrum's acid can act as the XB donor, and a Lewis basic group at the *ortho*-position of the benzyl moiety can act as the XB acceptor (Figure 4.6a). Two potential modes of interaction were also predicted; where the lone pair of electrons

of Y can donate into the σ-hole generated by the X group (Figure 4.6b anti conformation). In this scenario, X would be at the pseudo axial position of the Meldrum's acid ring and acting as the electron withdrawing group resulting a σ-hole along the extension of the C_5–X bond. Alternatively, a less ideal conformation would allow for a "direct" RX⋯Y interaction, where the Meldrum's acid moiety acts as the electron withdrawing substituent in the same manner as it did in HB interactions (Figure 4.6b direct). Molecular orbital calculations by Ohwada revealed that the electron-accepting ability of the acidic CH group was related to the magnitude of overlap of the σ^*_{CH} orbital and the adjacent carbonyl π^* orbital.[153] Ohwada rationalized that when Meldrum's acid is being deprotonated, the base such as an amine attacks with its lone pair of electrons at the unoccupied orbital of the hydrogen atom, σ^*_{CH} orbital, which leads to CH bond cleavage. Based on the same rationale, there is potential for XB interactions since the same antibonding orbitals are involved. Figure 4.6c illustrates an adaptation of the models proposed by Ohwada in HB, and shows the orbitals available for the "direct" XB interaction. It is worth noting that this second mode, the direct mode, of interaction does not allow for the ideal 180° overlap thereby making it the less favorable mode of interaction. ^{13}C NMR spectroscopy will be employed to conduct solution based studies and X-ray crystallography will be used to observe solid state interactions.
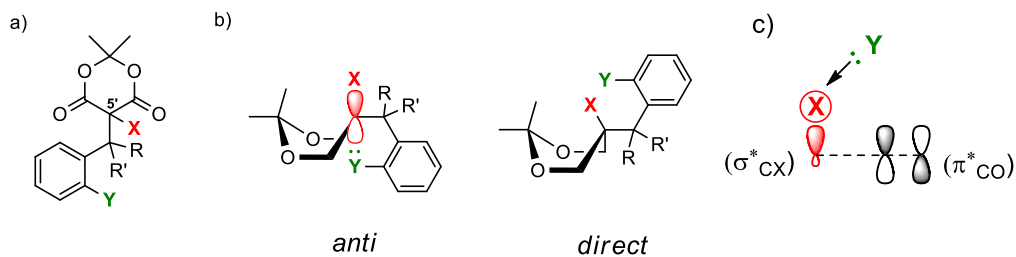
Figure 4.6. a) Proposed Models of Meldrum's Acid Derivatives Bearing XB Donor (X) and XB Acceptor (Y) Groups; b) Potential Modes of XB Interactions (*Note:* Oxygen Atoms for the Carbonyl Groups were Omitted for Clarity); c) Atomic Orbitals Representation for "Direct" XB Interaction

4.3. Results and Discussion

4.3.1. In Solution ^{13}C NMR Studies Exploring Intramolecular Halogen Bonding Interactions Using Meldrum's Acid Derivatives

Meldrum's acid derivatives were readily prepared by the protocols described in chapter 1 starting with corresponding ortho- substituted aldehyde or ketone. Halogenation at the 5-position of Meldrum's acid can be achieved using either *N*-chlorosuccinimide or PhICl$_2$ for chlorination, and Br$_2$ for bromination (Scheme 4.1). Several different models were prepared with XB acceptors ranging from Cl, Br, OMe, and S; and Cl or Br as the XB donor. The limitation for XB donors was quickly apparent where substitution at the *ortho* position of the aromatic moiety hindered the bromination at the 5-position of Meldrum's acid and resulted in the recovery of starting material. Running the reaction at higher temperatures, up to 60 °C, afforded inseparable mixture of compounds. Given the ability to prepare **4.7a**, which has a Br

Scheme 4.1. Halogenation of Meldrum's Acid Derivatives.

a)

4.5b, R, R' = H
4.9b, R, R' = Me

Br$_2$
NaHCO$_3$, H$_2$O
0 °C to rt

4.5, R = H; Y = H
4.6, R = H; Y = Cl
4.7, R = H; Y = Br
4.8, R = H; Y = OMe
4.9, R = Me; Y = H
4.10, R = Me; Y = Cl

NCS or PhICl$_2$
K$_2$CO$_3$, DMF

4.5a, R = H; Y = H
4.6a, R = H; Y = Cl
4.7a, R = H; Y = Br
4.8a, R = H; Y = OMe
4.9a, R = Me; Y = H
4.10a, R = Me; Y = Cl

b)

4.11

PhICl$_2$
K$_2$CO$_3$, DMF

4.11a
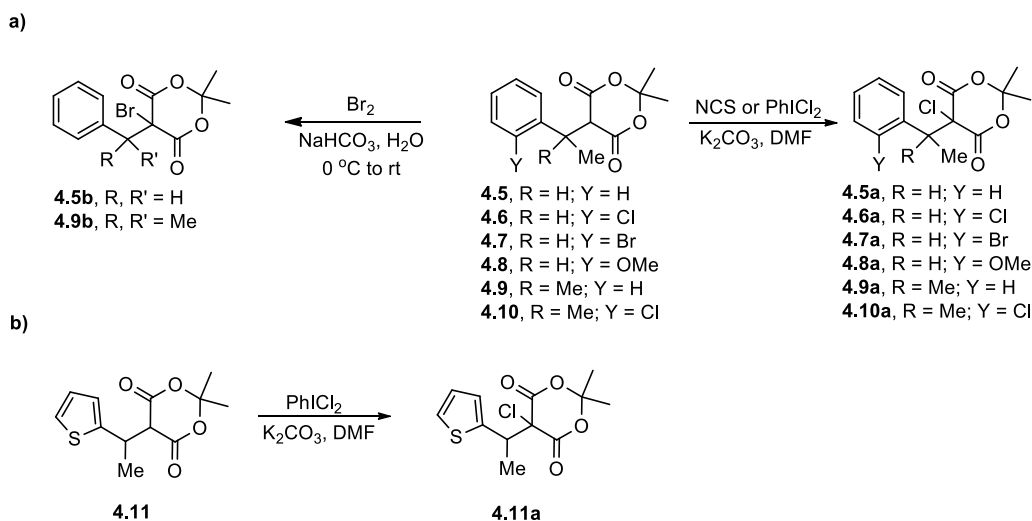
atom on the aromatic group and a Cl atom at the 5-position of Meldrum's acid, and the inability to prepare the reverse, where the Cl atom is on the aromatic group and Br atom is at the 5-position of Meldrum's acid, implies halogenation at thr 5-position of Meldrum's acid is blocked by the steric effects of the *ortho*-substituent. The close proximity of the *ortho*-

substituent on the benzyl group position to the acidic hydrogen on Meldrum's acids has been shown by nOe between an ethyl group and the acidic hydrogen (Figure 4.7).[148]
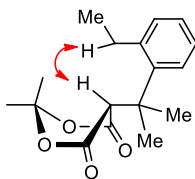
Figure 4.7. Close Proximity Between Methylene H and H at the 5-Position of Meldrum's Acid Shown By nOe in CDCl₃.

Models possessing sterically demanding groups at the benzylic position, such as **4.12**, may force XB interactions by taking advantage of the 1,3-allylic strain between the *ortho* substitute on the aromatic group and the largest group at the benzylic position. Noteworthy were chlorination reactions of **4.12** with PhICl₂, where halogenation took place at the desired 5-position of Meldrum's acid as well as the electron rich aromatic affording isomers **4.12a** and **4.12b** (Scheme 4.2).

Scheme 4.2. Chlorination of Benzyl Meldrum's Acid **4.12**
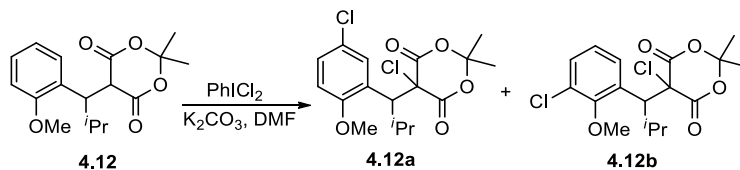
Solution based studies of intramolecular XB interactions began by investigating substitution effects of Y (XB acceptor) on X (XB donor) in CDCl₃ and C₆D₆. The results are summarized for compounds **4.5a–4.11a** in CDCl₃ in Table 4.1.[154] Model substrates with electronegative XB acceptors (Y = OMe, Cl), entries 2 and 4, showed downfield shifts of 2.34 and 0.24 ppm, respectively, at the C(5)–Cl position compared to the blank model C(5)–H. In contrast, for the larger and less electronegative XB acceptors (Y = Br, S), entries 3 and 5, upfield shifts of 0.04 and 1.74 ppm, respectively, were observed. Increasing the substitution at

the benzylic position, compounds **4.9a** and **4.10a**, show a downfield shift of 0.38 ppm for **4.10a** compared to control model **4.9a** (entry 7). However, a considerable difference of 8.36 ppm (entry 7) was observed when comparing the tertiary benzylic **4.6a** to quaternary benzylic **4.10a**. This difference can be attributed to the closer proximity of the Cl atom to that carbon as result of the gem-dimethyl substitution at the benzylic position. Based on these results, no correlation between the electronegativity or size of Y was observed on the C–X in the ^{13}C NMR.

Table 4.1. ^{13}C Chemical Shifts δ (ppm) of C(5) of Benzyl Meldrum`s Acid Derivatives in CDCl₃ .
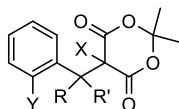
Entry	Compound (R / R')	X	Y	^{13}C(5) (ppm)	Δ ppm
1	**4.5a** (Me / H)	Cl	H	62.97	–
2	**4.6a** (Me / H)	Cl	Cl	63.21	0.24 (entry 2–1)
3	**4.7a** (Me / H)	Cl	Br	62.93	-0.04 (entry 3–1)
4	**4.8a** (Me / H)	Cl	OMe	65.31	2.34 (entry 4–1)
5	**4.11a** (Me / H)	Cl	2-thiophene	61.23	-1.74 (entry 5–1)
6	**4.9a** (Me / Me)	Cl	H	71.19	-
7	**4.10a** (Me / Me)	Cl	Cl	71.57	0.38 (entry 7–6) 8.36 (entry 7–2)

In addition to the 5-chloro derivatives, analogous 5-acetonitrile Meldrum's acid derivatives were also prepared (Scheme 4.3). Computational and gas phase studies have shown that the electron withdrawing power of cyano groups result in larger σ-holes and in turn form some of the strongest RX···Y interactions.[155] Alkylation at the 5-position of Meldrum's acid derivatives was achieved using K₂CO₃ and bromoacetonitrile in DMF (Scheme 4.3). Based on their proximity to the electron withdrawing group, two potential sites for σ-holes labeled C_a and C_b (Scheme 4.3) were probed and their chemical shifts δ in ppm are listed in Table 4.2. In these models (**4.6c**, **4.8c**, **4.13c**) a difference of ± 0.15 ppm at C_a was observed with respect to the control model **4.5c**. More interestingly, for all the models with a XB acceptor (Y ≠ H)

an upfield shift was observed for C_b, where OMe > Cl > SMe. A similar shielding effect was also observed in the ^{19}F NMR of XB bonding aryldiynes reported by Bowling.[156] Although it would be premature to insinuate that XB interactions are responsible for the trend, these results have more promise than the 5-chloroderivatives.

Scheme 4.3. Alkylation of Meldrum's acid derivatives.

4.5, Y = H
4.6, Y = Cl
4.8, Y = OMe
4.13, Y = SMe

4.5c, Y = H
4.6c, Y = Cl
4.8c, Y = OMe
4.13c, Y = SMe
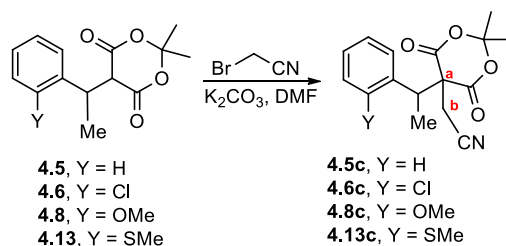
Table 4.2. [1]H/^{13}C chemical shifts δ (ppm) in CDCl$_3$.
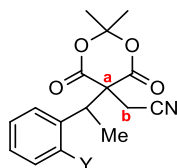
Entry	Y	[13]C(a) ppm	Δ^{13}C(a) ppm	[13]C(b) ppm	Δ [13]C(b) ppm
1	**4.5c** (H)	56.95	-	22.88	-
2	**4.8c** (OMe)	57.02	-0.07	21.32	1.56 (entry 2–1)
3	**4.13c** (SMe)	57.10	-0.15	21.79	1.09 (entry 3–1)
4	**4.6c** (Cl)	56.83	0.12	21.69	1.19 (entry 4–1)

4.3.2. Solid State Intramolecular Halogen Bonding Studies of Benzyl Meldrum`s Acid Derivatives Using X-Ray Crystallography

Benzyl Meldrum's acid models used for solution based studies were also investigated in solid state for XB interactions. However, only some substrates furnished single crystals that were of sufficient quality for x-ray analysis.
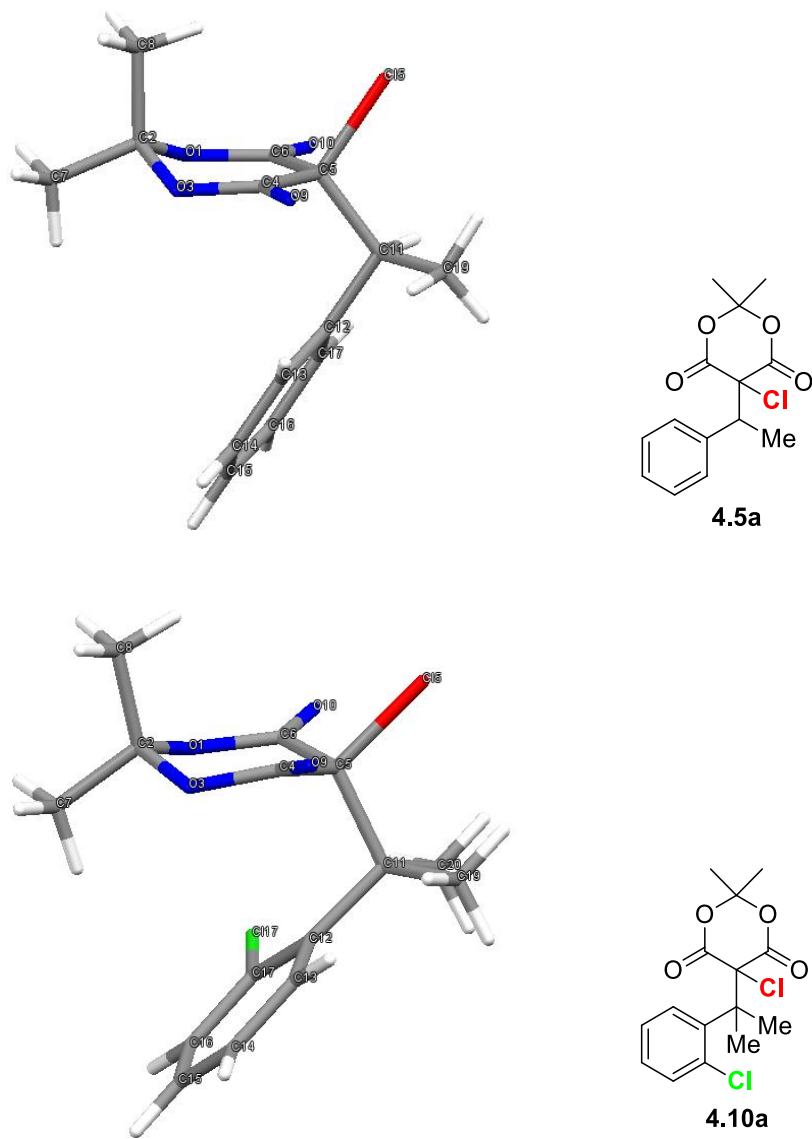
Figure 4.8. X-ray structures of Meldrum`s acids **4.5a** (top) and **4.10a** (bottom).

The x-ray structures of **4.5a** and **4.10a** are shown in Figure 4.8, where both structures have a Cl atom at the 5-position of Meldrum's acid and the aromatic group adopting an antiperiplanar conformation about the C(5)–C(11) bond. This conformation allows for the predicted "anti" XB interaction (Figure 4.6b); however, the x-ray structure of **4.10a** shows the XB acceptor, Cl(17), on the aromatic ring faces away from the potential σ-hole site. This orientation minimizes the allylic 1,3-strian[157] between Cl(17) and the Meldrum's acid ring, but also has the unfortunate consequence of impeding any intramolecular XB interactions. It is

also worth highlighting the half-chair and chair conformations of the Meldrum's acid ring in **4.5a** and **4.10a** respectively. Neither of these conformations were observed in Meldrum's acid derivatives prepared for the HB studies[148] or for Meldrum's acid,[158] where both adopt a boat conformation. One possible explanation for both the half-chair and chair conformations being favored in **4.5a** and **4.10a** may be due to the increased size of the substituents at the 5-position of Meldrum's acid, forcing the ring to adopt the conformations that minimize the 1,4-diaxial interactions of the boat conformation. In addition to reducing steric effects, destabilizing factors, such as $\sigma^*_{C-Cl} \rightarrow \pi^*_{C=O}$ overlap is also minimized by having the Cl atom at the pseudo-equatorial position in the Meldrum's acid ring (Figure 4.9).
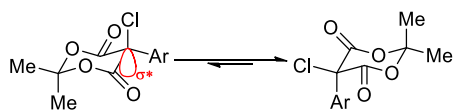
Figure 4.9. Potential $\sigma^*_{C-Cl} \rightarrow \pi^*_{C=O}$ Destabilizing Interactions of **4.10a**

Although intramolecular XB interactions were not observed in solid state for **4.10a**, intermolecular interactions between the XB donor of one molecule and the acceptor of another molecule were observed, Figure 4.10. Close contacts between the Cl(5) atom of one molecule and the Cl(17) atom of another were observed, with a bond length of 3.49 Å that is shorter than the sum of the van der Waals radii of 3.50 Å. Based on the bond angle of 167.3° for C(5)–Cl(5)···Cl(17), Cl(5) can be considered the XB donor which only deviates 13° from the ideal 180° for maximal overlap; and 28.4° for C(17)–Cl(17)···Cl(5) would suggest that Cl(17) is the XB acceptor. Further evidence for intermolecular XB was 0.01 Å shortening of the C(5)–Cl(5) bond for **4.10a** compared to **4.5a** (Table 4.3). XB interactions with Cl atoms have been shown to be weak compared to the more polarizable Br and I atoms both in solid state[140] and computationally.[143] However, these results are encouraging as no intermolecular interactions were observed for models that lacked a XB acceptor (**4.5a**).
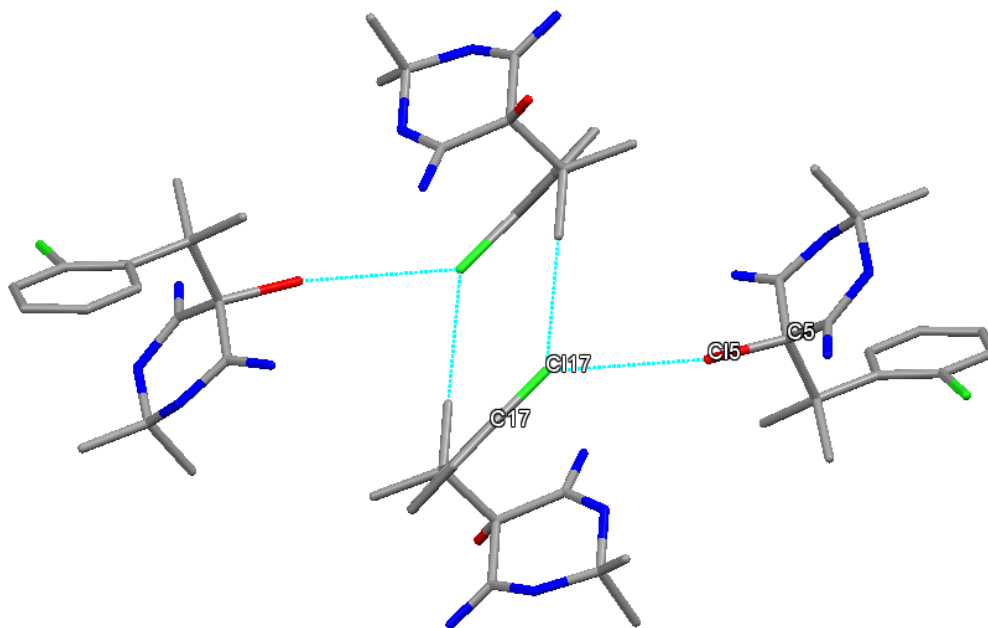
Figure 4.10. Intermolecular Interactions for **4.10a.**

More rigid Meldrum's acid derivatives **4.14a** were also prepared, where a cyclohexyl group is present at the benzylic position. X-ray crystallographic data collected for **4.14a** is illustrated in Figure 4.11 (top), and reveals that the Meldrum's acid moiety is again in the chair conformation with the Cl atom at the pseudo equatorial position, and the benzylic group at the pseudo axial position. Efforts to prepare related models with a XB acceptor, Y = OMe, lead to C–C bond cleavage between the benzylic carbon and Meldrum's acid carbon as evidenced by the isolation of **4.15a** and the olefin **4.16** (Scheme 4.3). The x-ray structure of **4.15a** shows that Meldrum's acid ring is in the boat conformation with the Cl group at the pseudo equatorial position (Figure 4.11 bottom). It should be noted that the C–Cl in **4.15a** bond is at least 0.03 Å shorter than those models that were in a chair conformation (**4.5a**, **4.10a** and **4.14a**) with Cl atom at the equatorial position.
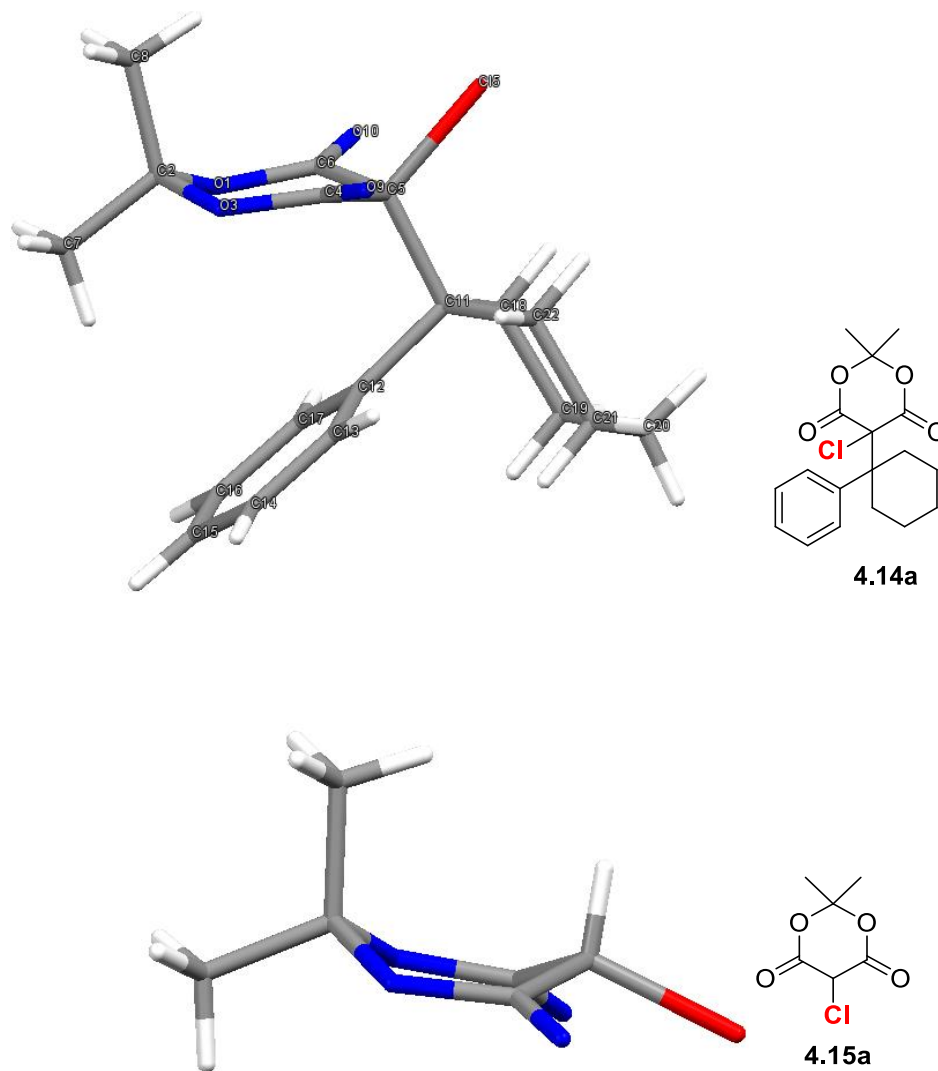
Figure 4.11. X-ray Structure of **4.14a** (top) and **4.15a** (bottom)

The difficulty of isolating halogenated derivatives of **4.15**, although structurally similar to **4.6a**, may be attributed to two factors, both of which promote the C–C bond cleavage (Scheme 4.4). Firstly, the donating ability of the methoxy group at the *ortho* position of the aromatic ring can help stabilize the formation of a tertiary benzylic carbocation through conjugation. Secondly, chlorination of the 5-position of Meldrum's acid ring renders it a better leaving group. Scheme 4.4 shows the proposed mechanism for the chlorination of **4.15** with NCS based on the two factors mentioned above, where chlorination of **4.15** presumably precedes bond cleavage. As alluded to in the previous chapter, our group has reported that Meldrum's acid can act as a carbon-based leaving group, where both electron rich aromatic

groups, as well as methylation of the 5-position of Meldrum's acid promote the cleavage of the C–C bond at the benzylic position.

Scheme 4.4. Proposed Mechanism for the C–C Bond Cleavage
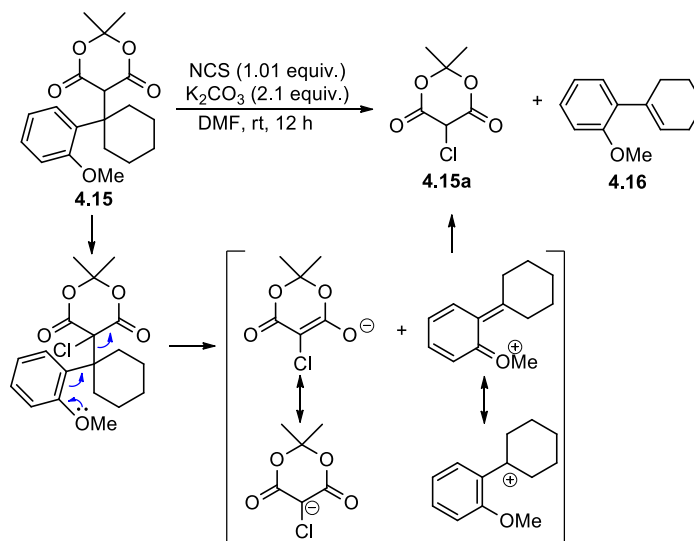
Meldrum's acid derivatives with multiple XB acceptor sites could increase the potential for XB interactions and were also pursued. Scheme 4.5 illustrates the strategy employed to access Meldrum's acid derivatives **4.17**, **4.19** and **4.20** that had either an ester or carbonyl moiety at the benzylic position. Chlorination of **4.17** was followed by an elimination of the benzylic proton resulting in olefin **4.18** as the only product (Scheme 4.5a). In order to avoid unwanted elimination reactions, compound **4.19** was prepared which has a quaternary center at the benzylic position, but the increase in steric bulk appears to also impede the chlorination and resulted in the complete recovery of starting material (Scheme 4.5b). As an alternative model for multiple XB sites, compound **4.20** which has a benzoyl group at the 5-position of Meldrum's acid was prepared. Compound **4.20** does not suffer from potential elimination reactions observed for **4.17**, and has the added advantage of introducing another electron withdrawing substituent next to the XB donor. However, chlorination reactions proved to be futile and starting material was isolated (Scheme 4.5c).

Table 4.3. X-ray Data of Meldrum's Acid Derivatives

Meldrum Acid	Bond Length (Å)	Δ (sum of van der Waals raddi – observed X-ray distance) (Å)
4.5a	C(5)–Cl(5) : 1.80 C(4)–O(9) : 1.19 C(6)–O(10) : 1.19	-
4.10a	C(5)–Cl(5) : 1.79 C(17)–Cl(17) : 1.75 C(4)–O(9) : 1.19 C(6)–O(10) : 1.18	0.01 (Cl⋯Cl)
4.14a	C(5)–Cl(5) : 1.79 C(4)–O(9) : 1.19 C(6)–O(10) : 1.19	-
4.15a	C(5)–Cl(5) : 1.76 C(4)–O(9) : 1.19 C(6)–O(10) : 1.19	-
4.6c	C(4A)–O(9A): 1.19 C(6A)–O(10A) : 1.15 C(17)–Cl(1) : 1.75 C(21A)–N(1A) : 1.15	-
4.18	C(13)–Cl(13) : 1.74 C(4)–O(9) : 1.20 C(6)–O(10) : 1.20 C(5)–C(14) : 1.34	-
4.22	C(13A)–Cl(13A) 1.74 C(13B)–Cl(13B) 1.74 C(5A)–Cl(5A) 1.78 C(5B)–Cl(5B) 1.78 C(5A)–C(5B) 1.56 C(4A)–O(9A) 1.18 C(4B)–O(9B) 1.20 C(6A)–O(10A) 1.20 C(6B)–O(10B) 1.18	-

Scheme 4.5. Chlorination Reactions of Meldrum's acid derivatives a) **4.17**, b) **4.19** and c) **4.20**

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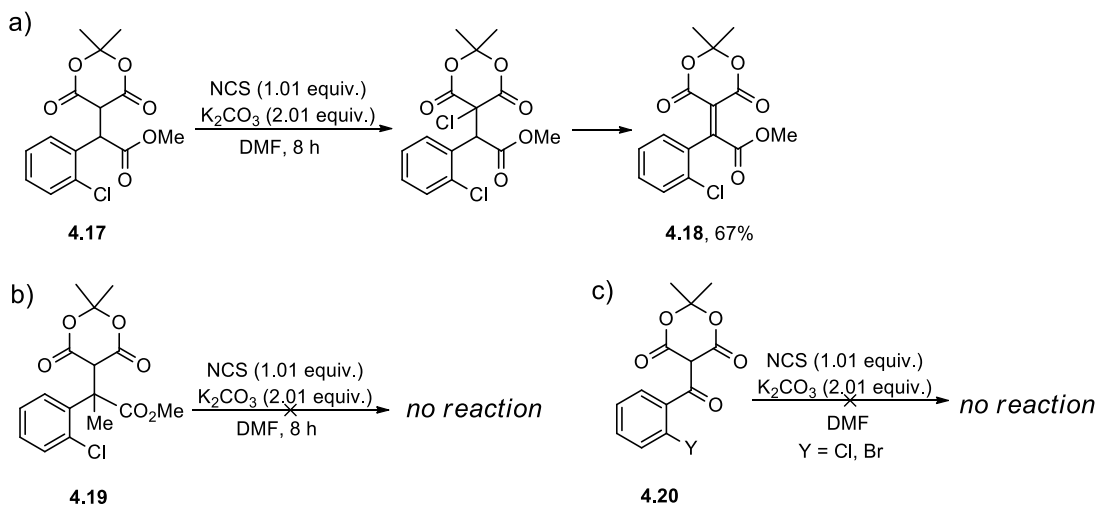
The solid state structure of **4.6c** was also determined using X-ray crystallography and shown in Figure 4.12. Compound **4.6c** has the potential for multiple sites of XB and did show an upfield shift at the methylene carbon (C_b) in the ^{13}C-NMR compared to the control model (vide supra). However, X-ray analysis of **4.6c** does not show any intra- or intermolecular interactions (Figure 4.12). The Meldrum's acid ring is in a chair conformation with the acetonitrile group at the pseudo equatorial position and the benzyl group in the pseudo axial position. A survey of the pertinent bonds in **4.6c** revealed a shorten bond length 0.04 Å for one of the carbonyl groups in the Meldrum's acid ring, C(6A)–O(10A) (Table 4.3), compared to any of the other derivatives and Meldrum's acid itself.[158]
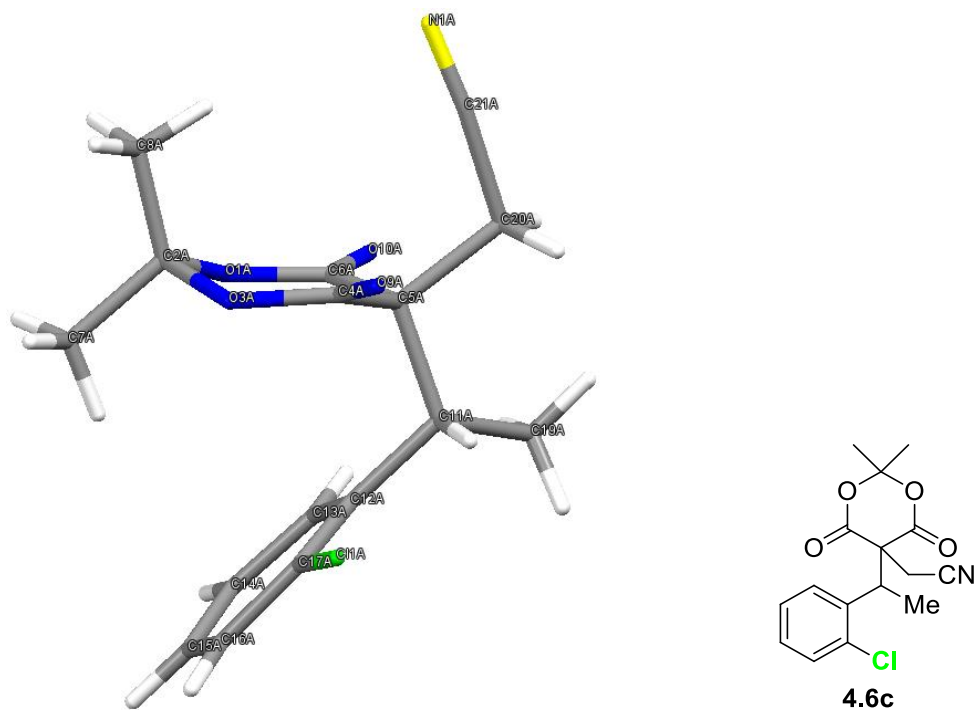
Figure 4.12. X-ray structure of **4.6c**.

Due to the absence of intramolecular XB interactions for Meldrum's acid derivatives halogenated at the 5-position, novel models were envisioned that would allow for the incorporation of the larger halogens (Figure 4.13). These models place the XB acceptor at the C(2) position of Meldrum's acid and the XB donor at the 5-position. We have already observed that the Meldrum's acid group can adopt a boat, chair and half-chair conformation that could

allow for the flexibility needed to incorporate larger halogens at the 5-position, and a broader angle necessary for the directionality of XB. Moreover, it has been reported that the 5-position of Meldrum's acid can be fluorinated[159], chlorinated[160] and brominated[161] which should give a more comprehensive range of studies. These derivatives can be accessed by the acid catalyzed condensation of malonic acid and corresponding carbonyl.[162]
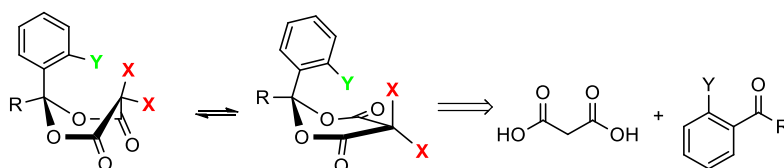
Figure 4.13. C(2)-Derivatives of Meldrum's Acid.

With these new models in mind, compound **4.21** was prepared in a modest yield of 31% after 60 h (Scheme 4.6). Efforts were made to improve the yield by diluting reactions in various solvents and using dehydrative conditions such using a Dean-Stark trap and the addition of molecular sieves to shift the equilibrium towards right; however, those modifications did not improve the efficiency of the reaction. On the contrary, molecular sieves completely halted the reaction and afforded the ketone in quantitative yields. Furthermore, attempts to prepare the 2'-bromo- and 2'-methoxy analogous of **4.21** failed to give any condensed products. It was apparent that new conditions needed to be developed to promote the condensation, but model **4.21** was a good starting point to probe for RX···Cl interactions.

Scheme 4.6. Acid Catalyzed Condensation of Malonic Acid and 2`-Chloroacetophenone
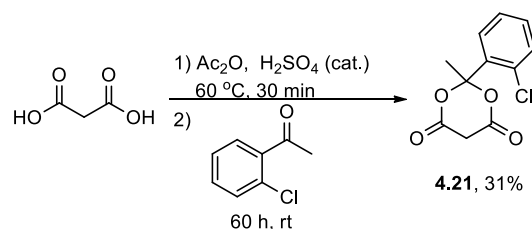
With these new potential models in hand, only the halogenation step of **4.21** remained to prepare the desired model. Surprisingly, chlorination at the 5-position of **4.21** was inaccessible using previous strategies that were successful for earlier models, and resulted in hydrolysis of **4.21** to 2'-chloroacetophenone with NCS (Scheme 4.7a), or the formation of complex mixtures for reactions with PhICl₂ (Scheme 4.7b). Alternate halogenation strategies were sought after and to this end a report by Weinreb *et al.* for the halogenation of *β*-dicarbonyl compounds using sodium hypochlorite and acetic acid in acetone offered an attractive mild approach.[163] However, under those conditions the Knovenagel condensation between **4.21** and acetone was favoured, and **4.22** was isolated (Scheme 4.7c). The X-ray structure of **4.22** was obtained, Figure 4.14, and shows the Meldrum's acid ring is in a boat conformation with the aryl group at the axial position. Bond lengths for **4.22** are summarized in Table 4.3.

Scheme 4.7. Halogenation Reactions of **4.21** with a) NCS, b) PhICl₂ and c) HOAc/NaOCl
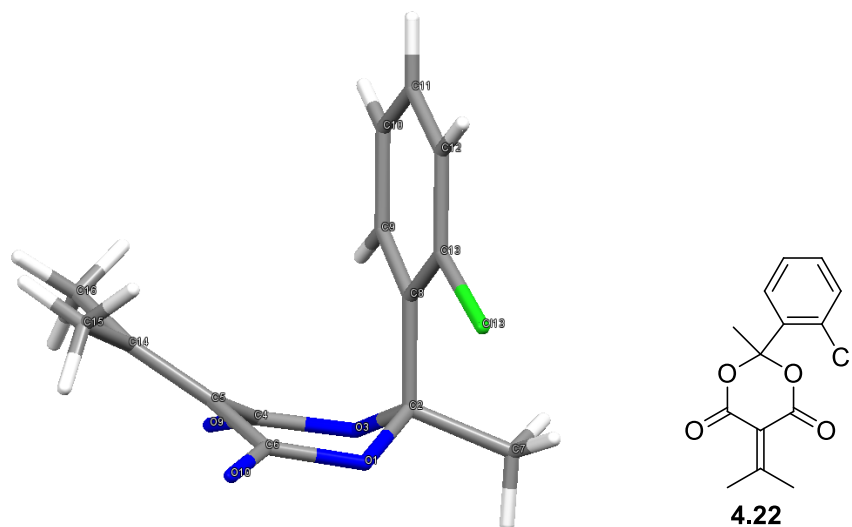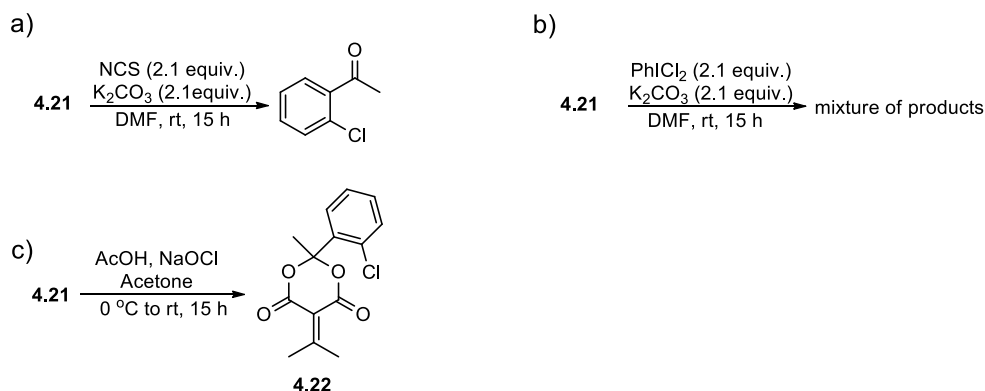
Figure 4.14. X-ray structure of **4.22**.

Instead of halogenating **4.21** directly, a different precursor was targeted after coming across a report by the Murphy group here at the University of Waterloo. They recently expanded on their chlorination methodology of diazoacetates[164] to phenyliodonium ylides with hypervalent iodine reagents, Scheme 4.8a and b respectively. Utilizing the same strategy, **4.21** was treated with PhI(OAc)$_2$ in the presence of catalytic base affording ylide **4.23** in excellent yield of 93% (Scheme 4.8 c). Ylide **4.23** has an electron deficient I atom at the 5-position of Meldrum's acid, which would be the best XB donor, but efforts to obtain single crystals for X-ray analysis failed and an amorphous white solid was isolated. Treating **4.23** with a slight excess of PhICl$_2$ unexpectedly gave **4.24** (Scheme 4.8c). Initially, it was believed that the desired 5,5-dichlorinated product was formed based on the disappearance of the phenyl peaks corresponding to the iodobenzene in **4.23**. However, upon running HRMS analyses of **4.24**, no Cl atoms were present based on the absence of the characteristic M+2 peak, and ^{13}C NMR analyses was not informative. Fortunately single crystals were obtained for X-ray analysis and the structure of **4.24** was unambiguously determined (Figure 4.15).

Scheme 4.8. a) Chlorination of Diazoacetate with Iodobenzene Dichloride; b) Chlorination of Phenyliodonium Ylides with Iodobenzene Dichloride; c) Chlorination of **4.17** with Iodobenzene Dichloride
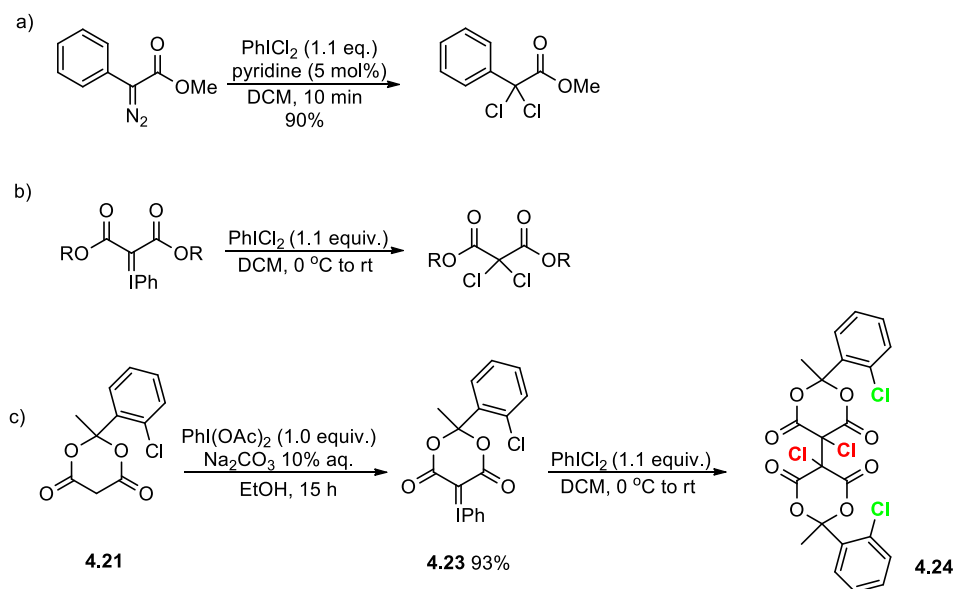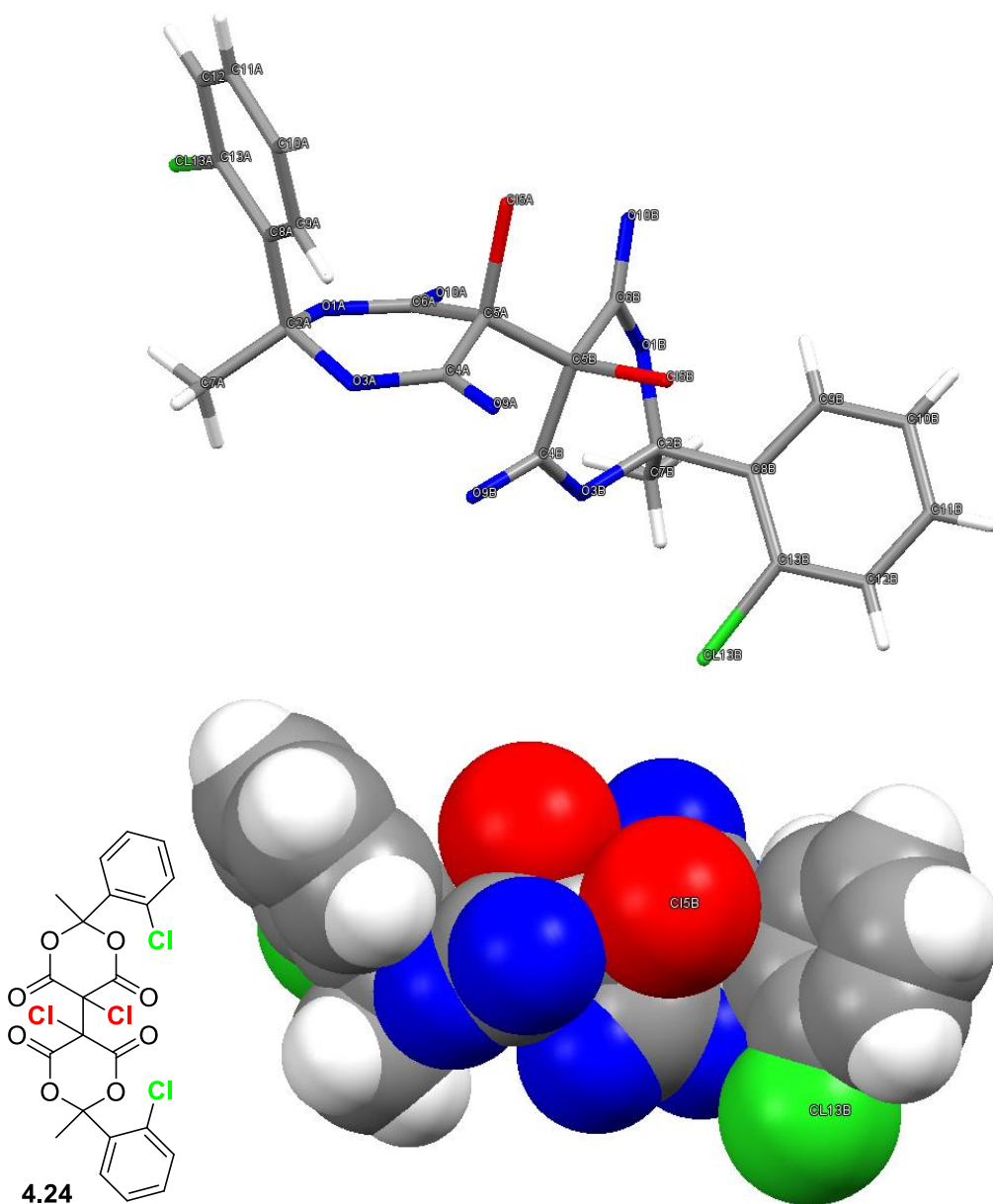
Figure 4.15. X-ray Structure of **4.24**

Compound **4.24** has two Meldrum's acid rings coupled at the 5-position with vicinal Cl atoms (Figure 4.15). Both Meldrum's acid rings are in a boat conformation with their Cl(5A/B) atoms at the pseudo axial position. The two Cl(5A/B) atoms are eclipsing about the C(5A)–C(5B) bond, while the 2-aryl groups are gauche relative to each other. Though both XB partners have the correct orientation for intramolecular interactions, the aromatic ring is again rotated away from XB donor. Pertinent bond lengths are summarized in Table 4.3, where

each half of the molecule has nearly identical bond lengths. A closer examination of the space filling diagram of **4.24**, Figure 4.14 bottom, revealed that the 1,4-interactions do not allow for XB interaction to occur. This oversight suggests that although there is flexibility in the ring, the angle for correct overlap between the XB donor and acceptor is not attainable by these models.

Another inherent problem with these models may be their stability where dihalogenated Meldrum's acid derivatives can function as excellent halogenating agents themselves,[165] and therefore can be more challenging to isolate. This could also explain the numerous side products that are formed in these reactions. As a result, instead of halogenating as the last step, dibromomalonic acid was first prepared using a procedure reported by Snyder and Kruse,[161b] followed by condensation conditions with the vinyl acetate (Scheme 4.9). Unfortunately, after monitoring the reaction for several days,[166] the only compound identified was the unprotected ketone.

Scheme 4.9. Condensation of Dibromomalonic Acid
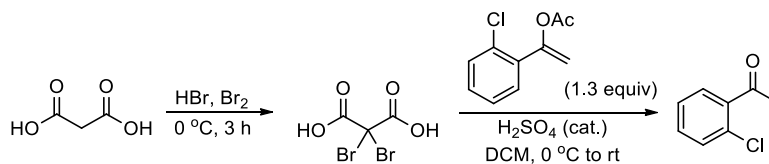
Based on these results, novel models **M1** and **M2** were proposed (Figure 4.16), which place the XB acceptor further away to avoid steric interactions while still allowing for the optimal bond angle of 180° for RX···Y. As a starting point, three aldehydes (**4.25**-**4.27**) were prepared with either an aromatic or alkynyl group acting as a spacer for the XB acceptor (Scheme 4.10). The synthetic approach to these aldehydes are shown in Scheme 4.10 where **4.25** was prepared in 68% yield after three steps by a Corey-Fuchs homologation of 2-methoxybenzaldehyde (Scheme 4.10a); compounds **4.26** and **4.27** were both prepared by the Suzuki coupling of 4-formylphenylboronic acid and the corresponding aryl halide (Scheme 4.10b-c).
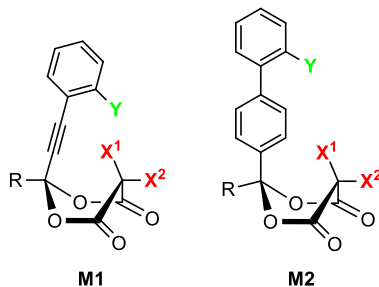
Figure 4.16. Proposed models with rigid spacers between XB donor and acceptor.

Scheme 4.10. Synthesis of a) **4.25**; b) **4.26**; and c) **4.27**; d) Condensation Conditions of **4.25–4.27** with Malonic Acid
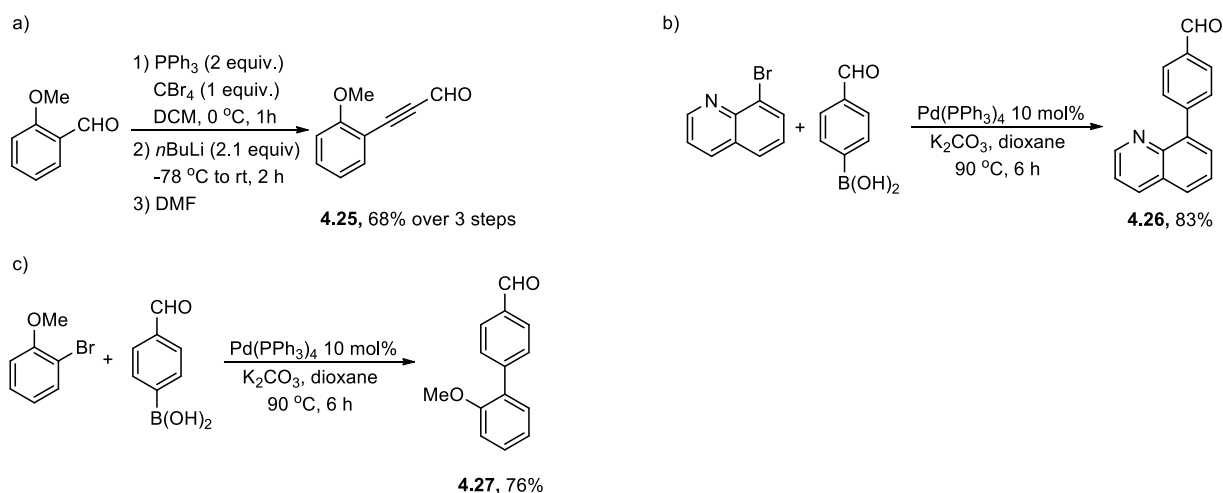
Condensation conditions used to prepare **4.21** were applied to aldehydes **4.25**-**4.27**, but proved to be ineffective and did not produce the desired Meldrum's acid adducts (Scheme 4.11a). Rather, complex mixtures of products as well as starting material was observed in the crude ^{1}H NMR. Particularly for condensations with **4.26**, which possess a basic amino group, resulted in recovery of quantitative amounts of starting material. Modifications to the procedure were made to account for the presence a basic amine functional group, and poor solubility of aldehydes **4.25**-**4.27**. For example, a viscous medium is formed in the first step of the condensation when malonic acid is acylated with acetic anhydride complicating the addition of the aldehydes which are solids. To ensure the formation of a homogeneous mixture, different solvents (CH$_2$Cl$_2$, Et$_2$O, toluene) were screened; however, no condensed products were observed and significant amounts of unreacted aldehydes remained. For

aldehyde **4.26**, the basic/nucleophilic quinoline group may interfere with catalytic acid present; therefore 1.1 equivalents of sulfuric acid was added to allow for the acid to catalyze the reaction, conversely, no condensation was obtained. Finally, several Brønsted acids were screened based on a report by Xu *et al*, [167] who claimed that H_3BO_4 and acetic anhydride were superior condensing reagents compared to other Brønsted and Lewis acids in the condensation of malonates and various ketones for synthesis of 1,3-dioxane-4,6-diones, including **4.28** (Scheme 4.11b). Brønsted acids including H_2SO_4, H_3PO_4 and H_3BO_3 were screened but did not afford any adducts.

Scheme 4.11 Condesation Conditions for Malonates and Various Carbonyls
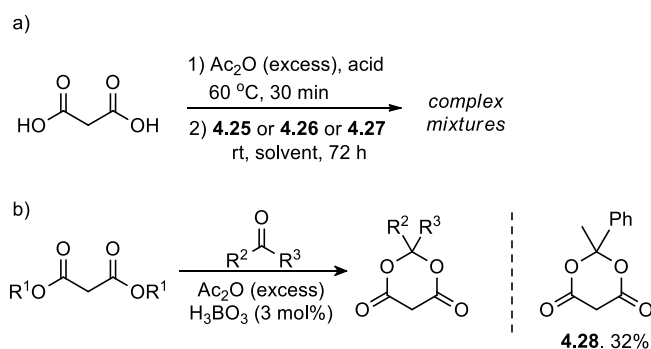
Non-acidic conditions for the synthesis of the new XB models were explored. The thermolysis of Meldrum's acid in the presence of cyclic ketones to afford the spiro adduct **4.29** is known (Scheme 4.12). [168] These reactions proceed through a retro-hetero-Diels–Alder cycloaddition with the loss of acetone to give an acyl ketene intermediate that rapidly undergoes a successive Diels–Alder cycloaddition with the ketone resulting in **4.29**.[169] This reaction has only been reported for cyclic ketones, cyclohexanone and cyclopentanone, in modest 40-50% yields. In order to develop conditions for aldehydes **4.25**-**4.27**, benzaldehyde and acetophenone were used as carbonyl sources. Under thermal decomposition conditions, both neat mixtures and 1 M solutions of benzaldehyde or acetophenone did not result in the condensed adducts. Based on the crude ^{1}H-NMR spectra, the Meldrum`s acid had been consumed and significant amounts of the carbonyl were present, but no other compounds were isolated or identified.

Scheme 4.12. Thermolysis of Meldrum`s acid.
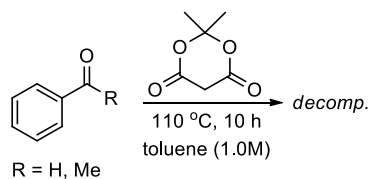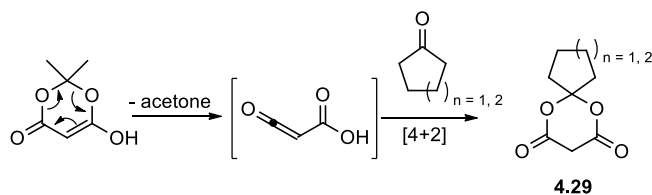
It was determined that in order to prepare the desired **M1** and **M2** models, new conditions were required. Since the acid catalyzed condensation of malonic acid was the only strategy that afforded the condensed product **4.21**, similar strategies may offer the most potential. As a starting point, a mechanism for the condensation was proposed, Figure 4.17, to determine modifications for the procedure. In this mechanism: protonation of the malonate **SM** activates the carbonyl for nucleophilic attack by the oxygen of the aryl ketone or aldehyde. An intramolecular nucleophilic attack closes the ring and give rise to intermediate **I1**. Proton transfer and loss of acetic acid results in **I2**, which can undergo another series of proton transfers and the loss of another molecule of acetic acid or acetic anhydride affording the desired Meldrum's acid derivative. One possible reason the condensation stalls may be due to the poor reactivity between electrophile generated by the protonation of **SM**, and the poor nucleophilicity of the carbonyl oxygen. In order shift the equilibrium towards the products, bis(trimethylsilyl) malonate (BTM) can function as an irreversible electrophile by forming hexamethyldisiloxane (HMDSO) as a byproduct.
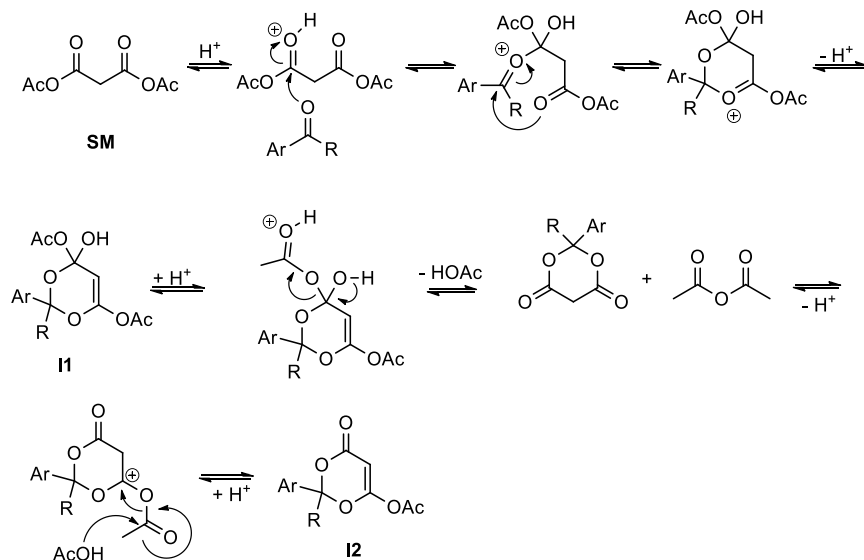
Figure 4.17. Proposed Mechanism for the Condensation of Malonate **SM** and Aromatic Carbonyls

The viability of BTM in condensation reactions for the synthesis of 1,3-dioxane-4,6-diones was screened and the preliminary results are summarized in Table 4.4. For economical reasons and ease of identification of products by investigating aromatic region of the ^{1}H NMR, 4'-chloroacetophenone and 4-chlorobenzaldehyde were used as carbonyl sources for developing and optimizing condensation conditions. Additionally, Lewis acids have been used to prepare silyl ketene acetals from enolizable esters in the presence of a base,[170] but in the absence of a base, it is plausible that BTM can be activated by a Lewis acid and become susceptible to nucleophilic attack. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was used as the Lewis acid to activate the BTM for nucleophilic attack because not only is it an excellent Lewis acid but hexamethyldisiloxane (HMDSO) is volatile and can be easily removed.

Table 4.4. Reaction Conditions of BTM and Aromatic Ketones and Aldehydes.
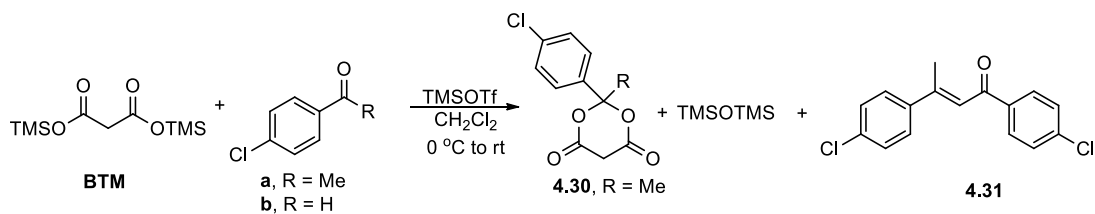
Entry	Carbonyl	Method	% Conv.[a]
1	a	a (0.7 mmol) was added to **BTM** (0.7 mmol) + TMSOTf (0.7 mmol)	20 : 10 : 70 **a** : **4.30** : **4.31**
2	a	TMSOTf (0.7 mmol) was added to **BTM** (0.7 mmol) + c (0.7 mmol)	10 : 10 : 80 **a** : **4.30** : **4.31**
3	a	a (0.7 mmol) was added to **BTM** (0.7 mmol) + TMSOTf (0.2 mmol)	65 : 0 : 35 **a** : **4.30** : **4.31**
4	a	a (0.7 mmol) was added to **BTM** (1.4 mmol) + TMSOTf (0.7 mmol)	90 : 0 : 10 **a** : **4.30** : **4.31**
5	b	b (0.7 mmol) was added to **BTM** (1.4 mmol) + TMSOTf (0.7 mmol)	complex mixture

[a]Based on the relative ratios in the crude ^{1}H-NMR.

Reactions where the acetophenone was added to a mixture of BTM and TMSOTf did result in the formation of the desired adduct **4.30** but as minor product compared to the aldol adduct **4.31** (Table 4.5, entry 1).[171] Changing the order of addition where the TMSOTf was added to a mixture of BTM and the ketone, did not show any improvements (entry 2). Moreover, evidence for the favorable formation of **4.31** was observed when catalytic amounts of TMSOTf was used, where only the starting material **a** and **4.31** were seen in the crude ^{1}H-NMR. In the presence of excess BTM, entry 4, a reduction in the formation of **4.31** was observed but no condensed product was formed. To prevent the aldol reaction, 4-chlorobenzaldehyde was used as the nucleophile, entry 5, which resulted in complete consumption of the aldehyde but complex mixtures were obtained that lacked the characteristic diastereotopic protons, suggesting the desired product was formed.

4.3.3. Halogen Bond Directed Diels–Alder Cycloadditions

In addition to investigating intramolecular XB interactions, we were also interested in applications of XB, and began studies on XB directed Diels-Alder cycloadditions. We propose that a diene and dienophile can coordinate through XB interactions and undergo regioselective Diels– Alder cycloaddition as illustrated in Figure 4.18.
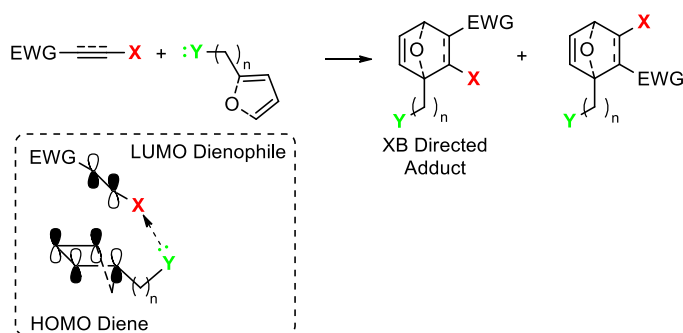
Figure 4.18. Halogen Bond Directed Diels–Alder Cycloadditions

Iodoacetylenes have been studied in both solid state and in solution and have shown to participate in XB interactions with various Lewis bases. [172] The strongest association constants in solution for O bearing XB acceptors were found to be PO > SO > CO, and quinuclidine > Et_3N > pyridine for N bearing acceptors.[172] Furthermore, Laurence found that the association of 1-iodoacetylenes derivatives with various Lewis bases followed the trend ICN > IC≡CCN > IC≡CCOOEt > IC≡CC$_6$H$_4$NO$_2$ > IC≡CPh > IC≡CPr.[173] With these studies in mind, alkynyl groups bearing a halogen could act as a XB donating dienophile, and a substituted furan can act as the XB accepting diene. Scheme 4.13 outlines the synthesis of both the diene and dienophiles that were tested for XB directed Diels-Alder cycloadditions.

Scheme 4.13. Synthesis of XB Acceptors and Donors.

<u>XB Acceptor - Dienes</u>

<u>XB Acceptor - Dienophile</u>
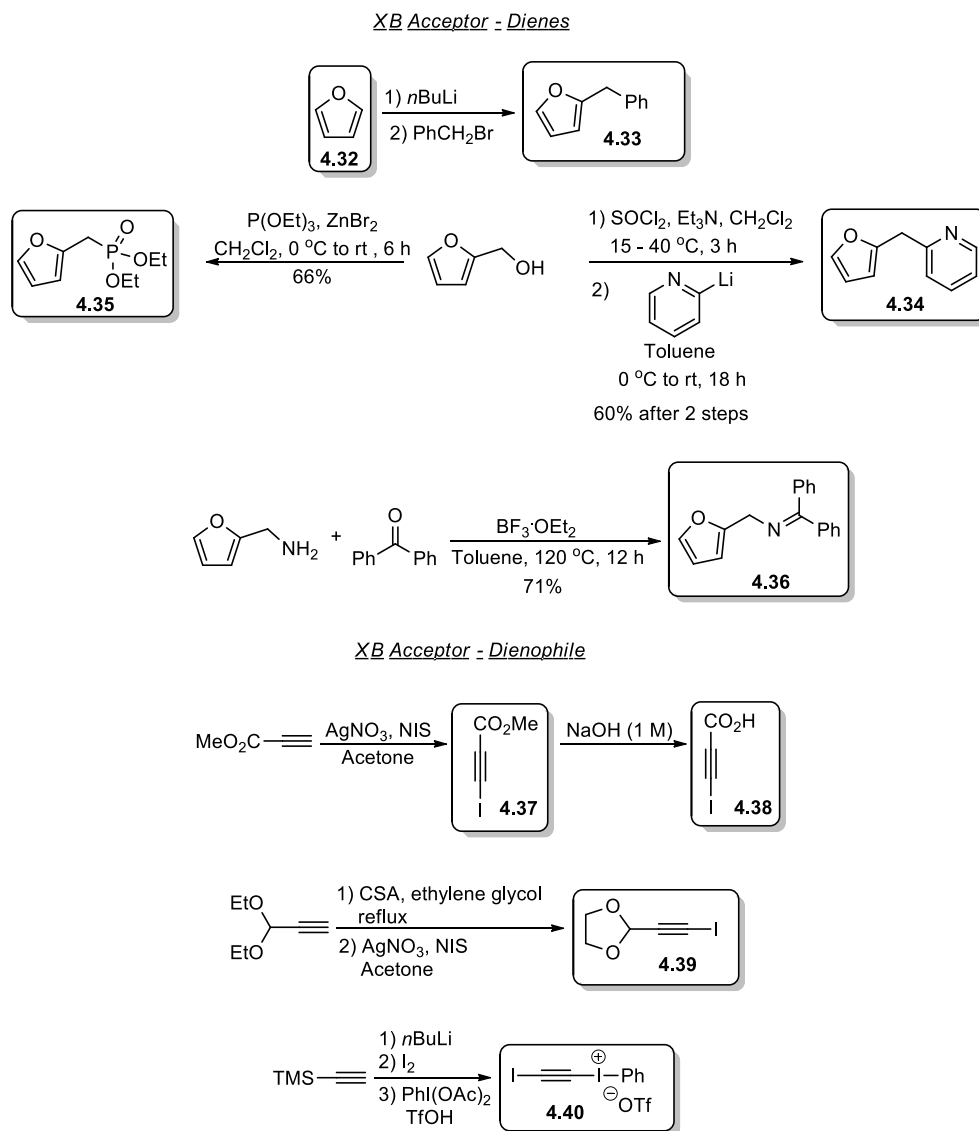
The [4+2] cycloaddition of furans and bromopropiolate is known and results in 7-oxabicyclo[2.2.1]heptadiene frameworks in moderate to low yields, and have then been used in subsequent transformations to access natural products. [174] Table 4.5 summarizes the substrates that were tested and conditions screened. Initially conditions reported for the cycloaddition of bromopropiolate and furan were employed (Table 4.5, entry1),[174a] where a 10:1 mixture of furan **4.32** to iodopropiolate **4.37** was heated at 80 °C for 24 h to obtain 18% of the adduct **4.41**. The isolation of **4.41** was promising showing that a Diels-Alder reaction was possible between the simplest diene, no XB acceptor, and dienophile. However, mild

reaction conditions would be preferable to allow XB to direct the regioselectivity of the reaction and minimize the formation of regioisomers. Screening dienes **4.33–4.36** showed no reactivity for in all cases at room temperature after 96 h, but more concerning was that no products could be detected at 100 °C after 96h, entries 2, 7, and 9. Diluting reagents in different solvents and repeating reactions at 100 °C still showed significant amounts of starting material as well as signs of decomposition in the crude ^{1}H NMR, entries 3, 8, 10–11.

In order to improve reactivity, the attention was shifted to Lewis acid catalyzed Diels-alder reactions that not only increase the rate of reaction, but can also increase the regioselectivity at lower temperatures.[175] The addition of two different Lewis acids, Me$_2$AlCl or TiCl$_4$, both resulted in the consumption of the diene but recovery of the dienophile, entries 4 and 5. This result was somewhat puzzling because the dienophile bears a more nucleophilic ester moiety compared the benzyl furan, and was therefore expected to be activated by forming a coordination complex with the Lewis acid. Inline with the same strategy, a report by Hall recently disclosed a protocol for the boronic acid-catalyzed Diels-alder cycloadditions to propiolic acids under mild reaction conditions. [176] Using the same conditions with iodopropiolic acid **4.38** and furan resulted in the cycloadduct **4.42**. Running the same reaction at elevated temperatures, entry 13, gave a mixture of **4.42** as the major product and trace amounts of an aromatic compound believed to be **4.43**.[177] Repeating reactions with substituted dienes **4.33** and **4.35**, entries 14 and 15, showed no reactivity after 96 h at elevated temperatures. It is possible that boronic acid complexes to the phosphonate for reactions with **4.35**, no longer activating the propiolate for the cycloaddition to take place; but the same rationale cannot be used for reactions with benzyl furan **4.33**, which lacks the nucleophilic site to interact with the Lewis acid.

More reactive dienophiles could circumvent the lack of reactivity observed with **4.37** and **4.38**. Gassman used allyl cation intermediates in Diels-Alder reactions with 1,3-dienes,[178a] and later expanded to cycloaddition of acetals of acrolein to various dienes at low temperatures.[178b] The importance of the catalyst was shown where in its absence no or poor reactivity was observed, but upon addition of the catalyst a dramatic increase in reactivity at significantly lower temperatures was observed by the formation of the product. Furthermore, nearly twice the yields were obtained by utilizing the dioxolane derivatives of acrolein than for

Table 4.5. XB directed Diels–Alder cycloadditions.
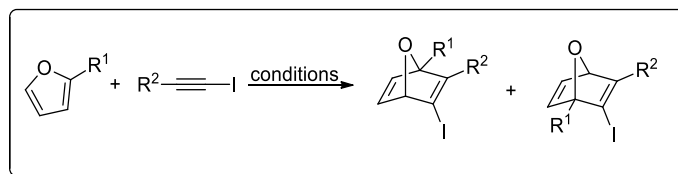
Entry	XB Donor (Diene)	XB Acceptor (Dienophile)	Conditions	Additives	Result
1	4.32	4.37	80 °C, 24 h	-	**4.41**, 18%
2	4.33	4.37	rt–100 °C, 96 h	-	no reaction
3	4.33	4.37	Benzene (1.0 M), 100 °C, 24 h	-	decomp.
4	4.33	4.37	DCM (0.1 M), -78°C to 0 °C	Me$_2$AlCl	4.30 recovered
6	4.33	4.37	DCM (0.1M), -78 °C to 0 °C	TiCl$_4$	4.30 recovered
7	4.34	4.37	rt – 100 °C, 96 h	-	no reaction
8	4.34	4.37	Benzene (1.0M), 100 °C, 48 h	-	decomp.
9	4.35	4.37	rt – 100 °C, 96 h	-	no reaction
10	4.35	4.37	Benzene (1.0M), 100 °C, 48 h	-	decomp.
11	4.36	4.37	Benzene (1.0M), 100 °C, 48 h	-	decomp.
12	4.32	4.38	DCE (1.0 M), rt, 24 h	o-Br-C$_6$H$_4$B(OH)$_2$ (30 mol%)	**4.42**
13	4.32	4.38	DCE (1.0 M), 50 °C, 24 h	o-Br-C$_6$H$_4$B(OH)$_2$ (30 mol%)	**4.42** (major) **4.43** (minor)
14	4.33	4.38	DCE (1.0 M), rt –50 °C, 96 h	o-Br-C$_6$H$_4$B(OH)$_2$	no reaction
15	4.35	4.38	DCE (1.0 M), rt –50 °C, 96 h	o-Br-C$_6$H$_4$B(OH)$_2$	no reaction
16	4.32	4.39	DCM (0.1M), –78 °C to rt, 24 h	TMSOTf (1.4 equiv.)	Insoluble black solid
17	4.33	4.39	DCM (0.1M), –78 °C to 0 °C, 24 h	TMSOTf (1.0 equiv.)	decomp.
18	4.33	4.39	DCM (0.1M), –78 °C to 0 °C, 48 h	TMSOTf (15 mol%)	no reaction
19	4.35	4.39	DCM (0.1M), –78 °C to rt, 48 h	TMSOTf (15 mol%)	no reaction
20	4.35	4.39	DCM (0.1M), –78 °C to 0 °C, 48 h	TMSOTf (1.0 equiv.)	no reaction
21	4.32	4.40	CD$_3$CN, –30 °C to rt, 24 h	-	Shiny black plastic

the diethyl acetals.[178b] Danishefsky later utilized this strategy in the total synthesis of dysidiolide **1**, where a key step was the Diels-Alder reaction between dioxolane **4.44** and diene **4.45** catalyzed by TMSOTf at very low temperatures affording the adduct **4.46** in a 67% yield (Scheme 4.14).[179] The true utility of the Gassman dioxolenium dienophile strategy was highlighted by the fact that the analogues dienophile of **4.44** bearing an ester moiety instead of the acetal was ineffective in the Diels-Alder reactions.[179] Employing this strategy to our system, dienophile **4.39** was prepared (Scheme 4.13) bearing a terminal iodine atom at one end and the dioxolane group at the other end of an alkyne. Repeating reactions with **4.32**, **4.39** and TMSOTf as the catalyst, entry 16, resulted in the formation of an insoluble black precipitate. Efforts to run the reaction at temperatures below 0 °C resulted in consumption of starting material after 24 h, however, no isolatable product could be obtained, entry 17. Using catalytic amounts of TMSOTf did not show any reactivity after 48 h, entry 18, suggesting that TMSOTf does not act as a catalyst. Reactions with other dienes such as **4.35** did not fare any better and resulted in the isolation of starting material after 48 h, entries 19–20. Substituted furans **4.33-4.36** appear to hinder any reactivity that was previously observed with furan.

Scheme 4.14. Application of Dioxolenium Mediated Diels–Alder Reaction in the Total Synthesis of Dysidiolide.
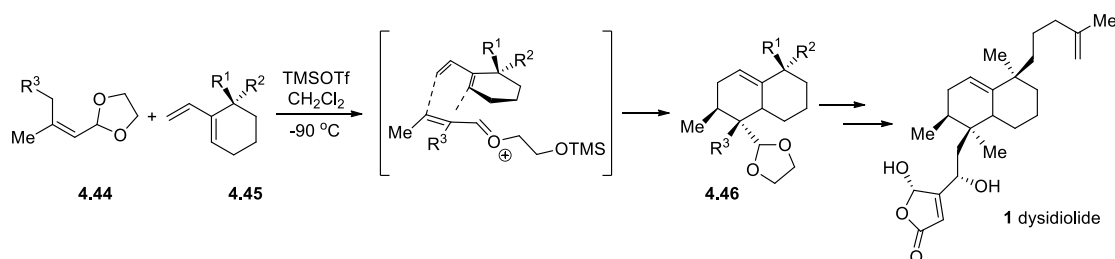
The final substrates tested were highly activated bis(iodonium) acetylene dienophiles prepared by Stang, and reported to undergo various reactions with nucleophiles including Diels–Alder reactions under mild reaction conditions in the absence of Lewis acids (Scheme 4.15a).[180] Cycloadducts were crystalline solids and characterized by single-crystal X-ray analysis as well as NMR spectroscopy. Although these bis(iodonium) alkynes are excellent dienophiles, their symmetry does not allow for the ability to differentiate between XB directed Diels-Alder adducts and a non-directed Diels-Alder adducts. Fortunately Camps has reported the synthesis

of **4.40** and its reactivity towards the Diels–Alder reaction with 1,3-diphenylisobenzofuran (Scheme 4.15b).[181] Using the same conditions reported by Stang and Camps, **4.32** and **4.40** were mixed in a solution of MeCN at –30 °C and allowed to warm to room temperature over 24 hours which resulted in the formation of a shiny black plastic (Table 4.5, entry 21). Evidently **4.40** is more reactive than the other dienophiles tested, and the instability of cycloadducts using these iodonium salts has been noted by both Stang and Camps.[180,181]

Scheme 4.15. Reactions of Bis(iodonium) Alkynes by a) Stang *et al.* and b) Camps *et al.*
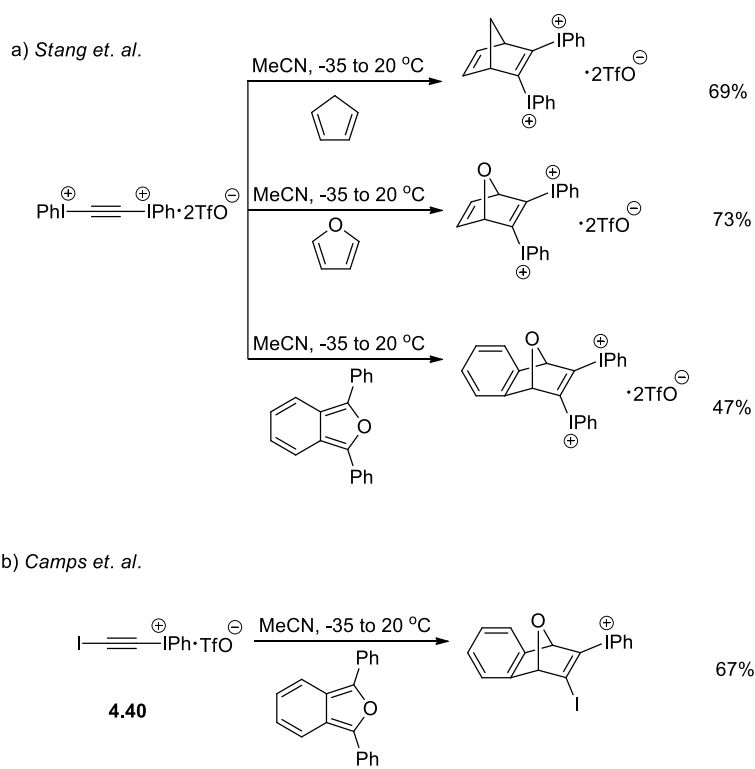
4.4. Summary and Future Outlook

In summary, several different Meldrum's acid derivatives were prepared for intramolecular XB studies in solution and solid states. ^{13}C NMR and X-ray data did not show any intramolecular XB interactions for the models prepared. Compound **4.10a** gave the most promising lead where intermolecular XB interactions between the XB acceptor of one molecule and the XB donor of another were observed. Further evidence for XB was seen by the shortening of the RX bond and the directionality of the RX···Y interaction. Also, no RX···XR or Y···Y contacts were observed minimizing the chance of random interactions based on proximity of halogen atoms. Efforts to extend the XB interactions to larger and more polarizable Br atoms were unsuccessful due to the steric interactions between the 5-position of Meldrum's acid and the *ortho* position on the aromatic moiety, only allowing for chlorination.

Novel models that placed the XB acceptor at the 2-position of Meldrum's acid to reduce the steric hindrance did not result in either intra- or intermolecular interactions as evidenced by X-ray analyses of **4.24**. This model highlighted the need to redesign models with the capacity for halogens to interact with the correct orientation with minimal steric influences. Preparation of models **M1** and **M2**, Figure 4.16, were then focused on but progress towards their synthesis was thwarted by the inability to condense the malonic ester with the corresponding carbonyl. To overcome this challenge, a methodology using bis(trimethylsilyl) malonate was developed and gave some promising initial results, however, further screening of various Lewis acids and reaction conditions is required for optimization. Although this would be a project on its own, the condensation of malonates would give access to new Meldrum's acid derivatives such as **M1** and **M2**. The importance of a rigid framework for **M1** and **M2** models was recently shown by Bowling where substituted 1,2-aryldiynes were used as templates to study intramolecular XB interactions in both solution and solid state, figure 4.19.[182] Cavity size, distance between R–X and Y, and bond angle were crucial to observing XB interactions.
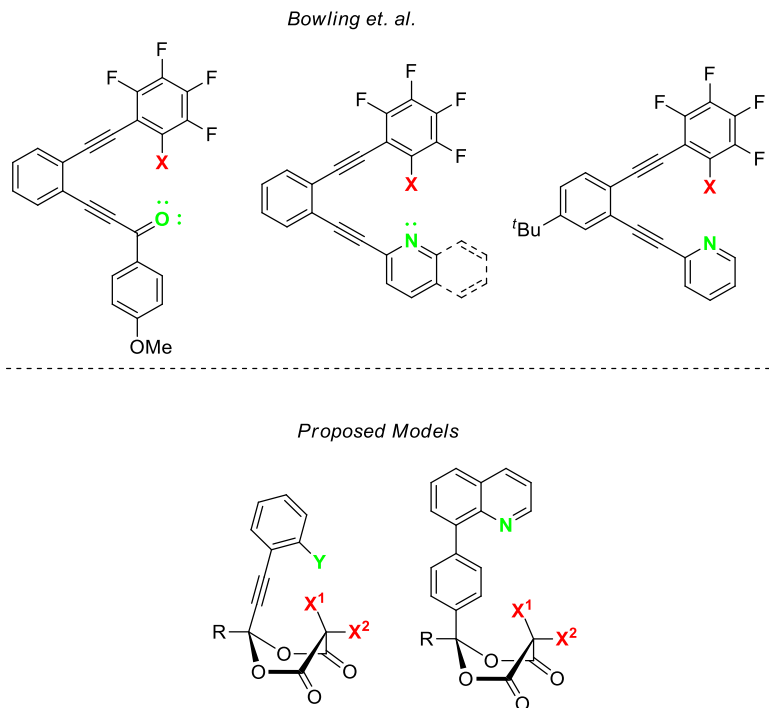
Figure 4.19. Aryl alkyne templates for intramolecular XB studies.

XB-directed Diels–Alder cycloadditions requires different diene and dienophiles than those tested. Other than furan, poor to no reactivity was observed with all substituted dienes. Computational studies and modeling would be invaluable to gain further insight into designing models with the greatest potential for XB interactions. It is worth mentioning that collaborative efforts with professor Scott Hopkins here at the University of Waterloo have already begun, and the results of their computational studies searching for XB interactions in Meldrum's acid derivatives can help guide synthetic efforts down the road.

4.5. Experimental
General Considerations
Reactions

All reactions were performed in flame-dried glassware under a nitrogen atmosphere. Benzene, 1,4-dioxane and THF were distilled over sodium/benzophenone ketyl before use. Toluene, dichloromethane and DMF were distilled over CaH_2 and stored in Schlenk flasks.

1,2-Dichloroethane, MeCN and Et₂O were obtained from a solvent purification system based on the published procedure.[42] All other reagents were purchased from commercial sources and used without further purification. Reactions were monitored by TLC on commercially prepared plates. Developed plates were viewed under a UV lamp (254 nm) and with ceric ammonium molybdate stain. Flash chromatography was performed using 230-400 mesh silica gel.

The following compounds were prepared according to literature procedures and spectral data obtained were in agreement to those reported and data will not be repeated here: 2,2-dimethyl-5-(1-phenylethyl)-1,3-dioxane-4,6-dione (**4.5**),[148] 5-(1-(2-chlorophenyl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.6**), 5-(1-(2-bromophenyl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.7**), 5-(1-(2-methoxyphenyl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.8**), 2,2-dimethyl-5-(2-phenylpropan-2-yl)-1,3-dioxane-4,6-dione (**4.9**), 5-(2-(2-chlorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.10**), 2,2-dimethyl-5-(1-(thiophen-2-yl)ethyl)-1,3-dioxane-4,6-dione (**4.11**), 2,2-dimethyl-5-(1-(2-(methylthio)phenyl)ethyl)-1,3-dioxane-4,6-dione (**4.13**), 5-(1-(2-methoxyphenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.15**),[148] 3-(2-methoxyphenyl)propiolaldehyde (**4.25**), [183] 2'-methoxy-[1,1'-biphenyl]-4-carbaldehyde (**4.27**),[184] 2-benzylfuran (**4.33**),[185] *N*-(diphenylmethylene)-1-(furan-2-yl)methanamine (**4.36**),[186] and (iodoethynyl)(phenyl)iodonium triflate (**4.40**).[180,181]

Characterization

¹H (300 MHz) and ¹³C NMR (75 MHz) spectra for all compounds were obtained in CDCl₃ or C₆D₆ unless otherwise noted. Chemical shifts are reported in parts per million (ppm, δ). Proton spectra were calibrated to residual CHCl₃ (7.24 ppm) or C₆D₅H (7.15 ppm), and carbon spectra were calibrated to CDCl₃ (77.0 ppm). Multiplicities in ¹³C spectra (C, CH, CH₂, CH₃) were determined by combined DEPT 90/135 experiments. Melting points are uncorrected. High resolution mass spectra were run at the University of Waterloo Mass Spectrometry facility. X-ray structure data was collected and determined at the University of Waterloo X-ray facility b Dr. Jalil Assound.

Preparation of 5-(1-(2-Methoxyphenyl)-2-methylpropyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.12)
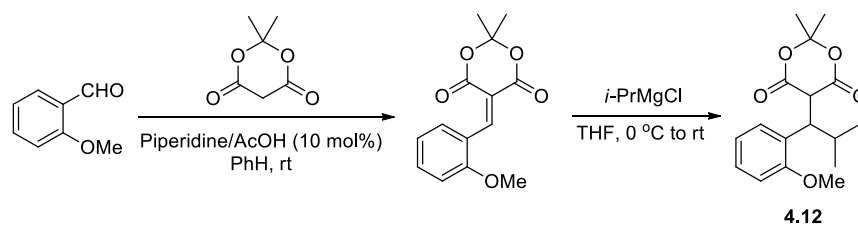
5-(2-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione was prepared according a reported procedure:[114a] A round bottom flask charged with 2-methoxybenzaldehyde (2.66 mL, 22.03 mmol), Meldrum's acid (3.49 g, 24.23 mmol), freshly distilled benzene (110 mL), and 4.4 mL of a 0.5 mM solution of pyrrolidinium acetate in benzene. The resulting solution was stirred at room temperature for 18 h. The reaction mixture was then diluted with EtOAc and washed with saturated $NaHCO_3$ solution (3×), dried over $MgSO_4$ and concentrated. The product was purified by recrystallizing crude solid from MeOH affording 3.35 g (58% yield) of yellow solid. Characterization data matched that reported.

5-(1-(2-methoxyphenyl)-2-methylpropyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**4.12**) was prepared according to a reported procedure:[187] A round bottom flask charged with 5-(2-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (3.35 g, 12.78 mmol) was dissolved in 65 mL of freshly distilled THF and cooled in an ice bath. A 2.0 M solution of iPrMgCl in THF (16.0 mL, 31.95 mmol) was slowly added dropwise and gradually warmed to room temperature, and stirred for 16 h. The reaction was diluted with Et_2O and quenched by the addition of H_2O. The layers were partitioned and aqueous was extracted with EtOAc (3×). Combined organic fractions were washed with brine (1×), dried over $MgSO_4$, filtered and concentrated. The crude solid was purified by recrystallizing from MeOH affording **4.12** (2.54 g, 65% yield) as a yellow solid. M.p. 109-111 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) 7.37 (d, J = 7.2 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 3.92 (dd, J = 11.1, 2.4 Hz, 1H), 3.78 (s, 3H), 3.73 (d, J = 2.4 Hz, 1H), 2.74-2.62 (m, 1H), 1.59 (s, 3H), 1.27 (s, 3H), 1.09 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 168.5 (C), 168.1 (C), 158.1 (C), 129.5 (CH), 128.6 (C), 127.7 (CH), 120.1 (CH), 115.5 (CH),

105.1 (C), 56.1 (CH$_3$), 54.4 (CH), 33.2 (CH), 30.3 (CH), 28.8 (CH$_3$), 27.3 (CH$_3$), 16.1 (CH$_3$), 15.5 (CH$_3$).

Preparation of Iodobenzene Dichloride (PhICl$_2$)

PhICl$_2$ was prepared according to reported procedure:[164] To a mixture of PhI (1.64 mL, 14.70 mmol) in 5% NaOCl (Chlorox® bleach, 90 mL) was added conc. HCl (30 mL) dropwise at rt. The mixture was stirred vigorously for 10 min, then filtered and washed with H$_2$O and petroleum ether. The yellow solid was dried in a desiccator overnight in the dark. PhICl$_2$ (3.39 g, 84%) was isolated as a yellow solid and characterization data matched that reported.

General Procedure A – Chlorination of Benzyl Meldrum's Acid Derivatives with PhICl$_2$ or *N*-Chlorosuccinimide

A conical vial charged with benzyl Meldrum's acid (0.55 mmol, 1.0 equiv), PhICl$_2$ or NCS (0.60 mmol, 1.1 equiv) and K$_2$CO$_3$ (1.10 mmol, 2.0 equiv) were dissolved in 1.10 mL of DMF (0.5M). The vial was capped and the reaction mixture was stirred at rt. The progress of the reaction was monitored by TLC and the workup consisted of diluting the reaction with H$_2$O (16.5 mL) and extracting with Et$_2$O (3×). Combined organic layers were dried over MgSO$_4$, filtered and concentrated. The crude product was purified by flash column chromatography using silica gel with the indicated solvent gradient.

General Procedure B – Alkylation of Benzyl Meldrum's Acid Derivatives with Bromoacetonitrile

A conical vial charged with benzyl Meldrum's acid (0.55 mmol, 1.0 equiv), BrCH$_2$CN (0.82 mmol, 1.5 equiv) and K$_2$CO$_3$ (1.10 mmol, 2.0 equiv) were dissolved in 1.10 mL of DMF (0.5M). The vial was capped and the reaction mixture was stirred at rt. The progress of the reaction was monitored by TLC and the workup consisted of diluting the reaction with H$_2$O (16.5 mL) and extracting with Et$_2$O (3×). Combined organic layers were dried over MgSO$_4$,

filtered and concentrated. The crude product was purified by flash column chromatography using silica gel with the indicated solvent gradient.

5-Chloro-2,2-dimethyl-5-(1-phenylethyl)-1,3-dioxane-4,6-dione (4.5a)
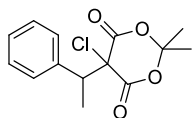
Prepared according to General Procedure A from Meldrum's derivative **4.5** (136 mg, 0.55 mmol) and PhICl$_2$ (165 mg, 0.60 mmol) as the chlorinating agent and MeCN as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.5a** (93 mg, 60% yield) as a beige solid. M.p. 137-140 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.29-7.27 (m, 3H), 7.19-7.17 (m, 2H), 3.88 (q, J = 7.2 Hz, 1H), 1.76 (d, J = 7.2 Hz, 3H), 1.69 (s, 3H), 1.11 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 164.9 (C), 163.1 (C), 136.7 (C), 129.2 (CH), 128.9 (CH), 128.5 (CH), 106.1 (C), 63.0 (CCl), 48.9 (CH), 29.2 (CH$_3$), 27.3 (CH$_3$), 15.5 (CH$_3$). HRMS (DART) m/z calcd for C$_{14}$H$_{19}$ClNO$_4$ (M + NH$_4$)$^+$: 300.10026. Found: 300.10041.

2-(2,2-Dimethyl-4,6-dioxo-5-(1-phenylethyl)-1,3-dioxan-5-yl)acetonitrile (4.5c)
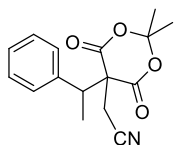
Prepared according to General Procedure B from Meldrum's derivative **4.5** (136 mg, 0.55 mmol). Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.5c** (105 mg, 67% yield) as a beige solid. M.p. 122-125 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.31-7.29 (m, 3H), 7.12-7.10 (m, 2H), 3.43 (q, J = 7.2 Hz, 1H), 3.19 (d, J = 16.1 Hz, 1H), 2.97 (d, J = 16.1 Hz, 1H), 1.66 (s, 3H), 1.50 (d, J = 7.2 Hz, 3H), 0.98 (s, 3H); ^{13}C HMR (75 MHz, CDCl$_3$) 166.9 (C), 165.4 (C), 137.9 (C), 128.8 (CH), 128.6 (CH), 124.5 (CH), 116.2 (C), 107.0 (C), 56.9 (C), 49.1 (CH), 31.2 (CH$_3$), 26.9 (CH$_3$), 22.9 (CH$_2$), 15.3 (CH$_3$). HRMS (DART) m/z calcd for C$_{16}$H$_{21}$N$_2$O$_4$ (M + NH$_4$)$^+$: 305.15013. Found: 305.15025.

5-Chloro-5-(1-(2-chlorophenyl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.6a)

Prepared according to General Procedure A from Meldrum's derivative **4.6** (155 mg, 0.55 mmol) and PhICl$_2$ (165 mg, 0.60 mmol) as the chlorinating agent and DMF as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded
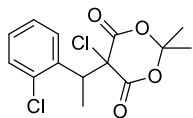
4.6a (71 mg, 43% yield) as a beige solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.35-7.29 (m, 1H), 7.27-7.18 (m, 3H), 4.55 (q, J = 7.1 Hz, 1H), 1.74 (s, 3H), 1.60 (d, J = 7.1 Hz, 3H), 1.45 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 163.7 (C), 163.5 (C), 135.5 (C), 134.8 (C), 130.3 (CH), 129.4 (CH), 128.8 (CH), 127.0 (CH), 106.2 (C), 63.2 (CCl), 44.6 (CH), 29.3 (CH$_3$), 27.3 (CH$_3$), 16.7 (CH$_3$).

2-(5-(1-(2-Chlorophenyl)ethyl)-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)acetonitrile (4.6c)
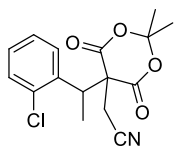
Prepared according to General Procedure B from Meldrum's derivative **4.6** (155 mg, 0.55 mmol). Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.6c** (113 mg, 64% yield) as a beige solid. M.p. 136-138 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.39-7.36 (m, 1H), 7.27-7.20 (m, 2H), 7.16-7.13 (m, 1H), 4.17 (q, J = 7.2 Hz, 1H), 3.27 (d, J = 16.1 Hz, 1H), 2.81 (d, J = 16.1 Hz, 1H), 1.75 (s, 3H), 1.45 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H); ^{13}C HMR (75 MHz, CDCl$_3$) 166.4 (C), 165.5 (C), 135.3 (C), 134.5 (C), 129.9 (CH), 129.6 (CH), 129.5 (CH), 127.1 (CH), 116.3 (C), 107.0 (C), 56.8 (C), 43.4 (CH), 31.4 (CH$_3$), 27.2 (CH$_3$), 21.7 (CH$_2$), 17.0 (CH$_3$).

5-Chloro-5-(1-(2-bromophenyl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.7a)
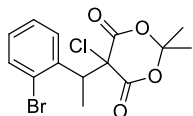
Prepared according to General Procedure A from Meldrum's derivative **4.7** (180 mg, 0.55 mmol) and PhICl$_2$ (165 mg, 0.60 mmol) as the chlorinating agent and DMF as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.7a** (89 mg, 45% yield) as a waxy solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.58 (d, J = 8.1 Hz, 1H), 7.27-7.25 (m, 2H), 7.15-7.09 (m, 1H), 7.55 (q, J = 7.1 Hz, 1H), 1.77 (s, 3H), 1.62 (d, J = 7.2 Hz, 3H), 1.49 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 163.6 (C), 163.5 (C), 134.1 (C), 133.8 (C), 129.0 (CH), 128.9 (CH), 128.4 (CH), 127.0 (CH), 106.2 (C), 62.9 (CCl), 47.5 (CH), 28.9 (CH$_3$), 28.1 (CH$_3$), 16.8 (CH$_3$).

5-Chloro-5-(1-(2-methoxyphenyl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.8a)
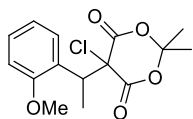
Prepared according to General Procedure A from Meldrum's derivative **4.8** (153 mg, 0.55 mmol) and PhICl$_2$ (165 mg, 0.60 mmol) as the chlorinating agent and MeCN as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.8a** (51 mg, 30% yield) as a yellow solid. M.p. 151-155 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.26-7.21 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 4.29 (q, J = 7.2 Hz, 1H), 3.75 (s, 3H), 1.68 (s, 3H), 1.64 (d, J = 7.2 Hz, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 164.6 (C), 163.2 (C), 157.2 (C), 129.7 (CH), 129.5 (CH), 125.7 (C), 120.8 (CH), 110.8 (CH), 105.7 (C), 65.3 (CCl), 55.0 (CH$_3$), 43.4 (CH), 29.7 (CH$_3$), 27.1 (CH$_3$), 15.7 (CH$_3$); HRMS (DART) m/z calcd for C$_{15}$H$_{21}$ClNO$_5$ (M + NH$_4$)$^+$ 330.11083. Found: 330.11095.

2-(5-(1-(2-Methoxyphenyl)ethyl)-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)acetonitrile (4.8c)
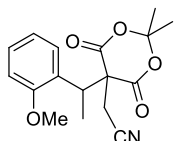
Prepared according to General Procedure B from Meldrum's derivative **4.8** (153 mg, 0.55 mmol). Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.8c** (92 mg, 53% yield) as a yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.28-7.23 (m, 1H), 7.04 (d, J =7.6 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 4.09 (br s, 1H), 3.76 (s, 3H), 3.17 (d, J = 16.2 Hz, 1H), 2.86 (d, J = 16.2 Hz, 1H), 1.71 (s, 3H), 1.40 (d, J = 7.2 Hz, 3H), 1.36 (s, 3H); ^{13}C HMR (75 MHz, CDCl$_3$) 166.3 (C), 157.0 (C), 129.4 (CH), 128.7 (CH), 126.0 (C), 120.7 (CH), 116.8 (C), 110.6 (CH), 106.6 (C), 57.0 (C), 55.2 (CH$_3$), 39.3 (CH), 31.3 (CH$_3$), 27.0 (CH$_3$), 21.3 (CH$_2$), 15.8 (CH$_3$). HRMS (DART) m/z calcd for C$_{17}$H$_{23}$N$_2$O$_5$ (M + NH$_4$)$^+$ 335.16070. Found: 335.16084.

5-Chloro-2,2-dimethyl-5-(2-phenylpropan-2-yl)-1,3-dioxane-4,6-dione (4.9a)

Prepared according to General Procedure A from Meldrum's derivative **4.9** (144 mg, 0.55 mmol) and PhICl$_2$ (165 mg, 0.60 mmol) as the chlorinating agent and DMF as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded
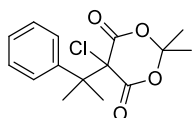
4.9a (97 mg, 60% yield) as a beige waxy solid. ^{1}H NMR (300 MHz, CDCl$_3$) 7.35-7.27 (m, 5H), 1.73 (s, 6H), 1.54 (s, 3H), 0.97 (s, 3H); ^{13}C HNMR (75 MHz, CDCl$_3$) 163.8 (C), 139.8 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 105.2 (C), 71.2 (CCl), 48.1 (C), 30.4 (CH$_3$), 26.0 (CH$_3$), 24.6 (CH$_3$); HRMS (DART) m/z calcd for C$_{15}$H$_{21}$ClNO$_5$ (M + NH$_4$)$^{+}$ 296.08154. Found 296.08169.

5-Chloro-5-(2-(2-chlorophenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.10a)
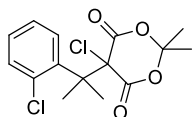
Prepared according to General Procedure A from Meldrum's derivative **4.10** (144 mg, 0.55 mmol) and PhICl$_2$ (165 mg, 0.60 mmol) as the chlorinating agent and DMF as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.10a** (97 mg, 60% yield) as a white solid. M.p. 166-169 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.46-7.43 (m, 1H), 7.32-7.31 (m, 1H), 7.21-7.18 (m, 2H), 1.90 (s, 6H), 1.57 (s, 3H), 1.13 (s, 3H); ^{13}C (75 MHz, CDCl$_3$)163.6 (C), 137.0 (C), 135.0 (C), 132.6 (CH), 132.2 (CH), 129.4 (CH), 126.6 (CH), 105.4 (C), 71.6 (CCl), 50.1 (C), 30.2 (CH$_3$), 26.9 (CH$_3$), 26.1 (CH$_3$).

5-Chloro-2,2-dimethyl-5-(1-(thiophen-2-yl)ethyl)-1,3-dioxane-4,6-dione (4.11a)
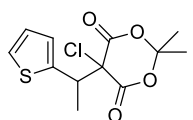
Prepared according to General Procedure A from Meldrum's derivative **4.11** (140 mg, 0.55 mmol) and NCS (80 mg, 0.60 mmol) as the chlorinating agent and DMF as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.11a** (82 mg, 52% yield) as a yellow film. ^{1}H NMR (300 MHz, CDCl$_3$)7.23-7.21 (m, 1H), 6.93-6.91 (m, 2H), 4.23 (q, J = 7.2 Hz, 1H), 1.81 (d, J = 7.2 Hz, 3H), 1.74 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 164.8 (C), 162.8 (C), 139.2 (C), 128.2 (CH), 127.0 (CH), 126.1 (CH), 106.4 (C), 61.3 (CCl), 43.7 (CH), 28.8 (CH$_3$), 27.8 (CH$_3$), 17.1 (CH$_3$); HRMS (DART) m/z calcd for C$_{12}$H$_{17}$ClNO$_4$S (M + NH$_4$)$^{+}$: 306.05668. Found 306.05682.

5-Chloro-5-(1-(5-chloro-2-methoxyphenyl)-2-methylpropyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.12a) and 5-Chloro-5-(1-(3-chloro-2-methoxyphenyl)-2-methylpropyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4.12b)
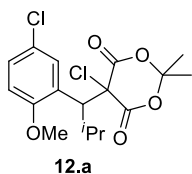
Prepared according to General Procedure A from Meldrum's derivative **4.12** (168 mg, 0.55 mmol) and PHICl$_2$ (165 mg, 0.60 mmol) as the chlorinating agent and MeCN as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.12a** (37 mg, 18% yield) as a yellow film. ^{1}H NMR (300 MHz, CDCl$_3$) 7.46 (br s, 1H), 7.19 (dd, J = 8.7, 2.4 Hz, 1H), 6.78 (d, J = 9.0 Hz, 1H), 4.36 (br s, 1H), 3.79 (s, 3H), 2.49 (br s, 1H), 1.86 (s, 3H), 1.68 (s, 3H), 1.10 (d, J = 6.6 Hz, 3H), 0.69 (d, J = 6.3 Hz, 3H); ^{13}C (75 MHz, CDCl$_3$)
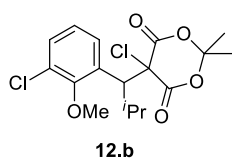
Compound **4.12b** (45 mg, 22% yield) was also isolated from above reaction as a yellow film. ^{1}H NMR (300 MHz, CDCl$_3$) 7.73 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 3.95 (s, 3H), 2.44-2.33 (m, 1H), 1.92 (s, 3H), 1.77 (s, 3H), 1.01 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.6 Hz, 3H); ^{13}C (75 MHz, CDCl$_3$)

2-(2,2-Dimethyl-5-(1-(2-(methylthio)phenyl)ethyl)-4,6-dioxo-1,3-dioxan-5-yl)acetonitrile (4.13c)
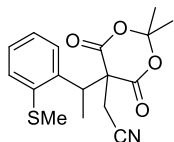
Prepared according to General Procedure B from Meldrum's derivative **4.13** (162 mg, 0.55 mmol). Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.13c** (69 mg, 38% yield) as a yellow film. ^{1}H NMR (300 MHz, CDCl$_3$) 7.27-7.23 (m, 2H), 7.18-7.13(m, 1H), 7.09-7.06 (m, 1H), 4.19 (q, J = 7.1 Hz, 1H), 3.36 (d, J = 16.1 Hz, 1H), 2.79 (d, J = 16.1 Hz, 1H), 2.43 (s, 3H), 1.76 (s, 3H), 1.48 (s, 3H), 1.41 (d, J = 7.2 Hz, 3H); ^{13}C HMR (75 MHz, CDCl$_3$) 166.8 (C), 166.0 (C), 138.6 (C), 136.4 (C), 128.9 (CH), 128.3 (CH), 127.6 (CH), 125.6 (CH), 116.6 (C), 107.0 (C), 57.1 (C), 43.9 (CH), 31.4 (CH$_3$), 27.2 (CH$_3$), 21.8 (CH$_2$), 17.5 (CH$_3$), 17.2 (CH$_3$). HRMS (DART) m/z calcd for C$_{17}$H$_{23}$N$_2$O$_4$S (M + NH$_4$)$^+$ 351.13785. Found: 351.13793.

5-Chloro-2,2-dimethyl-5-(1-phenylcyclohexyl)-1,3-dioxane-4,6-dione (4.14a)
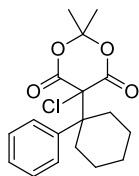
Prepared according to General Procedure A from Meldrum's derivative **4.14** (166 mg, 0.55 mmol) and NCS (80 mg, 0.60 mmol) as the chlorinating agent and DMF as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.14a** (82 mg, 52% yield) as a white solid. M.p. 119-121 °C. ^{1}H NMR (300 MHz, CDCl$_3$)737-7.27 (m, 5H), 2.65 (d, J = 13.5 Hz, 2H), 2.06 (t, J = 13.2 Hz, 2H), 1.66-1.58 (m, 2H), 1.51 (s, 3H), 1.50-1.46 (m, 2H), 1.30-1.06 (m, 3H), 0.89 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 163.4 (C), 135.5 (C), 129.2 (CH), 128.9 (CH), 127.9 (CH), 105.1 (C), 72.5 (CCl), 52.4 (C), 30.4 (CH$_3$), 29.6 (CH$_2$), 25.8 (CH$_3$), 25.5 (CH$_2$), 22.1 (CH$_2$).

5-Chloro-2,2-dimethyl-1,3-dioxane-4,6-dione (4.15a)
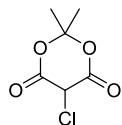
Prepared according to General Procedure A from Meldrum's derivative **4.15** (183 mg, 0.55 mmol) and NCS (80 mg, 0.60 mmol) as the chlorinating agent and DMF as the solvent. Recrystallization from Et$_2$O:hexanes afforded **4.15a** (18 mg, 18% yield) as colourless crystals. M.p. 117-121 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 5.32 (s, 1H), 1.84 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 163.0 (C), 105.2 (C), 68.2 (CH), 33.5 (CH$_3$), 27.1 (CH$_3$).

Preparation of 2-(2-Chlorophenyl)-2-methyl-1,3-dioxane-4,6-dione (4.21)
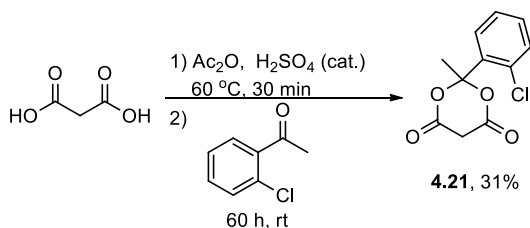
The preparation of **4.21** was based on report by Shi-Zheng:[162a] Malonic acid (3.00 g, 28.83 mmol), acetic anhydride (2.73 mL, 28.83 mmol) and conc. H$_2$SO$_4$ (2-3 drops) were mixed and stirred at 60 °C for 30 min. The reaction was then cooled back down to room temperature and 2-chloroacetophenone (3.74 mL, 28.83 mmol) was added dropwise by syringe pump over

60 min. The progress of the reaction was monitored by TLC and afer stirring for 60 h at room temperature, the reaction was stopped and excess AcOH and ketone were removed under high vacuum resulting in dark orange paste. Flash column chromatography on silica gel eluting with EtOAc:hexanes (1:6) afforded **4.21** (2.15 g, 31% yield) as a white solid. M.p. 97-99 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.51-7.47 (m, 2H), 7.40-7.30 (m, 2H), 3.46 (d, J = 19.5 Hz, 1H), 3.07 (d, J = 19.5 Hz, 1H), 2.09 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 162.8 (C), 135.7 (C), 132.8 (CH), 131.5 (CH), 127.6 (CH), 126.8 (CH), 105.4 (C), 38.1 (CH$_2$), 27.0 (CH$_3$).

Preparation of 2-(2-Chlorophenyl)-2-methyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (4.22)
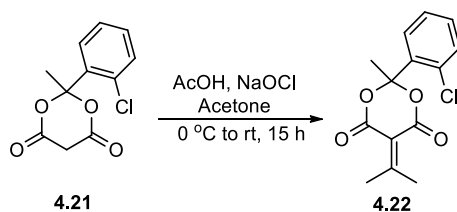
The synthesis of **4.22** was based on a modified procedure by Weinreb:[163] To a solution of **4.21** (131 mg, 0.54 mmol) in acetone (2.3 mL) and glacial acetic acid (0.91 mL, 15.70 mmol) at 0 °C was added NaOCl (0.40 mL, 0.82 mmol, 5% v/v Chlorox®) dropwise. The mixture was gradually warmed to room temperature and stirred for 15 h. The reaction was cooled back down and saturated Na$_2$CO$_3$ was added. The mixture was transferred to a separatory funnel and extracted with CH$_2$Cl$_2$ (3×). Combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel eluting with EtOAc:hexanes (1:5) and afforded **4.22** (50 mg, 33% yield) as a white solid. M.p. 140-144 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.46-7.39 (m, 2H), 7.30-7.25 (m, 2H), 2.17 (s, 6H), 2.01 (s, 1H); ^{13}C (75 MHz, CDCl$_3$) 176.3 (C), 161.2 (C), 137.7 (C), 132.4 (CH), 131.3 (C), 130.8 (CH), 127.1 (CH), 126.9 (CH), 117.3 (C), 103.4 (C), 26.6 (CH$_3$), 25.9 (CH$_3$).

Preparation of 5,5'-Dichloro-2,2'-bis(2-chlorophenyl)-2,2'-dimethyl-[5,5'-bi(1,3-dioxane)]-4,4',6,6'-tetraone (4.24)
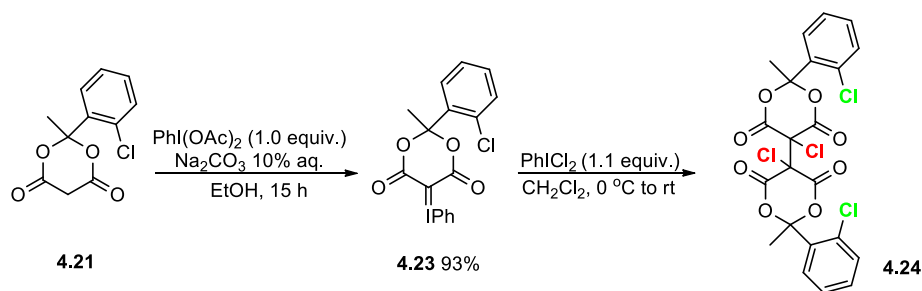
The synthesis of **4.24** was achieved in two steps procedure starting from **4.21**, where the first step was based on a procedure reported by Müller:[188] To a round flask charged with **4.21** (403 mg, 1.67 mmol) and 5 mL of 10% aq. Na$_2$CO$_3$ was added a 4.2 mL mixture of PhI(OAc)$_2$ (538 mg, 1.67 mmol) in EtOH. The resulting mixture was stirred for 15 h at room temperature. The reaction was poured into a separatory funnel with ice water and extracted with CH$_2$Cl$_2$ (3×). Combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Compound **4.23** (686 mg, 93% yield) was isolated as a white solid and sufficiently pure for the next step. 1H NMR (300 MHz, CDCl$_3$) 7.64-7.61 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 8.1 Hz, 4H), 7.27-7.22 (m, 4H), 2.02 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 163.1 (C), 134.5 (C), 132. 7 (CH), 132.6 (C), 131.5 (CH), 131.4 (CH), 130.9 (CH), 128.1 (CH), 127.1 (CH), 115.1 (C), 105.7 (C), 28.1 (CH$_3$). HRMS (ESI) m/z calcd for C$_{17}$H$_{13}$ClIO$_4$ (M + H)$^+$: 442.95470. Found 442.95466.

Compound **4.24** was prepared according to General procedure A from Meldrum's derivative **4.23** (313 mg, 0.71 mmol) and PHICl$_2$ (408 mg, 1.48 mmol) as the chlorinating agent and CH$_2$Cl$_2$ as the solvent. Flash column chromatography eluting with a gradient of EtOAc:hexanes (1:14 to 1:4) afforded **4.24** (128 mg, 33% yield) as a beige solid. M.p. 155-157 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 7.57 (dd, J = 7.58, 1.8 Hz, 1H), 7.46-7.43 (m, 1H), 7.36-7.29 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) 135.7 (C), 132.2 (CH), 131.3 (CH), 130.8 (C), 127.4 (CH), 127.1 (CH), 106.9 (C), 57.6 (CCl), 29.0.

Preparation of 4-(Quinolin-8-yl)benzaldehyde (4.26)

4.26, 83%
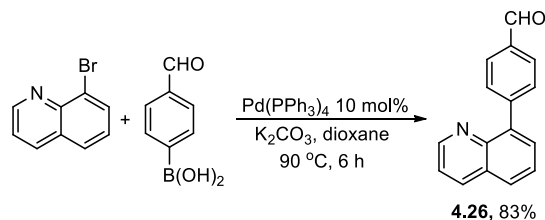
The procedure is based on the Suzuki-Miyaura Reaction reported by Langer:[189] A round bottom flask equipped with a reflux condenser was charged with 8-bromoquinoline (1.25 g, 6.0 mmol), 4-formylphenylboronic acid (1.35 g, 9.0 mmol), Pd(PPh$_3$)$_4$ (0.62 g, 0.54 mmol) and 30 mL of freshly distilled 1,4-dioxane. A solution of K$_2$CO$_3$ (1.24 g, 9.0 mmol) in 4.5 mL of 1,4-dioxane was then added and the reaction was placed in a preheated oil bath at 100 °C stirring for 6 h. The reaction mixture was cooled back down to room temperature and quenched by the addition of H$_2$O. The layers were partitioned and the aqueous was extracted with CH$_2$Cl$_2$ (3×). Combined organic layers were washed with a saturated solution of brine (1×), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel eluting with EtOAc:hexanes (1:4) afforded **4.26** (917 mg, 89% yield) as a beige solid. M.p. 69-72 °C. ^{1}H NMR (300 MHz, CDCl$_3$) 10.09 (s, 1H), 8.94 (dd, J = 4.05, 1.8 Hz, 1H), 8.20 (dd, J = 8.1, 1.5 Hz, 1H), 8.0 (d, J = 8.1 Hz, 2H), 7.89-7.85 (m, 3H), 7.74 (d, J = 7.2 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.44-7.40 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) 192.1 (CHO), 150.4 (CH), 145.9 (C), 145.6 (C), 139.3 (C), 136.3 (CH), 135.1 (C), 131.3 (CH), 130.3 (CH), 129.2 (CH), 128.6 (C), 128.5 (CH), 126.2 (CH), 121.2 (CH); MS (ESI) m/z for C$_{16}$H$_{12}$NO (M + H)$^+$ 234.1.

Preparation of Diethyl (furan-2-ylmethyl)phosphonate (4.35)

4.35
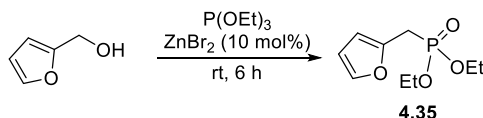
Phosphonate **4.35** was prepared according to modified Arbuzov reaction reported by Mohanakrishnan:[190] To a round bottom flask charged with furfuryl alcohol (0.49 mL, 5.0

mmol), triethyl phosphite (4.29 mL, 25.0 mmol) in 16 mL of CH_2Cl_2 was added freshly dried $ZnBr_2$ (1.35 g, 6.0 mmol) in one portion at room temperature. After consumption of starting material (monitored by TLC), the reaction was quenched by the addition of crushed ice conc. HCl mixture. The layers were partitioned and the aqueous layer was extracted with CH_2Cl_2. (3×). Combined organic layers were washed with a saturated solution of brine (1×), dried over $MgSO_4$ and concentrated. Distillation of crude oil afforded **4.35** (654 mg, 60% yield) as a yellow oil at 90-102 °C at 2 mmHg. ^1H NMR (300 MHz, $CDCl_3$) 7.30 (s, 1H), 6.28 (s, 1H), 6.19 (s, 1H), 4.07-4.00 (m, 6H), 3.18 (d, J = 20.7 Hz, 2H), 1.31-1.21 (m, 9H); ^{13}C (75 MHz, $CDCl_3$) 152.7 (C), 141.9 (CH), 110.8 (CH), 108. 1 (CH), 62.3 (CH_2), 27.5 (CH_2), 16.1 (CH_3); MS (ESI) m/z for $C_9H_{16}O_4P$ $(M + H)^+$ 219.1.

Preparation of Methyl 3-iodopropiolate (4.37)
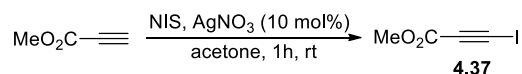
Propiolate **4.37** was prepared according to a procedure reported by Leroy:[191] To a solution of methyl propiolate (3.17 mL, 35.68 mmol) in 112 mL of acetone at room temperature was added $AgNO_3$ (606 mg, 3.57 mmol), followed by *N*-iodosuccinimide (9.27 g, 41.22 mmol). The reaction was stirred for 1 h at room temperature. The reaction was stopped by filtering over a pad of celite and concentrating down under vacuum (0.5 mmHg), affording **4.37** (6.41 g, 86% yield) as a beige solid that did not require further purification. ^1H NMR (300 MHz, $CDCl_3$) 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 152.7 (C), 86.7 (C), 53.0 (CH_3), 13.8 (CI). MS (ESI) m/z for $C_4H_3IO_2$ $(M)^+$ 209.1.

Preparation of 3-Iodopropiolic acid (4.38)
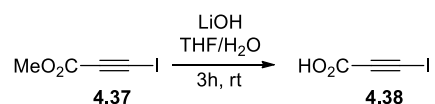
Propiolic acid **4.38** was prepared by the saponification of **4.37**:[192] A round bottom charged with **4.37** (4.00 g, 19.06 mmol), LiOH (1.36 g, 57.16 mmol) and 27 mL of THF/H_2O

(5:1) were stirred at rt for 3 h. The reaction was quenched by cooling the mixture in an ice bath and adding conc. HCl to adjust the pH ~ 1–2. The layers were separated and the organic layer was concentrated onto a small amount of silica gel that was loaded onto a column and purified by flash chromatography eluting with CH₂Cl₂:MeOH (10:1 to 5:1). Propiolic acid **4.38** (3.16 g, 85% yield) was isolated as a beige solid. ¹H NMR (300 MHz, MeOD) 7.63 (s, 1H); ¹³C NMR (75 MHz, MeOD) 158.1 (C), 90.4 (C), 22.1 (C).

Preparation of 2-(Iodoethynyl)-1,3-dioxolane (4.39)
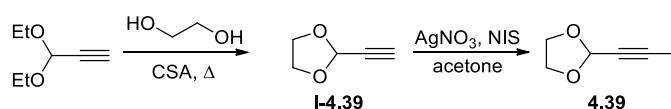
Alkyne **4.39** was prepared in 2 steps starting from commercially available propiolaldehyde diethyl acetal:[193] A mixture of propiolaldehyde diethyl acetal (2.0 mL, 13.95 mmol) and ethylene glycol (1.6 mL, 27.90 mmol) was treated with camphorsulfornic acid (10 mg, 0.042 mmol). The reaction was gradually heated, first to 85 °C to distill off the ethanol, then to 140 °C to afford alkyne **I-4.39** (957 mg, 70% yield) as clear oil that matched characterization data reported.[193] Alkyne **4.39** (1.51 g, 94% yield) was prepared using the same procedure for **4.37** (vide supra) from **I-4.39** (706 mg, 7.20 mmol). ¹H NMR (300 MHz, CDCl₃) 5.70 (s, 1H), 4.11-4.06 (m, 2H), 3.98-3.93 (m, 2H); ¹³C (75 MHz, CDCl₃) 93.4 (CH), 90.8 (C), 64.5 (CH₂), 5.11 (CI). MS (ESI) m/z for C₅H₅IO₂ (M)⁺ 223.9.

Preparation of Methyl 3-iodo-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (4.41)
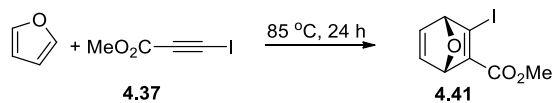
Compound **4.41** was prepared according to a procedure reported by Rainier:[174a] A Schlenk flask charged with furan (1.73 mL, 23.81 mmol) and **4.37** (500 mg, 2.38 mmol) was capped and placed in a preheated oil bath at 85 °C and stirred for 24 h. The mixture was cooled back down and excess furan was removed under vacuum. Purification by flash column

chromatography on silica gel afforded **4.41** (119 mg, 18% yield) as a yellow film. ^{1}H NMR (300 MHz, CDCl$_3$) 7.16 (s, 2H), 5.63 (s, 1H), 5.43 (s, 1H), 3.77 (s, 3H); ^{13}C (75 MHz, CDCl$_3$) 163.1 (C), 149.6 (C), 143.6 (CH), 141.2 (CH), 120.8 (C), 92.8 (CH), 84.3 (CH), 51.7 (CH$_3$); HRMS (ESI) *m/z* calcd for C$_8$H$_{10}$IO$_3$ (M + H)$^+$ 280.96746. Found 280.96733.

Appendix A

Crystallographic Data for 1.10aa
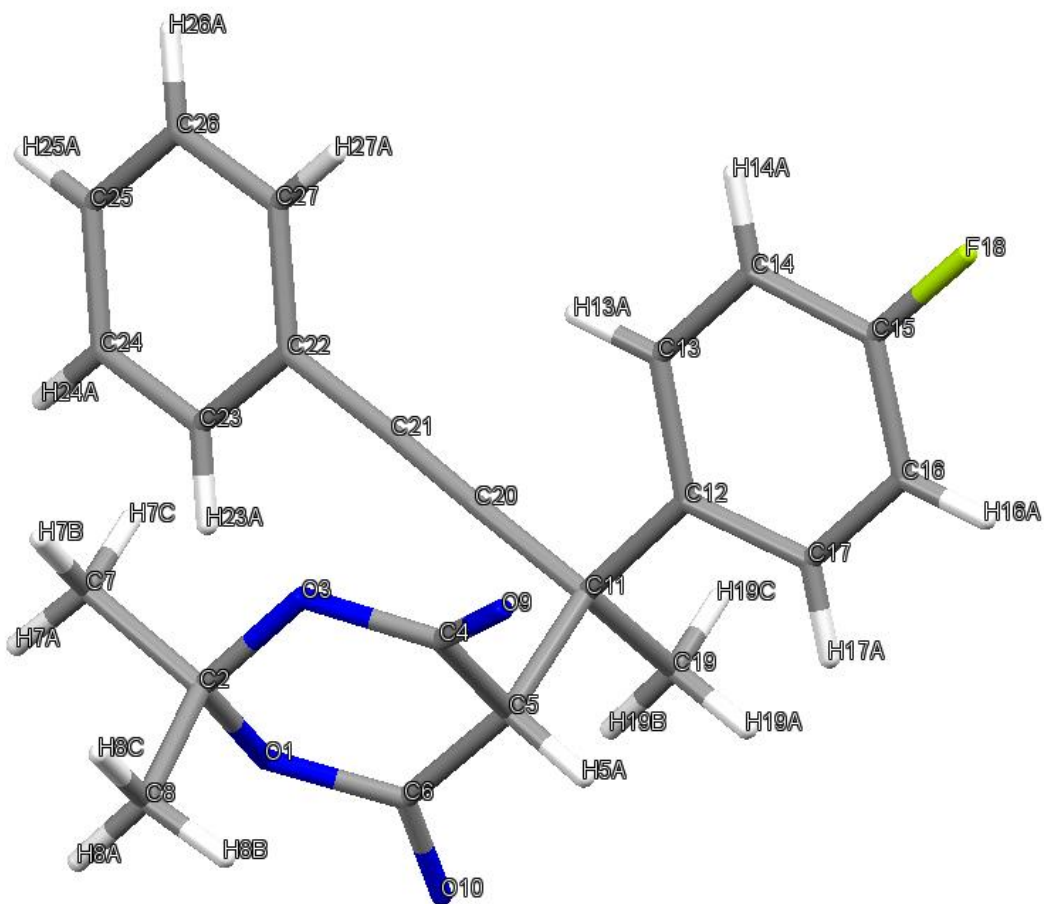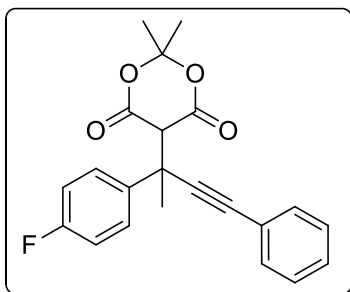
Table S1 - Crystal Data and Details of the Structure Determination for: 1.10aa   R = 0.04

Crystal Data

Formula	$C_{22} H_{19} F O_4$
Formula Weight	366.37
Crystal System	triclinic
Space group	P-1 (No. 2)
a, b, c [Å]	7.5328(2) 10.4878(3) 12.3102(3)
α, β, γ[°]	107.062(1) 91.716(1) 91.689(1)
V [Å³]	928.57(4)
Z	2
D(calc) [g/cm³]	1.310
Mu(MoKa) [/mm]	0.096
F(000)	384
Crystal Size [mm]	0.04 x 0.24 x 0.42

Data Collection

Temperature (K)	296
Radiation [Å]	MoKa 0.71073
Theta Min-Max [°]	1.7, 26.0
Dataset	-9: 9 ; -12: 12 ; -15: 15
Tot., Uniq. Data, R(int)	16167, 3642, 0.021
Observed data [I > 2.0 sigma(I)]	2919

Refinement

Nref, Npar	3642, 245
R, wR2, S	0.0368, 0.1057, 1.71

w = ^2^(FO^2^)+(0.0237P)^2^+0.1312P] WHERE P=(FO^2^+2FC^2^)/3'

Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.25, 0.28

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: 1.10aa

Atom	x	y	z	U(eq) [Å^2]
F18	-0.10130(17)	0.15756(12)	0.87581(9)	0.0564(4)
O1	-0.23472(17)	0.30075(12)	0.23038(9)	0.0395(4)
O3	0.00893(15)	0.25514(12)	0.34003(9)	0.0337(4)
O9	0.03257(15)	0.35556(12)	0.52443(9)	0.0362(4)
O10	-0.45966(18)	0.41364(13)	0.31251(11)	0.0477(5)
C2	-0.0477(2)	0.27769(17)	0.23484(13)	0.0334(5)
C4	-0.0601(2)	0.32440(15)	0.43939(13)	0.0259(5)
C5	-0.2564(2)	0.34506(15)	0.43544(13)	0.0253(5)
C6	-0.3249(2)	0.35986(15)	0.32349(14)	0.0317(5)
C7	-0.0168(3)	0.15192(19)	0.14201(15)	0.0479(7)
C8	0.0526(3)	0.39930(19)	0.22399(17)	0.0497(7)
C11	-0.3632(2)	0.22449(15)	0.46265(13)	0.0260(4)
C12	-0.2872(2)	0.20625(15)	0.57369(13)	0.0248(4)
C13	-0.1973(2)	0.09345(16)	0.57572(14)	0.0324(5)
C14	-0.1343(3)	0.07597(18)	0.67690(15)	0.0401(6)
C15	-0.1612(2)	0.17371(18)	0.77556(14)	0.0361(6)
C16	-0.2467(2)	0.28744(17)	0.77777(14)	0.0354(6)
C17	-0.3102(2)	0.30317(16)	0.67641(13)	0.0308(5)
C19	-0.5614(2)	0.25675(18)	0.47509(15)	0.0376(6)
C20	-0.3502(2)	0.10161(15)	0.36741(13)	0.0287(5)
C21	-0.3531(2)	0.00068(16)	0.29057(14)	0.0316(5)
C22	-0.3593(2)	-0.11824(16)	0.19522(14)	0.0334(5)
C23	-0.4385(3)	-0.1157(2)	0.09290(16)	0.0488(7)
C24	-0.4489(3)	-0.2288(2)	0.00048(17)	0.0632(8)
C25	-0.3819(3)	-0.3446(2)	0.0096(2)	0.0643(8)
C26	-0.3038(3)	-0.3493(2)	0.1100(2)	0.0615(8)
C27	-0.2913(3)	-0.23640(18)	0.20406(17)	0.0446(6)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 1.10aa

Atom	x	y	z	U(iso) [Å^2]
H5A	-0.28000	0.42730	0.49510	0.0300
H7A	-0.05300	0.16280	0.06990	0.0720
H7B	0.10730	0.13340	0.14190	0.0720
H7C	-0.08470	0.07910	0.15480	0.0720
H8A	0.01630	0.41570	0.15410	0.0750
H8B	0.02780	0.47510	0.28680	0.0750
H8C	0.17780	0.38460	0.22420	0.0750
H13A	-0.17890	0.02820	0.50770	0.0390
H14A	-0.07510	-0.00040	0.67770	0.0480
H16A	-0.26180	0.35290	0.84620	0.0420
H17A	-0.36940	0.37990	0.67680	0.0370
H19A	-0.57340	0.33660	0.53680	0.0560
H19B	-0.60820	0.26970	0.40590	0.0560
H19C	-0.62590	0.18400	0.49040	0.0560
H23A	-0.48510	-0.03700	0.08640	0.0590
H24A	-0.50160	-0.22590	-0.06800	0.0760

Atom						
H25A	-0.38930	-0.42070	-0.05280	0.0770		
H26A	-0.25860	-0.42890	0.11540	0.0740		
H27A	-0.23790	-0.24010	0.27210	0.0540		

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for: 1.10aa

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
F18	0.0697(9)	0.0712(8)	0.0360(6)	0.0270(6)	-0.0018(5)	0.0144(6)
O1	0.0424(8)	0.0498(7)	0.0274(6)	0.0137(6)	-0.0065(5)	0.0037(6)
O3	0.0317(7)	0.0441(7)	0.0258(6)	0.0103(5)	0.0022(5)	0.0074(5)
O9	0.0268(7)	0.0520(8)	0.0288(6)	0.0115(5)	-0.0053(5)	-0.0034(5)
O10	0.0457(8)	0.0452(8)	0.0547(8)	0.0190(6)	-0.0123(6)	0.0145(6)
C2	0.0391(10)	0.0371(9)	0.0253(8)	0.0113(7)	0.0010(7)	0.0023(8)
C4	0.0271(9)	0.0255(8)	0.0265(8)	0.0104(6)	-0.0006(7)	-0.0014(6)
C5	0.0266(9)	0.0213(7)	0.0265(8)	0.0051(6)	-0.0027(6)	0.0011(6)
C6	0.0347(10)	0.0256(8)	0.0347(9)	0.0097(7)	-0.0070(7)	0.0010(7)
C7	0.0710(15)	0.0401(11)	0.0306(10)	0.0066(8)	0.0042(9)	0.0064(10)
C8	0.0612(14)	0.0419(11)	0.0473(11)	0.0146(9)	0.0125(10)	-0.0034(9)
C11	0.0233(8)	0.0228(7)	0.0302(8)	0.0053(6)	-0.0010(6)	-0.0002(6)
C12	0.0212(8)	0.0235(7)	0.0296(8)	0.0080(6)	0.0024(6)	-0.0015(6)
C13	0.0358(10)	0.0278(8)	0.0322(9)	0.0061(7)	0.0023(7)	0.0064(7)
C14	0.0449(11)	0.0357(10)	0.0436(10)	0.0167(8)	0.0019(8)	0.0124(8)
C15	0.0381(10)	0.0453(10)	0.0300(9)	0.0190(8)	0.0003(7)	0.0019(8)
C16	0.0406(11)	0.0358(9)	0.0276(9)	0.0056(7)	0.0063(7)	0.0024(8)
C17	0.0332(10)	0.0269(8)	0.0326(9)	0.0087(7)	0.0047(7)	0.0047(7)
C19	0.0251(9)	0.0412(10)	0.0443(10)	0.0095(8)	-0.0020(7)	0.0007(7)
C20	0.0276(9)	0.0265(8)	0.0316(8)	0.0085(7)	-0.0029(7)	-0.0023(6)
C21	0.0331(10)	0.0287(9)	0.0318(9)	0.0078(7)	-0.0019(7)	-0.0051(7)
C22	0.0342(10)	0.0271(8)	0.0338(9)	0.0018(7)	0.0039(7)	-0.0081(7)
C23	0.0655(14)	0.0408(11)	0.0357(10)	0.0064(8)	-0.0051(9)	-0.0113(9)
C24	0.0804(17)	0.0630(15)	0.0337(11)	-0.0023(10)	0.0002(11)	-0.0259(13)
C25	0.0670(16)	0.0471(13)	0.0564(14)	-0.0192(11)	0.0226(12)	-0.0212(11)
C26	0.0512(14)	0.0320(11)	0.0893(18)	-0.0022(11)	0.0189(13)	0.0005(9)
C27	0.0395(11)	0.0348(10)	0.0551(12)	0.0063(9)	0.0035(9)	-0.0011(8)

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms
T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for: 1.10aa

F18	-C15	1.360(2)	C22	-C27	1.387(3)
O1	-C2	1.439(2)	C23	-C24	1.380(3)
O1	-C6	1.347(2)	C24	-C25	1.362(3)
O3	-C2	1.4378(19)	C25	-C26	1.368(3)
O3	-C4	1.3539(19)	C26	-C27	1.391(3)
O9	-C4	1.1967(19)	C5	-H5A	0.9800
O10	-C6	1.199(2)	C7	-H7A	0.9600
C2	-C7	1.500(3)	C7	-H7B	0.9600
C2	-C8	1.505(3)	C7	-H7C	0.9600
C4	-C5	1.502(2)	C8	-H8A	0.9600
C5	-C6	1.509(2)	C8	-H8B	0.9600
C5	-C11	1.601(2)	C8	-H8C	0.9600
C11	-C12	1.532(2)	C13	-H13A	0.9300
C11	-C19	1.543(2)	C14	-H14A	0.9300
C11	-C20	1.474(2)	C16	-H16A	0.9300
C12	-C13	1.387(2)	C17	-H17A	0.9300
C12	-C17	1.390(2)	C19	-H19A	0.9600
C13	-C14	1.383(2)	C19	-H19B	0.9600
C14	-C15	1.365(3)	C19	-H19C	0.9600
C15	-C16	1.366(3)	C23	-H23A	0.9300
C16	-C17	1.379(2)	C24	-H24A	0.9300
C20	-C21	1.194(2)	C25	-H25A	0.9300
C21	-C22	1.439(2)	C26	-H26A	0.9300
C22	-C23	1.385(3)	C27	-H27A	0.9300

Table S6 - Bond Angles   (°) for: 1.10aa

C2	-O1	-C6	122.83(12)	F18	-C15	-C14	118.98(17)
C2	-O3	-C4	120.60(13)	F18	-C15	-C16	118.47(15)
O1	-C2	-O3	112.23(12)	C14	-C15	-C16	122.55(16)
O1	-C2	-C7	106.94(14)	C15	-C16	-C17	118.62(16)
O1	-C2	-C8	108.18(15)	C12	-C17	-C16	121.08(16)
O3	-C2	-C7	106.79(14)	C11	-C20	-C21	175.10(16)
O3	-C2	-C8	108.44(14)	C20	-C21	-C22	177.85(18)
C7	-C2	-C8	114.35(15)	C21	-C22	-C23	119.35(16)
O3	-C4	-O9	119.40(14)	C21	-C22	-C27	121.49(16)
O3	-C4	-C5	115.88(13)	C23	-C22	-C27	119.14(17)
O9	-C4	-C5	124.46(14)	C22	-C23	-C24	120.65(19)
C4	-C5	-C6	113.44(13)	C23	-C24	-C25	120.0(2)
C4	-C5	-C11	110.03(13)	C24	-C25	-C26	120.3(2)
C6	-C5	-C11	109.66(12)	C25	-C26	-C27	120.7(2)
O1	-C6	-O10	118.93(15)	C22	-C27	-C26	119.25(19)
O1	-C6	-C5	117.30(13)	C4	-C5	-H5A	108.00
O10	-C6	-C5	123.60(15)	C6	-C5	-H5A	108.00
C5	-C11	-C12	109.27(12)	C11	-C5	-H5A	108.00
C5	-C11	-C19	109.37(13)	C2	-C7	-H7A	109.00
C5	-C11	-C20	109.65(12)	C2	-C7	-H7B	109.00
C12	-C11	-C19	109.61(13)	C2	-C7	-H7C	109.00
C12	-C11	-C20	111.04(13)	H7A	-C7	-H7B	109.00
C19	-C11	-C20	107.88(13)	H7A	-C7	-H7C	110.00
C11	-C12	-C13	121.82(14)	H7B	-C7	-H7C	109.00
C11	-C12	-C17	120.04(14)	C2	-C8	-H8A	109.00
C13	-C12	-C17	118.14(15)	C2	-C8	-H8B	110.00

C12	-C13	-C14	121.34(16)	C2	-C8	-H8C	109.00
C13	-C14	-C15	118.26(18)	H8A	-C8	-H8B	109.00
H8A	-C8	-H8C	109.00	H19A	-C19	-H19B	110.00
H8B	-C8	-H8C	109.00	H19A	-C19	-H19C	109.00
C12	-C13	-H13A	119.00	H19B	-C19	-H19C	109.00
C14	-C13	-H13A	119.00	C22	-C23	-H23A	120.00
C13	-C14	-H14A	121.00	C24	-C23	-H23A	120.00
C15	-C14	-H14A	121.00	C23	-C24	-H24A	120.00
C15	-C16	-H16A	121.00	C25	-C24	-H24A	120.00
C17	-C16	-H16A	121.00	C24	-C25	-H25A	120.00
C12	-C17	-H17A	119.00	C26	-C25	-H25A	120.00
C16	-C17	-H17A	119.00	C25	-C26	-H26A	120.00
C11	-C19	-H19A	109.00	C27	-C26	-H26A	120.00
C11	-C19	-H19B	109.00	C22	-C27	-H27A	120.00
C11	-C19	-H19C	109.00	C26	-C27	-H27A	120.00

Table S7 - Torsion Angles (°) for: 1.10aa

C6	-O1	-C2	-O3	31.2(2)	C5	-C11	-C12	-C13	-112.80(16)
C6	-O1	-C2	-C7	148.00(15)	C5	-C11	-C12	-C17	68.35(18)
C6	-O1	-C2	-C8	-88.38(18)	C19	-C11	-C12	-C13	127.37(16)
C2	-O1	-C6	-O10	156.56(16)	C19	-C11	-C12	-C17	-51.5(2)
C2	-O1	-C6	-C5	-28.0(2)	C20	-C11	-C12	-C13	8.3(2)
C4	-O3	-C2	-O1	-37.8(2)	C20	-C11	-C12	-C17	-170.57(14)
C4	-O3	-C2	-C7	-154.71(15)	C11	-C12	-C13	-C14	-177.84(16)
C4	-O3	-C2	-C8	81.61(17)	C17	-C12	-C13	-C14	1.0(2)
C2	-O3	-C4	-O9	-144.85(16)	C11	-C12	-C17	-C16	178.42(14)
C2	-O3	-C4	-C5	40.8(2)	C13	-C12	-C17	-C16	-0.5(2)
O3	-C4	-C5	-C6	-33.3(2)	C12	-C13	-C14	-C15	-0.7(3)
O3	-C4	-C5	-C11	90.01(16)	C13	-C14	-C15	-F18	179.49(16)
O9	-C4	-C5	-C6	152.75(16)	C13	-C14	-C15	-C16	-0.3(3)
O9	-C4	-C5	-C11	-84.0(2)	F18	-C15	-C16	-C17	-178.96(15)
C4	-C5	-C6	-O1	27.0(2)	C14	-C15	-C16	-C17	0.8(3)
C4	-C5	-C6	-O10	-157.74(16)	C15	-C16	-C17	-C12	-0.4(2)
C11	-C5	-C6	-O1	-96.42(16)	C21	-C22	-C23	-C24	-178.98(18)
C11	-C5	-C6	-O10	78.8(2)	C27	-C22	-C23	-C24	-0.4(3)
C4	-C5	-C11	-C12	52.06(16)	C21	-C22	-C27	-C26	178.70(18)
C4	-C5	-C11	-C19	172.04(13)	C23	-C22	-C27	-C26	0.2(3)
C4	-C5	-C11	-C20	-69.86(16)	C22	-C23	-C24	-C25	0.4(3)
C6	-C5	-C11	-C12	177.50(12)	C23	-C24	-C25	-C26	-0.2(3)
C6	-C5	-C11	-C19	-62.52(16)	C24	-C25	-C26	-C27	-0.1(3)
C6	-C5	-C11	-C20	55.58(16)	C25	-C26	-C27	-C22	0.1(3)

Table S8 - Contact Distances(Å) for: 1.10aa

F18	.C7_a	3.337(2)	O3	.H14A_b	2.6800	O1	.C20	3.164(2)	O10	.H19A_g	2.7300
F18	.C7_b	3.338(2)	O3	.H8C	2.5800	O3	.C20	3.185(2)	C2	.C5	2.888(2)
F18	.C27_b	3.302(3)	O3	.H7B	2.5400	O3	.C6	2.7990(19)	C4	.O1	2.7956(19)
F18	.H16A	2.5200	O9	.H5A	2.5400	O3	.C11	3.2749(19)	C4	.C8	3.112(3)
F18	.H7A_a	2.3900	O9	.H8B_e	2.5400	O9	.C19_d	3.2751(19)	C4	.C12	2.906(2)
F18	.H14A	2.5300	O10	.H5A	2.5500	O9	.C5_e	3.417(2)	C4	.C13	3.478(2)
F18	.H7C_b	2.8200	O10	.H8C_f	2.8800	O9	.C12	3.007(2)	C4	.C17	3.577(2)
O1	.C4	2.7956(19)	O10	.H19B	2.4200	O9	.C4_e	3.253(2)	C4	.C20	3.064(2)
O1	.C11	3.3487(19)	O10	.H17A_g	2.5200	O9	.C17	3.3583(19)	C4	.O9_e	3.253(2)

O9	.C11	3.2195(19)	C5	.C13	3.583(2)	C5	.H19A	2.7400	H5A	.O10	2.5500
O10	.C19	3.041(2)	C5	.C2	2.888(2)	C5	.H19B	2.7300	H5A	.C12	2.7600
O10	.C11	3.168(2)	C5	.O9_e	3.417(2)	C6	.H19B	2.6600	H5A	.C17	2.9100
O1	.H8A	2.5600	C5	.C17	3.160(2)	C6	.H8B	2.9900	H5A	.C19	2.6900
O1	.H7C	2.5500	C5	.C21	3.570(2)	C7	.H8A	2.7300	H5A	.H17A	2.5400
O1	.H8B	2.5900	C6	.C20	2.915(2)	C7	.H8C	2.7200	H5A	.H19A	2.5100
O1	.H24A_c	2.7000	C6	.O3	2.7990(19)	C8	.H7B	2.7200	H7A	.F18_h	2.3900
O1	.H7A	2.5400	C6	.C7	3.589(3)	C8	.H7A	2.7200	H7A	.O1	2.5400
O3	.H8B	2.5800	C6	.C19	3.016(2)	C11	.H13A	2.7000	H7A	.C8	2.7200
O3	.H7C	2.5400	C6	.C8	3.193(3)	C11	.H17A	2.6600	H7A	.H8A	2.5800
C7	.F18_b	3.338(2)	C17	.C8_e	3.502(3)	C12	.H19C	2.7000	H7B	.O3	2.5400
C7	.F18_h	3.337(2)	C17	.C4	3.577(2)	C12	.H19A	2.6800	H7B	.C8	2.7200
C7	.C6	3.589(3)	C17	.C19	2.986(2)	C12	.H5A	2.7600	H7B	.H8C	2.5600
C8	.C4	3.112(3)	C17	.O9	3.3583(19)	C13	.H19C_i	3.0400	H7C	.O1	2.5500
C8	.C6	3.193(3)	C17	.C27_i	3.523(3)	C17	.H8B_e	3.0300	H7C	.O3	2.5400
C8	.C16_e	3.563(3)	C17	.C14	2.762(3)	C17	.H19A	2.6800	H7C	.C21	2.9100
C8	.C17_e	3.502(3)	C17	.C5	3.160(2)	C17	.H5A	2.9100	H7C	.C22	3.0400
C11	.O9	3.2195(19)	C19	.C17	2.986(2)	H7C	.F18_b	2.8200	H17A	.H16A	2.3100
C11	.O3	3.2749(19)	C19	.C6	3.016(2)	H8A	.O1	2.5600	H17A	.H19A	2.2100
C11	.O10	3.168(2)	C19	.C21	3.423(2)	H8A	.C7	2.7300	H17A	.O10_g	2.5200
C11	.O1	3.3487(19)	C19	.O10	3.041(2)	H8A	.H7A	2.5800	H19A	.C5	2.7400
C12	.C21	3.531(2)	C19	.O9_f	3.2751(19)	H8B	.O1	2.5900	H19A	.C12	2.6800
C12	.O9	3.007(2)	C20	.C6	2.915(2)	H8B	.O3	2.5800	H19A	.C17	2.6800
C12	.C4	2.906(2)	C20	.C13	2.805(2)	H8B	.C4	2.8700	H19A	.H5A	2.5100
C12	.C15	2.751(2)	C20	.C27	3.574(3)	H8B	.C6	2.9900	H19A	.H17A	2.2100
C13	.C21	3.511(2)	C20	.C4	3.064(2)	H8B	.O9_e	2.5400	H19A	.O10_g	2.7300
C13	.C16	2.756(2)	C20	.C23	3.509(2)	H8B	.C17_e	3.0300	H19B	.O10	2.4200
C13	.C4	3.478(2)	C20	.O1	3.164(2)	H8C	.O3	2.5800	H19B	.C5	2.7300
C13	.C20	2.805(2)	C20	.O3	3.185(2)	H8C	.O10_d	2.8800	H19B	.C6	2.6600
C13	.C5	3.583(2)	C21	.C12	3.531(2)	H8C	.C7	2.7200	H19B	.C20	2.6200
C14	.C17	2.762(3)	C21	.C19	3.423(2)	H8C	.H7B	2.5600	H19C	.C12	2.7000
C15	.C12	2.751(2)	C21	.C13	3.511(2)	H13A	.C11	2.7000	H19C	.C20	2.6200
C15	.C27_b	3.440(3)	C21	.C5	3.570(2)	H13A	.C20	2.4400	H19C	.C13_i	3.0400
C15	.C23_i	3.584(3)	C22	.C25	2.767(3)	H13A	.C21	2.8700	H23A	.C21	2.5900
C16	.C22_i	3.488(2)	C22	.C16_i	3.488(2)	H13A	.H14A	2.3200	H23A	.H24A	2.3100
C16	.C8_e	3.563(3)	C23	.C20	3.509(2)	H14A	.F18	2.5300	H23A	.H23A_c	2.4800
C16	.C13	2.756(2)	C23	.C26	2.741(3)	H14A	.H13A	2.3200	H24A	.H23A	2.3100
C16	.C27_i	3.529(3)	C23	.C15_i	3.584(3)	H14A	.O3_b	2.6800	H24A	.H25A	2.2900
C24	.C27	2.764(3)	C19	.H17A	2.7800	H16A	.F18	2.5200	H24A	.O1_c	2.7000
C25	.C22	2.767(3)	C19	.H5A	2.6900	H16A	.H17A	2.3100	H25A	.H16A_k	2.5700
C26	.C23	2.741(3)	C20	.H19B	2.6200	H16A	.H25A_j	2.5700	H25A	.H24A	2.2900
C27	.C20	3.574(3)	C20	.H19C	2.6200	H17A	.C5	3.0400	H25A	.H26A	2.2900
C27	.C16_i	3.529(3)	C20	.H13A	2.4400	H17A	.C11	2.6600	H26A	.H25A	2.2900
C27	.C15_b	3.440(3)	C21	.H7C	2.9100	H17A	.C19	2.7800	H26A	.H27A	2.3200
C27	.C24	2.764(3)	C21	.H27A	2.6400	H17A	.H5A	2.5400	H27A	.C21	2.6400
C27	.C17_i	3.523(3)	C21	.H13A	2.8700	H27A	.H26A	2.3200			
C27	.F18_b	3.302(3)	C21	.H23A	2.5900						
C4	.H8B	2.8700	C22	.H7C	3.0400						
C5	.H17A	3.0400	H5A	.O9	2.5400						

Translation of Symmetry Code to Equiv.Pos

a =[1556.00] = [1_556] =x,y,1+z
b =[2556.00] = [2_556] =-x,-y,1-z
c =[2455.00] = [2_455] =-1-x,-y,-z
d =[1655.00] = [1_655] =1+x,y,z
e =[2566.00] = [2_566] =-x,1-y,1-z
f =[1455.00] = [1_455] =-1+x,y,z
g =[2466.00] = [2_466] =-1-x,1-y,1-z
h =[1554.00] = [1_554] =x,y,-1+z
i =[2456.00] = [2_456] =-1-x,-y,1-z
j =[1566.00] = [1_566] =x,1+y,1+z
k =[1544.00] = [1_544] =x,-1+y,-1+z

Crystallographic Data for 4.5a
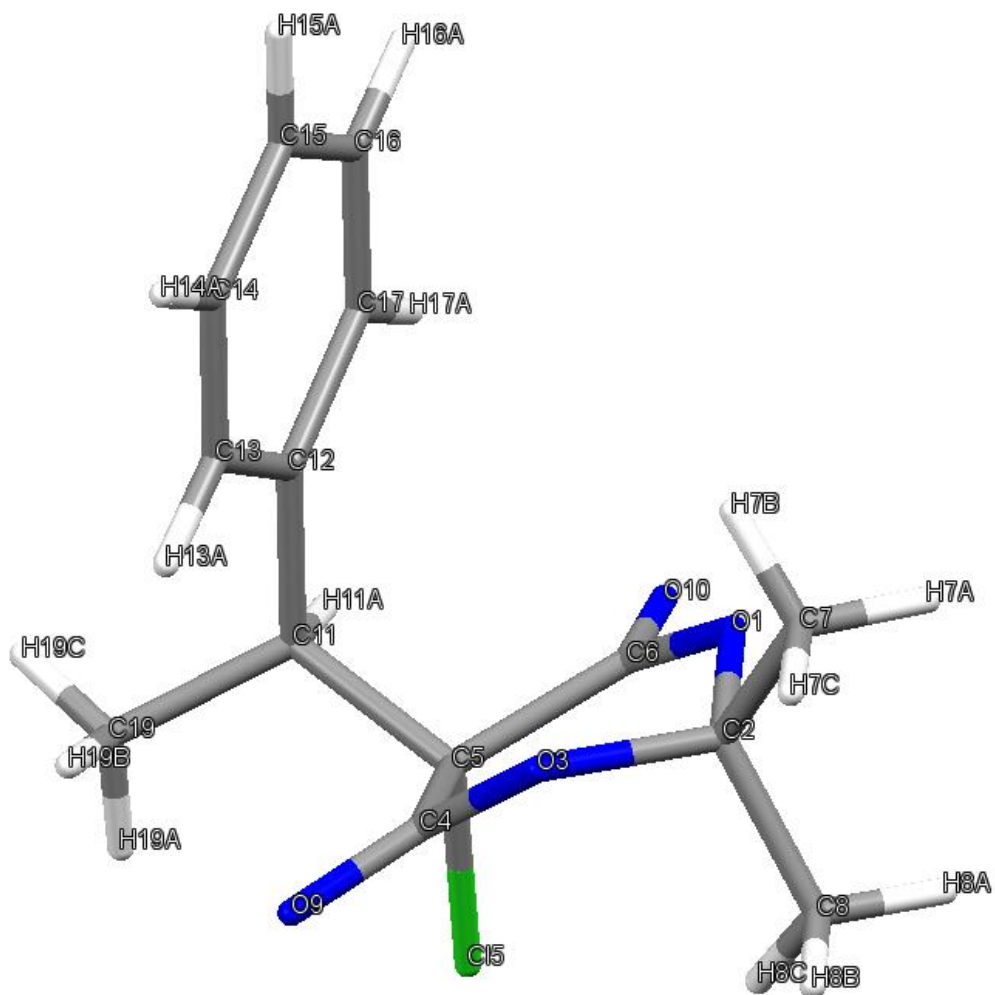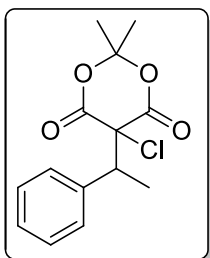
Table S1 - Crystal Data and Details of the Structure Determination for: 4.5a   R = 0.04

Crystal Data

Formula	$C_{14} H_{15} Cl O_4$
Formula Weight	282.71
Crystal System	triclinic
Space group	P-1 (No. 2)
a, b, c [Å]	7.6047(4) 9.0984(5) 10.7173(6)
α, β, γ [°]	88.569(4) 88.055(4) 71.660(3)
V [Å^3]	703.39(7)
Z	2
D(calc) [g/cm^3]	1.335
Mu(MoKa) [/mm]	0.278
F(000)	296
Crystal Size [mm]	0.05 x 0.18 x 0.24

Data Collection

Temperature (K)	200
Radiation [Å]	MoKa 0.71073
Theta Min-Max [°]	2.4, 28.0
Dataset	-10: 10 ; -12: 11 ; -14: 14
Tot., Uniq. Data, R(int)	11618, 3350, 0.024
Observed data [I > 2.0 sigma(I)]	2331

Refinement

Nref, Npar	3350, 172
R, wR2, S	0.0417, 0.0830, 1.10

w = ^2^(FO^2^)+(0.0140P)^2^+0.2171P] WHERE P=(FO^2^+2FC^2^)/3'

Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.30, 0.24

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: 4.5a

Atom	x	y	z	U(eq) [Ang^2]
Cl5	0.25994(7)	0.39756(6)	0.38847(5)	0.0728(2)
O1	0.74676(16)	0.36196(14)	0.32246(11)	0.0546(4)
O3	0.60322(16)	0.37466(13)	0.12936(10)	0.0510(4)
O9	0.34463(19)	0.32099(16)	0.10814(12)	0.0708(5)
O10	0.6536(2)	0.26433(15)	0.49072(11)	0.0683(5)
C2	0.6980(2)	0.44868(18)	0.20804(14)	0.0439(5)
C4	0.4612(2)	0.33103(18)	0.17561(15)	0.0460(5)
C5	0.4695(2)	0.28033(18)	0.31252(14)	0.0438(5)
C6	0.6279(2)	0.30446(18)	0.38416(15)	0.0469(5)
C7	0.8762(3)	0.4408(3)	0.14046(19)	0.0683(7)
C8	0.5772(3)	0.6105(2)	0.23515(19)	0.0647(7)
C11	0.4849(2)	0.10536(18)	0.32649(15)	0.0480(5)
C12	0.6690(2)	0.00594(17)	0.27110(15)	0.0458(5)
C13	0.6990(3)	-0.0164(2)	0.14381(18)	0.0612(7)
C14	0.8669(3)	-0.1076(3)	0.0955(2)	0.0791(8)
C15	1.0082(3)	-0.1797(3)	0.1730(2)	0.0792(9)
C16	0.9827(3)	-0.1605(2)	0.2990(2)	0.0726(8)
C17	0.8147(3)	-0.0683(2)	0.34805(18)	0.0585(7)
C19	0.3199(3)	0.0636(2)	0.2799(2)	0.0663(7)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 4.5a

Atom	x	y	z	U(iso) [Å^2]
H7A	0.94680	0.49000	0.19050	0.1020
H7B	0.94880	0.33220	0.12700	0.1020
H7C	0.84950	0.49490	0.05970	0.1020
H8A	0.64260	0.66040	0.28890	0.0970
H8B	0.54780	0.66950	0.15670	0.0970
H8C	0.46220	0.60730	0.27760	0.0970
H11A	0.48940	0.08180	0.41820	0.0580
H13A	0.60180	0.03220	0.08870	0.0730
H14A	0.88450	-0.12040	0.00780	0.0950
H15A	1.12360	-0.24300	0.13950	0.0950
H16A	1.08070	-0.21050	0.35320	0.0870
H17A	0.79870	-0.05560	0.43590	0.0700
H19A	0.20540	0.13120	0.31870	0.0990
H19B	0.31440	0.07710	0.18900	0.0990
H19C	0.33360	-0.04450	0.30220	0.0990

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for: 4.5a

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
Cl5	0.0633(3)	0.0723(3)	0.0744(3)	-0.0086(3)	0.0106(2)	-0.0101(2)
O1	0.0574(7)	0.0646(7)	0.0485(7)	0.0119(6)	-0.0180(5)	-0.0281(6)
O3	0.0627(7)	0.0595(7)	0.0369(6)	0.0030(5)	-0.0065(5)	-0.0278(6)
O9	0.0742(9)	0.0912(10)	0.0591(8)	0.0234(7)	-0.0336(7)	-0.0420(8)
O10	0.0981(10)	0.0771(9)	0.0386(7)	0.0102(6)	-0.0214(6)	-0.0391(8)
C2	0.0491(9)	0.0453(9)	0.0398(9)	0.0030(7)	-0.0062(7)	-0.0183(7)
C4	0.0509(10)	0.0443(9)	0.0444(9)	0.0079(7)	-0.0136(8)	-0.0167(7)
C5	0.0462(9)	0.0456(9)	0.0397(9)	0.0039(7)	-0.0048(7)	-0.0146(7)
C6	0.0622(11)	0.0408(8)	0.0385(9)	0.0009(7)	-0.0108(8)	-0.0166(8)
C7	0.0523(11)	0.0838(14)	0.0685(13)	0.0046(11)	0.0042(9)	-0.0220(10)
C8	0.0748(13)	0.0473(10)	0.0697(13)	-0.0026(9)	0.0055(10)	-0.0167(9)
C11	0.0552(10)	0.0479(9)	0.0453(9)	0.0103(7)	-0.0087(8)	-0.0228(8)
C12	0.0547(10)	0.0375(8)	0.0511(10)	0.0045(7)	-0.0126(8)	-0.0221(7)
C13	0.0671(12)	0.0550(11)	0.0576(12)	-0.0059(9)	-0.0173(9)	-0.0117(9)
C14	0.0830(16)	0.0771(14)	0.0689(14)	-0.0199(11)	-0.0050(12)	-0.0114(12)
C15	0.0606(13)	0.0714(14)	0.1008(18)	-0.0189(13)	-0.0058(12)	-0.0124(11)
C16	0.0584(12)	0.0635(12)	0.0956(17)	0.0035(11)	-0.0285(11)	-0.0163(10)
C17	0.0631(12)	0.0575(11)	0.0593(11)	0.0099(9)	-0.0200(9)	-0.0241(9)
C19	0.0627(12)	0.0665(12)	0.0801(14)	0.0118(10)	-0.0124(10)	-0.0352(10)

The Temperature Factor has the Form of Exp(-T) Where
$T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2$ for Isotropic Atoms
$T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j))$, for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for: 4.5a

Cl5	-C5	1.7960(17)	C15	-C16	1.365(3)
O1	-C2	1.4360(19)	C16	-C17	1.384(3)
O1	-C6	1.330(2)	C7	-H7A	0.9800
O3	-C2	1.435(2)	C7	-H7B	0.9800
O3	-C4	1.339(2)	C7	-H7C	0.9800
O9	-C4	1.190(2)	C8	-H8A	0.9800
O10	-C6	1.194(2)	C8	-H8B	0.9800
C2	-C7	1.497(3)	C8	-H8C	0.9800
C2	-C8	1.499(2)	C11	-H11A	1.0000
C4	-C5	1.524(2)	C13	-H13A	0.9500
C5	-C6	1.525(2)	C14	-H14A	0.9500
C5	-C11	1.563(2)	C15	-H15A	0.9500
C11	-C12	1.518(2)	C16	-H16A	0.9500
C11	-C19	1.523(3)	C17	-H17A	0.9500
C12	-C13	1.385(3)	C19	-H19A	0.9800
C12	-C17	1.388(3)	C19	-H19B	0.9800
C13	-C14	1.377(3)	C19	-H19C	0.9800
C14	-C15	1.366(3)			

Table S6 - Bond Angles (°) for: 4.5a

Atoms			Angle	Atoms			Angle
C2	-O1	-C6	121.36(13)	C14	-C15	-C16	119.7(2)
C2	-O3	-C4	120.16(12)	C15	-C16	-C17	120.2(2)
O1	-C2	-O3	110.28(12)	C12	-C17	-C16	121.10(18)
O1	-C2	-C7	106.61(14)	C2	-C7	-H7A	109.00
O1	-C2	-C8	110.14(13)	C2	-C7	-H7B	109.00
O3	-C2	-C7	106.11(14)	C2	-C7	-H7C	109.00
O3	-C2	-C8	109.84(14)	H7A	-C7	-H7B	109.00
C7	-C2	-C8	113.74(16)	H7A	-C7	-H7C	110.00
O3	-C4	-O9	119.93(15)	H7B	-C7	-H7C	110.00
O3	-C4	-C5	116.73(13)	C2	-C8	-H8A	109.00
O9	-C4	-C5	123.04(15)	C2	-C8	-H8B	109.00
Cl5	-C5	-C4	107.13(11)	C2	-C8	-H8C	109.00
Cl5	-C5	-C6	105.88(10)	H8A	-C8	-H8B	109.00
Cl5	-C5	-C11	109.97(11)	H8A	-C8	-H8C	109.00
C4	-C5	-C6	115.25(13)	H8B	-C8	-H8C	109.00
C4	-C5	-C11	111.13(13)	C5	-C11	-H11A	106.00
C6	-C5	-C11	107.31(12)	C12	-C11	-H11A	106.00
O1	-C6	-O10	119.83(16)	C19	-C11	-H11A	106.00
O1	-C6	-C5	118.24(14)	C12	-C13	-H13A	119.00
O10	-C6	-C5	121.75(15)	C14	-C13	-H13A	119.00
C5	-C11	-C12	109.85(13)	C13	-C14	-H14A	120.00
C5	-C11	-C19	115.05(13)	C15	-C14	-H14A	120.00
C12	-C11	-C19	113.13(14)	C14	-C15	-H15A	120.00
C11	-C12	-C13	122.29(15)	C16	-C15	-H15A	120.00
C11	-C12	-C17	120.45(15)	C15	-C16	-H16A	120.00
C13	-C12	-C17	117.25(16)	C17	-C16	-H16A	120.00
C12	-C13	-C14	121.37(19)	C12	-C17	-H17A	119.00
C13	-C14	-C15	120.4(2)	C16	-C17	-H17A	119.00
C11	-C19	-H19A	109.00	H19A	-C19	-H19B	109.00
C11	-C19	-H19B	110.00	H19A	-C19	-H19C	109.00
C11	-C19	-H19C	109.00	H19B	-C19	-H19C	109.00

Table S7 - Torsion Angles (°) for: 4.5a

Atoms				Angle	Atoms				Angle
C6	-O1	-C2	-O3	-43.42(18)	C4	-C5	-C6	-O10	-177.21(15)
C6	-O1	-C2	-C7	-158.18(16)	C11	-C5	-C6	-O1	122.41(15)
C6	-O1	-C2	-C8	77.98(19)	C11	-C5	-C6	-O10	-52.9(2)
C2	-O1	-C6	-O10	-163.07(15)	Cl5	-C5	-C11	-C12	-175.61(11)
C2	-O1	-C6	-C5	21.6(2)	Cl5	-C5	-C11	-C19	55.36(17)
C4	-O3	-C2	-O1	49.32(18)	C4	-C5	-C11	-C12	65.94(17)
C4	-O3	-C2	-C7	164.40(15)	C4	-C5	-C11	-C19	-63.09(18)
C4	-O3	-C2	-C8	-72.25(18)	C6	-C5	-C11	-C12	-60.89(16)
C2	-O3	-C4	-O9	153.85(15)	C6	-C5	-C11	-C19	170.08(14)
C2	-O3	-C4	-C5	-32.30(19)	C5	-C11	-C12	-C13	-79.32(19)
O3	-C4	-C5	-Cl5	124.67(13)	C5	-C11	-C12	-C17	101.44(17)
O3	-C4	-C5	-C6	7.2(2)	C19	-C11	-C12	-C13	50.8(2)
O3	-C4	-C5	-C11	-115.19(15)	C19	-C11	-C12	-C17	-128.50(17)
O9	-C4	-C5	-Cl5	-61.69(19)	C11	-C12	-C13	-C14	-179.73(19)
O9	-C4	-C5	-C6	-179.21(15)	C17	-C12	-C13	-C14	-0.5(3)
O9	-C4	-C5	-C11	58.5(2)	C11	-C12	-C17	-C16	179.36(17)
Cl5	-C5	-C6	-O1	-120.17(13)	C13	-C12	-C17	-C16	0.1(3)
Cl5	-C5	-C6	-O10	64.58(18)	C12	-C13	-C14	-C15	0.6(3)
C4	-C5	-C6	-O1	-2.0(2)	C13	-C14	-C15	-C16	-0.3(4)

C14	-C15	-C16	-C17	-0.1(3)		C15	-C16	-C17	-C12	0.2(3)

Table S8 - Contact Distances(Å) for: 4.5a

Cl5	.O9	3.1012(14)	O9	.H19B	2.4400	C15	.C12	2.788(3)	C19	.H13A	2.8700
Cl5	.O10	3.0830(16)	O9	.H13A	2.7500	C16	.C13	2.738(3)	H7A	.Cl5_e	3.1400
Cl5	.C19	3.1722(19)	O9	.H7C_b	2.5900	C17	.C14	2.738(3)	H7A	.O1	2.5600
Cl5	.H7A_a	3.1400	O10	.H11A	2.5200	C17	.C5	3.445(2)	H7A	.C8	2.7100
Cl5	.H8C	3.0000	O10	.H17A	2.8400	C17	.O10	3.282(2)	H7A	.H8A	2.5500
Cl5	.H11A	2.8700	O10	.H8C_c	2.7700	C17	.C6	3.266(2)	H7B	.O1	2.5200
Cl5	.H19A	2.7100	O10	.H16A_d	2.5900	C19	.C4	3.123(3)	H7B	.O3	2.5300
O1	.C4	2.813(2)	C2	.C5	2.842(2)	C19	.Cl5	3.1722(19)	H7B	.H14A_f	2.4300
O3	.C6	2.7879(19)	C4	.O1	2.813(2)	C19	.C13	3.069(3)	H7C	.O3	2.5300
O3	.C13	3.401(2)	C4	.C8	3.030(3)	C19	.O9	2.991(2)	H7C	.C8	2.7200
O9	.C19	2.991(2)	C4	.C12	3.051(2)	C4	.H13A	2.7600	H7C	.H8B	2.5500
O9	.Cl5	3.1012(14)	C4	.C13	3.129(2)	C4	.H8C	2.7700	H7C	.O9_b	2.5900
O9	.C7_a	3.390(3)	C4	.C19	3.123(3)	C4	.H19B	2.8600	H8A	.O1	2.6000
O9	.C13	3.411(2)	C5	.C2	2.842(2)	C5	.H19A	2.7500	H8A	.C7	2.7200
O9	.C11	3.014(2)	C5	.C8	3.429(2)	C5	.H19B	2.8600	H8A	.H7A	2.5500
O10	.Cl5	3.0830(16)	C5	.C13	3.266(2)	H8B	.O3	2.6000	H14A	.H15A	2.3200
O10	.C17	3.282(2)	C5	.C17	3.445(2)	H8B	.C7	2.7000	H14A	.H7B_f	2.4300
O10	.C8_c	3.401(2)	C6	.O3	2.7879(19)	H8B	.H7C	2.5500	H14A	.H19B_h	2.5900
O10	.C11	2.878(2)	C6	.C7	3.592(3)	H8C	.Cl5	3.0000	H15A	.H14A	2.3200
O10	.C12	3.341(2)	C6	.C17	3.266(2)	H8C	.O1	2.6200	H15A	.H16A	2.3200
O1	.H8A	2.6000	C6	.C12	2.924(2)	H8C	.O3	2.6000	H16A	.H15A	2.3200
O1	.H7B	2.5200	C6	.C8	3.098(2)	H8C	.C4	2.7700	H16A	.H17A	2.3200
O1	.H8C	2.6200	C7	.O9_e	3.390(3)	H8C	.C5	2.9700	H16A	.O10_d	2.5900
O1	.H7A	2.5600	C7	.C6	3.592(3)	H8C	.C6	2.8700	H17A	.O10	2.8400
O3	.H8B	2.6000	C8	.C6	3.098(2)	H8C	.O10_c	2.7700	H17A	.C11	2.6700
O3	.H7C	2.5300	C8	.C4	3.030(3)	H11A	.Cl5	2.8700	H17A	.H11A	2.3000
O3	.H7B	2.5300	C8	.C5	3.429(2)	H11A	.O10	2.5200	H17A	.H16A	2.3200
O3	.H8C	2.6000	C8	.O10_c	3.401(2)	H11A	.C6	2.5700	H19A	.Cl5	2.7100
C11	.O9	3.014(2)	C5	.H8C	2.9700	H11A	.C17	2.5200	H19A	.C5	2.7500
C11	.O10	2.878(2)	C6	.H11A	2.5700	H11A	.H17A	2.3000	H19A	.H11A	2.3500
C12	.C4	3.051(2)	C6	.H8C	2.8700	H11A	.H19A	2.3500	H19B	.O9	2.4400
C12	.O10	3.341(2)	C7	.H8B	2.7000	H11A	.H19C	2.3000	H19B	.C4	2.8600
C12	.C6	2.924(2)	C7	.H8A	2.7200	H11A	.H11A_g	2.2500	H19B	.C5	2.8600
C12	.C15	2.788(3)	C8	.H7C	2.7200	H13A	.O9	2.7500	H19B	.C12	2.7400
C13	.C5	3.266(2)	C8	.H7A	2.7100	H13A	.C4	2.7600	H19B	.C13	2.8100
C13	.O9	3.411(2)	C11	.H13A	2.7000	H13A	.C11	2.7000	H19B	.H13A	2.3200
C13	.C4	3.129(2)	C11	.H17A	2.6700	H13A	.C19	2.8700	H19B	.H14A_h	2.5900
C13	.C16	2.738(3)	C12	.H19C	2.7400	H13A	.H14A	2.3100	H19C	.C12	2.7400
C13	.O3	3.401(2)	C12	.H19B	2.7400	H13A	.H19B	2.3200	H19C	.H11A	2.3000
C13	.C19	3.069(3)	C13	.H19B	2.8100	H14A	.H13A	2.3100			
C14	.C17	2.738(3)	C17	.H11A	2.5200						

Translation of Symmetry Code to Equiv.Pos

a =[1455.00] = [1_455] =-1+x,y,z
b =[2665.00] = [2_665] =1-x,1-y,-z
c =[2666.00] = [2_666] =1-x,1-y,1-z
d =[2756.00] = [2_756] =2-x,-y,1-z
e =[1655.00] = [1_655] =1+x,y,z

f =[2755.00] = [2_755] =2-x,-y,-z
g =[2656.00] = [2_656] =1-x,-y,1-z
h =[2655.00] = [2_655] =1-x,-y,-z

Appendix C

Crystallographic Data for 4.6c
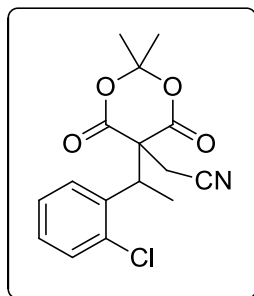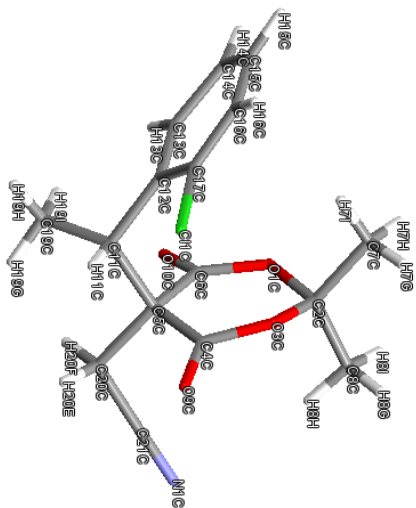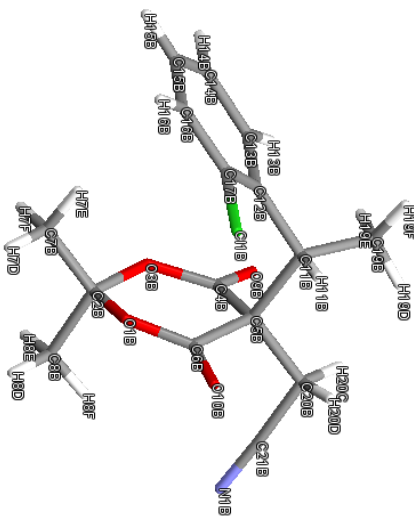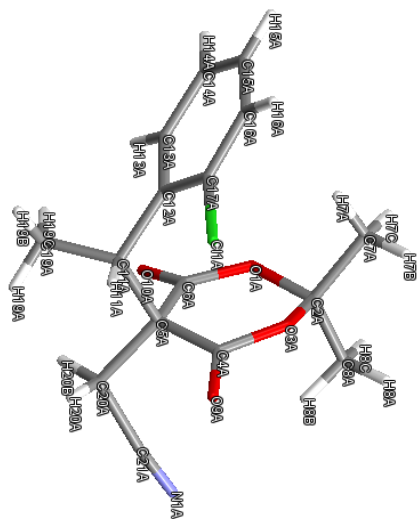
Table S1 - Crystal Data and Details of the Structure Determination for: 4.6c   R = 0.11

Crystal Data

Formula	$C_{16} H_{16} Cl N O_4$
Formula Weight	321.75
Crystal System	triclinic
Space group	P-1 (No. 2)
a, b, c [Å]	9.5883(9) 16.0222(14) 16.2329(15)
α, β, γ[°]	74.607(5) 88.915(6) 89.179(6)
V [Å³]	2403.8(4)
Z	6
D(calc) [g/cm³]	1.334
Mu(MoKa) [/mm]	0.255
F(000)	1008
Crystal Size [mm]	0.06 x 0.18 x 0.26

Data Collection

Temperature (K)	200
Radiation [Å]	MoKa 0.71073
Theta Min-Max [°]	1.3, 26.0
Dataset	-13: 13 ; -18: 22 ; -22: 22
Tot., Uniq. Data, R(int)	27166, 9408, 0.052
Observed data [I > 2.0 sigma(I)]	2569

Refinement

Nref, Npar	9408, 587
R, wR2, S	0.1131, 0.2504, 1.20

w = ^2^(FO^2^)+(0.0511P)^2^] WHERE P=(FO^2^+2FC^2^)/3'

Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.53, 0.66

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: 4.6c   R = 0.11

Atom	x	y	z	U(eq) [Ang^2]
Cl1A	0.2798(3)	1.15581(12)	-0.52269(14)	0.1127(12)
O1A	0.1857(6)	1.4101(3)	-0.4056(3)	0.066(2)
O3A	0.1253(6)	1.2613(3)	-0.3770(3)	0.081(2)
O9A	0.2664(6)	1.1604(3)	-0.3161(3)	0.084(2)
O10A	0.3879(5)	1.4484(3)	-0.3856(3)	0.0723(15)
N1A	0.3259(9)	1.2783(5)	-0.1517(4)	0.103(4)
C2A	0.0719(9)	1.3510(5)	-0.3823(7)	0.080(4)
C4A	0.2543(8)	1.2355(4)	-0.3513(4)	0.045(3)
C5A	0.3655(7)	1.2979(4)	-0.3700(4)	0.046(3)
C6A	0.3132(9)	1.3934(4)	-0.3885(4)	0.047(3)
C7A	-0.0231(8)	1.3695(4)	-0.4602(5)	0.090(4)
C8A	0.0094(10)	1.3500(5)	-0.3024(6)	0.112(4)
C11A	0.4453(7)	1.2900(4)	-0.4512(4)	0.053(3)
C12A	0.3632(8)	1.3186(5)	-0.5325(4)	0.063(3)
C13A	0.3609(9)	1.4071(4)	-0.5757(5)	0.076(4)
C14A	0.2877(9)	1.4397(5)	-0.6497(5)	0.075(4)
C15A	0.2196(10)	1.3854(6)	-0.6835(5)	0.099(5)
C16A	0.2176(9)	1.2969(5)	-0.6453(5)	0.084(4)
C17A	0.2862(9)	1.2676(4)	-0.5688(5)	0.070(3)
C19A	0.5880(7)	1.3265(5)	-0.4631(4)	0.067(3)
C20A	0.4734(8)	1.2823(4)	-0.2943(4)	0.064(3)
C21A	0.3929(9)	1.2750(4)	-0.2100(6)	0.065(4)
Cl1B	0.1693(3)	0.83049(11)	0.13479(13)	0.1284(15)
O1B	0.3643(6)	0.9210(3)	0.2813(3)	0.075(2)
O3B	0.3171(6)	1.0736(3)	0.2592(3)	0.064(2)
O9B	0.1155(6)	1.1249(3)	0.2851(3)	0.070(2)
O10B	0.1997(5)	0.8288(3)	0.3350(3)	0.0634(13)
N1B	0.1712(8)	0.9385(4)	0.5082(4)	0.091(4)
C2B	0.4209(8)	1.0065(5)	0.2730(5)	0.063(3)
C4B	0.1859(9)	1.0617(4)	0.2821(4)	0.049(3)
C5B	0.1226(7)	0.9751(3)	0.2950(4)	0.044(3)
C6B	0.2374(10)	0.9045(4)	0.3090(4)	0.060(3)
C7B	0.5136(8)	1.0206(5)	0.1971(5)	0.092(4)
C8B	0.4974(9)	1.0043(5)	0.3553(5)	0.097(4)
C11B	0.0351(7)	0.9733(4)	0.2125(4)	0.047(3)
C12B	0.1240(8)	0.9983(4)	0.1311(4)	0.054(3)
C13B	0.1393(8)	1.0855(4)	0.0907(4)	0.058(3)
C14B	0.2195(9)	1.1127(4)	0.0181(5)	0.075(3)
C15B	0.2841(10)	1.0540(6)	-0.0173(5)	0.099(4)
C16B	0.2708(10)	0.9674(5)	0.0188(5)	0.099(4)
C17B	0.1875(9)	0.9412(4)	0.0911(5)	0.069(3)
C19B	-0.1025(8)	1.0256(4)	0.2072(5)	0.080(3)
C20B	0.0249(7)	0.9538(4)	0.3728(4)	0.058(3)
C21B	0.1036(9)	0.9450(4)	0.4495(5)	0.062(3)
Cl1C	0.3201(3)	0.49331(11)	0.80716(12)	0.0997(12)
O1C	0.1324(6)	0.7311(3)	0.9295(3)	0.068(2)
O3C	0.1326(6)	0.5775(3)	0.9559(3)	0.082(3)
O9C	0.2999(5)	0.4958(2)	1.0130(3)	0.0650(18)
O10C	0.3276(5)	0.7955(3)	0.9389(3)	0.074(2)
N1C	0.3035(8)	0.6209(5)	1.1776(5)	0.107(4)

C2C	0.0498(8)	0.6560(5)	0.9517(6)	0.067(3)
C4C	0.2652(8)	0.5697(5)	0.9785(4)	0.046(3)
C5C	0.3521(7)	0.6465(4)	0.9586(4)	0.037(3)
C6C	0.2681(9)	0.7312(4)	0.9401(4)	0.042(3)
C7C	-0.0479(8)	0.6631(4)	0.8759(5)	0.079(3)
C8C	-0.0179(9)	0.6479(5)	1.0353(5)	0.096(4)
C11C	0.4400(7)	0.6458(4)	0.8753(4)	0.056(3)
C12C	0.3507(8)	0.6645(4)	0.7951(4)	0.065(3)
C13C	0.3200(9)	0.7528(4)	0.7535(4)	0.078(4)
C14C	0.2303(9)	0.7729(6)	0.6816(4)	0.083(4)
C15C	0.1864(10)	0.7100(6)	0.6492(5)	0.094(4)
C16C	0.2172(10)	0.6230(5)	0.6897(5)	0.088(4)
C17C	0.2909(9)	0.6046(4)	0.7596(4)	0.064(3)
C19C	0.5651(7)	0.7013(5)	0.8622(4)	0.072(3)
C20C	0.4546(8)	0.6411(5)	1.0340(5)	0.069(3)
C21C	0.3718(10)	0.6309(5)	1.1142(6)	0.071(4)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 4.6c

Atom	x	y	z	U(iso) [Ang^2]
H7A	0.03250	1.36840	-0.51120	0.1350
H7B	-0.09550	1.32530	-0.45090	0.1350
H7C	-0.06690	1.42670	-0.46820	0.1350
H8A	-0.06730	1.30840	-0.29030	0.1680
H8B	0.07910	1.33290	-0.25750	0.1680
H8C	-0.02700	1.40780	-0.30400	0.1680
H11A	0.45980	1.22640	-0.44260	0.0630
H13A	0.41210	1.44600	-0.55300	0.0910
H14A	0.28590	1.50020	-0.67620	0.0900
H15A	0.17090	1.40780	-0.73530	0.1190
H16A	0.17120	1.25820	-0.67070	0.1010
H19A	0.63880	1.30690	-0.40950	0.1010
H19B	0.63740	1.30680	-0.50800	0.1010
H19C	0.58190	1.38990	-0.47970	0.1010
H20A	0.52750	1.22840	-0.29090	0.0760
H20B	0.53940	1.33110	-0.30500	0.0760
H7D	0.58470	0.97460	0.20650	0.1370
H7E	0.45860	1.01960	0.14710	0.1370
H7F	0.55890	1.07690	0.18730	0.1370
H8D	0.56880	0.95860	0.36550	0.1450
H8E	0.54170	1.06030	0.34980	0.1450
H8F	0.43060	0.99270	0.40330	0.1450
H11B	0.00790	0.91170	0.22010	0.0560
H13B	0.09330	1.12720	0.11380	0.0700
H14B	0.23020	1.17290	-0.00780	0.0900
H15B	0.33930	1.07370	-0.06780	0.1180
H16B	0.31750	0.92640	-0.00500	0.1190
H19D	-0.15430	1.00640	0.26140	0.1200
H19E	-0.08150	1.08730	0.19620	0.1200
H19F	-0.15880	1.01630	0.16080	0.1200
H20C	-0.04580	1.00050	0.36750	0.0690

H20D	-0.02440	0.89910	0.37590	0.0690		
H7G	-0.10830	0.61230	0.88790	0.1180		
H7H	-0.10550	0.71560	0.86760	0.1180		
H7I	0.00780	0.66580	0.82400	0.1180		
H8G	-0.07510	0.59570	1.05040	0.1430		
H8H	0.05350	0.64380	1.07870	0.1430		
H8I	-0.07720	0.69880	1.03270	0.1430		
H11C	0.47560	0.58520	0.88420	0.0680		
H13C	0.35890	0.79790	0.77350	0.0940		
H14C	0.20200	0.83110	0.65690	0.1000		
H15C	0.13370	0.72410	0.59830	0.1130		
H16C	0.18510	0.57820	0.66680	0.1060		
H19G	0.61950	0.68760	0.91470	0.1080		
H19H	0.62230	0.69060	0.81540	0.1080		
H19I	0.53610	0.76230	0.84800	0.1080		
H20E	0.51910	0.59120	1.03950	0.0820		
H20F	0.51060	0.69450	1.02240	0.0820		

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for: 4.6c

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
Cl1A	0.221(3)	0.0397(12)	0.0764(17)	-0.0125(11)	-0.0153(16)	-0.0094(14)
O1A	0.060(4)	0.048(3)	0.082(4)	-0.002(3)	0.012(3)	-0.012(3)
O3A	0.075(4)	0.050(3)	0.114(5)	-0.014(3)	-0.017(3)	-0.011(3)
O9A	0.135(5)	0.018(3)	0.089(4)	0.003(3)	-0.009(3)	-0.003(3)
N1A	0.179(9)	0.082(5)	0.040(5)	-0.003(4)	0.023(5)	-0.042(5)
C2A	0.052(6)	0.059(6)	0.125(9)	-0.015(5)	0.002(6)	-0.017(5)
C4A	0.055(6)	0.028(4)	0.050(5)	-0.007(3)	-0.021(4)	-0.011(4)
C5A	0.058(5)	0.046(4)	0.029(4)	-0.002(3)	-0.008(4)	0.012(4)
C6A	0.066(6)	0.026(4)	0.049(5)	-0.009(3)	-0.025(4)	-0.016(4)
C7A	0.089(7)	0.061(5)	0.108(7)	0.000(5)	-0.039(6)	-0.010(5)
C8A	0.136(9)	0.088(7)	0.091(7)	0.008(5)	0.075(7)	0.026(6)
C11A	0.045(5)	0.041(4)	0.067(6)	-0.004(4)	-0.013(4)	0.018(4)
C12A	0.093(7)	0.054(5)	0.040(5)	-0.008(4)	0.000(4)	-0.016(4)
C13A	0.129(8)	0.043(5)	0.047(5)	0.005(4)	-0.004(5)	-0.030(4)
C14A	0.120(8)	0.050(5)	0.043(5)	0.010(4)	-0.020(5)	-0.016(5)
C15A	0.160(10)	0.088(7)	0.040(6)	-0.002(5)	-0.020(5)	0.001(6)
C16A	0.149(9)	0.069(6)	0.037(5)	-0.017(5)	-0.006(5)	-0.019(5)
C17A	0.116(7)	0.038(4)	0.060(6)	-0.021(4)	-0.001(5)	-0.017(4)
C19A	0.063(6)	0.081(5)	0.044(5)	0.007(4)	0.007(4)	0.015(5)
C20A	0.081(6)	0.051(4)	0.052(5)	-0.002(4)	-0.018(5)	0.018(4)
C21A	0.080(7)	0.041(4)	0.066(7)	0.002(5)	-0.035(5)	-0.010(4)
Cl1B	0.286(4)	0.0285(11)	0.0699(16)	-0.0143(11)	0.0430(18)	-0.0081(15)
O1B	0.082(4)	0.029(3)	0.106(5)	-0.003(3)	0.017(3)	-0.015(3)
O3B	0.058(4)	0.029(3)	0.095(4)	0.002(2)	-0.001(3)	-0.004(3)
O9B	0.120(5)	0.024(3)	0.063(3)	-0.008(2)	-0.007(3)	0.017(3)
N1B	0.146(8)	0.070(5)	0.043(5)	0.010(4)	-0.001(4)	0.017(4)
C2B	0.066(6)	0.047(5)	0.071(6)	-0.007(4)	0.015(5)	-0.015(5)
C4B	0.071(6)	0.034(5)	0.034(4)	0.005(3)	-0.015(4)	0.004(5)
C5B	0.066(5)	0.013(3)	0.047(5)	0.001(3)	-0.004(4)	0.004(3)

C6B	0.097(7)	0.007(4)	0.065(5)	0.010(3)	0.000(5)	-0.004(4)
C7B	0.091(7)	0.058(5)	0.113(8)	-0.002(5)	0.031(6)	-0.021(5)
C8B	0.111(8)	0.083(6)	0.083(7)	0.003(5)	-0.014(6)	-0.005(5)
C11B	0.075(6)	0.031(4)	0.031(4)	0.000(3)	-0.006(4)	-0.012(4)
C12B	0.098(6)	0.031(4)	0.028(4)	-0.001(3)	-0.013(4)	0.000(4)
C13B	0.117(7)	0.028(4)	0.024(4)	0.001(3)	0.007(4)	0.001(4)
C14B	0.143(8)	0.026(4)	0.050(5)	-0.001(4)	0.018(5)	-0.001(4)
C15B	0.177(10)	0.065(6)	0.039(5)	0.011(5)	0.028(5)	0.002(6)
C16B	0.204(11)	0.055(6)	0.039(5)	-0.017(5)	0.027(6)	0.008(6)
C17B	0.137(8)	0.031(4)	0.029(5)	0.006(4)	0.014(5)	-0.007(4)
C19B	0.103(7)	0.059(5)	0.072(6)	-0.005(4)	-0.017(5)	0.004(5)
C20B	0.077(6)	0.060(5)	0.025(4)	0.006(3)	0.022(4)	0.013(4)
C21B	0.087(7)	0.052(5)	0.033(5)	0.011(4)	0.004(5)	0.020(4)
Cl1C	0.199(3)	0.0354(11)	0.0641(14)	-0.0113(10)	-0.0335(15)	0.0214(13)
O1C	0.063(4)	0.042(3)	0.087(4)	0.003(3)	-0.016(3)	0.002(3)
O3C	0.081(5)	0.037(3)	0.120(5)	-0.006(3)	-0.017(4)	-0.002(3)
O9C	0.097(4)	0.021(2)	0.063(3)	0.013(2)	-0.006(3)	0.010(2)
O10C	0.094(4)	0.055(3)	0.071(4)	-0.015(3)	-0.005(3)	0.003(3)
N1C	0.121(7)	0.149(7)	0.039(5)	-0.004(5)	-0.011(5)	0.020(5)
C2C	0.068(6)	0.041(5)	0.097(7)	-0.027(5)	0.001(5)	-0.012(5)
C4C	0.054(6)	0.048(5)	0.036(4)	-0.010(4)	-0.014(4)	0.011(4)
C5C	0.052(5)	0.036(4)	0.024(4)	-0.008(3)	-0.011(4)	0.007(4)
C6C	0.088(7)	0.003(3)	0.030(4)	0.003(3)	-0.015(4)	-0.007(4)
C7C	0.093(7)	0.053(5)	0.088(6)	-0.013(4)	-0.043(5)	0.014(4)
C8C	0.117(8)	0.095(7)	0.079(7)	-0.031(5)	0.014(6)	-0.006(6)
C11C	0.064(6)	0.041(4)	0.057(5)	0.000(4)	-0.015(4)	0.006(4)
C12C	0.120(7)	0.031(4)	0.035(5)	0.004(4)	0.008(4)	0.013(4)
C13C	0.119(8)	0.048(5)	0.056(6)	0.004(4)	0.009(5)	0.022(5)
C14C	0.122(8)	0.083(6)	0.028(5)	0.015(4)	-0.021(5)	0.026(6)
C15C	0.163(10)	0.084(7)	0.033(5)	-0.013(5)	-0.014(5)	0.030(6)
C16C	0.155(9)	0.070(6)	0.039(5)	-0.013(5)	-0.006(5)	0.011(6)
C17C	0.115(7)	0.042(4)	0.034(5)	-0.011(4)	-0.006(5)	0.022(4)
C19C	0.058(6)	0.079(5)	0.066(6)	0.003(4)	0.016(4)	-0.013(5)
C20C	0.078(6)	0.067(5)	0.057(6)	-0.011(4)	0.005(5)	0.012(4)
C21C	0.093(8)	0.050(5)	0.073(7)	-0.017(5)	-0.036(6)	-0.003(5)

The Temperature Factor has the Form of Exp(-T) Where

$T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2$ for Isotropic Atoms

$T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j))$, for Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for: 4.6c

Cl1A	-C17A	1.750(7)	C5A	-C6A	1.557(10)
Cl1B	-C17B	1.737(7)	C5A	-C11A	1.545(9)
Cl1C	-C17C	1.766(7)	C11A	-C12A	1.510(9)
O1A	-C2A	1.433(10)	C11A	-C19A	1.485(10)
O1A	-C6A	1.268(10)	C12A	-C13A	1.405(10)
O3A	-C4A	1.337(9)	C12A	-C17A	1.360(11)
O3A	-C2A	1.500(10)	C13A	-C14A	1.377(11)
O9A	-C4A	1.192(8)	C14A	-C15A	1.330(13)
O10A	-C6A	1.155(9)	C15A	-C16A	1.389(13)
O1B	-C6B	1.295(11)	C16A	-C17A	1.381(11)

O1B	-C2B	1.453(10)	C20A	-C21A	1.536(11)
O3B	-C2B	1.431(10)	C7A	-H7B	0.9800
O3B	-C4B	1.307(10)	C7A	-H7C	0.9800
O9B	-C4B	1.220(9)	C7A	-H7A	0.9800
O10B	-C6B	1.231(9)	C8A	-H8B	0.9800
O1C	-C6C	1.316(10)	C8A	-H8C	0.9800
O1C	-C2C	1.411(10)	C8A	-H8A	0.9800
O3C	-C2C	1.465(10)	C11A	-H11A	1.0000
O3C	-C4C	1.325(9)	C13A	-H13A	0.9500
O9C	-C4C	1.212(9)	C14A	-H14A	0.9500
O10C	-C6C	1.180(9)	C15A	-H15A	0.9500
N1A	-C21A	1.146(12)	C16A	-H16A	0.9500
N1B	-C21B	1.144(11)	C19A	-H19A	0.9800
N1C	-C21C	1.185(12)	C19A	-H19B	0.9800
C2A	-C8A	1.415(14)	C19A	-H19C	0.9800
C2A	-C7A	1.534(13)	C20A	-H20A	0.9900
C4A	-C5A	1.444(10)	C20A	-H20B	0.9900
C5A	-C20A	1.588(9)	C2B	-C7B	1.475(11)
C2B	-C8B	1.528(11)	C20B	-H20C	0.9900
C4B	-C5B	1.484(9)	C20B	-H20D	0.9900
C5B	-C20B	1.525(9)	C2C	-C7C	1.540(12)
C5B	-C6B	1.543(10)	C2C	-C8C	1.468(12)
C5B	-C11B	1.601(9)	C4C	-C5C	1.456(10)
C11B	-C19B	1.544(10)	C5C	-C6C	1.530(10)
C11B	-C12B	1.523(9)	C5C	-C11C	1.582(9)
C12B	-C17B	1.383(10)	C5C	-C20C	1.568(10)
C12B	-C13B	1.385(9)	C11C	-C12C	1.532(9)
C13B	-C14B	1.369(11)	C11C	-C19C	1.482(10)
C14B	-C15B	1.362(12)	C12C	-C13C	1.426(9)
C15B	-C16B	1.362(13)	C12C	-C17C	1.380(10)
C16B	-C17B	1.380(12)	C13C	-C14C	1.427(10)
C20B	-C21B	1.442(10)	C14C	-C15C	1.331(13)
C7B	-H7D	0.9800	C15C	-C16C	1.404(13)
C7B	-H7E	0.9800	C16C	-C17C	1.312(11)
C7B	-H7F	0.9800	C20C	-C21C	1.484(12)
C8B	-H8D	0.9800	C7C	-H7G	0.9800
C8B	-H8E	0.9800	C7C	-H7H	0.9800
C8B	-H8F	0.9800	C7C	-H7I	0.9800
C11B	-H11B	1.0000	C8C	-H8G	0.9800
C13B	-H13B	0.9500	C8C	-H8H	0.9800
C14B	-H14B	0.9500	C8C	-H8I	0.9800
C15B	-H15B	0.9500	C11C	-H11C	1.0000
C16B	-H16B	0.9500	C13C	-H13C	0.9500
C19B	-H19D	0.9800	C14C	-H14C	0.9500
C19B	-H19E	0.9800	C15C	-H15C	0.9500
C19B	-H19F	0.9800	C16C	-H16C	0.9500
C19C	-H19G	0.9800	C20C	-H20E	0.9900
C19C	-H19H	0.9800	C20C	-H20F	0.9900
C19C	-H19I	0.9800			

Table S6 - Bond Angles (°) for: 4.6c

C2A	-O1A	-C6A	126.5(6)	C11A	-C12A	-C13A	118.3(7)
C2A	-O3A	-C4A	122.3(6)	C11A	-C12A	-C17A	126.8(7)
C2B	-O1B	-C6B	119.6(6)	C12A	-C13A	-C14A	122.7(7)
C2B	-O3B	-C4B	124.6(6)	C13A	-C14A	-C15A	119.1(8)
C2C	-O1C	-C6C	124.1(6)	C14A	-C15A	-C16A	121.9(8)
C2C	-O3C	-C4C	122.8(6)	C15A	-C16A	-C17A	117.1(7)
O1A	-C2A	-O3A	108.6(6)	C12A	-C17A	-C16A	124.3(7)
O1A	-C2A	-C7A	106.1(7)	Cl1A	-C17A	-C16A	115.4(6)
C7A	-C2A	-C8A	117.5(7)	Cl1A	-C17A	-C12A	120.2(6)
O3A	-C2A	-C8A	107.7(8)	C5A	-C20A	-C21A	109.0(6)
O1A	-C2A	-C8A	113.5(8)	N1A	-C21A	-C20A	172.3(8)
O3A	-C2A	-C7A	102.7(6)	C2A	-C7A	-H7A	109.00
O9A	-C4A	-C5A	125.9(7)	H7B	-C7A	-H7C	109.00
O3A	-C4A	-C5A	119.0(6)	H7A	-C7A	-H7C	110.00
O3A	-C4A	-O9A	115.1(7)	C2A	-C7A	-H7B	109.00
C6A	-C5A	-C20A	107.5(5)	C2A	-C7A	-H7C	109.00
C4A	-C5A	-C20A	111.9(5)	H7A	-C7A	-H7B	109.00
C6A	-C5A	-C11A	106.5(5)	C2A	-C8A	-H8C	110.00
C4A	-C5A	-C11A	109.0(5)	C2A	-C8A	-H8B	109.00
C4A	-C5A	-C6A	113.5(6)	H8B	-C8A	-H8C	109.00
C11A	-C5A	-C20A	108.1(5)	C2A	-C8A	-H8A	109.00
O1A	-C6A	-C5A	118.9(6)	H8A	-C8A	-H8B	109.00
O10A	-C6A	-C5A	121.1(7)	H8A	-C8A	-H8C	109.00
O1A	-C6A	-O10A	120.0(7)	C19A	-C11A	-H11A	105.00
C5A	-C11A	-C12A	114.6(6)	C12A	-C11A	-H11A	105.00
C12A	-C11A	-C19A	111.2(6)	C5A	-C11A	-H11A	105.00
C5A	-C11A	-C19A	115.8(6)	C12A	-C13A	-H13A	119.00
C13A	-C12A	-C17A	114.9(7)	C14A	-C13A	-H13A	119.00
C15A	-C14A	-H14A	120.00	C6B	-C5B	-C20B	108.0(5)
C13A	-C14A	-H14A	120.00	C4B	-C5B	-C20B	111.4(5)
C16A	-C15A	-H15A	119.00	C6B	-C5B	-C11B	109.2(5)
C14A	-C15A	-H15A	119.00	C11B	-C5B	-C20B	108.5(5)
C17A	-C16A	-H16A	121.00	O1B	-C6B	-C5B	122.4(6)
C15A	-C16A	-H16A	121.00	O10B	-C6B	-C5B	117.1(7)
C11A	-C19A	-H19A	109.00	O1B	-C6B	-O10B	119.5(7)
C11A	-C19A	-H19B	109.00	C12B	-C11B	-C19B	113.7(6)
H19B	-C19A	-H19C	109.00	C5B	-C11B	-C12B	111.8(5)
C11A	-C19A	-H19C	109.00	C5B	-C11B	-C19B	112.0(5)
H19A	-C19A	-H19C	110.00	C13B	-C12B	-C17B	116.1(6)
H19A	-C19A	-H19B	109.00	C11B	-C12B	-C17B	125.7(6)
C5A	-C20A	-H20B	110.00	C11B	-C12B	-C13B	118.1(6)
C21A	-C20A	-H20A	110.00	C12B	-C13B	-C14B	121.3(6)
C5A	-C20A	-H20A	110.00	C13B	-C14B	-C15B	120.4(7)
H20A	-C20A	-H20B	108.00	C14B	-C15B	-C16B	120.9(8)
C21A	-C20A	-H20B	110.00	C15B	-C16B	-C17B	117.9(8)
O1B	-C2B	-O3B	113.6(6)	Cl1B	-C17B	-C12B	119.6(6)
O3B	-C2B	-C7B	109.4(6)	C12B	-C17B	-C16B	123.3(7)
O1B	-C2B	-C7B	103.7(6)	Cl1B	-C17B	-C16B	117.1(6)
O1B	-C2B	-C8B	107.9(6)	C5B	-C20B	-C21B	109.9(6)
C7B	-C2B	-C8B	113.6(7)	N1B	-C21B	-C20B	177.0(9)
O3B	-C2B	-C8B	108.7(6)	C2B	-C7B	-H7F	109.00
O9B	-C4B	-C5B	121.5(7)	C2B	-C7B	-H7D	109.00
O3B	-C4B	-O9B	118.0(6)	C2B	-C7B	-H7E	109.00

O3B	-C4B	-C5B	120.2(6)	H7E	-C7B	-H7F	109.00
C4B	-C5B	-C11B	109.4(5)	H7D	-C7B	-H7F	110.00
C4B	-C5B	-C6B	110.2(6)	H7D	-C7B	-H7E	109.00
C2B	-C8B	-H8E	109.00	O1C	-C2C	-O3C	111.9(6)
C2B	-C8B	-H8F	109.00	O1C	-C2C	-C7C	105.8(7)
H8D	-C8B	-H8F	109.00	O1C	-C2C	-C8C	109.8(7)
H8E	-C8B	-H8F	109.00	O3C	-C2C	-C7C	104.4(6)
H8D	-C8B	-H8E	109.00	O3C	-C2C	-C8C	108.6(7)
C2B	-C8B	-H8D	110.00	C7C	-C2C	-C8C	116.3(7)
C19B	-C11B	-H11B	106.00	O3C	-C4C	-O9C	113.3(7)
C5B	-C11B	-H11B	106.00	O3C	-C4C	-C5C	119.0(6)
C12B	-C11B	-H11B	106.00	O9C	-C4C	-C5C	127.6(7)
C12B	-C13B	-H13B	119.00	C4C	-C5C	-C6C	113.4(6)
C14B	-C13B	-H13B	119.00	C4C	-C5C	-C11C	107.0(5)
C15B	-C14B	-H14B	120.00	C4C	-C5C	-C20C	109.3(6)
C13B	-C14B	-H14B	120.00	C6C	-C5C	-C11C	107.8(5)
C16B	-C15B	-H15B	120.00	C6C	-C5C	-C20C	110.3(6)
C14B	-C15B	-H15B	120.00	C11C	-C5C	-C20C	108.9(5)
C17B	-C16B	-H16B	121.00	O1C	-C6C	-O10C	121.4(7)
C15B	-C16B	-H16B	121.00	O1C	-C6C	-C5C	120.5(6)
C11B	-C19B	-H19D	109.00	O10C	-C6C	-C5C	118.1(7)
H19D	-C19B	-H19E	109.00	C5C	-C11C	-C12C	112.7(5)
C11B	-C19B	-H19E	109.00	C5C	-C11C	-C19C	113.8(5)
C11B	-C19B	-H19F	109.00	C12C	-C11C	-C19C	111.7(5)
H19E	-C19B	-H19F	110.00	C11C	-C12C	-C13C	117.6(6)
H19D	-C19B	-H19F	110.00	C11C	-C12C	-C17C	127.0(6)
C5B	-C20B	-H20D	110.00	C13C	-C12C	-C17C	115.3(6)
C5B	-C20B	-H20C	110.00	C12C	-C13C	-C14C	119.4(7)
H20C	-C20B	-H20D	108.00	C13C	-C14C	-C15C	119.9(8)
C21B	-C20B	-H20C	110.00	C14C	-C15C	-C16C	120.5(8)
C21B	-C20B	-H20D	110.00	C15C	-C16C	-C17C	119.0(8)
Cl1C	-C17C	-C12C	119.0(5)	C12C	-C13C	-H13C	120.00
Cl1C	-C17C	-C16C	115.6(6)	C14C	-C13C	-H13C	120.00
C12C	-C17C	-C16C	125.4(7)	C13C	-C14C	-H14C	120.00
C5C	-C20C	-C21C	108.8(6)	C15C	-C14C	-H14C	120.00
N1C	-C21C	-C20C	178.1(10)	C14C	-C15C	-H15C	120.00
C2C	-C7C	-H7G	109.00	C16C	-C15C	-H15C	120.00
C2C	-C7C	-H7H	109.00	C15C	-C16C	-H16C	120.00
C2C	-C7C	-H7I	110.00	C17C	-C16C	-H16C	121.00
H7G	-C7C	-H7H	109.00	C11C	-C19C	-H19G	109.00
H7G	-C7C	-H7I	109.00	C11C	-C19C	-H19H	109.00
H7H	-C7C	-H7I	110.00	C11C	-C19C	-H19I	109.00
C2C	-C8C	-H8G	109.00	H19G	-C19C	-H19H	109.00
C2C	-C8C	-H8H	109.00	H19G	-C19C	-H19I	109.00
C2C	-C8C	-H8I	110.00	H19H	-C19C	-H19I	110.00
H8G	-C8C	-H8H	109.00	C5C	-C20C	-H20E	110.00
H8G	-C8C	-H8I	109.00	C5C	-C20C	-H20F	110.00
H8H	-C8C	-H8I	109.00	C21C	-C20C	-H20E	110.00
C5C	-C11C	-H11C	106.00	C21C	-C20C	-H20F	110.00
C12C	-C11C	-H11C	106.00	H20E	-C20C	-H20F	108.00
C19C	-C11C	-H11C	106.00				

Table S7 - Torsion Angles (°) for: 4.6c

C6A	-O1A	-C2A	-O3A	-29.4(11)	C5A	-C11A	-C12A	-C17A	-93.7(9)
C6A	-O1A	-C2A	-C7A	-139.2(7)	C19A	-C11A	-C12A	-C13A	-49.1(9)
C6A	-O1A	-C2A	-C8A	90.3(9)	C13A	-C12A	-C17A	-C16A	4.4(12)
C2A	-O1A	-C6A	-O10A	-155.6(7)	C11A	-C12A	-C17A	-C16A	-177.3(8)
C2A	-O1A	-C6A	-C5A	23.3(10)	C11A	-C12A	-C13A	-C14A	-179.2(7)
C4A	-O3A	-C2A	-O1A	33.2(10)	C13A	-C12A	-C17A	-Cl1A	179.6(6)
C4A	-O3A	-C2A	-C7A	145.3(6)	C11A	-C12A	-C17A	-Cl1A	-2.2(11)
C4A	-O3A	-C2A	-C8A	-90.1(8)	C17A	-C12A	-C13A	-C14A	-0.7(12)
C2A	-O3A	-C4A	-O9A	149.7(7)	C12A	-C13A	-C14A	-C15A	-2.1(13)
C2A	-O3A	-C4A	-C5A	-32.2(9)	C13A	-C14A	-C15A	-C16A	1.5(14)
C6B	-O1B	-C2B	-C8B	93.7(7)	C14A	-C15A	-C16A	-C17A	1.9(13)
C2B	-O1B	-C6B	-O10B	-163.1(6)	C15A	-C16A	-C17A	-Cl1A	179.6(7)
C2B	-O1B	-C6B	-C5B	29.1(9)	C15A	-C16A	-C17A	-C12A	-5.1(13)
C6B	-O1B	-C2B	-C7B	-145.5(6)	O3B	-C4B	-C5B	-C11B	-100.4(7)
C6B	-O1B	-C2B	-O3B	-26.8(9)	O9B	-C4B	-C5B	-C11B	73.2(7)
C4B	-O3B	-C2B	-C7B	139.7(7)	O3B	-C4B	-C5B	-C20B	139.6(6)
C4B	-O3B	-C2B	-O1B	24.4(9)	O9B	-C4B	-C5B	-C6B	-166.7(6)
C2B	-O3B	-C4B	-C5B	-22.9(9)	O3B	-C4B	-C5B	-C6B	19.8(8)
C4B	-O3B	-C2B	-C8B	-95.7(8)	O9B	-C4B	-C5B	-C20B	-46.8(8)
C2B	-O3B	-C4B	-O9B	163.3(6)	C20B	-C5B	-C11B	-C12B	177.2(5)
C2C	-O1C	-C6C	-O10C	-162.8(7)	C20B	-C5B	-C11B	-C19B	48.4(7)
C6C	-O1C	-C2C	-O3C	-22.2(10)	C6B	-C5B	-C11B	-C19B	165.8(6)
C2C	-O1C	-C6C	-C5C	14.3(10)	C6B	-C5B	-C20B	-C21B	55.1(7)
C6C	-O1C	-C2C	-C8C	98.4(8)	C11B	-C5B	-C20B	-C21B	173.4(5)
C6C	-O1C	-C2C	-C7C	-135.3(6)	C4B	-C5B	-C20B	-C21B	-66.1(7)
C4C	-O3C	-C2C	-O1C	31.1(10)	C4B	-C5B	-C6B	-O1B	-24.0(8)
C4C	-O3C	-C2C	-C7C	145.1(6)	C4B	-C5B	-C6B	-O10B	167.8(6)
C4C	-O3C	-C2C	-C8C	-90.2(8)	C11B	-C5B	-C6B	-O1B	96.2(7)
C2C	-O3C	-C4C	-C5C	-31.1(9)	C11B	-C5B	-C6B	-O10B	-71.9(7)
C2C	-O3C	-C4C	-O9C	150.4(7)	C20B	-C5B	-C6B	-O1B	-146.0(6)
O3A	-C4A	-C5A	-C20A	143.0(6)	C20B	-C5B	-C6B	-O10B	45.9(7)
O9A	-C4A	-C5A	-C6A	-161.1(6)	C4B	-C5B	-C11B	-C12B	55.5(7)
O9A	-C4A	-C5A	-C20A	-39.1(9)	C4B	-C5B	-C11B	-C19B	-73.4(7)
O9A	-C4A	-C5A	-C11A	80.4(8)	C6B	-C5B	-C11B	-C12B	-65.3(7)
O3A	-C4A	-C5A	-C11A	-97.5(7)	C19B	-C11B	-C12B	-C13B	43.5(9)
O3A	-C4A	-C5A	-C6A	21.0(8)	C19B	-C11B	-C12B	-C17B	-133.7(8)
C20A	-C5A	-C11A	-C12A	-169.7(6)	C5B	-C11B	-C12B	-C13B	-84.5(8)
C20A	-C5A	-C11A	-C19A	-38.2(8)	C5B	-C11B	-C12B	-C17B	98.3(8)
C4A	-C5A	-C20A	-C21A	-50.7(7)	C11B	-C12B	-C17B	-Cl1B	-0.5(11)
C6A	-C5A	-C11A	-C19A	77.1(7)	C11B	-C12B	-C13B	-C14B	178.9(7)
C6A	-C5A	-C11A	-C12A	-54.4(8)	C17B	-C12B	-C13B	-C14B	-3.6(11)
C4A	-C5A	-C6A	-O10A	162.5(6)	C13B	-C12B	-C17B	-C16B	4.9(12)
C11A	-C5A	-C6A	-O1A	103.7(7)	C11B	-C12B	-C17B	-C16B	-177.8(8)
C11A	-C5A	-C6A	-O10A	-77.5(7)	C13B	-C12B	-C17B	-Cl1B	-177.8(6)
C20A	-C5A	-C6A	-O1A	-140.7(6)	C12B	-C13B	-C14B	-C15B	1.4(12)
C20A	-C5A	-C6A	-O10A	38.2(8)	C13B	-C14B	-C15B	-C16B	-0.3(13)
C4A	-C5A	-C11A	-C19A	-160.1(6)	C14B	-C15B	-C16B	-C17B	1.4(13)
C4A	-C5A	-C6A	-O1A	-16.3(8)	C15B	-C16B	-C17B	-Cl1B	178.8(7)
C11A	-C5A	-C20A	-C21A	-170.8(5)	C15B	-C16B	-C17B	-C12B	-3.9(13)
C4A	-C5A	-C11A	-C12A	68.4(7)	O3C	-C4C	-C5C	-C6C	19.0(8)
C6A	-C5A	-C20A	-C21A	74.6(7)	O3C	-C4C	-C5C	-C11C	-99.7(7)
C5A	-C11A	-C12A	-C13A	84.5(8)	O3C	-C4C	-C5C	-C20C	142.5(6)
C19A	-C11A	-C12A	-C17A	132.6(8)	O9C	-C4C	-C5C	-C6C	-162.7(7)

O9C	-C4C	-C5C	-C11C	78.6(8)	C11C	-C5C	-C20C	-C21C	-173.1(6)
O9C	-C4C	-C5C	-C20C	-39.2(9)	C5C	-C11C	-C12C	-C13C	82.3(8)
C4C	-C5C	-C6C	-O1C	-10.9(8)	C5C	-C11C	-C12C	-C17C	-95.0(9)
C4C	-C5C	-C6C	-O10C	166.3(6)	C19C	-C11C	-C12C	-C13C	-47.4(9)
C11C	-C5C	-C6C	-O1C	107.3(7)	C19C	-C11C	-C12C	-C17C	135.4(8)
C11C	-C5C	-C6C	-O10C	-75.5(7)	C11C	-C12C	-C13C	-C14C	-176.3(7)
C20C	-C5C	-C6C	-O1C	-133.8(6)	C17C	-C12C	-C13C	-C14C	1.3(11)
C20C	-C5C	-C6C	-O10C	43.4(8)	C11C	-C12C	-C17C	-Cl1C	-1.8(11)
C4C	-C5C	-C11C	-C12C	70.6(7)	C11C	-C12C	-C17C	-C16C	-178.5(8)
C4C	-C5C	-C11C	-C19C	-160.8(6)	C13C	-C12C	-C17C	-Cl1C	-179.1(6)
C6C	-C5C	-C11C	-C12C	-51.7(7)	C13C	-C12C	-C17C	-C16C	4.2(12)
C6C	-C5C	-C11C	-C19C	76.9(7)	C12C	-C13C	-C14C	-C15C	-6.1(12)
C20C	-C5C	-C11C	-C12C	-171.4(6)	C13C	-C14C	-C15C	-C16C	5.8(13)
C20C	-C5C	-C11C	-C19C	-42.8(8)	C14C	-C15C	-C16C	-C17C	-0.6(14)
C4C	-C5C	-C20C	-C21C	-56.6(8)	C15C	-C16C	-C17C	-Cl1C	178.4(7)
C6C	-C5C	-C20C	-C21C	68.7(8)	C15C	-C16C	-C17C	-C12C	-4.7(14)

Translation of Symmetry Code to Equiv.Pos

a =[2675.00] = [2_675] =1-x,2-y,-z
b =[2575.00] = [2_575] =-x,2-y,-z
c =[1564.00] = [1_564] =x,1+y,-1+z
d =[2684.00] = [2_684] =1-x,3-y,-1-z
e =[2676.00] = [2_676] =1-x,2-y,1-z
g =[1554.00] = [1_554] =x,y,-1+z
h =[1655.00] = [1_655] =1+x,y,z
i =[1455.00] = [1_455] =-1+x,y,z
j =[1563.00] = [1_563] =x,1+y,-2+z
k =[2575.00] = [2_575] =-x,2-y,-z
m =[2575.00] = [2_575] =-x,2-y,-z
o =[1556.00] = [1_556] =x,y,1+z
p =[2576.00] = [2_576] =-x,2-y,1-z
q =[2576.00] = [2_576] =-x,2-y,1-z
r =[1546.00] = [1_546] =x,-1+y,1+z
s =[2667.00] = [2_667] =1-x,1-y,2-z
t =[2567.00] = [2_567] =-x,1-y,2-z
u =[1556.00] = [1_556] =x,y,1+z
v =[2676.00] = [2_676] =1-x,2-y,1-z
w =[1547.00] = [1_547] =x,-1+y,2+z
x =[2676.00] = [2_676] =1-x,2-y,1-z

Appendix D

Crystallographic Data for 4.10a
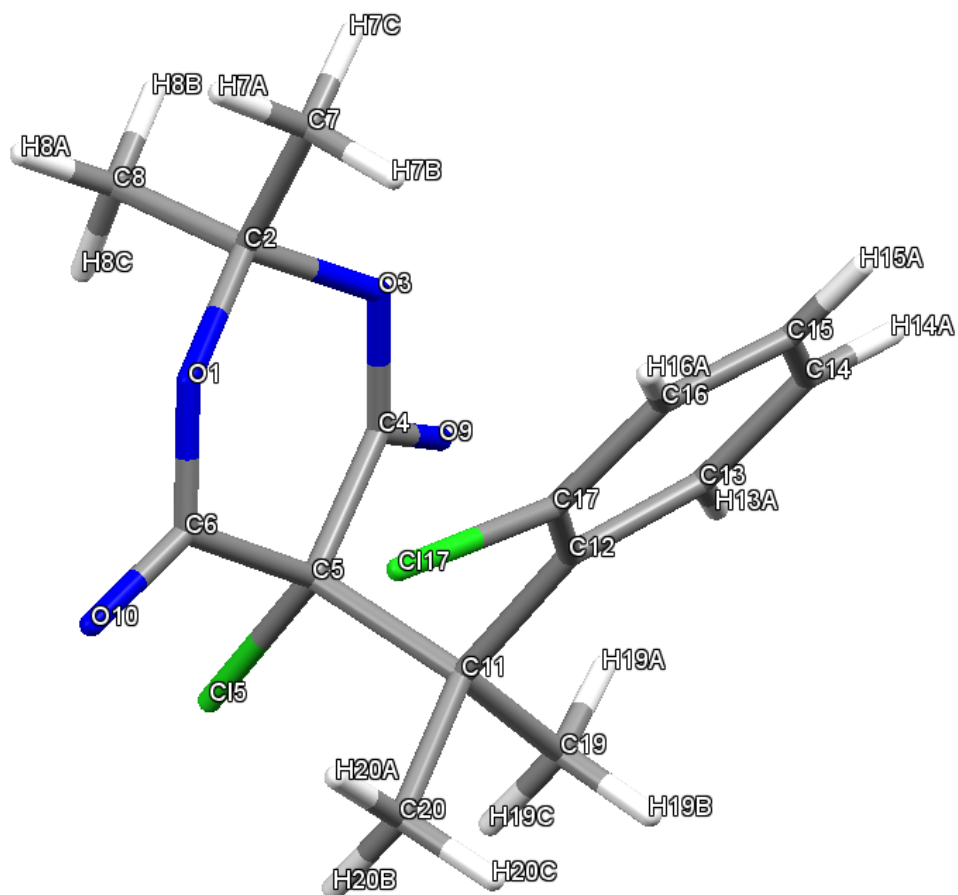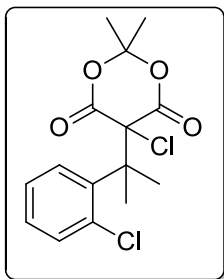
Table S1 - Crystal Data and Details of the Structure Determination for: 4.10a   R = 0.04

Formula	$C_{15}H_{16}Cl_2O_4$
Formula Weight	331.18
Crystal System	monoclinic
Space group	P21/c (No. 14)
a, b, c [Å]	9.3376(3) 12.8166(4) 12.8361(4)
α, β, γ[°]	90 94.9459(19) 90
V [Å³]	1530.46(8)
Z	4
D(calc) [g/cm³]	1.437
Mu(MoKa) [/mm]	0.436
F(000)	688
Crystal Size [mm]	0.02 x 0.30 x 0.42
Temperature (K)	200
Radiation [Å]	MoKa 0.71073
Theta Min-Max [°]	2.3, 28.0
Dataset	-12: 12 ; -16: 16 ; -16: 16
Tot., Uniq. Data, R(int)	14399, 3687, 0.018
Observed data [I > 2.0 sigma(I)]	2771
Refinement	
Nref, Npar	3687, 190
R, wR2, S	0.0401, 0.0924, 1.13
w = ^2^(FO^2^)+(0.0245P)^2^+0.7519P] WHERE P=(FO^2^+2FC^2^)/3'	
Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.35, 0.37

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: 4.10a

Atom	x	y	z	U(eq) [Ang^2]
Cl5	0.47883(6)	0.71070(4)	0.18603(5)	0.0565(2)
Cl17	0.29229(6)	0.39521(4)	0.41168(5)	0.0608(2)
O1	0.34213(15)	0.43273(10)	0.16419(12)	0.0559(5)
O3	0.15182(14)	0.54098(11)	0.09850(11)	0.0485(4)
O9	0.17494(18)	0.71129(11)	0.09835(11)	0.0601(6)
O10	0.53681(14)	0.49361(12)	0.24809(13)	0.0558(5)
C2	0.2298(2)	0.44753(15)	0.08285(15)	0.0407(6)
C4	0.2204(2	0.62936(15)	0.12950(13)	0.0381(6)
C5	0.34497(17)	0.61700(13)	0.21368(13)	0.0310(5)
C6	0.41924(18)	0.51077(14)	0.20958(14)	0.0361(5)
C7	0.1271(3)	0.3592(2)	0.0925(2)	0.0788(10)
C8	0.2914(3)	0.4550(2)	-0.02001(19)	0.0815(11)
C11	0.28785(17)	0.64050(13)	0.32595(12)	0.0306(5)
C12	0.15040(17)	0.57437(13)	0.33709(12)	0.0306(5)
C13	0.0154(2)	0.61962(15)	0.30679(15)	0.0418(6)
C14	-0.1131(2)	0.56980(18)	0.31521(17)	0.0507(7)
C15	-0.1152(2)	0.47007(18)	0.35496(16)	0.0508(7)
C16	0.0124(2)	0.42203(16)	0.38409(15)	0.0448(7)
C17	0.14235(19)	0.47233(14)	0.37462(13)	0.0360(6)
C19	0.2506(2)	0.75779(14)	0.33241(15)	0.0434(6)
C20	0.4080(2)	0.62304(17)	0.41379(15)	0.0482(7)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 4.10a

Atom	x	y	z	U(iso) [Ang^2]
H7A	0.17620	0.29290	0.08230	0.1180
H7B	0.09180	0.36030	0.16220	0.1180
H7C	0.04580	0.36660	0.03940	0.1180
H8A	0.34560	0.39140	-0.03230	0.1220
H8B	0.21340	0.46320	-0.07560	0.1220
H8C	0.35570	0.51550	-0.01990	0.1220
H13A	0.01340	0.68840	0.27900	0.0500
H14A	-0.20080	0.60420	0.29360	0.0610
H15A	-0.20380	0.43540	0.36200	0.0610
H16A	0.01230	0.35310	0.41130	0.0540
H19A	0.17390	0.77490	0.27810	0.0650
H19B	0.21820	0.77330	0.40140	0.0650
H19C	0.33610	0.79950	0.32180	0.0650
H20A	0.43750	0.54960	0.41450	0.0720
H20B	0.49050	0.66730	0.40170	0.0720
H20C	0.37260	0.64100	0.48120	0.0720

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for: 4.10a

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
Cl5	0.0595(3)	0.0435(3)	0.0707(4)	-0.0041(3)	0.0303(3)	-0.0173(2)
Cl17	0.0544(3)	0.0511(3)	0.0760(4)	0.0226(3)	0.0009(3)	0.0101(2)
O1	0.0582(9)	0.0331(7)	0.0715(10)	-0.0097(7)	-0.0219(7)	0.0073(6)
O3	0.0403(7)	0.0525(8)	0.0507(8)	-0.0153(7)	-0.0081(6)	0.0096(6)
O9	0.0889(12)	0.0482(9)	0.0414(8)	0.0028(7)	-0.0055(8)	0.0287(8)
O10	0.0310(7)	0.0565(9)	0.0784(10)	-0.0055(8)	-0.0035(7)	0.0094(6)
C2	0.0440(11)	0.0373(10)	0.0400(10)	-0.0070(8)	-0.0009(8)	0.0000(8)
C4	0.0473(11)	0.0403(10)	0.0273(9)	-0.0021(8)	0.0071(8)	0.0121(8)
C5	0.0312(8)	0.0281(8)	0.0344(9)	-0.0011(7)	0.0063(7)	-0.0028(7)
C6	0.0305(9)	0.0366(9)	0.0416(10)	-0.0015(8)	0.0055(8)	0.0018(7)
C7	0.0798(18)	0.0654(16)	0.0876(19)	0.0007(14)	-0.0132(15)	-0.0294(14)
C8	0.097(2)	0.096(2)	0.0557(15)	-0.0136(14)	0.0305(14)	0.0145(17)
C11	0.0319(9)	0.0323(9)	0.0276(8)	-0.0029(7)	0.0024(7)	-0.0026(7)
C12	0.0319(9)	0.0343(9)	0.0258(8)	-0.0037(7)	0.0038(7)	-0.0015(7)
C13	0.0401(10)	0.0422(10)	0.0436(11)	-0.0017(9)	0.0061(8)	0.0046(8)
C14	0.0312(10)	0.0666(14)	0.0540(12)	-0.0141(11)	0.0014(9)	0.0058(9)
C15	0.0396(11)	0.0639(14)	0.0504(12)	-0.0155(11)	0.0126(9)	-0.0170(10)
C16	0.0496(12)	0.0444(11)	0.0413(11)	-0.0036(9)	0.0091(9)	-0.0136(9)
C17	0.0375(10)	0.0394(10)	0.0310(9)	-0.0005(7)	0.0032(7)	0.0001(7)
C19	0.0541(12)	0.0330(9)	0.0445(11)	-0.0114(8)	0.0118(9)	-0.0034(8)
C20	0.0425(11)	0.0608(13)	0.0392(10)	-0.0040(9)	-0.0080(8)	-0.0074(9)

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms
T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for: 4.10a

Cl5	-C5	1.7908(17)	C14	-C15	1.377(3)
Cl17	-C17	1.7460(19)	C15	-C16	1.364(3)
O1	-C2	1.427(2)	C16	-C17	1.389(3)
O1	-C6	1.336(2)	C7	-H7A	0.9800
O3	-C2	1.425(2)	C7	-H7B	0.9800
O3	-C4	1.345(2)	C7	-H7C	0.9800
O9	-C4	1.189(2)	C8	-H8A	0.9800
O10	-C6	1.185(2)	C8	-H8B	0.9800
C2	-C7	1.496(3)	C8	-H8C	0.9800
C2	-C8	1.488(3)	C13	-H13A	0.9500
C4	-C5	1.526(2)	C14	-H14A	0.9500
C5	-C6	1.531(2)	C15	-H15A	0.9500
C5	-C11	1.608(2)	C16	-H16A	0.9500
C11	-C12	1.555(2)	C19	-H19A	0.9800
C11	-C19	1.547(2)	C19	-H19B	0.9800
C11	-C20	1.537(2)	C19	-H19C	0.9800
C12	-C13	1.411(2)	C20	-H20A	0.9800
C12	-C17	1.398(2)	C20	-H20B	0.9800
C13	-C14	1.372(3)	C20	-H20C	0.9800

Table S6 - Bond Angles   (°) 4.10a

C2	-O1	-C6	123.63(14)	C13	-C12	-C17	113.96(15)
C2	-O3	-C4	120.92(15)	C12	-C13	-C14	123.61(18)
O1	-C2	-O3	111.15(15)	C13	-C14	-C15	120.12(18)
O1	-C2	-C7	105.95(17)	C14	-C15	-C16	118.71(18)
O1	-C2	-C8	109.98(17)	C15	-C16	-C17	121.03(19)
O3	-C2	-C7	106.59(17)	Cl17	-C17	-C12	123.90(13)
O3	-C2	-C8	108.20(17)	Cl17	-C17	-C16	113.55(14)
C7	-C2	-C8	114.95(19)	C12	-C17	-C16	122.54(17)
O3	-C4	-O9	119.83(17)	C2	-C7	-H7A	110.00
O3	-C4	-C5	115.89(15)	C2	-C7	-H7B	109.00
O9	-C4	-C5	123.92(17)	C2	-C7	-H7C	109.00
Cl5	-C5	-C4	107.01(12)	H7A	-C7	-H7B	109.00
Cl5	-C5	-C6	105.28(11)	H7A	-C7	-H7C	110.00
Cl5	-C5	-C11	110.07(11)	H7B	-C7	-H7C	109.00
C4	-C5	-C6	112.82(14)	C2	-C8	-H8A	110.00
C4	-C5	-C11	108.89(13)	C2	-C8	-H8B	109.00
C6	-C5	-C11	112.56(13)	C2	-C8	-H8C	109.00
O1	-C6	-O10	119.20(17)	H8A	-C8	-H8B	109.00
O1	-C6	-C5	116.87(14)	H8A	-C8	-H8C	109.00
O10	-C6	-C5	123.84(17)	H8B	-C8	-H8C	109.00
C5	-C11	-C12	108.70(12)	C12	-C13	-H13A	118.00
C5	-C11	-C19	108.88(13)	C14	-C13	-H13A	118.00
C5	-C11	-C20	110.66(13)	C13	-C14	-H14A	120.00
C12	-C11	-C19	109.49(13)	C15	-C14	-H14A	120.00
C12	-C11	-C20	114.16(14)	C14	-C15	-H15A	121.00
C19	-C11	-C20	104.80(14)	C16	-C15	-H15A	121.00
C11	-C12	-C13	118.38(15)	C15	-C16	-H16A	119.00
C11	-C12	-C17	127.66(15)	C17	-C16	-H16A	120.00
C11	-C19	-H19A	109.00	C11	-C20	-H20A	109.00
C11	-C19	-H19B	109.00	C11	-C20	-H20B	109.00
C11	-C19	-H19C	109.00	C11	-C20	-H20C	109.00
H19A	-C19	-H19B	109.00	H20A	-C20	-H20B	109.00
H19A	-C19	-H19C	109.00	H20A	-C20	-H20C	109.00
H19B	-C19	-H19C	109.00	H20B	-C20	-H20C	109.00

Table S7 - Torsion Angles (°) 4.10a

C6	-O1	-C2	-O3	-36.1(2)	O9	-C4	-C5	-C6	-157.60(18)
C6	-O1	-C2	-C7	-151.47(18)	O9	-C4	-C5	-C11	76.7(2)
C6	-O1	-C2	-C8	83.7(2)	Cl5	-C5	-C6	-O1	-139.61(14)
C2	-O1	-C6	-O10	-154.40(18)	Cl5	-C5	-C6	-O10	43.9(2)
C2	-O1	-C6	-C5	29.0(2)	C4	-C5	-C6	-O1	-23.3(2)
C4	-O3	-C2	-O1	42.4(2)	C4	-C5	-C6	-O10	160.29(18)
C4	-O3	-C2	-C7	157.38(17)	C11	-C5	-C6	-O1	100.47(18)
C4	-O3	-C2	-C8	-78.5(2)	C11	-C5	-C6	-O10	-76.0(2)
C2	-O3	-C4	-O9	145.24(18)	Cl5	-C5	-C11	-C12	167.77(11)
C2	-O3	-C4	-C5	-41.4(2)	Cl5	-C5	-C11	-C19	48.56(15)
O3	-C4	-C5	-Cl5	144.62(13)	Cl5	-C5	-C11	-C20	-66.12(16)
O3	-C4	-C5	-C6	29.3(2)	C4	-C5	-C11	-C12	50.76(17)
O3	-C4	-C5	-C11	-96.44(17)	C4	-C5	-C11	-C19	-68.45(17)
O9	-C4	-C5	-Cl5	-42.3(2)	C4	-C5	-C11	-C20	176.88(15)

C6	-C5	-C11	-C12	-75.12(16)	C17	-C12	-C13	-C14	1.4(3)
C6	-C5	-C11	-C19	165.67(14)	C11	-C12	-C17	-Cl17	-3.3(2)
C6	-C5	-C11	-C20	51.00(19)	C11	-C12	-C17	-C16	177.93(16)
C5	-C11	-C12	-C13	-92.41(17)	C13	-C12	-C17	-Cl17	176.83(13)
C5	-C11	-C12	-C17	87.68(19)	C13	-C12	-C17	-C16	-2.0(2)
C19	-C11	-C12	-C13	26.4(2)	C12	-C13	-C14	-C15	0.0(3)
C19	-C11	-C12	-C17	-153.49(16)	C13	-C14	-C15	-C16	-0.9(3)
C20	-C11	-C12	-C13	143.54(16)	C14	-C15	-C16	-C17	0.3(3)
C20	-C11	-C12	-C17	-36.4(2)	C15	-C16	-C17	-Cl17	-177.73(16)
C11	-C12	-C13	-C14	-178.50(18)	C15	-C16	-C17	-C12	1.2(3)

Table S8 - Contact Distances(Å) 4.10a

Cl5	.O9	2.9611(17)	O9	.Cl5	2.9611(17)	C7	.C4	3.592(3)	C19	.C4	3.074(3)
Cl5	.O10	2.9317(16)	O10	.Cl17	3.4698(16)	C8	.C4	3.056(3)	C19	.C13	2.818(3)
Cl5	.C19	3.021(2)	O10	.C11	3.217(2)	C8	.C6	3.165(3)	C19	.O9	3.085(2)
Cl5	.C20	3.253(2)	O10	.Cl5	2.9317(16)	C11	.O10	3.217(2)	C20	.Cl17_d	3.439(2)
Cl5	.Cl17_a	3.4921(8)	O10	.C20	3.027(3)	C11	.Cl17	3.3299(17)	C20	.O10	3.027(3)
Cl17	.C11	3.3299(17)	O1	.H8A	2.5800	C11	.O9	3.153(2)	C20	.C6	3.000(3)
Cl17	.C20	3.113(2)	O1	.H8C	2.6000	C11	.O3	3.335(2)	C20	.Cl17	3.113(2)
Cl17	.C6	3.2953(19)	O1	.H7A	2.5400	C12	.C15	2.844(3)	C20	.C17	3.150(3)
Cl17	.O1	3.2856(17)	O1	.H7B	2.5100	C12	.O3	3.094(2)	C20	.Cl5	3.253(2)
Cl17	.O10	3.4698(16)	O3	.H7C	2.5300	C12	.C6	3.218(2)	C4	.H8C	2.8000
Cl17	.C20_d	3.439(2)	O3	.H8B	2.5600	C12	.C4	2.885(2)	C4	.H19A	2.7300
Cl17	.Cl5_c	3.4921(8)	O3	.H7C_e	2.7200	C13	.C16	2.721(3)	C4	.H13A	2.9400
Cl5	.H19C	2.5500	O3	.H7B	2.5300	C13	.C4	3.100(3)	C5	.H19C	2.7200
Cl5	.H8A_b	2.9800	O3	.H8C	2.5600	C13	.C19	2.818(3)	C5	.H19A	2.7500
Cl5	.H20B	2.8200	O9	.H7C_e	2.7800	C13	.O9	3.383(2)	C5	.H20A	2.7800
Cl17	.H20A	2.4000	O9	.H19B_g	2.6000	C13	.O3	3.221(2)	C5	.H20B	2.7400
Cl17	.H16A	2.6700	O9	.H13A	2.8900	C6	.H20A	2.6700	H7B	.H13A_i	2.5500
Cl17	.H20B_d	3.1100	O9	.H19A	2.4500	C6	.H8C	2.9500	H7C	.O3	2.5300
O1	.Cl17	3.2856(17)	O9	.H16A_f	2.5200	C7	.H8B	2.7200	H7C	.C8	2.7300
O1	.C4	2.785(2)	O10	.H14A_h	2.8500	C7	.H8A	2.7300	H7C	.H8B	2.5600
O3	.C13	3.221(2)	O10	.H15A_h	2.8200	C7	.H13A_i	3.1000	H7C	.O3_e	2.7200
O3	.C6	2.794(2)	O10	.H20A	2.5100	C8	.H7A	2.7300	H7C	.O9_e	2.7800
O3	.C11	3.335(2)	C2	.C5	2.895(3)	C8	.H7C	2.7300	H8A	.O1	2.5800
O3	.C12	3.094(2)	C4	.O1	2.785(2)	C11	.H13A	2.6500	H8A	.C7	2.7300
O9	.C19	3.085(2)	C4	.C7	3.592(3)	C12	.H20A	2.8000	H8A	.H7A	2.5800
O9	.C11	3.153(2)	C4	.C8	3.056(3)	C12	.H19B	2.7400	H8A	.Cl5_b	2.9800
O9	.C16_f	3.236(2)	C4	.C12	2.885(2)	C12	.H19A	2.6900	H8B	.O3	2.5600
O9	.C13	3.383(2)	C4	.C13	3.100(3)	C12	.H20C	2.7900	H8B	.C7	2.7200
C4	.C19	3.074(3)	C13	.C5	3.396(2)	C13	.H19B	2.9200	H8B	.H7C	2.5600
C5	.C2	2.895(3)	C14	.C17	2.742(3)	C13	.H19A	2.5300	H8C	.O1	2.6000
C5	.C13	3.396(2)	C15	.C12	2.844(3)	C15	.H19A_i	3.0500	H8C	.O3	2.5600
C5	.C17	3.458(2)	C15	.C17_j	3.579(3)	C17	.H20A	2.9300	H8C	.C4	2.8000
C6	.C17	3.516(2)	C16	.O9_i	3.236(3)	C17	.H7B	3.0800	H8C	.C6	2.9500
C6	.C20	3.000(3)	C16	.C13	2.721(3)	C19	.H20C	2.6100	H13A	.O9	2.8900
C6	.O3	2.794(2)	C17	.C15_j	3.579(3)	C19	.H20B	2.6100	H13A	.C4	2.9400
C6	.C8	3.165(3)	C17	.C6	3.516(2)	C19	.H13A	2.4300	H13A	.C11	2.6500
C6	.C12	3.218(2)	C17	.C14	2.742(3)	C20	.H19B	2.6100	H13A	.C19	2.4300
C6	.C7	3.573(3)	C17	.C5	3.458(2)	C20	.H19C	2.6100	H13A	.H14A	2.2900
C6	.Cl17	3.2953(19)	C17	.C20	3.150(3)	H7A	.O1	2.5400	H13A	.H19A	1.8700
C7	.C6	3.573(3)	C19	.Cl5	3.021(2)	H7A	.C8	2.7300	H13A	.C7_f	3.1000

H7A	.H8A	2.5800	H13A	.H7B_f	2.5500
H7B	.O1	2.5100	H14A	.O10_k	2.8500
H7B	.O3	2.5300	H14A	.H13A	2.2900
H7B	.C17	3.0800	H14A	.H15A	2.3400
H15A	.O10_k	2.8200	H19C	.Cl5	2.5500
H15A	.H14A	2.3400	H19C	.C5	2.7200
H15A	.H16A	2.3200	H19C	.C20	2.6100
H16A	.Cl17	2.6700	H19C	.H20B	2.4000
H16A	.H15A	2.3200	H20A	.Cl17	2.4000
H16A	.O9_i	2.5200	H20A	.O10	2.5100
H19A	.O9	2.4500	H20A	.C5	2.7800

H19A	.C4	2.7300	H20A	.C6	2.6700
H19A	.C5	2.7500	H20A	.C12	2.8000
H19A	.C12	2.6900	H20A	.C17	2.9300
H19A	.C13	2.5300	H20B	.Cl5	2.8200
H19A	.H13A	1.8700	H20B	.C5	2.7400
H19A	.C15_f	3.0500	H20B	.C19	2.6100
H19B	.C12	2.7400	H20B	.H19C	2.4000
H19B	.C13	2.9200	H20B	.Cl17_d	3.1100
H19B	.C20	2.6100	H20C	.C12	2.7900
H19B	.H20C	2.4000	H20C	.C19	2.6100
H19B	.O9_l	2.6000	H20C	.H19B	2.4000

Translation of Symmetry Code to Equiv.Pos

a =[2655.00] = [2_655] =1-x,1/2+y,1/2-z
b =[3665.00] = [3_665] =1-x,1-y,-z
c =[2645.00] = [2_645] =1-x,-1/2+y,1/2-z
d =[3666.00] = [3_666] =1-x,1-y,1-z
e =[3565.00] = [3_565] =-x,1-y,-z
f =[2555.00] = [2_555] =-x,1/2+y,1/2-z
g =[4564.00] = [4_575] =x,3/2-y,-1/2+z
h =[1655.00] = [1_655] =1+x,y,z
i =[2545.00] = [2_545] =-x,-1/2+y,1/2-z
j =[3566.00] = [3_566] =-x,1-y,1-z
k =[1455.00] = [1_455] =-1+x,y,z
l =[4565.00] = [4_576] =x,3/2-y,1/2+z
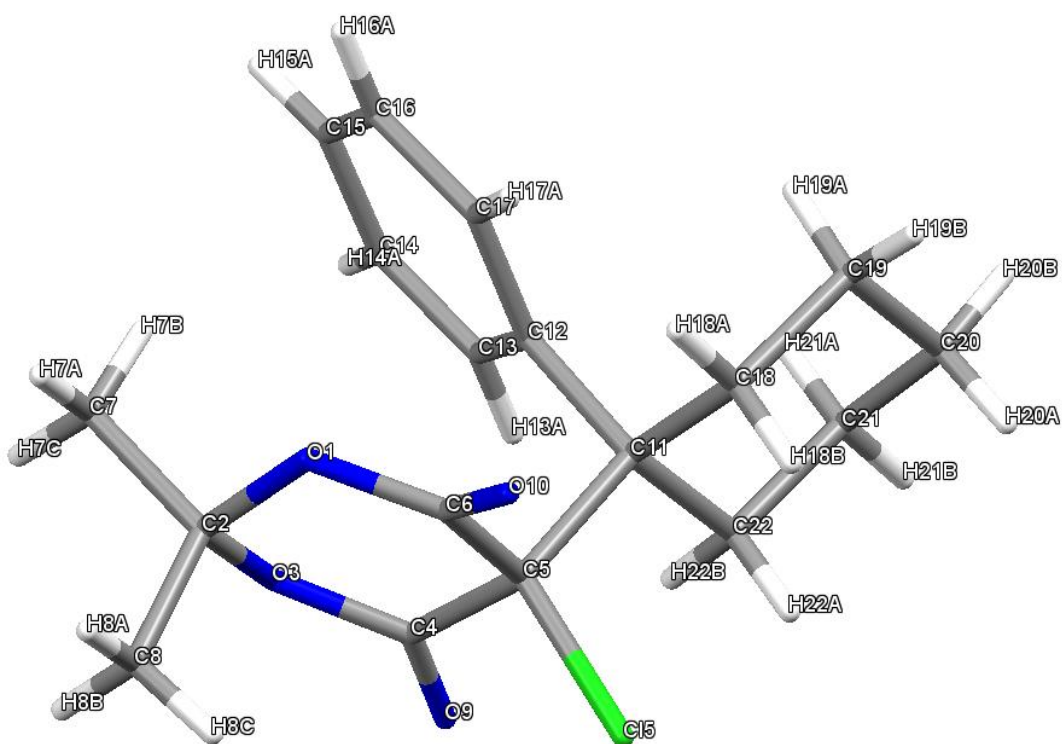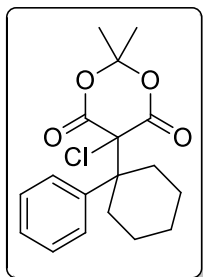
Table S1 - Crystal Data and Details of the Structure Determination for: 4.14a   R = 0.03

Crystal Data

Formula	$C_{18} H_{21} Cl O_4$
Formula Weight	336.80
Crystal System	orthorhombic
Space group	Pca21 (No. 29)
a, b, c [Å]	12.7415(2) 14.6484(3) 9.1996(2)
V [Å³]	1717.04(6)
Z	4
D(calc) [g/cm**3]	1.303
Mu(MoKa) [/mm]	0.240
F(000)	712
Crystal Size [mm]	0.04 x 0.24 x 0.42

Data Collection

Temperature (K)	296
Radiation [Å]	MoKa 0.71073
Theta Min-Max [°]	1.4, 28.0
Dataset	-16: 16 ; -19: 19 ; -7: 12
Tot., Uniq. Data, R(int)	16882, 2890, 0.025
Observed data [I > 2.0 sigma(I)]	2599

Refinement

Nref, Npar	2890, 208
R, wR2, S	0.0327, 0.0963, 1.51
w = ^2^(FO^2^)+(0.0366P)^2^+0.0872P] WHERE P=(FO^2^+2FC^2^)/3'	
Max. and Av. Shift/Error	0.00, 0.00
Flack x	0.01(2)
Min. and Max. Resd. Dens. [e/Ang^3]	-0.21, 0.28

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: 4.14a

Atom	x	y	z	U(eq) [Å^2]
Cl5	0.63703(6)	0.30785(6)	0.19944(8)	0.0670(3)
O1	0.36915(13)	0.34817(13)	0.3658(2)	0.0547(6)
O3	0.49643(15)	0.41379(13)	0.5200(2)	0.0600(7)
O9	0.66409(16)	0.38746(14)	0.4944(3)	0.0749(8)
O10	0.41263(17)	0.26552(16)	0.1780(2)	0.0718(8)
C2	0.3971(2)	0.42639(16)	0.4506(3)	0.0510(8)
C4	0.5767(2)	0.37010(17)	0.4587(3)	0.0484(8)
C5	0.55012(18)	0.29361(16)	0.3504(2)	0.0406(7)
C6	0.4393(2)	0.30272(18)	0.2867(3)	0.0451(8)
C7	0.3175(3)	0.4338(2)	0.5703(4)	0.0760(11)
C8	0.4030(3)	0.5086(2)	0.3535(4)	0.0812(14)
C11	0.56448(19)	0.19613(16)	0.4286(2)	0.0400(7)
C12	0.49906(19)	0.20038(14)	0.5690(3)	0.0409(7)
C13	0.5412(2)	0.23113(18)	0.6997(3)	0.0524(8)
C14	0.4807(3)	0.23910(19)	0.8238(3)	0.0663(12)
C15	0.3757(3)	0.2168(2)	0.8198(3)	0.0662(11)
C16	0.3332(2)	0.18502(19)	0.6950(4)	0.0614(10)
C17	0.3935(2)	0.17597(17)	0.5698(3)	0.0481(8)
C18	0.5296(2)	0.11822(17)	0.3273(3)	0.0533(8)
C19	0.5491(3)	0.0241(2)	0.3952(4)	0.0734(11)
C20	0.6632(3)	0.0103(2)	0.4347(4)	0.0838(15)
C21	0.7015(3)	0.0876(2)	0.5305(4)	0.0750(11)
C22	0.6822(2)	0.17959(19)	0.4606(4)	0.0560(9)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 4.14a

Atom	x	y	z	U(iso) [Å^2]
H7A	0.24900	0.44230	0.52900	0.1140
H7B	0.31820	0.37880	0.62710	0.1140
H7C	0.33440	0.48480	0.63130	0.1140
H8A	0.33650	0.51750	0.30650	0.1220
H8B	0.41980	0.56150	0.41050	0.1220
H8C	0.45640	0.49930	0.28140	0.1220
H13A	0.61190	0.24670	0.70370	0.0630
H14A	0.51080	0.25950	0.90990	0.0790
H15A	0.33440	0.22350	0.90240	0.0800
H16A	0.26260	0.16900	0.69280	0.0740
H17A	0.36280	0.15330	0.48550	0.0580
H18A	0.45540	0.12480	0.30620	0.0640
H18B	0.56770	0.12260	0.23630	0.0640
H19A	0.50640	0.01780	0.48200	0.0880
H19B	0.52780	-0.02290	0.32710	0.0880
H20A	0.70520	0.00780	0.34680	0.1000
H20B	0.67130	-0.04730	0.48550	0.1000
H21A	0.66560	0.08500	0.62330	0.0900
H21B	0.77610	0.08020	0.54840	0.0900

H22A	0.72140	0.18330	0.37050	0.0670
H22B	0.70770	0.22720	0.52480	0.0670

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for: 4.14a

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
Cl5	0.0585(4)	0.0846(5)	0.0578(4)	0.0065(4)	0.0253(3)	0.0050(3)
O1	0.0422(9)	0.0598(11)	0.0620(12)	-0.0087(9)	-0.0012(8)	0.0077(8)
O3	0.0659(12)	0.0589(11)	0.0552(11)	-0.0180(9)	-0.0074(9)	0.0129(9)
O9	0.0571(12)	0.0640(12)	0.1035(17)	-0.0157(13)	-0.0153(11)	-0.0183(10)
O10	0.0652(13)	0.1033(17)	0.0470(11)	-0.0192(11)	-0.0150(9)	0.0066(11)
C2	0.0556(14)	0.0435(13)	0.0539(15)	0.0007(12)	0.0025(12)	0.0104(12)
C4	0.0473(14)	0.0436(13)	0.0542(14)	-0.0037(12)	-0.0015(11)	-0.0079(11)
C5	0.0356(11)	0.0502(13)	0.0361(11)	-0.0057(9)	0.0062(9)	-0.0010(10)
C6	0.0440(13)	0.0529(15)	0.0385(12)	-0.0011(10)	-0.0014(10)	0.0010(11)
C7	0.088(2)	0.0609(18)	0.079(2)	0.0032(16)	0.0306(18)	0.0200(17)
C8	0.108(3)	0.0625(19)	0.073(2)	0.0197(17)	0.0052(19)	0.0020(19)
C11	0.0380(11)	0.0429(12)	0.0391(12)	-0.0081(9)	-0.0042(9)	0.0002(9)
C12	0.0472(13)	0.0375(11)	0.0381(11)	-0.0017(9)	-0.0016(9)	-0.0004(10)
C13	0.0649(16)	0.0498(14)	0.0425(13)	-0.0039(11)	-0.0047(12)	-0.0073(12)
C14	0.110(3)	0.0535(16)	0.0353(13)	-0.0020(12)	0.0030(14)	-0.0027(17)
C15	0.088(2)	0.0564(17)	0.0541(18)	0.0116(14)	0.0265(15)	0.0102(16)
C16	0.0569(15)	0.0578(16)	0.0695(19)	0.0178(14)	0.0160(17)	0.0042(12)
C17	0.0459(13)	0.0487(14)	0.0498(14)	0.0055(11)	-0.0005(11)	-0.0011(11)
C18	0.0579(15)	0.0529(15)	0.0492(14)	-0.0164(12)	-0.0060(11)	0.0011(12)
C19	0.094(2)	0.0463(15)	0.080(2)	-0.0188(15)	-0.0132(18)	0.0026(15)
C20	0.102(3)	0.0583(19)	0.091(3)	-0.0140(17)	-0.017(2)	0.0280(18)
C21	0.0690(19)	0.072(2)	0.084(2)	-0.0110(17)	-0.0222(17)	0.0261(16)
C22	0.0398(13)	0.0638(17)	0.0643(16)	-0.0120(14)	-0.0053(12)	0.0081(12)

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms
T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for: 4.14a

Cl5	-C5	1.788(2)	C20	-C21	1.516(5)
O1	-C2	1.431(3)	C21	-C22	1.513(4)
O1	-C6	1.331(3)	C7	-H7A	0.9600
O3	-C2	1.430(3)	C7	-H7B	0.9600
O3	-C4	1.332(3)	C7	-H7C	0.9600
O9	-C4	1.188(3)	C8	-H8A	0.9600
O10	-C6	1.188(3)	C8	-H8B	0.9600
C2	-C7	1.501(5)	C8	-H8C	0.9600
C2	-C8	1.501(4)	C13	-H13A	0.9300
C4	-C5	1.537(3)	C14	-H14A	0.9300
C5	-C6	1.535(3)	C15	-H15A	0.9300
C5	-C11	1.609(3)	C16	-H16A	0.9300

C11	-C12	1.539(3)		C17	-H17A	0.9300
C11	-C18	1.539(3)		C18	-H18A	0.9700
C11	-C22	1.548(4)		C18	-H18B	0.9700
C12	-C13	1.392(4)		C19	-H19A	0.9700
C12	-C17	1.392(3)		C19	-H19B	0.9700
C13	-C14	1.383(4)		C20	-H20A	0.9700
C14	-C15	1.378(5)		C20	-H20B	0.9700
C15	-C16	1.352(5)		C21	-H21A	0.9700
C16	-C17	1.391(4)		C21	-H21B	0.9700
C18	-C19	1.534(4)		C22	-H22A	0.9700
C19	-C20	1.512(5)		C22	-H22B	0.9700

Table S6 - Bond Angles   (°) for: 4.14a

C2	-O1	-C6	122.1(2)	C13	-C12	-C17	116.8(2)
C2	-O3	-C4	123.6(2)	C12	-C13	-C14	121.7(3)
O1	-C2	-O3	111.12(19)	C13	-C14	-C15	120.0(3)
O1	-C2	-C7	106.8(2)	C14	-C15	-C16	119.6(3)
O1	-C2	-C8	109.3(2)	C15	-C16	-C17	121.0(3)
O3	-C2	-C7	106.3(2)	C12	-C17	-C16	120.9(3)
O3	-C2	-C8	109.0(2)	C11	-C18	-C19	111.9(2)
C7	-C2	-C8	114.4(2)	C18	-C19	-C20	112.0(3)
O3	-C4	-O9	120.0(3)	C19	-C20	-C21	110.5(3)
O3	-C4	-C5	117.1(2)	C20	-C21	-C22	111.5(3)
O9	-C4	-C5	122.8(2)	C11	-C22	-C21	112.2(2)
Cl5	-C5	-C4	106.37(16)	C2	-C7	-H7A	109.00
Cl5	-C5	-C6	105.25(15)	C2	-C7	-H7B	109.00
Cl5	-C5	-C11	112.35(15)	C2	-C7	-H7C	110.00
C4	-C5	-C6	112.8(2)	H7A	-C7	-H7B	109.00
C4	-C5	-C11	109.39(17)	H7A	-C7	-H7C	110.00
C6	-C5	-C11	110.64(19)	H7B	-C7	-H7C	109.00
O1	-C6	-O10	119.8(2)	C2	-C8	-H8A	109.00
O1	-C6	-C5	116.9(2)	C2	-C8	-H8B	109.00
O10	-C6	-C5	123.0(2)	C2	-C8	-H8C	109.00
C5	-C11	-C12	106.13(17)	H8A	-C8	-H8B	109.00
C5	-C11	-C18	110.76(17)	H8A	-C8	-H8C	109.00
C5	-C11	-C22	109.5(2)	H8B	-C8	-H8C	110.00
C12	-C11	-C18	112.5(2)	C12	-C13	-H13A	119.00
C12	-C11	-C22	111.8(2)	C14	-C13	-H13A	119.00
C18	-C11	-C22	106.2(2)	C13	-C14	-H14A	120.00
C11	-C12	-C13	122.0(2)	C15	-C14	-H14A	120.00
C11	-C12	-C17	121.2(2)	C14	-C15	-H15A	120.00
C16	-C15	-H15A	120.00	C19	-C20	-H20A	110.00
C15	-C16	-H16A	120.00	C19	-C20	-H20B	110.00
C17	-C16	-H16A	119.00	C21	-C20	-H20A	110.00
C12	-C17	-H17A	120.00	C21	-C20	-H20B	110.00
C16	-C17	-H17A	119.00	H20A	-C20	-H20B	108.00
C11	-C18	-H18A	109.00	C20	-C21	-H21A	109.00
C11	-C18	-H18B	109.00	C20	-C21	-H21B	109.00
C19	-C18	-H18A	109.00	C22	-C21	-H21A	109.00
C19	-C18	-H18B	109.00	C22	-C21	-H21B	109.00
H18A	-C18	-H18B	108.00	H21A	-C21	-H21B	108.00
C18	-C19	-H19A	109.00	C11	-C22	-H22A	109.00
C18	-C19	-H19B	109.00	C11	-C22	-H22B	109.00

C20	-C19	-H19A	109.00		C21	-C22	-H22A	109.00	
C20	-C19	-H19B	109.00		C21	-C22	-H22B	109.00	
H19A	-C19	-H19B	108.00		H22A	-C22	-H22B	108.00	

Table S7 - Torsion Angles (°) for: 4.14a

C6	-O1	-C2	-O3	-39.9(3)		C6	-C5	-C11	-C12	-71.9(2)
C6	-O1	-C2	-C7	-155.4(2)		C6	-C5	-C11	-C18	50.4(2)
C6	-O1	-C2	-C8	80.4(3)		C6	-C5	-C11	-C22	167.2(2)
C2	-O1	-C6	-O10	-149.4(3)		C5	-C11	-C12	-C13	-89.7(3)
C2	-O1	-C6	-C5	36.4(3)		C5	-C11	-C12	-C17	88.4(2)
C4	-O3	-C2	-O1	36.6(3)		C18	-C11	-C12	-C13	149.1(2)
C4	-O3	-C2	-C7	152.5(2)		C18	-C11	-C12	-C17	-32.9(3)
C4	-O3	-C2	-C8	-83.8(3)		C22	-C11	-C12	-C13	29.7(3)
C2	-O3	-C4	-O9	154.1(3)		C22	-C11	-C12	-C17	-152.3(2)
C2	-O3	-C4	-C5	-30.0(3)		C5	-C11	-C18	-C19	176.3(2)
O3	-C4	-C5	-Cl5	136.5(2)		C12	-C11	-C18	-C19	-65.2(3)
O3	-C4	-C5	-C6	21.7(3)		C22	-C11	-C18	-C19	57.5(3)
O3	-C4	-C5	-C11	-101.9(2)		C5	-C11	-C22	-C21	-178.4(2)
O9	-C4	-C5	-Cl5	-47.7(3)		C12	-C11	-C22	-C21	64.3(3)
O9	-C4	-C5	-C6	-162.5(3)		C18	-C11	-C22	-C21	-58.7(3)
O9	-C4	-C5	-C11	73.9(3)		C11	-C12	-C13	-C14	176.7(2)
Cl5	-C5	-C6	-O1	-140.4(2)		C17	-C12	-C13	-C14	-1.4(4)
Cl5	-C5	-C6	-O10	45.6(3)		C11	-C12	-C17	-C16	-176.2(2)
C4	-C5	-C6	-O1	-24.9(3)		C13	-C12	-C17	-C16	2.0(4)
C4	-C5	-C6	-O10	161.2(3)		C12	-C13	-C14	-C15	-0.4(4)
C11	-C5	-C6	-O1	98.0(2)		C13	-C14	-C15	-C16	1.7(4)
C11	-C5	-C6	-O10	-76.0(3)		C14	-C15	-C16	-C17	-1.1(4)
Cl5	-C5	-C11	-C12	170.80(15)		C15	-C16	-C17	-C12	-0.8(4)
Cl5	-C5	-C11	-C18	-66.9(2)		C11	-C18	-C19	-C20	-57.4(3)
Cl5	-C5	-C11	-C22	49.9(2)		C18	-C19	-C20	-C21	53.8(4)
C4	-C5	-C11	-C12	52.9(2)		C19	-C20	-C21	-C22	-54.6(4)
C4	-C5	-C11	-C18	175.24(19)		C20	-C21	-C22	-C11	59.0(4)
C4	-C5	-C11	-C22	-68.0(2)						

Table S8 - Contact Distances(Å) for: 4.14a

Cl5	.O9	2.974(3)	O10	.C18	2.960(3)	O3	.C12	3.159(3)	O10	.H16A_g	2.6500
Cl5	.O10	2.932(2)	O1	.H8A	2.5700	O9	.C22	3.070(3)	C2	.C5	2.904(3)
Cl5	.C18	3.313(3)	O1	.H8C	2.6000	O9	.C11	3.136(3)	C4	.O1	2.798(3)
Cl5	.C22	3.104(3)	O1	.H7B	2.5300	O9	.Cl5_d	3.367(2)	C4	.C7	3.582(5)
Cl5	.O9_b	3.367(2)	O1	.H7A	2.5500	O9	.C13	3.356(4)	C4	.C8	3.155(4)
Cl5	.H22A	2.6400	O3	.H8B	2.5800	O9	.C7_e	3.341(4)	C4	.C12	2.862(3)
Cl5	.H7C_a	3.1200	O3	.H7B	2.5300	O9	.Cl5	2.974(3)	C4	.C13	3.044(4)
Cl5	.H18B	2.8700	O3	.H8C_c	2.7900	O10	.C15_f	3.404(3)	C4	.C22	3.098(4)
Cl5	.H22B_b	2.8100	O3	.H7C	2.5300	O10	.C14_f	3.394(3)	C5	.C2	2.904(3)
O1	.C4	2.798(3)	O3	.H8C	2.5800	O10	.C16_g	3.351(3)	C5	.C13	3.343(3)
O1	.C11	3.389(3)	O9	.H7A_e	2.7400	O10	.Cl5	2.932(2)	C5	.C17	3.321(3)
O1	.C12	3.305(3)	O9	.H22B	2.4300	O10	.C11	3.177(3)	C6	.C18	2.961(4)
O1	.C17	3.159(3)	O9	.H13A	2.9000	C6	.C17	3.251(4)	C13	.C4	3.044(4)
O3	.C13	3.197(3)	O10	.H15A_f	2.7900	C6	.C7	3.592(4)	C14	.C17	2.748(4)
O3	.C6	2.790(3)	O10	.H18A	2.4400	C6	.C12	3.094(4)	C14	.O10_i	3.394(3)
O3	.C11	3.410(3)	O10	.H14A_f	2.7700	C6	.O3	2.790(3)	C15	.C12	2.802(4)

C6	.C8	3.112(4)	C15	.C20_j	3.526(4)	C13	.H21A	2.7500	H7C	.C8	2.7200
C7	.O9_h	3.341(4)	C15	.O10_i	3.404(3)	C13	.H22B	2.6600	H7C	.H8B	2.5600
C7	.C6	3.592(4)	C16	.O10_k	3.351(3)	H7C	.Cl5_c	3.1200	H16A	.O10_k	2.6500
C7	.C4	3.582(5)	C16	.C13	2.735(4)	H8A	.O1	2.5700	H17A	.C6	3.0100
C8	.C4	3.155(4)	C17	.C18	2.950(4)	H8A	.C7	2.7300	H17A	.C11	2.7000
C8	.C6	3.112(4)	C17	.C6	3.251(4)	H8A	.H7A	2.5800	H17A	.C18	2.6300
C11	.C20	2.999(4)	C17	.O1	3.159(3)	H8B	.O3	2.5800	H17A	.H16A	2.3100
C11	.O1	3.389(3)	C17	.C14	2.748(4)	H8B	.C7	2.7100	H17A	.H18A	2.0700
C11	.O9	3.136(3)	C17	.C5	3.321(3)	H8B	.H7C	2.5600	H18A	.O10	2.4400
C11	.O10	3.177(3)	C17	.C19	3.385(4)	H8C	.O1	2.6000	H18A	.C5	2.7800
C11	.O3	3.410(3)	C18	.C21	2.914(5)	H8C	.O3	2.5800	H18A	.C6	2.6200
C12	.C6	3.094(4)	C18	.O10	2.960(3)	H8C	.C4	2.9300	H18A	.C12	2.7200
C12	.O1	3.305(3)	C18	.C17	2.950(4)	H8C	.C6	2.8900	H18A	.C17	2.6600
C12	.O3	3.159(3)	C18	.C6	2.961(4)	H8C	.O3_a	2.7900	H18A	.H17A	2.0700
C12	.C4	2.862(3)	C18	.Cl5	3.313(3)	H13A	.O9	2.9000	H18A	.H19A	2.3400
C12	.C15	2.802(4)	C19	.C22	2.903(4)	H13A	.C4	2.9200	H18A	.H19B	2.3600
C12	.C19	3.103(4)	C19	.C12	3.103(4)	H13A	.C11	2.7100	H18B	.Cl5	2.8700
C12	.C21	3.084(4)	C19	.C17	3.385(4)	H13A	.C21	3.0500	H18B	.C5	2.7300
C13	.O9	3.356(4)	C20	.C11	2.999(4)	H13A	.C22	2.6000	H18B	.C20	2.7400
C13	.C21	3.319(4)	C20	.C15_l	3.526(4)	H13A	.H14A	2.3000	H18B	.C22	2.6600
C13	.C16	2.735(4)	C21	.C18	2.914(5)	H13A	.H21A	2.5700	H18B	.H19B	2.3400
C13	.O3	3.197(3)	C21	.C13	3.319(4)	H13A	.H22B	2.0700	H18B	.H22A	2.4800
C13	.C5	3.343(3)	C21	.C12	3.084(4)	H14A	.O10_i	2.7700	H19A	.C11	2.7600
C13	.C22	2.939(4)	C22	.Cl5	3.104(3)	H14A	.H13A	2.3000	H19A	.C12	2.7900
C22	.O9	3.070(3)	C15	.H7B	3.0500	H14A	.H15A	2.3100	H19A	.C17	2.8400
C22	.C19	2.903(4)	C15	.H19B_j	3.1000	H15A	.O10_i	2.7900	H19A	.C21	2.7200
C22	.C13	2.939(4)	C15	.H20B_j	2.9700	H15A	.H14A	2.3100	H19A	.H18A	2.3400
C22	.C4	3.098(4)	C16	.H7B	2.9100	H15A	.H16A	2.2800	H19A	.H20B	2.3100
C4	.H8C	2.9300	C17	.H18A	2.6600	H16A	.H15A	2.2800	H19B	.H18A	2.3600
C4	.H22B	2.7500	C17	.H19A	2.8400	H16A	.H17A	2.3100	H19B	.H18B	2.3400
C4	.H13A	2.9200	C18	.H22A	2.6500	H19B	.H20A	2.3100	H21B	.H20A	2.3200
C5	.H22A	2.7200	C18	.H20A	2.7700	H19B	.H20B	2.3700	H21B	.H20B	2.3700
C5	.H18A	2.7800	C18	.H17A	2.6300	H19B	.C15_l	3.1000	H21B	.H22A	2.3300
C5	.H22B	2.7500	C19	.H21A	2.7200	H20A	.C18	2.7700	H21B	.H22B	2.3300
C5	.H18B	2.7300	C20	.H18B	2.7400	H20A	.C22	2.7400	H22A	.Cl5	2.6400
C6	.H17A	3.0100	C20	.H22A	2.7100	H20A	.H19B	2.3100	H22A	.C5	2.7200
C6	.H8C	2.8900	C21	.H19A	2.7200	H20A	.H21B	2.3200	H22A	.C18	2.6500
C6	.H18A	2.6200	C21	.H13A	3.0500	H20A	.H22A	2.5900	H22A	.C20	2.7100
C7	.H8A	2.7300	C22	.H13A	2.6000	H20B	.H19A	2.3100	H22A	.H18B	2.4800
C7	.H8B	2.7100	C22	.H18B	2.6600	H20B	.H19B	2.3700	H22A	.H20A	2.5900
C8	.H7C	2.7200	C22	.H20A	2.7400	H20B	.H21A	2.3200	H22A	.H21B	2.3300
C8	.H7A	2.7200	H7A	.O1	2.5500	H20B	.H21B	2.3700	H22B	.O9	2.4300
C11	.H17A	2.7000	H7A	.C8	2.7200	H20B	.C15_l	2.9700	H22B	.C4	2.7500
C11	.H19A	2.7600	H7A	.H8A	2.5800	H21A	.C11	2.7400	H22B	.C5	2.7500
C11	.H13A	2.7100	H7A	.O9_h	2.7400	H21A	.C12	2.7600	H22B	.C12	2.7200
C11	.H21A	2.7400	H7B	.O1	2.5300	H21A	.C13	2.7500	H22B	.C13	2.6600
C12	.H21A	2.7600	H7B	.O3	2.5300	H21A	.C19	2.7200	H22B	.H13A	2.0700
C12	.H19A	2.7900	H7B	.C15	3.0500	H21A	.H13A	2.5700	H22B	.H21A	2.3300
C12	.H18A	2.7200	H7B	.C16	2.9100	H21A	.H20B	2.3200	H22B	.H21B	2.3300
C12	.H22B	2.7200	H7C	.O3	2.5300	H21A	.H22B	2.3300	H22B	.Cl5_d	2.8100

Translation of Symmetry Code to Equiv.Pos

a =[2664.00] = [2_664] =1-x,1-y,-1/2+z

200

b =[3654.00] = [4_654] =3/2-x,y,-1/2+z
c =[2665.00] = [2_665] =1-x,1-y,1/2+z
d =[3655.00] = [4_655] =3/2-x,y,1/2+z
e =[4565.00] = [3_565] =1/2+x,1-y,z
f =[1554.00] = [1_554] =x,y,-1+z
g =[3554.00] = [4_554] =1/2-x,y,-1/2+z
h =[4465.00] = [3_465] =-1/2+x,1-y,z
i =[1556.00] = [1_556] =x,y,1+z
j =[2655.00] = [2_655] =1-x,-y,1/2+z
k =[3555.00] = [4_555] =1/2-x,y,1/2+z
l =[2654.00] = [2_654] =1-x,-y,-1/2+z

Table S1 - Crystal Data and Details of the Structure Determination for 4.15a

Formula	$C_6 H_7 Cl O_4$
Formula Weight	178.57
Crystal System	monoclinic
Space group	P21/n (No. 14)
a, b, c [Å]	10.758(5) 9.670(5) 15.675(8)
α, β, γ [°]	90 106.82(1) 90
V [Å³]	1560.9(13)
Z	8
D(calc) [g/cm³]	1.520
Mu(MoKa) [/mm]	0.452
F(000)	736
Crystal Size [mm]	0.04 x 0.20 x 0.28

Data Collection

Temperature (K)	296
Radiation [Å]	MoKa 0.71073
Theta Min-Max [°]	5.6, 26.0
Dataset	-12: 12 ; -7: 11 ; -19: 9
Tot., Uniq. Data, R(int)	3681, 3681, 0.000
Observed data [I > 2.0 sigma(I)]	2796

Refinement

Nref, Npar	3681, 201
R, wR2, S	0.0377, 0.0912, 1.02

$w = {}^2(FO^2) + (0.0337P)^2 + 0.6570P]$ WHERE $P = (FO^2 + 2FC^2)/3'$

Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.24, 0.22

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: 4.15a

Atom	x	y	z	U(eq) [Å^2]
Cl1A	0.19731(8)	0.50219(8)	0.89086(4)	0.0618(3)
O1A	0.14713(16)	0.76992(16)	0.69616(9)	0.0438(6)
O2A	-0.00543(15)	0.59025(17)	0.64564(10)	0.0462(6)
O3A	0.2542(2)	0.7814(2)	0.83805(12)	0.0692(8)
O4A	-0.0376(2)	0.4422(2)	0.74338(13)	0.0698(8)
C1A	0.1693(2)	0.5593(2)	0.78005(13)	0.0368(8)
C2A	0.1964(2)	0.7117(3)	0.77684(15)	0.0433(9)
C3A	0.0776(2)	0.6909(2)	0.61950(14)	0.0386(8)
C4A	0.0342(2)	0.5223(3)	0.72340(16)	0.0440(9)
C5A	0.1697(3)	0.6192(3)	0.57683(15)	0.0480(9)
C6A	-0.0132(3)	0.7908(3)	0.55902(17)	0.0578(10)
Cl1B	0.70507(9)	0.61759(9)	0.89337(4)	0.0754(3)
O1B	0.71582(16)	0.76341(16)	0.66379(10)	0.0426(5)
O2B	0.51465(15)	0.64602(18)	0.63961(10)	0.0461(6)
O3B	0.84954(19)	0.7860(2)	0.79751(11)	0.0645(7)
O4B	0.45521(19)	0.5817(2)	0.75684(13)	0.0735(8)
C1B	0.6831(2)	0.6128(2)	0.77758(13)	0.0384(8)
C2B	0.7587(2)	0.7274(2)	0.74954(14)	0.0392(8)
C3B	0.6152(2)	0.6864(3)	0.60024(14)	0.0398(8)
C4B	0.5413(2)	0.6116(3)	0.72642(15)	0.0434(8)
C5B	0.5528(3)	0.7868(3)	0.52788(17)	0.0689(11)
C6B	0.6740(3)	0.5623(3)	0.56862(17)	0.0566(10)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 4.15a

Atom	x	y	z	U(iso) [Å^2]
H1AA	0.23080	0.51060	0.75520	0.0440
H5AA	0.12070	0.56740	0.52600	0.0720
H5AB	0.22170	0.68700	0.55830	0.0720
H5AC	0.22520	0.55770	0.61920	0.0720
H6AA	-0.06250	0.74330	0.50630	0.0870
H6AB	-0.07110	0.82910	0.58930	0.0870
H6AC	0.03600	0.86380	0.54280	0.0870
H1BA	0.71980	0.52510	0.76480	0.0460
H5BA	0.61550	0.81740	0.49910	0.1030
H5BB	0.48180	0.74250	0.48500	0.1030
H5BC	0.52100	0.86480	0.55310	0.1030
H6BA	0.74030	0.59210	0.54290	0.0850
H6BB	0.71140	0.50220	0.61820	0.0850
H6BC	0.60780	0.51340	0.52470	0.0850

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for 4.15a

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
Cl1A	0.0860(6)	0.0628(5)	0.0415(3)	0.0126(3)	0.0262(3)	0.0211(4)
O1A	0.0541(11)	0.0314(10)	0.0429(8)	0.0000(7)	0.0095(8)	-0.0045(8)
O2A	0.0355(10)	0.0494(11)	0.0508(9)	0.0071(8)	0.0078(7)	-0.0082(8)
O3A	0.0910(16)	0.0511(13)	0.0521(10)	-0.0142(9)	-0.0004(10)	-0.0088(11)
O4A	0.0618(13)	0.0664(14)	0.0840(13)	0.0196(11)	0.0254(11)	-0.0178(11)
C1A	0.0430(14)	0.0347(14)	0.0349(11)	0.0033(10)	0.0147(10)	0.0076(11)
C2A	0.0499(16)	0.0384(16)	0.0411(12)	-0.0040(11)	0.0126(11)	0.0027(12)
C3A	0.0382(14)	0.0366(15)	0.0397(11)	0.0017(10)	0.0091(10)	-0.0052(11)
C4A	0.0443(16)	0.0404(16)	0.0523(14)	0.0042(11)	0.0218(12)	0.0004(12)
C5A	0.0507(16)	0.0539(17)	0.0409(12)	-0.0001(11)	0.0157(11)	0.0021(12)
C6A	0.0517(17)	0.0588(19)	0.0587(15)	0.0181(13)	0.0095(13)	0.0078(14)
Cl1B	0.0980(6)	0.0863(6)	0.0378(3)	0.0037(3)	0.0133(4)	-0.0184(5)
O1B	0.0442(10)	0.0397(10)	0.0446(8)	0.0001(7)	0.0138(7)	-0.0112(8)
O2B	0.0311(10)	0.0622(12)	0.0451(8)	0.0042(8)	0.0111(7)	-0.0054(8)
O3B	0.0585(13)	0.0593(13)	0.0629(11)	-0.0071(10)	-0.0026(9)	-0.0249(10)
O4B	0.0547(13)	0.1050(17)	0.0705(11)	0.0098(12)	0.0333(10)	-0.0190(12)
C1B	0.0437(15)	0.0335(14)	0.0360(11)	-0.0004(10)	0.0086(10)	-0.0017(11)
C2B	0.0382(14)	0.0330(14)	0.0450(13)	-0.0043(10)	0.0097(11)	-0.0024(11)
C3B	0.0321(13)	0.0498(16)	0.0371(11)	0.0002(10)	0.0096(10)	-0.0072(11)
C4B	0.0425(15)	0.0443(16)	0.0465(13)	0.0003(11)	0.0178(11)	-0.0063(12)
C5B	0.071(2)	0.077(2)	0.0534(15)	0.0203(15)	0.0097(14)	0.0037(17)
C6B	0.0434(16)	0.068(2)	0.0574(14)	-0.0218(14)	0.0129(12)	-0.0033(14)

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms
T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for 4.15a

Cl1A	-C1A	1.764(2)	C1A	-H1AA	0.9800
Cl1B	-C1B	1.762(2)	C5A	-H5AA	0.9600
O1A	-C2A	1.345(3)	C5A	-H5AB	0.9600
O1A	-C3A	1.438(3)	C5A	-H5AC	0.9600
O2A	-C4A	1.341(3)	C6A	-H6AA	0.9600
O2A	-C3A	1.458(3)	C6A	-H6AB	0.9600
O3A	-C2A	1.190(3)	C6A	-H6AC	0.9600
O4A	-C4A	1.198(3)	C1B	-C2B	1.513(3)
O1B	-C3B	1.447(3)	C1B	-C4B	1.504(3)
O1B	-C2B	1.335(3)	C3B	-C5B	1.496(4)
O2B	-C4B	1.349(3)	C3B	-C6B	1.506(4)
O2B	-C3B	1.446(3)	C1B	-H1BA	0.9800
O3B	-C2B	1.190(3)	C5B	-H5BA	0.9600
O4B	-C4B	1.193(3)	C5B	-H5BB	0.9600
C1A	-C4A	1.511(3)	C5B	-H5BC	0.9600
C1A	-C2A	1.506(4)	C6B	-H6BA	0.9600
C3A	-C6A	1.500(4)	C6B	-H6BB	0.9600
C3A	-C5A	1.514(4)	C6B	-H6BC	0.9600

Table S6 - Bond Angles (°) for 4.15a

C2A	-O1A	-C3A	122.11(18)	C3A	-C6A	-H6AB	109.00	
C3A	-O2A	-C4A	121.54(18)	C3A	-C6A	-H6AC	109.00	
C2B	-O1B	-C3B	122.04(18)	H6AA	-C6A	-H6AC	109.00	
C3B	-O2B	-C4B	122.04(17)	H6AB	-C6A	-H6AC	109.00	
C2A	-C1A	-C4A	112.01(19)	H6AA	-C6A	-H6AB	110.00	
Cl1A	-C1A	-C2A	111.09(14)	C3A	-C6A	-H6AA	109.00	
Cl1A	-C1A	-C4A	111.47(16)	Cl1B	-C1B	-C2B	110.91(14)	
O1A	-C2A	-C1A	114.43(19)	Cl1B	-C1B	-C4B	111.25(16)	
O1A	-C2A	-O3A	119.5(3)	C2B	-C1B	-C4B	113.47(18)	
O3A	-C2A	-C1A	126.0(2)	O1B	-C2B	-O3B	119.6(2)	
O1A	-C3A	-C5A	111.34(19)	O1B	-C2B	-C1B	115.17(18)	
O1A	-C3A	-O2A	109.44(16)	O3B	-C2B	-C1B	125.3(2)	
O2A	-C3A	-C6A	105.5(2)	O1B	-C3B	-O2B	110.38(17)	
C5A	-C3A	-C6A	113.9(2)	O1B	-C3B	-C5B	105.7(2)	
O1A	-C3A	-C6A	105.79(17)	O1B	-C3B	-C6B	109.6(2)	
O2A	-C3A	-C5A	110.54(18)	O2B	-C3B	-C5B	105.8(2)	
O4A	-C4A	-C1A	125.7(2)	O2B	-C3B	-C6B	111.3(2)	
O2A	-C4A	-O4A	119.7(2)	C5B	-C3B	-C6B	114.0(2)	
O2A	-C4A	-C1A	114.6(2)	O2B	-C4B	-O4B	120.0(2)	
C4A	-C1A	-H1AA	107.00	O2B	-C4B	-C1B	115.01(19)	
C2A	-C1A	-H1AA	107.00	O4B	-C4B	-C1B	125.0(2)	
Cl1A	-C1A	-H1AA	107.00	Cl1B	-C1B	-H1BA	107.00	
C3A	-C5A	-H5AB	110.00	C2B	-C1B	-H1BA	107.00	
C3A	-C5A	-H5AA	109.00	C4B	-C1B	-H1BA	107.00	
H5AA	-C5A	-H5AC	109.00	C3B	-C5B	-H5BA	110.00	
C3A	-C5A	-H5AC	109.00	C3B	-C5B	-H5BB	109.00	
H5AA	-C5A	-H5AB	109.00	C3B	-C5B	-H5BC	109.00	
H5AB	-C5A	-H5AC	109.00	H5BA	-C5B	-H5BB	109.00	
H5BA	-C5B	-H5BC	110.00	C3B	-C6B	-H6BC	109.00	
H5BB	-C5B	-H5BC	109.00	H6BA	-C6B	-H6BB	109.00	
C3B	-C6B	-H6BA	109.00	H6BA	-C6B	-H6BC	110.00	
C3B	-C6B	-H6BB	109.00	H6BB	-C6B	-H6BC	109.00	

Table S7 - Torsion Angles (°) for 4.15a

C3A	-O1A	-C2A	-O3A	179.3(2)	C3B	-O2B	-C4B	-O4B	178.4(2)
C3A	-O1A	-C2A	-C1A	-1.6(3)	C3B	-O2B	-C4B	-C1B	-2.4(3)
C2A	-O1A	-C3A	-O2A	39.8(3)	C4A	-C1A	-C2A	-O3A	140.3(3)
C2A	-O1A	-C3A	-C5A	-82.7(2)	Cl1A	-C1A	-C4A	-O2A	164.43(17)
C2A	-O1A	-C3A	-C6A	153.0(2)	Cl1A	-C1A	-C4A	-O4A	-13.9(3)
C4A	-O2A	-C3A	-O1A	-39.0(3)	C2A	-C1A	-C4A	-O2A	39.3(3)
C4A	-O2A	-C3A	-C5A	84.0(2)	C2A	-C1A	-C4A	-O4A	-139.0(3)
C4A	-O2A	-C3A	-C6A	-152.4(2)	Cl1A	-C1A	-C2A	-O1A	-164.06(16)
C3A	-O2A	-C4A	-O4A	178.6(2)	Cl1A	-C1A	-C2A	-O3A	14.9(3)
C3A	-O2A	-C4A	-C1A	0.2(3)	C4A	-C1A	-C2A	-O1A	-38.7(3)
C2B	-O1B	-C3B	-O2B	40.8(3)	Cl1B	-C1B	-C2B	-O1B	-157.83(16)
C3B	-O1B	-C2B	-O3B	173.2(2)	Cl1B	-C1B	-C2B	-O3B	21.4(3)
C3B	-O1B	-C2B	-C1B	-7.6(3)	C4B	-C1B	-C2B	-O1B	-31.8(3)
C2B	-O1B	-C3B	-C5B	154.7(2)	C4B	-C1B	-C2B	-O3B	147.5(2)
C2B	-O1B	-C3B	-C6B	-82.1(2)	Cl1B	-C1B	-C4B	-O2B	162.54(18)
C4B	-O2B	-C3B	-C6B	86.8(3)	Cl1B	-C1B	-C4B	-O4B	-18.3(3)
C4B	-O2B	-C3B	-O1B	-35.1(3)	C2B	-C1B	-C4B	-O2B	36.7(3)
C4B	-O2B	-C3B	-C5B	-148.9(2)	C2B	-C1B	-C4B	-O4B	-144.2(3)

Table S8 - Contact Distances (Å) for 4.15a

Cl1A	.O3A	2.940(3)	O4B	.C2A	3.152(4)
Cl1A	.O4A	2.947(3)	O4B	.C1A	3.207(3)
Cl1A	.O1A_a	3.321(2)	O1A	.H5AC	2.6400
Cl1A	.C5B_d	3.623(4)	O1A	.H1AA	2.7300
Cl1A	.Cl1B_c	3.439(2)	O1A	.H6AC	2.5200
Cl1B	.O4B	2.932(3)	O1A	.H6AB	2.5200
Cl1B	.O3B	2.946(3)	O1A	.H1AA_e	2.6700
Cl1B	.Cl1A_j	3.439(2)	O1A	.H5AB	2.6400
Cl1A	.H5BC_b	3.0400	O1B	.H5BC	2.5000
Cl1A	.H6AC_a	3.0600	O1B	.H5BA	2.5500
Cl1A	.H5BA_d	2.7500	O1B	.H6BA	2.5900
O1A	.C4A	2.774(3)	O1B	.H6BB	2.6200
O1A	.Cl1A_e	3.321(2)	O1B	.H1BA	2.7900
O1A	.C1A_e	3.383(3)	O1B	.H1BA_k	2.7700
O1B	.O4A_e	3.224(3)	O2A	.H6AA	2.5600
O1B	.C4B	2.777(3)	O2A	.H6BA_f	2.7400
O2A	.C6B_f	3.319(4)	O2A	.H1AA	2.7300
O2A	.C2A	2.782(3)	O2A	.H5AC	2.6500
O2B	.C2B	2.804(3)	O2A	.H6AB	2.5000
O3A	.Cl1A	2.940(3)	O2A	.H5AA	2.6200
O3B	.C1B_k	3.355(3)	O2B	.H5BC	2.5200
O3B	.C4B_k	3.419(4)	O2B	.H5BB	2.5200
O3B	.Cl1B	2.946(3)	O2B	.H6BC	2.6300
O4A	.O1B_b	3.224(3)	O2B	.H1BA	2.7500
O4A	.C4B_b	3.234(4)	O2B	.H6BB	2.6300
O4A	.C2B_b	3.184(3)	O3A	.H6AA_g	2.8100
O4A	.Cl1A	2.947(3)	O3A	.H5AC_e	2.7500
O4B	.Cl1B	2.932(3)	O3A	.H1AA	2.9000
O3A	.H1AA_e	2.6900	C4A	.C5A	3.197(4)
O3B	.H1BA	2.8600	C4A	.C6A	3.589(4)
O3B	.H1BA_k	2.5400	C4A	.O1A	2.774(3)
O3B	.H6BB_k	2.6500	C4B	.C6B	3.229(4)
O3B	.H5BB_l	2.8800	C4B	.O4A_e	3.234(4)
O4A	.H6BB_f	2.9000	C4B	.O1B	2.777(3)
O4A	.H1AA	2.9200	C4B	.C5B	3.577(4)
O4A	.H1BA_f	2.8400	C4B	.O3B_m	3.419(4)
O4B	.H1AA	2.5000	C5A	.C4A	3.197(4)
O4B	.H5AC	2.7800	C5A	.C1A	3.239(4)
O4B	.H1BA	2.8700	C5A	.C2A	3.192(4)
C1A	.C3A	2.737(3)	C5B	.Cl1A_n	3.623(4)
C1A	.C5A	3.239(4)	C5B	.C2B	3.585(4)
C1A	.O4B	3.207(3)	C5B	.C4B	3.577(4)
C1A	.O1A_a	3.383(3)	C6A	.C2A	3.588(4)
C1B	.C6B	3.285(4)	C6A	.C4A	3.589(4)
C1B	.O3B_m	3.355(3)	C6B	.C4B	3.229(4)
C1B	.C3B	2.755(3)	C6B	.C2B	3.151(4)
C2A	.O2A	2.782(3)	C6B	.O2A_o	3.319(4)
C2A	.O4B	3.152(4)	C6B	.C1B	3.285(4)
C2A	.C5A	3.192(4)	C1A	.H5AC	2.7600
C2B	.O4A_e	3.184(3)	C2A	.H1AA_e	3.0700
C2B	.C5B	3.585(4)	C2A	.H5AC	2.9800
C2B	.O2B	2.804(3)	C2B	.H6BB	2.9400
C2B	.C6B	3.151(4)	C2B	.H1BA_k	2.9000
C3A	.C1A	2.737(3)	C3A	.H1AA	2.8700
C3B	.C1B	2.755(3)	C3B	.H1BA	2.9400
C4A	.H5AC	2.9900	H5AB	.H6AC	2.5900
C4B	.H6BB	3.0200	H5AB	.C6A	2.7200
C5A	.H6AA	2.7000	H5AB	.O1A	2.6400
C5A	.H1AA	2.8800	H5AC	.O1A	2.6400
C5A	.H6AC	2.7400	H5AC	.H1AA	2.1600
C5B	.H6BC	2.7100	H5AC	.O3A_a	2.7500
C5B	.H6BA	2.7200	H5AC	.O2A	2.6500
C6A	.H5AA	2.7300	H5AC	.O4B	2.7800
C6A	.H5AB	2.7200	H5AC	.C1A	2.7600
C6B	.H5BB	2.7300	H5AC	.C2A	2.9800
C6B	.H6BC_h	3.0500	H5AC	.C4A	2.9900
C6B	.H5BA	2.7000	H6AA	.C5A	2.7000
C6B	.H1BA	2.9900	H6AA	.H5AA	2.5500
H1AA	.O4A	2.9200	H6AA	.O2A	2.5600
H1AA	.O3A	2.9000	H6AA	.O3A_i	2.8100
H1AA	.O1A	2.7300	H6AB	.O2A	2.5000
H1AA	.O2A	2.7300	H6AB	.O1A	2.5200
H1AA	.O3A_a	2.6900	H6AC	.Cl1A_e	3.0600
H1AA	.C2A_a	3.0700	H6AC	.H5AB	2.5900
H1AA	.O4B	2.5000	H6AC	.O1A	2.5200
H1AA	.C3A	2.8700	H6AC	.C5A	2.7400
H1AA	.C5A	2.8800	H1BA	.O1B	2.7900
H1AA	.H5AC	2.1600	H1BA	.O2B	2.7500
H1AA	.O1A_a	2.6700	H1BA	.O3B	2.8600
H5AA	.C6A	2.7300	H1BA	.O4A_o	2.8400
H5AA	.H6AA	2.5500	H1BA	.O4B	2.8700
H5AA	.O2A	2.6200	H1BA	.C3B	2.9400

H5AA .H6BA_h 2.5900 H1BA .C6B 2.9900

H1BA .H6BB 2.2800 H6BA .C5B 2.7200

H1BA .O1B_m 2.7700 H6BA .H5BA 2.5500

H1BA .O3B_m 2.5400 H6BA .H5AA_q 2.5900

H1BA .C2B_m 2.9000 H6BB .O1B 2.6200

H5BA .O1B 2.5500 H6BB .O2B 2.6300

H5BA .C6B 2.7000 H6BB .O4A_o 2.9000

H5BA .H6BA 2.5500 H6BB .C1B 2.8100

H5BA .Cl1A_n 2.7500 H6BB .C2B 2.9400

H5BB .O2B 2.5200 H6BB .C4B 3.0200

H5BB .C6B 2.7300 H6BB .H1BA 2.2800

H5BB .H6BC 2.5800 H6BB .O3B_m 2.6500

H5BB .O3B_p 2.8800 H6BC .O2B 2.6300

H5BC .O1B 2.5000 H6BC .C5B 2.7100

H5BC .O2B 2.5200 H6BC .H5BB 2.5800

H5BC .Cl1A_e 3.0400 H6BC .C6B_h 3.0500

H6BA .O1B 2.5900 H6BC .H6BC_h 2.2400

H6BA .O2A_o 2.7400

Translation of Symmetry Code to Equiv.Pos

a =[2546.00] = [2_546] =1/2-x,-1/2+y,3/2-z
b =[2546.00] = [2_546] =1/2-x,-1/2+y,3/2-z
c =[3667.00] = [3_667] =1-x,1-y,2-z
d =[4465.00] = [4_576] =-1/2+x,3/2-y,1/2+z
e =[2556.00] = [2_556] =1/2-x,1/2+y,3/2-z
f =[1455.00] = [1_455] =-1+x,y,z
g =[4565.00] = [4_676] =1/2+x,3/2-y,1/2+z
h =[3666.00] = [3_666] =1-x,1-y,1-z
i =[4464.00] = [4_575] =-1/2+x,3/2-y,-1/2+z
j =[3667.00] = [3_667] =1-x,1-y,2-z
k =[2656.00] = [2_656] =3/2-x,1/2+y,3/2-z
l =[4565.00] = [4_676] =1/2+x,3/2-y,1/2+z
m =[2646.00] = [2_646] =3/2-x,-1/2+y,3/2-z
n =[4564.00] = [4_675] =1/2+x,3/2-y,-1/2+z
o =[1655.00] = [1_655] =1+x,y,z
p =[4464.00] = [4_575] =-1/2+x,3/2-y,-1/2+z
q =[3666.00] = [3_666] =1-x,1-y,1-z
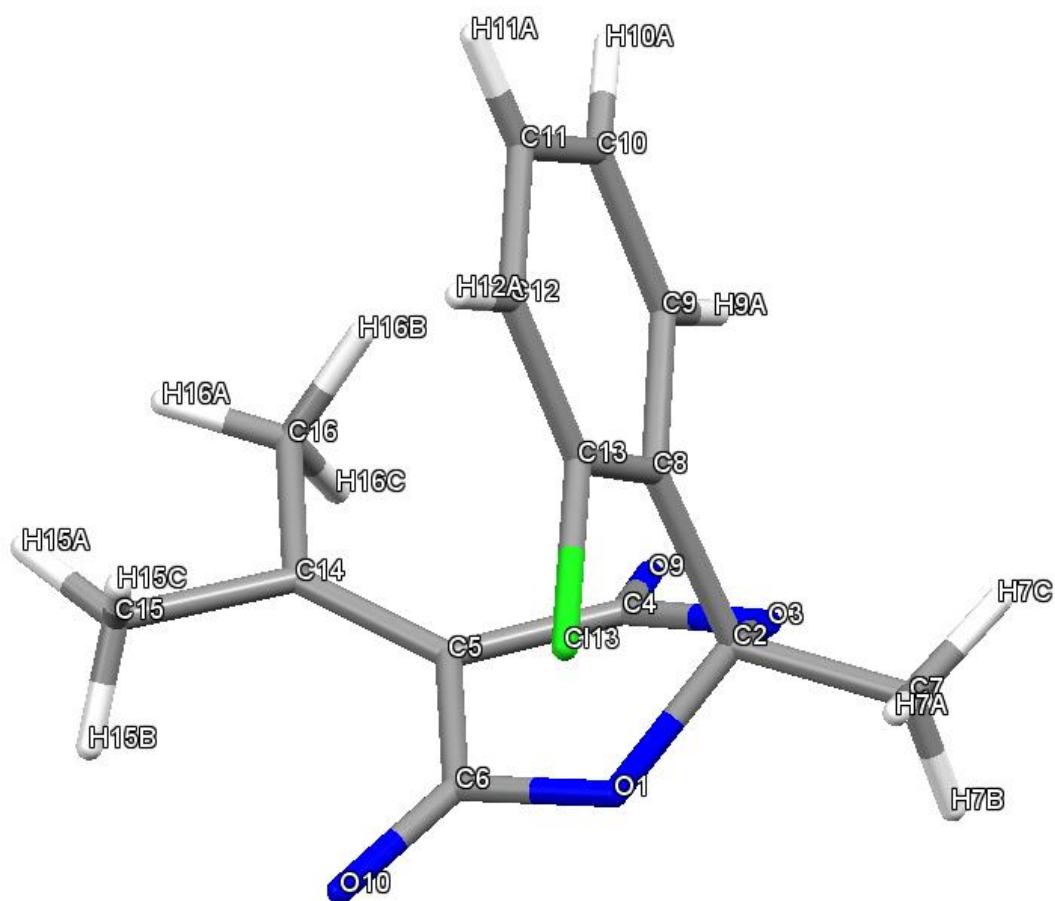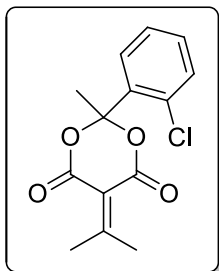
Table S1 - Crystal Data and Details of the Structure Determination 4.22   R = 0.05

Crystal Data

Formula	C14 H13 Cl O4
Formula Weight	280.69
Crystal System	monoclinic
Space group	C2/c (No. 15)
a, b, c [Å]	8.6786(16) 13.491(3) 22.967(5)
α, β, γ [°]	90 93.677(13) 90
V [Å^3]	2683.5(10)
Z	8
D(calc) [g/cm^3]	1.390
Mu(MoKa) [/mm]	0.291
F(000)	1168
Crystal Size [mm]	0.04 x 0.13 x 0.20

Data Collection

Temperature (K)	200
Radiation [Å]	MoKa 0.71073
Theta Min-Max [°]	1.8, 28.0
Dataset	-11: 11 ; -17: 17 ; -30: 28
Tot., Uniq. Data, R(int)	9160, 3244, 0.024
Observed data [I > 2.0 sigma(I)]	2011

Refinement

Nref, Npar	3244, 172
R, wR2, S	0.0492, 0.1155, 1.15
w = ^2^(FO^2^)+(0.0259P)^2^+2.7416P] WHERE P=(FO^2^+2FC^2^)/3'	
Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	-0.27, 0.26

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms 4.22

Atom	x	y	z	U(eq) [Ang^2]
Cl13	0.20261(9)	0.60380(7)	0.51120(3)	0.0770(3)
O1	0.04323(17)	0.57566(12)	0.39443(7)	0.0463(5)
O3	0.17569(18)	0.49925(12)	0.32212(6)	0.0455(5)
O9	0.1849(2)	0.56909(13)	0.23633(7)	0.0571(6)
O10	-0.05752(19)	0.72413(13)	0.38325(7)	0.0547(6)
C2	0.1746(3)	0.51546(17)	0.38373(10)	0.0428(8)
C4	0.1668(2)	0.58072(18)	0.28714(10)	0.0413(8)
C5	0.1291(2)	0.67452(17)	0.31614(9)	0.0369(7)
C6	0.0319(2)	0.66428(19)	0.36662(10)	0.0411(7)
C7	0.1475(3)	0.41500(19)	0.40975(12)	0.0608(10)
C8	0.3256(2)	0.56380(17)	0.40674(9)	0.0382(7)
C9	0.4527(3)	0.56533(18)	0.37234(10)	0.0455(8)
C10	0.5924(3)	0.6058(2)	0.39142(11)	0.0548(9)
C11	0.6097(3)	0.6469(2)	0.44588(12)	0.0598(10)
C12	0.4888(3)	0.6459(2)	0.48155(11)	0.0592(10)
C13	0.3483(3)	0.60427(19)	0.46230(10)	0.0479(8)
C14	0.1812(3)	0.76183(19)	0.29790(10)	0.0464(8)
C15	0.1466(4)	0.8586(2)	0.32642(13)	0.0721(11)
C16	0.2850(3)	0.7721(2)	0.24835(13)	0.0681(11)

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 4.22

Atom	x	y	z	U(iso) [Ang^2]
H7A	0.14550	0.42100	0.45220	0.0910
H7B	0.04850	0.38860	0.39370	0.0910
H7C	0.23090	0.37000	0.40030	0.0910
H9A	0.44220	0.53740	0.33430	0.0550
H10A	0.67650	0.60520	0.36690	0.0660
H11A	0.70540	0.67600	0.45900	0.0720
H12A	0.50110	0.67390	0.51950	0.0710

Atom						
H15A	0.19610	0.91260	0.30610	0.1080		
H15B	0.03470	0.86920	0.32450	0.1080		
H15C	0.18650	0.85710	0.36730	0.1080		
H16A	0.30860	0.84230	0.24250	0.1020		
H16B	0.38110	0.73560	0.25760	0.1020		
H16C	0.23300	0.74520	0.21260	0.1020		

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for: 4.22

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
Cl13	0.0726(5)	0.1180(7)	0.0423(4)	-0.0042(4)	0.0179(3)	0.0113(5)
O1	0.0399(8)	0.0516(11)	0.0485(9)	0.0081(8)	0.0109(7)	0.0051(8)
O3	0.0578(10)	0.0366(9)	0.0418(9)	-0.0026(8)	0.0007(7)	0.0033(8)
O9	0.0745(12)	0.0597(12)	0.0378(9)	-0.0064(8)	0.0084(8)	0.0134(9)
O10	0.0492(9)	0.0608(12)	0.0550(10)	-0.0091(9)	0.0101(8)	0.0164(9)
C2	0.0471(13)	0.0408(14)	0.0409(13)	0.0044(11)	0.0056(10)	0.0047(11)
C4	0.0400(12)	0.0433(14)	0.0403(13)	-0.0007(11)	0.0010(10)	0.0045(10)
C5	0.0361(11)	0.0384(13)	0.0359(11)	-0.0013(10)	0.0005(9)	0.0046(10)
C6	0.0369(11)	0.0473(15)	0.0387(12)	-0.0045(11)	0.0001(9)	0.0040(11)
C7	0.0680(17)	0.0478(17)	0.0665(17)	0.0156(14)	0.0041(14)	-0.0045(13)
C8	0.0427(12)	0.0354(13)	0.0367(11)	0.0052(10)	0.0038(9)	0.0082(10)
C9	0.0461(13)	0.0490(15)	0.0416(13)	-0.0013(11)	0.0047(10)	0.0101(11)
C10	0.0428(14)	0.0634(18)	0.0587(16)	0.0068(14)	0.0066(12)	0.0046(12)
C11	0.0509(15)	0.0581(18)	0.0690(19)	0.0033(15)	-0.0070(14)	-0.0026(13)
C12	0.0675(18)	0.0617(18)	0.0467(15)	-0.0072(13)	-0.0088(13)	0.0054(14)
C13	0.0532(14)	0.0527(16)	0.0382(12)	0.0029(12)	0.0060(10)	0.0110(12)
C14	0.0484(13)	0.0440(15)	0.0462(13)	0.0028(12)	-0.0011(11)	0.0033(11)
C15	0.099(2)	0.0419(16)	0.076(2)	-0.0053(15)	0.0106(17)	0.0000(16)
C16	0.0706(18)	0.066(2)	0.0694(18)	0.0103(16)	0.0188(15)	-0.0091(16)

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms
T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for: 4.22

Cl13 -C13	1.744(3)	C12 -C13	1.389(4)		C4 -C5	1.477(3)	C12 -H12A	0.9500
O1 -C2	1.434(3)	C14 -C15	1.500(4)		C5 -C6	1.483(3)	C15 -H15A	0.9800
O1 -C6	1.356(3)	C14 -C16	1.502(4)		C5 -C14	1.339(3)	C15 -H15B	0.9800
O3 -C2	1.432(3)	C7 -H7A	0.9800		C8 -C9	1.398(3)	C15 -H15C	0.9800
O3 -C4	1.361(3)	C7 -H7B	0.9800		C8 -C13	1.390(3)	C16 -H16A	0.9800
O9 -C4	1.198(3)	C7 -H7C	0.9800		C9 -C10	1.376(4)	C16 -H16B	0.9800
O10 -C6	1.199(3)	C9 -H9A	0.9500		C10 -C11	1.368(4)	C16 -H16C	0.9800
C2 -C7	1.506(3)	C10 -H10A	0.9500		C11 -C12	1.372(4)		
C2 -C8	1.527(3)	C11 -H11A	0.9500					

Table S6 - Bond Angles (°) 4.22

C2	-O1	-C6	116.94(16)		C5	-C14	-C16	123.3(2)
C2	-O3	-C4	117.14(17)		C15	-C14	-C16	113.4(2)
O1	-C2	-O3	108.15(18)		C2	-C7	-H7A	110.00
O1	-C2	-C7	107.2(2)		C2	-C7	-H7B	109.00
O1	-C2	-C8	111.89(18)		C2	-C7	-H7C	109.00
O3	-C2	-C7	105.41(19)		H7A	-C7	-H7B	109.00
O3	-C2	-C8	110.31(19)		H7A	-C7	-H7C	109.00
C7	-C2	-C8	113.5(2)		H7B	-C7	-H7C	110.00
O3	-C4	-O9	117.6(2)		C8	-C9	-H9A	119.00
O3	-C4	-C5	115.58(19)		C10	-C9	-H9A	119.00
O9	-C4	-C5	126.8(2)		C9	-C10	-H10A	120.00
C4	-C5	-C6	115.24(19)		C11	-C10	-H10A	120.00
C4	-C5	-C14	121.60(19)		C10	-C11	-H11A	120.00
C6	-C5	-C14	123.2(2)		C12	-C11	-H11A	120.00
O1	-C6	-O10	118.19(19)		C11	-C12	-H12A	120.00
O1	-C6	-C5	115.00(19)		C13	-C12	-H12A	120.00
O10	-C6	-C5	126.8(2)		C14	-C15	-H15A	109.00
C2	-C8	-C9	120.1(2)		C14	-C15	-H15B	109.00
C2	-C8	-C13	123.58(19)		C14	-C15	-H15C	109.00
C9	-C8	-C13	116.3(2)		H15A	-C15	-H15B	110.00
C8	-C9	-C10	122.5(2)		H15A	-C15	-H15C	109.00
C9	-C10	-C11	119.7(2)		H15B	-C15	-H15C	110.00
C10	-C11	-C12	119.9(2)		C14	-C16	-H16A	109.00
C11	-C12	-C13	120.2(2)		C14	-C16	-H16B	109.00
Cl13	-C13	-C8	121.58(19)		C14	-C16	-H16C	110.00
Cl13	-C13	-C12	117.03(18)		H16A	-C16	-H16B	109.00
C8	-C13	-C12	121.4(2)		H16A	-C16	-H16C	109.00
C5	-C14	-C15	123.3(2)		H16B	-C16	-H16C	110.00

Table S7 - Torsion Angles (°) for: 4.22

C6	-O1	-C2	-O3	-56.6(2)		C4	-C5	-C6	-O1	26.3(2)
C6	-O1	-C2	-C7	-169.77(19)		C4	-C5	-C6	-O10	-150.7(2)
C6	-O1	-C2	-C8	65.1(2)		C14	-C5	-C6	-O1	-153.1(2)
C2	-O1	-C6	-O10	-165.26(19)		C14	-C5	-C6	-O10	29.9(3)
C2	-O1	-C6	-C5	17.4(3)		C4	-C5	-C14	-C15	-179.5(2)
C4	-O3	-C2	-O1	52.6(2)		C4	-C5	-C14	-C16	-1.9(3)
C4	-O3	-C2	-C7	166.96(18)		C6	-C5	-C14	-C15	-0.2(4)
C4	-O3	-C2	-C8	-70.1(2)		C6	-C5	-C14	-C16	177.4(2)
C2	-O3	-C4	-O9	171.86(19)		C2	-C8	-C9	-C10	-178.5(2)
C2	-O3	-C4	-C5	-10.5(2)		C13	-C8	-C9	-C10	-1.0(4)
O1	-C2	-C8	-C9	-134.9(2)		C2	-C8	-C13	-Cl13	-0.4(3)
O1	-C2	-C8	-C13	47.9(3)		C2	-C8	-C13	-C12	178.9(2)
O3	-C2	-C8	-C9	-14.5(3)		C9	-C8	-C13	-Cl13	-177.73(18)
O3	-C2	-C8	-C13	168.3(2)		C9	-C8	-C13	-C12	1.5(4)
C7	-C2	-C8	-C9	103.6(3)		C8	-C9	-C10	-C11	-0.3(4)
C7	-C2	-C8	-C13	-73.6(3)		C9	-C10	-C11	-C12	1.2(4)
O3	-C4	-C5	-C6	-29.9(2)		C10	-C11	-C12	-C13	-0.7(4)
O3	-C4	-C5	-C14	149.5(2)		C11	-C12	-C13	-Cl13	178.6(2)
O9	-C4	-C5	-C6	147.5(2)		C11	-C12	-C13	-C8	-0.7(4)
O9	-C4	-C5	-C14	-33.2(3)						

Table S8 - Contact Distances(Å) for: 4.22

Cl13	.O1	2.9621(19)	O9	.H16B	2.8400	C7	.C13	3.278(4)	C4 .H16C	2.8800
Cl13	.C2	3.156(3)	O9	.H16C	2.4800	C7	.C9	3.487(4)	C4 .H9A	2.6300
Cl13	.C6	3.641(2)	O10	.H10A_f	2.8200	C7	.Cl13	3.465(3)	C4 .H16B	2.9100
Cl13	.C7	3.465(3)	O10	.H11A_f	2.8500	C8	.C4	3.002(3)	C5 .H16C	2.7700
Cl13	.C7_a	3.647(3)	O10	.H15B	2.5400	C8	.C11	2.804(3)	C5 .H15C	2.7600
Cl13	.H7A	2.8400	O10	.H15C	2.8200	C8	.C6	2.980(3)	C5 .H16B	2.7700
Cl13	.H12A	2.7500	O10	.H16C_d	2.6100	C8	.C5	3.002(3)	C5 .H15B	2.7600
Cl13	.H15C_b	2.9400	O10	.H7C_g	2.7400	C9	.C4	3.067(3)	C6 .H16C_d	3.0400
O1	.Cl13	2.9621(19)	O10	.H12A_b	2.6400	C9	.O3	2.748(3)	C6 .H15C	2.9300
O1	.C4	2.751(3)	C2	.Cl13	3.156(3)	C9	.C15_h	3.457(4)	C6 .H15B	2.9300
O1	.C13	3.010(3)	C2	.C5	2.663(3)	C9	.C5	3.355(3)	C8 .H7C	2.7400
O3	.C9	2.748(3)	C4	.C9	3.067(3)	C9	.C7	3.487(4)	C8 .H7A	2.7300
O3	.C6	2.779(3)	C4	.O1	2.751(3)	C9	.C12	2.733(3)	C9 .H15B_h	2.9700
O9	.C14	2.961(3)	C4	.C8	3.002(3)	C10	.C13	2.753(4)	C13 .H7A	3.0400
O9	.C6_d	3.195(3)	C4	.C4_d	3.265(3)	C11	.C8	2.804(3)	C15 .H9A_g	3.0100
O9	.C4_d	3.069(3)	C4	.C16	2.938(4)	C12	.C9	2.733(3)	C15 .H16A	2.4700
O9	.C5_d	3.237(3)	C4	.O9_d	3.069(3)	C13	.C7	3.278(4)	C16 .H15A	2.4700
O9	.C16	2.881(3)	C5	.C2	2.663(3)	C13	.C10	2.753(4)	C16 .H16B_e	2.9500
O10	.C15	2.903(4)	C5	.C9	3.355(3)	C13	.O1	3.010(3)	H7A .Cl13	2.8400
O10	.C14	2.986(3)	C5	.C8	3.002(3)	C13	.C6	3.500(3)	H7A .O1	2.6000
O1	.H7B	2.5200	C5	.O9_d	3.237(3)	C14	.O10	2.986(3)	H7A .C8	2.7300
O1	.H7A	2.6000	C6	.C15	2.972(4)	C14	.O9	2.961(3)	H7A .C13	3.0400
O3	.H7B	2.5300	C6	.C13	3.500(3)	C15	.C6	2.972(4)	H7B .O1	2.5200
O3	.H7C	2.5300	C6	.O3	2.779(3)	C15	.O10	2.903(4)	H7B .O3	2.5300
O3	.H9A	2.3700	C6	.C8	2.980(3)	C15	.C9_g	3.457(4)	H7C .O3	2.5300
O3	.H16A_c	2.5900	C6	.O9_d	3.195(3)	C16	.C4	2.938(4)	H7C .C8	2.7400
O9	.H10A_e	2.7700	C6	.Cl13	3.641(2)	C16	.O9	2.881(3)	H7C .O10_h	2.7400
O9	.H15A_c	2.5700	C7	.Cl13_a	3.647(3)	C2	.H9A	2.6700	H9A .O3	2.3700

H9A	.C2	2.6700	H15B .C6	2.9300	H11A .H10A	2.3200	H16B .O9	2.8400
H9A	.C4	2.6300	H15B .C9_g	2.9700	H11A .H12A	2.3200	H16B .C4	2.9100
H9A	.H10A	2.3100	H15B .H9A_g	2.4200	H12A .Cl13	2.7500	H16B .C5	2.7700
H9A	.C15_h	3.0100	H15C .O10	2.8200	H12A .H11A	2.3200	H16B .C16_e	2.9500
H9A	.H15B_h	2.4200	H15C .C5	2.7600	H12A .O10_b	2.6400	H16B .H16B_e	2.1200
H10A	.O10_i	2.8200	H15C .C6	2.9300	H15A .C16	2.4700	H16C .O9	2.4800
H10A	.H9A	2.3100	H15C .Cl13_b	2.9400	H15A .H16A	2.0400	H16C .C4	2.8800
H10A	.H11A	2.3200	H16A .C15	2.4700	H15A .O9_j	2.5700	H16C .C5	2.7700
H10A	.O9_e	2.7700	H16A .H15A	2.0400	H15B .O10	2.5400	H16C .O10_d	2.6100
H11A	.O10_i	2.8500	H16A .O3_j	2.5900	H15B .C5	2.7600	H16C .C6_d	3.0400

Appendix H

Crystallographic Data for 4.24

Table S1 - Crystal Data and Details of the Structure Determination for: 4.24

Crystal Data

Formula	$C_{22} H_{14} Cl_4 O_8$
Formula Weight	548.13
Crystal System	triclinic
Space group	P-1 (No. 2)
a, b, c [Å]	9.1114(3) 11.5298(5) 12.6921(5)
α, β, γ [°]	106.280(3) 101.717(2) 110.676(3)
V [Ang**3]	1127.68(9)
Z	2
D(calc) [g/cm**3]	1.614
Mu(MoKa) [/mm]	0.574
F(000)	556
Crystal Size [mm]	0.02 x 0.16 x 0.20

Data Collection

Temperature (K)	296
Radiation [Angstrom]	MoKa 0.71073
Theta Min-Max [Deg]	0.0, 0.0
Dataset	999:-99 ; 999:-99 ; 999:-99
Tot., Uniq. Data, R(int)	0, 0, 0.000
Observed data [I > 0.0 sigma(I)]	0

Refinement

Nref, Npar	0, 0
R, wR2, S	0.0000, 0.0000, 0.00
w =	
Max. and Av. Shift/Error	0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3]	0.00, 0.00

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: 4.24

Atom	x	y	z	U(eq) [Ang^2]
CL13A	0.59039	0.34431	0.34645	0.0705
CL13B	0.27710	0.91377	-0.08332	0.0664
Cl5A	0.60521	0.80247	0.46595	0.0518
Cl5B	0.54005	0.99378	0.31749	0.0468
O1A	0.55946	0.53497	0.24200	0.0438
O1B	0.15087	0.73279	0.18135	0.0488
O3A	0.80306	0.72291	0.27308	0.0407
O3B	0.29867	0.74838	0.05117	0.0490
O9A	0.82547	0.92724	0.32308	0.0624
O9B	0.53773	0.74042	0.09550	0.0536
O10A	0.32408	0.55139	0.21426	0.0579
O10B	0.26240	0.76840	0.36449	0.0624
C2A	0.73968	0.59437	0.28035	0.0381
C2B	0.16441	0.76968	0.08450	0.0414
C4A	0.74318	0.81345	0.30374	0.0374
C4B	0.43453	0.76676	0.12817	0.0380
C5A	0.56726	0.75917	0.31378	0.0328
C5B	0.45325	0.81492	0.25751	0.0333
C6A	0.47354	0.60674	0.25374	0.0384
C6B	0.28248	0.77036	0.27592	0.0411
C7A	0.78253	0.50719	0.19084	0.0542
C7B	0.00655	0.67005	-0.01573	0.0655
C8A	0.81169	0.60443	0.40347	0.0334
C8B	0.18829	0.91294	0.11087	0.0351
C9A	0.95090	0.72034	0.48260	0.0405
C9B	0.14703	0.97477	0.20315	0.0488
C10A	1.02414	0.73142	0.59295	0.0486
C10B	0.15978	1.10247	0.22812	0.0617
C11A	0.96149	0.62723	0.62742	0.0519
C11B	0.21347	1.17174	0.16134	0.0630
C12	0.82670	0.51029	0.55066	0.0513
C12B	0.24985	1.11215	0.06747	0.0571
C13A	0.75357	0.49889	0.43929	0.0414
C13B	0.23576	0.98280	0.04149	0.0416

U(eq) = 1/3 of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters for: 4.24

Atom	x	y	z	U(iso) [Ang^2]
H7AA	0.74277	0.41848	0.19148	0.0813
H7AB	0.73093	0.50273	0.11500	0.0813
H7AC	0.90118	0.54481	0.20901	0.0813
H7BA	0.00921	0.69049	-0.08382	0.0983
H7BB	-0.00220	0.58101	-0.03122	0.0983
H7BC	-0.08778	0.67528	0.00409	0.0983
H9A	0.99523	0.79178	0.46023	0.0486
H9B	0.10988	0.92872	0.24917	0.0585
H10A	1.11672	0.81006	0.64452	0.0583

H10B	0.13179	1.14198	0.29070	0.0740	
H11A	1.01014	0.63563	0.70272	0.0622	
H11B	0.22518	1.25922	0.17979	0.0756	
H12A	0.78465	0.43889	0.57351	0.0615	
H12B	0.28412	1.15839	0.02091	0.0685	

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms

Table S4 - (An)isotropic Displacement Parameters for: 4.24

Atom	U(1,1) or U	U(2,2)	U(3,3)	U(2,3)	U(1,3)	U(1,2)
CL13A	0.0575	0.0471	0.0846	0.0329	0.0069	0.0023
CL13B	0.0698	0.0921	0.0473	0.0336	0.0282	0.0358
Cl5A	0.0489	0.0782	0.0382	0.0251	0.0164	0.0355
Cl5B	0.0405	0.0377	0.0627	0.0158	0.0183	0.0199
O1A	0.0317	0.0353	0.0596	0.0172	0.0069	0.0148
O1B	0.0291	0.0600	0.0659	0.0400	0.0140	0.0175
O3A	0.0378	0.0451	0.0577	0.0296	0.0267	0.0244
O3B	0.0538	0.0615	0.0385	0.0149	0.0111	0.0384
O9A	0.0371	0.0424	0.1142	0.0340	0.0348	0.0162
O9B	0.0590	0.0816	0.0506	0.0353	0.0325	0.0482
O10A	0.0276	0.0448	0.0907	0.0286	0.0066	0.0098
O10B	0.0474	0.1061	0.0672	0.0559	0.0361	0.0430
C2A	0.0322	0.0364	0.0496	0.0182	0.0164	0.0166
C2B	0.0339	0.0479	0.0449	0.0207	0.0091	0.0204
C4A	0.0309	0.0414	0.0460	0.0201	0.0160	0.0181
C4B	0.0410	0.0383	0.0408	0.0201	0.0147	0.0196
C5A	0.0276	0.0389	0.0354	0.0170	0.0131	0.0148
C5B	0.0285	0.0354	0.0390	0.0182	0.0141	0.0127
C6A	0.0340	0.0416	0.0430	0.0234	0.0109	0.0159
C6B	0.0334	0.0499	0.0536	0.0316	0.0189	0.0215
C7A	0.0676	0.0587	0.0510	0.0213	0.0278	0.0388
C7B	0.0520	0.0488	0.0717	0.0212	-0.0082	0.0135
C8A	0.0291	0.0380	0.0408	0.0170	0.0166	0.0188
C8B	0.0269	0.0433	0.0389	0.0175	0.0105	0.0183
C9A	0.0343	0.0387	0.0540	0.0192	0.0183	0.0190
C9B	0.0432	0.0683	0.0511	0.0291	0.0214	0.0340
C10A	0.0380	0.0494	0.0507	0.0094	0.0084	0.0220
C10B	0.0581	0.0747	0.0579	0.0132	0.0130	0.0481
C11A	0.0596	0.0675	0.0417	0.0216	0.0170	0.0414
C11B	0.0582	0.0512	0.0730	0.0183	0.0025	0.0317
C12	0.0575	0.0574	0.0583	0.0353	0.0288	0.0307
C12B	0.0465	0.0558	0.0697	0.0384	0.0113	0.0164
C13A	0.0343	0.0403	0.0525	0.0202	0.0171	0.0161
C13B	0.0320	0.0524	0.0409	0.0212	0.0095	0.0179

The Temperature Factor has the Form of Exp(-T) Where
T = 8*(Pi**2)*U*(Sin(Theta)/Lambda)**2 for Isotropic Atoms
T = 2*(Pi**2)*Sumij(h(i)*h(j)*U(i,j)*Astar(i)*Astar(j)), for
Anisotropic Atoms. Astar(i) are Reciprocal Axial Lengths and
h(i) are the Reflection Indices.

Table S5 - Bond Distances (Å) for: 4.24

CL13A	-C13A	1.7365	C8A	-C13A	1.3860
CL13B	-C13B	1.7413	C8B	-C9B	1.3861
Cl5A	-C5A	1.7791	C8B	-C13B	1.3848
Cl5B	-C5B	1.7837	C9A	-C10A	1.3723
O1A	-C2A	1.4479	C9B	-C10B	1.3728
O1A	-C6A	1.3251	C10A	-C11A	1.3683
O1B	-C2B	1.4230	C10B	-C11B	1.3666
O1B	-C6B	1.3504	C11A	-C12	1.3724
O3A	-C2A	1.4256	C11B	-C12B	1.3652
O3A	-C4A	1.3415	C12	-C13A	1.3822
O3B	-C2B	1.4491	C12B	-C13B	1.3861
O3B	-C4B	1.3189	C7A	-H7AA	0.9600
O9A	-C4A	1.1805	C7A	-H7AB	0.9600
O9B	-C4B	1.1991	C7A	-H7AC	0.9600
O10A	-C6A	1.2011	C7B	-H7BA	0.9600
O10B	-C6B	1.1800	C7B	-H7BB	0.9600
C2A	-C7A	1.5068	C7B	-H7BC	0.9600
C2A	-C8A	1.5212	C9A	-H9A	0.9300
C2B	-C7B	1.5091	C9B	-H9B	0.9300
C2B	-C8B	1.5147	C10A	-H10A	0.9300
C4A	-C5A	1.5480	C10B	-H10B	0.9300
C4B	-C5B	1.5299	C11A	-H11A	0.9300
C5A	-C5B	1.5588	C11B	-H11B	0.9300
C5A	-C6A	1.5244	C12	-H12A	0.9300
C5B	-C6B	1.5460	C12B	-H12B	0.9300
C8A	-C9A	1.3916			

Table S6 - Bond Angles　(°) for: 4.24

C2A	-O1A	-C6A	123.20	Cl5B	-C5B	-C4B	109.10
C2B	-O1B	-C6B	123.72	Cl5B	-C5B	-C5A	113.04
C2A	-O3A	-C4A	124.32	Cl5B	-C5B	-C6B	103.81
C2B	-O3B	-C4B	122.27	C4B	-C5B	-C5A	105.61
O1A	-C2A	-O3A	110.08	C4B	-C5B	-C6B	111.83
O1A	-C2A	-C7A	105.52	C5A	-C5B	-C6B	113.54
O1A	-C2A	-C8A	111.01	O1A	-C6A	-O10A	119.73
O3A	-C2A	-C7A	105.45	O1A	-C6A	-C5A	119.05
O3A	-C2A	-C8A	111.01	O10A	-C6A	-C5A	121.18
C7A	-C2A	-C8A	113.50	O1B	-C6B	-O10B	120.12
O1B	-C2B	-O3B	109.12	O1B	-C6B	-C5B	115.10
O1B	-C2B	-C7B	106.01	O10B	-C6B	-C5B	124.78
O1B	-C2B	-C8B	111.46	C2A	-C8A	-C9A	119.45
O3B	-C2B	-C7B	105.90	C2A	-C8A	-C13A	123.09
O3B	-C2B	-C8B	111.97	C9A	-C8A	-C13A	117.26
C7B	-C2B	-C8B	112.05	C2B	-C8B	-C9B	118.97
O3A	-C4A	-O9A	119.73	C2B	-C8B	-C13B	123.49
O3A	-C4A	-C5A	116.07	C9B	-C8B	-C13B	117.30
O9A	-C4A	-C5A	124.18	C8A	-C9A	-C10A	121.37
O3B	-C4B	-O9B	119.64	C8B	-C9B	-C10B	121.46
O3B	-C4B	-C5B	119.11	C9A	-C10A	-C11A	120.26
O9B	-C4B	-C5B	121.18	C9B	-C10B	-C11B	120.23

Cl5A	-C5A	-C4A	104.28		C10A	-C11A	-C12	119.87
Cl5A	-C5A	-C5B	113.45		C10B	-C11B	-C12B	119.80
Cl5A	-C5A	-C6A	107.88		C11A	-C12	-C13A	119.84
C4A	-C5A	-C5B	113.24		C11B	-C12B	-C13B	120.06
C4A	-C5A	-C6A	112.19		CL13A	-C13A	-C8A	122.25
C5B	-C5A	-C6A	105.83		CL13A	-C13A	-C12	116.38
C8A	-C13A	-C12	121.35		C8A	-C9A	-H9A	119.00
CL13B	-C13B	-C8B	122.60		C10A	-C9A	-H9A	119.00
CL13B	-C13B	-C12B	116.35		C8B	-C9B	-H9B	119.00
C8B	-C13B	-C12B	121.05		C10B	-C9B	-H9B	119.00
C2A	-C7A	-H7AA	109.00		C9A	-C10A	-H10A	120.00
C2A	-C7A	-H7AB	109.00		C11A	-C10A	-H10A	120.00
C2A	-C7A	-H7AC	109.00		C9B	-C10B	-H10B	120.00
H7AA	-C7A	-H7AB	109.00		C11B	-C10B	-H10B	120.00
H7AA	-C7A	-H7AC	109.00		C10A	-C11A	-H11A	120.00
H7AB	-C7A	-H7AC	109.00		C12	-C11A	-H11A	120.00
C2B	-C7B	-H7BA	109.00		C10B	-C11B	-H11B	120.00
C2B	-C7B	-H7BB	109.00		C12B	-C11B	-H11B	120.00
C2B	-C7B	-H7BC	109.00		C11A	-C12	-H12A	120.00
H7BA	-C7B	-H7BB	109.00		C13A	-C12	-H12A	120.00
H7BA	-C7B	-H7BC	109.00		C11B	-C12B	-H12B	120.00
H7BB	-C7B	-H7BC	109.00		C13B	-C12B	-H12B	120.00

Table S7 - Torsion Angles (°) for: 4.24

C6A	-O1A	-C2A	-O3A	-30.13		C7B	-C2B	-C8B	-C9B	100.25
C6A	-O1A	-C2A	-C7A	-143.44		O3B	-C2B	-C8B	-C9B	-140.92
C6A	-O1A	-C2A	-C8A	93.19		C7B	-C2B	-C8B	-C13B	-73.88
C2A	-O1A	-C6A	-C5A	-1.99		O1B	-C2B	-C8B	-C9B	-18.38
C2A	-O1A	-C6A	-O10A	175.92		O9A	-C4A	-C5A	-Cl5A	-78.66
C6B	-O1B	-C2B	-C8B	-77.98		O3A	-C4A	-C5A	-Cl5A	100.01
C2B	-O1B	-C6B	-C5B	-19.79		O3A	-C4A	-C5A	-C6A	-16.47
C2B	-O1B	-C6B	-O10B	159.75		O3A	-C4A	-C5A	-C5B	-136.20
C6B	-O1B	-C2B	-O3B	46.19		O9A	-C4A	-C5A	-C5B	45.12
C6B	-O1B	-C2B	-C7B	159.85		O9A	-C4A	-C5A	-C6A	164.85
C4A	-O3A	-C2A	-C7A	154.55		O3B	-C4B	-C5B	-C5A	152.16
C4A	-O3A	-C2A	-O1A	41.19		O3B	-C4B	-C5B	-C6B	28.20
C4A	-O3A	-C2A	-C8A	-82.12		O9B	-C4B	-C5B	-Cl5B	96.98
C2A	-O3A	-C4A	-O9A	161.03		O9B	-C4B	-C5B	-C5A	-24.80
C2A	-O3A	-C4A	-C5A	-17.71		O3B	-C4B	-C5B	-Cl5B	-86.05
C4B	-O3B	-C2B	-C8B	89.72		O9B	-C4B	-C5B	-C6B	-148.76
C2B	-O3B	-C4B	-C5B	-1.25		C4A	-C5A	-C5B	-C4B	61.83
C4B	-O3B	-C2B	-O1B	-34.15		C4A	-C5A	-C5B	-C6B	-175.30
C4B	-O3B	-C2B	-C7B	-147.87		C4A	-C5A	-C5B	-Cl5B	-57.38
C2B	-O3B	-C4B	-O9B	175.76		Cl5A	-C5A	-C5B	-Cl5B	61.22
O1A	-C2A	-C8A	-C9A	-137.87		Cl5A	-C5A	-C5B	-C4B	-179.57
O3A	-C2A	-C8A	-C9A	-15.09		Cl5A	-C5A	-C5B	-C6B	-56.69
C7A	-C2A	-C8A	-C13A	-71.21		Cl5A	-C5A	-C6A	-O10A	93.78
O1A	-C2A	-C8A	-C13A	47.44		C4A	-C5A	-C6A	-O1A	25.95
O3A	-C2A	-C8A	-C13A	170.22		C4A	-C5A	-C6A	-O10A	-151.93
C7A	-C2A	-C8A	-C9A	103.48		C5B	-C5A	-C6A	-O1A	149.91
O3B	-C2B	-C8B	-C13B	44.95		C5B	-C5A	-C6A	-O10A	-27.97
O1B	-C2B	-C8B	-C13B	167.50		C6A	-C5A	-C5B	-C4B	-61.48

C6A	-C5A	-C5B	-C6B	61.40		C13B	-C8B	-C9B	-C10B	-2.86	
Cl5A	-C5A	-C6A	-O1A	-88.34		C2B	-C8B	-C13B	-CL13B	-1.20	
C6A	-C5A	-C5B	-Cl5B	179.31		C2B	-C8B	-C13B	-C12B	177.61	
C5A	-C5B	-C6B	-O1B	-137.27		C9B	-C8B	-C13B	-CL13B	-175.41	
C5A	-C5B	-C6B	-O10B	43.21		C9B	-C8B	-C13B	-C12B	3.39	
C4B	-C5B	-C6B	-O10B	162.59		C8A	-C9A	-C10A	-C11A	0.37	
Cl5B	-C5B	-C6B	-O1B	99.59		C8B	-C9B	-C10B	-C11B	0.26	
Cl5B	-C5B	-C6B	-O10B	-79.93		C9A	-C10A	-C11A	-C12	1.17	
C4B	-C5B	-C6B	-O1B	-17.89		C9B	-C10B	-C11B	-C12B	1.91	
C2A	-C8A	-C9A	-C10A	-177.20		C10A	-C11A	-C12	-C13A	-0.78	
C13A	-C8A	-C9A	-C10A	-2.20		C10B	-C11B	-C12B	-C13B	-1.37	
C2A	-C8A	-C13A	-CL13A	-0.58		C11A	-C12	-C13A	-CL13A	176.93	
C2A	-C8A	-C13A	-C12	177.39		C11A	-C12	-C13A	-C8A	-1.15	
C9A	-C8A	-C13A	-CL13A	-175.38		C11B	-C12B	-C13B	-CL13B	177.53	
C9A	-C8A	-C13A	-C12	2.59		C11B	-C12B	-C13B	-C8B	-1.34	
C2B	-C8B	-C9B	-C10B	-177.35							

Table S8 - Contact Distances(Å) for: 4.24

A1	A2	d	A1	A2	d	A1	A2	d	A1	A2	d
CL13A	.O1A	2.9307	Cl5B	.O10B	3.2168	Cl5B	.C4A	3.2286	O9A	.C5B	3.0032
CL13A	.C2A	3.1491	Cl5B	.O9A	2.9532	Cl5B	.O9B	3.4337	O9A	.C4B	3.3812
CL13A	.C7A	3.4139	Cl5B	.C2B	3.5349	O9A	.Cl5A	3.2073	O3A	.H7AC	2.5200
CL13A	.C10B_a	3.5996	CL13A	.H12A	2.7300	O9A	.Cl5B	2.9532	O3A	.H9A	2.3700
CL13A	.C11B_a	3.2480	CL13A	.H7AA	2.7800	O9A	.O9B	3.0504	O3A	.H7AB	2.5200
CL13A	.Cl5A_b	3.6827	CL13B	.H7BA	2.8500	O9B	.Cl5B	3.4337	O3B	.H7BB	2.5100
CL13B	.O3B	2.9226	CL13B	.H10A_c	3.1500	O9B	.O3A	3.0581	O3B	.H7BA	2.5700
CL13B	.C2B	3.1652	CL13B	.H12B	2.7300	O9B	.O9A	3.0504	O9A	.H10A_e	2.7800
CL13B	.CL13B_d	3.6572	Cl5B	.H10A_e	2.9800	O9B	.C5A	2.6674	O9B	.H12B_d	2.6000
CL13B	.C7B	3.4681	O1A	.CL13A	2.9307	O9B	.C6A	2.8858	O10A	.H7BB_h	2.9000
Cl5A	.C2A	3.5898	O1A	.Cl5A	3.3854	O9B	.C4A	2.6132	O10B	.H12A_b	2.6400
Cl5A	.O10B	2.9639	O1A	.C4A	2.8261	O10A	.O10B	2.9942	C2A	.CL13A	3.1491
Cl5A	.O10A	3.3766	O1A	.C13A	2.9792	O10A	.C7B_h	3.1340	C2A	.Cl5A	3.5898
Cl5A	.O1A	3.3854	O1B	.O10A	3.0972	O10A	.C5B	2.6824	C2A	.C5A	2.8610
Cl5A	.O9A	3.2073	O1B	.C4B	2.7260	O10A	.O1B	3.0972	C2B	.C5B	2.8393
Cl5A	.Cl5B	3.4014	O1B	.Cl5B	3.4170	O10A	.C6B	2.6112	C2B	.CL13B	3.1652
Cl5A	.C6B	3.2327	O1B	.C9B	2.7389	O10A	.C4B	2.9285	C2B	.Cl5B	3.5349
Cl5A	.O3A	3.4329	O3A	.C9A	2.7394	O10A	.Cl5A	3.3766	C4A	.O9B	2.6132
Cl5A	.CL13A_b	3.6827	O3A	.O9B	3.0581	O10B	.O10A	2.9942	C4A	.C9A	3.3082
Cl5A	.C8A	3.4650	O3B	.C7A_g	3.3358	O10B	.C9A_f	3.4195	C4A	.Cl5B	3.2286
Cl5A	.C9A	3.5791	O3B	.Cl5B	3.3900	O10B	.Cl5B	3.2168	C4A	.O1A	2.8261
Cl5B	.O3B	3.3900	O3B	.C13B	2.9833	O10B	.Cl5A	2.9639	C4A	.C8A	3.2018
Cl5B	.O1B	3.4170	O3B	.CL13B	2.9226	O10B	.C6A	3.3633	C4A	.C4B	2.9795
Cl5B	.C9B	3.4833	O3B	.C6B	2.8311	O10B	.C5A	3.0062	C4A	.C7A	3.5940
Cl5B	.C8B	3.3352				O1A	.H7AA	2.5600	C4B	.O10A	2.9285
Cl5B	.Cl5A	3.4014				O1A	.H7AB	2.5000	C4B	.C8B	3.2557
						O1B	.H9B	2.3700	C4B	.C7B	3.5609
						O1B	.H7BB	2.5300	C4B	.O1B	2.7260
						O1B	.H7AC_f	2.7000	C4B	.O9A	3.3812
						O1B	.H7BC	2.5300	C4B	.C4A	2.9795
						C4B	.C6A	2.8200	C7B	.C4B	3.5609
						C5A	.C2A	2.8610	C7B	.C9B	3.4070
						C5A	.O10B	3.0062	C7B	.O10A_h	3.1340
						C5A	.O9B	2.6674	C7B	.CL13B	3.4681

C5A	.C8A	3.5148	C7B	.C13B	3.2387	
C5B	.C2B	2.8393	C8A	.C11A	2.7863	
C5B	.C8B	3.4424	C8A	.C6A	3.2883	
C5B	.O10A	2.6824	C8A	.Cl5A	3.4650	
C5B	.O9A	3.0032	C8A	.C4A	3.2018	
C6A	.C4B	2.8200	C8A	.C5A	3.5148	
C6A	.C8A	3.2883	C8B	.C11B	2.7843	
C6A	.O10B	3.3633	C8B	.C6B	3.1661	
C6A	.O3A	2.7468	C8B	.C5B	3.4424	
C6A	.O9B	2.8858	C8B	.Cl5B	3.3352	
C6A	.C7A	3.5443	C8B	.C4B	3.2557	
C6A	.C6B	2.9813	C9A	.C12	2.7435	
C6B	.C6A	2.9813	C9A	.Cl5A	3.5791	
C6B	.Cl5A	3.2327	C9A	.C7A	3.4690	
C6B	.O10A	2.6112	C9A	.O3A	2.7394	
C6B	.O3B	2.8311	C9A	.C4A	3.3082	
C6B	.C9B	3.2775	C9A	.O10B_i	3.4195	
C6B	.C8B	3.1661	C9B	.Cl5B	3.4833	
C7A	.CL13A	3.4139	C9B	.O1B	2.7389	
C7A	.C13A	3.2422	C9B	.C12B	2.7366	
C7A	.C4A	3.5940	C9B	.C6B	3.2775	
C7A	.C6A	3.5443	C9B	.C7B	3.4070	
C7A	.C9A	3.4690	C10A	.C13A	2.7418	
C7A	.O3B_g	3.3358	C10B	.C13B	2.7389	
C10B	.CL13A_k	3.5996	H7AA	.C8A	2.7100	
C11A	.C8A	2.7863	H7AA	.C13A	2.9900	
C11A	.C13A_l	3.5271	H7AB	.O1A	2.5000	
C11B	.C8B	2.7843	H7AB	.O3A	2.5200	
C11B	.CL13A_k	3.2480	H7AC	.O1B_i	2.7000	
C12	.C9A	2.7435	H7AC	.O3A	2.5200	
C12B	.C9B	2.7366	H7AC	.C8A	2.7400	
C13A	.O1A	2.9792	H7BA	.CL13B	2.8500	
C13A	.C7A	3.2422	H7BA	.O3B	2.5700	

C13A	.C10A	2.7418	H7BA	.C8B	2.6800
C13A	.C11A_l	3.5271	H7BA	.C13B	2.9800
C13B	.C10B	2.7389	H7BA	.H11B_m	2.5700
C13B	.C7B	3.2387	H7BB	.O1B	2.5300
C13B	.O3B	2.9833	H7BB	.O3B	2.5100
C2A	.H9A	2.6500	H7BB	.O10A_h	2.9000
C2B	.H9B	2.6300	H7BB	.H7BB_h	2.2300
C4A	.H9A	2.8500	H7BC	.O1B	2.5300
C6B	.H9B	2.8400	H7BC	.C8B	2.7100
C8A	.H7AA	2.7100	H9A	.O3A	2.3700
C8A	.H7AC	2.7400	H9A	.C2A	2.6500
C8B	.H7BC	2.7100	H9A	.C4A	2.8500
C8B	.H7BA	2.6800	H9A	.H10A	2.2900
C10A	.H10B_j	2.7300	H9B	.O1B	2.3700
C11A	.H10B_j	3.0500	H9B	.C2B	2.6300
C13A	.H7AA	2.9900	H9B	.C6B	2.8400
C13B	.H7BA	2.9800	H9B	.H10B	2.2900
H7AA	.CL13A	2.7800	H10A	.CL13B_n	3.1500
H7AA	.O1A	2.5600	H10A	.H9A	2.2900
H10A	.H11A	2.3000	H11B	.H10B	2.3000
H10A	.Cl5B_e	2.9800	H11B	.H12B	2.3000
H10A	.O9A_e	2.7800	H11B	.H7BA_m	2.5700
H10B	.H9B	2.2900	H12A	.CL13A	2.7300
H10B	.H11B	2.3000	H12A	.H11A	2.3000
H10B	.C10A_j	2.7300	H12A	.O10B_b	2.6400
H10B	.C11A_j	3.0500	H12B	.CL13B	2.7300
H11A	.H10A	2.3000	H12B	.H11B	2.3000
H11A	.H12A	2.3000	H12B	.O9B_d	2.6000

Translation of Symmetry Code to Equiv.Pos

a =[1545.00] =   x,-1+y,z
b =[2666.00] =   1-x,1-y,1-z
c =[1454.00] =   -1+x,y,-1+z
d =[2675.00] =   1-x,2-y,-z
e =[2776.00] =   2-x,2-y,1-z
f =[1455.00] =   -1+x,y,z
g =[2665.00] =   1-x,1-y,-z
h =[2565.00] =   -x,1-y,-z
i =[1655.00] =   1+x,y,z
j =[2676.00] =   1-x,2-y,1-z
k =[1565.00] =   x,1+y,z
l =[2766.00] =   2-x,1-y,1-z
m =[2575.00] =   -x,2-y,-z
n =[1656.00] =   1+x,y,1+z

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