Asymmetric synthesis of pharmaceutically important lactones and cyclic ketones

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School of Chemical Sciences

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Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of (Master of Science) is entirely my own work, and that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge breach any law of copyright, and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

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Abbreviations

δ	Chemical shift in parts per million relative to deuterated chloroform
d	Doublet (NMR spectra)
D-A	Donor-acceptor
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMSO	Dimethyl sulfoxide
DMF	Dimethyl formamide
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent
EtOAc	Ethyl acetate
H	Hours
HPLC	High performance liquid chromatography
Hz	Hertz
LDA	Lithium Diisopropylamide
i	Iso
IR	Infrared
J	Coupling constant (NMR spectra)
M	Moles per litre
m	multiplet (NMR spectra)
MHz	Megahertz
n-BuLi	*n*-butyllithium
NMR	Nuclear magnetic resonance (spectroscopy)
ppm	Parts per million (NMR spectra)
PPTS	Pyridinium *p*-toluenesulfonate

q	Quartet (NMR spectra)
rt	Room temperature
s	Singlet (NMR spectra)
t	Triplet (NMR spectra)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilane or trimethylsilyl
TLC	Thin layer chromatography

Abstract

The work in this thesis is divided into three parts: (A) Investigation of the synthesis of lactones from sulfoxonium salts; (B) Investigation of the synthesis of cyclohexanones from donor-acceptor cyclobutanes and ketenes; (C) The synthesis of cyclopentanones from donor-acceptor cyclopropanes and ketenes.

A synthetic route to formation of a delta-lactone from cyclopropylamino sulfoxonium salts was initially explored. Multiple reactant partners (e.g. lithium enediolate, lithium enolates, ketene) were tested and although lactone formation was not achieved, ring-opening of the cyclopropyl salt was observed under much milder conditions than previous literature findings (0°C to RT vs >65°C).

Research into the synthesis of monocyclic gamma-lactones from vinyl sulfoxonium salts was also pursued. This was inspired by previous work from the group and aimed to introduce new substitution patterns on the gamma-lactone ring. Both the phenyl-substituted vinyl sulfoxonium salt and the isopropyl-substituted vinyl sulfoxonium salt were investigated for this reaction. Carboxylic acids such as dichloroacetic acid, α-methoxyphenylacetic acid, methoxyacetic acid, 4-methyl-2-phenylpentanoic acid and 4-methylvaleric acid were tested as enediolate precursors. Different bases such as LDA, NaHDMS and *n*-Butyllithium were tested to verify their ability to deprotonate the carboxylic acid to enable gamma-lactone formation to occur.

Other significant research was carried out on the development of a synthetic route to cyclohexanones from donor-acceptor cyclobutanes and ketenes. The reactant partners for this reaction have been synthesized in good yields, the phenyl-substituted donor-acceptor cyclobutane being synthesized in 54% yield, and its precursor 1,3-dibromopropylbenzene synthesized in yields of up to 82%. A variety of Lewis acids including $InBr_3$, $AlCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$ and $GaCl_3$ were explored for their effectiveness in promoting the [4+2]-cycloaddition reaction.

Most significantly, through the reaction of a donor-acceptor cyclopropane and a ketene generated in-situ from propionyl chloride a range of substituted cyclopentanones were also synthesized in yields ranging between 56-92% with excellent diastereoselectivity.

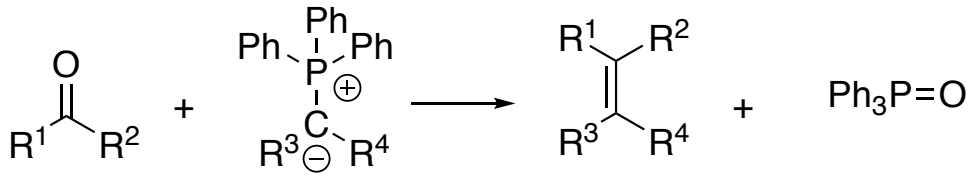
Chapter 1:

Application of sulfoxonium salts to the synthesis of lactones

1.1 Introduction to Sulfoxonium Salts

Sulfoxonium salts have found many uses in organic synthesis. The most important and widely used sulfoxonium salts include alkyl-substituted sulfoxonium salts, vinyl sulfoxonium salts and cyclopropyl sulfoxonium salts.

Ylides were first defined in the 1920's by Staudinger as a neutral dipolar molecule containing a negatively charged atom, most often a carbanion, that is attached to a heteroatom with a formal positive charge. Although discovered by Staudinger, it wasn't until later in the 1950s and 1960s that their use became popularized, and in 1979 Georg Wittig won a Nobel prize for his work concerning the employment of phosphonium ylides in the synthesis of alkenes.[1,2] This reaction, named the Wittig-reaction after its inventor, produces substituted alkenes from aldehydes and ketones through attack of the carbonyl by phosphorous ylides (Scheme 1).



SCHEME 1: WITTIG REACTION

Not long after the discovery of the Wittig reaction, interest began to emerge regarding the wide scope and importance of other types of ylide.

Sulfur ylides, which were first discovered in 1930 by Ingold and Jessop[3], were popularized by A.W. Johnson along with Corey and Chaykovksy. Their work on the use of sulfur ylides for the synthesis of epoxides, aziridines and cyclopropanes has undoubtably become one of the most well-known examples of the application of sulfur ylide chemistry. Since then, the uses for these popular ylides have expanded to show its ability to act as an integral part in insertion reactions, cycloaddition reactions and annulation reactions. Sulfur ylides can be divided into

two main classes: sulfonium ylides and sulfoxonium ylides. The difference between these two classes depend on the oxidation state of the sulfur atom, with the sulfonium ylide being less stabilized and having greater nucleophilicity at the α-carbon. On the other hand, the sulfoxonium ylide displays better delocalization of the negative charge leading to lower C-nucleophilicity. Another property that makes the sulfoxonium ion attractive to synthetic chemists is the availability of the oxygen atom to coordinate to Lewis acids and facilitate asymmetric catalysis.

Sulfonium ylide Sulfoxonium ylide

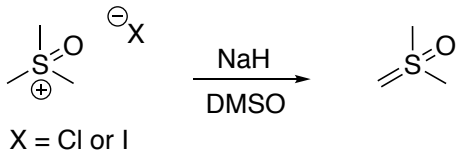
SCHEME 2: SULFONIUM YLIDE VS SULFOXONIUM YLIDE

It is not surprising that sulfur ylides generated such traction considering sulfur's ability to stabilize the adjacent negatively charged carbanion. It was originally presumed in some of Johnson's earlier published work regarding sulfur ylides that this stabilization was due to the availability of empty low-lying d-orbitals for stabilization of delocalized electron density of the carbanion.[4] Thanks to modern computational chemistry, our understanding of this has changed. Instead, it is understood that the stabilization is mostly due to large electrostatic attraction, as well as an overlap between the carbanion lone pair orbital *n* with the σ* orbital of the sulfur-carbon bond (negative hyperconjugation).[5–7]

Sulfur ylides can be defined as "stabilized" or "unstabilised". Stabilized ylides have an electron-withdrawing group at the nucleophilic α-carbon that can delocalize the electron density of the carbanion. These ylides are storable and have much longer half-life's than their unstabilised counterpart. In comparison, unstabilised sulfur ylides do not have groups capable of delocalizing the anionic charge and are therefore only suited to in situ reactions at low temperatures. Although these sulfur ylides present the challenge of being more difficult to handle, their enhanced reactivity in contrast to their stabilized analogues is an important asset to synthetic chemists.

1.1.1 Preparation of Sulfoxonium ylides and sulfoxonium salts

In 1962, Corey and Chaykovsky reported the first synthesis of dimethylsulfoxonium methylide, formed through the reaction of trimethylsulfoxonium iodide or chloride in the presence of sodium hydride in DMSO (Scheme 3).[8,9] It was noted that tetrahydrofuran or 1,4-dioxane were also suitable solvent systems for an efficient reaction.



SCHEME 3: COREY AND CHAYKOVSKY'S PREPARATION OF SULFOXONIUM YLIDE

The four most common methods of sulfoxonium ylide preparation are as follows; (1) base-mediated deprotonation of sulfoxonium salt (as above)(1) nucleophilic addition of methylide 1 to acyl derivatives, (2) conjugate addition of methylide 1 to alkynes with electron withdrawing substitutents, (3) conjugate addition of methylide 1 to β-chloro substituted unsaturated ketones or imidoyl chlorides and (4) addition of sulfoxides to metal carbenoids.[10]

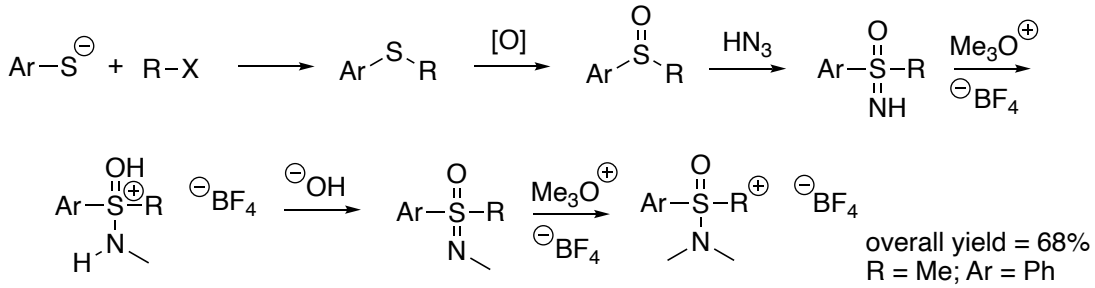
Only a few years later in 1970, the first reported synthesis of aminosulfoxonium salts was published by C.R. Johnson and co-workers.[11]

Originally, Johnson and co-workers noted the limitations regarding accessing a range of trialkylsulfoxonium salts from previously published methods. Previously, access to the trimethylsulfoxonium salt occurred through S-methylation of dimethyl sulfoxide. It was noted that this method produced a limited range of substituted sulfoxonium salts, so the group focused on a new method of preparation.

This work proved successful and allowed access to a new-type of sulfoxonium salt, one that could offer extensive structural variation-, namely the -(dialkylamino)sulfoxonium salt.

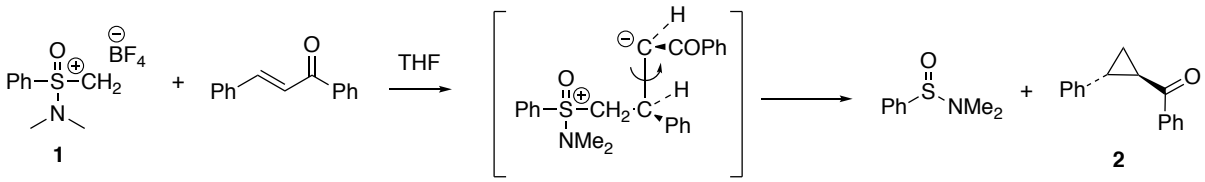
The first step in this synthesis, the alkylation of an arenethiolate, produced a range of aryl-alkyl sulfides with tolerance for a range of alkyl groups. Subsequent oxidation of this sulfide produces the corresponding sulfoxide, followed by conversion of the sulfoxide to the sulfoximine. It was found that in the case of methylphenylsulfoxide this last step occurred in

high yield (92%) when conducted in the presence of hydrazoic acid. Alkylation of the synthesized sulfoximines to give (dimethylamino)sulfoxonium fluoroborates was accomplished in high yield when the methylating agent, trimethyloxonium tetrafluoroborate, was utilized.



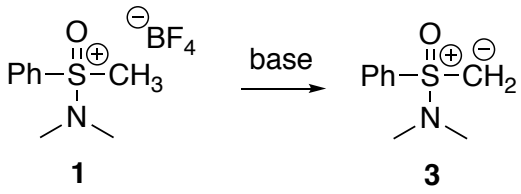
SCHEME 4: PREPARATION OF ALKYLARYLAMINOSULFOXONIUM SALTS

Johnson et al also demonstrated access to cyclopropane **2** in the same publication, through reaction of sulfoxonium salt **1** with benzalacetophenone in THF (Scheme 4). This reaction occurred at room temperature and had an impressive 100% yield, requiring only 4 hours reaction time.



SCHEME 5: PREPARATION OF TRANS-1-BENZOYL-2-PHENYLCYCLOPROPANE

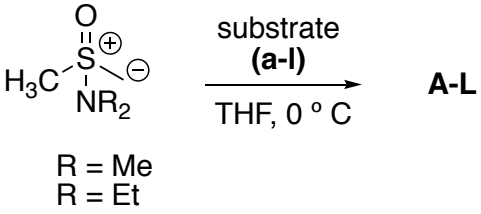
Sulfoxonium salt **1** was treated with a base to obtain ylide **3** which was subsequently subjected to a reaction with a range of electrophilic olefins to investigate its reactivity. It was found that reaction with *p*-chlorobenzaldehyde and 4-*tert*-butylcyclohexanone produced the corresponding oxiranes, while reaction with benzalaniline gave the corresponding aziridine. Access to stable ylides could be afforded through reaction of ylide **3** with benzoyl chloride or phenyl isocyanate.

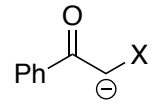
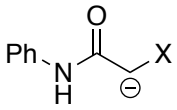
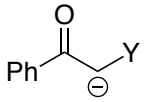
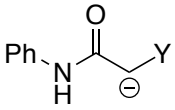
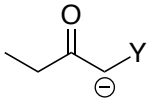
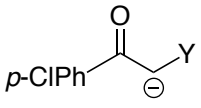


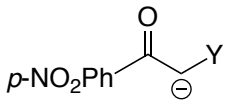
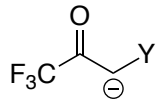
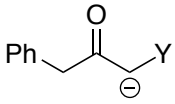
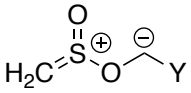
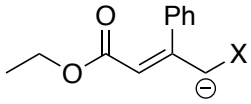
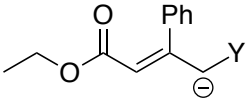
1 **3**

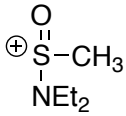
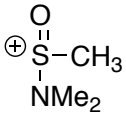
In 1973 Johnson and co-workers published a more expansive scope demonstrating the variety of stabilized sulfoxonium ylides available from (dialkylamino)sulfoxonium salts.[12] The results of this work are outlined in table 1.

TABLE 1: PREPARATION OF STABILIZED YLIDES



Substrate	***Stabilized ylide***	***Yield, %***
(a) Benzoic anhydride	**(A)** 	53
(b) Phenyl isocyanate	**(B)** 	83
(c) Benzoyl chloride	**(C)** 	60
(d) Phenyl isocyanate	**(D)** 	75
(e) Acetic anhydride	**(E)** 	65
(f) *p*-Chlorobenzoyl chloride	**(F)** 	65

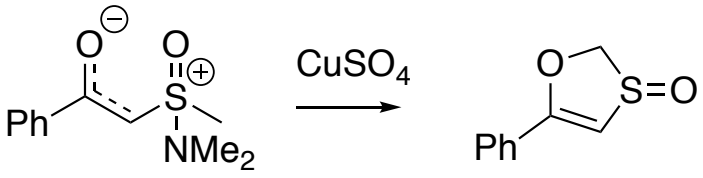
(g) *p*-Nitrobenzoyl chloride	**(G)** 	82
(h) Trifluoroacetic anhydride	**(H)** 	31
(i) Phenylacetyl chloride	**(I)** 	52
(j) Methanesulfonyl chloride	**(J)** 	58
(k) Ethyl phenylpropiolate	**(K)** 	38
(l) Ethyl phenylpropiolate	**(L)** 	55

X =  Y = 

In all cases, better yields were afforded with the sulfoximine with N-methylation rather than the ethyl substituted counterpart. O-alkylation of the benzoyl- and acetyl-stabilized ylides using trimethyl- and triethyloxonium tetrafluororborate was also tolerated.

It was found that a mixture of diastereomeric vinyl salts were obtained for all cases studied.

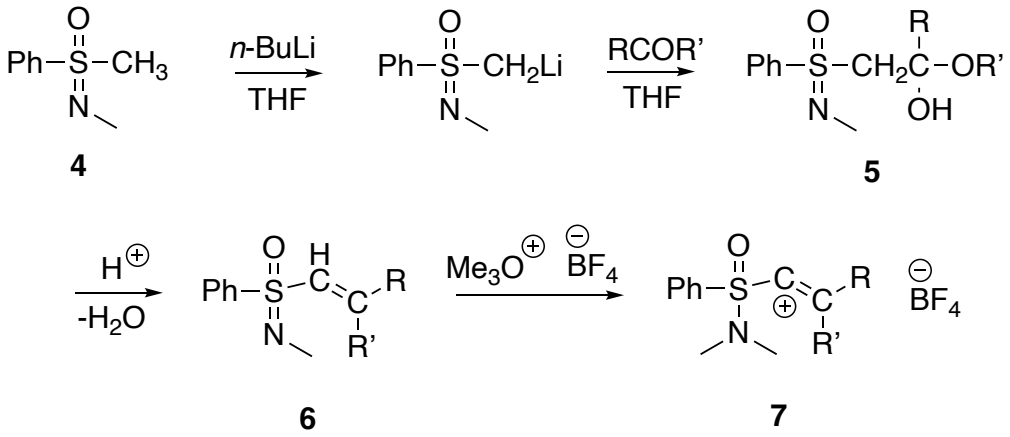
This work also described facile access to 1,3-oxathiole 3-oxides through reaction of various ylides with 2 equivalents of anhydrous cupric sulfate in benzene.



SCHEME 6: SYNTHESIS OF 1,3-OXATHIOLE 3-OXIDES

Johnson and co-workers also published work detailing the synthesis and characterization of vinylsulfoxonium salts.[13]

Sulfoximine **4** was deprotonated through treatment with a strong base and subsequently submitted to an addition reaction in the presence of an aldehyde or a ketone to produce **5**. Dehydration of this intermediate with acid afforded vinyl sulfoximine **6** which was then N-methylated through use of Meerwein's salt to afford **7**.

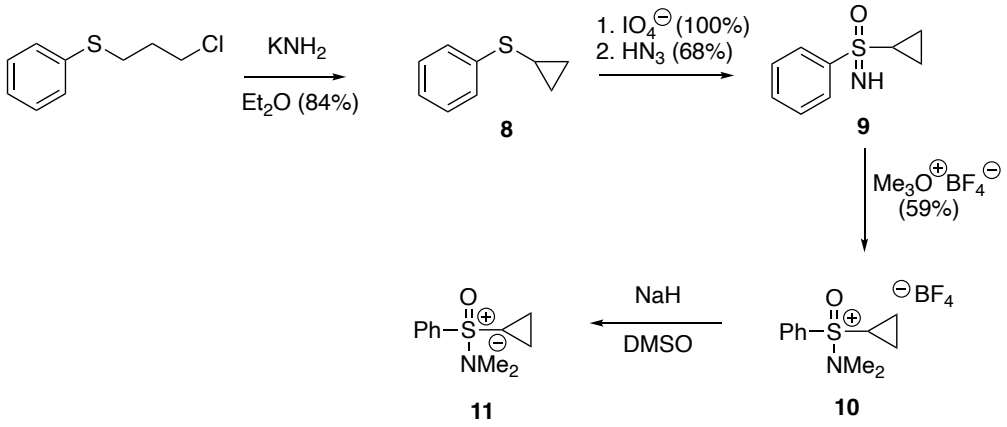


SCHEME 7: SYNTHESIS OF VINYLAMINOSULFOXONIUM SALTS

This article also detailed that this method is applicable to asymmetric synthesis, with optically pure (-)-(S)-N,S-dimethyl-S-phenylsulfoximine producing the optically active (-)-(S)-N,S-dimethyl-S-phenylsulfoxonium salt. Reaction of optically active compound (-)-(S)-**7** (where R' = H, R = Ph) with methyl cyanoacetate in methanol and sodium methoxide allowed access to exclusively the (E)-isomer in 81% yield.

1.1.2 Preparation of cyclopropylsulfoxonium salts

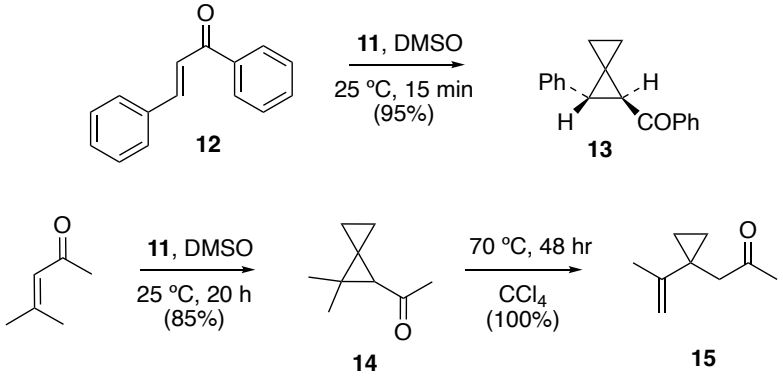
One of the earliest examples of the synthesis of cyclopropylaminosulfoxonium salts came from C.R Johnson in 1971 which occurred through the base-induced cyclization of (3-halopropyl)sulfoxonium salts.[14,15] Treatment of 3-chloropropyl phenyl sulfide with potassium amide in diethyl ether generated cyclopropane **8** in 84% yield. Subsequent reaction with a periodate ion followed by treatment with hydrazoic acid afforded cyclopropylaminosulfoximine **9** in 68% yield. Methylation of this compound with Meerwein's salt afforded cyclopropylsulfoxonium salt **10** in 59% yield. Treatment with sodium hydride in DMSO afforded stable cyclopropylide **11**, which was found to have a half-life of approximately 4 days (Scheme 8).



SCHEME 8: SYNTHESIS OF CYCLOPROPYLAMINOSULFOXONIUM SALT

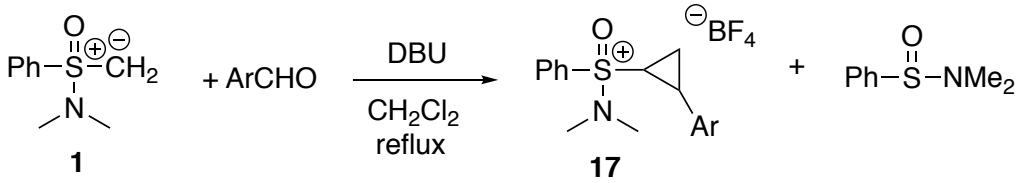
Johnson demonstrated the significance of this compound by describing the synthesis of a range of spiropentanes from the reaction of ylide **11** with unsaturated carbonyl compounds (or Mannich bases). Impressively, reaction of ylide **11** with chalcone (**12**) in DMSO at 25 °C requiring only 15 minutes reaction time afforded spiropentane **13** in 95% yield (Scheme 9).

Reflux of spiropentane **14** in carbon tetrachloride allowed for a quantitative rearrangement to 1-acetonyl-1-isopropenylcyclopropane **15**, which imitated a similar thermolysis published some years prior.[16]



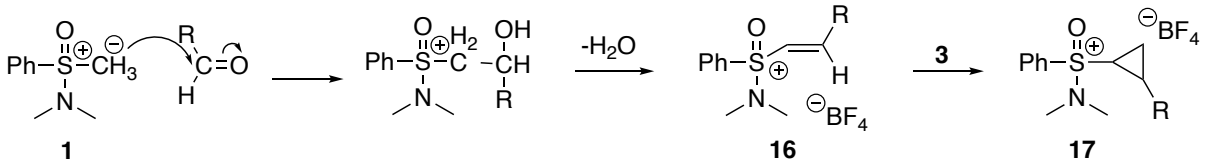
SCHEME 9: REACTION OF YLIDE 11 WITH α,β-UNSATURATED CARBONYL COMPOUNDS

In 1994, Okuma and co-workers published an article describing the synthesis of cyclopropylaminosulfoxonium salts from (Dimethylamino)phenylsulfoxonium methylide.[17] Cyclopropylaminosulfoxonium salt **17** was obtained in good yield through treatment of sulfoxonium salt **1** with DBU, followed by the addition of an aldehyde in refluxing dichloromethane (Scheme 10). Cyclopropylaminosulfoxonium salts **17** were obtained as a mixture of *cis* and *trans* isomers in a 2:3 ratio.



SCHEME 10: SYNTHESIS OF CYCLOPROPYLAMINOSULFOXONIUM SALT

Using CH_2Cl_2 as the reaction solvent was found to be essential for successful synthesis of the cyclopropyl salt, as was the use of DBU as a base. When stronger bases such as dimsyl sodium or sodium *tert*-butoxide were employed in the reaction the corresponding epoxides were afforded. As DBU is not a strong base, DBU:HBF_4 can act as a proton source for the betaine intermediate which can subsequently result in the formation of (2-hydroxyalkyl)sulfoxonium salts. Dehydration of these salts can produce vinylsulfoxonium salts **16** which subsequently react with additional ylide **3** to give the salts **17** (Scheme 11). Refluxing dichloromethane also plays an essential role in this process as it allows for the dehydration step to occur faster, reducing the likelihood of reversion back to starting materials.



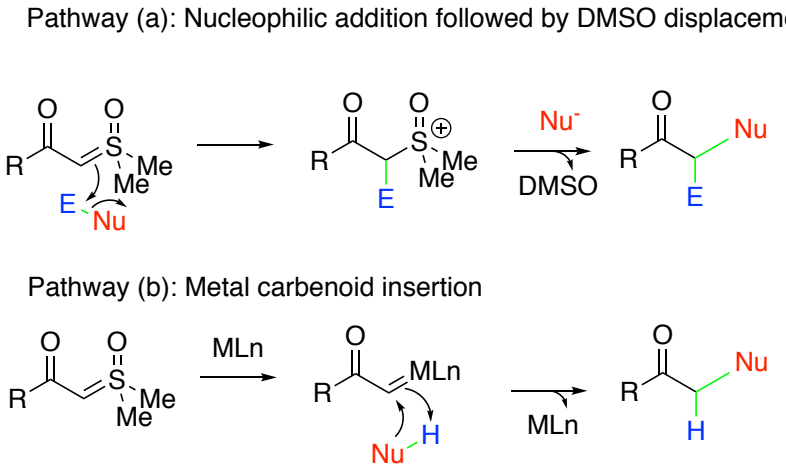
SCHEME 11: MECHANISTIC PATHWAY FOR THE SYNTHESIS OF CYCLOPROPYLAMINOSULFOXONIUM SALTS

1.1.3 Reactions of sulfoxonium salts

1.1.3.1 Insertion Reactions of Sulfoxonium Ylides

Despite the large advancements in the area of insertion reactions using diazo compounds, the toxicity and potential explosive property of diazo compounds and the side products of their reactions, such as N_2 gas, have always been a concern particularly regarding large scale production. Sulfoxonium ylides have been investigated as more stable and less toxic substitutes for carbenoid transfer reactions.[18]

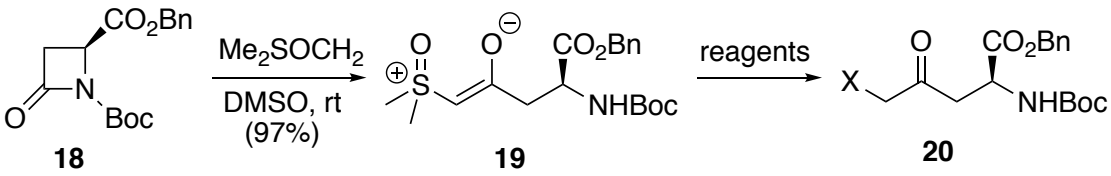
The use of sulfoxonium ylides in formal insertion reactions has been widely reported in recent years and has proven capable of facilitating reactions into X-H, C-H, C-X and X-Y bonds. There are two main pathways by which this reaction occurs. The first (pathway (a)) is through reaction of the electrophilic portion of a polarized Nu-E bond with the nucleophilic carbon of the sulfoxonium ylide, followed by DMSO displacement by the nucleophilic species. The second pathway (pathway (b)) sees sulfoxonium ylides combined with transition metals to afford metal carbenoids (Scheme 12).



SCHEME 12: SULFOXONIUM YLIDE INSERTION PATHWAYS

Pathway A, in general, is more straight forward and less likely to form the undesired dimer of the sulfoxonium ylide. In contrast, pathway B is more susceptible to the formation of this dimer. This is because after replacement of the ylide with the MLn species, the α-carbon becomes electrophilic and reaction with the nucleophilic α-carbon of the original starting ylide structure becomes far more likely.[19,20]

The first reported use of a metal-catalysed insertion reaction with sulfoxonium ylides was by Baldwin and co-workers in 1993.[21–23] This group had previously reported the utilization of pathway (a) for insertion of various X-H reagents into a β-ketosulfoxonium ylide (**19**) formed from ring-opening of an *N*-Boc lactam with dimethylsulfoxonium methylide. This produced a series of δ-substituted γ-oxo-α-aminoacids (Scheme 13)(Table 2).

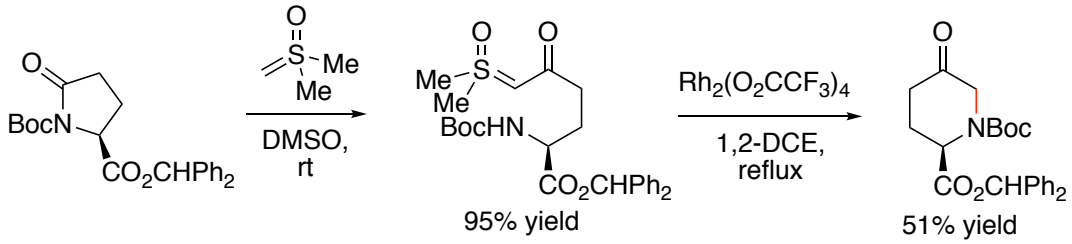


SCHEME 13: SYNTHESIS OF δ-SUBSTITUTED γ-OXO-α-AMINOACIDS (BALDWIN ET AL.)

TABLE 2: SYNTHESIS OF δ-SUBSTITUTED γ-OXO-α-AMINOACIDS

Reagents	***Products (20)***	***Yield (%)***
1M HCl/AcOH (1 eq), DMF	X = Cl	74
47% HBr/AcOH (1eq),DMF	X = Br	62
35% HI/H_2O (1eq), DMF	X = H	48
TFA (cat.), NaBr (cat), H_2O, DMF then acetic formic anhydride, pyridine	X= OCHO	62
57% HBr/H_2O (1 eq), DMF, 50 °C	X = OCHO X = OH	47 28
MeI, DMF then Zn/AcOH	X = Me X = H	65 8

The group's 1993 work was inspired by the inability to cyclize this δ-substituted γ-oxo-α-aminoacid (X = Br) directly to a substituted 4-oxopyrrolidine. They hypothesized that conversion of the β-ketosulfoxonium ylide into a rhodium carbenoid would allow for intramolecular N-H insertion to form the desired product. The rhodium catalyst $Rh_2(O_2CCF_3)_4$ was found to work well affording a one carbon ring expansion of the gamma-lactam in 51% yield. (Scheme 14).

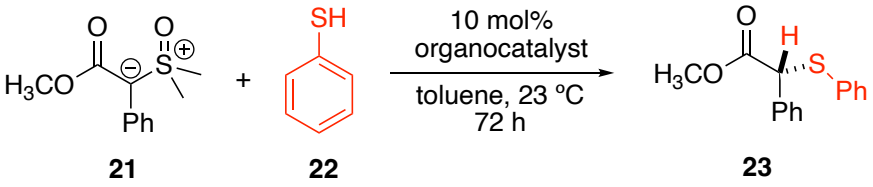


SCHEME 14: SYNTHESIS OF CARBENOID SPECIES FROM β-KETOSULFOXONIUM YLIDES (BALDWIN ET AL.)

A more recent advancement in the area of insertion reactions of sulfoxonium ylides comes from Momo and co-workers on their developments in the enantioselective S-H insertion of α-carbonyl sulfoxonium ylides.[24] Over the past decade there have been increasing numbers of publications involving non-enantioselective N-H, S-H and O-H insertion reactions, mostly involving transition metal catalyst systems. Mangion and co-workers contributed significantly to this area regarding their work with Iridium and Gold catalyst systems. More recent work involving copper catalyst systems for N-H insertion was reported by Furniel and Burtoloso and Zhang reported P-H insertion.[19,25–28]

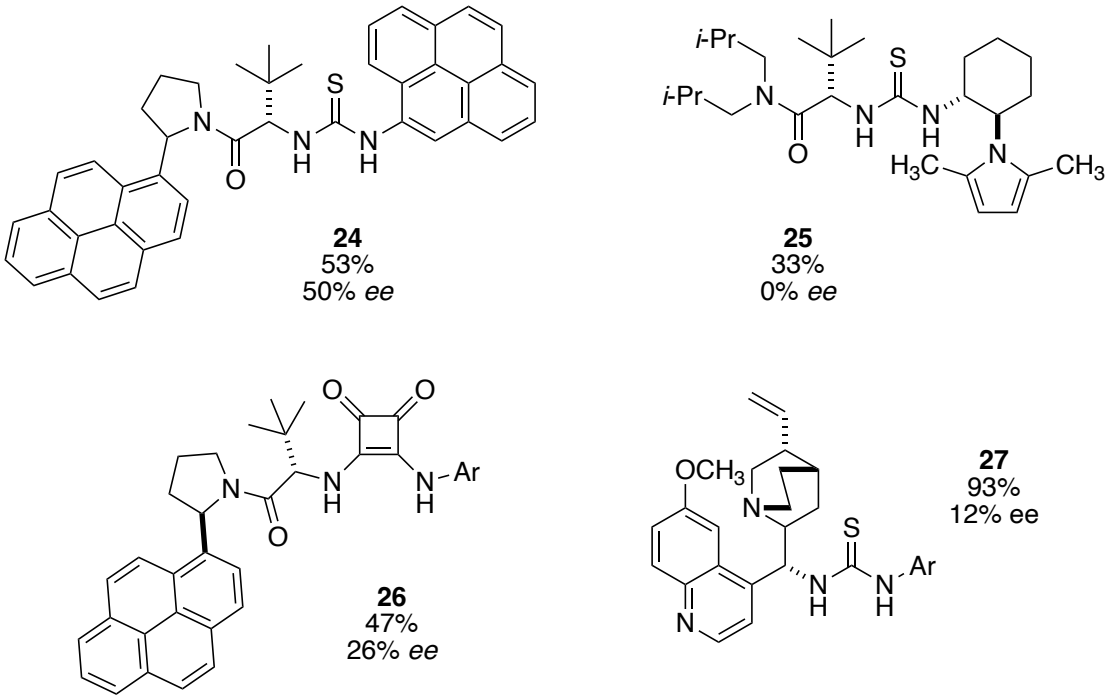
Inspired by their previous work on catalyst-free S-H bond insertion reactions, they hypothesized that this work could be coupled with that of reported dual hydrogen bond donor catalysts systems such as thioureas, ureas, silanediols and squaramides.[29]

Sulfoxonium ylide **21** was inserted into the S-H bond of thiophenol **22** in the presence of a range of organocatalysts to produce **23** and determine the optimal dual hydrogen bond donor catalyst.



SCHEME 15: ORGANOCATALYST SCREENING FOR ENANTIOSELECTIVE S-H INSERTION

Thiourea **24** proved to provide the best yield and enantioselectivity (53% yield, 50% ee). Interestingly thiourea **25** only produced racemic product **23** in lower yield (33%). Thiourea **27** produced the corresponding product in excellent yield (93%) but provided little enantiocontrol (12% ee). Squaramide **26** furnished product **23** in 47% yield but with limited enantiomeric excess (26%). BINOL-based silanediols were not capable of providing any control in enantioselectivity.



SCHEME 16: EXAMPLES OF SELECTED CATALYSTS (Ar = 3,5-BIS(TRIFLUOROMETHYL)PHENYL)

When carrying out reaction optimization it was found that the solvent selection was crucial for both improving the yield and the enantiomeric excess. Ethereal solvent methyl *t*-butyl ether (MTBE) not only improved the yield to 74% but also increased enantioselectivity to 64% ee. However, halogenated solvents such as dichloromethane and chloroform offered the best results with CH_2Cl_2 producing **23** in 85% yield with 62% ee and chloroform yielding **23** in 82% yield with 74% ee. Lowering the reaction temperature to -25 °C and extending reaction time from 24 to 96 hours offered yields of up to 87% with 85% ee. The absolute stereochemistry of **23** was assigned to be (*R*) by specific rotation.

With the reaction conditions optimized, the scope of the reaction was investigated to determine if substitution of the thiophenol could be tolerated. Both electron withdrawing groups such as nitro-, bromo- and chloro- and electron donating groups such as o- and p-methoxy- were tolerated with very good eneantioselectivity. 2,6-Disubstitution of the thiophenol ring with bulky methyl groups was also tolerated with excellent enantioselectivity, albeit in low yield.

Use of an unprotected thiophenol was also tolerated with yields of 97% and 63% ee, as was 2-Naphthalenethiol in 87% yield with 81% ee. Aliphatic substitution of the thiol was not tolerated in any case.

Substitution of the sulfoxonium ylide was also tolerated well in most cases. Halogens on the para-position of the aryl ring on the sulfoxonium ylide generated products in good yields with enantioselectivity between 66-87%. Para-substitution with a methyl group was tolerated for three different cases and gave good yield with high enantiomeric excess.

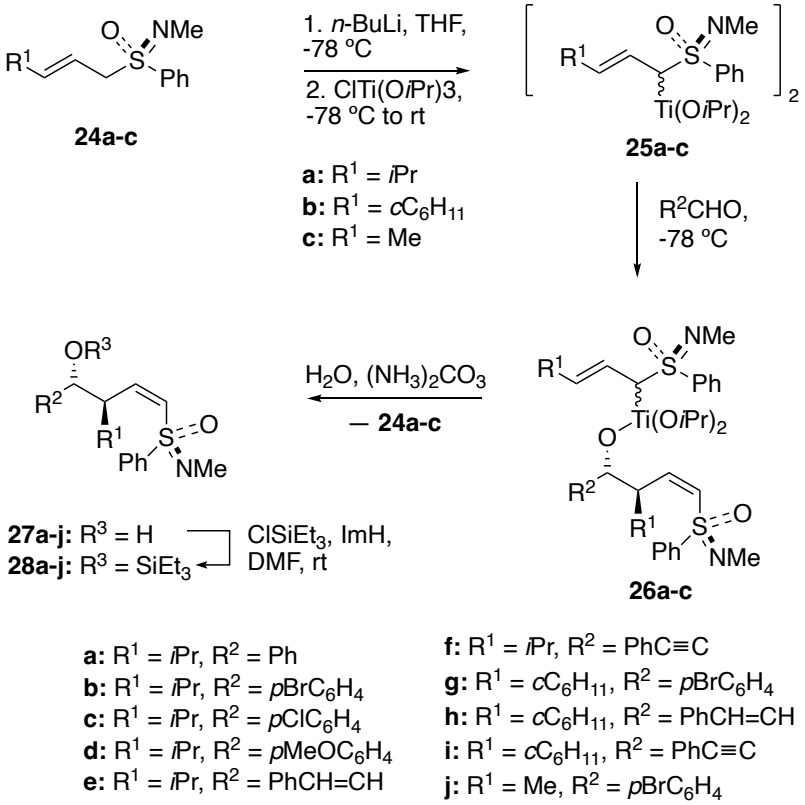
Interestingly, it was found that the type of ester on the sulfoxonium ylide could influence the % ee. A methyl ester yielded the product in 94% yield with 80% ee, but when an ethyl ester was employed the % ee increased to 89% with only a slight loss in yield (90%). Benzyl ester achieved yields of 86% and 87% ee, and t-butyl ester showed the highest enantiocontrol (90% ee) with some loss in yield in some cases (63-87% yield).

Momo et. al. also conducted a mechanistic investigation of their reaction through NMR studies and DFT calculations. This data suggested that the thiourea catalyst hydrogen bonds to the sulfoxonium ylide through the sulfooxnium oxygen, and this hydrogen-bonded complex then promotes protonation of the ylide's *re* face by the thiophenol.The thiolate can then participate in a substitution reaction (with DMSO as leaving group) to generate product **23**, while simultaneously releasing the catalyst back into the catalytic cycle.

1.1.3.2 Asymmetric synthesis of anti-homopropargylic alcohols

Homopropargylic alcohols have been reported as important building blocks in the synthesis of natural products due to their terminal alkyne being one of the most versatile functional groups for further development of the carbon skeleton. Gais and co-workers detail a method of synthesis of enantiomerically pure anti-homopropargylic alcohols from sulfonimidoyl-substituted homoallylic alcohols.[30]

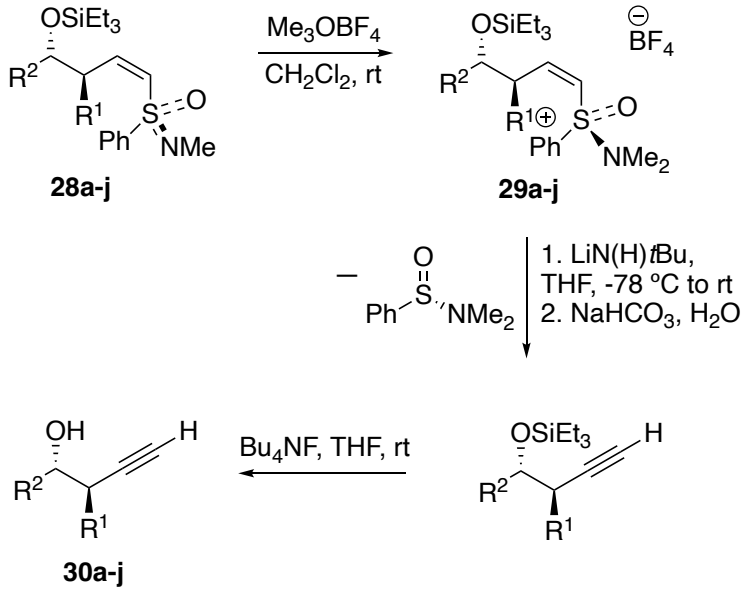
Enantiomerically pure sulfoximines **24a-c** were prepared from (S)-N,S-dimethyl-S-phenylsulfoximine and the corresponding aldehydes according to procedure published by Johnson.[31] These sulfoximines were subjected to a reaction with 1.1 equiv of n-BuLi in THF and subsequently titanated with 1.1 equiv of $ClTi(O\textit{i}Pr)_3$ to give the isopropyl-, cyclohexyl- and methyl- substituted bis(allyl)titanium complexes **25a-c**. Reaction of these complexes with aldehydes a-e at -78 °C proceeded to generate homoallylic alcohols **26a-j** with high regio- and diastereoselectivity. Upon hydrolysis with ammonium carbamate, starting material **24a-c** was lost from the intermediate to afford diastereomerically pure anti-homoallylic alcohols **27a-j**. Silylation of these homoallylic alcohols afforded the triethylsilyl ethers **28a-j** (Scheme 17).



a: R^1 = *i*Pr, R^2 = Ph
b: R^1 = *i*Pr, R^2 = *p*BrC_6H_4
c: R^1 = *i*Pr, R^2 = *p*ClC_6H_4
d: R^1 = *i*Pr, R^2 = *p*$MeOC_6H_4$
e: R^1 = *i*Pr, R^2 = PhCH=CH
f: R^1 = *i*Pr, R^2 = PhC≡C
g: R^1 = *c*C_6H_{11}, R^2 = *p*BrC_6H_4
h: R^1 = *c*C_6H_{11}, R^2 = PhCH=CH
i: R^1 = *c*C_6H_{11}, R^2 = PhC≡C
j: R^1 = Me, R^2 = *p*BrC_6H_4

SCHEME 17: SYNTHESIS OF SULFONIMIDOYL SUBSTITUTED HOMOALLYLIC ALCOHOLS

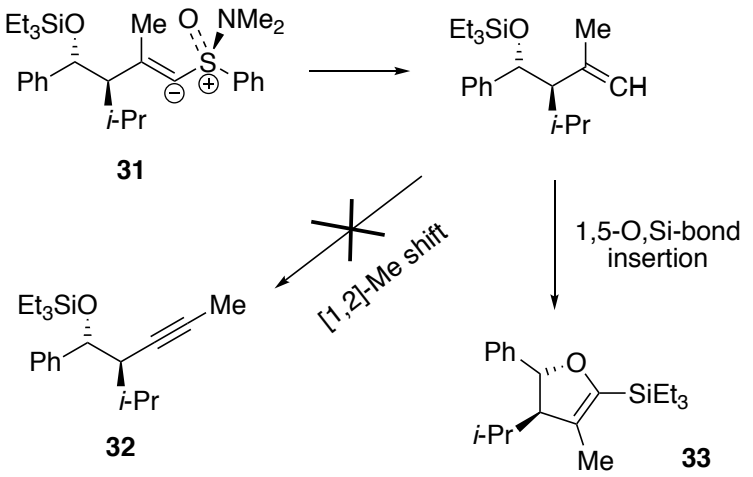
Conversion of these homoallylic alcohols to homopropargylic alcohols begins with methylation of **28a-j** with Meerwein's salt to afford the aminosulfoxonium salts **29a-j**. Treatment with LiN(H)*t*Bu at -78 °C afforded the corresponding alkynes in high yields. Finally, deprotection of the silyl ethers gave the homopropargylic alcohols in high total yields (85-98%).



SCHEME 18: SYNTHESIS OF HOMOPROPARGYLIC ALCOHOLS THROUGH ELIMINATION OF ALKENYL AMINOSULFOXONIUM SALTS

1.1.3.3 Asymmetric Synthesis of 2,3-Dihydrofurans and Fused Bicylic Tetrahydrofurans

Gais and co-workers also had success in the synthesis of 2,3-dihydrofurans through α-elimination and migratory cyclization of the same silyloxy alkenyl aminosulfoxonium salts previously described.[32] While investigating their method of synthesis of homopropargylic alcohols they noted that the β-Me-substituted alkenyl sulfoxonium salt intermediate carbene **31** had undergone a 1,5-O,Si-bond insertion to afford the 2,3-dihydrofuran **33**, rather than the expected 1,2-Me shift.

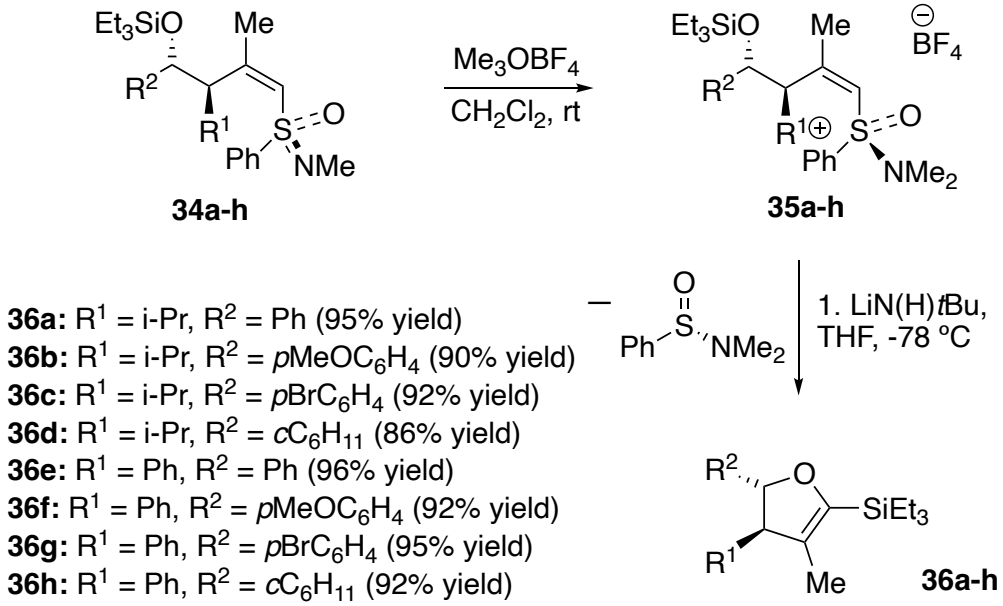


SCHEME 19: 1,5-O,Si-BOND INSERTION OF SILYLOXY ALKENYL AMINOSULFOXONIUM SALTS

This immediately became of interest due to the potential for highly substituted 2,3-dihydrofurans to act as starting materials for the synthesis of tetrahydrofurans, which are important structural motifs in many natural products.

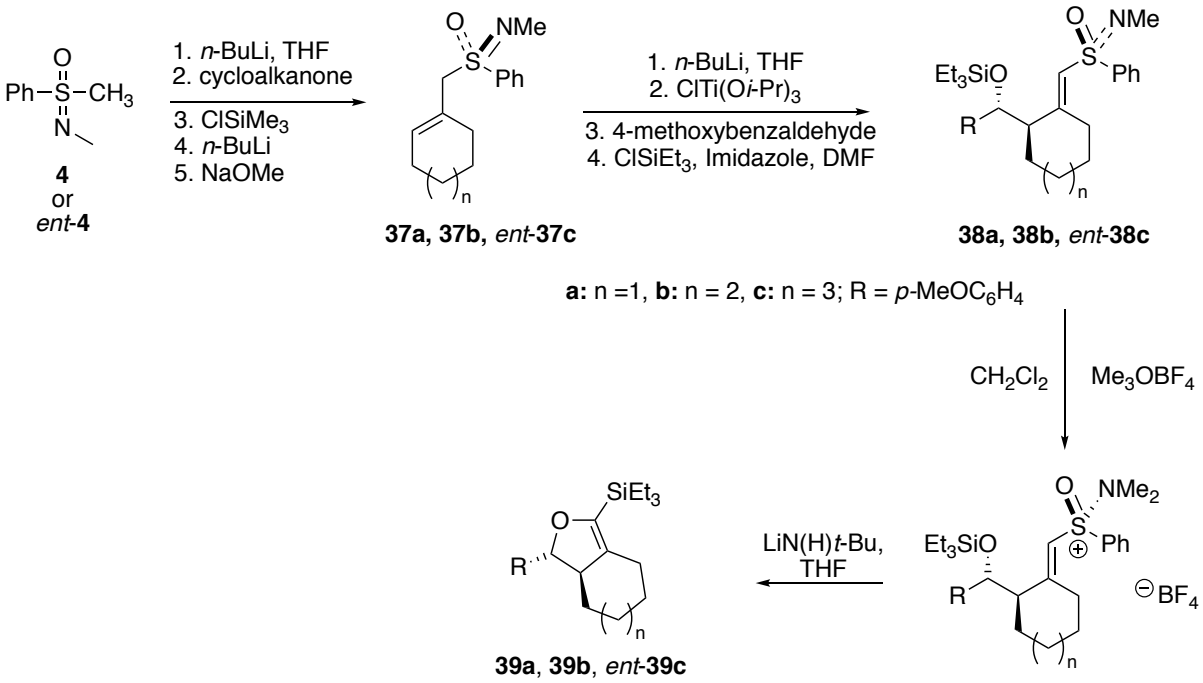
To further examine this generation of 2,3-dihydrofurans, methyl substituted salts where the O,Si-bond insertion was expected to be faster than the methyl 1,2-migration were chosen.

Diastereomerically pure (anti,Z)-configured silyl ethers **34a-h** were prepared through treatment of sulfoximine 4 with phenylacetone or methyl isobutyl ketone, methyl chloroformate and DBU. Without isolation, this was subsequently treated with DBU in MeCN at high temperatures to afford a mixture of the E and Z configured allylic sulfoximines. The resulting *E*/*Z*-mixture was separated by preparative HPLC to obtain the E-isomer and subsequently converted to the diastereomerically pure (anti,Z)-configured silyl ethers. This intermediate was subjected to the same reaction conditions outlined in Scheme 17 to afford silyl ethers **34a-h**. Methylation of silyl ethers **34a-h** followed by subsequent reaction with LiN(H)t-Bu afforded monocyclic 2,3-dihydrofurans **36a-h** in excellent yields (86-95%) and with very high diastereoselectivity >98:2 for all examples (Scheme 20).



SCHEME 20: ASYMMETRIC SYNTHESIS OF 2,3 DIHYDROFURANS 27A-H

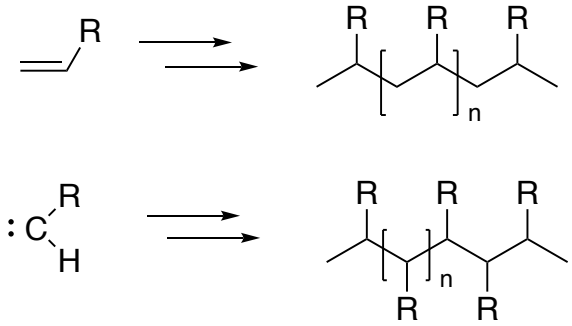
Bicyclic 2,3-Dihydrofurans were synthesized according to Scheme 21. The first step involves conversion of sulfoximine **4** to the allylic sulfoximines **37a** and **37b** by inverse Peterson-olefination followed by isomerisation. Cyclic allylic sulfoximine *ent*-**37c** was prepared by the same method from sulfoximine *ent*-**4**. Treatment of **37a**, **37b** and *ent*-**37c** with n-BuLi, $ClTi(O\textit{i}\text{-}Pr)_3$ and 4-methoxybenzaldehyde afforded the intermediate homoallylic alcohols which subsequently underwent silylation to afford silyl ethers **38a**, **38b** and *ent*-**38c** each as a single diastereomer in good yield (77-79%). Methylation of these sulfoxomines followed by treatment with LiN(H)-t-Bu as previously described, afforded enantio- and diastereomerically pure bicyclic 2,3-dihydrofurans **39a**, **39b** and *ent*-**39c** in very good yields (89-91%).



SCHEME 21: THE SYNTHESIS OF BICYCLIC 2,3-DIHYDROFURANS

1.1.3.4 Polymerisation reactions of sulfoxonium ylides

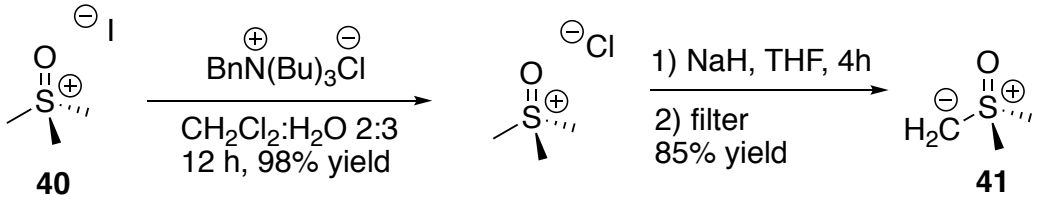
Polymers are large chain molecules created through the repetition of smaller molecular units called monomers. Synthetic polymers have revolutionized the modern world and have become essential to daily life in the form of Teflon for non-stick pans, polyvinyl chloride for pipe and wire insulation, medical prosthetics and stationary, and polyester for clothing and upholstery to name but a few. These macromolecules not only have significant industrial importance but they are also essential structural compounds for many biological materials, e.g. cellulose, DNA and RNA. The most common polymers such as polystyrene, polymethacrylate and polyvinyl chloride are prepared through a polymerization method that grows the polymer chain in two carbon increments from their constituent olefinic monomers (Scheme 22).



SCHEME 22: POLYMERISATION OF C2 MONOMERS VS C1 MONOMERS

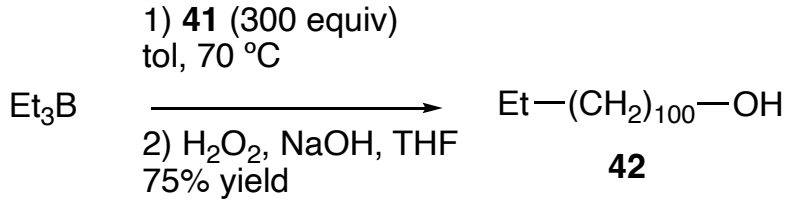
The monomers utilized in such polymerizations are currently sourced from crude oil, and though this currently offers cheap and abundant access to these alkenes, the supply of crude oil is finite and its extraction is often at the center of environmental debate. Therefore, long-term strategies for the renewable and environmentally friendly production of olefins will become necessary for the continued supply of polymeric materials in the future.[33] C1 polymerization offers important synthetic benefits and alternatives that are not available via C2 polymerization, including access to more structurally diverse polymers as well as increased reactivity toward polymerization.[34] Diazo compounds have commonly been used as monomers for C1 polymerizations in recent years due to the release of nitrogen as a by-product which further drives the reaction.[35,36] Due to the hazards previously discussed associated with diazo compounds, attention has shifted to the use of sulfoxonium ylides as C1 polymerization monomers.

Shea and co-workers have had great success in the use of sulfoxonium ylides for non-olefin polymerization.[37,38] Their 2002 work documents the first use of dimethylsulfoxonium methylide for polymerization through the use of a boron-catalyst. Ylide **41** was synthesized according to Scheme 23. Ion-exchange of trimethylsulfoxonium iodide (**40**) was carried out with benzyltributylammonium chloride to afford trimethylsulfoxonium chloride in 98% yield. Conversion of the iodide salt to the chloride salt is preferred due to its increased stability and solubility. Reflux of trimethylsulfoxonium chloride with sodium hydride in THF or toluene produces ylide **41** in 85% yield. The resulting ylide is stable and can be stored for months at 0 °C.



SCHEME 23: SYNTHESIS OF DIMETHYLSULFOXONIUM METHYLIDE

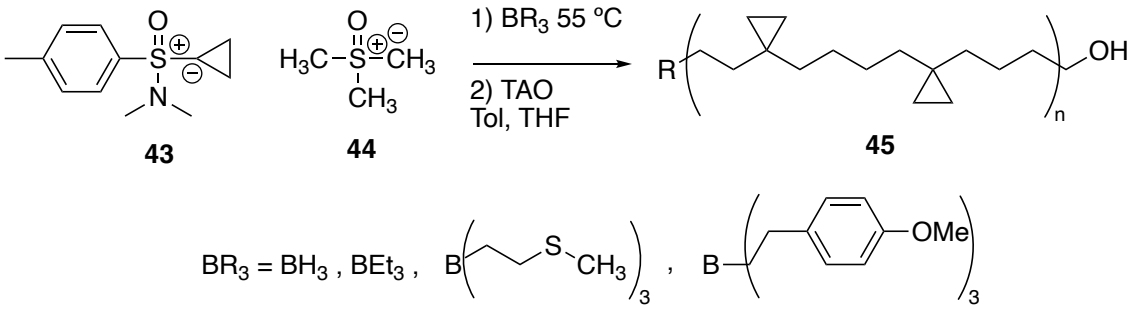
Toluene was selected as the solvent for the polymerization reaction due to linear polyethylene having significantly higher solubility at higher temperatures in toluene than in THF. A catalytic amount of triethylborane was injected into a solution of ylide **41** in toluene at 70 °C. After 5 min, sampling indicated complete consumption of ylide. Toluene was removed in vacuum and THF, hydrogen peroxide and sodium hydroxide were added. The resulting polymer could then be isolated through precipitation with acetonitrile to afford α-hydroxymethylene **42** (9) in 75% yield (Scheme 24). This type of polymerization occurs whereby the carbon source is the carbon of the sulfoxonium ylide and it binds to the electrophilic organoborane. This is immediately followed by 1,2-migration with elimination of dimethylsulfoxide. This type of polymerization is called 'polyhomologation', and the first example of borane-mediated polymerization of sulfoxonium ylides by this method was reported in 1966 by Tufariello and Lee.[39]



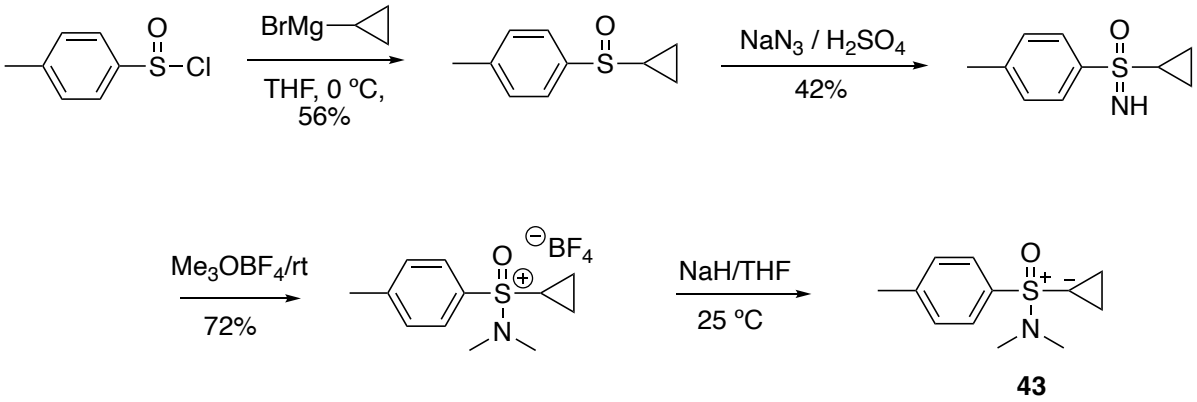
SCHEME 24: SYNTHESIS OF α-HYDROXYPOLYMETHYLENE 42

In 2006 Shea and co-workers demonstrated the first copolymerization with tertiary ylides resulting in polymers with tailored end groups. This described the use of cyclopropylaminosulfoxonium salts for the controlled synthesis of cyclopropyl containing carbon backbone polymers. Functional groups along the carbon backbone are important methods of controlling properties such as solvent adhesion, barrier performance and adhesion. The introduction of a cyclopropane moiety can not only provide a conformational restraint in the backbone, it also allows for the possibility of further chemical modification such as facilitating copolymer formation or the introduction of other functional groups to modify solubility.[40–42]

Poly(cyclopropylidine-co-methylidine) polymers **45** were afforded through the copolymerization of (dimethylamino)-p-tolyl-oxosulfonium cyclopropylide **43** and dimethyl sulfoxonium methylide **44** monomers (Scheme 25). Monomers **43** and **44** supply the cylcopropylidene and methylene groups to the growing polymer chain. Cyclopropylide **43** was synthesized according to Scheme 26. This ylide was prepared in situ for each reaction due to its increased reactivity in comparison to that of methyl ylide **44**. The monomers were added in precise aliquots in order to introduce one cyclopropylide group followed by a spacer chain of polymethylene groups. It was important to introduce **44** to begin so that a polymethylene spacer could form from the end group. The last addition must also be an aliquot of dimethylsulfoxonium methylide **44** to ensure the terminus chain doesn't contain a cyclopropyl group. When triethylborane was used as an initiator the copolymer composition was found to be 1:18 (cyclopropyl:methyl).



SCHEME 25: SYNTHESIS OF POLY(CYCLOPROPYLIDINE-CO-METHYLIDINE) POLYMERS

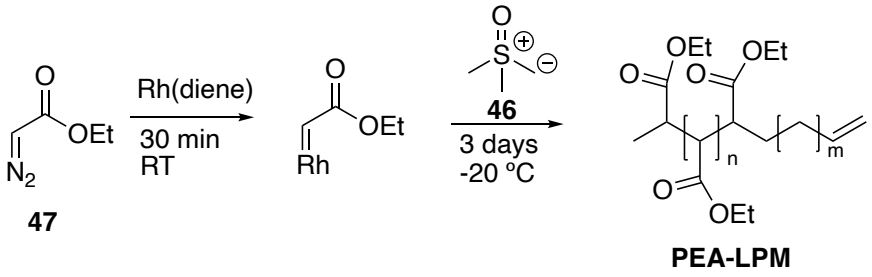


SCHEME 26: PREPARATION OF CYCLOPROPYLIDE 43

This work was very successful in showcasing the incorporation of sterically hindered functional groups into a hydrocarbon polymer chain. It successfully demonstrated that by changing the alkyl groups in (dimethyalmino)phenylsulfoxonium alkylide, it is possible to generate a variety of copolymers by the polyhomologation reaction.

However, one limitation of these boron homologation reactions is that they are not compatible with the use of polar-functionalized reagents. When sulfoxonium ylides and ethyl diazoacetate (EDA) were used for attempts at (co)polymerization with the boron catalyst it led to deactivation of the catalyst.[43]

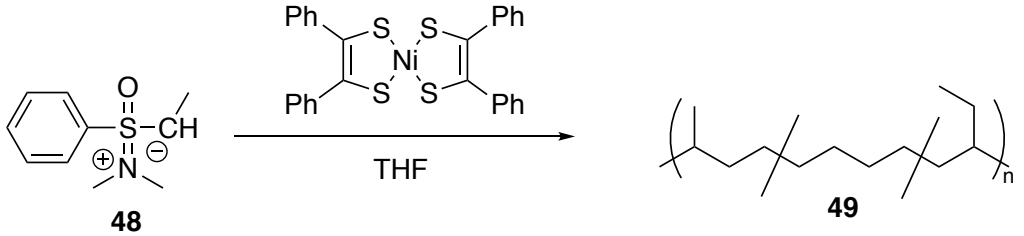
In 2012, Bruin et al. sought to identify a solution to these issues through the use of a transition metal catalyst to generate copolymers from diazoesters and methylene sulfoxonium ylides.[44] Rh^{I}(diene) complexes were chosen due to their success in EDA polymerization reactions. Copolymerization of sulfoxonium ylide **46** with diazoester **47** was carried out according to Scheme 27.



SCHEME 27: BRUIN ET AL POLYMERIZATION OF A SULFOXONIUM YLIDE WITH A DIAZOESTER

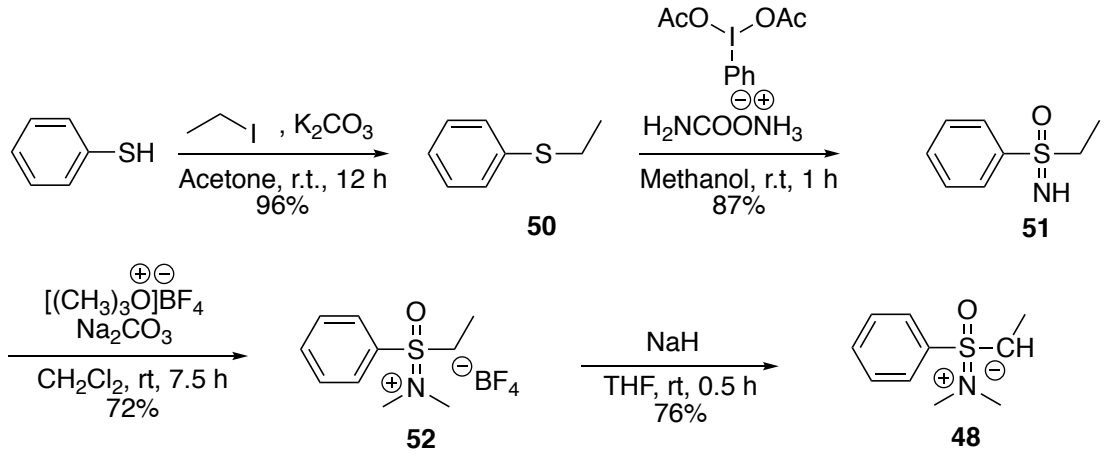
Even in the absence of catalyst it was found that EDA and sulfoxonium ylide **46** react strongly in an exothermic manner producing a complex mixture of products even at lower temperatures (0°C, -20°C and -50°C). The best results were found when the catalyst was preactivated by EDA for 30 minutes at -20°C before addition of the ylide. The reaction was then allowed to come to room temperature and react for 3 days to produce copolymer PEA-LPM. Efforts at reaction optimization found the copolymer could only be synthesized in yields 15-18%. However, despite low yield, this procedure still provides an attractive synthetic protocol for preparation of diblock copolymers containing both a polar ester-functionalized carbon chain-block as well as a nonfunctionalized, non-polar polymethylene block.

A more recent example of the advancement of the polymerization of sulfoxonium ylides comes from Bielawski and co-workers.[45] They describe the use of a readily available Ni(II) catalyst, bis(dithiobenzil)nickel (II), to polymerize (dimethylamino)phenylsulfoxonium ethylide **48** to afford the substitued polymer poly[1(1-butene)-*ran*-2-butene)-*ran*-(ethylene)] **49** in good yield with high molecular weight.



SCHEME 28: SYNTHESIS OF POLY[1(1-BUTENE)RAN-2-BUTENE-RAN-(ETHYLENE)]

(Dimethylamino)phenylsulfoxonium ethylide **48** was synthesized according to Scheme 29. Treatment of thiophenol with iodoethane in the presence of potassium carbonate affords ethyl phenyl thioether **50** in 96% yield. Sulfoximine **51** was generated through oxidation-imination of thioether **50** in the presence of ammonium carbamate and diacetoxyiodobenzene followed by methylation with Meerwein's salt to afford **52** in 72% yield.[15,46,47] Finally, ethylide **48** could be generated in situ through treatment with sodium hydride in a THF solution.[48]



SCHEME 29: PREPARATION OF (DIMETHYLAMINO)PHENYL SULFOXONIUM ETHYLIDE

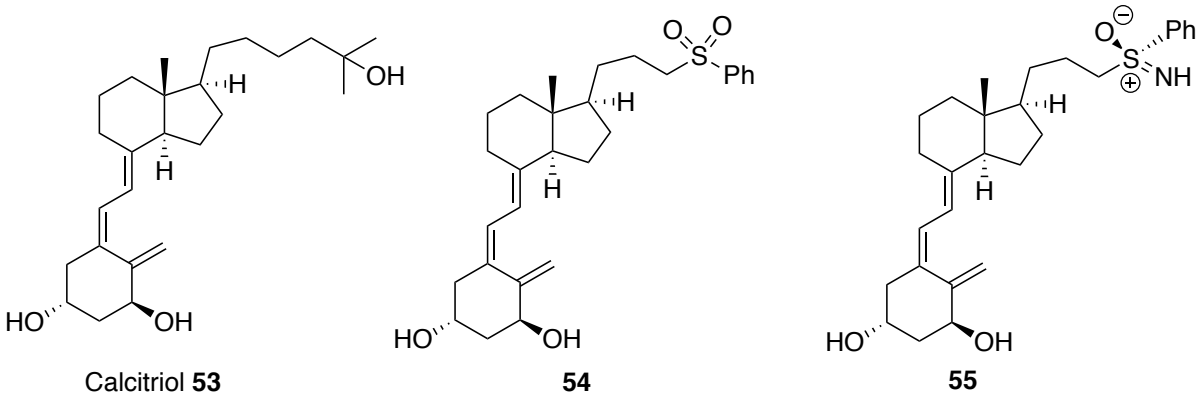
The polymerization reaction was carried out by addition of the nickel catalyst to a solution of **48** in THF at 50 °C. After 16 h the reaction was quenched and a yield of 78% of polymer **49** was obtained.

During reaction optimization it was found that increasing the reaction temperature to 70 °C resulted in slightly higher yields of 85% in significantly shorter reaction times (4 h). However, these conditions produced polymers of greatly reduced molecular weight with broader polydispersity.

These examples of polymerization reactions of sulfoxonium ylides not only showcase the versatility of the sulfoxonium ylide, but also demonstrate the significant advancements that can be made in chemical synthesis in just 20 years.

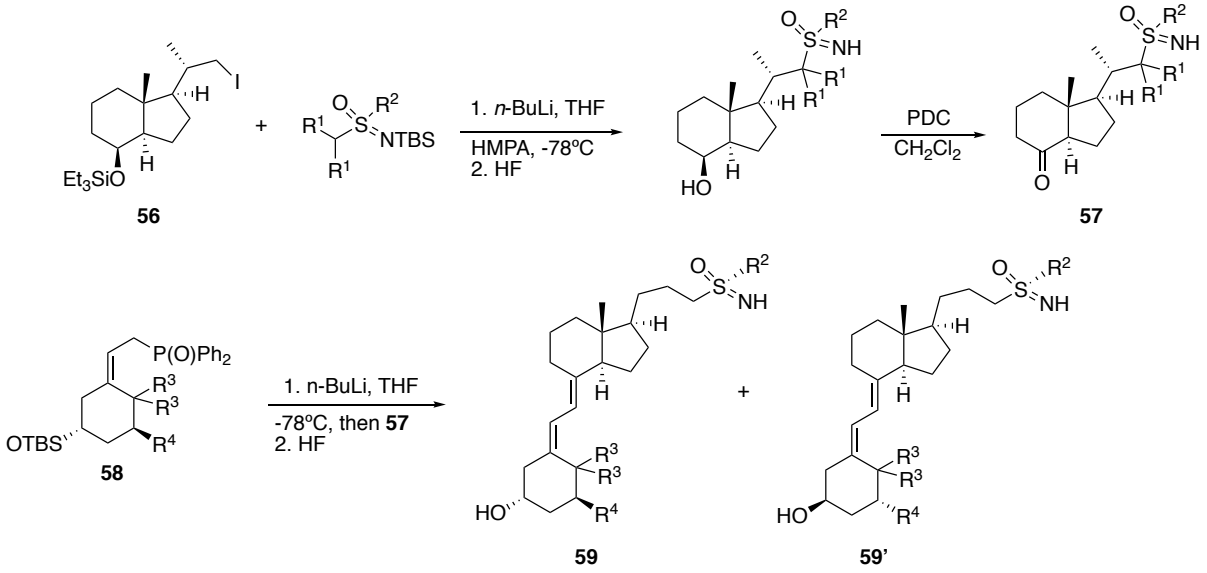
1.1.3.5 Application to the synthesis of sulfoximine analogues of the hormone 1α,25-dihydroxyvitamin D_3

An interesting application of sulfoximines and their benefits to medicinal chemistry is highlighted by Posner and co-workers in their publication concerning the natural hormone 1α,25-dihydroxyvitamin D_3 (calcitriol, **53**) that is frequently investigated for its potential as an anticancer agent.[49] Inspired by their success in developing 24-sulfone Vitamin D analogues that are transcriptionally active and low-calcemic, the group sought to investigate sulfoximine analogues in which the tertiary OH group of Calcitriol **53** is replaced with a sulfoximine NH group in **55** (Scheme 30).



SCHEME 30: 1α,25-DIHYDROXYVITAMIN D_3 AND ITS ANALOGUES (POSNER ET AL)

Unfortunately, the dozen 24-Sulfoximine analogues of this hormone that were generated proved to be only weakly antiproliferative. However, they were also found to be powerful hydroxylase enzyme inhibitors with low calcemic activity. The 24-sulfoximine analogues of 1α,25-dihydroxyvitamin D_3 were synthesized according to Scheme 31 and Table 3.



SCHEME 31:SYNTHESIS OF CALCITRIOL SULFOXIMINE ANALOGUE

TABLE 3: SYNTHESIS OF CALCITRIOL SULFOXIMINE ANALOGUE

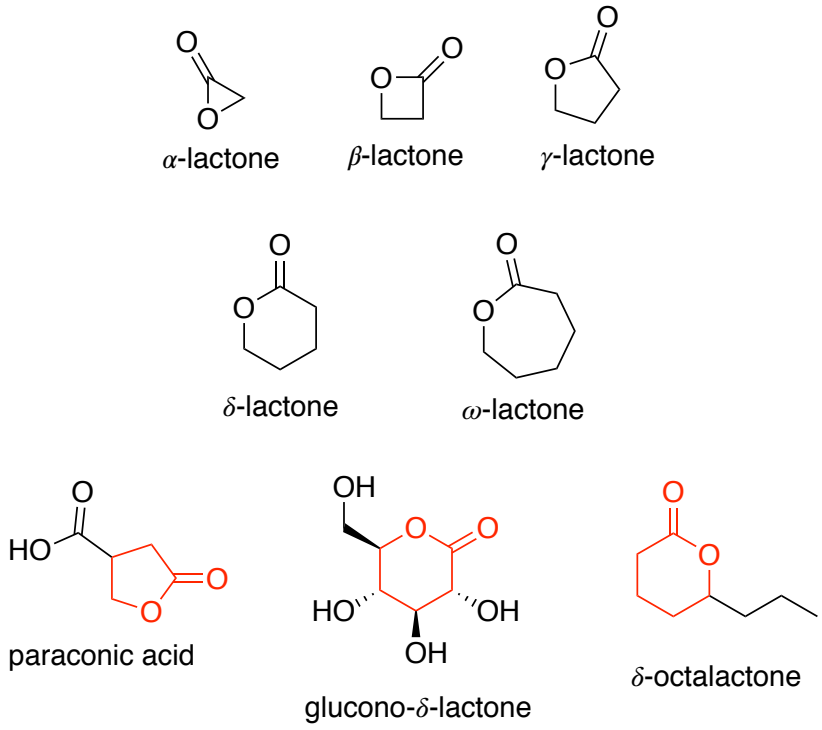
Entry	***Configuration of sulfoximine***	***R^1,R^1***	***R^2***	***R^3***	***R^4***	***59 + 59' yield (%)***
a	(+)-(*S*)	H,H	Ph	$=CH_2$	OH	47
b	(-)-(*R*)	H,H	Ph	$=CH_2$	OH	44
c	(-)-(*R*)	H,H	Ph	H,H	OH	55
d	(+)-(*S*)	H,H	Ph	H,H	OH	23
e	(+)-(*S*)	H,H	Ph	$=CH_2$	H	68
f	(+/-)-(*R/S*)	$-(CH_2)_2-$	Ph	$=CH_2$	OH	40

To begin, 22-iodide (+)-**56** underwent substitution by N-*tert*-butyldimethylsilylprotected sulfoximines followed by subsequent bisdesilylation to form C,D-ring side chain NH-sulfoximines as C-8 secondary alcohols. Oxidation at the C-8 produced the corresponding C-8 ketones **57**. Horner-Wadsworth-Emmons coupling of ketones **57** with A-ring phosphine oxide **58** α-anion, followed by HF-promoted desilylation, generated the target sulfoximine analogues **59a-59g** in yields ranging from 23-68%.

1.2 Introduction to lactones

Gaining access to natural products and their synthons is essential for the development and discovery of new pharmacologically active molecules. For this reason, lactones have been of interest to chemists since their discovery due to their remarkable biological activities. IUPAC defines lactones as "cyclic esters of hydroxy carboxylic acids, containing a 1-oxacycloalkan-2-one structure, or analogs having unsaturation or heteroatoms replacing one or more carbon atoms on the ring."[50,51]

Lactones can range in size from the smallest three-membered ring α-lactones, to macrolactones which have 12 or more members. α-Lactones do not exist naturally due to their high instability. However, they can be detected as transient intermediates in mass spectrometry experiments.[52] Other important extensions to this family of compounds include α,β-unsaturated lactones and aromatic-fused lactone ring systems such as sesquiterpene lactones and spirolactones.



SCHEME 32: STRUCTURE OF LACTONES

By far, the most commonly found lactones in nature are γ-lactones and δ-lactones because of the high stability of their rings. It is estimated that more than 3000 γ-lactones can be found in nature and occur in about 10% of all naturally occurring products including pesticides, antibiotics, plant and fungal growth inhibitors, paraconic acids and large rings of macrocyclic esters.[53–55] γ-Lactones have also been shown to possess strong antitumour, antifungal, antibacterial, antiviral and anti-inflammatory activity suggesting their potential as leads in

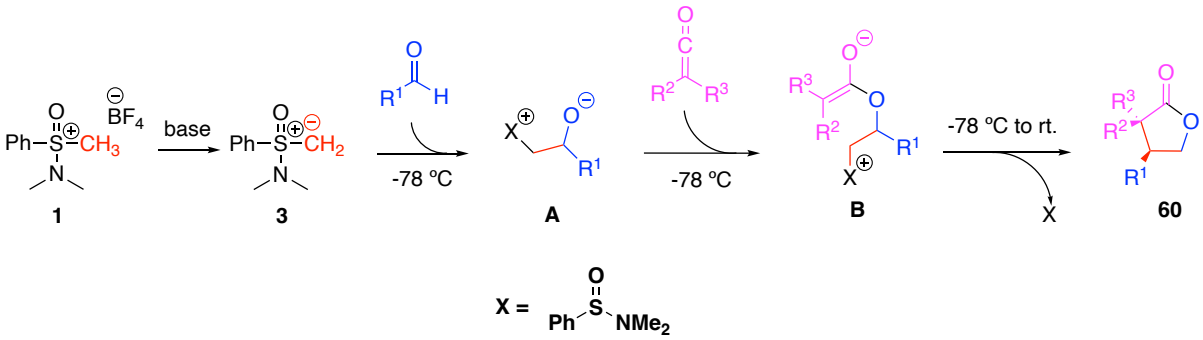
pharmaceutical development.[56–60] Butyrolactones have also been utilized in the perfume industry for their sweet, caramel-like fragrance.[61]

Like γ-lactones, δ-lactones are also important flavor and aroma consituents in many natural products including δ-hexalactone in coconut, raspberry and tea, δ-octalactone in apricot, blue cheese and pineapple and δ-nonalactone in cooked beef and pork, and whiskey.[62,63] Glucono δ-lactone is an important food preservative used as an acidifier or for pickling or curing and works by inhibiting bacterial growth by lowering the pH.[64] The δ-lactone moiety is also an important structural feature for natural compounds with biological activities, such as HIV protease inhibition, apoptosis induction, as well as a range of antitumour, anti-inflammatory and anticancer activities.[65–69]

1.2.1 Preparation of γ-lactones

1.2.1.1 Diastereoselective synthesis of γ-lactones through reaction of sulfoxonium ylides, aldehydes and ketenes

In 2013 Mondal et al. published work describing the synthesis of a γ-lactone through reaction with aldehydes and ketenes.[70,71] Preliminary studies showed that the chiral amino-sulfoxonium ylide **3**, generated through treatment of salt **1** with a strong base, was the superior onium ylide for γ-lactone formation. By carrying out betaine generation at -78 °C epoxide formation from reaction of sulfoxonium ylide **3** and the aldehyde is slowed, and the betaine intermediate can be intercepted by the ketene to generate enolate B. Enolate B then undergoes 5-exo-tet cyclization with resulting loss of the sulfinamide leaving group to generate the 3,4-disubstituted γ-lactone **60**.



SCHEME 33: SYNTHESIS OF γ-LACTONES FROM AMINOSULFOXONIUM YLIDES, ALDEHYDES AND KETENES

For all reactions tetrafluoroborate was used as the counterion for the sulfoxonium ylide in order to limited possible side reactions of other more nucleophilic counterions (e.g. iodide) with the ketene.

n-Butyllithium was found to be the best base and facilitated the highest yield of γ-lactone. It was therefore used in combination with a range of metal salt additives to investigate the effect on yield and diastereoselectivity (Table 4). Best results were found when $MgCl_2$ was used as an additive. It was proposed that it activated the aliphatic aldehydes which aided in their reaction with sulfoxonium ylide **3** whereas more reactive aldehydes did not require this additive for the reaction to progress efficiently.

TABLE 4: OPTIMIZATION OF THE DIASTEREOSELECTIVE SYNTHESIS OF γ-LACTONES

Entry	***Base (metal salt additive)***	***M^+***	***Metal salt (equiv)***	***Yield (%)***	***dr***
1	NaHDMS	Na		15	88:12
2	KHDMS	K		Trace	
3	*n*-BuLi	Li		32	88:12
4	*n*-BuLi	Li (50 °C)		61	79:21
5	*n*-BuLi ($ZnCl_2$)	ZnCl	1	45	70:30
6	*n*-BuLi ($MgCl_2$)	MgCl	1	77	86:14
7	*n*-BuLi ($MgCl_2$)	MgCl	2	93	88:12
8	*n*-BuLi ($MgCl_2$)	MgCl (50 °C)	1	95	85:15
9	*n*-BuLi ($MgBr_2$)	MgBr	1	30	86:14
10	*n*-BuLi (MgI_2)	MgI	1	56	86:14
11	*n*-BuLi ($AlCl_3$)	$AlCl_2$	1	60	64:36
12	*n*-BuLi (CuI)	Cu	1	79	74:26

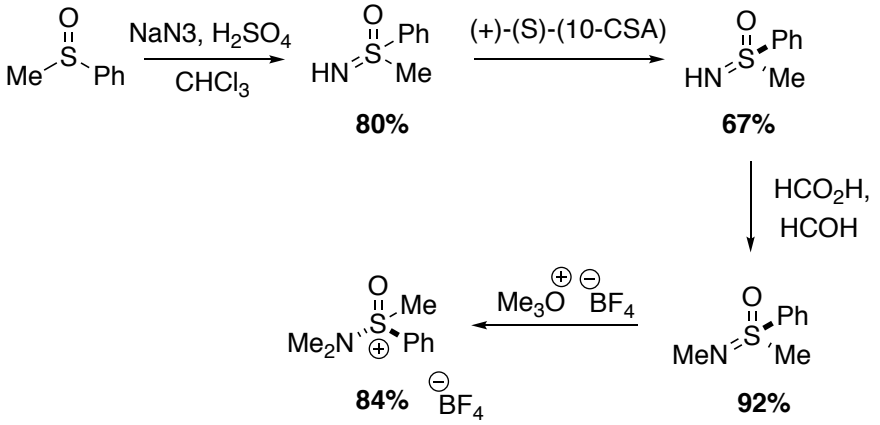
The scope of the reaction with regard to ketene structure and aldehyde substitution pattern was also investigated (Table 3). The use of unsymmetrical ketenes showed very good diastereoselectivity (dr up to 92:8), and it was confirmed by x-ray crystallography that the trans-isomer was the major diastereomer from the reaction. This reaction was also found to tolerate a range of different ketenes with varying degrees of reactivity, including dimethylketene, alkylarylketenes and diphenylketene were all tolerated.

Ortho-substituted aromatic aldehydes, heteroaromatic substituted aldehydes and isobutyraldehyde were also well tolerated with good diastereoselectivity. The most moderate results were found with aliphatic aldehydes (30-40% yield), where the low yields were attributed to competing enolization and aldol side reactions of the aldehyde, and incomplete conversion to betaine due to a sterically bulky *i*PrCHO being used.

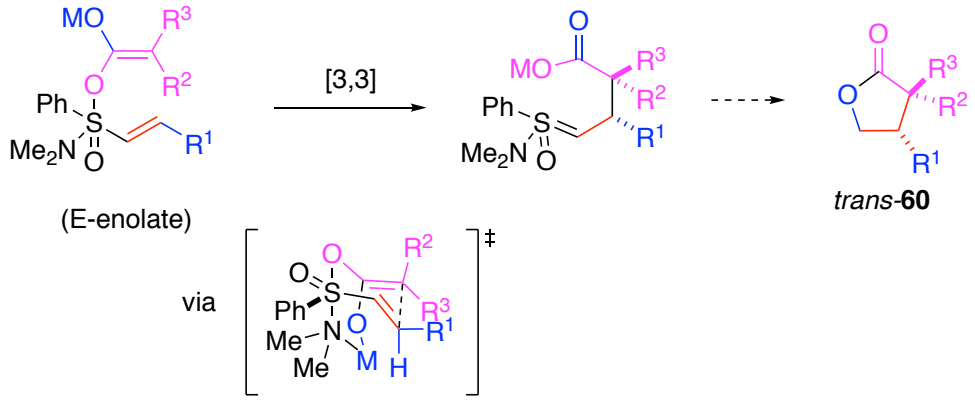
TABLE 5: SUBSTRATE SCOPE OF THE DIASTEREOSELECTIVE SYNTHESIS OF γ-LACTONES

Entry	***R^1***	***R^2***	***R^3***	***Yield (%)***	***dr***
1	*i*-Pr	*i*-Bu	Ph	93	88:12
2	Ph	*i*-Bu	Ph	60	83:17
3	2-NO_2Ph	*i*-Bu	Ph	70	87:13
4	2-ClPh	*i*-Bu	Ph	43	83:17
5	2-FPh	*i*-Bu	Ph	56	75:25
6	2-MePh	*i*-Bu	Ph	40	91:9
7	3-furyl	*i*-Bu	Ph	82	84:16
8	3-thienyl	*i*-Bu	Ph	69	81:19
9	2-NO_2Ph	Et	Ph	73	85:15
10	2-MePh	Et	Ph	70	82:18
11	*i*-Pr	Et	Ph	39	83:17
12	2-NO_2Ph	Me	Ph	62	90:10
13	*i*-Pr	Me	Ph	33	92:8
14	4-NO_2Ph	Me	Me	48	

The following year this work was expanded on to demonstrate its ability as an asymmetric reaction.[70] To obtain an enantioenriched aminosulfoxonium salt methylphenyl sulfoxide was converted to the sulfoximine by reaction with sodium azide under acidic conditions. The resulting racemic methylphenyl sulfoximine was resolved using (+)-(S)-10-camphorsulfonic acid (10-CSA) which was subsequently subjected to methylation according to the Eschweiler-Clarke reaction. Finally, Meerwein's salt was used for selective N-methylation to (dimethylamino)methylphenyl oxosulfonium fluoroborate (98% ee).



SCHEME 34: SYNTHESIS OF ENANTIOENRICHED SULFOXONIUM SALT FOR ASYMMETRIC SYNTHESIS



SCHEME 35: PROPOSED TRANSITION STATE FOR [3,3]-SIGMATROPIC REARRANGEMENT OF E-ENOLATE

Isobutyraldehyde and isobutylphenylketene were chosen as the reactants due to their success as reactant partners in the previous work (dr 88:12). As with the previous findings, the reaction proceeded smoothly when *n*-BuLi was used as a base (60% ee), the addition of $MgCl_2$ also showed slight improvement in enantioselectivity (76% ee). However, it was found with subsequent investigation that the best results were obtained when *n*-BuLi was used on its own, without the addition of an additive. Copper iodide was also investigated as an additive, interestingly, this had no major impact on the yield but resulted in the loss of some diastereoselectivity (dr 80:20 vs dr 77:23).

It was found that aromatic aldehydes also performed best in this reaction (up to 65%), as was the case with the previous work outlined above. The increased electron withdrawing effect of the aromatic groups creates a more reactive intermediate which subsequently shows preference for [3,3]-sigmatropic rearrangement, meaning intermolecular sider reactions such as aldol reactions become less favorable. The opposite trend is seen when aliphatic aldehydes are used, increasing the likelihood of intermolecular side reactions and reducing the preference for [3,3]-sigmatropic rearrangement, resulting in more moderate yields (up to 41%). Interestingly, when diphenylketene and isobuyraldehyde were subjected to this reaction the intermediate enolate E was too stabilized and the β-position of the α,β-unsaturated sulfurane oxide was too sterically hindered and electronically less activated, resulting in the formation of no γ-lactone.

It was hypothesized that diastereoselectivity occurs through a six-membered chair like transition state with the larger, higher priority substituents preferentially occupying the pseudoequatorial positions.

Unsurprisingly, it was found that highest diastereoselectivity was found when sterically bulky substituents were located at the β-position of the α,β-unsaturated sulfurane oxide intermediate, demonstrating that the inclusion of sterically bulky R^1 groups increases the preference for those groups to adopt pseudoequatorial positions in the chair-like transition state.

The major diastereomer was found to be the *trans*-diastereomer through X-ray crystallography, which is consistent with the outcome favoured during [3,3]-sigmatropic rearrangement through the *E*-isomeric form of the enolate (Scheme 35).

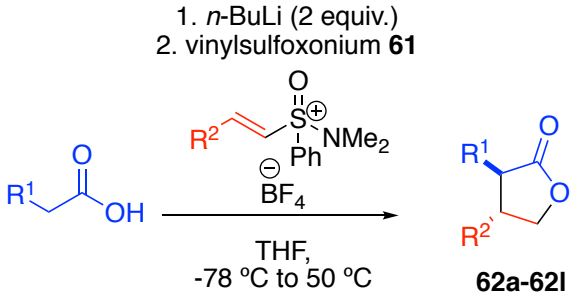
1.2.1.2 Diastereoselective synthesis of γ-lactones through reaction of enediolates and α,β-unsaturated sulfoxonium salts

In 2015, Kerrigan's group had hypothesized that the same sulfurane oxide intermediate (Scheme 35) could be accessed through reaction of a lithium enediolate with α,β-unsaturated sulfoxonium salts, offering an alternative route to γ-lactone synthesis.[72]

This reaction was first investigated with a phenyl-substituted vinylsulfoxonium salt which was prepared according to the work previously described by Johnson and co-workers.[73] Optimization of the reaction found that highest yield and dr was achieved when 2 equivalents of the enediolate was used. The yield was also significantly improved (71% vs 91%) when the reaction was warmed to 50 °C before quenching.

Substituent variation in both the carboxylic acid and the vinyl sulfoxonium salt were well tolerated, with the results of this investigation outlined in Table 6.

TABLE 6: SUBSTRATE SCOPE OF LACTONE-SYNTHESIS



Entry	*R^1*	*R^2*	*Yield (%)*	*dr*	*62*
1	2-Naph	Ph	91	94:6	62a
2	Ph	Ph	89	97:3	62b
3	2-MeOPh	Ph	99	92:8	62c
4	3-MeOPh	Ph	92	96:4	62d
5	2-MePh	Ph	89	88:12	62e
6	3-MePh	Ph	82	97:3	62f
7	2-ClPh	Ph	92	89:11	62g
8	*t*-Bu	Ph	33	>99:1	62h
9	2-Naph	*i*-Pr	98	92:8	62i
10	Ph	*i*-Pr	>99	92:8	62j
11	2-ClPh	*i*-Pr	54	94:6	62k
12	3-MePh	*i*-Pr	83	92:8	62l

This reaction was found to be tolerant to a range of aryl substituents on the carboxylic acid, including electron-donating substituents, electron-withdrawing substituents and even tolerated substitution on the aromatic ring. In contrast, when *t*-Bu was used as a substituent on the carboxylic acid it was not tolerated well (Table 6, entry 8). There was a dramatic loss in yield, however the *dr* remained impressively high.

Substitution with an *i*-Pr group at the β-position on the vinylsulfoxonium salt was also well tolerated with similar yielding results for most cases. Interestingly, though the *i*-Pr-substituted

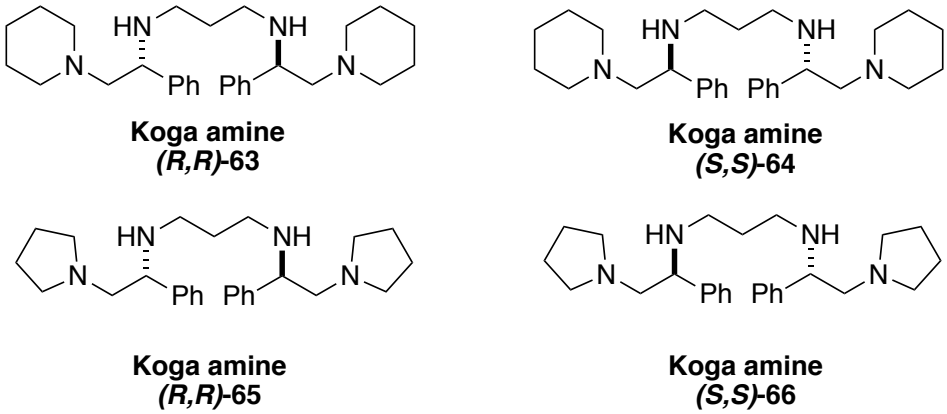
vinylsulfoxonium salt was tolerated where R^1 = 2-Naph and 3-MePh, there was a dramatic loss in yield in the case of the 2-chloro substituted phenyl ring (Table 6, entry 7 vs 11).

α,α-Disubstituted acetic acids also proved to be successful in this reaction and gave access to γ-lactones bearing a quaternary centre. Of those tested 2-phenylpropionic acid gave the highest yield when reacted with a phenyl substituted vinylsulfoxonium salt (82%), albeit with moderate diastereoselectivity (*dr* 73:27). When 2-phenyl propionic acid was reacted with isopropyl substituted vinylsulfoxonium salt slightly better diastereoselectivity was found with a loss in yield (62%, *dr* 80:20), and diphenyl acetic acid was also tolerated with moderate yield (56%).

1.2.1.3 Koga Amine-Controlled diastereoselective synthesis of γ-lactones through reaction of enediolates and α,β-unsaturated sulfoxonium salts

Having had such success in accessing the *trans*-isomer of the γ-lactone, the group became interested in developing an asymmetric variant of this reaction and, also, gaining access to the *cis*-isomer.[74] Their use of chiral Koga amine ligands to achieve these two goals was inspired by Zakarian's group, who had recently reported the use of chiral Koga amine ligands for enantioselective alkylation of lithium enediolates and in the conjugate addition of lithium enediolates to acrylates.[75,76]

To begin 2-methoxyphenylacetic acid **67a** was reacted with phenyl-substituted sulfoxonium salt **68a** under the reaction conditions previously outlined as optimal. *n*-BuLi was used as the base for enediolate generation and four different chiral Koga amines were investigated (scheme 36).



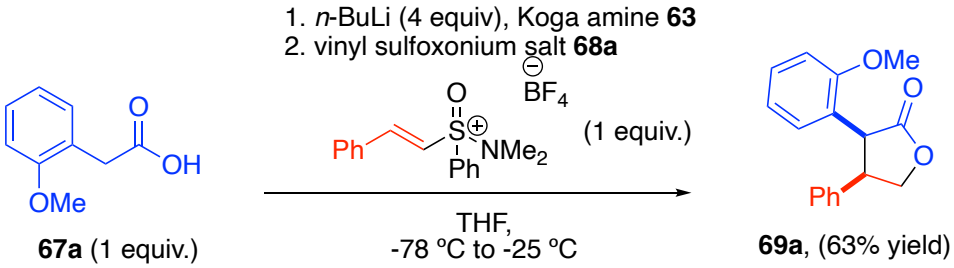
SCHEME 36: CHIRAL KOGA AMINES

Interestingly, the reaction conditions that were previously successful for the generation of the *trans*-lactone were not applicable to this reaction. The elevated quench temperature along with the use of excess carboxylic acid (2 equiv.) in the presence of Koga amines only provided trace yield. Highest yields were obtained when the carboxylic acid and sulfoxonium salt were in

equal equivalents (1 equiv), with 1.03 equivalents of Koga amine **63** and excess *n*-BuLi (4 equiv). For a moderate yield to be obtained it was essential that the reaction was quenched at -25 °C and the time the reaction was kept at this temperature was limited to 5 min. Allowing 30 minutes for enediolate generation also slightly improved the yield in comparison to 15 min generation time (51% vs 60%). Appropriate acid concentration for reaction quench was also determined to be important. Using glacial acetic acid rather than dilute HCl slightly improved the yield (63%).

The pyrrolidine-substituted Koga amines **65** and **66** provided significantly lower enantioselectivity in comparison to their six-membered ring counterparts **63** and **64** (46-52% ee vs 68-78% ee).

Interestingly, all Koga amines produced the *cis*-isomer as the major isomer, however, Koga amine **63** produced the highest yield levels of enantiocontrol so was selected as the most suitable additive for this reaction.



67a (1 equiv.) **69a**, (63% yield)

SCHEME 37: KOGA AMINE ASSISTED SYNTHESIS OF γ-LACTONE

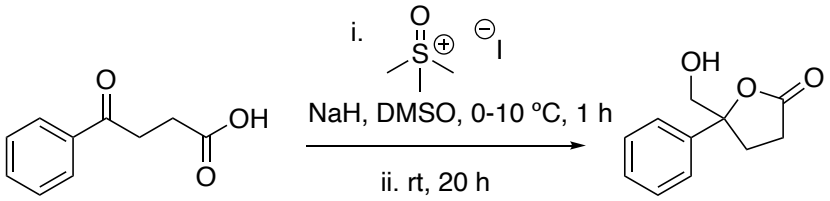
Examining the scope of this reaction in relation to substitution of the carboxylic acid and sulfoxonium salt provided similar results to those found for that of the trans-isomer albeit in slightly lower yields. Acids containing both electron-donating (MeO or Me) and electron-withdrawing (e.g., F) at the 2-position of the enediolate aryl ring were tolerated. Aryl-substituted α,β-unsaturated sulfoxonium salts where R^2 = 2-MeOPh, 4-ClPh and *i*-Pr were also tolerated, though the presence of the more sterically demanding and electron-donating substituent 2-MeOPh did lead to a drop in yield (30-40%) but maintained good diastereoselectivity and enantioselectivity (*dr* 7:1, 68-75% ee). Alkyl substitution of the α,β-unsaturated sulfoxonium salt (R^2 = *i*-Pr) also produced similar results in that a lower yield was obtained (39%) though high diastereoselectivity and % ee was maintained (*dr* 7:1, 80% ee).

Interestingly, when enantioenriched sulfoxonium salts (in combination with a Koga amine) were employed for this reaction, a significant improvement in enantioselectivity was seen, with some examples formed with significantly-increased ee from 64% to 85% ee. This improvement was due to a match between chirality of the sulfoxonium centre and that of the Koga amine.

1.2.1.4 Synthesis of γ-Lactones Utilizing Ketoacids and Trimethylsulfoxonium Iodide

In 2019 Kokotos' group had success in the synthesis of γ-lactones using ketoacids and trimethylsulfoxonium iodide.[77] This reaction occurs via a two-step process involving Johnson-Corey-Chaykovsky type reaction followed by cyclization.

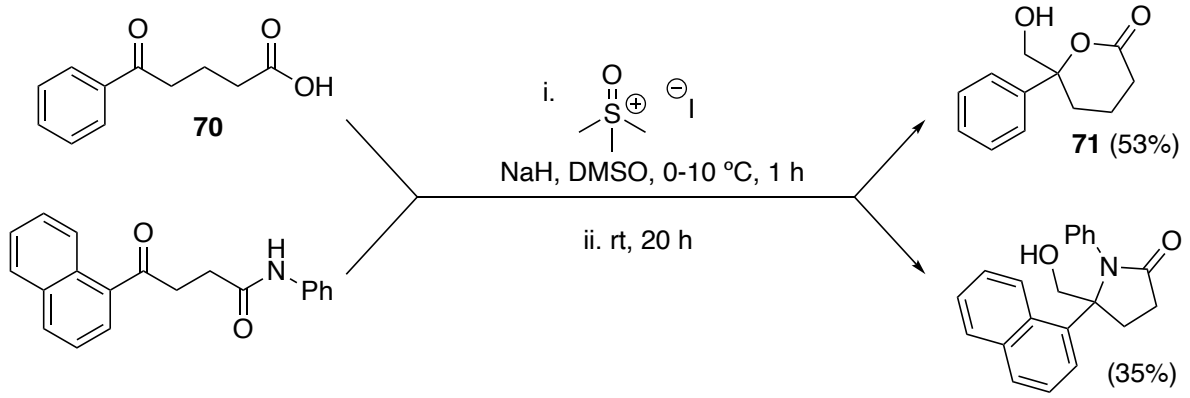
This reaction was found to obtain highest yields when 1 equiv. of ketoacid was subjected to reaction with 3 equiv. of trimethylsulfoxonium iodide in the presence of 3.6 equiv of NaH in DMSO.



SCHEME 38: SYNTHESIS OF γ-LACTONES FROM KETOACIDS

The reaction was found to tolerate substitution at the para position of the aromatic ring, substitution with a naphthyl group, branched aliphatic chains as well as aliphatic side chains with phenyl or other functional groups. Ortho-substitution of the aromatic ring was not tolerated well presumably due to increased steric hindrance close to the carbonyl moiety.

Use of ketoacid **70** under the same reaction conditions afforded δ-lactone **71** in 53% yield. This reaction was also found to tolerate the use of ketoamides as a starting material to afford γ-lactams in moderate yield.

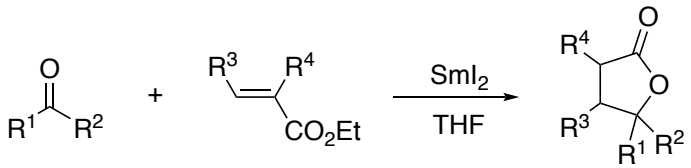


SCHEME 39: SYNTHESIS OF δ-LACTONE FROM KETOACID AND γ-LACTAM FROM KETOAMIDE

1.2.1.5 Samarium(II) Di-iodide induced Reductive Coupling of α,β-Unsaturated Esters with Carbonyl Compounds Leading to a Facile Synthesis of γ-Lactone

Fuzukawa et al. detailed a method of γ-lactone synthesis utilizing samarium(II) di-iodide, a strong one-electron transfer reducing agent.[78] Reaction of an α,β-unsaturated ester with various ketones and aldehydes in the presence of SmI_2 was found to afford a range of γ-lactones (**72**) under mild reaction conditions. The reaction was found to tolerate both aliphatic and aromatic ketones and aldehydes. For ketones, this reaction could be carried out at room temperature in THF employing equal equivalents of acrylate/crotonate ester to carbonyl compounds and 2 equivalents of SmI_2. For aldehydes, the same reaction conditions were used with a change in reaction temperature to 0 °C, and this was necessary to reduce the number of by-products formed. An asymmetric variant, using an ephedrinyl chiral auxiliary, was later reported in 1997 and it provided access to mainly 4,5-disubstituted γ-lactones in moderate to high enantiomeric excess (93-97 % ee) with diastereoselectivity up to 99:1 (*cis:trans*) and in 55-76% yield.[79]

TABLE 7: REDUCTIVE COUPLING OF CARBONYL COMPOUND WITH α,β-UNSATURATED ESTERS



72

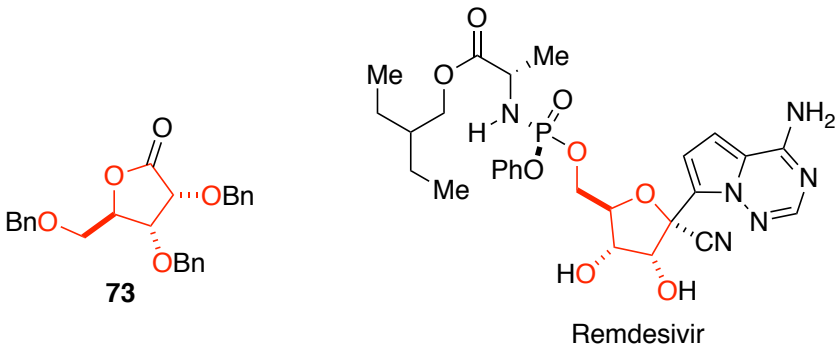
Entry	***α,β-Unsaturated ester***	***Carbonyl compound***	***(72) Isolated yield (%)***
1	Ethyl acrylate	Acetophenone	70
2	Ethyl acrylate	Benzophenone	47
3	Ethyl acrylate	Diethyl ketone	40
4	Ethyl acrylate	Octan-2-one	71
5	Ethyl acrylate	Cyclohexanone	76
6	Ethyl acrylate	Cyclodecanone	76
7	Ethyl acrylate	4-t-butylcyclohexanone	71
8	Ethyl acrylate	Hex-5-en-2-one	70

9	Ethyl acrylate	Benzaldehyde	82
10	Ethyl acrylate	Propanal	65
11	Ethyl acrylate	Isobutyraldehyde	63
12	Ethyl acrylate	Hexanal	57
13	Ethyl methacrylate	Acetophenone	75
14	Ethyl methacrylate	Benzaldehyde	75
15	Ethyl methacrylate	Cyclohexanone	63
16	Ethyl crotonate	Pentanal	70
17	Ethyl crotonate	Hexanal	70

(Ethyl acrylate: R^3 = H, R^4 = H, Ethyl methacrylate: R^3 = H, R^4 = Me, Ethyl crotonate: R^3 = Me, R^4 = H)

1.2.2 Applications of γ-lactones

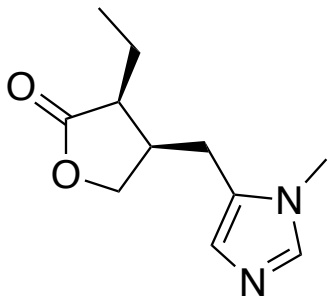
Perhaps one of the most important recent applications of γ-lactones as key intermediates in synthesis has been in the preparation of Remdesivir for the treatment of COVID-19.[80,81] The protected D-ribono-1,4-lactone **73** acts as an important synthetic intermediate as highlighted in Scheme 40. In addition, Remdesivir has been used for the treatment of Ebola virus disease and Marburg virus infections.[82,83]



SCHEME 40: γ-LACTONE AS IMPORTANT INTERMEDIATE FOR THE SYNTHESIS OF REMDESIVIR

The emergence of 2'-C-branched nucleosides that are derived from ribose analogues as therapeutics, e.g. Gilead's Sofosbuvir for the treatment of chronic Hapatitis C, underscores the need for new enantioselective methods to γ-lactones.[84,85]

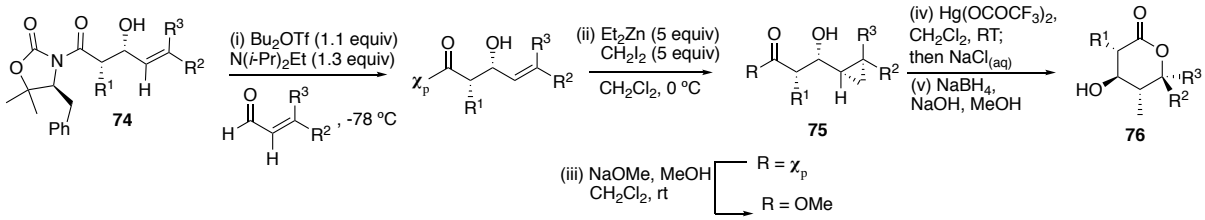
Pilocarpine is an important example of a drug that contains a γ-lactone motif. It is sold as an ophthalmic solution for the treatment of various types of glaucoma and is also available orally for the treatment of dry mouth.[86]



SCHEME 41: STRUCTURE OF PILOCARPINE

1.2.3 Preparation of δ-lactones

1.2.3.1 Asymmetric synthesis of chiral δ-lactones containing multiple contiguous stereocenters through regioselective ring-opening of cyclopropane esters

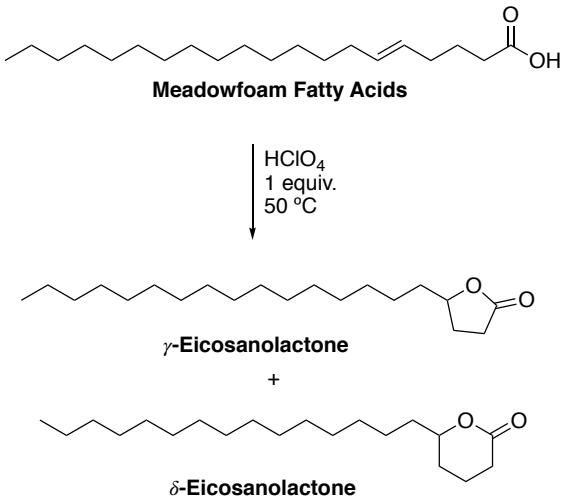


SCHEME 42: SYNTHESIS OF δ-LACTONES (BULL AND CO-WORKERS)

Bull and co-workers describe a method of synthesis of δ-lactones that employs chiral N-acyl-oxazolidin-2-one to prepare enantiomerically pure cyclopropane esters. Hydroxyl directed cyclopropanation of **74** followed by methanolysis afforded cyclopropane **75**. These cyclopropane esters can then undergo Hg(II) mediated ring-opening followed by subsequent reductive demercuration to afford δ-lactones **76**.

1.2.3.2 Regioselective synthesis of δ-lactones from meadowfoam fatty acids

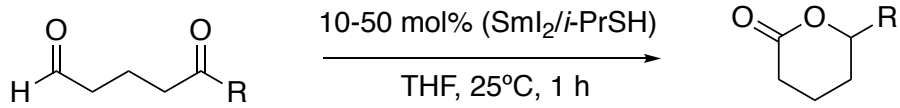
Isbell and Plattner describe a method of synthesis of δ-lactones from meadowfoam oil, a highly oxidatively stable oil due to its unique combination of monoenoic fatty acids. Taking advantage of the natural proximal relationship of the Δ5 double bond and carboxyl group meant that δ-lactone synthesis could occur in just two steps. The first step involved protonation of the Δ5 double bond to form a carbocation, stabilized by the carboxylate. Subsequent ring-closure afforded the product as a mixture of δ/γ-lactone. Reduction of reaction temperature to room temperature (vs previous literature publications with reaction temperature 85-150 °C) found a dramatic increase in regioselectivity of the reaction in favour of δ-lactones with δ/γ ratios up to 20:1.



SCHEME 43: ISBELL AND PLATTNER LACTONE SYNTHESIS FROM MEADOWFOAM FATTY ACIDS

1.2.3.3 Stereoselective synthesis of δ-lactones from 5-Oxapentanals

Fang and Hsu documented the preparation of δ-lactones through conversion of various 5-oxopentanals by synergistic catalysis of samarium diiodide and 1-propanethiol (mercaptan).[87] Mercaptan was chosen as a reactant partner preferentially to alcohols due to its facilitation of the catalytic cycle. Simple δ-substituted-δ-lactones were prepared in excellent yield (91-99 %) through cyclization of a series of 5-alkyl- and 5-phenyl- 5-oxopentanals facilitated by SmI_2/*i*-PrSH (10-50 mol %) with merely 1 hour of stirring at rt in THF. More complex δ-lactones, such as α-dimethyl-δ-lactone and 5,6- and 4,6-substituted δ-lactones were also synthesized in very good to excellent yields (80-97 %).



SCHEME 44: SYNTHESIS OF δ-LACTONES FROM 5-OXAPENTANALS

1.2.4 Applications of δ-lactones

1.2.4.1 Poly(glucono-δ-lactone) based nanocarriers as novel biodegradable drug delivery platforms

Xu and co-workers describe the ring-opening polymerization of glucono-δ-lactone (GDL) to generate a highly branched polymer (PGDL) that is capable of forming stable nanoparticles via emulsification, which can carry the anticancer agent 5-fluorouracil effectively.[88]

Polyethylene glycol is the most frequently researched hydrophilic material for drug delivery of therapeutic agents, however the repeating CH_2CH_2O unit results in a lack of sites available for functionalization for introduction targeting structures or dye labelling. For this reason, Xu and co-workers sought an alternative biocompatible and biodegradable polymer for drug delivery applications.

GDL is a widely used food additive and is administered with some drugs in the form of gluconates. Xu et al. were able to demonstrate that PGDL has very low cytotoxicity and multiple groups valuable for functionalization.

To prepare the PGDL, 10.0 g of glucono-δ-lactone, tetrabutyl titanate (0.4 mL) and ethylene glycol (0.4 mL) were refluxed under N_2 at 160 °C for 3 h. The product was cooled under N2 and 20 mL of dimethylformamide was added and heated at 80 °C until the product was completely dissolved. The product was precipitated and washed using THF and subsequently dried under vacuum.

To prepare drug-free PDGL particles, 100.0 mg of PGDL was dissolved in 5.0 mL of water to make a 2% (w/v) aqueous phase. The oil phase was prepared by homogenisation of 40.0 mL of paraffin oil and 2.0 mL of 5% (w/v) emulsifier span-80. 4.0 mL of the aqueous phase was added dropwise through a 0.22 μm microporous filter to the oil phase at 50 °C while stirring under reflux. After the mixture was agitated for 4 h the solution was added to an equal volume of petroleum ether and mixed. After allowing to settle for 15 minutes the upper layer was removed, and the remaining supernatant was removed via centrifuge. The polymer particles were purified via multiple washes with petroleum ether and isopropyl alcohol, centrifuged, dispersed in isopropyl alcohol and then dried under vacuum.

To prepare the drug-loaded PGDL particles the same process as above was followed with the addition of 10.0 mg of 5-fluorouracil in the aqueous phase of the first step.

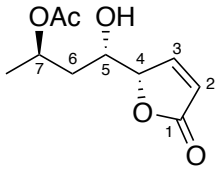
The highly branched monomer is formed through the attack of each hydroxy group to the lactone ester of another monomer. The molecular weight was determined by GPC analysis and had a weight-average of $1.58x10^4$ and a low polydispersity index of 1.13. The GPC trace indicated unimodal distribution of PGDL.

The PGDL scaffold allows for high drug-loading capacity, polyvalency and high permeability across biological barriers. In vitro studies showed that the controlled release of 5-fluorouracil from PGDL was possible with an enhanced release at tumoral pH.

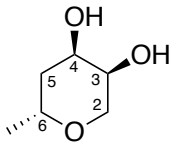
Human ovarian cancer cells were used to compare the viability of PDGL particles with and without 5-fluorouracil. The polymer was found to have good biocompatibility After 24 h incubation the drug-free PGDL particles showed a lethal concentration of 4587±58 μg/mL.

1.2.4.2 Synthesis of botryolide E and Ophiocerin A, B and C.

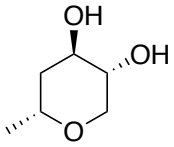
Recently Chen, Zhou and co-workers published a method of synthesis of botryolide E and Ophiocerins A, B and C from D-glucono-δ-lactone.[89] (-)-Botryolide E **77** is an important subunit in many biologically active natural products and has exhibited promising antibacterial activity and antifungal activity.[90] Ophiocerins **78a-c** are another important structural motif in biological natural products and have been isolated from the aquatic fungus *Ophioceras venezuelenser*.[91]



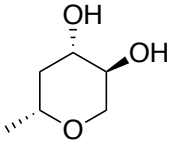
(-)-botryolide E (**77**)



(-)-ophiocerin A (**78a**)



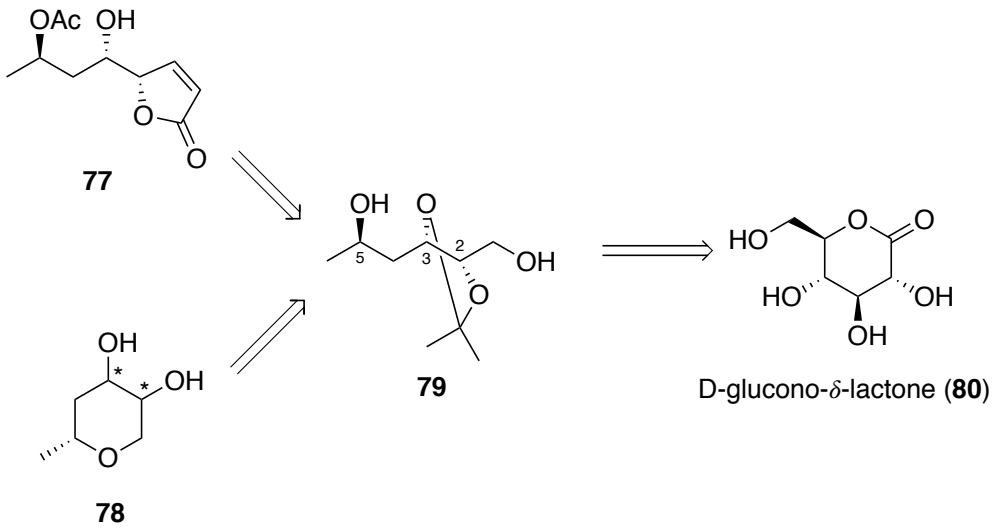
(-)-ophiocerin B (**78b**)



(+)-ophiocerin C (**78c**)

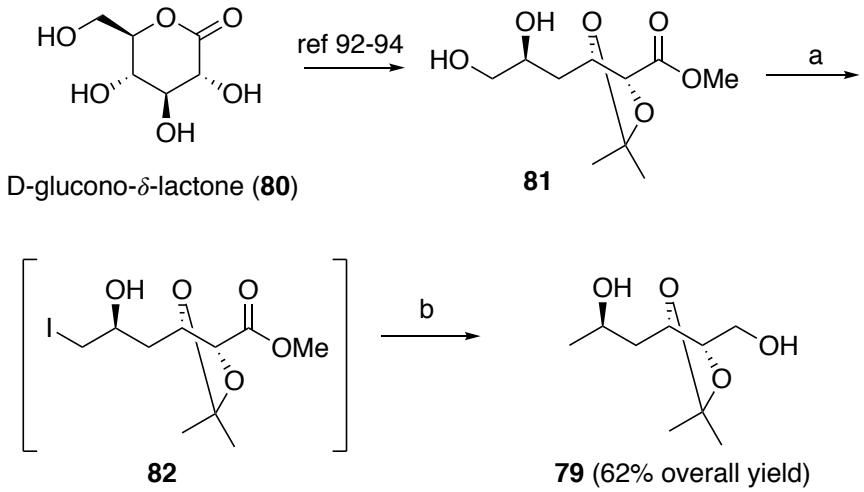
SCHEME 45: IMPORTANT STRUCTURAL MOTIFS IN BIOLOGICALLY ACTIVE PRODUCTS

It was envisioned that (-)-botryolide E **77** and Ophiocerins **78a-c** could be prepared from the common intermediate **79** via lactonization or S_N2 cyclization, and intermediate **79** could be generated through selective deoxygenation of D-glucono-δ-lactone **80** (Scheme 46).



SCHEME 46: CHEN, ZHOU AND CO-WORKERS RETROSYNTHETIC ANALYSIS OF D-GLUCONO-δ-LACTONE

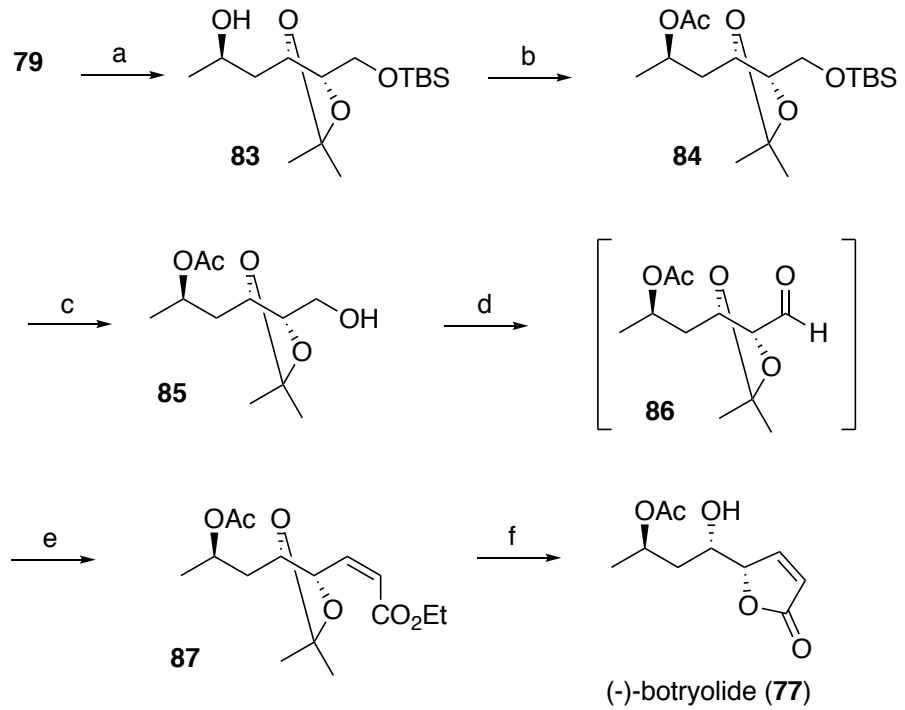
To begin, D-glucono-δ-lactone was converted to hydroxyl ester **81** following literature procedure which involved a 4-step sequence with protection as isopropylidene derivative, Barton-McCombie deoxygenation and selective hydrolysis of the terminal acetonide.[92–94] Selective iodination of the primary alcohol group in diol **81** under Appel reaction conditions affords Iodide **82**, simultaneous reduction of the ester and the iodo functional groups with excess $LiAlH_4$ affords the intermediate in 62% overall yield.



SCHEME 47: REAGENTS AND CONDITIONS: (A) I_2, PPh_3, IMIDAZOLE, THF, RT; (B) $LiALH_4$, THF, 0 ° C, 62% OVER TWO STEPS

The primary alcohol of **79** was masked with TBSCl first and acetylation of the secondary alcohol in **83** using Ac_2O afforded acetate **84**. Removal of the protecting group afforded alcohol **85** which was subjected to oxidation with Dess-Martin periodinane to afford corresponding

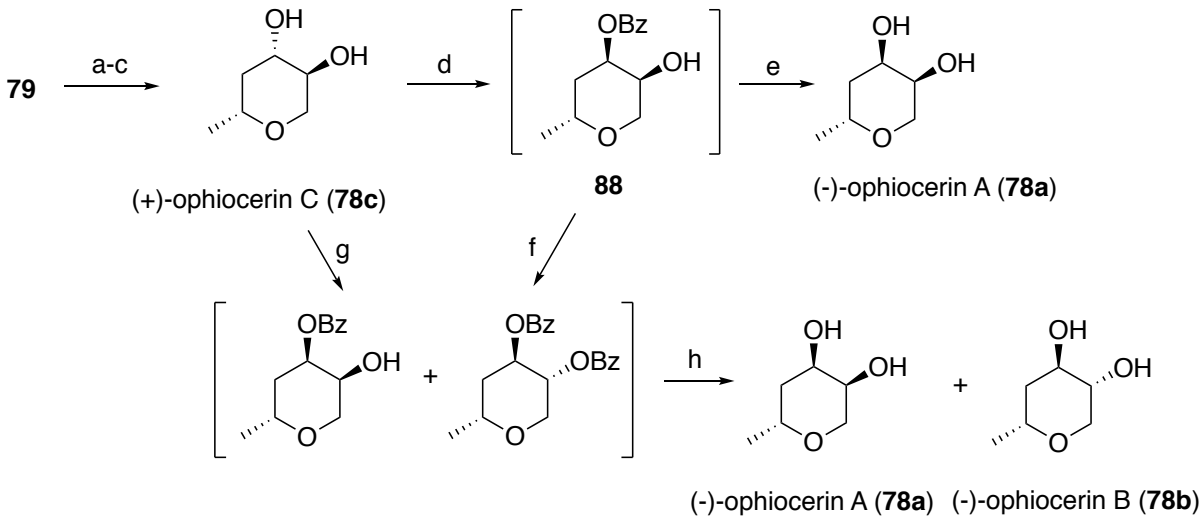
aldehyde **86**. Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane generated Z-conjugated ester **87** which then underwent one-pot acetonide deprotection and lactonization to afford (-)-botryolide E (Scheme 48).



SCHEME 48: REAGENTS AND CONDITIONS: (A) TBSCl, IMIDAZOLE, CH_2Cl_2, 0 ° C, 92%; (B) Ac_2O, Et_3N, DMAP. RT, 92%; (C) TBAF, THF, 0 ° C, 96%; (D) DESS-MARTIN PERIODINANE, CH_2Cl_2, rt; e) $Ph_3P{=}CHCO_2Et$, MeOH, 0 ° C, 72% OVER TWO STEPS; (F) 80% aq. AcOH, RT, 91%.

(+)-Ophiocerin C was readily accessed from intermediate **79** following Kumar's strategy which included sequential tosylation of the primary alcohol, base-induced cyclization and deprotection of acetonide.[95] (+)-Ophiocerin C was subjected to Mitsunobu reaction at room temperature to afford **88**. Hydrolysis of impure benzoate **88** afforded (-)-ophiocerin A (**78a**) in 78% overall yield.

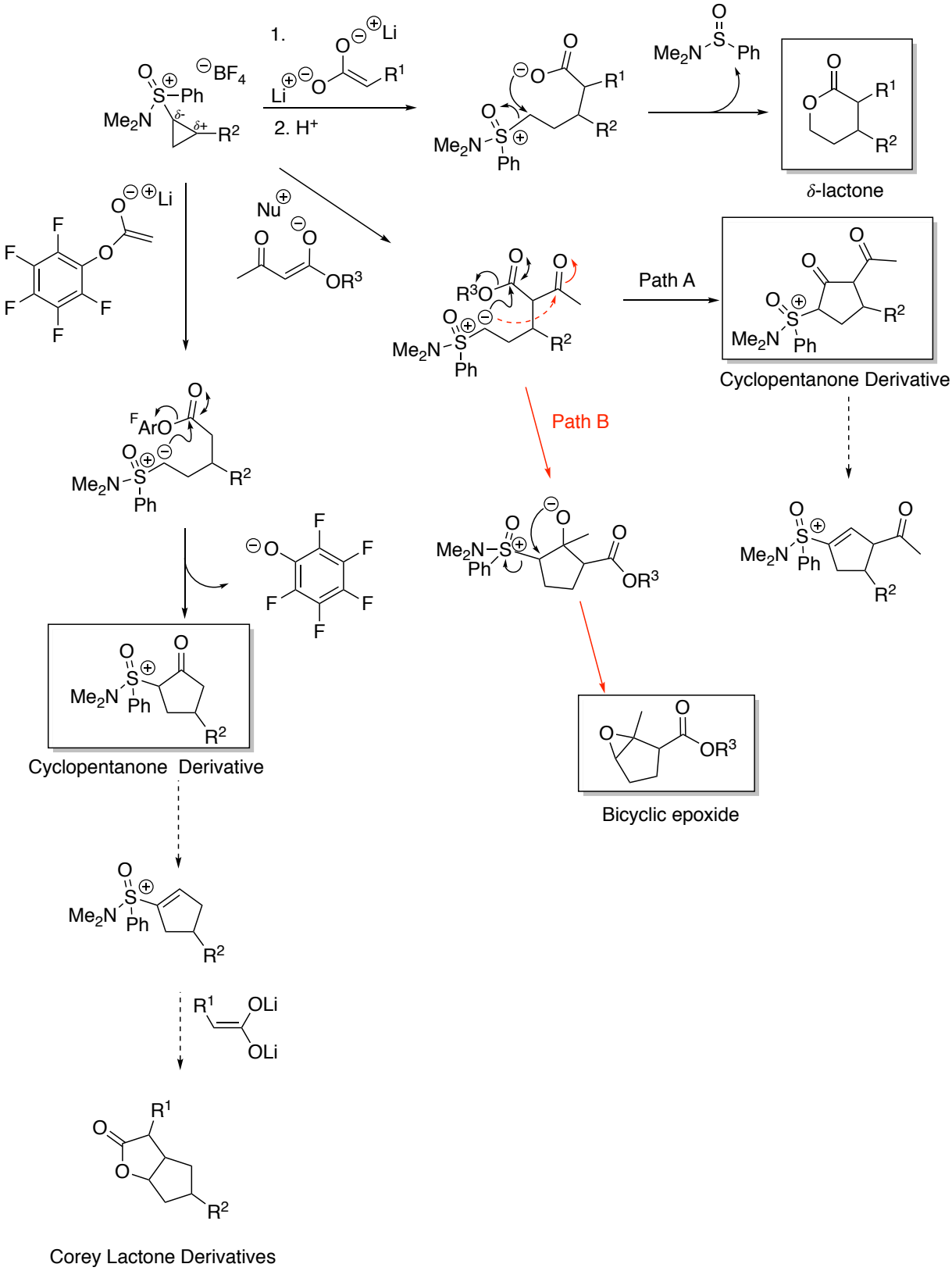
One pot double Mitsunobu reaction of **78c** performed in refluxing toluene or THF in the presence of excess reagents (4.0 equiv.) followed by subsequent hydrolysis furnished a mixture of (-)-ophiocerin B (**78b**) in 41% yield and (-)-ophiocerin A in 33% yield (Scheme 49).



SCHEME 49: REAGENTS AND CONDITIONS: (A) TsCl, NaH, THF, 0 ° C; (B) tBuOK, Et_2O, 0 ° C; (C) pTsOH, MeOH, RT, 80% OVER THREE STEPS; (D) DIAD, Ph_3P, BzOH, THF, RT; (E) K_2CO_3, MeOH, RT, 78% OVER 2 STEPS; (F) DIAD, Ph_3P, BzOH, THF, 50 ° C; (G) DIAD, Ph_3P, BzOH, TOLUENE, 110 ° C; (H) K_2CO_3, MeOH, RT, 45% FOR 78A AND 22% FOR 78B OVER THREE STEPS (D, F, H), 33% FOR 78A AND 41% FOR 78B OVER TWO STEPS (G, H).

1.3: Results and Discussion

1.3.1 Synthetic plan



SCHEME 50: SYNTHETIC PLAN

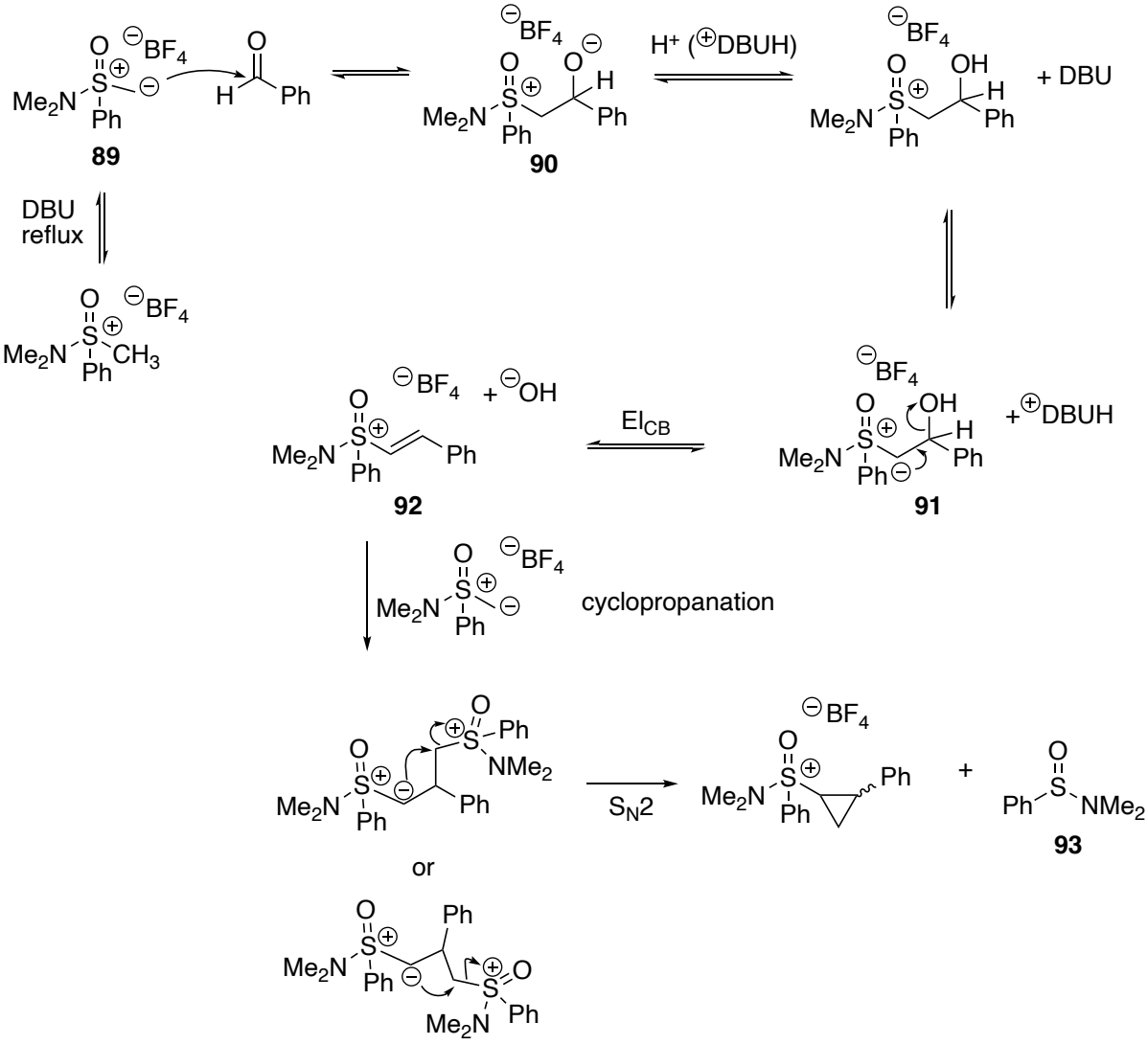
The synthetic plan for this work is outlined in Scheme 50. Access to various important structural motifs was envisioned through the reaction of the cyclopropylamino sulfoxonium salt and various enolates/enediolates. Access to δ-lactones was visualized to occur through reaction with lithium enediolates. Alternatively, reaction of cyclopropyl sulfoxonium salts and an acetoacetic ester was expected to react through two possible pathways; the first, pathway A, would involve ring-closure via attack of the ester carbonyl to afford a cyclopentanone derivative. Selective reduction of the cyclopentanone derivative would afford a cyclopentene intermediate suitable for the preparation of a Corey Lactone.

The second possible mechanism, pathway B, would involve ring-closure via attack of the ketone carbonyl. A subsequent secondary ring-closure would form an epoxide, generating a bicyclic epoxide.

Reaction of the cyclopropyl sulfoxonium salt with the enolate of pentafluorophenyl acetate was envisioned to also provide access to a cyclopentanone derivative. Increased electronegativity from the fluorine atoms would encourage attack of the carbanion to the ketone carbonyl, and subsequent loss of the pentafluorophenol anion was hoped to afford the desired product.

1.3.2 Preparation of cyclopropyl salt

The preparation of the cyclopropyl sulfoxonium salt followed the mechanism outlined in Scheme 51. To begin, DBU acts as a base to abstract a proton from the sulfoximine forming ylide **89**. The carbanion then attacks the carbonyl of benzaldehyde to form intermediate **90**. Intermediate **90** abstracts a proton from $DBUH^+$ in solution, the base also acts to abstract a proton to form the ylide intermediate **91**. The free electron flows into the adjacent bond to form the carbon-carbon double bond while an OH^- is simultaneously ejected to afford the unsaturated sulfoxonium **92**. Reaction of **92** with another ylide **89** in solution followed by cyclopropane ring formation with simultaneous loss of sulfinamide **93** afforded the desired cyclopropane.

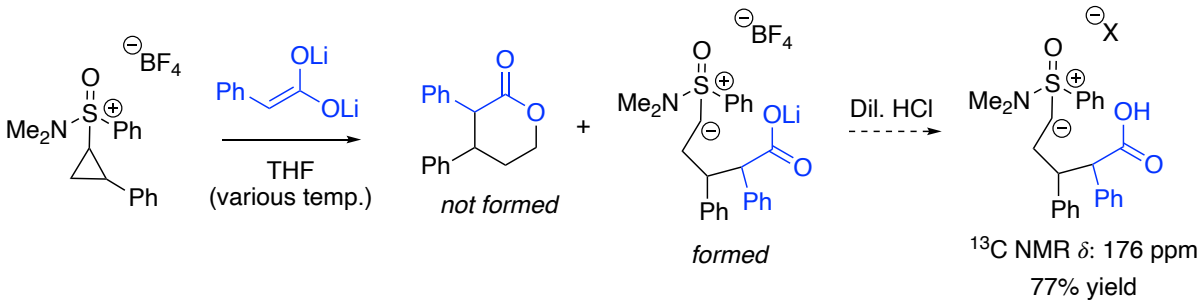


SCHEME 51: MECHANISTIC PATHWAY FOR THE SYNTHESIS OF CYCLOPROPYL SULFOXONIUM SALT

1.3.3 Investigation into the synthesis of δ-lactones/cyclopentyl sulfoxonium salts

With the desired cyclopropane at hand, a route to the synthesis of δ-lactones/cyclopentyl sulfoxonium salts was investigated through its reaction with various enolates/enediolates.

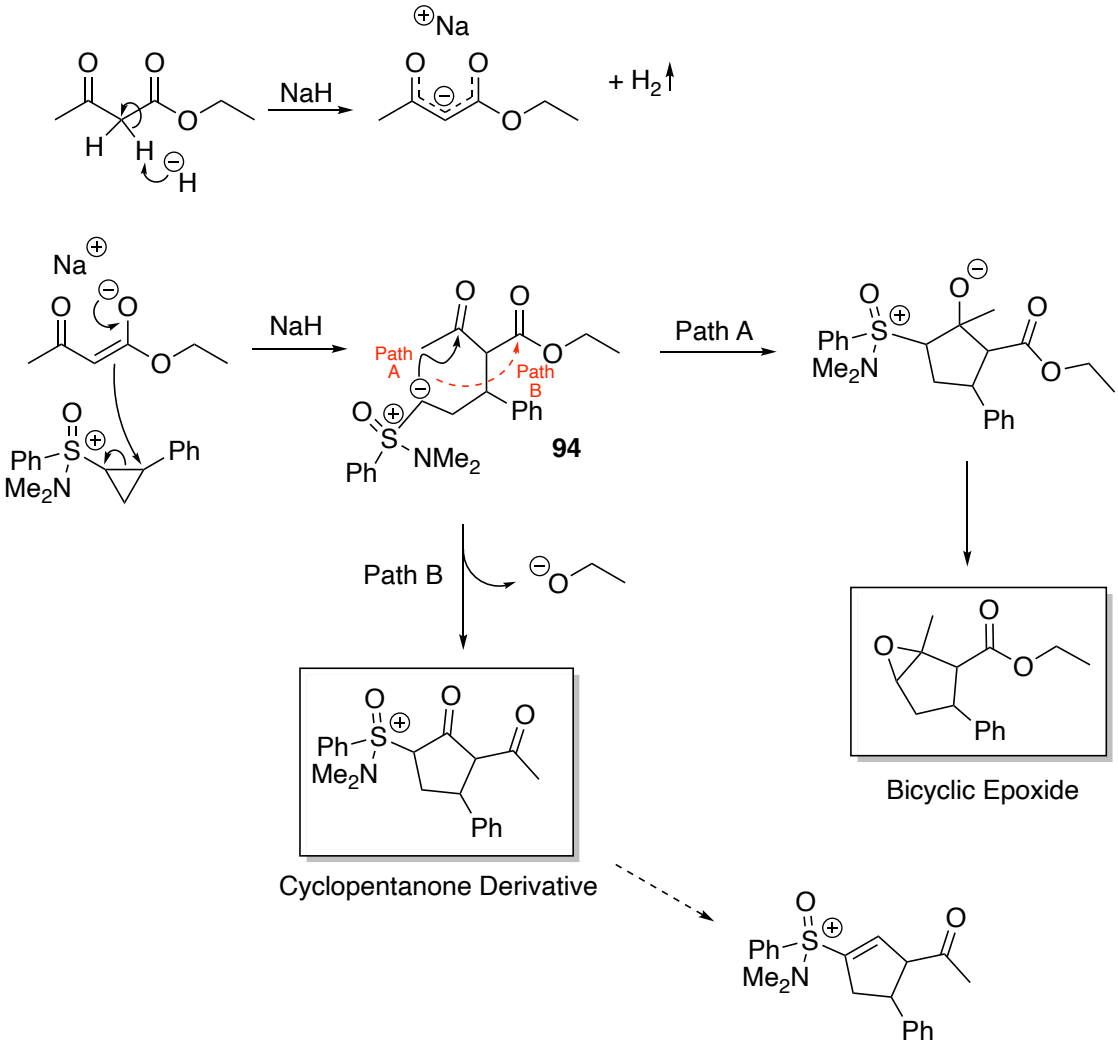
Access to δ-lactones through reaction with lithium enediolates was first investigated by another member of our group, Chrismae Bergado. This researched achieved ring-opening of the cyclopropyl sulfoxonium salt under much milder conditions (0 °C to RT) than in previous literature findings (>65 °C). All carboxylic acid starting material was consumed and the crude product ^{13}C NMR showed a carbonyl peak at 176 ppm. The product was found to be very polar and deduced to be the uncyclized sulfoxonium salt-carboxylic acid adduct. Although cyclization of the intermediate into a delta-lactone was our preliminary goal, achieving ring-opening under such mild conditions was very promising (Scheme 52). This encouraged us to try ester enolates and other enolates with a good leaving group so that cyclization through nucleophilic attack of the sulfoxonium ylide on the pendant carbonyl carbon would be more likely.



SCHEME 52: REACTION OF CYCLOPROPYL SULFOXONIUM SALT AND LITHIUM ENEDIOLATES

We then investigated the reaction of ethyl acetoacetate with cyclopropyl sulfoxonium salt. An enolate (carbanion) of ethyl acetoacetate would be prepared through treatment of ethyl acetoacetate with NaH (Scheme 53). The most acidic proton (pKa = 11) of the ketoester is located on the carbon between the two carbonyl groups and is readily removed by treatment with the relatively strong base NaH.

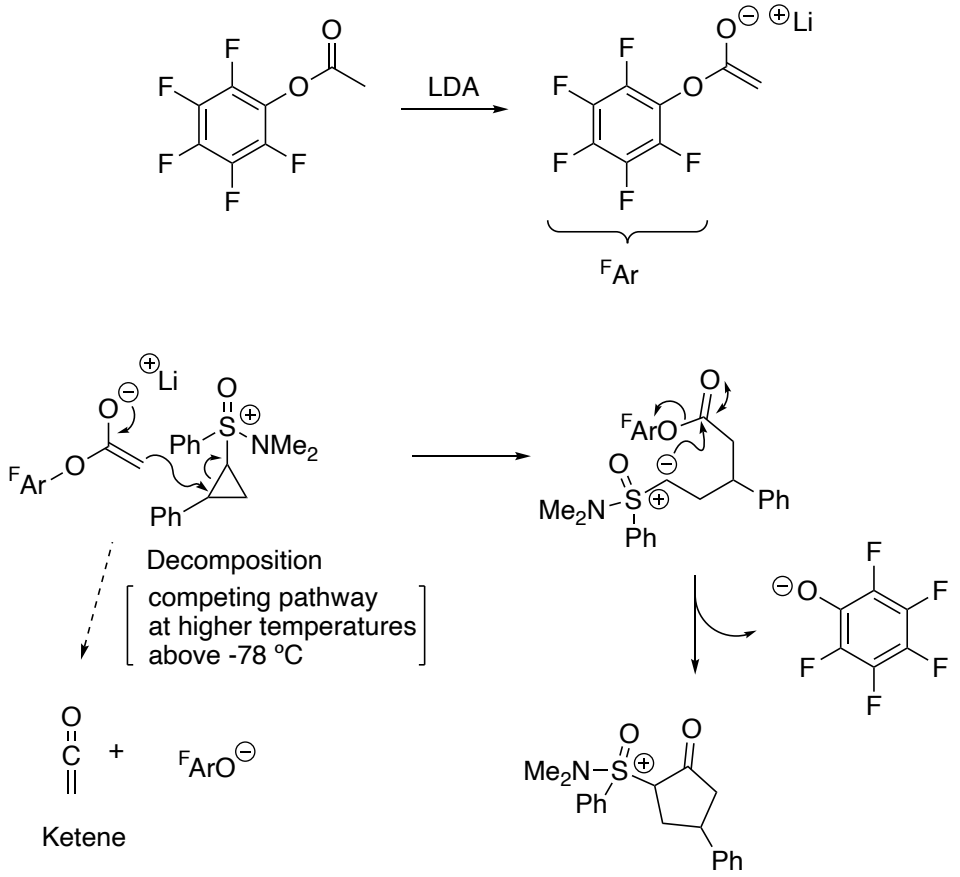
The reaction was expected to follow the reaction pathway outlined in Scheme 53. Ring-opening of the cyclopropyl salt was expected to occur upon nucleophilic attack of the enolate of ethyl acetoacetate to the sulfoxonium ylide to form intermediate **94**. From this point it was envisioned that two different pathways could be followed. Path A would involve attack of the carbanion to the ketone carbonyl, a secondary ring-closure reaction was expected to follow furnishing a bicyclic epoxide with the loss of a sulfinamide group. Path B would involve attack of the ester carbonyl furnishing a cyclopentanone derivative.



SCHEME 53: EXPECTED MECHANISTIC PATHWAY FOR REACTION OF CYCLOPROPY SULFOXONIUM SALT AND ETHYL ACETOACETATE

Unfortunately, this reaction did not proceed as expected. A large amount of unreacted cyclopropyl sulfoxonium salt was recovered as well as unreacted ethyl acetoacetate. It was hypothesized that this reaction did not progress because ethyl acetoacetate enolate was too stabilized to effect ring-opening reaction of the cyclopropyl salt under these conditions. To further investigate this possibility, pentafluorophenyl acetate was synthesized to use as a reactant partner. Fluorine is extremely electronegative, so it was hypothesized that the introduction of the pentafluorophenyl motif (^{F}ArO-) would encourage enolate formation, and would be expected to act as a good leaving group for subsequent cyclization. Unfortunately, the same results were again obtained, in that mostly unreacted starting materials were recovered. It was then presumed that the base (NaH) was not strong enough to deprotonate which was supported by the fact that no colour change was observed during reaction that would suggest presence of an enolate. The experiment was then repeated using in situ generated LDA generated through treatment of diisopropylamine with *n*-Butyllithium and diisopropylamine. The initial temperature of the reaction was dropped to -78 °C with the temperature being brought up to 0 °C after the addition of LDA and pentafluorophenyl acetate.

Interestingly, it appeared that this caused the reversion of pentafluorophenyl acetate back to pentafluorophenol. ^{1}H-NMR showed the presence of unreacted cyclopropyl salt as well as two -OH peaks at around 5 ppm. ^{13}C-NMR showed no carbonyl stretch which further suggests the reversion back to pentafluorophenol. ^{19}F-NMR showed only 3 unique fluorines which indicates complete reversion. Decomposition of the enolate to ketene and ^{F}ArO- can occur at elevated temperatures (above -78 °C).

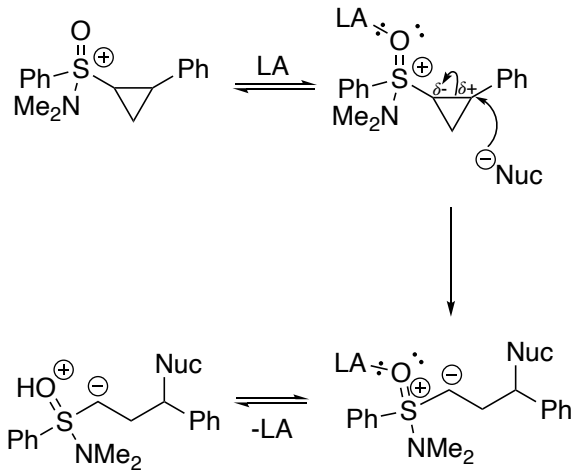


SCHEME 54: EXPECTED MECHANISTIC PATHWAY FOR REACTION OF CYCLOPROPYL SULFOXONIUM SALT AND PENTAFLUOROPHENYL ACETATE

Unfortunately, due to time constraints it was not possible to further investigate cyclopropyl salt ring-opening. However, there are many other routes that are worth investigating. Similar to the pentafluorophenyl acetate reaction, it may be worth repeating using ethyl 4,4,4-trifluoroacetoacetate. Ethyl 4,4,4-trifluoroacetoacetate would have a similar electron withdrawing effect. However, the fluorines are localized on one carbon, in comparison to pentafluorophenyl acetate where they are located around the phenyl ring which may provide better results. If successful, introduction of electron-withdrawing fluorine should encourage the reaction to proceed through path A in Scheme 53.

Another modification to this experiment that would be worth investigating would be to repeat the experiment with pentafluorophenyl acetate and LDA while stirring at -78 °C for several more hours. Maintaining this reaction at a lower temperature for longer would inhibit enolate decomposition, and allow for more time for the enolate and cyclopropyl salt to react in the expected fashion.

Finally, employing Lewis acid catalysis may encourage the formation of δ-lactones/cyclopentyl sulfoxonium salts. Complexation of a Lewis acid at the sulfoxonium oxygen oxygen would increase the electron withdrawing effect and weaken adjacent sigma bonds making them more likely to break when undergoing nucleophilic attack (Scheme 55).



SCHEME 55: INTRODUCTION OF A LEWIS ACID INCREASES POSITIVE CHARGE AT THE CARBONYL OXYGEN, MAKING THE CARBONYL CARBON MORE SUSCEPTIBLE TO NUCLEOPHILIC ATTACK

1.3.4 Synthesis of γ-lactones

As the group had previous success with the synthesis of γ-lactones through reaction of enediolates and α,β-unsaturated sulfoxonium salts (discussed in section 1.2.1.2), the substrate scope of this reaction was investigated to determine its tolerance towards a range of other substituted acetic acids. The results of which are outlined in Table 8.

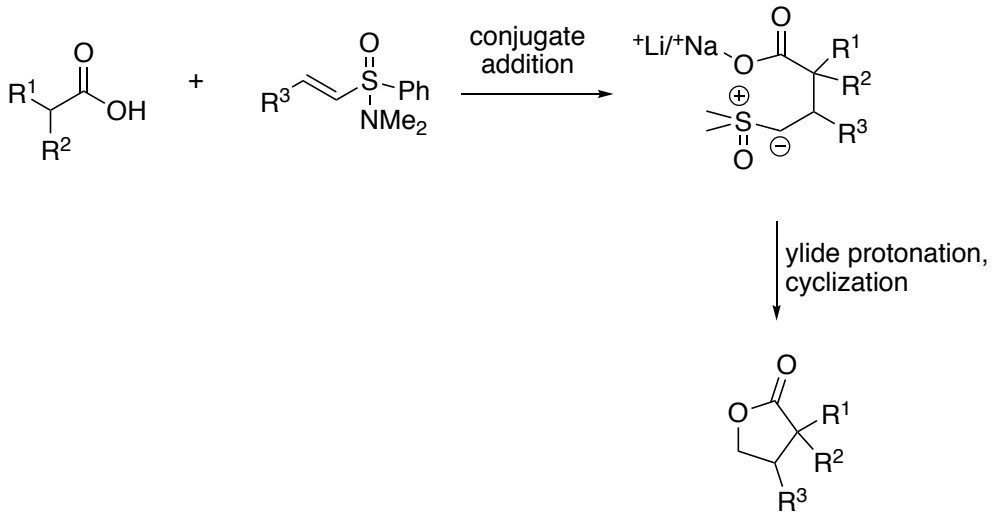
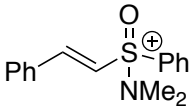
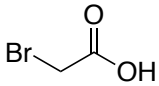
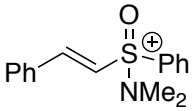
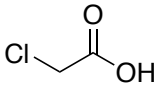
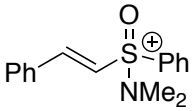
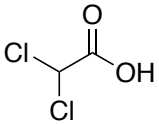
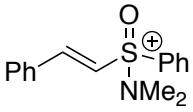
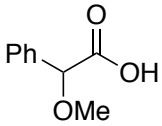
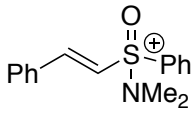
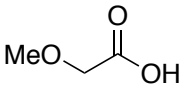
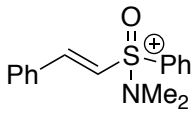
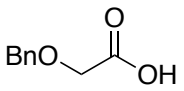
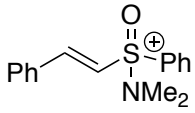
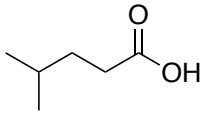
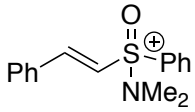
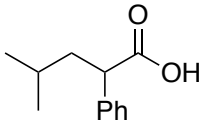
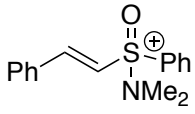
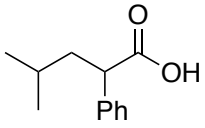
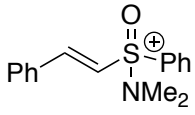
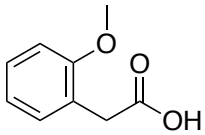
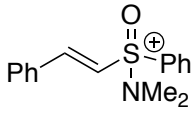
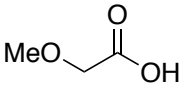
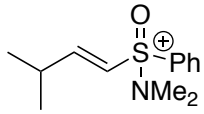
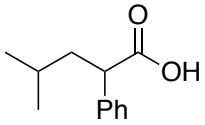
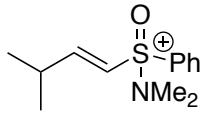
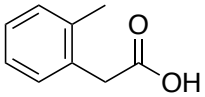
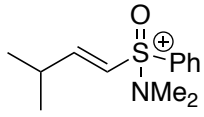
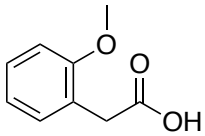


TABLE 8: INVESTIGATION OF γ-LACTONE SYNTHESIS

entry	*salt*	*acetic acid*	*base*	*Reaction no.*
1[b]			NaHDMs	SC1-55
2			NaHDMs	SC1-57
3			n-BuLi	SC1-67
4			n-BuLi	SC1-68

5			n-BuLi	SC1-69
6			n-BuLi	SC1-70
7			n-BuLi	SC1-80
8			n-BuLi	SC1-79
9[a]			n-BuLi	SC1-84
10[b]			n-BuLi	SC1-85
11			LDA	SC1-71
12			n-BuLi	SC1-82
13			n-BuLi	SC1-73
14			n-BuLi	SC1-74

In all cases BF_4^- was the salt couterion. In all cases procedure 1.3.7 was followed with the exception of: [a] followed procedure 1.3.8, [b] followed procedure 1.3.9.

When NaHDMS was used as a base (Table 8, entry 1 and 2), no colour change was observed upon its addition to the carboxylic in the reaction at -78 °C. This indicated that deprotonation was not occurring, which was confirmed by TLC and showed the starting materials remained after completion of reaction.

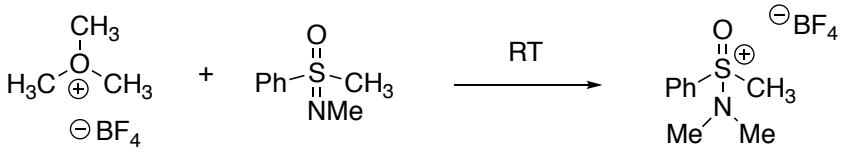
n-Butyllithium was believed to have the most likely success with this reaction given its use in previously published work (section 1.2.1.2). Unfortunately, this did not appear to yield the desired γ-lactone in any of the cases. ^{13}C-NMR did not indicate the presence of a carbonyl and no splitting patterns that would indicate new ring formation were noted in any case.

1.4: Experimental

General Information

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard inert atmosphere technique unless otherwise stated. THF was dried using a sodium/benzophenone ketyl still, and N,N,N-triethylamine was distilled from potassium hydroxide under nitrogen. Diphenylacetic acid, bromoacetic acid, chloroacetic acid, dichloroacetic acid, 2-methoxyphenylacetic acid, 2-phenylacetic acid, (+)-α-methoxyphenyl acetic acid, o-tolylacetic acid, benzyloxyacetic acid, methoxyacetic acid, 4-methylvaleric acid, o-methoxyphenyl acetic acid, α-isopropylphenylacetic acid, methylphenyl sulfoxide, sodium hydride (60% dispersion in oil), trimethyloxonium tetrafluoroborate, acetyl chloride, pentafluorophenol, DBU, 1-bromo-2-methylpropane, and n-butyllithium (2.5M in hexanes) were purchased from Aldrich Chemical Co. and used as received. Benzaldehyde, diisopropylamine, and ethyl acetoacetate were purchased from Aldrich Chemical Co. and distilled prior to use. The α,β-unsaturated sulfoxonium salts were previously prepared by Dylan Twardy. Iatrobeads (neutral silica, Bioscan, 6RS-8060, 60 μM particle size) and TLC plates (Sorbent Technologies, UV254, 250 μM) were used as received. NMR spectra were recorded on a Bruker Avance III 600 spectrometer (600 MHz for ^{1}H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to $CDCl_3$ (17.26 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra.

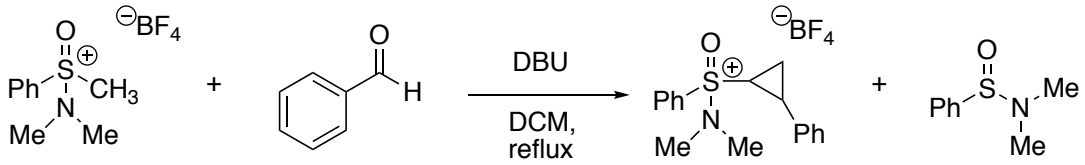
1.4.1 Methylation of N-(methyl)-S-methyl-S-phenyl sulfoxonimine



To a solution of trimethyloxonium tetrafluoroborate (2.26 g, 14.4 mmol, 1.2 equiv) in dry CH_2Cl_2 (18.5 mL) a solution of N-(methyl)-S-methyl-S-phenylsulfoximine (2.00 g, 11.82 mmol, 1.0 equiv) previously prepared by Chrismae Bergado in dry CH_2Cl_2 (18.5 mL) was added. After stirring for 4 hr at room temperature an additional portion of trimethyloxonium tetrafluoroborate (0.44 g, 0.2 equiv) was added and allowed to react overnight. The next day, an additional portion of trimethyloxonium tetrafluoroborate (0.2 equiv) was added and the reaction was stirred for a further 3 h. The solvent was removed under reduced pressure to afford compound number SC1-06 (1.43 g, 65%). The product was recrystallized from absolute ethanol to afford a white solid.

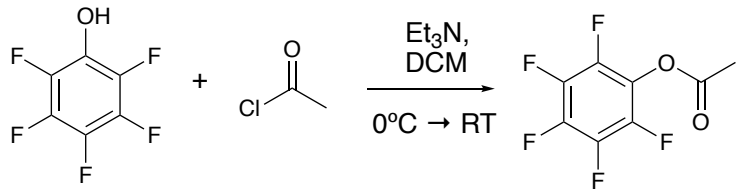
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.29 – 8.28 (d, 2H), 7.96 (t, 1H, J = 7.5 Hz), 7.87 – 7.84 (t, 2H, J = 8.0 Hz), 4.06 (s, 3H), 3.16 (s, 6H)^{13}C NMR (150 MHz, $CDCl_3$): 137.7, 131.5, 129.4, 40.9, 38.2

1.4.2 Synthesis of N,N-dimethyl-S-phenyl-S-(2-phenylcyclopropyl)sulfoxonium tetrafluoroborate



To a solution of N-(methyl)-S-methyl-S-phenyl sulfoximine (0.85 g, 3.1 mmol, 2.0 equiv) in dry CH_2Cl_2 (8.50 mL) was added DBU (0.56 mL, 3.7 mmol, 2.4 equiv), and this was allowed to stir. After 30 minutes, benzaldehyde (0.16 mL, 1.6 mmol, 1.0 equiv) was added and the solution was allowed to reflux for 2 h. The reaction was washed twice with HCl (0.1M, 2 × 10 mL) followed by washes with deionized water (2 × 10 mL). The organics were dried over Na_2SO_4, filtered and the solvent was evaporated. The product was purified through column chromatography with CH_2Cl_2 to afford an impure mixture of N,N-dimethyl-S-phenyl-S-(2-phenylcyclopropyl)sulfoxonium tetrafluoroborate and sulfinamide (0.37 g, ~63% (calc. by NMR peak integration) as a pale yellow solid.

1.4.3 Synthesis of pentafluorophenyl acetate

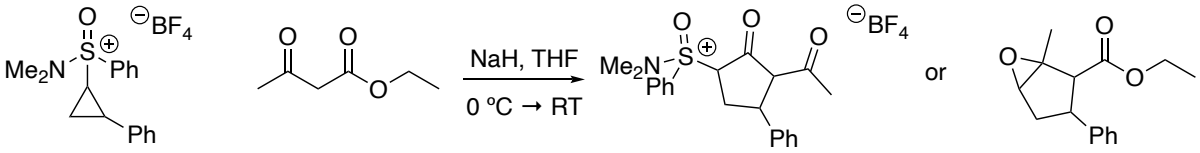


Pentafluorophenol (0.50 g, 2.7 mmol, 0.9 equiv) and triethylamine (0.41 mL, 3.0 mmol, 1.0 equiv) were added to a flask and cooled to 0 °C. To this was added CH_2Cl_2 (8 mL) and after the solution cooled to 0 °C, acetyl chloride (0.21 mL, 3.0 mmol, 1.0 equiv) was added dropwise. After the addition was complete the ice bath was removed and the reaction was stirred at room temperature for 3 h. CH_2Cl_2 (10 mL) was added to the reaction and was then washed with water (3 × 10 mL) followed by a wash with brine solution (10 mL). The organics were dried over Na_2SO_4, filtered and the solvent was evaporated. The resulting crude product

was purified by flash column chromatography (using 10% EtOAc in hexane) to afford product pentafluorophenyl acetate (0.53 g, 87%) as a colourless liquid.

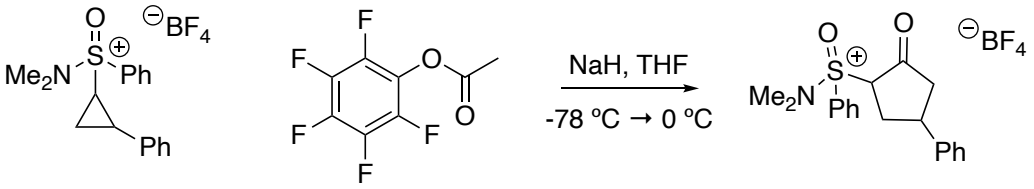
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.38 (s, 3H) ^{13}CNMR (150 MHz, $CDCl_3$): 171.1, 166.5, 19.7

1.4.4 Investigation of reaction of ethyl acetoacetate anion with cyclopropyl sulfoxonium salt



NaH (60% dispersion in oil, 5.5 mg, 0.13 mmol, 1.0 equiv) was added to a flask and washed with dry hexanes (2 × 1 mL). Dry THF (1 mL) was added and the solution was allowed to cool to 0 °C. The ethyl acetoacetate (0.017 mL, 0.13 mmol, 1.0 equiv) was added dropwise and allowed to stir for 20 minutes. Parallelly, in a separate flask THF (1 mL) was added to the cyclopropyl sulfoxonium salt (0.050 g, 0.13 mmol, 1.0 equiv) and allowed to cool to 0 °C. After stirring for 20 min the flask containing the ethyl acetoacetate-NaH solution was transferred by syringe to the second flask, and the reaction was allowed to proceed overnight. The reaction was quenched with HCl (0.1M, 10 mL). The reaction mass was washed with CH_2Cl_2 (3 × 10 mL) and the combined organics were then washed with brine solution (10 mL). The organics were dried over Na_2SO_4, filtered and the solvent was evaporated.

1.4.5 Procedure A for investigation of reaction of Pentafluorophenyl acetate anion with cyclopropyl sulfoxonium salt



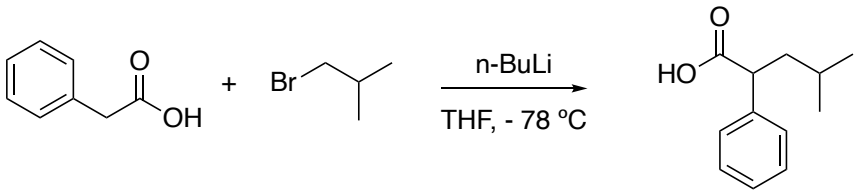
Diisopropylamine (0.020 mL, 0.16 mmol, 1.2 equiv) in THF (1 mL) was allowed to cool to -78 °C. *n*-BuLi (2.5M in hexanes, 64 µL, 0.16 mmol, 1.2 equiv) was added dropwise and the reaction was allowed to stir for 20 min. Parallelly THF (1 mL) was added to a flask containing cyclopropyl sulfoxonium salt (0.060 g, 0.13 mmol, 1.0 equiv) and the suspension was allowed to cool to -78 °C. Pentafluorophenyl acetate (0.040 g, 0.16 mmol, 1.2 equiv) was added dropwise to the LDA solution and the reaction stirred for 20 min at -78 °C. The reaction mixture

was then transferred to the cyclopropyl sulfoxonium salt suspension and stirred at -78 °C for 20 min and at 0 °C for 3.5 h. The reaction was quenched with saturated ammonium chloride solution (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organics were washed with brine solution (10 mL). The organics were dried over Na_2SO_4, filtered and the solvent was evaporated.

1.4.6 Procedure B for investigation of reaction of Pentafluorophenyl acetate anion with cyclopropyl sulfoxonium salt

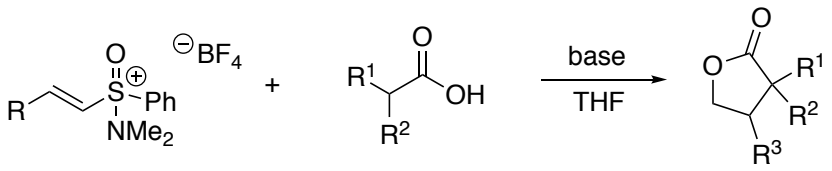
Reaction procedure repeated as described above in 1.4.5, however, after addition of the pentafluorophenyl acetate-LDA solution to the cyclopropyl salt the reaction mass was allowed to stir for 2.5 h at -78 °C before allowing the reaction to warm to rt overnight.

1.4.7 Synthesis of 4-methyl-2-phenylpentanoic acid



2-phenylacetic acid (1.00 g, 7.30 mmol, 1 equiv) in THF (28.5 mL) was cooled to -78 °C. Once cooled, n-BuLi (2.5M in hexanes, 5.9 mL, 2 equiv) was added dropwise and stirred. After 15 min, a solution of 1-bromo-2-methylpropane (1.00 g, 7.30 mmol, 1 equiv) was added and the reaction was allowed to warm to rt overnight. After stirring overnight, the reaction was quenched through dropwise addition of HCl (0.1M, 10 mL). The reaction mass was extracted with EtOAc (3 × 30 mL) and the collected organics were washed with brine solution (30 mL) and dried over Na_2SO_4. This was used for the next step without need for further purification as proven by ^{1}H NMR (1.26 g, 90%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 – 7.21 (m, 4H), 7.21 – 7.16 (m, 1H), 3.56 (t, 1H, J = 15.60 Hz), 1.91 – 1.84 (m, 1H), 1.64 – 1.58 (m, 1H), 0.85 – 0.81 (d, 1H).

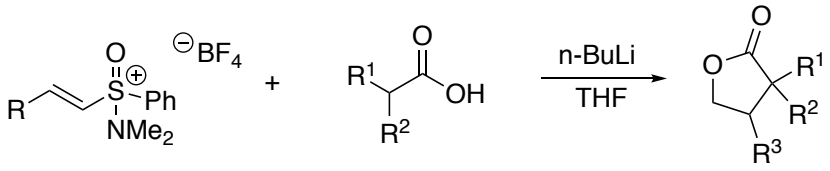
1.4.8 General procedure A for investigation of γ-lactone synthesis from unsaturated sulfoxonium salts



The sulfoxonium salt (45.0 mg, 0.125 mmol, 1.0 equiv) was added to a flask and dried under vacuum. In a second flask the acetic acid (0.25 mmol, 2.0 equiv) was added and allowed to dry under vacuum for 5 minutes. Dry THF (1 mL) was added to the acetic acid derivative and the solution was allowed to cool to -78 °C. Base (*n*-BuLi in most cases, 2 equiv) was added and the solution was stirred at -78 °C for 2 h. After 2 h dry THF (0.75 mL) was added to the sulfoxonium salt and the suspension was cooled to -78 °C. Once cooled the lithium enediolate solution was quickly added to the salt and the reaction mass was allowed to stir for 4 h at -78 °C before allowing the solution to come to rt and stir overnight. The reaction was quenched through dropwise addition of HCl (0.1M, 10 mL). The reaction mass was extracted with CH_2Cl_2 (3 × 10 mL) and the collected organics were washed with brine solution (10 mL) and

dried over Na_2SO_4. The crude product was purified through column chromatography with neutral silica using a 5-20% EtOAc/Hexane solvent system.

1.4.9 General procedure B for investigation of γ-lactone synthesis from unsaturated sulfoxonium salts



To a solution of acetic acid derivative (0.19 mmol, 1.0 equiv) in THF at -78 °C was added n-BuLi (2 equiv) and the solution was stirred for 2 h. The lithium enediolate solution was then added via syringe pump over 1 h to the vinyl sulfoxonium salt in THF at -78 °C. The reaction was allowed to warm to rt overnight. The solvent was removed by evaporation and the crude product was purified by passing through a plug of neutral silica (50-100 × crude weight), eluting with an EtOAc/hexane solvent system.

1.4.10 General procedure C for investigation of γ-lactone synthesis from unsaturated sulfoxonium salts

Reaction procedure repeated as described in 1.4.8 General procedure A with the modification that the reaction was heated to 50 °C for 30 minutes before quenching.

Chapter 2:

Synthesis of cyclohexanones from donor-acceptor cyclobutanes and ketenes

2.1 Introduction to Cyclohexanones

Six membered-ring carbocycles have been recognized as important structural units due to their frequent occurrence in many biologically interesting natural products.

Cyclohexanone is an important raw material that is used for the production of caprolactam and adipic acid, which are key intermediates for the production of the polymers nylon 6 and nylon 66. Billions of kilograms of cyclohexanone are produced every year for the nylon industry, making it one of the largest mass produced chemicals in industry.[96,97] The industrial production of cyclohexanone can be separated into three methods including the Asahi process, the oxidation of cyclohexane and the hydrogenation of phenol.

2.1.1 Preparation of cyclohexanones

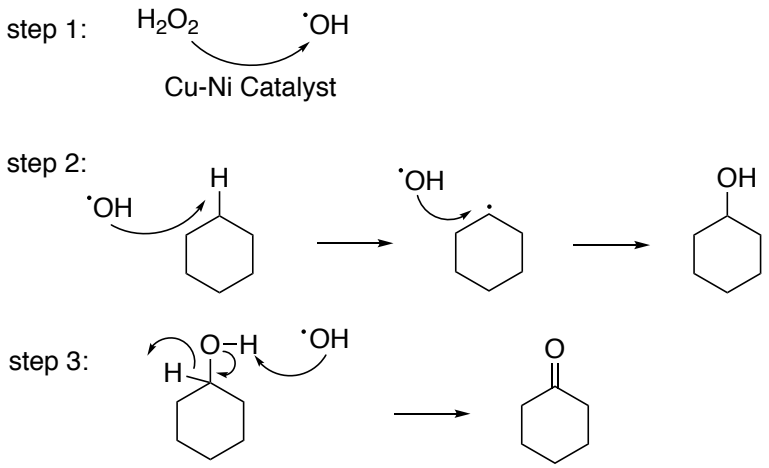
2.1.1.1 Cyclohexane oxidation

Cyclohexane oxidation is one of the most prevalent methods in industry for the synthesis of cycohexanones due to its low cost. However, despite its frequent use in industry, there is recurrent research into the development of new methods of cyclohexane oxidation that improve some of the route's major drawbacks, including harsh reaction conditions, such as high temperature and pressure, and the generation of undesirable side products that complicate purification steps, while also lowering the yield.

There have been many attempts to develop new catalytic approaches to cyclohexane oxidation with mild conditions. One of these that has been found to be important is the use of hydrogen peroxide as an oxidant and, significantly, hydrogen peroxide is an environmentally friendly oxidant as it only leads to the production of water as a by-product. Multicopper complexes have frequently been investigated as promising reaction accelerators for cyclohexane oxidation since copper is widely available and cheap.[98–100]

Das and co-workers have recently described a method of oxidation utilizing a copper-nickel catalyst.[99] They proposed that since the reaction proceeds through formation of a cyclohexyl-hydroperoxide (CHHP) intermediate species, a bimetallic catalyst would promote the homo-cleavage of the O-O bond which would in turn increase the conversion of the cyclohexane significantly. Facilitated by the catalyst, hydrogen peroxide decomposes into its radicals followed by the formation of cyclohexyl radicals. $FeAl_2O_4$ spinel oxide aids in the dispersion of active sites of CuO nanocrystallites while simultaneously the spinel support reduces the leaching of Cu^{2+} ions during the liquid-phase cyclohexane oxidation reaction.

They determined from their studies that the most active copper-nickel catalyst $25Cu_{50}Ni_{50}/Al_2O_3$ gave the highest cyclohexane conversion at ~13%. The reaction was proposed to follow the mechanism outlined in Scheme 56 below.



SCHEME 56: PROPOSED MECHANISM FOR THE OXIDATION OF CYCLOHEXANE TO CYCLOHEXANONE

Scorpionate complexes of vanadium(III or IV) as catalysts for solvent-free cyclohexane oxidation have also been investigated.[101] Complex $[VCl_3\{HC(pz)_3\}]$ (pz = pyrazolyl) was found to catalyze cyclohexane oxidation with dioxygen to cyclohexanol and cyclohexanone with 13% conversion at O2 pressure of 15 atm, at 140 °C with 18 h reaction time. The introduction of pyrazinecarboxylic acid (PCA) further improved the conversion to 15%.

2.1.1.2 Hydrogenation of Phenol to Cyclohexanone

The hydrogenation of phenol to cyclohexanone has been frequently described as a possible solution to some of the drawbacks mentioned prior for cyclohexane oxidation. Hydrogenation of phenol can occur as a "one-step" reaction (known as selective hydrogenation), or a "two-step" process that involves the hydrogenation of phenol to cyclohexanol, followed by subsequent dehydrogenation to cyclohexanone. The increasing interest in catalyst-mediated reactions has provided a bright future for selective hydrogenation, and it can be expected that it will applied in industry in the future.

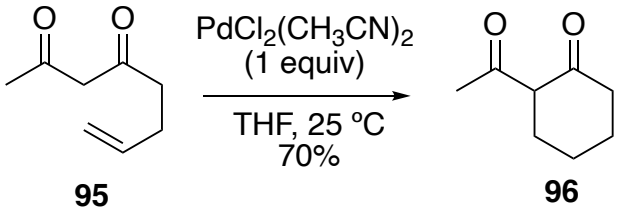
Liu et al. describe a method of selective hydrogenation of phenol to cyclohexanone using a bifunctional Pd/C-heteropoly acid catalyst in liquid phase.[102] Impressively, this work yielded 100% conversion of phenol with 93.6% selectivity for cyclohexanone within just 3 h under 80 °C and 1.0 MPa hydrogen pressure. The synergetic effect of Pd/C and heteropoly acid enhanced the catalytic performance of the composite catalytic system, which suppressed the hydrogenation of cyclohexanone to cyclohexanol.

The best results were found when the amount of catalyst was 5% of the starting material and the composite catalyst system was found to be stable and could be reused up to 5 times before a decrease in activity was noted.

2.1.1.3 Palladium catalyzed intramolecular addition of 1,3-diones to unactivated olefins

Widenhoefer and co-workers describe a method of synthesis of cyclohexanones through the regioselective palladium-catalyzed hydroalkylation intramolecular cyclization of β-keto esters with unactivated olefins.[103] Widenhoefer hypothesized that because silyl enol ethers were able to react readily with olefins in the presence of Pd(II), a 1,3-diketone may be nucleophilic enough to attack the olefin in the presence of Pd(II) while remaining resistant to oxidation.

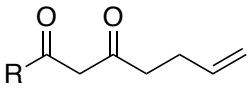
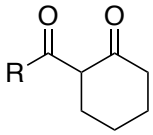
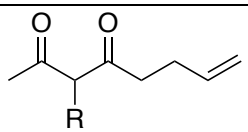
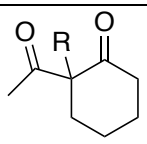
To investigate this, Widenhoefer stirred an equimolar solution of 7-octene-2,4-dione (1) and $PdCl_2(CH_3CN)_2$ in THF. After 15 minutes, the dione was completely consumed and 2-acetylcyclohexanone was afforded in 70% isolated yield. Interestingly, the lack of C=C double-bond in **96** suggested that no reduction of Pd(II) had occurred and therefore the addition of a stoichiometric oxidant for the catalytic conversion of **95** to **96** was not necessary. Optimization of the reaction conditions determined that yields of up to 81% could be achieved with 10 mol% of catalyst in dioxane with 16 h reaction time.

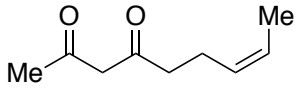
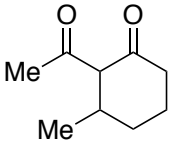
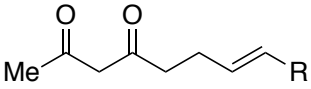
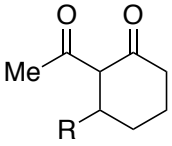
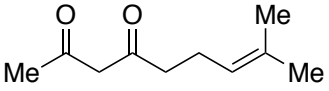
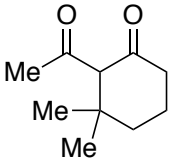
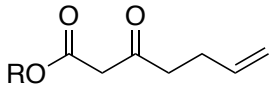
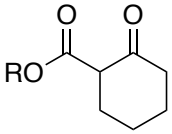


SCHEME 57: PALLADIUM CATALYZED INTRAMOLECULAR SYNTHESIS OF CYCLOHEXANONE

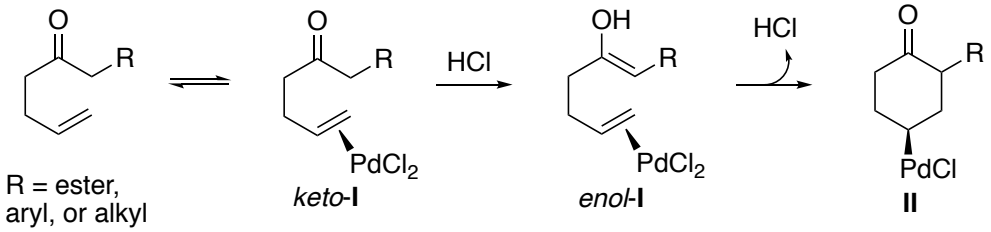
The reaction tolerated substitution at the terminal methyl group as well as at the carbon located between the two carbonyl groups with some loss in yield (66%-70%) (entries 3-6). Terminal olefinic substitution was also tolerated, as was di-methyl substitution of the terminal olefin, leading to a tri-substituted cyclohexanone, although in much lower yield than previous examples (38%)(Table 9, entries 7-11). Alkenyl-β-keto esters were tolerated though they produced the corresponding 2-carboalkoxycyclohexanones in lower yields (Table 9, entries 12 and 13).

TABLE 9: WIDENHOEFER PALLADIUM CATALYZED INTRAMOLECULAR SYNTHESIS OF CYCLOHEXANONE

entry	***substrate***	***Catalyst load (mol%)***	***cyclohexanone***	***yield (%)***
				
1	R = Me	10	R = Me	81
2	R = Me	5	R = Me	72
3	R = Et	10	R = Et	67
4	R = *t*-Bu	10	R = *t*-Bu	66
				
5	R = Me	10	R = Me	61
6	R = Bn	20	R = Bn	70

7		10		71
				
8	R = Me	20	R = Me	81
9	R = *n*-Bu	20	R = *n*-Bu	89
10	R = Ph	10	R = Ph	82
11		20		38
				
12	R = Et	10	R = Et	45
13	R = Bn	10	R = Bn	32

Some years later Widenhoefer and co-workers detailed an explanation for the mechanism of this reaction on the basis of deuterium-labeling, kinetic and in situ NMR experiments.[104] They proposed that the first step involves attack of the pendant enol on the palladium-complexed olefin I to form the palladium-cyclohexyl species II. Subsequent isomerization of II through β-hydride elimination/addition followed by protonolysis of the palladium-enolate species forms the 2-carboalkoxycyclohexanone with regeneration of the palladium catalyst (Scheme 58).

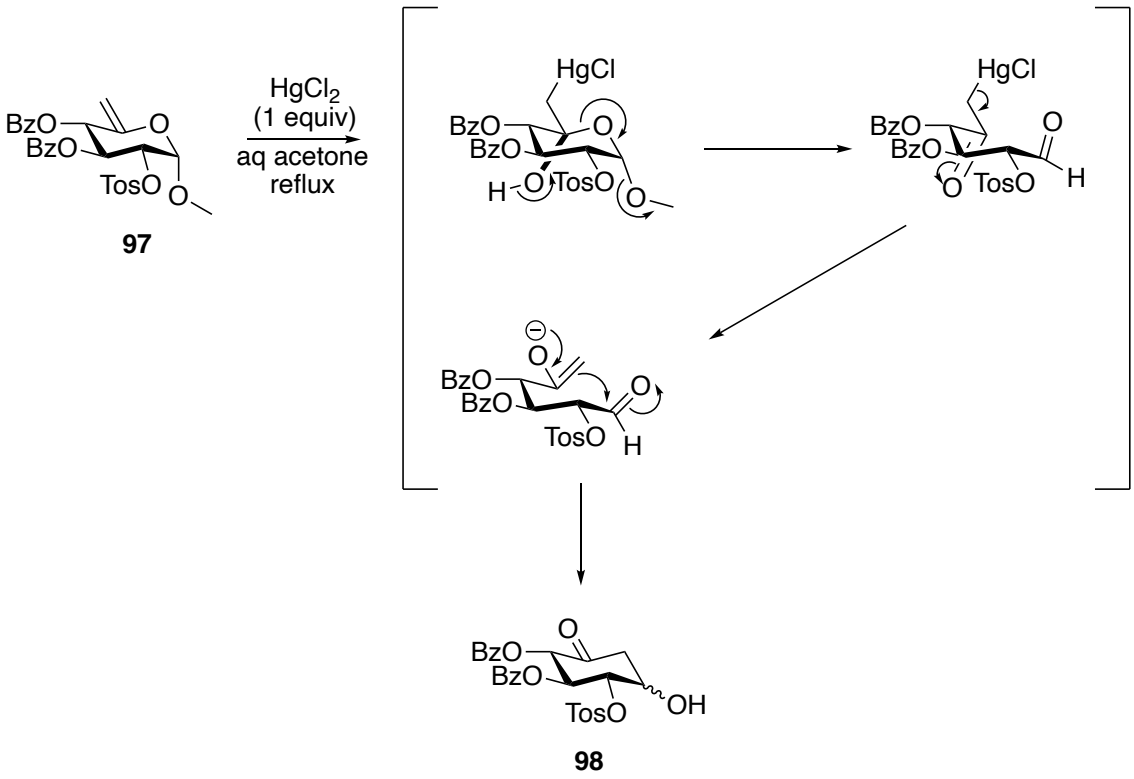


SCHEME 58: ROLE OF HCL IN PALLADIUM-CATALYZED HYDROALKYLATION

In 2005, Li and co-workers sought to develop a method to more easily reuse the catalyst systems from these reactions.[105] They hypothesized that immobilizing the catalyst in a liquid phase by dissolving it into a non-volatile and non-mixing liquid would satisfy environmental concerns as well as reduce costs. The system they found to operate the most efficiently involved utilizing the same palladium catalyst described by Widenhoefer, with the addition of $CuCl_2$ and PEG-400. A lower reaction temperature of 55 °C was also achieved, and it was found that the catalyst system could be recycled 5 times before there was a noted loss in catalytic activity.

2.1.1.4 Ferrier-II rearrangement

R.J Ferrier reported an interesting rearrangement reaction for the transformation of 6-deoxy-hex-5 -enopyranoside **97** into its cyclohexanone derivative **98**.[106] Ferrier proposed that in this mechanism the terminal olefin undergoes hydroxymercuration to afford a hemiacetal, methanol is subsequently lost. The dicarbonyl compound cyclizes via attack on the electrophilic acldehyde to form the cyclohexanone **98** as a mixture of α- and β-anomers.



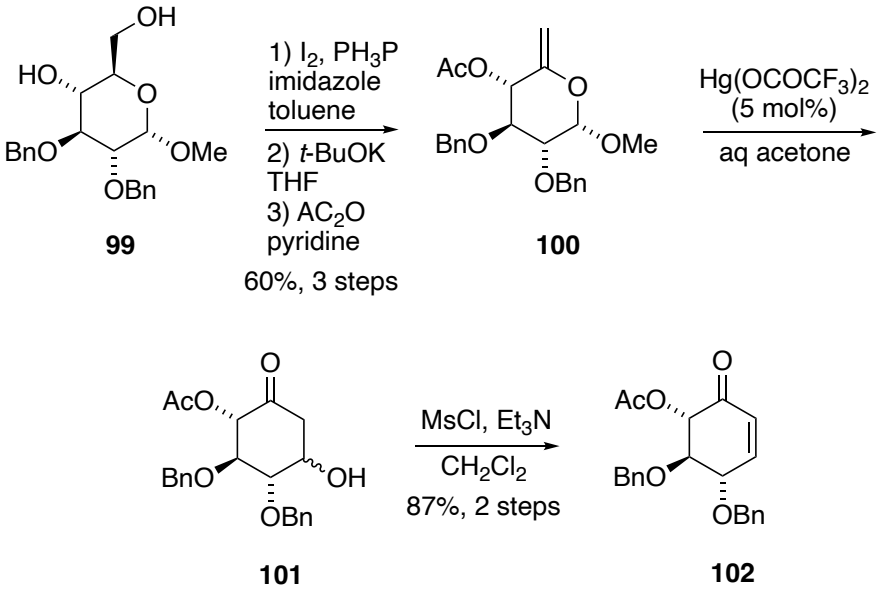
97 **98**

SCHEME 59: FERRIER-II REARRANGEMENT MECHANISM

2.1.2 Reactions and applications of cyclohexanones

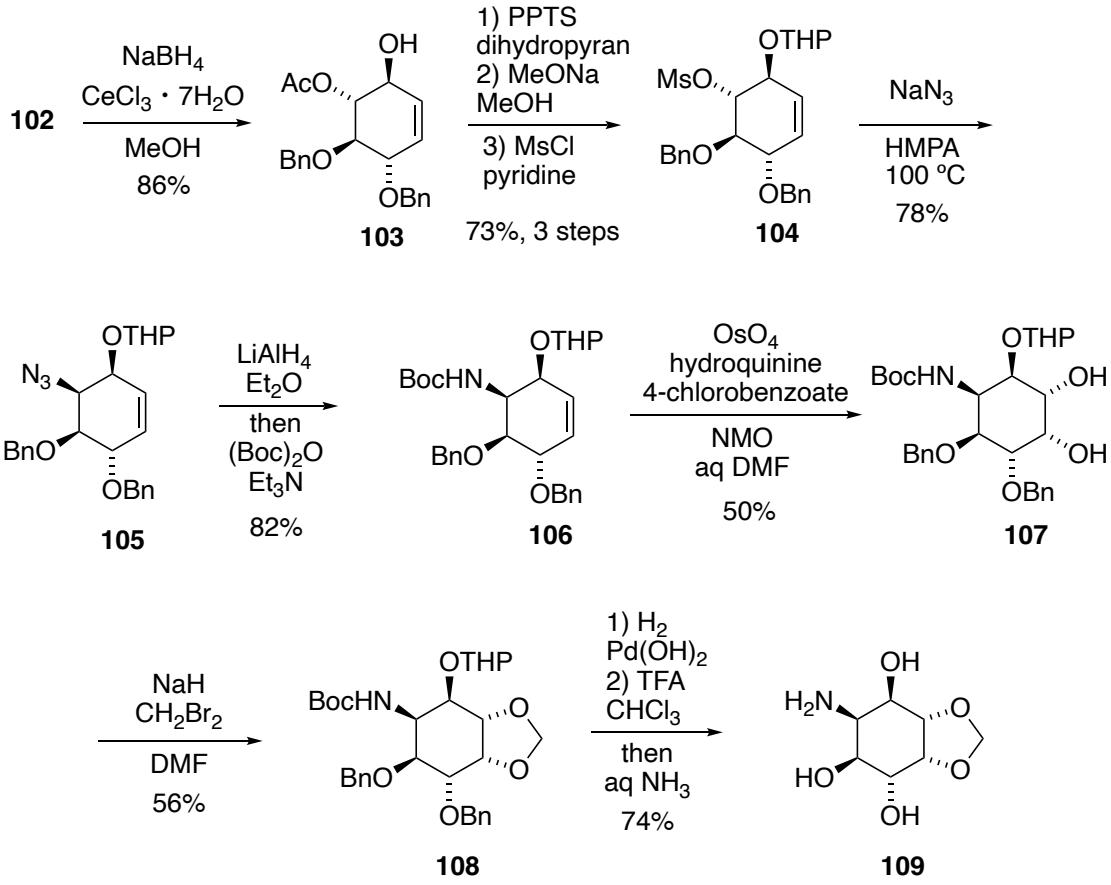
2.1.2.1 Synthesis of Hygromycin A

Cyclohexanones are importantly structural intermediates for a range of natural products, such as morphine, Hygromycin is an antibiotic that was first isolated from Streptomyces in 1953.[107] In 1991 Chida et. al reported the first total synthesis of Hygromycin A utilizing a cyclohexanone as a key intermediate.[108,109] The aminocyclitol moiety 94 of the antibiotic contains an important structural feature, the C-4/C-5 methylene ketal, which is responsible for making the molecule optically active. Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **99** was converted to 5-enopyranoside **100** as outlined in Scheme 60. The Ferrier rearrangement was employed for the conversion of **100** to its cyclohexanone derivative **101**, which was subsequently converted to cyclohexenone **102** through β-elimination of the hydroxy group.

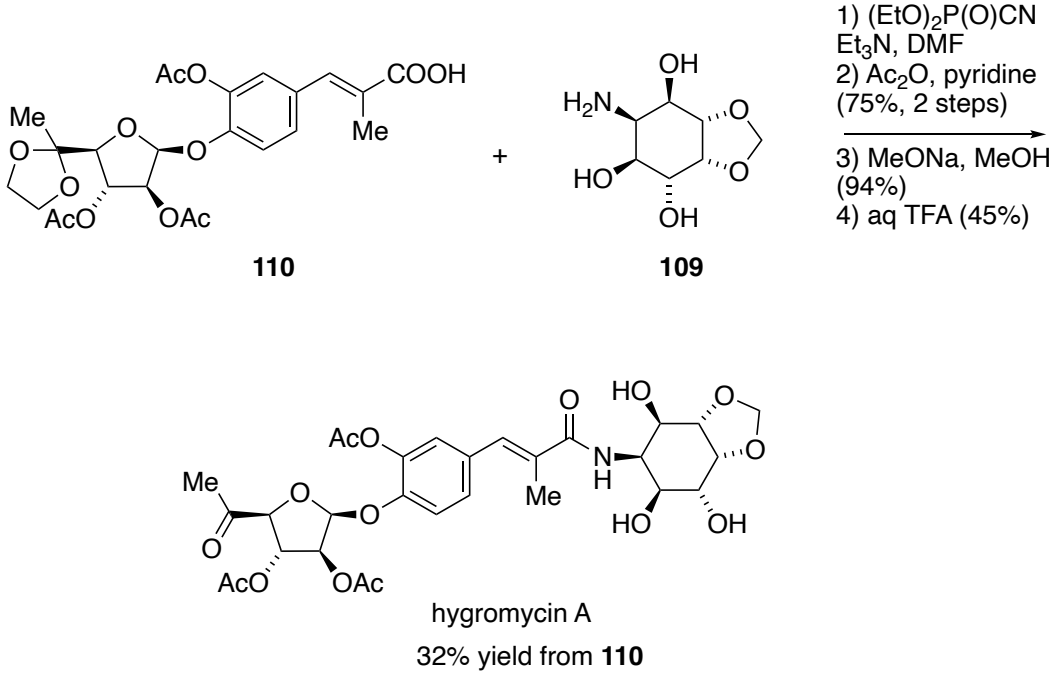


SCHEME 60: PREPARATION OF AMINOCYCLITOL PRECURSOR

1,2-reduction of the ketone carbonyl in **102** afforded **103**, subsequent introduction of a protection group afforded mesylate **104** which was treated with NaN_3 to afford **105**. The azide function was converted into a tert-butyl carbamate and the resulting compound **106** was oxidized to diol **107**. Treatment of **107** with CH_2Br_2 afforded methylene ketal **108** and subsequent deprotection generated 1L-2-amino-2-deoxy-4,5-*O*-methylene-*neo*-inositol **109**. Condensation of **109** with **110** by the Shioiri procedure followed by O-acetylation afforded Hygromycin A after removal of the protecting groups.



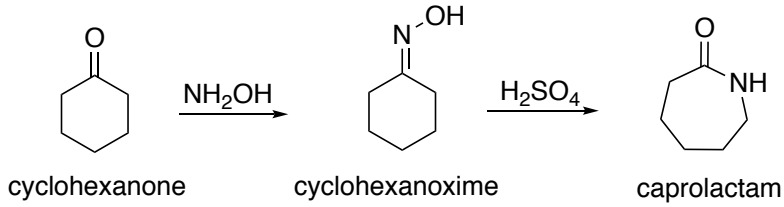
SCHEME 61: SYNTHESIS OF THE AMINOCYCLITOL MOIETY OF HYGROMYCIN A



SCHEME 62: SYNTHESIS OF HYGROMYCIN A

2.1.2.2 Synthesis of caprolactam

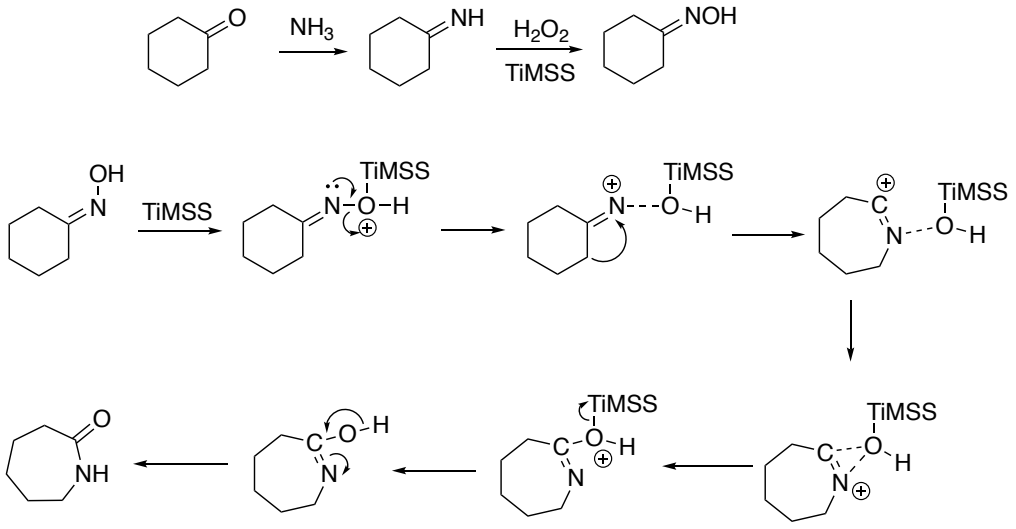
ε-Caprolactam is the monomeric unit of Nylon-6, unlike most other nylons it is formed through ring-opening polymerization rather than condensation polymerisation. Caprolactam is most commonly synthesized from cyclohexanoxime, which is afforded through a condensation reaction of cyclohexanone and hydroxylamine.[110]



SCHEME 63: SYNTHESIS OF CAPROLACTAM FROM CYCLOHEXANONE

In recent years many modifications to this reaction have been developed to improve its efficiency. Venkatathri et al. demonstrate the use of a titanium containing solid core mesoporous silica shell (TiMSS) as an efficient catalyst for the reaction.[111] The use of metallo-silicates offers an eco-friendly alternative to many industrially important oxidative reactions, and can act as a replacement to the use of hazardous acids and harmful oxidizing agents.

The Ti-containing catalyst offered conversion >92% and selectivity of 98% for the synthesis of caprolactam from cyclohexanone with only a very minimal loss in conversion rate and selectivity upon its 2nd and 3rd use. Venkatathri et al. provided a plausible mechanistic pathway for the conversion of cyclohexanone to caprolactam in the presence of this catalyst (Scheme 64).



SCHEME 64: PROPOSED MECHANISM FOR Ti-CONTAINING MESOPOROUS CORE SHELL SILICA CATALYSED SYNTHESIS OF CAPROLACTAM FROM CYCLOHEXANONE

Another modification of this reaction is described by Y. Wang and co-workers and utilizes ammonium chloride as the nitrogen source for the ammoximation of cyclohexanone.[112] Various reaction parameters were investigated and it was found that the best results were obtained with a NH_4Cl/H_2O_2/cyclohexanone molar ratio of 2:1.3:1, in a solution of 3.5 mol/L aqueous NaOH at 70 °C for 1.5 h. The catalyst used for this reaction is Titanium Silicalite-1 (TS-1) and is the most common catalyst used for this reaction and has frequent use in industrial application. Their modications to this reaction provided almost 99.4% conversion of cyclohexanone with 99.7% selectivity of cyclohexanone oxime.

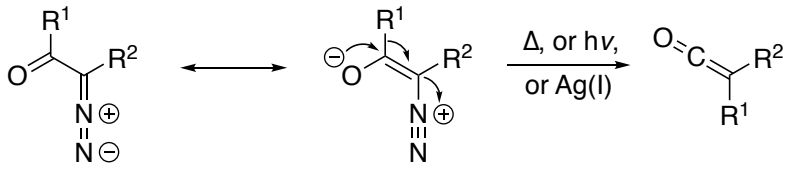
2.2 Introduction to Ketenes

Ketenes are very important and versatile synthetic compounds with a unique range of chemical reactivity. In 1905, Staudinger published the first example of the synthesis of a ketene. His attempted reaction to generate a radical species through the dechlorination of chlorodiphenyl acyl chloride was unsuccessful, though through its failure one of the most synthetically interesting and useful compounds had come to light. Ketenes have unusual properties and are characterized by a 'heteroallenic' bond structure. This structure is the source of the distinct high reactivity of ketenes. In this heteroallenic structure, the highest occupied molecular orbital (HOMO) of a ketene is located perpendicular to the plane of the ketene while the lowest unoccupied molecular orbital lies in the plane.[113] This arrangement results in significant negative charge on both the oxygen and the β-carbon, while the α-carbon subsequently has a similarly substantial positive charge making it highly susceptible to nucleophilic attack. The R group substituents of the ketene play an essential role in determining its reactivity. Any substituent that is capable of donating electron density will stabilize the ketene, while electron-withdrawing groups will further destabilize it. Introducing large sterically bulky groups can stabilize the ketene through steric shielding of reaction sites. In contrast, difluoroketenes in theory would enhance electron density withdrawal from the β-carbon. However this species is so reactive that it has not been observed in solution, although it has been hypothesized to be an intermediate in several reactions.[114,115]

2.2.1 Preparation of ketenes

2.2.1.1 Wolff rearrangement

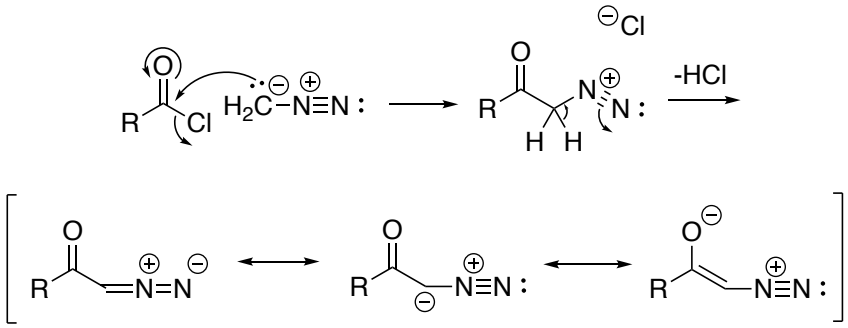
Wolff rearrangement is a method of ketene preparation whereby an α-diazocarbonyl compound undergoes loss of dinitrogen through a 1,2-rearrangment. This reaction can be induced via thermolysis, photolysis or transition metal catalysis.[116,117]



SCHEME 65: WOLFF REARRANGEMENT FOR PREPARATION OF KETENES

In 1902, Wolff discovered that upon treatment of diazoacetophenone with silver (I) oxide and water phenylacetic acid was formed, rather than the expected hydroxy ketone. A few years later Schröeter published similar results.[118,119] This reaction was termed the Wolff-Schröeter reaction and it wasn't until the 1930's that chemists began to employ it's use in ketene synthesis as facile diazo ketone synthesis became more available.[120]

One of the most common methods of preparation of α-diazo ketones is for utilization as part of the Arndt-Eistert homologation.[121–123] This method involves the C-acylation of a primary diazoalkane ($RCHN_2$) with acyl chlorides or, less commonly, with acid anhydrides.[120] In the procedure the diazo ketones are formed by slow addition of the acyl chloride to an ice-cold ethereal solution of diazomethane in nearly quantitative yield.



SCHEME 66: FORMATION OF α-DIAZOCARBONYL

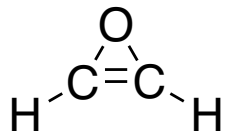
As mentioned previously, Wolff rearrangement can be initiated thermally, by photolysis or by transition metal catalysis. Thermal methods are not as frequently used as reaction temperatures of 180 °C are often required, and this can cause issues if the products are sensitive to high temperatures, and can often generate side products without causing rearrangmenent.[124]

The use of transition metal catalysts can offer a solution to these problems. However, many transition metal catalysts can interfere with the reactivity of the carbene intermediate by forming intermediate complexes which can lead to low yield or no reaction at all. Examples of such catalysts are Rh, Pd and some Cu catalysts. Silver (I) oxide has been the most frequently used catalyst since Wolff discovered its capabilities over 100 years ago.

Photolysis has become one of the more popular methods of Wolff rearrangement in recent years, and is especially useful when both thermal and catalytic methods fail. However, photolysis cannot be carried out if the product itself is photolabile under the same reaction conditions.

In 1950, Newman and Beal developed a modification to the Wolff rearrangement reaction in which it could be carried out under milder conditions than previously reported.[125] This method involved the use of a homogeneous medium of silver(I) salts (silver benzoate) in triethylamine. The addition of a few milliliters of this reagent can be added to a solution of diazomethyl ketone in methanol at room temperature. Nitrogen evolution takes place with the precipitation of metallic silver. As nitrogen evolution slows, repeated additions of silver salt in triethylamine are introduced until a theoretical amount of nitrogen is evolved and measured on an azotometer. The methyl ester of the acid can then be isolated from the reaction mixture.

Some of the best known evidence for the formation of ketene intermediates in the Wolff rearrangement comes from the detection of oxirenes as intermediates in kinetic studies, as well as from the effects of substitution upon nitrogen elimination.[124,126,127]



SCHEME 67: OXIRENE

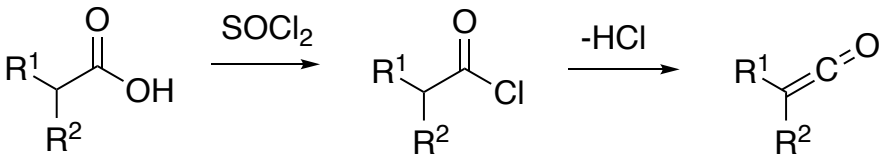
However, a more recent publication by Phelps and Ewing describes the direct observation of carbene ketene intermediates during the Wolff rearrangement of photoexcited ethyl diazoacetoacetate.[128] Spectroscopic evidence for ylide formation comes from the production of a singlet α-carbonyl carbene at 1625 cm^{-1} in acetonitrile and at 1586 and 1635 cm^{-1} in THF.

Some years earlier Platz and co-workers also provided notable spectroscopic evidence for reactive intermediates through the photoexcitation of p-biphenylyl diazo ketone.[129] Interestingly, the observed lifetime of the singlet carbene was dependent upon the solvent, with acetonitrile and THF being proposed to stabilize the carbene and suppress Wolff rearrangement.

2.2.1.2 Dehydrohalogenation of acyl chlorides

Although Staudinger was the first to publish the results and characterization of a ketene, four years prior to this Eduard Wedekind had already obtained diphenylketene through the dehydrohalogenation of diphenyl-acetyl chloride with triethylamine though it was not isolated or characterized.[130] However, this method of ketene preparation is still widely used to this day.

In this reaction, acyl chlorides are usually generated through treatment of a carboxylic acid with thionyl chloride or oxalyl chloride. The resulting acyl chloride is treated with a base (commonly triethylamine or diisopropylethylamine) which removes the proton α- to the carbonyl through an elimination reaction.

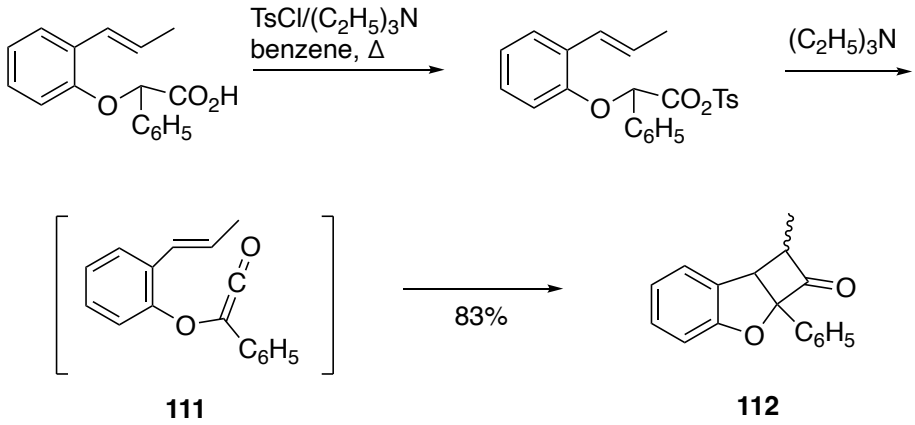


SCHEME 68: DEHYDROGENATION OF ACYL CHLORIDES

An interesting modification to this reaction was described by Olah and Farooq.[131] This method provides access to stable ketenes with bulky groups such as tert-butyl and 1-adamantyl from their corresponding acyl chlorides through treatment with triethylamine, assisted by ultrasonic radiation.

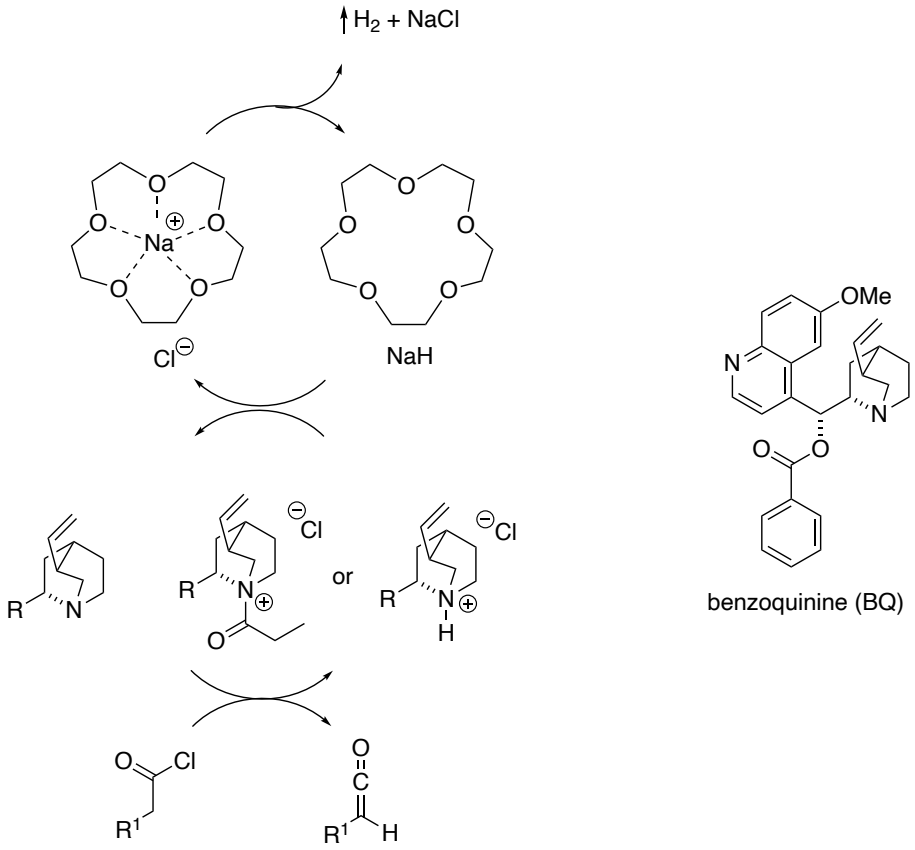
When a solution of bis-(1-adamantyl)acetyl chloride in dry ether and triethylamine was subjected to ultrasound for one hour and then filtered, bis(1-adamantyl)ketene was obtained in 90% yield. Under the same procedure using (1-adamantyl)-*tert*-butylacetyl chloride the corresponding ketene was synthesized in comparable yield.

Brady and co-workers also describe an adaptation to this reaction through employment of tosylate as a leaving group rather than the traditional halide.[132] The use of tosylate as a leaving group eliminates the need for preparation, isolation and purification that is required for the acid chloride derivatives, meaning the ketene can be prepared through a one-pot synthesis. This method is outlined in Scheme 69. (*o*-Propenylphenoxy)phenylacetic acid (readily obtained from *o*-propenylphenol and α-bromo-phenylacetic acid) is converted to the tosylate and subsequent triethylamine-promoted elimination of *p*-toluenesulfonic acid results in the formation of the corresponding phenoxyketene **111**. Subsequent [2+2]-cycloaddition affords the corresponding tricyclic ketone **112**. Although isolation of the ketene intermediate is not accessible through this method, it highlights an effective method of in situ generation.



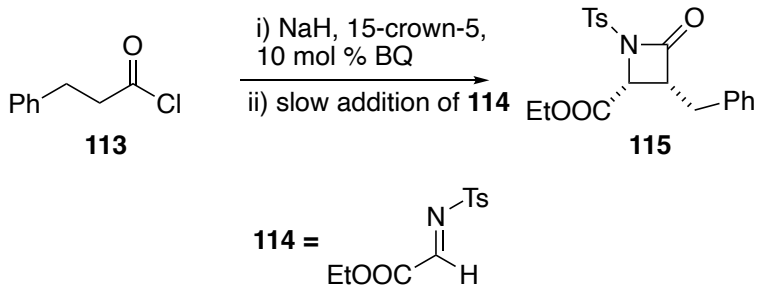
SCHEME 69: BRADY AND CO-WORKERS IN SITU GENERATION OF KETENE

More recently, Lectka and co-workers have described the in situ generation of reactive monosubstituted ketenes from acid chlorides through shuttle deprotonation mediated by NaH and a crown ether catalyst.[133] The hypothesis for the mechanism of this reaction is outlined in Scheme 70. Benzoylquinine (BQ) acts as a catalytic "shuttle" base effecting dehydrohalogenation of an acid chloride either by forming an acylammonium salt with BQ and is deprotonation by NaH or BQ deprotonates the acid chloride and then shuttles the proton to NaH.



SCHEME 70: PROPOSED CATALYTIC SHUTTLE DEPROTONATION OF ACID CHLORIDES TO GENERATE KETENES

One example provided for the use of this procedure is its application in the catalytic, asymmetric synthesis of β-lactams previously developed by their group. Hydrocinnamoyl chloride **113** was stirred with 15-crown-5 and 10 mol % benzoylquinine in toluene at -78°C for 7 h. A solution of α-imino ester **114** in toluene was added via syringe pump over 1 h, and the reaction was slowly warmed to room temperature. After reaction workup the reaction was purified through column chromatography to afford the cis-(3R,4R)-β-lactam **115** in 60% yield with 6:1 diastereomeric ratio and 99% ee. Recrystallisation from diethyl ether/hexanes increased the dr to 49:1.

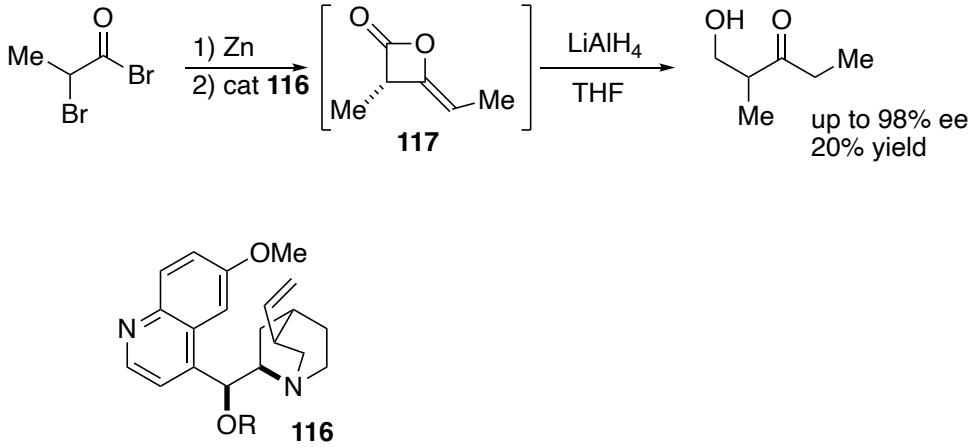


SCHEME 71: LECTKA AND CO-WORKERS SYNTHESIS OF β-LACTAM

2.2.2 Reactions of ketenes

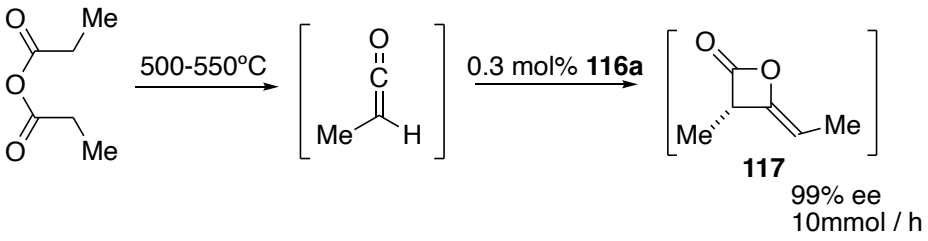
2.2.2.1 Asymmetric ketene dimerization

Although ketene dimers are commonly an unwanted side product as a consequence of its high reactivity, their complex structure and chirality have spiked the interest of synthetic chemists. Calter and co-workers describe a method of enantioselective synthesis of methylketene dimers utilizing cinchona alkaloid catalysts.[113,134] Out of the number of cinchona alkaloid catalysts screened, quinidine derivative **116** proved to be most effective, yielding excellent enantioselectivity (98%) although with low overall low yield (20%) for the three step synthesis of the ketene dimer derivative.



SCHEME 72: CALTER GROUP KETENE DIMERIZATION

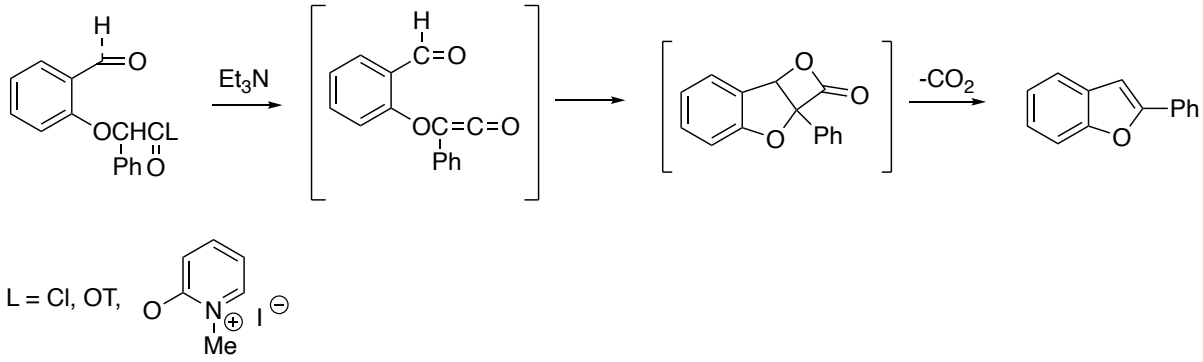
Due to the high reactivity of the ketene dimer intermediate **117** it was not isolated, but rather converted into a stable β-hydroxyketone. The group then continued this research in a slightly different direction by developing a thermolytic method of ketene generation from propionic anhydride and **116a** (a silylated derivative of catalyst **116)** to form dimer **117** at a reproducible rate with even higher enantioselectivity.



SCHEME 73: CALTER GROUP THERMOLYTIC KETENE DIMER GENERATION

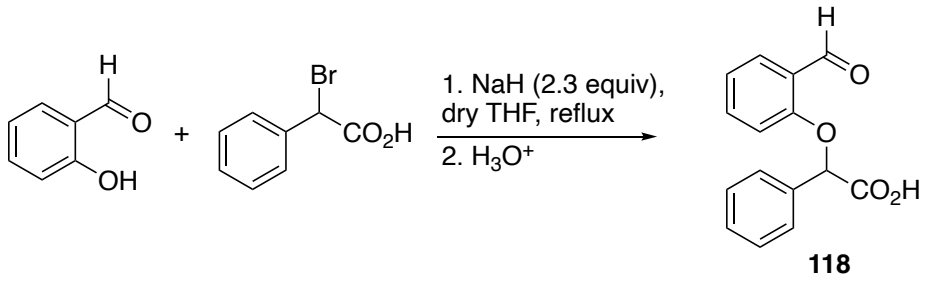
2.2.2.2 Intramolecular [2+2] cycloaddition to substituted benzofurans

Brady, Marchand and co-workers describe the synthetic application of ketenes for the synthesis of substituted benzofurans.[135] This group had previously reported the dehydrochlorination of (*o*-carbonylphenoxy)acetyl chloride to afford ketenes which can then undergo facile intramolecular [2+2] cycloaddition to afford the corresponding tricyclic β-lactones Decarboxylation of these lactones was reported to occur spontaneously and generated a range of benzofurans in 53-82% yield (Scheme 74).[136] Benzofurans are important structural motifs for a range of drugs in the pharmaceutical industry so further investigation of this unexpected reaction sequence was of great interest.



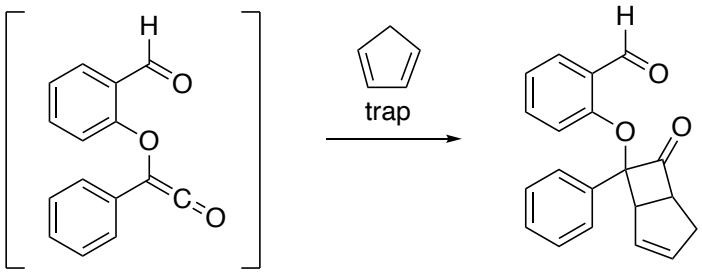
SCHEME 74: BRADY, MARCHARD AND CO-WORKERS SYNTHESIS OF BENZOFURANS

The method of synthesis for the (*o*-carbonylphenoxy)acetic acids **118** is outlined in Scheme 75. The pure salt of these acids was utilized in three different methods of ketene generation to determine if any had an impact on the yield of benzofuran. Method A involved base-promoted dehydrohalogenation of the acyl chloride, method B employed tosylate in place of the chloride as a leaving group and method C utilized 2-chloro-1-methyl-pyridinium iodide (Mukaiyama's reagent) to generate an ester via reaction with the (o-acylphenoxy)acetic acid which was subsequently treated with triethylamine to generate the ketene in situ. Interestingly, the methods by which the ketene was generated in situ had little to no effect on the yield of the benzofuran.



SCHEME 75: (O-CARBONYLPHENOXY)ACETIC ACID SYNTHESIS

It was determined that unlike intermolecular ketene cycloadditions, the intramolecular ketene cycloaddition proceeded with equal ease regardless of whether the pendant carbonyl was a ketone or an aldehyde group. To prove the presence of a ketene intermediate a cyclopentadiene trapping experiment was carried out. When the reaction was repeated in the presence of excess cyclopentadiene the corresponding [2+2] cycloadduct **119** was afforded.

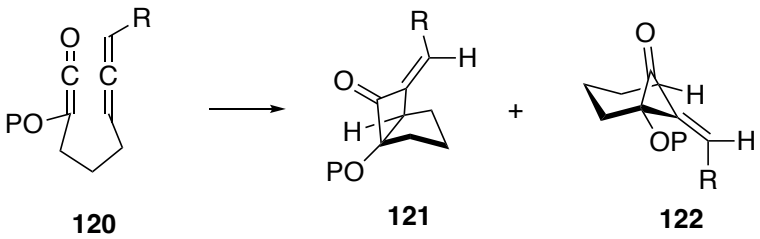


119

SCHEME 76: CYCLOPENTADIENE TRAPPING OF KETENE

2.2.2.3 Intramolecular ketene-allene cycloadditions

In 2000, Halcomb and McCaleb reported a method of synthesis for 7-methylidinebicyclo[3.2.0]heptanones and 7-methylidinebicyclo[3.1.1]heptanones through an intramolecular thermal [2+2] cycloaddition between ketenes and allenes.[137]



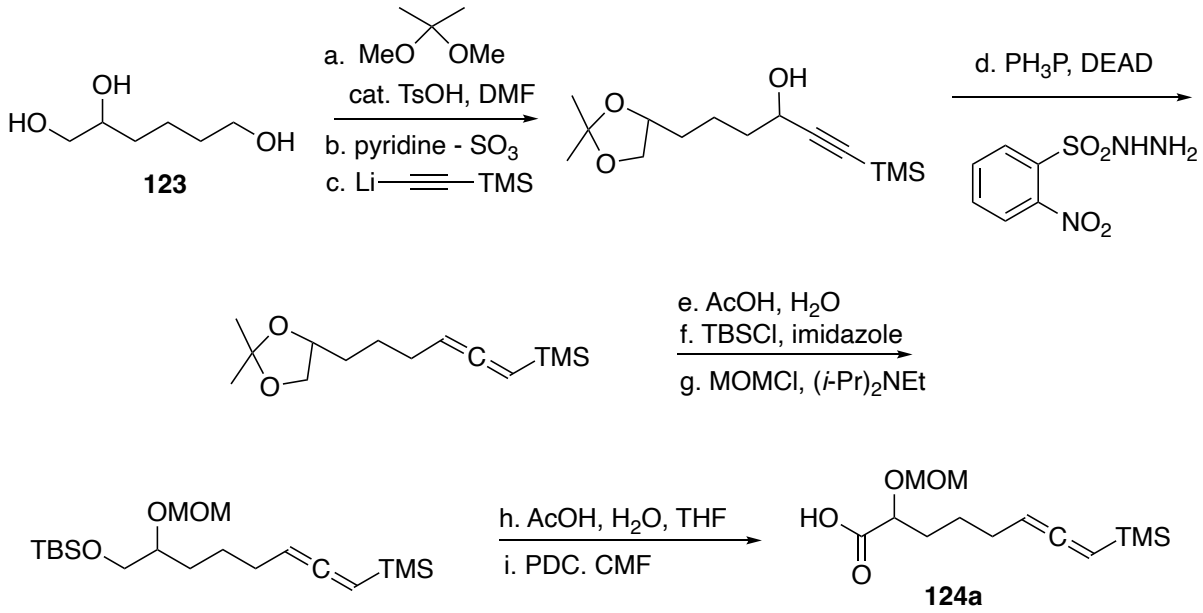
120 **121** **122**

SCHEME 77: HALCOMB AND MCCALEB INTRAMOLECULAR KETENE-ALLENE CYCLOADDITION

The alkoxy functionality was built into **120** to exploit the possibility that heteroatoms could encourage the cycloaddition. It was hypothesized that the oxygen lowers the energy of the ketene LUMO, possibly due to the electronegative nature of oxygen, which results in a better match with the allene HOMO.

Three different substituted allenes were investigated to determine the effects of substituents on the reaction. The first allene contained a large electron-donating group (**124a**, R = TMS), the second had a dialkyl intermediate (**124b**, R = *n*-Bu) and finally one with an unsubstituted allene terminus (**124c**, R = H).

The ketene cyclization precursors **124a-c** were synthesized from 1,2,6-trihydroxyhexane **123** according to Scheme 78. Two different methods for ketene generation were studied, the first method, developed by Funk and co-workers, which involved the addition of a carboxylic acid to a solution of triethylamine and 2-chloro-1-methyl-pyridinium iodide (Mukaiyama reagent) in acetonitrile heated at reflux.[138] The second method followed was the dehydrohalogenation of an acyl chloride with triethylamine in benzene heated at reflux. Both methods produced the cycloaddition products in approximately the same ratios and yields, which agreed with the results published by Brady and co-workers discussed previously.



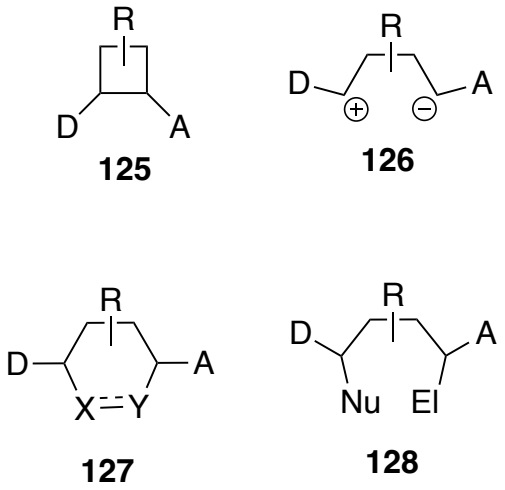
SCHEME 78: SYNTHESIS OF HALCOMB AND MCCALEB KETENE PRECURSOR 124

The two major products, **121** and **122**, were obtained through both methods of ketene generation. The [3.2.0] fused bicyclic system **121** arose from the formation of a bond between the central ketene carbon and the central allene carbon. In compound **122**, the alkoxy substituted carbon of the ketene bonded with the central allene carbon and the central ketene carbon with the internal allene carbon to generate the bridged bicyclic [3.1.1] system of **122**. Both **124b** and **124c** yielded the [3.2.0] bicyclic adduct as the major isomer. The selectivity of the cycloaddition of **124a** was different with the [3.1.1]bicycloheptanone **122** being the major product, with the *E*-olefin isomer being the major isomer observed in both cases.

2.3 Introduction to Donor-Acceptor Cyclobutanes

The concept of ring strain was first described by Adolf Von Baeyer in 1855 when he noted the higher reactivity of cyclopropanes in comparison to their unstrained congeners.[139] Vinylcyclopropane rearrangements leading to cyclopentene are a well-documented classic in this area, but it was soon recognized that this ring-strain could be even further exploited through the introduction of suitable donor/acceptor substituents to afford a variety of interesting cyclic or acylic products.

Donor-acceptor cyclopropane chemistry is well established in literature, however examples of such chemistry with D-A cyclobutanes is far more limited. Examples of D-A cyclobutane annulations can be found back to the early 1990's,[140] however, it wasn't until 2009 that reports of the [4+2] cycloaddition of donor-acceptor cyclobutanes were documented.[141,142] D-A cyclobutanes possess a similar bond strain to that of D-A cyclopropanes (ca. 120 kJ mol^{-1}), but it is distributed over 4 centers.[143] For this reason they have been of great interest to synthetic chemists as important four-membered carbon building blocks in the construction of cycloadducts **127** and compounds **128**. The high ring strain and the polarization of the carbon-carbon bond by the vicinal donor-acceptor substituents allow for the cyclobutane to behave as 1,4-zwitterionic synthons **126**.

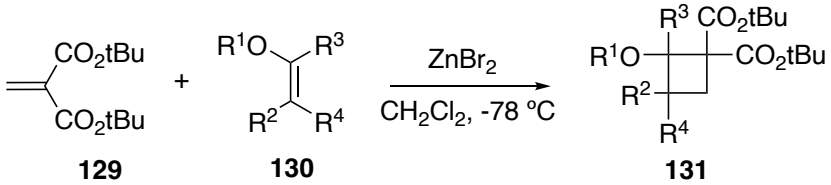


SCHEME 79: REACTIVITY PATTERN OF D-A CYCLOBUTANES[143]

2.3.1 Preparation of Donor-Acceptor Cyclobutanes

2.3.1.1 [2+2] annulation of alkyl enol ethers and methylidene malonates

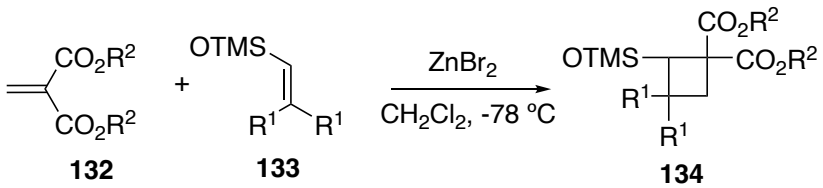
The first documented synthesis of donor-acceptor cyclobutanes dates back to 1986 when Roberts reported that the treatment of methylene malonate **129** with stoichiometric amounts of $ZnBr_2$ and enol ether **130** afforded cyclobutanes **131** in good yield.[144] Despite being the first documented synthesis of D-A cyclobutanes this method has remained the most popular among synthetic chemists since the required alkyl enol ethers are commercially available or readily prepared, and the methylidene malonates can be simply prepared through Knoevenagel condensation.



129 **130** **131**

SCHEME 80: ROBERTS $ZnBr_2$ CATALYSED SYNTHESIS OF D-A CYCLOBUTANES

This method of synthesis is frequent in literature and is often modified to expand the substitution of the cyclobutane to allow for more functionalized products. Lupton and co-workers adapted Roberts method of synthesis in their work detailing the [4+2] annulation of D-A cyclobutanes by n-heterocyclic carbene catalysis.[145] Cyclobutane **134** was synthesized through the addition of methylene malonate **132** in CH_2Cl_2 to a suspension of $ZnBr_2$ in CH_2Cl_2 at -78 °C, followed by a solution of trimethylsilyl enol ether **133** in CH_2Cl_2. After stirring at -78 °C for 2 hours the reaction was quenched by the addition of a cold (-78 °C) solution of pyridine in CH_2Cl_2. this was allowed to warm to room temperature then washed with saturated Na_2EDTA solution, water and brine. The organic layer was dried and purified by column chromatography.

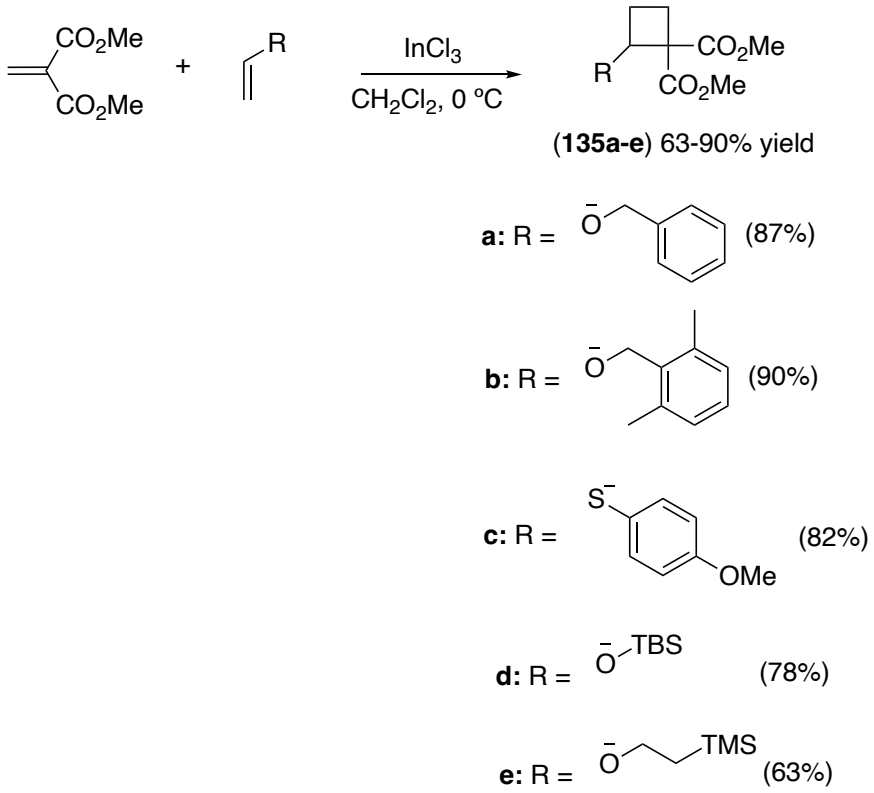


132 **133** **134**

SCHEME 81: LUPTON AND CO-WORKERS D-A CYCLOBUTANE SYNTHESIS

In 2017 Wang, Tang and co-workers documented a modification of Roberts reaction in their work describing the reaction of D-A cyclobutanes with indoles for the synthesis of (±)-

Strychnine.[146] Their modifications included the use of $InCl_3$ as a catalyst instead of $ZnBr_3$, which allowed for the reaction to take place under less harsh reaction conditions (0 °C, 1 hr) and produced cyclobutanes **135a-e** in yields 63-90%.



SCHEME 82: WANG, TANG AND CO-WORKERS D-A CYCLOBUTANE SYNTHESIS

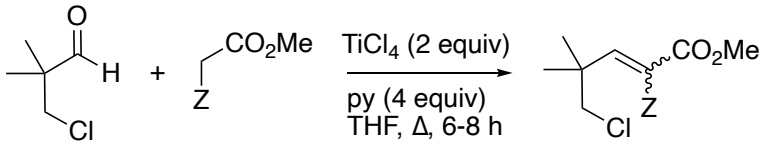
2.3.1.2 Michael induced ring closure of acylic substrates

Despite research into Michael induced ring closure (MIRC)-based cyclobutane synthesis having some success, there is significantly less research into this method of preparation of donor-acceptor cyclobutanes. Early research by Zabel and co-workers detail the synthesis of 1,1,-dicanocyclobutanes and alkyl 1-cyanobutane-1-carboxylates through reaction of doubly activated ω-tosyloxyolefins with hydride or alkoxide.[147] More recently, De Kimpe's group demonstrated the synthesis of functionalized dialkyl cyclobutane-1,1-dicarboxylates via MIRC of δ-chloro-α,β-unsaturated diesters and ketoesters.[148]

MIRC-based cyclobutane synthesis involves the intramolecular 1,4-substitution of an in situ generated δ-halocarbanion. This can be a relatively slow process and so is prone to competitive side reactions such as conjugate addition without cyclization, direct nucleophilic displacement of the δ-leaving group, and β-elimination of the δ-leaving group.[148–151]

De Kimpe's group proposed that utilizing doubly activated γ,γ-dimethyl-α,β-unsaturated esters with a δ-chlorosubstituent as a weaker leaving group would be suitable for MIRC reactions to cyclobutane-1,1-dicarboxylates. They predicted that the δ-chloro group would disfavour direct S_N2 displacement, while the γ,γ-dimethyl substitution would block β-elimination of the leaving group, disfavour direct S_N2 displacement while also favouring the cyclization of the Michael adducts due to the Thorpe-Ingold effect.[152]

ω-chloroalkylidenes **137a** and **137b** were prepared via modified Knoevenagel condensation of 3-chloro-2,2-dimethylpropanol with dimethyl malonate (a) or methyl acetoacetate (b) in the presence of titanium(IV) chloride (yield 72% and 69% respectively).

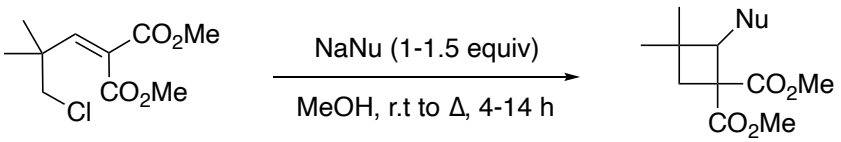


136a: Z = CO_2ME
136b: Z = COMe

137a/1373b

SCHEME 83: DE KIMPE ET AL. PREPARATION OF ω-CHLOROALKYLIDENES

Reaction of **137a** with one equivalent of sodium tert-butylthiolate in methanol at room temperature for 4 hours afforded **138** in 79% yield. When sodium methoxide was used as the nucleophilic reactant partner under the same conditions, a mixture of unreacted **137a**, unidentified methoxy compounds and cyclobutane **139** were obtained. However, the pure cyclobutane could be obtained upon reflux of **137a** in the presence of one equivalent of sodium methoxide in methanol (67% yield). It was found that reaction with sodium cyanide also required reflux of the reaction to obtain the desired cyclobutane (63% yield).



137a

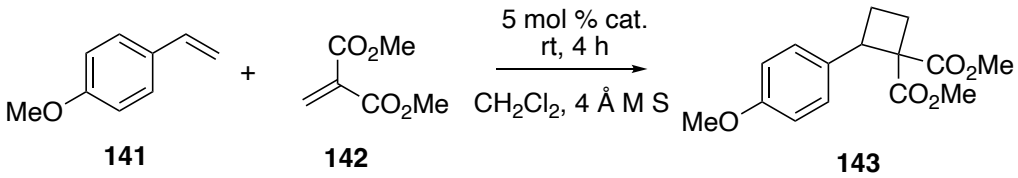
138 Nu = S*t*-Bu
139 Nu = OMe
140 Nu = CN

SCHEME 84: DE KIMPE ET AL. SYNTHESIS OF D-A CYCLOBUTANES

2.3.1.3 The synthesis of donor-acceptor cyclobutanes by $Cu(OAc)_2$ or $FeCl_3$ catalyzed [2+2] cycloaddition

Although [2+2] annulation is the most prevalent method of synthesis of D-A cyclobutanes, it does not come without its flaws. Requiring the use of purified dialkyl methylidenemalonates its practicality of synthesis has room for improvement. Noticing this, Luo and co-workers became interested in developing a method of synthesis that could utilize unpurified dialkyl methylidenemalonates, and envisioned this could be possible through a catalyzed [2+2]-cycloaddition with substituted styrenes.[153]

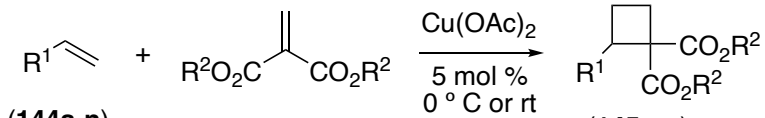
1-methoxy-4-vinylbenzene **141** and crude dimethyl methylidenemalonate **142** were used as model substrates. Of the catalysts tested $Cu(Otf)_3$ and $Cu(OAc)_2$ gave the desired cycloadducts in greatest yields (73 and 85% respectively) when the reaction was carried out in CH_2Cl_2 at room temperature. Interestingly, it was reported that when the reaction was performed without the use of 4 Å molecular sieves only 41 % ^{1}HNMR yield was detected, indicating that trace amounts of water resulted in the side product.



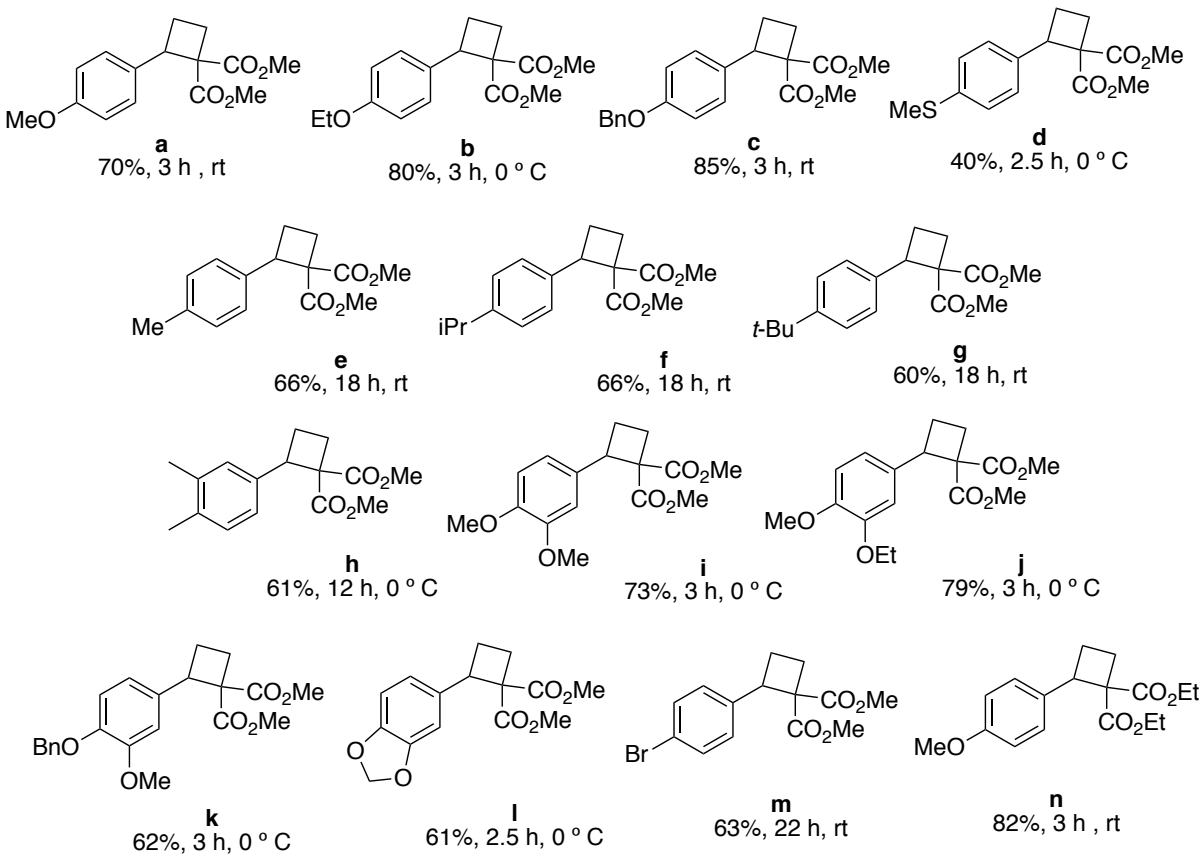
141 **142** **143**

SCHEME 85: LUO AND CO-WORKERS D-A CYCLOBUTANE SYNTHESIS

The scope of the reaction was investigated with the optimized reaction conditions. A broad range of alkenes were tolerated including substituted styrenes with electron-donating groups (**144a-d**) or alkyl substituents at the para position of the phenyl group (**144e-g**), 3,4-disubstituted alkenes with electron donating groups (**144h-l**) and the weak electron-withdrawing 4-bromostyrene (**144m**). This reaction was also reported to be suitable for gram-scale synthesis, with D-A cyclobutanes **145a-c** and **145i** obtained in 68-85% yields within a few hours.



(**144a-n**) (**145a-n**)



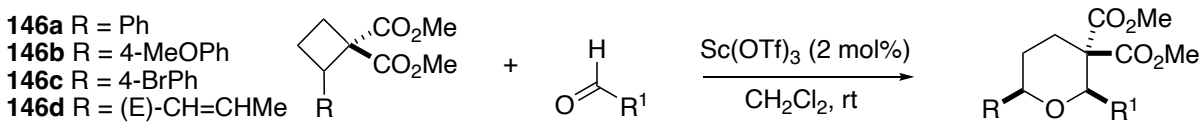
SCHEME 86: REACTION SCOPE OF LUO AND CO-WORKERS D-A CYCLOBUTANE SYNTHESIS

2.3.2 Reactivity of Donor-Acceptor Cyclobutanes

2.3.2.1 Formal [4+2] Cycloaddition of Donor-Acceptor Cyclobutanes and Aldehydes: Stereoselective Access to Substituted Tetrahydropyrans

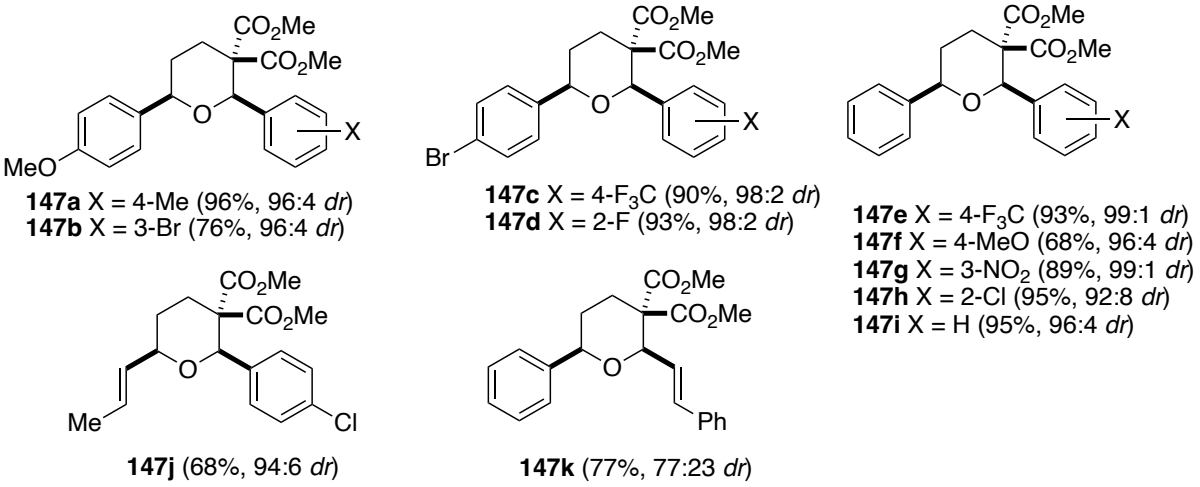
One of the first examples of [4+2] cycloaddition of D-A cyclobutanes was by Parsons and Johnson in 2009.[141] Inspired by publications showcasing the use of D-A cyclopropanes for the synthesis of tertrahydrofurans, Parons and Johnson envisioned a similar access route to tetrahydropyrans through reaction of malonate derived cyclobutanes and aldehydes.

Their studies found that of the Lewis acids examined, both $Hf(OTf)_4$ and $Sc(OTf)_3$ were suitably effective catalysts, providing 2,6-disubstituted tertahydropurans in high yield with high diastereoselectivity. However, $Sc(OTf)_3$ was selected for further studies due to the potential for asymmetric catalysis with chiral Sc(III) Lewis acids in future work.



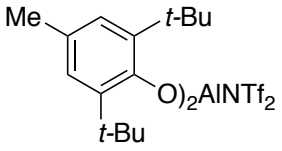
SCHEME 87: JOHNSON AND PARSONS [4+2]-CYCLOADDITION OF D-A CYCLOBUTANES

Several malonate derived cyclobutanes underwent [4+2] cycloaddition with cinnamyl and other substituted aryl halides (Scheme 88). With the exception of cinnamaldehyde and 2-chlorobenzaldehyde, all 2,6-*cis*-diastereomers were formed in greater than 94:6 selectivity.

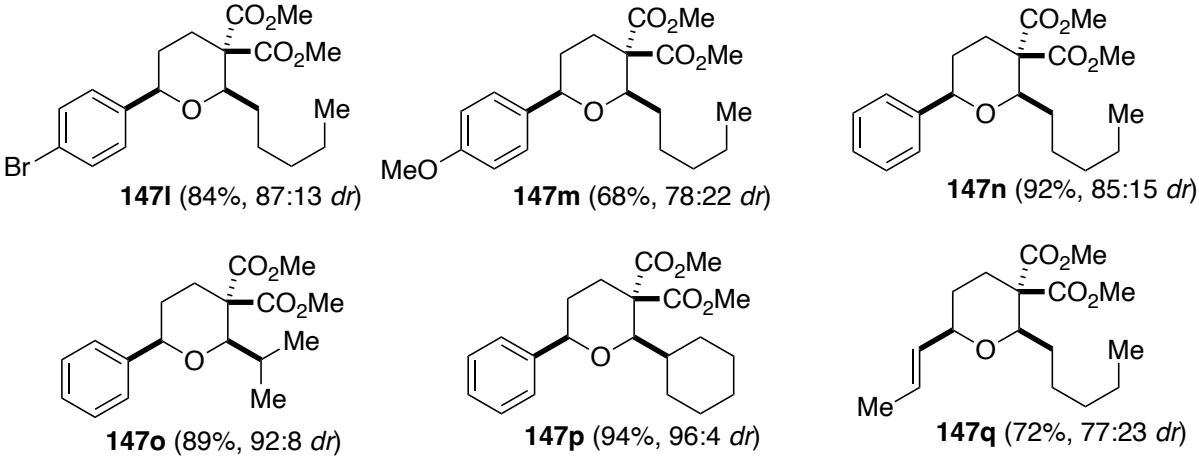


SCHEME 88: SUBSTRATE SCOPE OF [4+2]-CYCLOADDITION OF D-A CYCLOBUTANES WITH AROMATIC SUBSTITUTION

When attempting to expand the substrate scope to include branched aliphatic aldehydes $Sc(OTf)_3$ was found to be an unsuitable catalyst. However, it was found that $MADNTf_2$ was effective in catalyzing the cycloaddition of linear, branched and cyclic aliphatic aldehydes while avoiding the decomposition of any materials (Scheme 89).



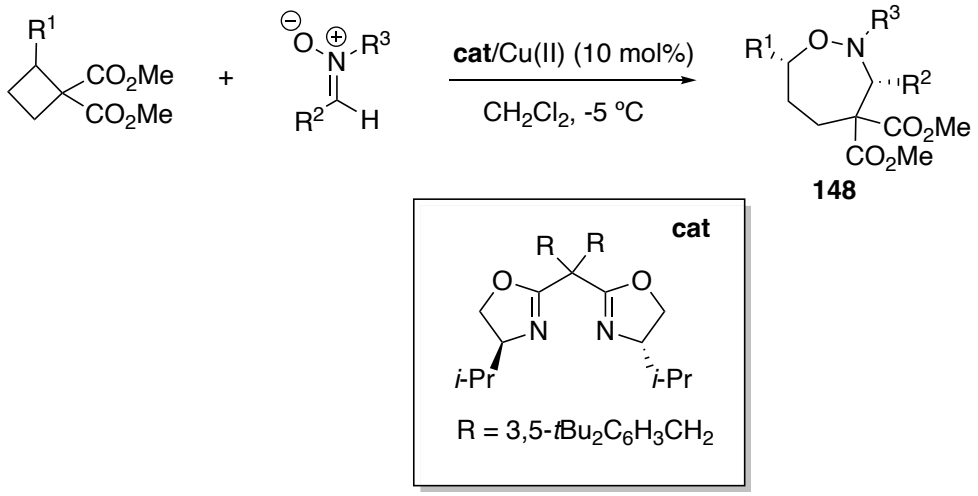
SCHEME 89: STRUCTURE OF $MADNTf_2$



SCHEME 90: SUBSTRATE SCOPE OF [4+2]-CYCLOADDITION OF D-A CYCLOBUTANES WITH ALIPHATIC SUBSTITUTION

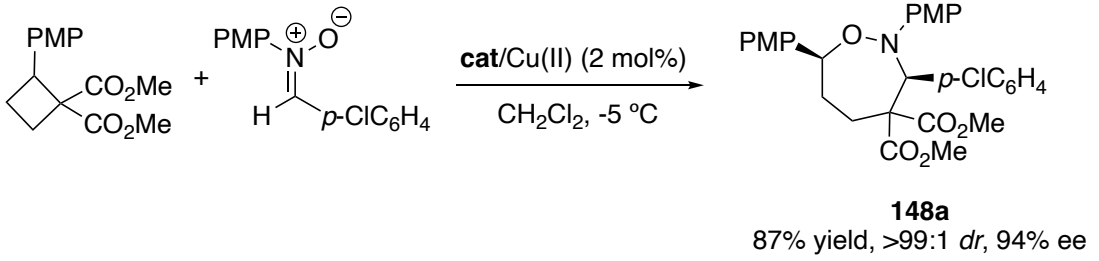
2.3.2.2 Enantioselective [4+3] Annulations of Donor-Acceptor Cyclobutanes

In 2016 Wang and Tang documented the first asymmetric [4+3] cycloaddition of 1,1-cyclobutane diester with nitrone, catalysed by the SaBOX/Cu(II) complex producing a broad range of multifunctionalized optically active 1,2-oxazepanes with yields up to 96% with excellent stereocontrol (up to >99/1 *dr* and 97% ee)(Scheme 91).[154] The reaction was found to tolerate a range of donor-acceptor cyclobutanes bearing different functional groups including phenyl, 2-thienyl, benzo[b]thiophenyl and alkoxy motifs. Though diastereoselectivity was not high for alkoxy-substituted cyclobutanes, both the *cis*- and *trans*- isomers could be readily isolated through column chromatography in high yield with excellent enantioselectivity.



SCHEME 91: WANG AND TANG [4+3] ANNULATION OF D-A CYCLOBUTANES

Gram scale investigation of the reaction showed that not only could the reaction be scaled up without loss of yield, it also required lower catalyst loading. Using 2 mol% of 37/$Cu(ClO_4)_2 \cdot 6H_2O$, 1.41g of product **148a** was obtained in 87% yield (>99/1 *dr* and 94% *ee*).

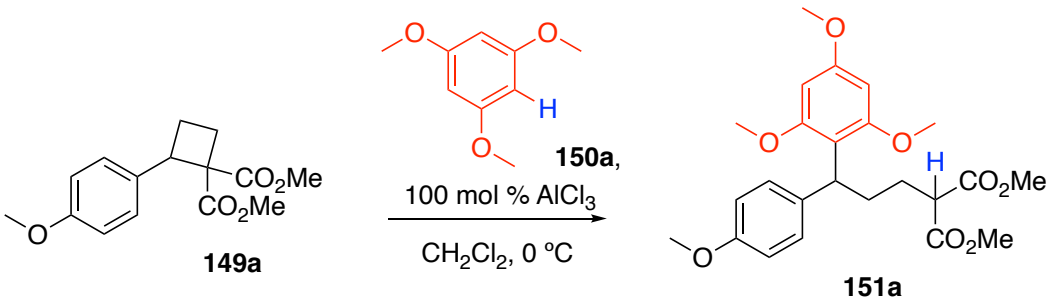


SCHEME 92: GRAM SCALE SYNTHESIS

2.3.2.3 Ring-Opening Reactions of Donor-Acceptor Cyclobutanes with Electron-Rich Arenes, Thiols and Selenols

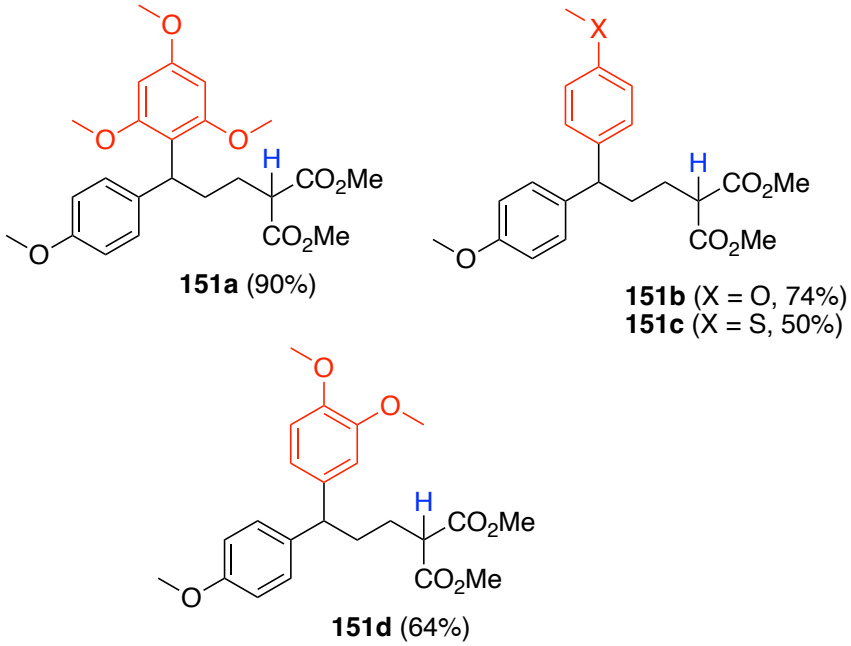
Inspired by the work of France, whereby electron-rich indole derivatives can open their four-membered ring motif, Kreft and co-workers investigated whether this intermolecular Friedel-Crafts type ring-opening was a feature of other arenes with particular interest in nucleophiles such as phenols.[155]

Various D-A cyclobutanes were synthesized beginning from their respective dihalides, which were obtained through chlorination of the corresponding alcohols. Subsequent double nucleophilic substitution with dimethyl malonate afforded the desired four-membered rings. Reaction optimization was carried out with D-A cyclobutane **149a** and trimethoxybenzene **150a** as model substrates. The reaction was determined to provide the best results when carried out at 0 °C in CH_2Cl_2 with the addition of 100 mol % of $AlCl_3$, which was necessary to activate the D-A cyclobutane, and stirred for 15 minutes.



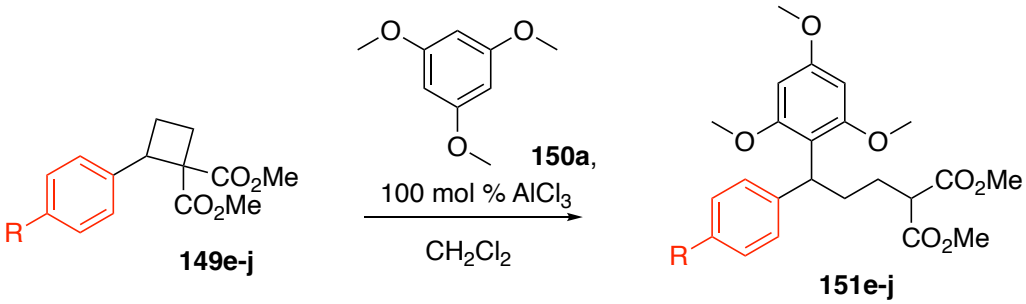
SCHEME 93: KREFT AND CO-WORKERS RING OPENING OF D-A CYCLOBUTANES

The reaction was determined to tolerate a broad variety of arenes including trimethoxybenzene (**151a**), (thio-)anisole (**151b**,**151c**) and veratrole (**151d**) with yields up to 90% (Scheme 94). Notably, the possible competitive attack of the nucleophilic hydroxy group was not observed under these reaction conditions.



SCHEME 94: SUBSTRATE SCOPE W.R.T NUCLEOPHILE FOR KREFT AND CO-WORKERS RING-OPENING OF D-A CYCLOBUTANES

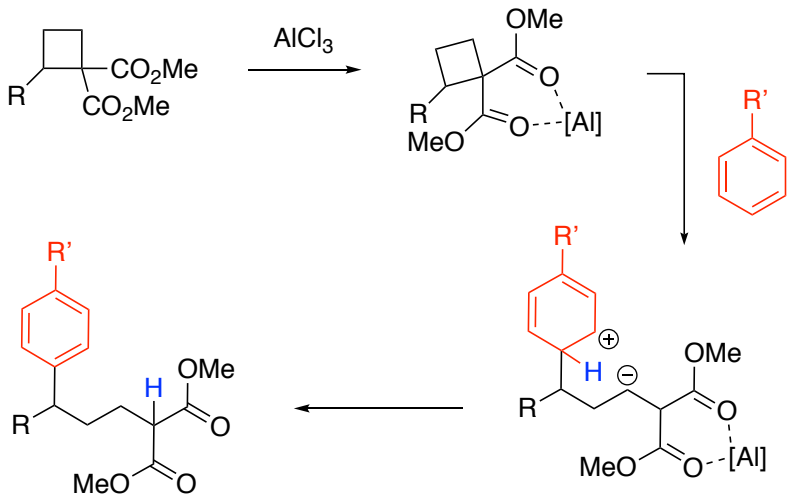
The scope with regard to different D-A cyclobutanes was also investigated. The products from the reactions of D-A cyclobutanes with electron-poor and neutral donors could be isolated in yields up to 83%. D-A cyclobutanes with highly electron-rich arene substituents, such as D-A cyclobutanes with *p*-O_2N-C_6H_4 or *p*-F_3C-C_6H_4, required drastically elevated temperature and reaction time to achieve any conversion.



e (R = H, 68%)[a]
f (R = Me, 83%)[a]
g (R = O_2N, 10%)[b]
h (R = F3C, 65%)[b]
i (R = Br, 55%)[a]
j (R = F, 78%)[c]

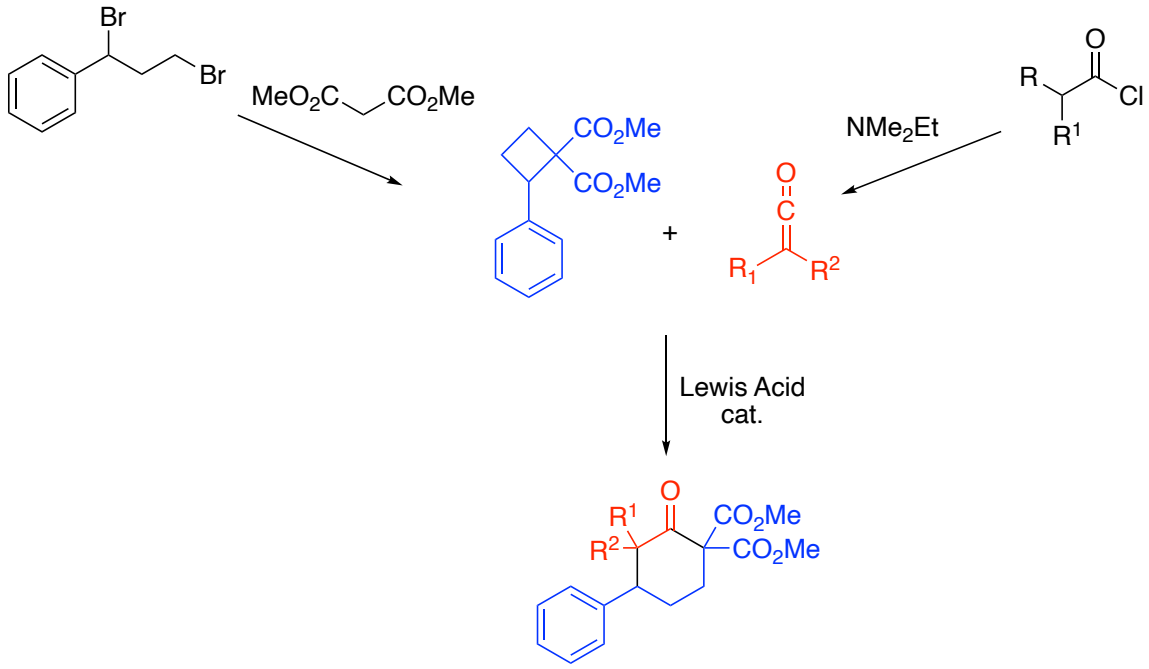
SCHEME 95: [A]REACTION CONDITIONS: 149 (0.1-0.2 MMOL) AND 150A (3.0 EQUIV), $AlCl_3$ (1.0 EQUIV), CH_2Cl_2 (0.05 M), REACTION TIME: 15 MIN-1 H. [B]ROOM TEMPERATURE, 14 H. [C]ROOM TEMPERATURE, 4 H.

The following mechanism was proposed for the transformation: Firstly, the D-A cyclobutane is activated by the co-ordination of the esters to the Lewis acid. The nucleophilic attack of the electron-rich arene followed by a proton shift leads to the desired product (Scheme 96).



SCHEME 96: MECHANISM PROPOSED BY KREFT AND CO-WORKERS

2.4: Results and Discussion



SCHEME 97: OVERALL PLAN FOR THE SYNTHESIS OF CYCLOHEXANONES

Access to synthetically important cyclohexanones was envisioned to occur through Lewis-acid catalyzed [4+2]-cycloaddition of a donor-acceptor cyclobutane with ketenes. Due to the group's previous success in the [3+2]-cycloaddition of cyclopropanes and ketenes to afford cyclopentanones, this work was expected to follow a similar synthetic procedure which will be discussed below.

2.4.1 Synthesis of 1,3-dibromopropyl benzene

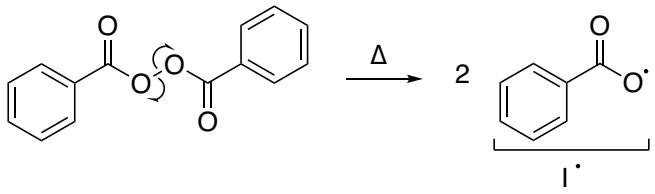
The synthesis of 1,3-dibromopropyl benzene was carried out via the Wohl-Ziegler reaction. Typical Wohl-Ziegler set-up was followed whereby a stoichiometric amount of N-bromosuccinimide (NBS) alongside an initiator (benzoyl peroxide, BPO) was added to a solution of the substrate ((3-bromopropyl)benzene) in CCl_4. While the reaction was stirring a heat gun was used to initiate the reaction, and initiation was indicated by a sudden more vigorous boil. The reaction was then allowed to react under reflux. An additional portion of benzoyl peroxide (0.1 equivalent) was added after 6 hours and it was allowed to react overnight. The crude product was purified by column chromatography to afford 1,3-dibromopropylbenzene in 79% yield.

Purification of the compound was difficult in some cases due to the similar polarity of the starting material (3-bromopropyl)benzene and the product. In cases where the product co-eluted with the starting material the mixed fractions were collected and repurified. The product was eluted using petroleum ether.

A benefit of using NBS is that it maintains a low concentration of molecular bromine which helps to limit the formation of the tribromopropyl benzene derivative of the starting material. To validate the importance of this on the yield of the desired product, addition of a further 0.5 equivalent of NBS after 6 hours was investigated. Unsurprisingly, this caused for the conversion of some product to a tribrominated derivative benzene as determined by NMR.

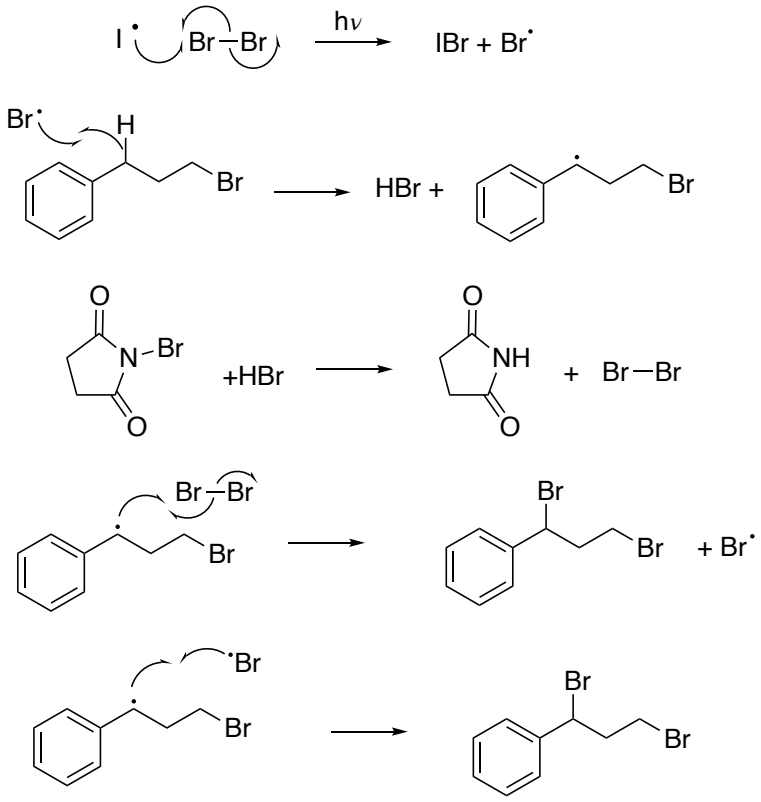
In all other cases 1,3-dibromopropylbenzene was the only product. This is because bromination is more highly favoured for C_1 as the resulting intermediate radical is better stabilized by the adjacent phenyl ring.

The mechanism by which this reaction proceeds was proposed by Paul Goldfinger in 1953.[156] Upon heating benzoyl peroxide it readily undergoes symmetrical fission (homolysis), forming two benzoyloxy radicals. The unpaired electrons act as free radical initiators.



SCHEME 98: BENZOYLOXY RADICALS

The initiator radicals then initiate a series of chain reactions called the propagation phase. Diatomic bromine (which is present in NBS in trace amounts) reacts with the initiator to form a bromine free radical. A proton from the C_1 carbon of the (3-bromopropyl)benzene is abstracted by the bromine radical to generate HBr and the 3-bromopropylbenzene free radical. At this point the 3-bromopropylbenzene free radical can either cause bond cleavage in diatomic bromine, generating another bromine free radical, or it can react with bromine free radical in solution, both of which will form the desired product 1,3-dibromopropylbenzene. The purpose of NBS in this reaction is to maintain a low concentration of the initial radical and to reform diatomic bromine. Maintaining low molecular bromine concentration is essential for promoting substitution reactions over addition reactions.



SCHEME 99: MECHANISM FOR THE SYNTHESIS OF 1,3-DIBROMOPROPYL BENZENE

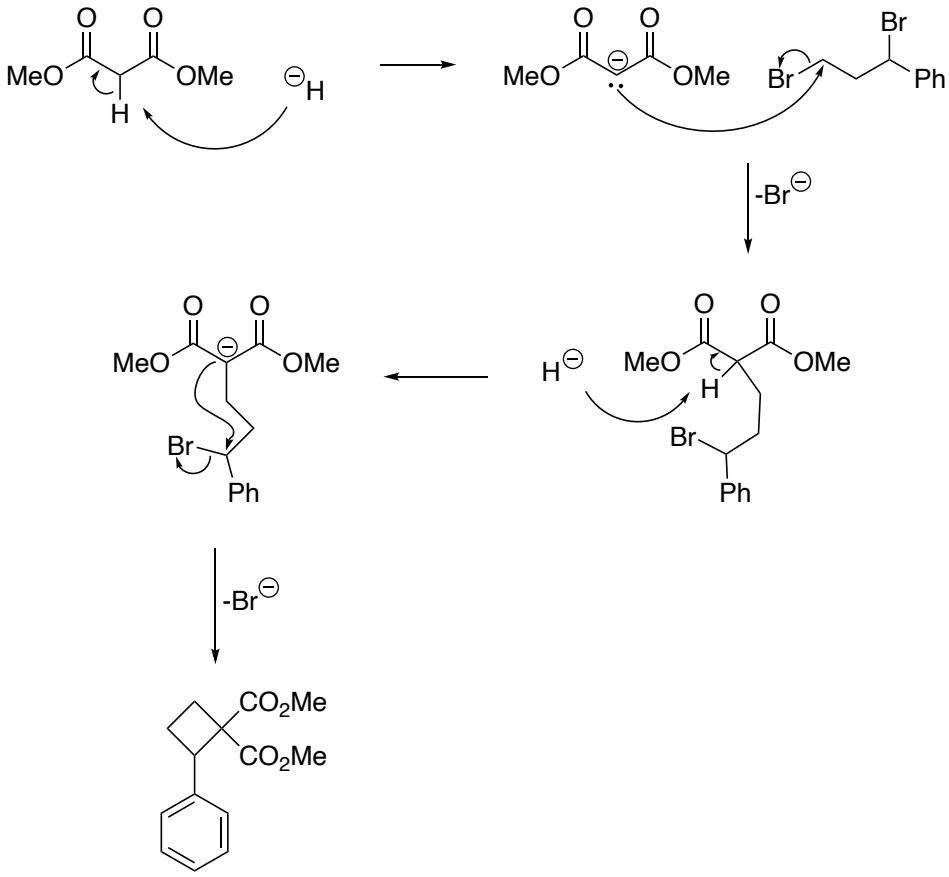
Using CCl_4 as the solvent also plays a role in maintaining low molecular bromine concentration. NBS is poorly soluble in CCl_4 and the resulting succinimide is insoluble and floats to the surface. This helps keep concentration of the reagents low, which limits bromination of the product.

TABLE 10: OPTIMIZATION OF THE SYNTHESIS OF 1,3-DIBROMOPROPYLBENZENE

Equiv. of NBS for second addition	*Time allowed to reflux after initial benzoyl peroxide addition (h)*	*Time allowed to reflux after 2nd benzoyl peroxide addition (h)*	*Yield (%)*
N/A	20	5	52
N/A	6	16	79
0.5	6	16	58
N/A	3	20	61

2.4.2 Synthesis of donor-acceptor cyclobutane

The synthesis of dimethyl 2-phenylcyclobutane-1,1-dicarboxylate followed the mechanism outlined in Scheme 100. To begin, a strong base (sodium hydride) abstracts one of the two acidic α-carbon protons. The resulting carbanion/enolate attacks the C_3 primary carbon of the 1,3-dibromopropyl benzene in a S_N2 reaction with loss of a bromine anion. The base abstracts the second acidic α-carbon proton forming another carbanion, which can effect ring-closure through intramolecular attack on the C_1 secondary carbon.



SCHEME 100: MECHANISM FOR THE SYNTHESIS OF DIMETHYL 2-PHENYLCYCLOBUTANE-1,1-DICARBOXYLATE

TABLE 11: OPTIMISATION OF REACTION CONDITIONS FOR DONOR-ACCEPTOR CYCLOBUTANE SYNTHESIS

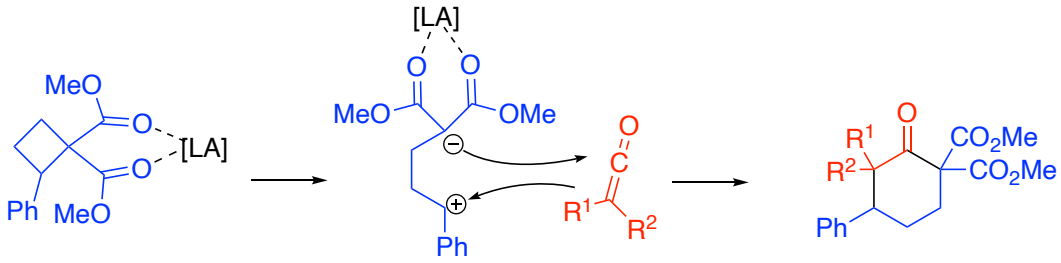
Entry no.	***No. of NaH additions (1.1 equiv)***	***Time between start of reaction and second addition (h)***	***Time between second and third addition (h)***	***Time between third and fourth addition (h)***	***Time between fourth and fifth addition (h)***	***Total reaction time (h)***	***Yield (%)***
1	3	3	16	N/A	N/A	40	60
2	3	3	16	N/A	N/A	25	39
3	3	20	6	N/A	N/A	42	57
4	4	3	14	8	N/A	41	71
5	4	16	5	3	N/A	38	67
6	5	3	16	5	5	48	69

For reaction optimization the effect of total reaction time as well as the number of sodium hydride additions (equivalents) was investigated. The time between supplementary additions was also investigated. It was found that best results were obtained when four additions (4.4 equivalents) of sodium hydride were introduced to the reaction. Best results were found when the second addition was added 3 hours after the reaction was initiated. Interestingly, addition of a fifth equivalent of sodium hydride did not improve the yield and required longer reaction times for similar yield (Table 11, entry 4 &5 vs 6). In contrast, when three additions of sodium hydride were used, increasing the total reaction time was essential to obtain satisfactory yields (Table 11, entry 1 vs entry 2). It is worth noting that initial attempts at this reaction were significantly lower yielding (20-40%). The higher yields noted above in Table 11 were obtained when sodium hydride that was newly opened (<3 months old) was used for the reaction. For earlier attempts (not shown in Table 11), it is likely that degradation of the sodium hydride occurred over time which meant that a lower concentration of base was being introduced to the reaction than was calculated.

2.4.3 Optimization of [4+2] cycloaddition of donor-acceptor cyclcobutanes with ketenes

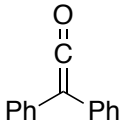
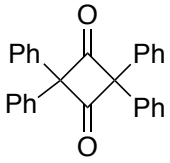
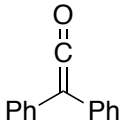
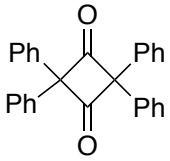
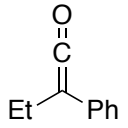
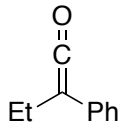
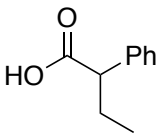
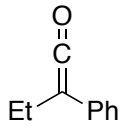
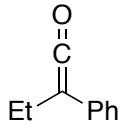
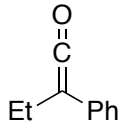
The donor-acceptor cyclobutane was synthesized from 1,3-dibromopropyl benzene and dimethyl malonate in good yield (70%).

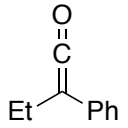
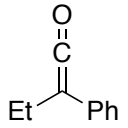
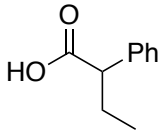
The cyclobutane dimethyl 2-phenylcyclobutane-1,1-dicarboxylate was subjected to reaction with a ketene in the presence of various Lewis acids. The effective use of the ring-strain of donor-acceptor cyclobutanes was hoped to encourage the formal [4+2]-cycloaddition of the ketenes to form substituted cyclohexanones. This was expected to occur by the mechanism outlined in Scheme 101.



SCHEME 101: EXPECTED PATHWAY FOR CYCLOHEXANONE SYNTHESIS

TABLE 12: INVESTIGATION OF CYCLOHEXANONE SYNTHESIS

entry	*Equiv. of cyclobutane*	*Ketene*	*Lewis acid*	*addition of ketene over (h)*	*quench temp.*	*major product of reaction*	*Yield (%)*
1	1.35	 (1.0 equiv)	$InBr_3$ (0.2 equiv)	2	NA		31
2	1.35	 (1.0 equiv)	$InBr_3$ (0.2 equiv)	4	NA		20
3	1.0	 (2.0 equiv)	$Sc(OTf)_3$ (0.5 equiv)	4	NA	NA	NA
4	1.0	 (3.0 equiv)	$In(OTf)_3$ (0.2 equiv)	2	NA		NA
5[a]	1.0	 (3.0 equiv)	$In(OTf)_3$ (0.2 equiv)	1	rt	NA	NA
6	1.0	 (1.5 equiv)	$Yb(OTf)_3$ (0.1 equiv)	1	NA	NA	NA
7	1.0		$AlCl_3$ (1.0 equiv)	1	0 °C and rt	NA	NA

		(3.0 equiv)					
8	1.0	 (1.5 equiv)	$GaCl_3$ (1.5 equiv)	3	0 °C	NA	NA
9	1.0	 (1.5 equiv)	$GaCl_3$ (1.5 equiv)	3	-30 °C		NA

Note in reactions where quench is NA the reaction was not quenched and work up was carried out as in section 2.3.5.

[a] addition of $EtAlCl_2$ and reaction allowed to stir overnight at -25 °C before being allowed to warm to room temperature for quenching

Both diphenylketene and ethylphenylketene were investigated as reaction partners for phenyl-substituted cyclobutane under a variety of Lewis acid-catalyzed conditions (Table 12). Diphenylketene is more stable than the unsymmetrical ketene, so it would be less reactive in solution. For this reason, ethylphenylketene was investigated more thoroughly. Ethylphenylketene is also a more attractive reaction partner as it would offer disubstitution with two different substituents, and the ethyl phenyl disubstitution would not be as sterically demanding, therefore it was predicted that it would be more likely to form the cyclohexanone.

One of the major drawbacks of ketene addition, is the probability of ketene dimerization/polymerization as background reaction if the desired reaction does not proceed quickly enough. Indeed Lewis acid-catalyzed homodimerizations of ketenes have been known since the 1960s.[157,158] Ironically, this is a consequence of the high reactivity of ketenes which is what makes them such attractive substrates. Unfortunately, evidence of this can be found from the formation of ketene dimers highlighted in entries 1 and 2. Although ketene dimerization is unwelcomed in terms of cyclohexanone synthesis, there has been large interest in the study of these dimerization reactions as outlined in section 2.2.2.1. It is possible to recover the desired ketene through thermal cracking of the ketene dimer.[159] Although impractical for this research considering it is carried out on milligram scale (<1 mmol scale), it is worth mentioning as it may offer a possible solution in the future for the regeneration of starting materials from unwanted side products.

In the case of diphenylketene it was initially hypothesized that dimerization may be preferred due to the steric interaction that could present between the two phenyl rings and the acceptor motif of the cyclobutane. It was hoped that ethylphenylketene would yield better results. Unfortunately, ketene polymerization was found in most of the other examples, indicated by TLC analysis (by spots very high up the plate close to the solvent line). This was confirmed by TLC comparison to an authentic sample of ethylphenylketene dimer standard prepared by Shubhanjan Mitra. For efficiency, these products were not analysed by NMR and instead the spots that were lower lying were isolated and analysed to determine if cyclohexanone had been synthesized.

It was hypothesized that polymerization of the ketene could be more likely to occur when the ketene is introduced to the reaction mixture within a shorter time frame. The larger the concentration of ketene within the reaction flask at one time, the more likely it is that two molecules will come in contact and polymerize. Increasing ketene addition time was thought to help keep ketene concentration low for long enough that it could react with the cyclobutane.

In two cases the major product from the reaction was 2-phenylbutanoic acid (Table 12, entries 4 and 9). This is unfortunate as this is most likely a product of the ketene reacting with moisture within the reaction flask. Although, care was taken to avoid this unfortunately it can be difficult especially in the reactions with longer addition times as there is an increased risk in air leaking into the reaction flask due to strain on the septa from the needle.

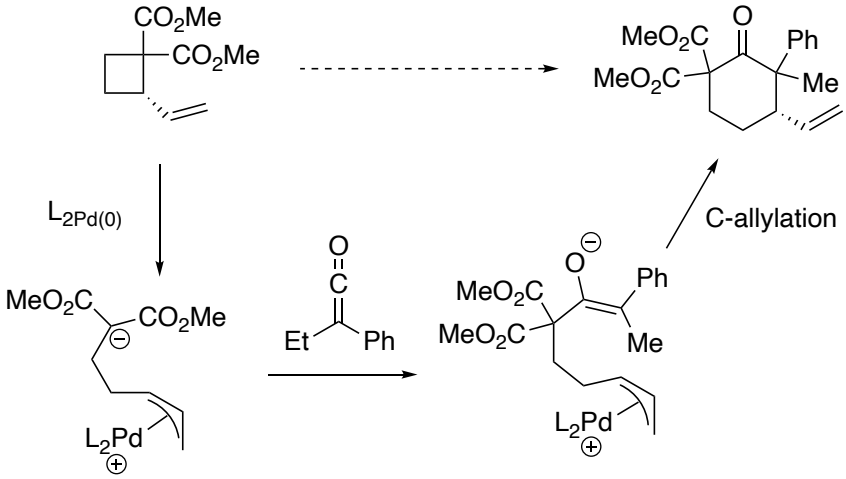
To investigate whether quenching at room temperature caused the loss of product, or if product was simply not formed during the reaction, approximately 1 mL of reaction mass was taken out and quenched while still at 0 °C while the rest was allowed to come up to rt overnight and quenched the following day (Table 12, entry 7). TLC of the samples suggested that there was no loss of any product of the reaction, however, upon quenching two new TLC spots were formed. Unfortunately, isolation of these compounds and analysis by NMR did not yield the desired cyclohexanone.

2.4.4 Future Work

It would be worth reinvestigating the use of $AlCl_3$ in this reaction due to its recent success mediating the reaction between the same D-A cyclobutane and a range of arenes, thiols and selenols.[155] More extensive investigation in regard to reaction temperature, quench temperature and reaction time may yield better results.

Given the previous successes of Lewis acid catalyzed reactions of D-A cyclobutanes/cyclopropanes from other groups it would be worth investigating a larger range of Lewis acids such as $SnCl_4$, $SbCl_5$, $TiCl_4$, $ZnBr_2$ and $FeCl_3$. It is not uncommon in literature to see that a reaction may be successful with a specific Lewis acid, but yield nothing or trace amounts when other Lewis acid catalysts are employed. $Sc(OTf)_3$ is a popular choice in this area with multiple publications showcasing its use mediating cycloaddition of D-A cyclobutanes and cyclopropanes.[160,161] However, Werz and co-workers found for their work involving D-A cyclobutanes and syndones that $Sc(OTf)_3$ yielded only trace amounts of product while use of $SbCl_5$ produced the desired product in yields of up to 91%.[162] Another example can be found in Pagenkopf and co-workers research on the [4+2]-cycloaddition of D-A cyclobutanes and nitriles, where $SnCl_4$ was found to facilitate the reaction and yield the desired product in 78% yield, while $Yb(OTf)_3$ did not facilitate any reaction.[163]

Our group has had previous success in the palladium(0)-catalyzed [3+2]-cycloaddition of vinylcyclopropanes and ketenes.[164] Use of vinylcyclobutanes in this reaction may offer access to cyclohexanones through a similar mechanism to that outlined in Scheme 102.



SCHEME 102: PROPOSED MECHANISM FOR PALLADIUM(0)-CATALYZED-CYCLOADDITION OF VINYLCYCLOBUTANES AND KETENES

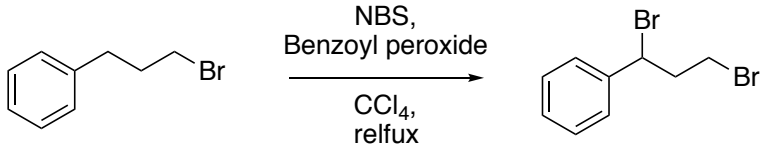
In addition, the investigation of more reactive ketene substrates such as in situ generated monosubstituted ketenes (as discussed in section 3), might lead to more promising results.

2.5: Experimental

General Information

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard inert atmosphere technique unless otherwise stated. THF was dried using a sodium/benzophenone ketyl still, and N,N-diethylamine was distilled from potassium hydroxide under nitrogen. Benzoyl peroxide, sodium hydride (60% dispersion in oil), dimethyl malonate, 1,4-dioxane, ethylaluminium dichloride, indium (III) bromide, scandium (III) trifluoromethanesulfonate, indium (III) trifluoromethanesulfonate, ytterbium (III) trifluoromethanesulfonate, aluminium trichloride and gallium trichloride were purchased from Aldrich Chemical Co. and used as received. N-bromosuccinimide was purchased from Aldrich Chemical Co. and purified prior to use.[165] Iatrobeads (neutral silica, Bioscan, 6RS-8060, 60 μM particle size) and TLC plates (Sorbent Technologies, UV254, 250 μM) were used as received. NMR spectra were recorded on a Bruker Avance III 600 spectrometer (600 MHz for ^{1}H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to $CDCl_3$ (17.26 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra.

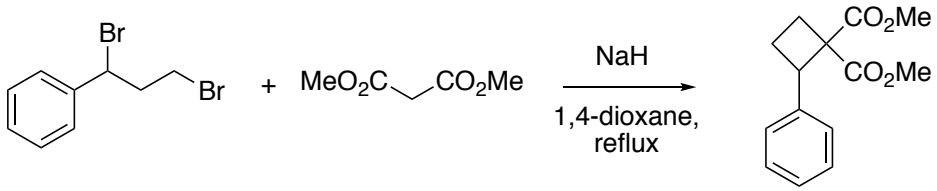
2.5.1 Synthesis of 1,3-dibromopropyl benzene



CCl_4 (10 mL) was added to 1-bromopropylbenzene (0.50 g, 2.5 mmol, 1.0 equiv), N-bromosuccinimide (0.53 g, 3.0 mmol, 1.2 equiv), and benzoyl peroxide (0.060 g, 0.25 mmol, 0.10 equiv). A heat gun was used to initiate the reaction by heating until a vigorous boil was noted, and the yellow solution was then allowed to reflux for 6 h in open air. After 6 h the solution was a pale yellow, an additional benzoyl peroxide (0.10 equiv) was added along with CCl_4 (1.5 mL) and the reaction was allowed to reflux overnight. The next day the reaction was allowed to cool to ambient temperature, filtered over celite and washed with CH_2Cl_2. The product was purified by silica column chromatography (indicate dimensions of column and amount of silica as was difficult purification) eluting slowly with petroleum ether to provide a yellow oil (79%). ^{1}H NMR (600 MHz, $CDCl_3$): 7.43 – 7.39 (m, 2H), 7.38 – 7.35 (m, 2H), 7.33 – 7.31 (m, 1H), 5.21 – 5.18 (dd, 1H, J_1 = 6.0 Hz, J_2 = 12.0 Hz), 3.59 – 3.53 (m, 1H), 3.46 – 3.40 (m, 1H), 2.83 – 2.74 (m, 1H), 2.60 – 2.51 (m, 1H)

^{13}C NMR (150 MHz, $CDCl_3$): 128.9, 128.7, 127.4, 52.5, 42.1, 31.0

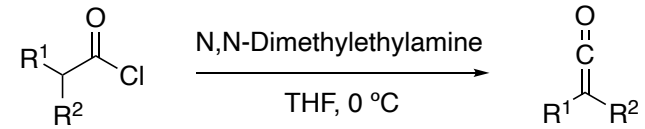
2.5.2 Synthesis of dimethyl 2-phenylcyclobutane-1,1-dicarboxylate



To a suspension of sodium hydride (60% dispersion in oil, 0.030 g, 0.79 mmol, 1.1 equiv) in 1,4-dioxane (2 mL), dimethylmalonate (0.11 g, 0.86 mmol, 1.2 equiv) was added and the reaction was stirred for 30 min. 1,3-Dibromopropylbenzene (0.20 g, 0.72 mmol, 1.0 equiv) was added along with 1,4-dioxane (3 mL) and the reaction was refluxed for 3 h. After 3h, a further portion of sodium hydride (1.1 equiv) along with 1,4-dioxane (3 mL) was added and the reaction allowed to reflux overnight. The next day a further portion of sodium hydride (1.1 equiv) was added along with 1,4-dioxane (1.5 mL) and the reaction was allowed to proceed for a further 6 h. A further portion of sodium hydride (1.1 equiv) and 1,4-dioxane (1.5 mL) was added and left to react overnight again. The next day the reaction was allowed to cool to room temperature and filtered over celite and washed with diethyl ether (50 mL). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography eluting with 2-5% EtOAc:hexane to provide dimethyl 2-phenylcyclobutane-1,1-dicarboxylate as a colourless oil. (71%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 – 7.28 (m, 4 H), 7.22 – 7.20 (m, 1H), 4.37 (t, 1H, J = 10.2 Hz), 3.78 (s, 3H), 3.23 (s, 3H), 2.72 – 2.69 (m, 1H), 2.65 – 2.59 (m, 1H), 2.30 – 2.25 (m, 1H), 2.20 – 2.15 (m, 1H)

^{13}C NMR (150 MHz, $CDCl_3$): 172.2, 169.8, 139.1, 128.1, 127.5, 127.0, 59.7, 52.6, 51.9, 45.1, 25.7, 20.7

2.5.3 Synthesis of disubstituted ketenes

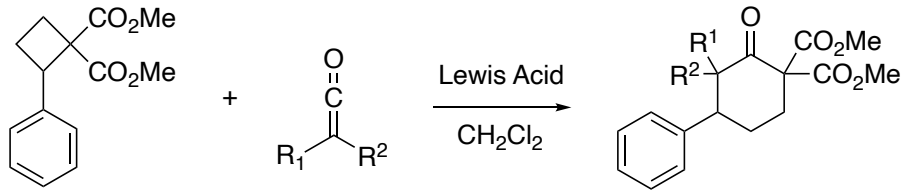


R^1 = Ph
R^2 = Ph or Et

Acyl chloride previously prepared by Shubhanjan Mitra (1.50 g, 1.0 equiv) in THF (22.0 mL) was cooled to 0 °C in an ice bath. At 0 °C freshly distilled N,N-dimethylethylamine (4 equiv) was added dropwise via syringe pump over 30 min. After complete addition the reaction was stirred at 0-5 °C for 5 h (a yellow coloured mixture was obtained). This mixture was stored overnight at -30 °C to -35 °C. The next day the reaction mass warmed to 0 °C while Schlenk-filtration was set-up. The reaction mass was quickly added to the Schlenk filter via syringe.

The vacuum was applied gently to filter the solution into the Schlenk flask and the filter was washed with anhydrous THF. The remaining THF was removed under controlled vacuum before proceeding to short-path distillation. The crude oil was distilled under vacuum with the aid of a heat gun to afford a yellow/orange oil for both ethylphenylketene and diphenylketene (55% and 69% respectively). Due to the sensitivity of the products to polymerization in air it was not analysed by NMR and was stored at -30 °C to -35 °C until its use in a subsequent step.

2.5.4 General procedure A for investigation of the synthesis of cyclohexanones from donor-acceptor cyclobutanes and ketenes



To a solution of Lewis acid in CH_2Cl_2 (1.5 mL) was added dimethyl 2-phenylcyclobutane-1,1-dicarboxylate in CH_2Cl_2 (2 mL). To a separate flask was quickly added the ketene via micropipette, the flask was weighed to determine precise equiv. of ketene added. To this flask was added CH_2Cl_2 (1 mL) and the resulting yellow solution was added to the cyclobutane solution over 1-4 h (see table 12). This was allowed to stir overnight at rt. The reaction mass was extracted with CH_2Cl_2 (3 × 30 mL) and the collected organics were washed with brine solution (30 mL) and dried over Na_2SO_4. **(Table 12, entry 1-4 and 6)**

2.5.5 General procedure B for investigation of the synthesis of cyclohexanones from donor-acceptor cyclobutanes and ketenes

To a solution of $In(OTf)_3$ in CH_2Cl_2 (1.5 mL) was added dimethyl 2-phenylcyclobutane-1,1-dicarboxylate (0.045 g, 0.18 mmol, 1 equiv) in CH_2Cl_2 (2 mL). To a separate flask was quickly added ethylphenylketene (0.08g, 0.54 mmol, 3 equiv) via micropipette followed by addition of CH_2Cl_2 (1 mL). The resulting yellow solution was added to the cyclobutane solution over 1 h. The solution was then cooled to -25 °C. Once cooled ethylaluminium dichloride (1.0M in hexanes, 0.27 mL, 0.27 mmol, 1.5 equiv) was added over 2 h and the reaction was allowed to stir at -25 °C overnight. The next day consumption of starting material was verified by TLC and the reaction mass was allowed to warm to rt. Excess triethylamine (10 mL) was added to quench the reaction, a white ppt was noted. 2 drops of water added to ensure reaction mass was safe to open to air. The reaction mass was neutralized with dil. HCl. The reaction mass was extracted with CH_2Cl_2 (3 × 30 mL) and the collected organics were washed with brine solution (30 mL) and dried over Na_2SO_4. **(Table 12, entry 5)**

2.5.6 General procedure C for investigation of the synthesis of cyclohexanones from donor-acceptor cyclobutanes and ketenes

Procedure followed as described in 2.3.5 with the addition of reaction quench after stirring overnight as described in Table 12. **(Table 12, entry 7-9)**

Chapter 3:

Stereoselective synthesis of cyclopentanones from donor-acceptor cyclopropanes and ketenes

3.1 Introduction to Cyclopentanones

Cyclopentanones have been found to be important intermediates across a range of different industries. Cyclopentanone derivatives such as cyclopentylamine and cyclopentanol are frequently used in the perfume industry. In particular, Magnolione is known for its floral, intense jasmine scent.[166] Cyclopentanones are also key structutal motifs for the manufacture of a range of insecticides and pesticides, as well as synthetic resins and rubber.

Cyclopentanones and cyclopentanone derivates are also frequently seen as pharmaceutical intermediates for drug synthesis.

3.1.1 Preparation of cyclopentanones

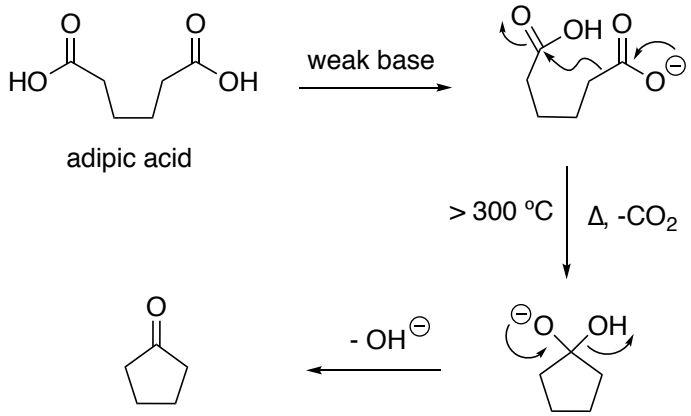
3.1.1.1 Ketonic decarboxylation from adipic acid

The most common method of cyclopentanone production in industry is through the ketonic decarboxylation of adipic acid in dry distillation at elevated temperatures (300-450 °C). Despite its presence in industry there is still frequent investigation into potential new catalysts that may offer increased productivity to industry.

One such example of this is described by Renz and Corma on the application of weak bases as catalysts for the production of optically pure cyclopentanone.[167] Their studies determined that the reaction rate could be increased through the introduction of increasing amounts of base. However, addition of more than 3.3 mol % of NaOH reduced the yield which was hypothesized to be due to the formation of disodium adipate. It was also noted that the NaOH could be reused for several distillations. 10 g of adipic acid was added to 0.5 g of NaOH and distilled, six more 10 g portions of adipic acid could be added to the flask without the need for addition of more base. Over 320 minutes, an accumulated yield of 90% in cyclopentanone yield was afforded.

When the weak base Na_2CO_3 was used a similar trend was observed. An increased quantity of Na_2CO_3 afforded carbonic acid and sodium adipate as intermediate side products and upon decomposition of carbonic acid into water and carbon dioxide the thermodynamic equilibrium is shifter towards sodium adipate. This demonstrated that the use of strong bases was not essential for reaction initiation. To confirm that the initial rate is not affected by the nature of the base but rather by its quantity, several different carbonates and hydroxides of alkali and alkaline-earth metals were tested and compared as additives.

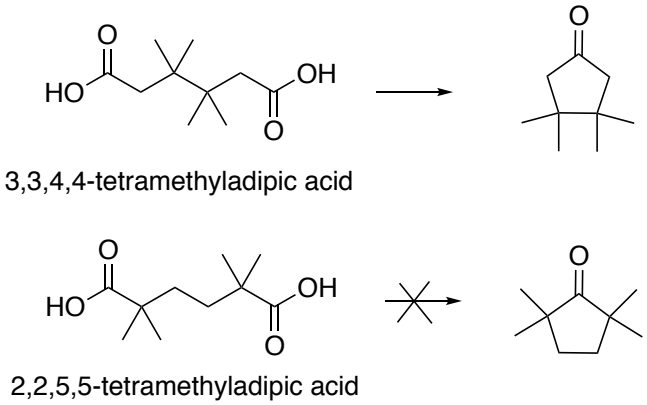
In terms of kinetics it was determined that they performed similarly, which disagreed with previous publications claiming that barium cations acted as reaction promoters.[168,169] For this reason, Renz and Corma concluded that only the cost, potential environmental impact and disposal facilities should influence the choice of metal salt additive. These findings also agreed with the mechanism proposed by Rand et. al. depicted in Scheme 103.[170]



SCHEME 103: RAND ET. AL. PROPOSED MECHANISM FOR CYCLOPENTANONE FORMATION FROM ADIPIC ACID

In earlier years the mechanism of this reaction was thought to occur through formation of a β-keto acid intermediate, for this mechanism to occur the compound required deprotonation at the α-position to occur.[171] Consequently, this would mean any substrates without α-hydrogen atoms would be incapable of cyclopentanone formation through this reaction pathway.

This was widely believed to have been true due to 2,2,5,5-tetramethyladipic acid, which has no α-hydrogen atoms, not forming the corresponding cyclopentanone under these reaction conditions where its 3,3,4,4-isomer was successful (Scheme 104).

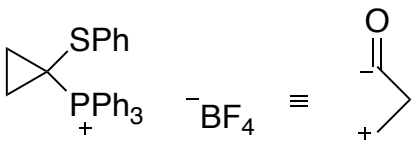


SCHEME 104: EFFECT OF SUBSTITUTION ON ADIPIC ACID WITH CYCLOPENTANONE FORMATION

However, in 1962 Rand and co-workers successfully reported the transformation of 2,2,5,5-tetramethyl adipic acid into the corresponding ketone in 52 to 72% yield in the presence of KF or BaO (Scheme 103).[170]

3.1.1.2 Synthesis of cyclopentanones from donor-acceptor cyclopropanes

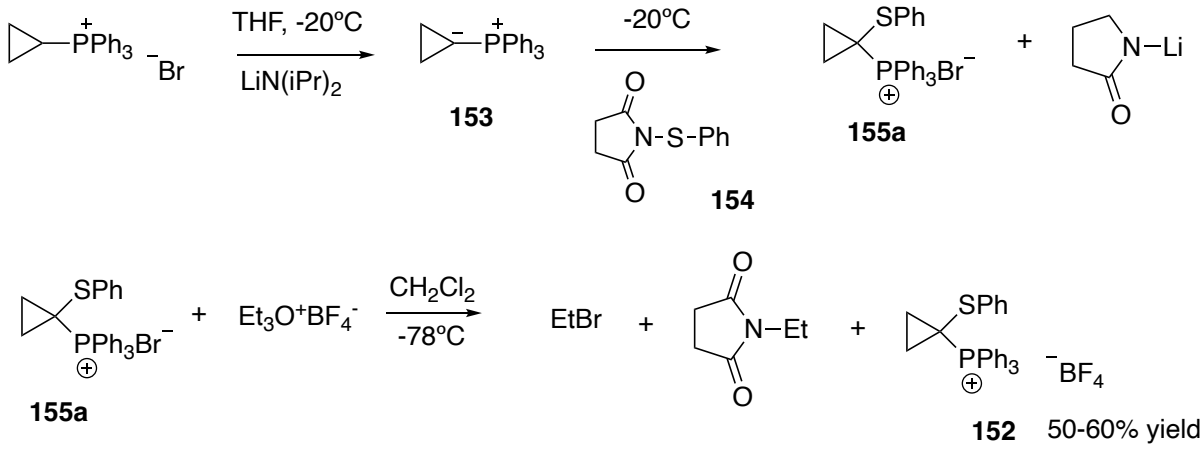
One of the most efficient methods of synthesis of five-membered ring systems involves initial nucleophilic attack of an activated cyclopropane with subsequent intramolecular ring closure. This use of donor-acceptor cyclopropanes constitutes an extremely important class of reactions and its importance in modern synthetic chemistry has been demonstrated through its reoccurrence throughout literature from the late 1960's to more recent publications.[172–175] J.P. Marino's 1975 publication describes the preparation of a 3-carbon synthon, 1-phenylthiocyclopropyltriphenylphosphonium tetrafluoroborate **152**, that is synthetically equivalent to the cyclopropane zwitterion **153**.[176]



152 **153**

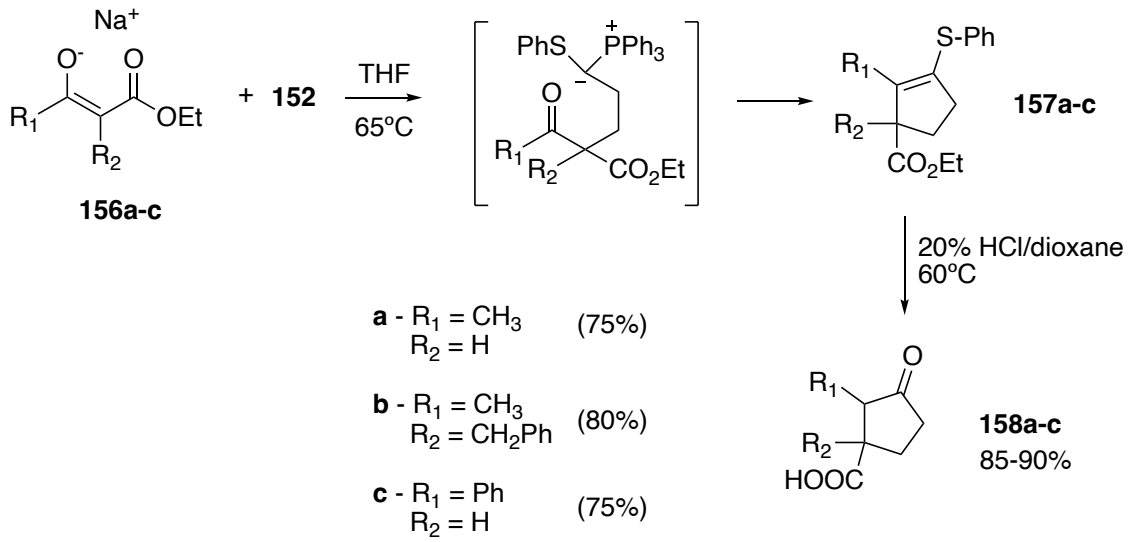
SCHEME 105: 1-PHENYLTHIOCYCLOPROPYLTRIPHENYLPHOSPHONIUM TETRAFLUOROBORATE

The preparation of synthon **152** is readily accomplished through sulfenylation of triphenylphosphonium cyclopropylide, **153**. Ylide **153** was prepared by treating the salt precursor cyclopropyltriphenylphosphonium bromide with lithium diisopropylamide at -20°C in THF, Once prepared this was subsequently added dropwise to a THF solution of one equivalent of N-phenylthiosuccinimide **154**, maintaining a temperature of -20°C. During the addition of **153**, the phosphonium bromide **155a** and succinimide salt precipitated out as a white solid. This was filtered under an inert atmosphere and washed with ether, and no further purification of the bromide was required for the next step. The phosphonium bromide **155a** in methylene chloride was treated with an excess of Meerwein's salt at -78°C to promote counterion exchange, producing the desired cyclopropyl synthon **152**, as well as ethyl bromide and N-ethyl-succinimide. After removal of the methylene chloride solvent, the product was washed with anhydrous ether to remove the non-salt by-products and provide the cyclopropylphosphonium salt in isolated yields ranging from 50-60% (Scheme 106).



SCHEME 106: SYNTHESIS OF 1-PHENYLTHIOCYCLOPROPYLTRIPHENYLPHOSPHONIUM TETRAFLUOROBORATE

More significantly, for the purpose of this review, the use of this synthon for the synthesis of cyclopentanones through its reaction with sodium enolates of β-keto esters is also described as a simple 2-step reaction. A range of substituted acetoacetic esters **156a-c** were refluxed with equimolar amounts of **152** in THF for an average of 72 hours and cyclopentenyl sulfides **157a**, **b** and **c** were obtained in good yields ranging from 75-80%. Subsequent conversion of this cyclopentenyl sulfide into cyclopentanone **158**, was carried out through hydrolysis of cyclopentenyl sulfide **157a-157c** in 20% HCl/dioxane at 60°C to provide cyclopentanone **158a-158c** in 85-90% (Scheme 107).

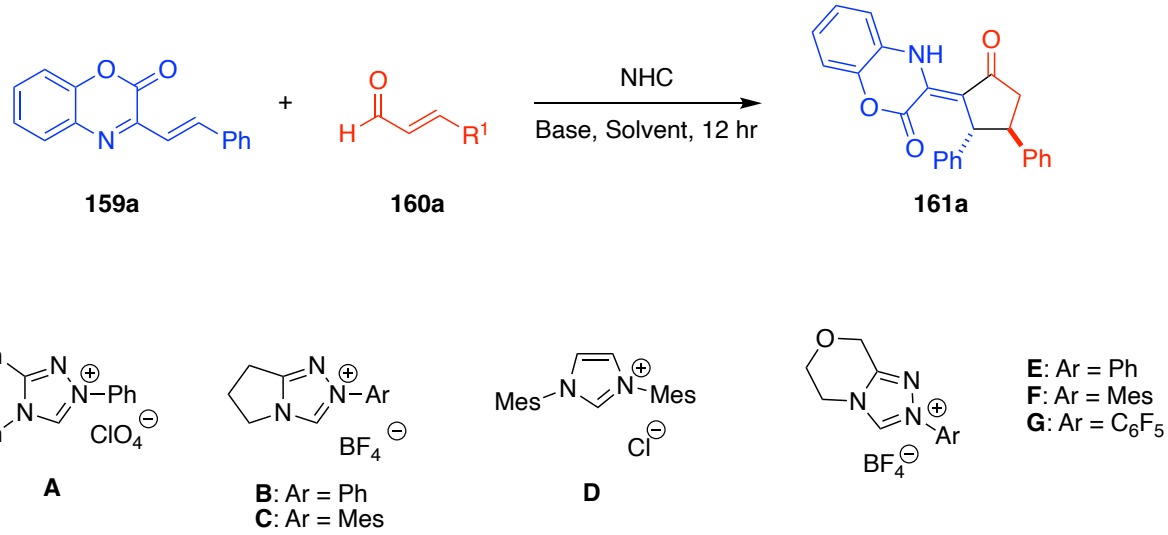


SCHEME 107: J.P. MARINO SYNTHESIS OF TRISUBSTITUTED CYCLOPENTANONE FROM 1-PHENYLTHIOCYCLOPROPYLTRIPHENYLPHOSPHONIUM TETRAFLUOROBORATE

3.1.1.3 NHC catalyzed [3+2] cycloaddition of enals with β,γ-unsaturated α-ketimino esters

Shi et al. describe an interesting method of NHC catalyzed [3+2] cycloaddition of enals with β,γ-unsaturated α-ketimino esters which provides convenient access to benzoxazinone derived cyclopentanone scaffolds under mild reaction conditions.[177] β,γ-unsaturated α-ketimino ester **159a** was first examined in the presence of cinnamaldehyde **160a**, DBU and THF. Catalyst screening found that catalyst C produced the highest yield of 80%, with catalyst E being the next most efficient with a yield of 76%. Reaction optimization also showed that the use of DBU and THF was the most effective, although substitution of THF for 1,4-dioxane also produced good yields. The other bases that were tested (DIPEA, TBD, K_2CO_3, Cs_2CO_3) also produced the desired product although it was in much less favorable yield. Product **161a** was generated as a single trans-diastereomer during this optimization process.

TABLE 13: REACTION OPTIMISATION FOR CYCLOPENTANONE SYNTHESIS

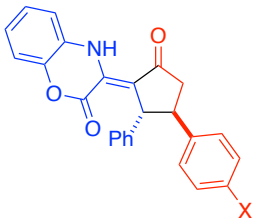


Entry	*NHC*	*Base*	*Solvent*	*Yield (%)[b]*
1	A	DBU	THF	37
2	B	DBU	THF	Trace
3	C	DBU	THF	80
4	D	DBU	THF	Trace
5	E	DBU	THF	76

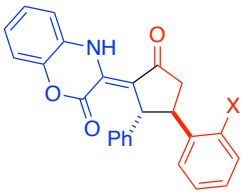
6	F	DBU	THF	13
7	G	DBU	THF	60
8	C	TBD	THF	58
9	C	DIPEA	THF	32
10	C	K_2CO_3	THF	47
11	C	Cs_2CO_3	THF	68
12	C	DBU	CH_2Cl_2	66
13	C	DBU	CH_3CN	55
14	C	DBU	1,4-dioxane	71
15	C	DBU	DME	66

[a)]Reaction conditions: 1a (0.1 mmol, 1.0 equiv), 2a (0.2 mmol, 2.0 equiv), NHC (20 mol %), base (20 mol %), solvent (1.0mL), room temperature, 12 h. [b)] Isolated yield after flash chromatography. DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene, DIPEA = N,N-diisopropylethylamine, Mes = mesityl, DME = 1,2-Dimethoxyethane.

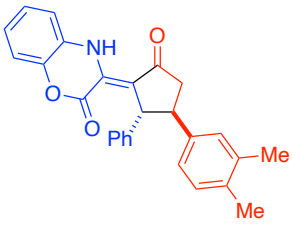
The substrate scope of this reaction is most impressive, 19 different β,γ-unsaturated α-ketimino esters with varying substitution were examined and all produced yields ranging from 73-99% (Scheme 108). These included enals derived from aryl aldehydes bearing various electron-withdrawing or electron-donating substituents **(161a-m)**, enals β-substituted with other heterocyclic units such as thienyl and furyl moeitys **(161n-o)**, an indole derived enal **161p**, an enal with a sterically demanding group **161q**, as well as β-alkyl and β-vinyl substituted enals **161r** and **161s**. Subsitution of an aryl unit on the β, γ-unsaturated α-ketoimino ester was also well tolerated (**161t-aa**). When the benzoxazinone unit bore an electron-donating or an electron-withdrawing group the reaction proceeded successfully with the desired product being formed in high yields (**161ab, 161ac**). It was also determined that the benzoxazinone unit could be replaced with a quinoxalinone unit with only a small loss in yield (**161ad**).



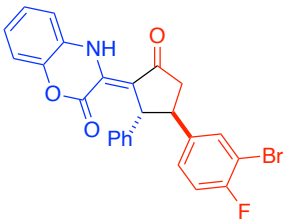
161a, X = H, 80%
161b, X = Me, 95%
161c, X = *t*Bu, 98%
161d, X = MeO, 94%
161e, X = F, 83%
161f, X = Cl, 99%
161g, X = Br, 89%
161h, X = CF_3, 95%
161i, X = NO_2, 73%



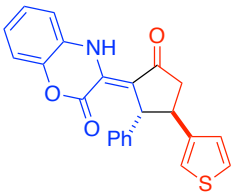
161j, X = Me, 73%
161k, X = Br, 76%



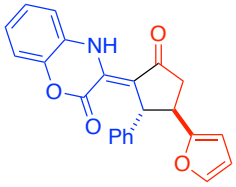
161l, 97%



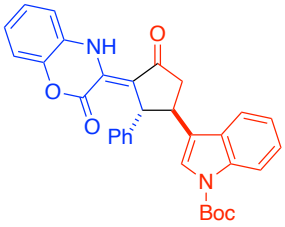
161m, 97%



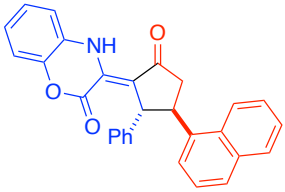
161n, 96%



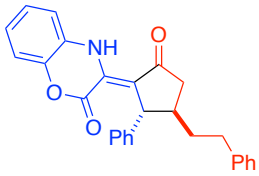
161o, 97%



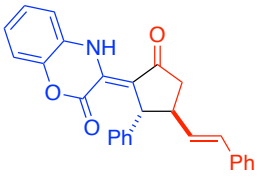
161p, dr = 7:1, 83%



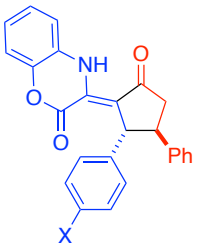
161q, 94%



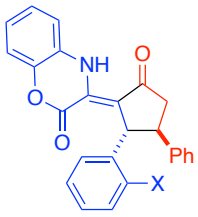
161r, dr = 8:1, 75%



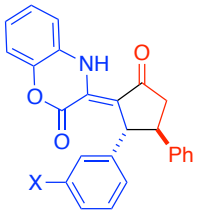
161s, dr = 8:1, 93%



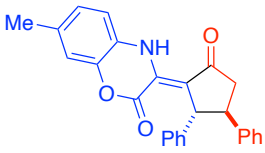
161t, X = Me, 97%
161u, X = MeO, 83%
161v, X = Cl, 86%
161w, X = Br, 86%



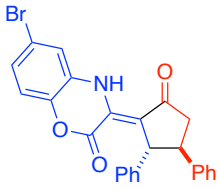
161x, X = Me, 92%
161y, X = Br, 76%



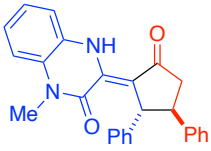
161z, X = Me, 91%
161aa, X = Cl, 82%



161ab, 92%

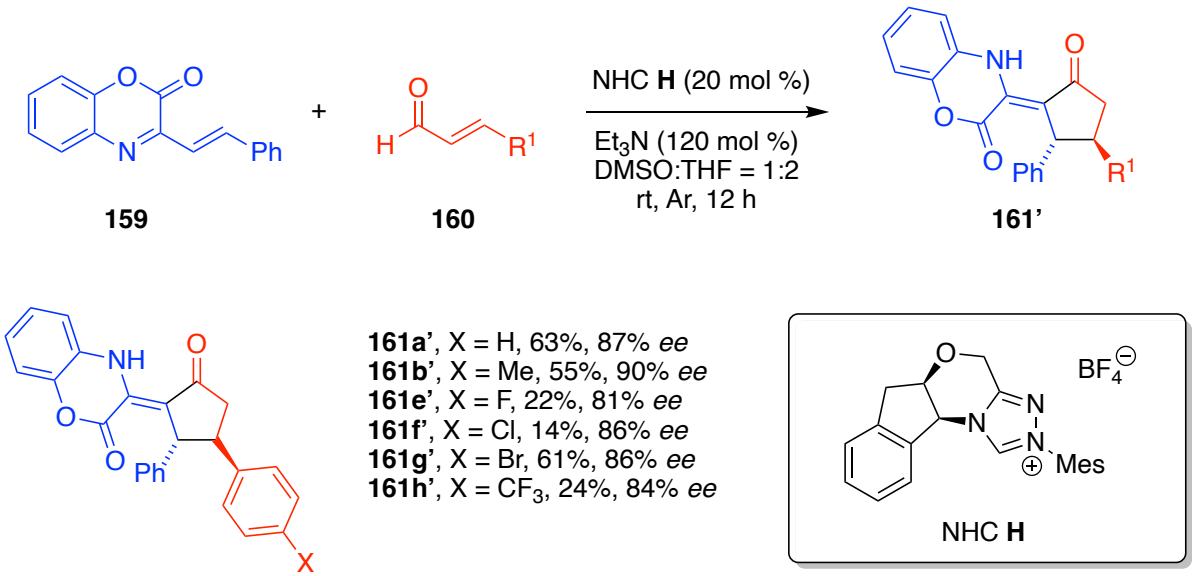


161ac, 84%



161ad, 75%

SCHEME 108: SHI ET AL. SUBSTRATE SCOPE FOR NHC CATALYSED CYCLOPENTANONE SYNTHESIS

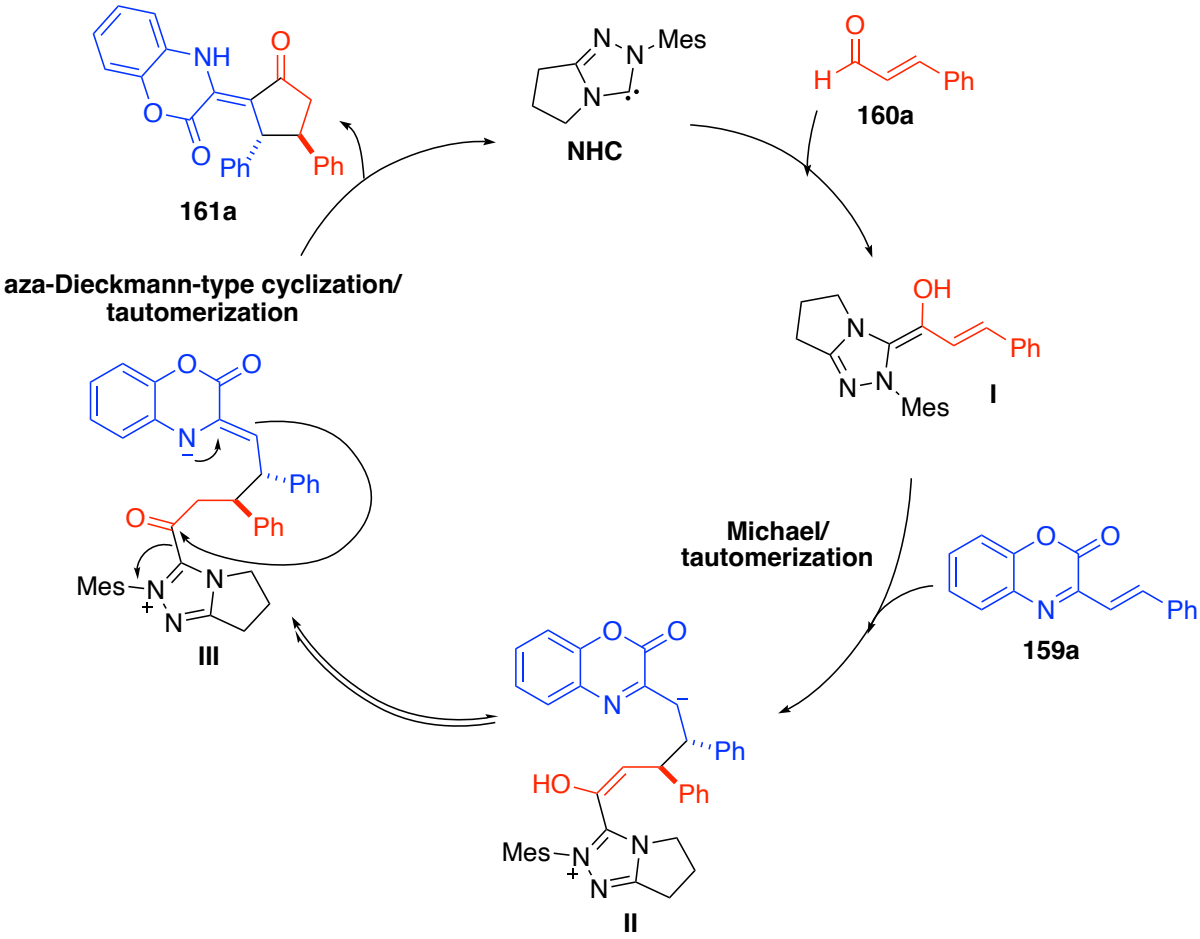


SCHEME 109: ENANTIOSELECTIVE STUDIES ON NHC CATALYSED CYCLOPENTANONE SYNTHESIS

Enantioselective studies of this reaction found that highest % ee was achieved using chiral triazolium salt NHC H as the catalyst, Et_3N as the base and a mixture of DMSO/THF (1:2 v/v) as the solvent afforded the product in 63% yield with 87 % ee (Scheme 109). Screening the substrate scope showed that all of the examples afforded low to moderate yields with acceptable ee values (**161b'-161h'**).

Compound **161a'** was determined to have stereogenic centres with absolute configuration (2R, 3R) when examined by X-ray crystallography.

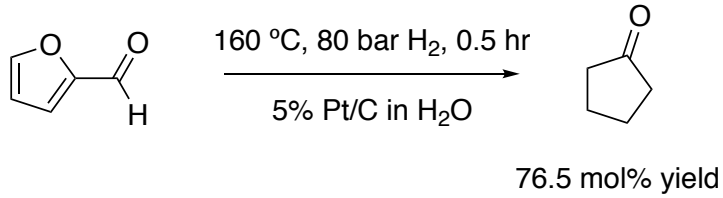
This article also proposes a reaction pathway for the [3+2] cycloaddition of β,γ-unsaturated α-ketimino esters as described in scheme 110.



SCHEME 110: PROPOSED MECHANISTIC PATHWAY FOR NHC CATALYSED CYCLOPENTANONE SYNTHESIS

3.1.1.4 Selective transformation of furfural to cyclopentanone

In 2012 Hronec and Fulajtarová published an article detailing a new highly selective preparation of cyclopentanone from furfural.[178] Not only does this work offer an effective route to cyclopentanone synthesis, but it also demonstrates a great example of the application of renewable materials for a more environmentally conscious chemical synthesis. Biomass derived furfural and 5-hydroxymethyl furfural are frequently used as starting materials and are converted into a range of different important chemical products.[179–181] However, Hronec and Fulajtarová's work is the first example of selective transformation to cyclopentanones.



SCHEME 111: CONVERSION OF FURFURAL TO CYCLOPENTANONE

It was found that highest cyclopentanone yield could be afforded through heating of furfural at 160 °C dissolved in water at reduced pressure of 80 bar in the presence of a platinum carbon catalyst. Water as the solvent medium was found to be essential for the transformation to cyclopentanone, other solvents resulted in the production of other well-known hydrogen derivatives of furfural such as furfural alcohol, tetrahydrofurfuryl alcohol, 2-methylfuran and 2-methylhydrofuran.

The influence of reaction temperature and hydrogen yield was found to differ significantly for each catalyst studied (Table 14).

TABLE 14: EFFECT OF REACTION SOLVENT ON THE TRANSFORMATION OF FURFURAL

Solvent	*Conv. %*	*C_{PON} mol%*	*C_{POL} mol%*	*FAL mol%*	*THFAL mol%*	*2-MeF mol%*	*2-MeTHF mol%*	*Σ*
Water	100	40.23	36.23	0	0.29	5.02	9.44	91.15
n-butanol	99.3	0.08	0.19	47.86	5.87	40.43	1.85	96.98
n-butanol/water (1:1 vol)	99.7	10.13	2.44	0.69	7.27	30.84	0	51.67
n-Decanol	94.5	0.18	0.13	26.34	4.78	23.17	1.09	61.10
Tetrahydrofuran	99.4	0.24	0.10	19.28	4.62	0	0	24.84

Reaction conditions: 1.0 g FA, 0.1 g 5% Pt/C, 20 mL solvent, reaction temperature 175 °C, hydrogen pressure 80 bar, reaction time 30 min; FA – furfural, CPON – cyclopentanone, CPOL – cyclopentanol, FAL – furfuryl alcohol, THFAL – tetrahydrofurfuryl alcohol, 2-MeF – 2-methylfuran, 2-MeTHF – 2-methyltetrahydrofuran, Σ - the sum of the yields and unconverted FA.

At lower reaction temperature and hydrogen pressure, palladium catalysts afforded higher yields of cyclopentanone than platinum and ruthenium catalysts. It was also discovered that at higher temperature and pressure Pd/C catalyst favoured hydrogenation of the furan ring and the aldehyde group, while Pt and Ru catalysts favoured furan ring rearrangement. Prolongation of the reaction time decreases the yield of cyclopentanone as the yield of cyclopentanol is almost proportionally increased.

TABLE 15: EFFECT OF CATALYST ON CONVERSION OF FURFURAL TO CYCLOPENTANONE

Exp. no.	*Catalyst*	*Reaction temp ℃*	*Hydrogen Pressure (bar)*	*Conversion %*	*Yield (mol%) of cyclopentanone*	*Yield (mol%) of cyclopentanol*
1	5% Pt/C	160	30	96.5	51.13	3.76
2	5% Pt/C	160[a]	80	100	76.50	4.82
3	5% Pt/C	160[a,b]	80	100	55.74	7.91
4	5% Pt/C	175	80	100	40.23	36.23
5	5% Pt/C	175[c]	80	98.08	48.40	6.45
6	5% Pd/C	160	30	97.80	67.08	0.74

7	5% Pd/C	175	80	100	38.89	3.54
8	5% Ru/C	160[d]	30	60.10	12.73	0.57
9	5% Ru/C	175	80	100	57.33	9.50
10	5% Ru/C	175[e]	80	100	4.48	48.83
11	CoMnCr	175	80	100	7.63	16.42
12	Raney Ni Actimet C	160[g]	30	100	17.46	40.01

Reaction conditions: 1.0 g FA, 20 ml water, catalyst 0.10 g, reaction time 60 min. [a] 0.05 g catalyst, 30 min. [b] reaction time 150 min. [c] The stirring speed ca. 350 rpm, [d] 30 min., [e] From the reaction mixture of exp. no. 9 Ru/C catalyst was separated and after the addition of 0.1 g of fresh 5% Pt/C catalyst the reaction. Proceeded for 60 min., [f] 0.5 g catalyst, 30 min. [g] 0.20 g catalyst.

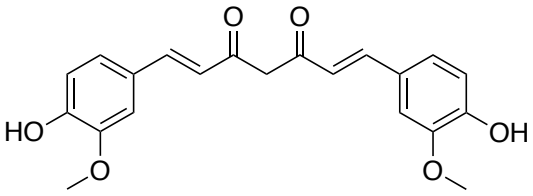
The experiments conducted with different stirring speeds (exp. no. 4 and 5) was said to suggest that the furan ring rearrangement is not cause by mass-transfer effects. It also supported the suggestion that hydrogen concentration in the liquid phase has a significant effect on the composition of cyclopentanol/cyclopentanone in the reaction mixture. The lower stirring speed was proposed to allow the majority of hydrogen dissolved in the liquid phase to be consumed during furan ring rearrangement and not for consecutive hydrogenation of primary formed cyclopentanone, which would explain the higher obtained yields for cyclopentanone at this stirring speed.

3.1.2 Reactions and applications of cyclopentanones

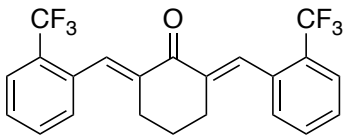
3.1.2.1 Synthesis of asymmetric C66 analogues

In 2015 Liu et al. published an article describing the use of a cyclopentanone for the synthesis of novel asymmetric C66 analogs as anti-inflammatory agents for the treatment of acute lung injury (ALI).[182] ALI is clinically proven to be a major cause of acute respiratory failure in critically-ill patients, however, despite this there is still no known effective treatment.[183] Clinical studies have shown that inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) play a key role in mediating the ALI process. Seeing this opportunity Liu and co-workers set to develop a range of anti-inflammatory candiates that would target these proinflammatory cytokines. Of the series of C66 analogues synthesized, the majority of them effectively inhibited lipopolysaccharide (LPS)-induced expression of TNF-α and IL-6. One compound was also found to effectively reduce LPS-induced pulmonary inflammation and *in vivo* administration of this compound resulted in remarkable improvement in histopathological changes of lung in rats.

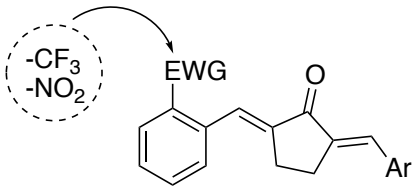
Previous work by the group on the development of curcumin analogues noted that introduction of tri-fluoromethyl or nitryl moieties dramatically improved stability and inhibitory effect.[184,185] Inspired by this they sought to introduce these moieties to C66 analogues in hopes it would also improve *in vitro* stability and improve pharmacokinetic profiles *in vivo*.



Curcumin



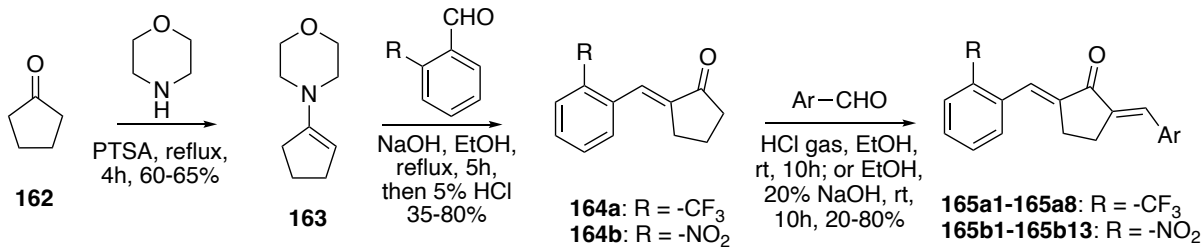
C66



asymmetric C66 analogues

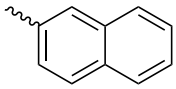
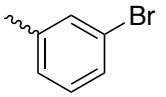
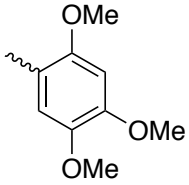
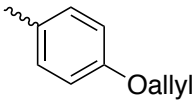
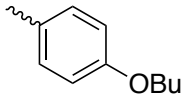
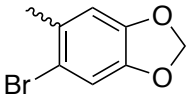
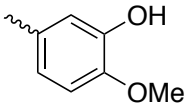
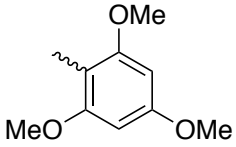
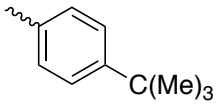
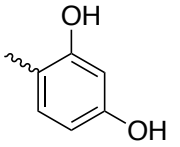
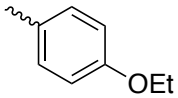
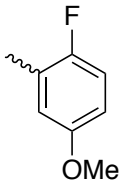
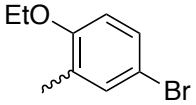
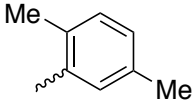
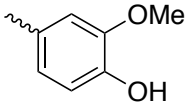
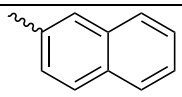
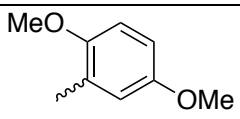
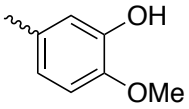
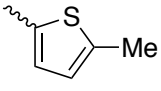
SCHEME 112: STRUCTURE OF CURCUMIN AND C66 ANALOGUES

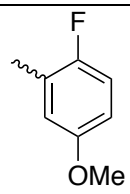
The synthesis of asymmetric C66 analogues was carried out as shown in Scheme 113. Stork reaction of cyclopentanone **162** with morpholine in the presence of *p*-Toluenesulfonic acid (*p*TSA) produced morpholine enamine **163**. Aldol condensation of this enamine with 2-CF_3 or 2-NO2 substituted benzaldehyde in ethanolic NaOH solution followed by subsequent acidation by hydrochloric acid afforded α,β-unsaturated ketones **164a**,**b** in satisfactory yield. Aldol condensation of the ketones with different aromatic aldehydes in a catalyst of 20% NaOH or HCl gases introduced various aromatic rings to the molecules and afforded the desired C66 cyclopentanone analogues in yields 30-84%.



SCHEME 113: GENERAL SYNTHETIC ROUTE FOR ASYMMETRIC C66 ANALOGUES

TABLE 16: SUBSTRATE SCOPE FOR ARYL SUBSTITUTION OF ASYMMETRIC C66 ANALOGUES

entry	Aryl substituent	Yield (%)	**entry**	Aryl substituent	Yield (%)
165a1		62.3	**165b4**		43.5
165a2		61.9	**165b5**		59.0
165a3		35.6	**165b6**		30.0
165a4		50.2	**165b7**		76.3
165a5		34.3	**165b8**		84.1
165a6		30.9	**165b9**		54.6
165a7		46.7	**165b10**		79.3
165a8		40.3	**165b11**		40.0
165b1		60.0	**165b12**		57.4
165b2		59.5	**165b13**		77.0

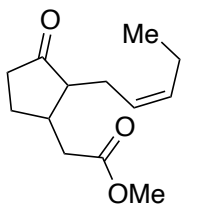
165b3		77.9			

3.1.2.2 Application for the synthesis of cyclopentanone perfumes and fragrances

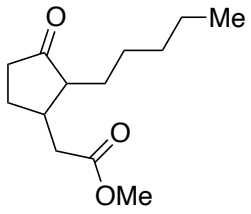
Another widely used application of cyclopentanones is their use as structural motifs in perfumes and fragrances. In 2014 Williams and Pan detailed an efficient synthesis of two such cyclopentanone derivatives; (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (**168**) and Magnolione (**169**) which are synthetic analogues of methyl jasmonate (**166**) and methyl dihydrojasmonate (**167**), respectively.[166]

Methyl jasmonate is a natural fragrant isolated from *Jasminum grandiflorum* and is frequently used in the perfume industry for its signature jasmine scent, but also interestingly, has recently been shown to display anticancer activity.[186,187] Methyl dihydrojasmonate is a naturally occurring analogue of methyl jasmonate and has been used for the manufacture of high grade perfumes, but is also found in fruits and vegetables such as cherry, asparagus, rhubarb and kiwi.[188] Magnolione has been commercialized by Givaudan, and is noted to be less biodegradable and exhibits a more intense jasminic scent than methyl dihydrojasmonate.[189]

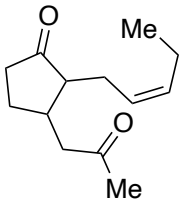
Interestingly, for **166**, **167** and **169** only the 2*S*,3*R*-isomers are found to possess an intense floral fragrance and consequently access to other jasmonoids with enriched 2*S*,3*R*-isomer content is highly desirable to synthetic chemists for use in the fragrance industry.[186]



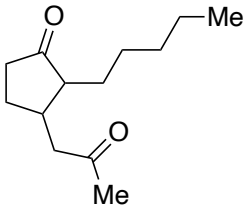
Methyl jasmonate (**166**)



Methyl dihydrojasmonate (**167**)



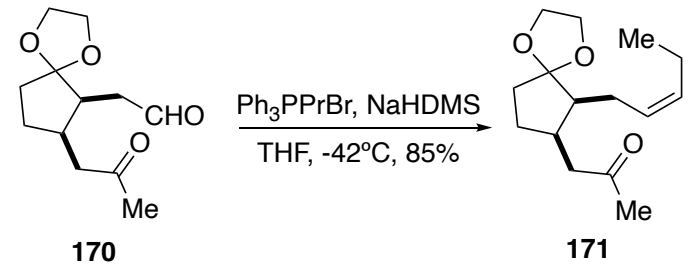
(*Z*)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (**168**)



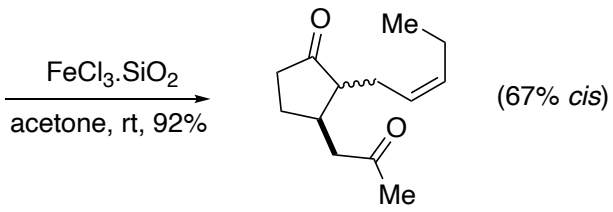
Magnolione® (**169**)

SCHEME 114: STRUCTURE OF SOME JASMONOID FRAGRANCES

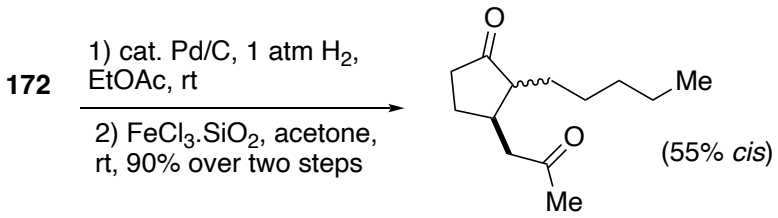
Keto-aldehyde **170** was treated with triphenyl(propylidene)phosphorane, generated in situ from *n*-propyltriphenylphosphonium bromide and NaHDMS, to afford *Z*-alkene **171** in 85% yield. De-ketalization of **171** with $FeCl_3.SiO_2$ in acetone provided (Z)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (67% cis). Catalystic dehydrogenation of **171** followed by treatment with $FeCl_3.SiO_2$ afforded Magnolione (**169**) (55% cis).



170 **171**



(*Z*)-3-(2-oxopropyl)-2-(pent-2-en-1-yl)cyclopentanone (**168**)



Magnolione® (**169**)

SCHEME 115: SYNTHESIS OF (Z)-3-(2-OXOPROPYL)-2-(PENT-2-EN-1-YL)CYCLOPENTANONE AND MAGNOLIONE

3.1.2.3 Synthesis of cyclopentamine

Cyclopentamine is classified as a vasoconstrictor, and was sold as an over the counter treatment for nasal congestion across Europe and Australia, however, has since been discontinued due to the increased safety, effectiveness and availability of a similar drug, propylhexedrine.[190,191] Cyclopentamine is structurally very similar to methamphetamine, with the phenyl ring of methamphetamine being placed with a cyclopentane ring. Like other amphetamine drugs, cyclopentamine is also a stimulant drug and can produce the same effects as amphetamine and methamphetamine in large enough doses.[192] Cylopentamine acts as a releasing agent to the catecholamine neurotransmitters noradrenaline, adrenaline and dopamine.[193,194]

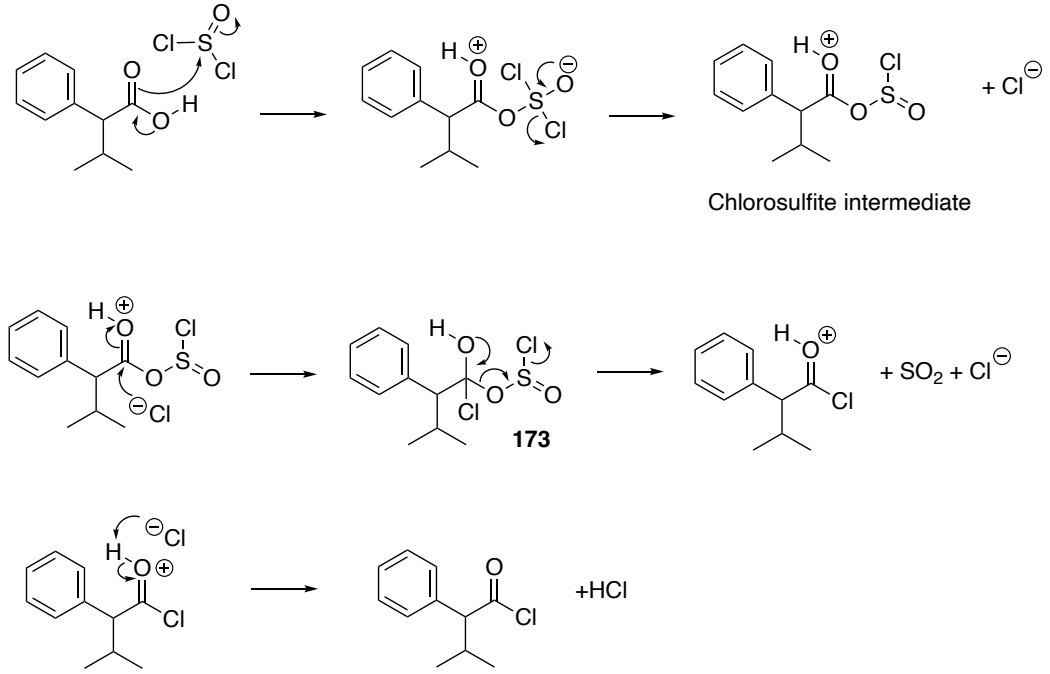
Despite being discontinued as a nasal decongestant, cyclopentamine still acts as an important industrial intermediate, particularly for the production of fungicides based on N-benzyl-cycloalkylamines.[195]

3.2: Results and Discussion

Though the group has previous success in the synthesis of cyclopentanones through dual Lewis acid-catalysed [3+2]-cycloaddition of donor acceptor cyclopropanes with ketenes, it is not without its difficulties. [196] As previously discussed, ketenes are extremely reactive compounds which is what makes them such attractive reactant partners. However, this reactivity also makes them difficult to handle, with a propensity for polymerization when exposed to air/moisture. *In situ* ketene generation offers a solution to this by limiting the ketenes opportunities to react with air or moisture by eliminating the need for storage between reactions and the transfer of the ketene from the storage to the reaction vessel. It was also envisioned that this reaction may offer a route to more substituted cyclopentanones through the use of disubstituted acyl chlorides for ketene generation.

3.2.1 Synthesis of starting materials and proposed mechanisms

α-Isopropylphenyl acetyl chloride was prepared as a precursor for ketene synthesis. It was successfully prepared in 89% yield through reflux of α-isopropylphenyl acetic acid in thionyl chloride. The mechanism for this reaction is shown in Scheme 116. Nucleophilic attack on thionyl chloride occurs and as the S=O double bond is reformed a Cl is lost. A chlorosulfite intermediate is formed at the hydroxy group of the carboxylic acid. Nucleophilic attack on the carbonyl by a chloride ion in solution forms intermediate **173**. The carbonyl double bond is reformed and the leaving group is lost from the molecule as SO_2 and a chloride ion. Finally, deprotonation occurs through abstraction of the hydrogen atom by free chlorine anions in solution to give the desired acyl chloride along with HCl byproduct.

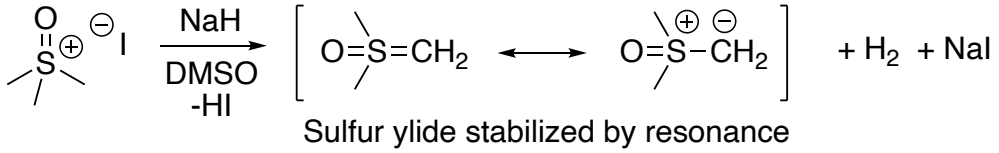


SCHEME 116: MECHANISM FOR THE SYNTHESIS OF α-ISOPROPYLPHENYL ACETYL CHLORIDE

With the exception of 1,1-diethyl 2-(2-thienyl)-1,1-cyclopropanedicarboxylate and diethyl 2-phenoxycyclopropane-1,1-dicarboxylate, all cyclopropanes used were previously prepared by Mukulesh Mondal.[196,197]

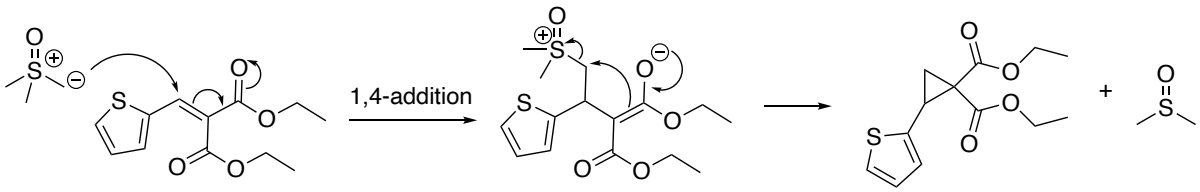
3.2.1.1 Synthesis of 1,1-diethyl 2-(2-thienyl)-1,1-cyclopropanedicarboxylate

1,1-Diethyl 2-(2-thienyl)-1,1-cyclopropanedicarboxylate was prepared via Corey-Chaykovksy cyclopropanation with Michael Inititated Ring Closure (MIRC). The sulfur ylide, dimethylsulfoxonium methylide, is generated *in situ* from trimethylsulfoxonium iodide in the presence of a strong base according to Scheme 117.



SCHEME 117: IN SITU GENERATION OF DIMETHYLSULFOXONIUM METHYLIDE

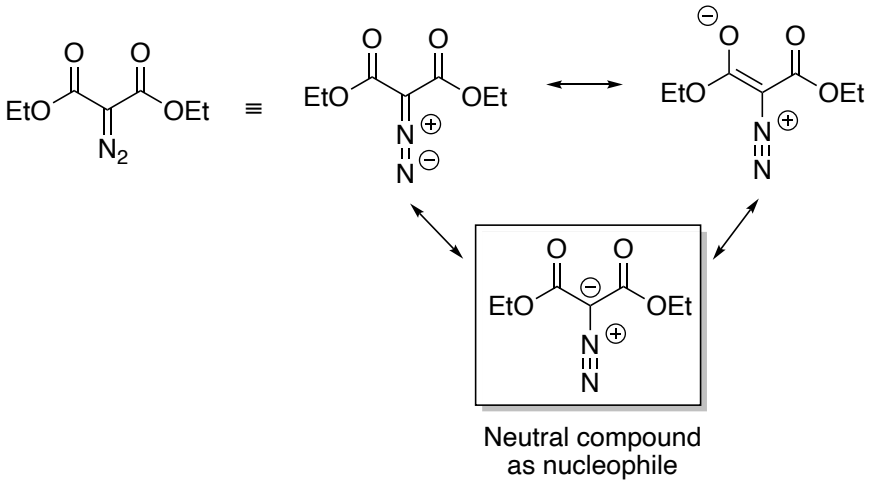
The first step is a 1,4-addition and involves the nucleophilic attack of the ylide carbon bearing the negative charge to the electrophilic carbon (β-position) in the carbon-carbon double bond of the starting material diethyl 2-(thiophen-2-ylmethylene)malonate. Michael induced intramolecular ring closure with loss of dimethyl sulfoxide affords the desired donor-acceptor cyclopropane.



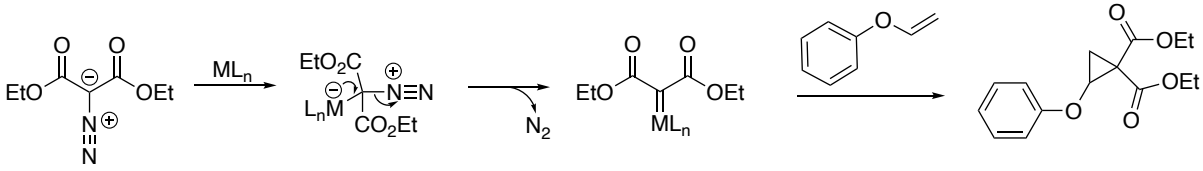
SCHEME 118: MECHANISM FOR THE SYNTHESIS OF 1,1-DIETHYL 2-(2-THIENYL)-1,1-CYCLOPROPANEDICARBOXYLATE VIA COREY-CHAYKOVKSY CYCLOPROPANATION

3.2.1.2 Synthesis of diethyl 2-phenoxycyclopropane-1,1-dicarboxylate

The synthesis of diethyl 2-phenoxycyclopropane-1,1-dicarboxylate was carried out according to literature publication by Garve and co-workers.[198] The proposed mechanism for this reaction is outlined in Scheme 119.



SCHEME 119: RESONANCE STRUCTURES FOR DIETHYL DIAZOMALONATE



SCHEME 120: RHODIUM CATALYZED SYNTHESIS OF DIETHYL 2-PHENOXYCYCLOPROPANE-1,1-DICARBOXYLATE

3.2.2 Synthesis of cyclopentanones

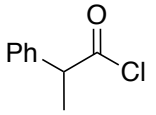
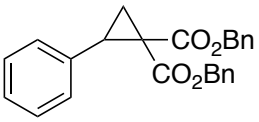
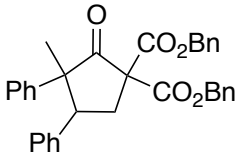
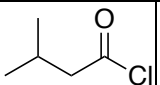
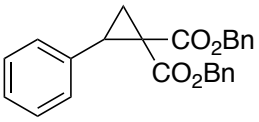
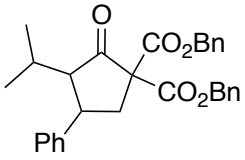
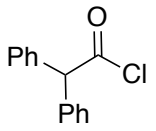
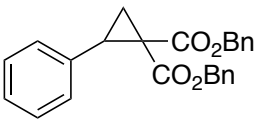
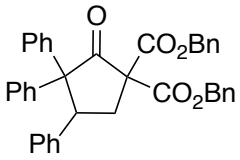
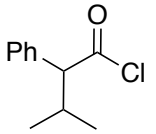
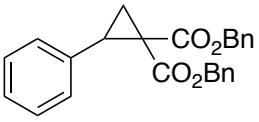
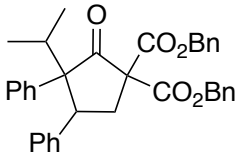
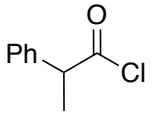
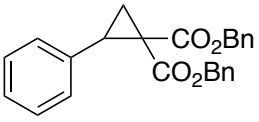
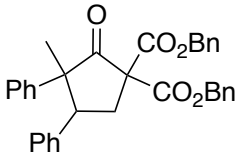
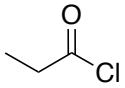
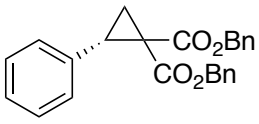
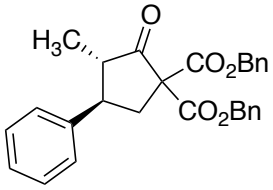
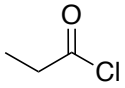
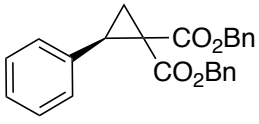
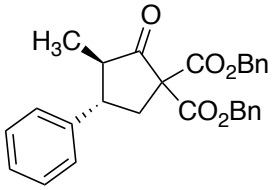
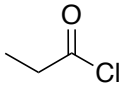
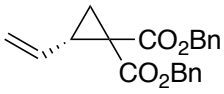
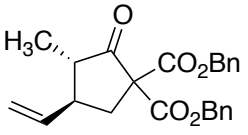
The use of disubstituted acyl chlorides for ketene generation was first investigated. It was hoped that, if successful, access to more substituted cyclopentanones would be possible. 2-phenylbutyryl chloride, diphenyl-acetyl chloride and α-isopropylphenyl acetyl chloride were all investigated for this purpose.

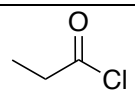
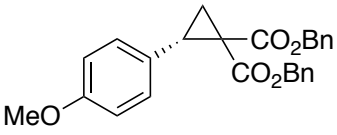
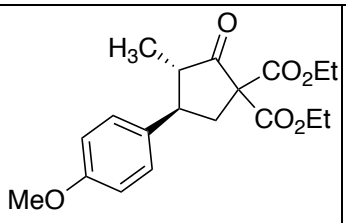
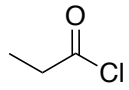
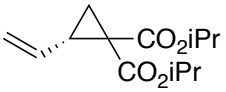
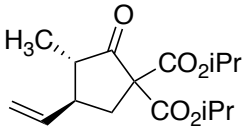
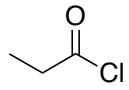
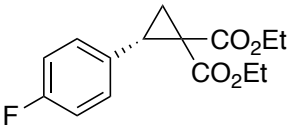
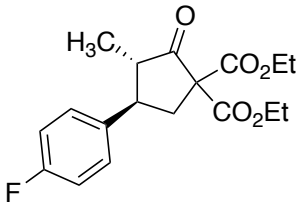
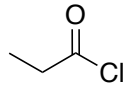
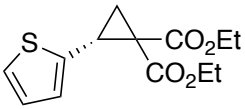
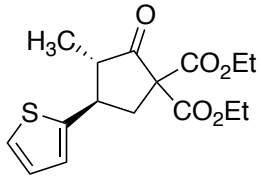
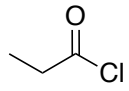
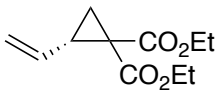
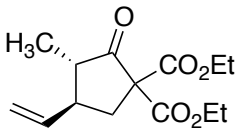
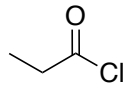
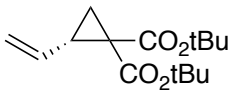
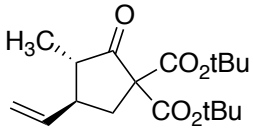
Unfortunately, this was not successful. There are a few possible reasons why this reaction did not progress as hoped. It is possible that the presence of an additional group alpha to the carbonyl in the acyl chloride causes some steric hindrance, making the necessary step of abstraction of an alpha-proton by the amine more difficult. If the ketene is generated in situ, absence of cyclopentanone ring-formation may be explained through a combination of other issues. Disubstituted alkylarylketenes are more stabilized than asymmetric monosubstituted ketenes, so if there is some steric hindrance between the ketene's substituents and the phenyl ring of the cyclopropane it is possible that remaining as a ketene in solution is more favoured than the desired ring-opening.

For the reactions investigated (Table 17, entries 1-5), the Lewis base triethylamine was added to facilitate ketene formation as it had previously proven successful in the literature.[199,200] Bearing these factors in mind some modifications to the reaction were made. Propionyl chloride was instead used as the ketene precursor, although this would mean substitution at the C_3 position of the cyclopentanone would be limited it would also reduce any unfavourable steric interactions and formation of an asymmetric monoketene would hopefully encourage cyclization. N-N-diisopropylethylamine (DIPEA) was investigated as a base.

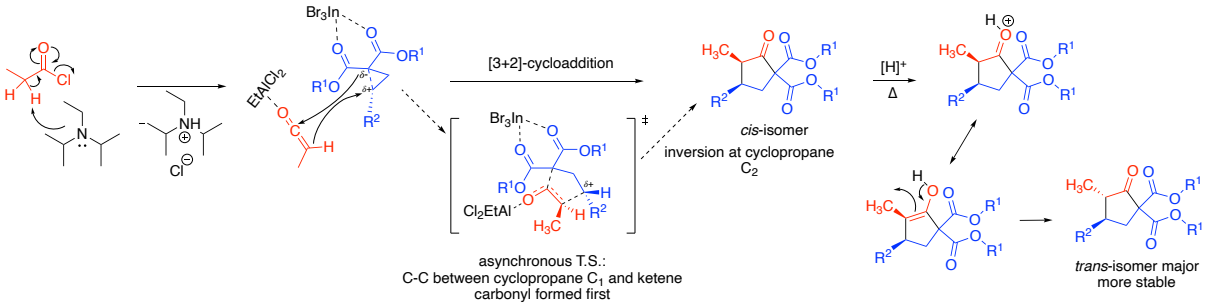
To our delight, reaction of dibenzyl (*S*)-2-phenylcyclopropane-1,1-dicarboxylate under these conditions afforded the desired cyclopentanone in excellent yield and diastereoselectivity (87%, 25.2 *dr*) (Table 17, entry 6). Access to more varied substitution on the cyclopentanones was achieved through reaction with various donor-acceptor cyclopropanes. The reaction was found to tolerate variation in both the donor and acceptor group within the cyclopropane. The C_4 of the cyclopentanone was very tolerant to a range of electron-withdrawing substituents including *p*-methoxyphenyl, *p*-fluorophenyl and thiophenyl (Table 17 entries 9, 11 and 12). Modification of the ester group of the acceptor portion of the cyclopropane was also well tolerated yielding the desired cyclopentanone in moderate to very good yields (56-81%, Table 17 entries 9-14). This reaction was also found to be suitable for gram scale synthesis with the desired cyclopentanone being formed in 92% yield.

TABLE 17: PREPARATION OF CYCLOPENTANONES

Entry	*Acyl chloride*	*Cyclopropane*	*Product*	*Yield*	*dr*
1[a]				N/A	N/A
2[a]				N/A	N/A
3[b]				N/A	N/A
4[a]				N/A	N/A
5[c]				N/A	N/A
6				87%	25.2:1
7				92%	26.5:1
8				81%	16.7:1

9				81%	20.0:1
10				68%	5.8:1
11				79%	12.2:1
12				74%	36.8:1
13				71%	3.6:1
14				56%	3.0:1

[a]follows procedure 3.3.6, [b] follows procedure 3.3.7, [c] follows procedure 3.3.8, all other entries follow procedure 3.3.5.

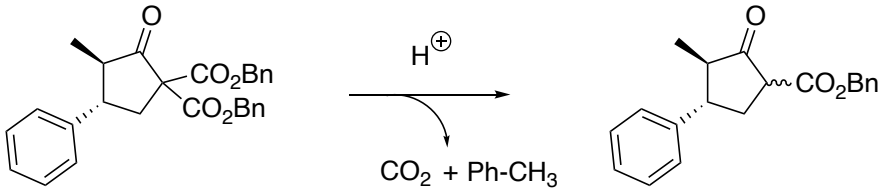


SCHEME 121: PROPOSED MECHANISM FOR CYCLOPENTANONE SYNTHESIS

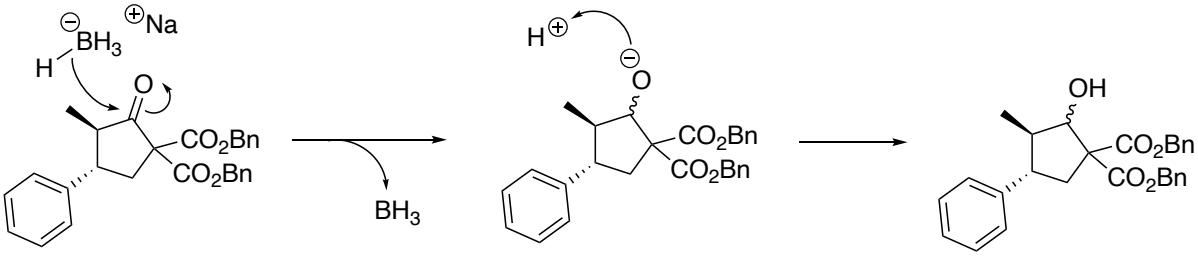
The proposed mechanism for the synthesis of cyclopentanones from monoketenes is outlined in Scheme 121. DIPEA abstracts a proton from the propionyl chloride which causes an α,β-carbon double bond to form in tandem with opening of the carbonyl double bond. The carbonyl double bond reforms with subsequent loss of the chlorine group. This chloride ion has a secondary function in stabilizing the DIPEA cation. Addition of the $InBr_3$ increases the electron-withdrawing effect of the acceptor portion of the D-A cyclopropane. However cycloaddition of the ketene to the cyclopropane does not occur until addition of $EtAlCl_2$. The addition of $EtAlCl_2$ activates the ketene, allowing the C_1-C_5 bond to form through attack of the ketene carbonyl by the C_1 carbon of the $InBr_3$-DA cyclopropane complex. The second C-C bond forming event takes place through the transition state outlined in Scheme 121, inversion of stereochemistry at cyclopropane C_2 occurs to initially provide the *cis*-product as the major diastereoisomer. Equilibrium under the basic conditions (use of excess *i*-Pr_2NEt) results in the formation of the *trans*-isomer as the major product. Exposure of the crude products to silica also lead to further improvements in diastereoselectivity to a useful level (dr .20:1), favouring the *trans*-isomer as the major isomer.

3.2.3 Reactions of cyclopentanone

Activated esters are often required functional groups for a variety of reactions, however it is important that it can be removed and replaced with a hydrogen once it's purpose has been fulfilled. For this reason, hydrolysis-decarboxylation of the ester-substituted cyclopentanone was carried out. The cyclopentanone was subjected to reaction with lithium hydroxide in a solution of THF and water. The water is essential for the lithium hydroxide to act as a strong base. This was allowed to stir at room temperature overnight and the next day the THF was evaporated and the pH was adjusted to be at least pH 3, this ensures that there is enough free hydrogen ions in solution to quench the reaction and supply C1 with a hydrogen source. This reaction was successful with a 43% yield and with excellent diastereoselectivity (dr 15.5:1).



Reduction of the cyclopentanone carbonyl to an alcohol was also investigated. This reaction occurred through two steps. The first step involves the 1,2-addition of a hydride ion to the cyclopentanone carbonyl, breaking the carbonyl double bond. The second step is protonation by which the free electron on the oxygen abstracts a proton from solution to form the alcohol group. The desired product was formed in 68% yield as a mixture of isomers.

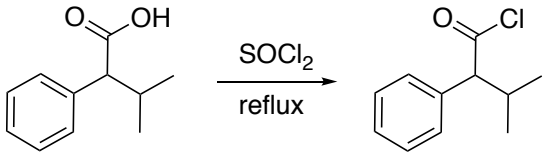


3.2 Experimental

General Information

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard inert atmosphere technique unless otherwise stated. THF was dried using a sodium/benzophenone ketyl still, and N,N,N-triethylamine and N,N-diisopropylethylamine were distilled from potassium hydroxide under nitrogen. Phenyl vinyl ether, 2-thiophenecarboxyaldehyde, piperidine, acetic acid, diethyl malonate, diphenylacetyl chloride, ethylphenylacetyl chloride were purchased from Aldrich Chemical Co. and used as received. Propionyl chloride and ethylaluminium dichloride were purchased from Aldrich Chemical Co. and distilled prior to use. With the exception of 1,1-diethyl 2-(2-thienyl)-1,1-cyclopropanedicarboxylate and diethyl 2-phenoxycyclopropane-1,1-dicarboxylate, all cyclopropanes used were previously prepared by Mukulesh Mondal.[196,197] Iatrobeads (neutral silica, Bioscan, 6RS-8060, 60 μM particle size) and TLC plates (Sorbent Technologies, UV254, 250 μM) were used as received. NMR spectra were recorded on a Bruker Avance III 600 spectrometer (600 MHz for ^{1}H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to $CDCl_3$ (17.26 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra.

3.3.1 Synthesis of α-isopropylphenyl acetyl chloride

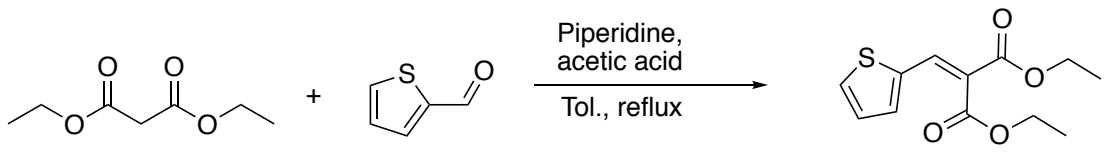


α-isopropylphenyl acetic acid (1.0g, 5.6 mmol) was refluxed in thionyl chloride (6.5 mL) at 75 °C overnight (not under inert reaction conditions). The next day the thionyl chloride was distilled off at 100 °C. When all of the thionyl chloride was removed the set-up was changed to short path distillation and the acyl chloride was collected under vacuum at 125 °C (0.89 g, 89% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 – 7.28 (m, 2H), 7.28 – 7.25 (m, 1H), 7.25 – 7.20 (m, 2H), 3.64 – 3.62 (d, 1H), 2.44 – 2.36 (m, 1H), 1.11 – 1.10 (d, 3H), 0.70 – 0.69 (d, 3H)

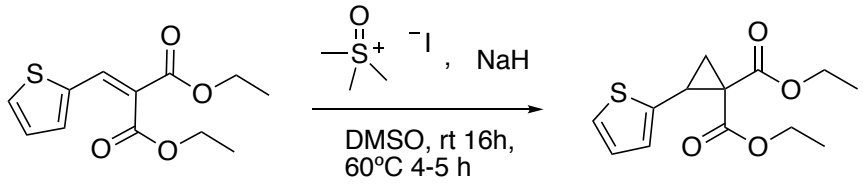
^{13}C NMR (150 MHz, $CDCl_3$): 174.7, 135.0, 129.0, 128.9, 128.3, 71.8, 32.1, 21.3, 19.8

3.3.2 Synthesis of diethyl 2-(thiophen-2-ylmethylene)malonate



To a flask set up with Dean-Stark apparatus was added diethyl malonate (7.80 g, 49.0 mmol, 1.10 equiv) and 2-thiophene carboxaldehyde (4.10 mL, 44.5 mmol, 1.0 equiv) in toluene (70 mL). Piperidine (0.57 g, 6.6 mmol, 0.15 equiv) and acetic acid (0.38 mL, 6.6 mmol, 0.15 equiv) were added to the flask. The solution was allowed to reflux overnight until the water level in the graduated arm of the Dean-stark apparatus indicated complete conversion to product. The reaction was extracted using water (3 × 50 mL) and the organic layer was dried over Na_2SO_4. The organics were evaporated under reduced pressure and the remaining toluene was removed from the product by running through a silica plug with hexane. The toluene was collected first along with the remaining starting material and then the product was removed with 2% EtOAc/hexane to afford diethyl 2-(thiophen-2-ylmethylene)malonate as a pink oil (7.96 g, 64% (determined by NMR)). Product determined impure by NMR analysis as removal of toluene was difficult without degradation of product. Impure product used for cyclopropane synthesis.

3.3.3 Synthesis of 1,1-diethyl 2-(2-thienyl)-1,1-cyclopropanedicarboxylate

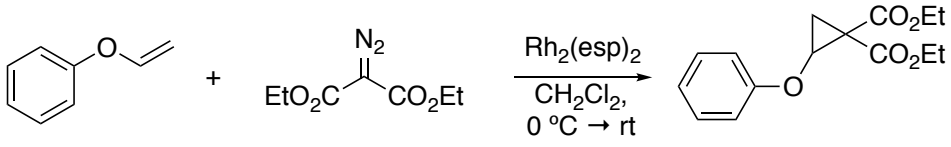


NaH (60% dispersion in oil, 0.420 g, 10.6 mmol, 1.8 equiv) was washed with hexanes (3 × 4mL) and the excess hexane was removed under vacuum. DMSO (5 mnL) was added and trimethylsulfoxonium iodide (2.33 g, 10.6 mmol, 1.8 equiv) was added quickly via funnel. The flask was cooled to 0 °C. Diethyl 2-(thiophen-2-ylmethylene)malonate (1.50 g, 5.89 mmol, 1.0 equiv) in DMSO (2 mL) was added and stirred overnight at rt. The next day the reaction was heated to 60°C and stirred for 4-5 h. The reaction was then cooled to rt and the reaction mass was added to ice-cold water. Pet. Ether (20 mL) was added and the layers separated. The aqueous layer was washed with pet. ether (2 × 20 mL) and the combined organics were washed with aqueous saturated brine solution (30 mL). The organics were dried over Na_2SO_4 and subsequently evaporated under reduced pressure to afford the product as a colourless oil (0.98 g, 62% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.15 – 7.14 (m, 1H), 6.89 – 6.88 (m, 1H), 6.83 – 6.82 (m, 1H), 4.28 – 4.23 (m, 1H), 4.22 – 4.16 (m, 2H), 3.98 – 3.90 (m, 2H), 2.13 – 2.11 (m, 1H), 1.80 – 1.77 (q, 1H, J_1 = 5.1 Hz, J_2 = 9.2 Hz), 1.28 (t, 3H, J = 7.1 Hz), 0.98 (t, 3H, J = 7.1 Hz)

^{13}C NMR (150 MHz, $CDCl_3$): 170.2, 169,4, 138.3, 126.6, 126.1, 124.9, 61.8, 61.4, 38.1, 26.9, 20.6, 14.1, 13.7

3.3.4 Synthesis of diethyl 2-phenoxycyclopropane-1,1-dicarboxylate



Procedure followed as published by Werz et al.[198]

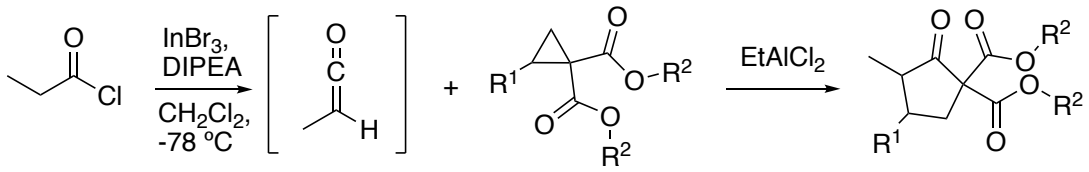
$Rh_2(esp)_2$ (2.0 mg, 0.1 mol%) was added to a flask and dried under vacuum for 15 minutes. Parallelly, phenyl vinyl ether (0.11g, 0.89 mmol, 1.0 equiv) was added to a flask and diethyl-2-diazomalonate (0.20 g, 0.11 mmol, 1.2 equiv) was added to a different flask and both were

dried under vacuum for 15 minutes. To the $Rh_2(esp)_2$ was added 2 mL of dry CH_2Cl_2 to afford a green/blue clear solution and the temperature was lowered to 0-5 °C. 3 mL of dry CH_2Cl_2 was added to the phenyl vinyl ether and this was added to the flask at 0-5 °C. The diethyl-2-diazomalonate in 2 mL CH_2Cl_2 was added dropwise to the solution over 10 minutes. After complete addition the reaction was stirred overnight at rt. The next day the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography with 2-3% EtOAc/Hexane (0.10 g, 40% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.28 (m, 2H), 7.03 – 7.01 (m, 3H), 4.51 – 4.49 (m, 1H), 4.31 – 4.23 (m, 2H), 4.11 – 4.04 (m, 2H), 2.19 – 2.17 (m, 1H), 1.74 – 1.72 (m, 1H), 1.34 – 1.31 (m, 3H), 1.0218 (t, 3H, J = 7.14 Hz)

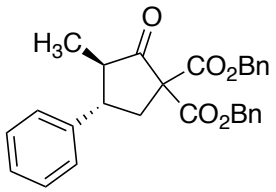
^{13}C NMR (150 MHz, $CDCl_3$): 168.7, 165.4, 157.4, 129.4, 130.0, 115.1, 61.8, 61.6, 60.4, 35.8, 20.4, 14.1, 13.7

3.3.5 General procedure A for synthesis of cyclopentanones



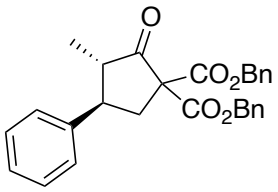
$InBr_3$ (0.06 mmol, 0.3 equiv) was added to a flask and dried under vacuum for 30 min. The flask was then N_2 flushed and dry CH_2Cl_2 (7 mL) was added and the solution was cooled to -78 °C. At -78 °C the acyl chloride (1.02 mmol, 5.0 equiv) was added to the solution, and then diisopropylethylamine (1.06 mmol, 5.2 equiv) was added dropwise over 15 min. A solution of the cyclopropane (0.21 mmol, 1.0 equiv) in dry CH_2Cl_2 (2 mL) was added to the main reaction flask via syringe pump over a period of 1 h. After addition of half of the cyclopropane solution, $EtAlCl_2$ (1.0M in hexanes, 0.51 mmol, 2.5 equiv) was added dropwise and the reaction was allowed to stir at -78 °C for 4 h. The reaction was quenched at -78 °C with 1:2 Et_3N:MeOH (1 mL) and the reaction mass was then added to 10% HCl (20 mL). The mixture was extracted with CH_2Cl_2 and the combined organics were washed with water (30 mL) followed by aqueous saturated brine solution (30 mL). The organics were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (15 mL) and sufficient silica (5.0 g) was added to saturate the solution. This was stirred at 50 °C for 2 h and then washed with CH_2Cl_2 (100 mL) over celite. The collected organics were evaporated under reduced pressure to afford desired cyclopentanone as a colourless/yellow gum. All products were purified by flash column chromatography.

Dibenzyl (3R,4S)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate



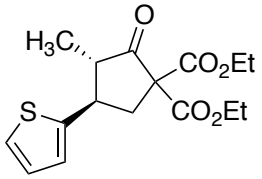
Colourless gum (71 mg of major isomer and 23 mg as mixture of isomers, 92%). Rf = 0.4 (EtOAc/hexanes 1:9); dr = 26.5:1 (by crude ^{1}H NMR analysis); HPLC analysis: 90% ee [Daicel Chiralcel AD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention times: 10.2 min (minor), 10.8 min (major)]; $[\alpha]_D^{24}$ = +33 (c = 0.1, CH_2Cl_2); IR (thin film) 3031, 2928, 1766, 1723, 1497, 1454, 1375, 1258, 1175, 959, 738, 696 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.34 – 7.27 (m, 13H), 7.19 (d, 2H, J = 7.3 Hz), 5.25 – 5.17 (m, 4H), 2.91 (dd, 1H, J_1 = 6.2 Hz, J_2 = 13.3 Hz), 2.86 – 2.80 (m, 1H), 2.58 (app. t, 1H, J = 12.8 Hz), 2.47 – 2.42 (m, 1H), 1.05 (d, 3H, J = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.3, 167.0, 166.7, 140.6, 135.2, 135.1, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 127.5, 127.3, 68.3, 68.2, 68.0, 51.5, 47.3, 39.0, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{28}H_{27}O_5)^+$: 443.1858; found: 443.1852.

Dibenzyl (3*S*,4*R*)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate



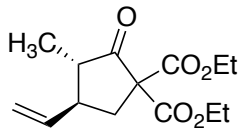
Colourless gum (42 mg of major isomer and 13 mg as mixture of isomers, 87%). Rf = 0.4 (EtOAc/hexanes 1:9); dr = 25.2:1 (by crude ^{1}H NMR analysis); HPLC analysis: 90% ee [Daicel Chiralcel AD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention times: 10.2 min (minor), 10.8 min (major)]; $[\alpha]_D^{24}$ = -41 (c = 0.07, CH_2Cl_2); IR (thin film) 3031, 2929, 1766, 1731, 1497, 1454, 1375, 1260, 1176, 960, 748, 697 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.35 – 7.29, (m, 12H), 7.29 – 7.27 (m, 1H), 7.29 – 7.19 (m, 2H), 5.26 – 5.19 (m, 4H), 2.92 (dd, 1H, J_1 = 6.2 Hz, J_2 = 13.3 Hz), 2.87 – 2.82 (m, 1H), 2.59 (dd, 1H, J_1 = 12.6 Hz, J_2 = 13.1 Hz), 2.49 – 2.43 (m, 1H), 1.06 (d, 3H, J = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.4, 167.0, 166.7, 140.6, 135.2, 135.1, 129.0, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 127.5, 127.3, 68.3, 68.2, 68.0, 39.0, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{28}H_{27}O_5)^+$: 443.1858; found: 443.1861.

Diethyl (3*S*,4*R*)-3-methyl-2-oxo-4-(thiophen-2-yl)cyclopentane-1,1-dicarboxylate



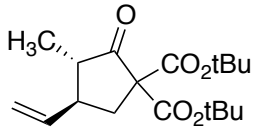
Yellow gum (75 mg of major isomer and 14 mg as mixture of isomers, 74%). Rf = 0.5 (EtOAc/hexanes 2:8); dr = 36.8:1 (by crude ^{1}H NMR analysis); IR (thin film) 2980, 1768, 1732, 1445, 1366, 1257, 1189, 1017, 938, 734 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.23 (dd, 1H, J_1 = 1.1 Hz, J_2 = 5.2 Hz), 7.00 – 6.98 (m, 1H), 6.94 – 6.93 (m, 1H), 4.30 – 4.25 (m, 4H), 3.23 – 3.18 (m, 1H), 3.03 (dd, 1H, J_1 = 6.1 Hz, J_2 = 13.4 Hz), 2.62 – 2.58 (m, 1H), 2.46 – 2.40 (m, 1H), 1.32 – 1.28 (m, 6H), 1.21 (d, 3H, J = 6.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): δ 206.1, 166.9, 166.8, 144.8, 127.2, 124.4, 124.0, 68.3, 62.7, 62.6, 53.6, 52.5, 42.6, 39.8, 14.1, 13.3; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{21}O_5S)^+$: 325.1110; found: 325.1106.

Diethyl (3*S*,4*S*)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate



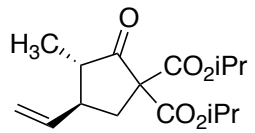
Colourless oil (40 mg of major isomer and 49 mg as mixture of isomers, 71%). Rf = 0.4 (EtOAc/hexanes 0.8:9.2); dr = 3.6:1 (by crude ^{1}H NMR analysis); $[\alpha]_D^{24}$ = +38 (c = 0.03, CH_2Cl_2); IR (thin film) 2981, 1767, 1733, 1454, 1366, 1256, 1191, 938, 860 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 5.76 – 5.71 (m, 1H), 5.19 – 5.13 (m, 2H), 4.27 – 4.22 (m, 4H), 2.74 (dd, 1H, J_1 = 5.8 Hz, J_2 = 13.2 Hz), 2.39 – 2.32 (m, 1H), 2.27 (dd, 1H, J_1 = 12.3 Hz, J_2 = 13.0 Hz), 2.12 – 2.07 (m, 1H), 1.28 (t, 3H, J = 7.1 Hz) 1.27 (t, 3H, J = 7.1 Hz), 1.12 (d, 3H, J = 6.8 Hz) ^{13}C NMR (150 MHz, $CDCl_3$): 207.1, 167.2, 167.0, 138.6, 116.9, 67.8, 62.5, 62.5, 49.8, 45.8, 37.1, 14.1, 12.7; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{21}O_5)^+$: 269.1389; found: 269.1390.

Di-tert-butyl (3*S*,4*S*)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate



Colourless gum (12 mg of major isomer and 29 mg as mixture of isomers, 56%). Rf = 0.5 (EtOAc/hexanes 1:9); dr = 3:1 (by crude ^{1}H NMR analysis); $[\alpha]_D^{24}$ = +2 (c = 0.09, CH_2Cl_2); IR (thin film) 2978, 1728, 1457, 1368, 1249, 1166, 1138, 1014, 847 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 5.77 – 5.71 (m, 1H), 5.18 – 5.12 (m, 2H), 2.64 (dd, 1H, J_1 = 5.9 Hz, J_2 = 13.1 Hz), 2.34 – 2.28 (m, 1H), 2.21 (app. t, 1H, J = 13.0 Hz), 2.06-2.02 (m, 1H), 1.49-1.45 (m, 18H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 207.6, 166.5, 166.3, 139.0, 116.5, 83.2, 82.8, 69.5, 49.7, 45.8, 37.1, 28.0, 28.0, 13.0; $(M + H)^+$ HRMS m/z calcd for $(C_{18}H_{28}NaO_5)^+$: 347.1834; found: 347.1830.

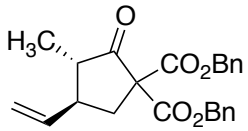
Diisopropyl (3*S*,4*S*)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate



Colourless gum (28 mg of major isomer and 54 mg as mixture of isomers, 68%). Rf = 0.4 (EtOAc/hexanes 1:9); dr = 5.8:1 (by crude ^{1}H NMR analysis); $[\alpha]_D^{24}$ = +27 (c = 0.07, CH_2Cl_2); IR (thin film) 2981, 1766, 1719, 1454, 1375, 1265, 1194, 1101, 946, 836 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 5.77 – 5.71 (m, 1H), 5.18 – 5.12 (m, 2H), 5.09 – 5.05

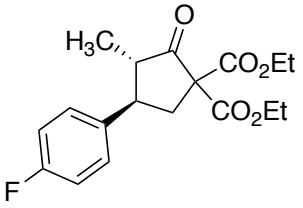
(m, 2H), 2.70 (dd, 1H, J_1 = 5.9 Hz, J_2 = 13.2 Hz), 2.35 – 2.33 (m, 1H), 2.25 (app. t, 1H, J = 13.1 Hz), 2.09-2.06 (m, 1H), 1.29-1.22 (m, 12H), 1.12 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 207.1, 166.8, 166.7, 138.8, 116.7, 70.2, 70.1, 68.0, 49.7, 45.8, 37.0, 21.7, 21.6, 21.6, 21.6, 12.8; $(M + H)^+$ HRMS m/z calcd for $(C_{16}H_{25}O_5)^+$: 297.1702; found: 297.1697.

Dibenzyl (3*S*,4*S*)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate



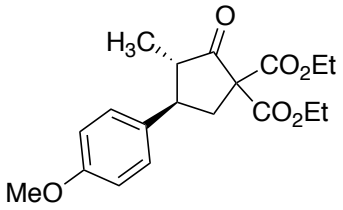
Colourless gum (36 mg of major isomer and 71 mg as mixture of isomers, 81%). Rf = 0.4 (EtOAc/hexanes 1:9); dr = 16.7:1 (by crude ^{1}H NMR analysis); $[\alpha]_D^{24}$ = -7 (c = 0.06, CH_2Cl_2); IR (thin film) 2968, 1767, 1733, 1498, 1454, 1374, 1258, 1186, 950, 737, 696 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, Major isomer): δ 7.33 – 7.30 (m, 6H), 7.29 – 7.26 (m, 4H), 5.72 – 5.67 (m, 1H), 5.21 – 5.17 (m, 4H), 5.16 – 5.11 (m, 2H), 2.76 – 2.74 (m, 1H), 2.35 – 2.31 (m, 1H), 2.30 – 2.26 (m, 1H), 2.12 – 2.07 (m, 1H), 1.08 (d, 3H, J = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, Major isomer): 206.6, 166.9, 166.7, 138.4, 135.2, 135.1, 128.7, 128.6, 128.4, 128.2, 128.1, 117.0, 68.1, 68.0, 67.8, 49.8, 45.8, 37.2, 12.6; $(M + H)^+$ HRMS m/z calcd for $(C_{24}H_{25}O_5)^+$: 393.1702; found: 393.1694.

Diethyl (3*S*,4*R*)-4-(4-fluorophenyl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate



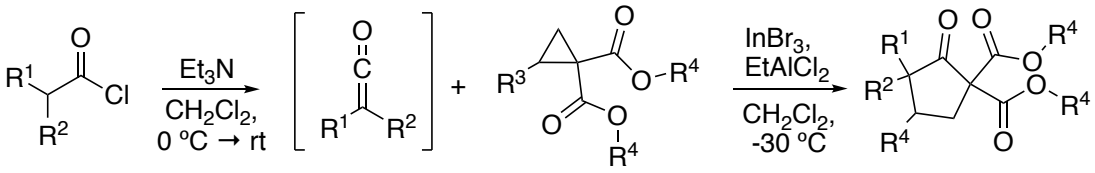
Colourless gum (32 mg of major isomer and 25 mg as mixture of isomers, 79%). Rf = 0.5 (EtOAc/hexanes 1:9); dr = 31:1 (by crude 1H NMR analysis); IR (thin film) 2981, 1767, 1733, 1511, 1454, 1367, 1257, 1187, 1015, 939, 836 cm^{-1}; 1H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.25 – 7.22 (m, 2H), 7.07 – 7.04 (m, 2H), 4.31 – 4.25 (m, 4H), 2.92 – 2.86 (m, 2H), 2.56 – 2.51 (m, 1H), 2.42-2.39 (m, 1H), 1.32-1.28 (m, 6H), 1.10 (d, 3H, J = 6.9 Hz); 13C NMR (150 MHz, $CDCl_3$, Major isomer): δ 206.4, 167.2, 166.9, 162.1 (d, J = 240 Hz, 1C), 136.4 (d, J = 2.9 Hz, 1C), 128.8 (d, J = 7.8 Hz, 1C), 115.9 (d, J = 21.0 Hz, 1C), 68.2, 62.7, 62.6, 51.6, 46.7, 39.1, 14.1, 12.9 ; $(M + H)^+$ HRMS m/z calcd for $(C_{18}H_{22}FO_5)^+$: 337.1451; found: 337.1447.

Diethyl (3*S*,4*R*)-4-(4-methoxyphenyl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate



Colourless gum (41 mg of major isomer and 17 mg as mixture of isomers, 81%). Rf = 0.4 (EtOAc/hexanes 1:9); dr = 26:1 (by crude 1H NMR analysis); IR (thin film) 2979, 1764, 1720, 1513, 1455, 1367, 1245, 1178, 1031, 938, 831 cm^{-1}; 1H NMR (600 MHz, $CDCl_3$, TMS, Major isomer): δ 7.19 – 7.17 (m, 2H), 6.91 – 6.89 (m, 2H), 4.30 – 4.25 (m, 4H), 3.81 (s, 3H), 2.91 – 2.87 (m, 1H), 2.83 (dd, 1H, J_1 = 6.2 Hz, J_2 = 12.2 Hz), 2.53 (app. t, 1H, J = 12.5 Hz), 2.42-2.39 (m, 1H), 1.32-1.28 (m, 6H), 1.09 (d, 3H, J = 6.8 Hz); 13C NMR (150 MHz, $CDCl_3$, Major isomer): δ 206.9, 167.3, 167.0, 158.9, 132.7, 128.2, 114.4, 68.3, 62.6, 62.5, 55.4, 51.6, 46.6, 39.2, 14.1, 12.9; $(M - H)^-$ HRMS m/z calcd for $(C_{19}H_{23}O_6)^-$: 347.1495; found: 347.1494.

3.3.6 General procedure B for synthesis of cyclopentanones



12 mL of dry CH_2Cl_2 was added to a flask followed by the acyl chloride (0.78 mmol, 5.0 equiv) the temperature was then lowered to 0 °C and the Et_3N (0.08 g, 0.81 mmol, 5.2 equiv) was added dropwise (canary yellow colour observed). This was raised to rt and stirred for 3 hours. To a flask was added $InBr_3$ (16.4 mg, 30.0 mol%) and dibenzyl 2-phenylcyclopropane-1,1-dicarboxylate (0.06 g, 0.16 mmol, 1.0 equiv) was added to a flask and dried under vacuum for 1 hour. 7 mL of dry CH_2Cl_2 was added to the cyclopropane and $InBr_3$ and brought down to -30 °C. An additional 5 mL of dry CH_2Cl_2 was added to the flask containing the acyl chloride to ensure the white precipitate (insoluble salt of triethylamine) did not clog the needle followed by the addition of $EtAlCl_2$ (1.0M in hexanes, 0.05 g, 2.5 equiv.) dropwise. The ketene solution was added to the flask containing the cyclopropane over 4 hours using an autopipette. This was allowed to stir at -30 °C overnight. The next day the reaction was quenched with 1 mL of 1:2 Et_3N:MeOH. The reaction mass was added into 20 mL of 10% HCl solution. It was extracted with CH_2Cl_2 (2 x 25 mL) and the combined organics were washed with 30 mL of H_2O followed by 30 mL of sat. brine solution. Dried over Na_2SO_4.

3.3.7 General procedure C for synthesis of cyclopentanones

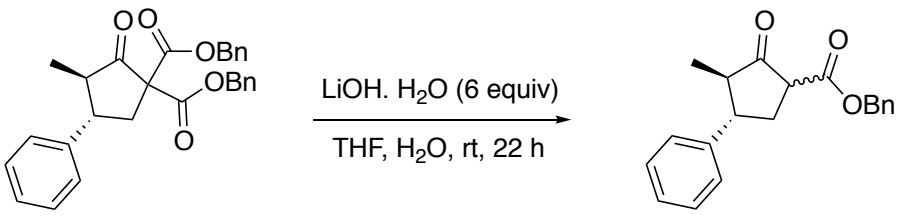
Reaction procedure as described above in general procedure B with the modification that the acyl chloride and Et_3N were allowed to stir overnight at room temperature.

3.3.8 General procedure D for synthesis of cyclopentanones

Reaction procedure as described above in general procedure B with diisobutylaluminium chloride (0.8M in hexanes) used in place of $EtAlCl_2$.

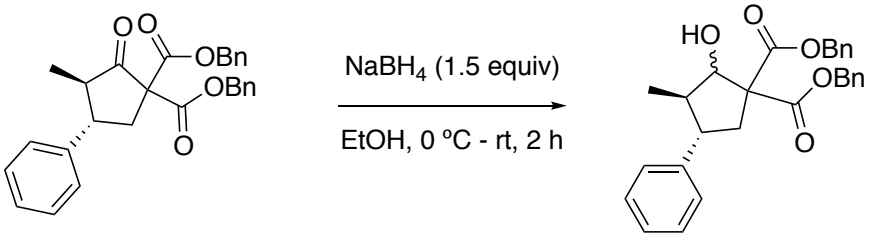
3.3.9 Reactions of cyclopentanones

Benzyl (3*R*,4*S*)-3-methyl-2-oxo-4-phenylcyclopentane-1-carboxylate



LiOH.H_2O (56 mg, 1.33 mmol) was added to a solution of dibenzyl (3*R*,4*S*)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate (100 mg, 0.22 mmol) in THF/H_2O (3:1, 4 mL) at room temperature. The reaction was then stirred at room temperature overnight (total reaction time = 22 h). After this time THF was removed under reduced pressure. Cooled water (2 mL) was added to the residue and the pH of the mixture was adjusted to at least pH = 3 by addition of 1M HCl (*ca*. 2 mL). The aqueous solution was extracted with EtOAc (3 x 5 mL), and the combined organics were dried over sodium sulfate, before filtration, and evaporation of the organics afforded the product as a colourless oil (29 mg, 43%), with *dr* = 15.5:1 (by crude ^{1}H NMR analysis); IR (thin film) 2924, 1752, 1722, 1495, 1453, 1146, 697 cm^{-1}; 1H NMR for major diastereomer (600 MHz, $CDCl_3$, TMS): δ 7.40 – 7.33 (m, 7H), 7.31 – 7.27 (m, 3H), 5.25 – 5.19 (m, 2H), 3.40 – 3.36 (m, 1H), 2.83 – 2.71 (m, 1H), 2.60 – 2.54 (m, 1H), 2.47 – 2.38 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR for major diastereomer (150 MHz, $CDCl_3$): δ 211.4, 169.3, 141.2, 135.7, 129.0, 128.8, 128.5, 128.3, 127.4, 127.3, 127.2, 67.4, 55.0, 53.6, 51.7, 48.5, 33.6, 12.3; $(M + Na)^+$ HRMS m/z calcd for $(C_{20}H_{20}NaO_3)$+: 331.1310; found: 331.1313.

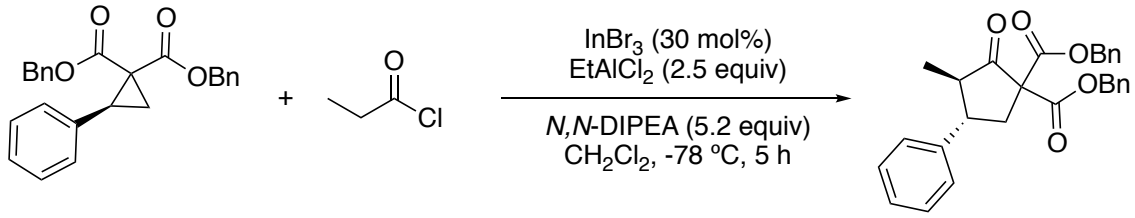
Dibenzyl (3R,4S)-2-hydroxy-3-methyl-4-phenylcyclopentane-1,1-dicarboxylate



$NaBH_4$ (13 mg, 0.34 mmol) was added in small lots to a stirring solution of dibenzyl (3*R*,4*S*)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate (100 mg, 0.22 mmol) in ethanol (3

mL) at 0-5 °C. The reaction was then stirred at room temperature for 2h. After this time cooled water (5 mL) was added to the residue in small lots and the pH of the mixture was adjusted to pH = 7 by addition of 1M HCl (*ca*. 2 mL). The ethanol was evaporated under reduced pressure. The aqueous solution was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with sat. brine solution (20 mL), dried over sodium sulfate, before filtration, and evaporation of the organic layer afforded the product as an off-white oil (23 mg of major isomer and 45 mg as mixture of isomers, 68%), with *dr* = 1.5:1 (by crude ^{1}H NMR analysis); IR (thin film) 3520, 3030, 2956, 1719, 1496, 1454, 1260, 1174, 696 cm^{-1}; ^{1}H NMR for major diastereomer (600 MHz, $CDCl_3$, TMS): δ 7.33 – 7.31 (m, 6H), 7.29 – 7.26 (m, 6H), 7.22 – 7.19 (m, 1H), 5.22 – 5.15 (m, 4H), 4.23 – 4.20 (m, 1H), 2.94 (dd, 1H, J_1 = 3.3 Hz, J_2 = 6.2 Hz), 2.65 – 2.63 (m, 1H), 2.61 – 2.59 (m, 1H), 2.57 - 2.53 (m, 1H), 2.21 - 2.19 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR for major diastereomer (150 MHz, $CDCl_3$): δ 171.8, 171.2, 142.5, 135.5, 135.3, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 128.2, 127.8, 126.8, 83.1, 67.6, 67.6, 62.7, 48.0, 47.4, 39.8, 15.4; $(M + Na)^+$ HRMS m/z calcd for $(C_{28}H_{28}NaO_5)^+$: 467.1834; found: 467.1830.

Gram scale synthesis



$InBr_3$ (0.280 g, 0.78 mmol, 0.3 equiv) was added to a flask and dried for 30 min. The flask was N_2 flushed and dry CH_2Cl_2 (70.0 mL) was added and the solution was cooled to -78 °C. At -78 °C propionyl chloride (1.12 mL, 12.9 mmol, 5.0 equiv) was added and then diisopropylethylamine (2.34 mL, 13.4 mmol) was added dropwise over 15 min. To this stirring reaction mixture, a solution of the dibenzyl (*S*)-2-phenylcyclopropane-1,1-dicarboxylate (1.00 gm, 2.6 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL) was added over a period of 1 h via syringe pump. After addition of the cyclopropane reaction mixture, $EtAlCl_2$ (1.0 M in hexanes, 6.47 mL, 6.47 mmol) was added and the reaction was stirred at -78 °C for another 4 h. The reaction was quenched at -78 °C with 1:2 Et_3N:MeOH (10.0 mL) and the reaction mass was then added into cold 10% HCl solution (200 mL). The mixture was extracted with CH_2Cl_2 (80 mL × 2) and the combined organics were washed with water (80 mL) followed by aqueous saturated brine solution (80 mL). The organics were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), added silica gel (for column chromatography, 40 g) and stirred for 2 h at 50 °C. The reaction mass was filtered and washed with CH_2Cl_2 (3 × 80 mL). The combined filtrate evaporated under reduced pressure to

afford the crude product for diastereomeric measurement. The final product was isolated as colourless gummy mass (1.122 gm, 98%), dr = 28.2:1 (by ^{1}H NMR). The product was purified by flash column chromatography with 10% EtOAc/hexane as eluent (1.05 g, 92%).

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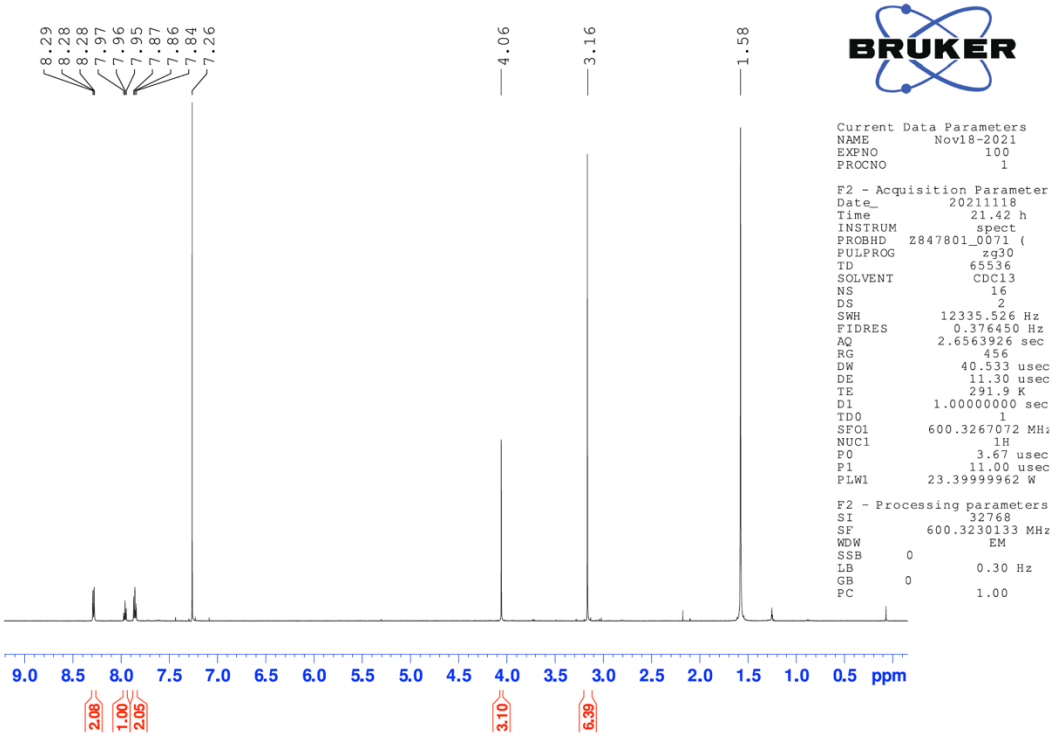
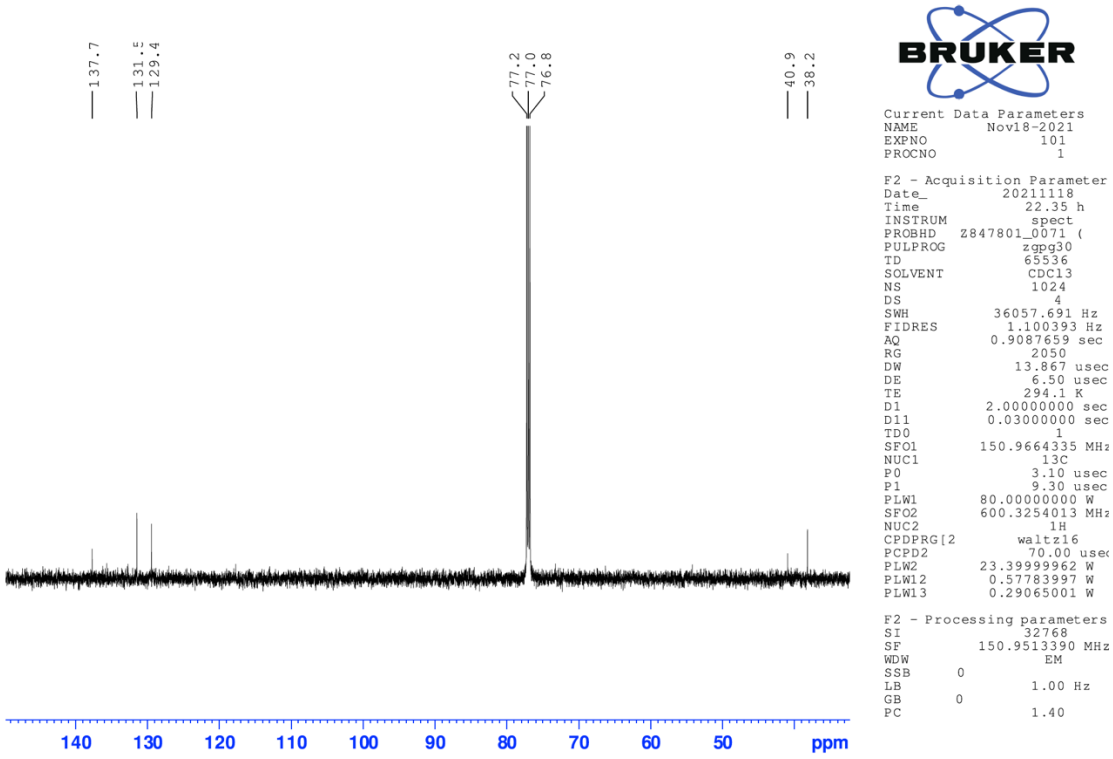
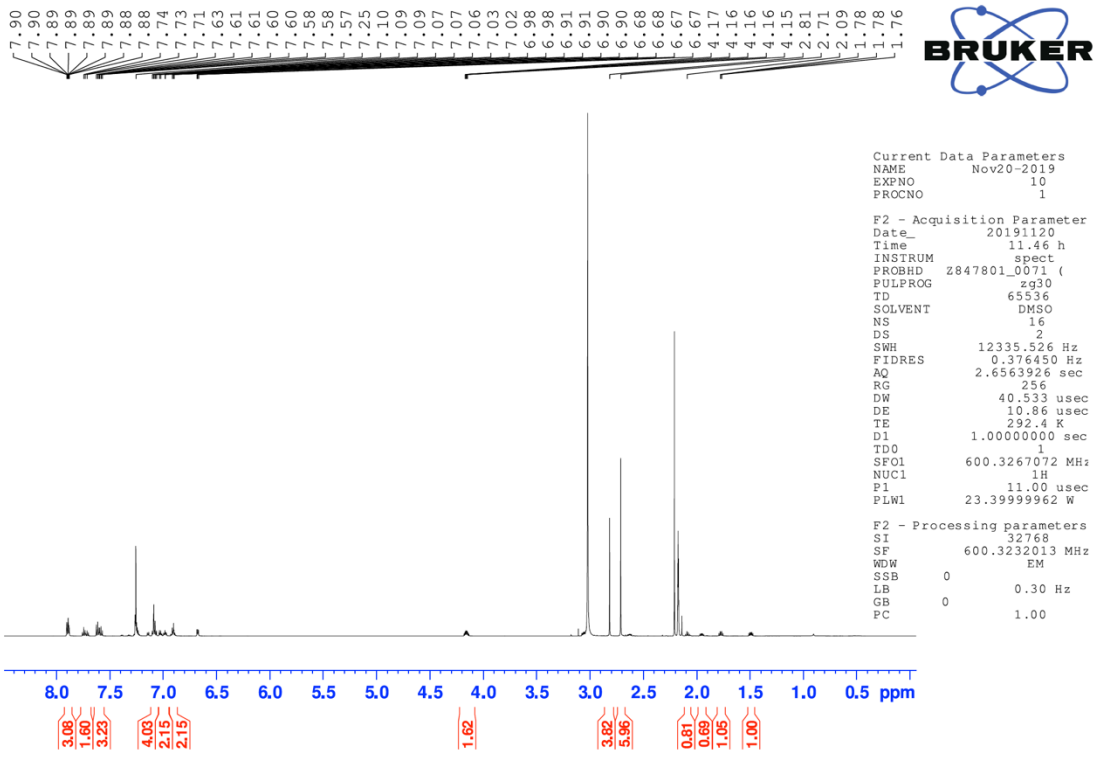
Supplementary data

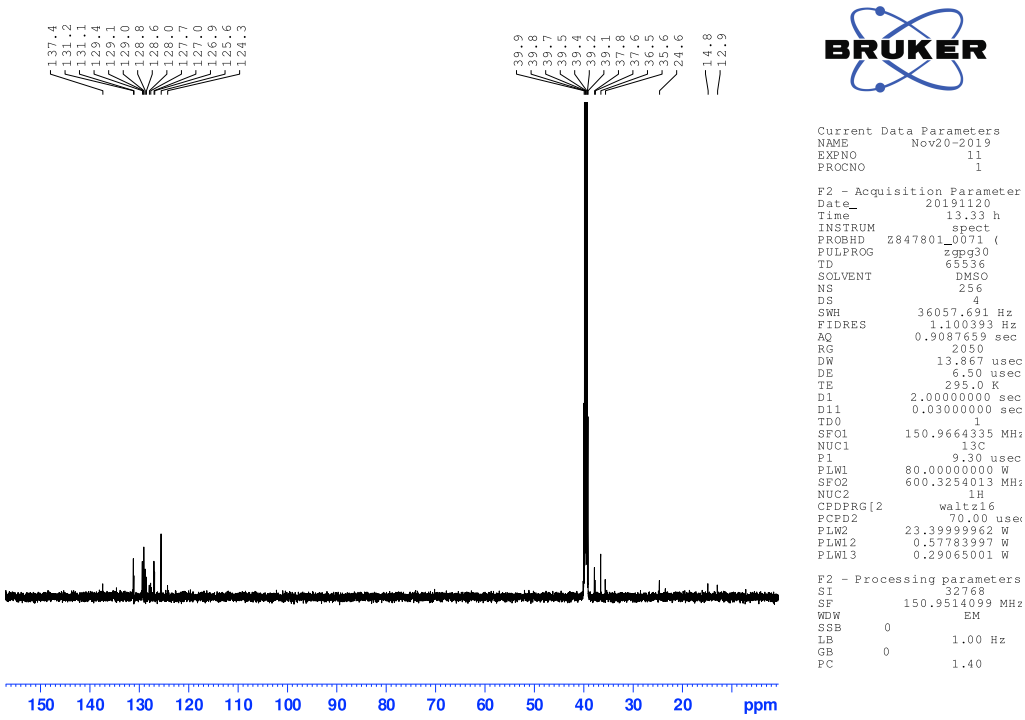
1.4.1 Methylation of N-(methyl)-S-methyl-S-phenyl sulfoxonimine



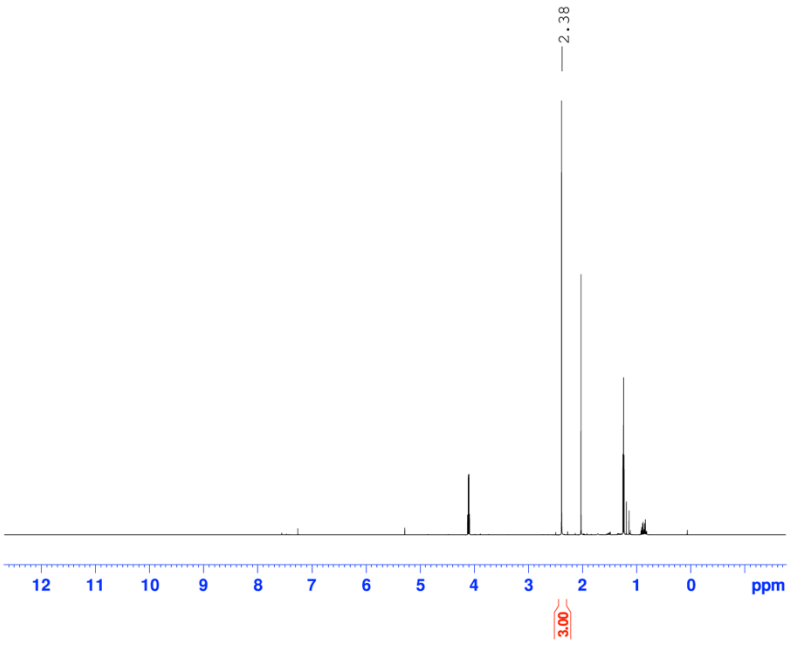


1.4.2 *N,N-dimethyl-S-phenyl-S-(2-phenylcyclopropyl)sulfoxonium tetrafluoroborate*





1.4.3 Pentafluorophenyl acetate

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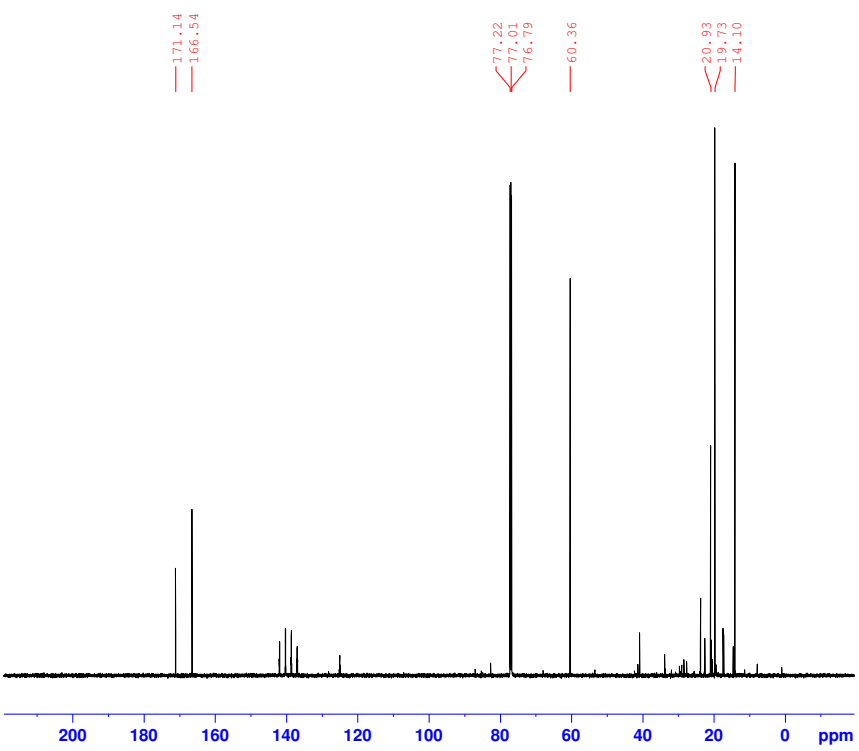
Current Data Parameters
NAME                  Dec13-2019
EXPNO                         20
PROCNO                         1

F2 - Acquisition Parameter
Date_                   20191213
Time                     12.47 h
INSTRUM                    spect
PROBHD   Z847801_0071 (
PULPROG                    zg30
TD                        65536
SOLVENT                   CDCl3
NS                           16
DS                            2
SWH                  12335.526 Hz
FIDRES                0.376450 Hz
AQ                   2.6563926 sec
RG                         90.5
DW                     40.533 usec
DE                     10.86 usec
TE                       292.9 K
D1                   1.00000000 sec
TD0                           1
SFO1               600.3267072 MHz
NUC1                         1H
P1                     11.00 usec
PLW1               23.39999962 W

F2 - Processing parameters
SI                        32768
SF                 600.3230144 MHz
WDW                          EM
SSB                           0
LB                     0.30 Hz
GB                            0
PC                         1.00
```

S968 - SC1-20-1 Pentafluorophenyl acetate

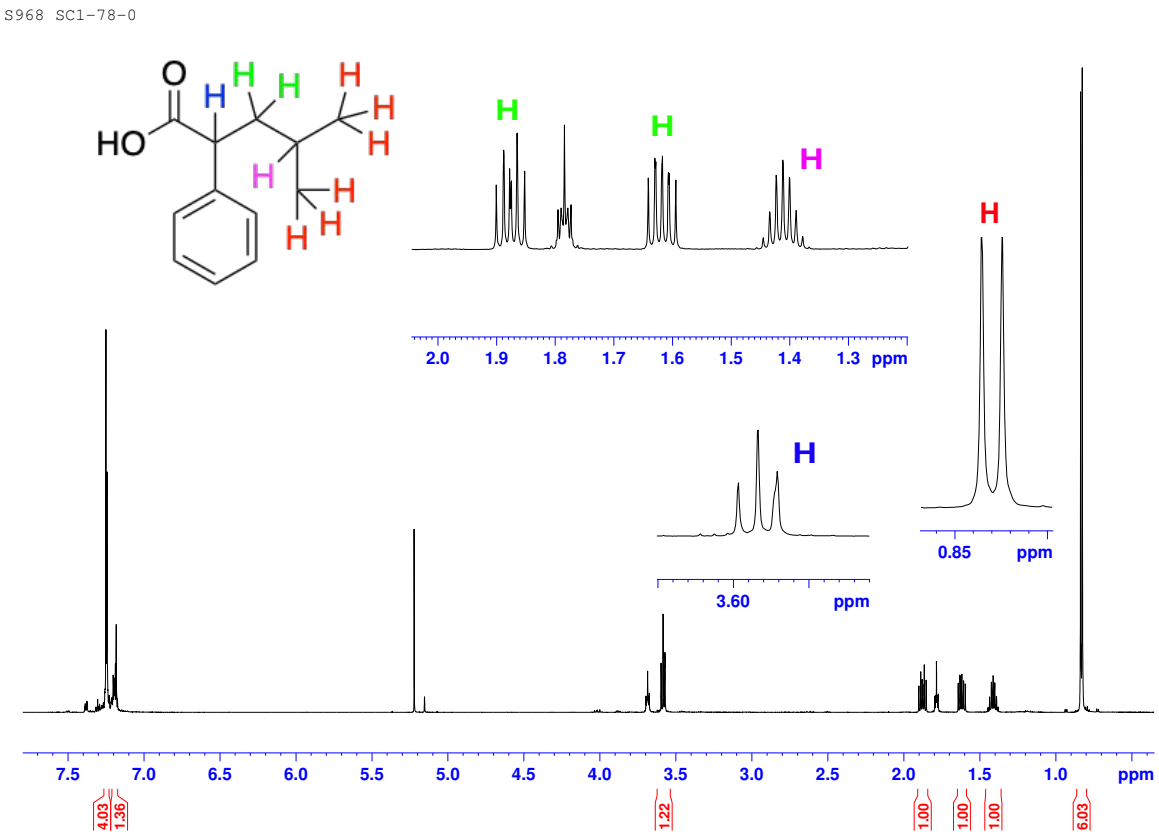



```
Current Data Parameters
NAME                  Dec13-2019
EXPNO                         21
PROCNO                         1

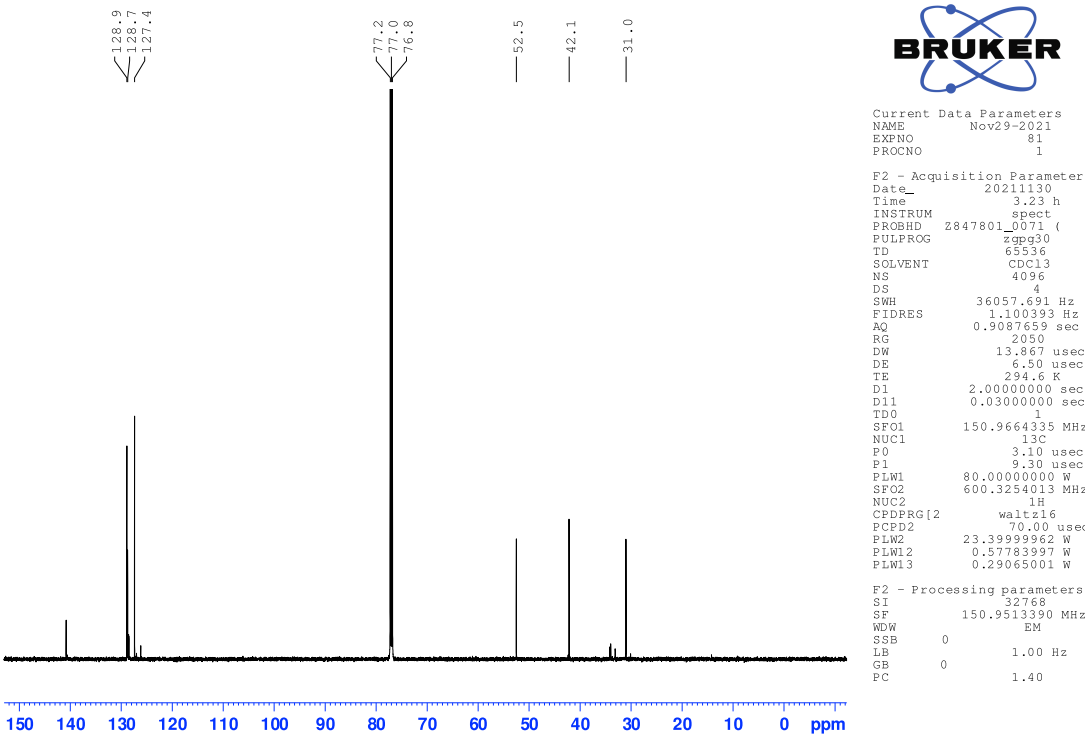
F2 - Acquisition Parameters
Date_                   20191213
Time                     13.40 h
INSTRUM                    spect
PROBHD   Z847801_0071 (
PULPROG                 zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                  36057.691 Hz
FIDRES                1.100393 Hz
AQ                   0.9087659 sec
RG                         2050
DW                     13.867 usec
DE                      6.50 usec
TE                       293.0 K
D1                   2.00000000 sec
D11                  0.03000000 sec
TD0                           1
SFO1               150.9664335 MHz
NUC1                         13C
P1                      9.30 usec
PLW1               80.00000000 W
SFO2               600.3254013 MHz
NUC2                         1H
CPDPRG[2                waltz16
PCPD2                  70.00 usec
PLW2               23.39999962 W
PLW12               0.57783997 W
PLW13               0.29065001 W

F2 - Processing parameters
SI                        32768
SF                 150.9513390 MHz
WDW                          EM
SSB                           0
LB                     1.00 Hz
GB                            0
PC                         1.40
```

1.4.7 4-methyl-2-phenylpentanoic acid



2.5.1 1,3-Dibromopropylbenzene

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Current Data Parameters
NAME          Nov29-2021
EXPNO                 81
PROCNO                 1

F2 - Acquisition Parameter
Date_          20211130
Time               3.23 h
INSTRUM            spect
PROBHD   Z847801_0071 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 4096
DS                    4
SWH           36057.691 Hz
FIDRES         1.100393 Hz
AQ            0.9087659 sec
RG                 2050
DW               13.867 usec
DE                6.50 usec
TE                294.6 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        150.9664335 MHz
NUC1               13C
P0                3.10 usec
P1                9.30 usec
PLW1        80.00000000 W
SFO2        600.3254013 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             70.00 usec
PLW2        23.39999962 W
PLW12        0.57783997 W
PLW13        0.29065001 W

F2 - Processing parameters
SI                32768
SF          150.9513390 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```
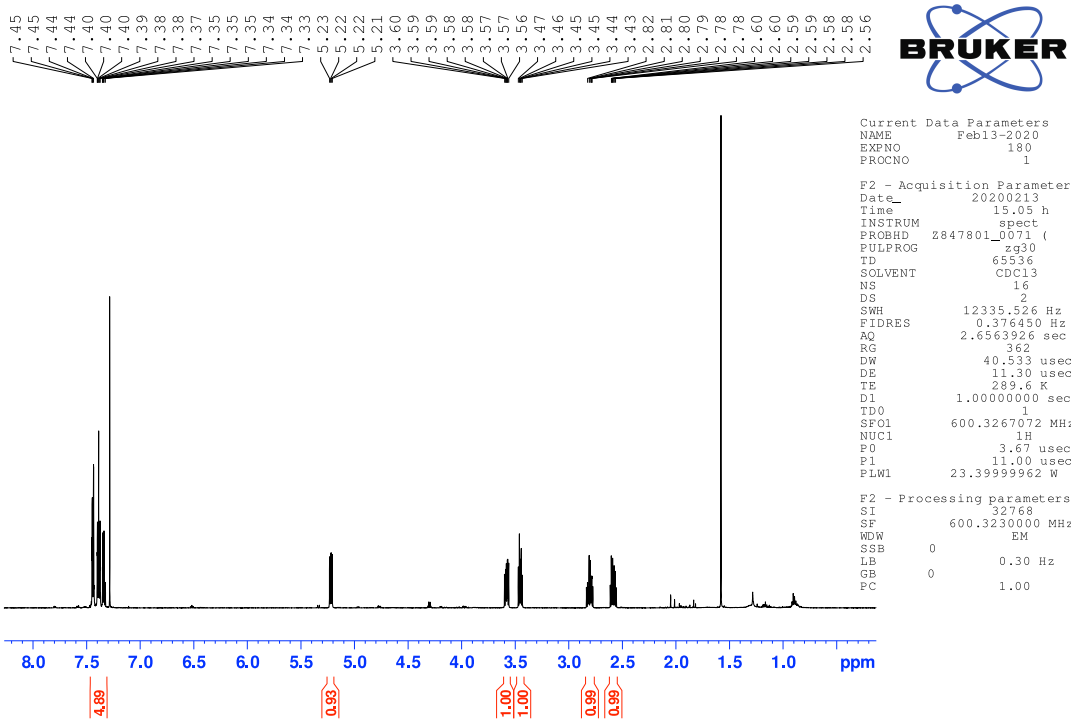
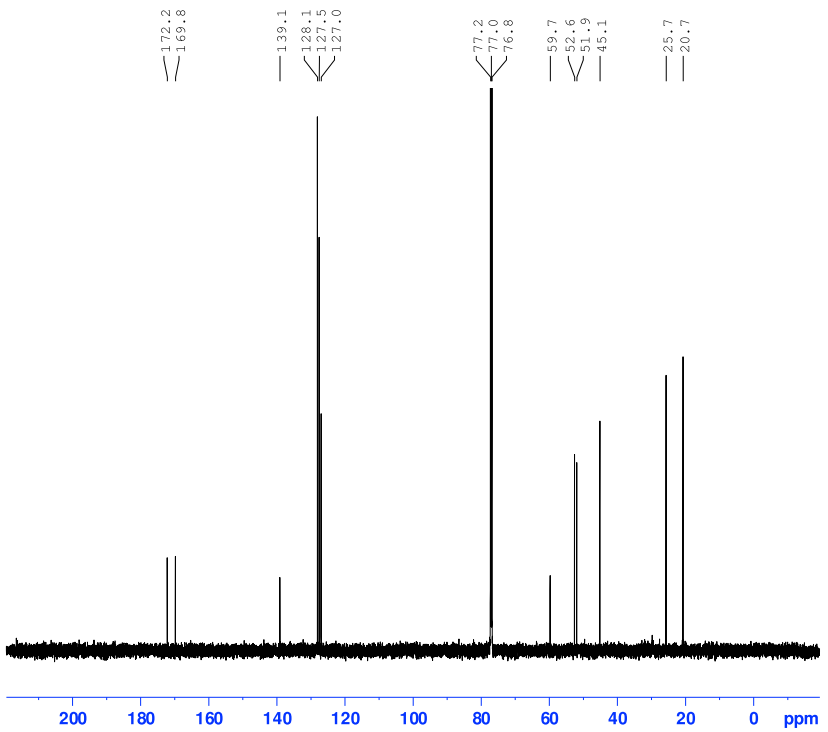
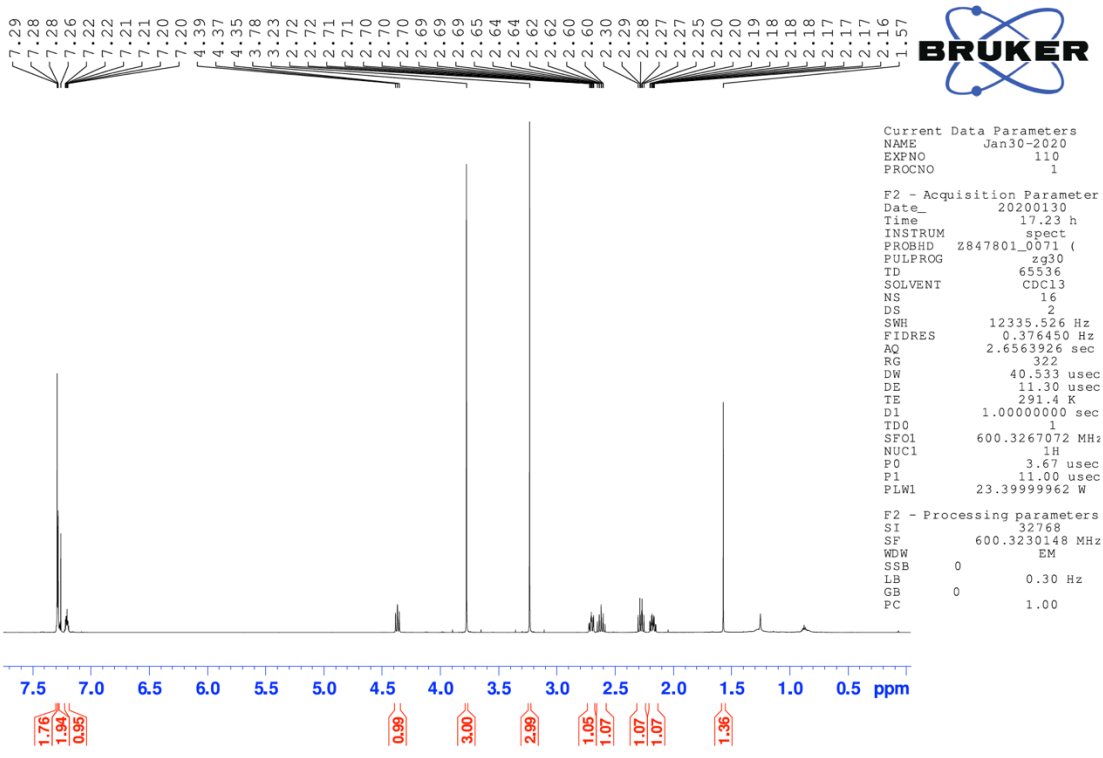




```
Current Data Parameters
NAME          Feb13-2020
EXPNO                180
PROCNO                 1

F2 - Acquisition Parameter
Date_          20200213
Time              15.05 h
INSTRUM            spect
PROBHD   Z847801_0071 (
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           12335.526 Hz
FIDRES         0.376450 Hz
AQ            2.6563926 sec
RG                  362
DW               40.533 usec
DE                11.30 usec
TE                289.6 K
D1           1.00000000 sec
TD0                   1
SFO1        600.3267072 MHz
NUC1               1H
P0                3.67 usec
P1               11.00 usec
PLW1        23.39999962 W

F2 - Processing parameters
SI                32768
SF          600.3230000 MHz
WDW                EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

2.5.2 dimethyl 2-phenylcyclobutane-1,1-dicarboxylate

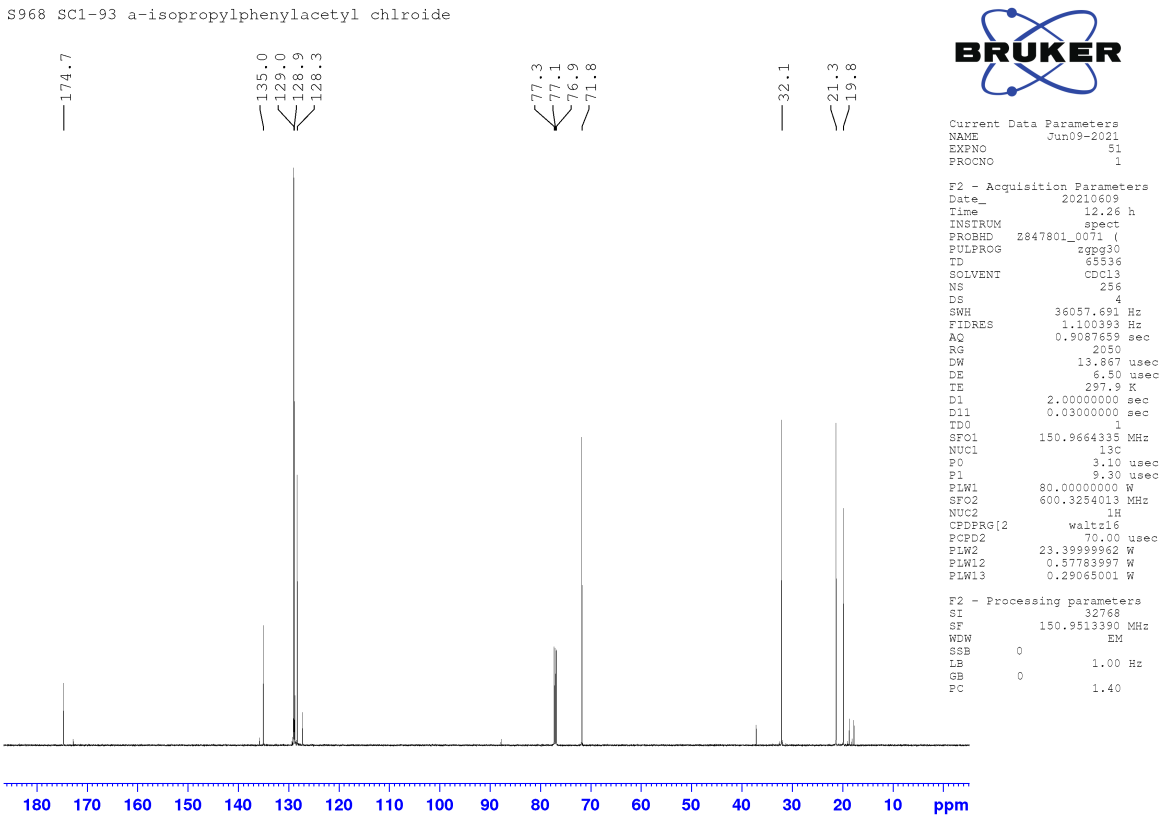


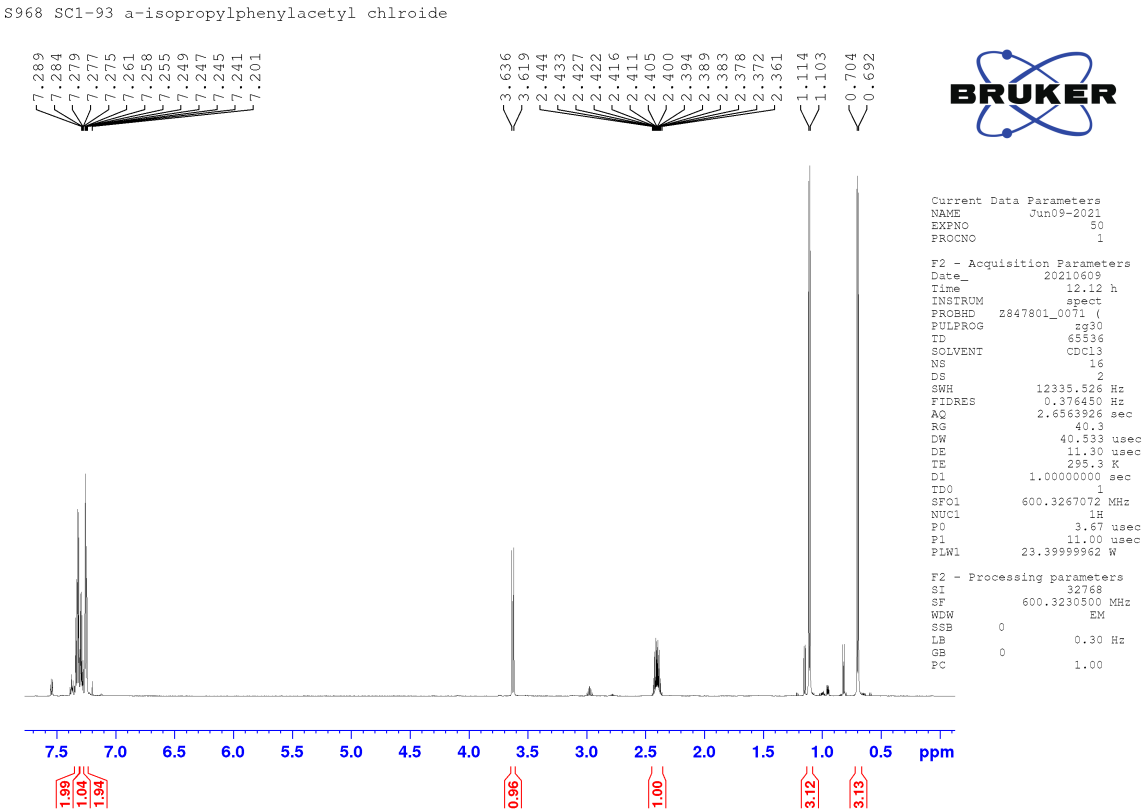

```
Current Data Parameters
NAME          Jan30-2020
EXPNO             81
PROCNO             1

F2 - Acquisition Parameter
Date_          20200130
Time             16.49 h
INSTRUM          spect
PROBHD   Z847801_0071 (
PULPROG          zgpg30
TD               65536
SOLVENT          CDCl3
NS               1024
DS                  4
SWH          36057.691 Hz
FIDRES        1.100393 Hz
AQ           0.9087659 sec
RG               2050
DW             13.867 usec
DE              6.50 usec
TE              293.9 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                 1
SFO1         150.9664335 MHz
NUC1               13C
P0               3.10 usec
P1               9.30 usec
PLW1         80.00000000 W
SFO2         600.3254013 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             70.00 use
PLW2         23.39999962 W
PLW12         0.57783997 W
PLW13         0.29065001 W

F2 - Processing parameters
SI                32768
SF           150.9513390 MHz
WDW                EM
SSB       0
LB               1.00 Hz
GB        0
PC               1.40
```



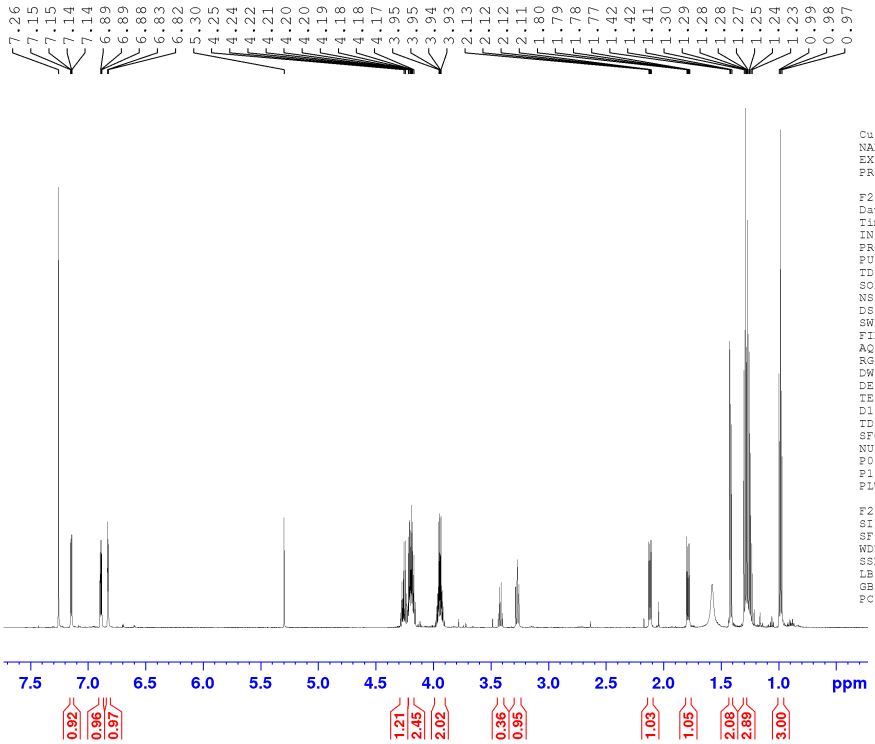

```
Current Data Parameters
NAME          Jan30-2020
EXPNO             110
PROCNO              1

F2 - Acquisition Parameter
Date_          20200130
Time             17.23 h
INSTRUM          spect
PROBHD   Z847801_0071 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                 16
DS                  2
SWH          12335.526 Hz
FIDRES        0.376450 Hz
AQ           2.6563926 sec
RG                322
DW             40.533 usec
DE              11.30 usec
TE              291.4 K
D1           1.00000000 sec
TD0                 1
SFO1         600.3267072 MHz
NUC1               1H
P0               3.67 usec
P1              11.00 usec
PLW1         23.39999962 W

F2 - Processing parameters
SI                32768
SF           600.3230148 MHz
WDW                EM
SSB       0
LB               0.30 Hz
GB        0
PC               1.00
```

3.3.1 α-isopropylphenyl acetyl chloride

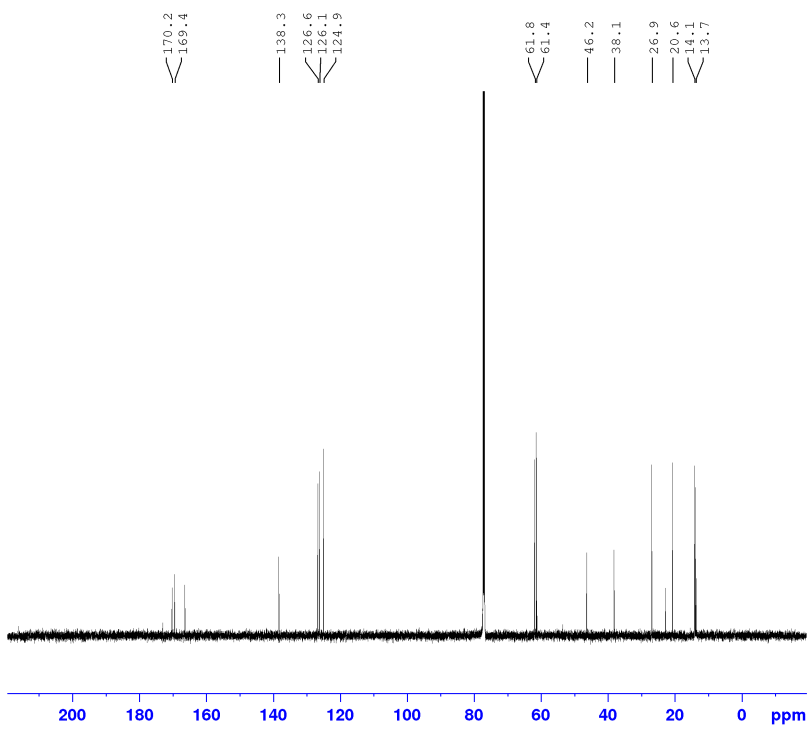




1,1-diethyl 2-(2-thienyl)-1,1-cyclopropanedicarboxylate

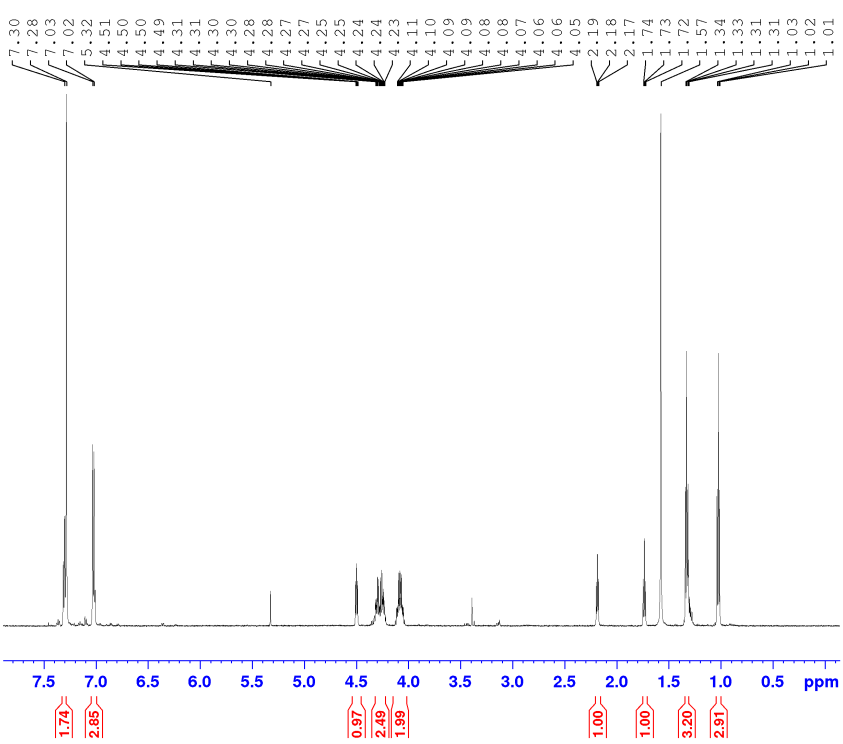



```
Current Data Parameters
NAME          Sep21-2021
EXPNO                120
PROCNO                 1

F2 - Acquisition Parameters
Date_           20210922
Time               9.19 h
INSTRUM            spect
PROBHD   Z847801_0071 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    64
DS                     2
SWH            12335.526 Hz
FIDRES          0.376450 Hz
AQ             2.6563926 sec
RG                   362
DW                40.533 usec
DE                11.30 usec
TE                292.8 K
D1            1.00000000 sec
TD0                    1
SFO1         600.3267072 MHz
NUC1                  1H
P0                 3.67 usec
P1                11.00 usec
PLW1         23.39999962 W

F2 - Processing parameters
SI                 32768
SF           600.3230159 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```




```
Current Data Parameters
NAME          Sep21-2021
EXPNO                121
PROCNO                 1

F2 - Acquisition Parameters
Date_           20210922
Time              20.26 h
INSTRUM            spect
PROBHD   Z847801_0071 (
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  4096
DS                     4
SWH            36057.691 Hz
FIDRES          1.100393 Hz
AQ             0.9087659 sec
RG                  2050
DW                13.867 usec
DE                 6.50 usec
TE                295.8 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1
SFO1         150.9664335 MHz
NUC1                  13C
P0                 3.10 usec
P1                 9.30 usec
PLW1         80.00000000 W
SFO2         600.3254013 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             70.00 usec
PLW2         23.39999962 W
PLW12         0.57783997 W
PLW13         0.29065001 W

F2 - Processing parameters
SI                 32768
SF           150.9513390 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

diethyl 2-phenoxycyclopropane-1,1-dicarboxylate




```
Current Data Parameters
NAME                  Dec13-2021
EXPNO                         80
PROCNO                         1

F2 - Acquisition Parameters
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Time                     14.08 h
INSTRUM                  spect
PROBHD     Z847801_0071 (
PULPROG                  zg30
TD                      65536
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                 12335.526 Hz
FIDRES                0.376450 Hz
AQ                    2.6563926 sec
RG                          456
DW                     40.533 usec
DE                     11.30 usec
TE                     292.1 K
D1                    1.00000000 sec
TD0                          1
SFO1               600.3267072 MHz
NUC1                        1H
P0                     3.67 usec
P1                     11.00 usec
PLW1               23.39999962 W

F2 - Processing parameters
SI                          32768
SF                 600.3230000 MHz
WDW                          EM
SSB                0
LB                     0.30 Hz
GB                 0
PC                     1.00
```
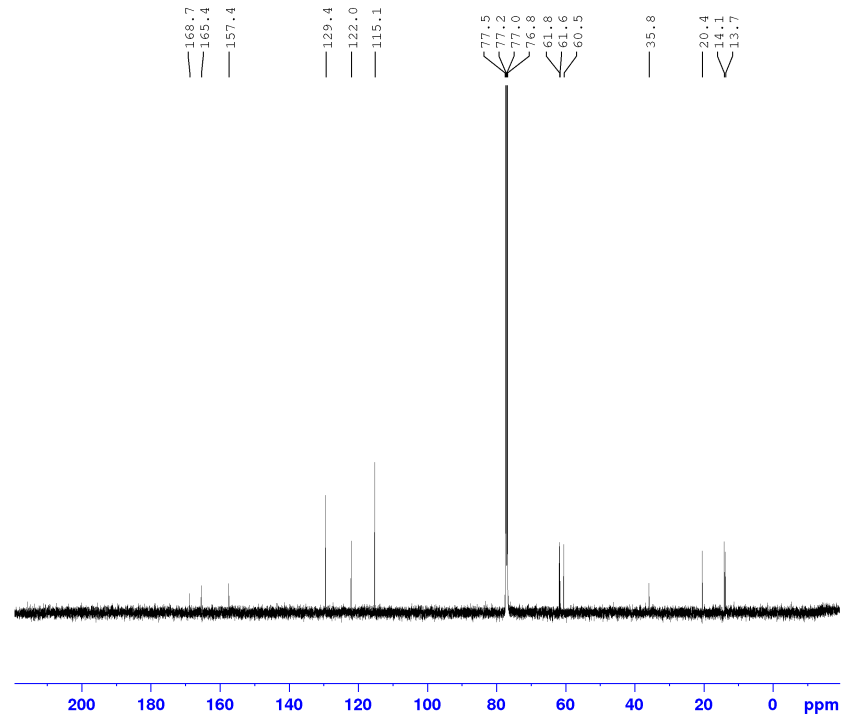
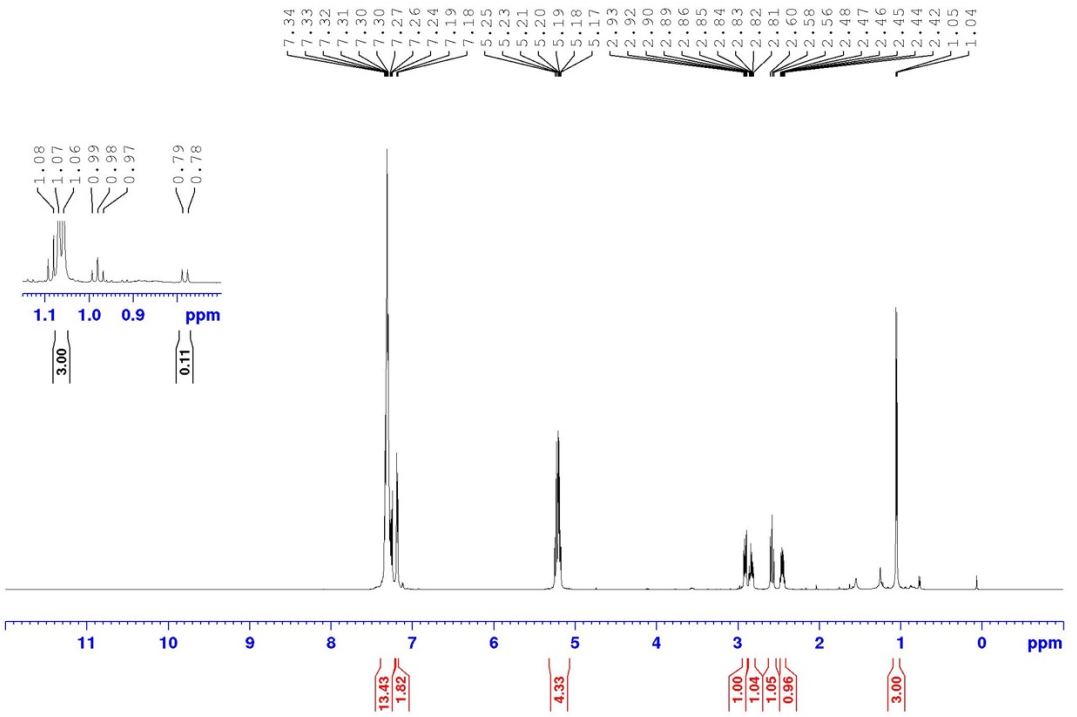
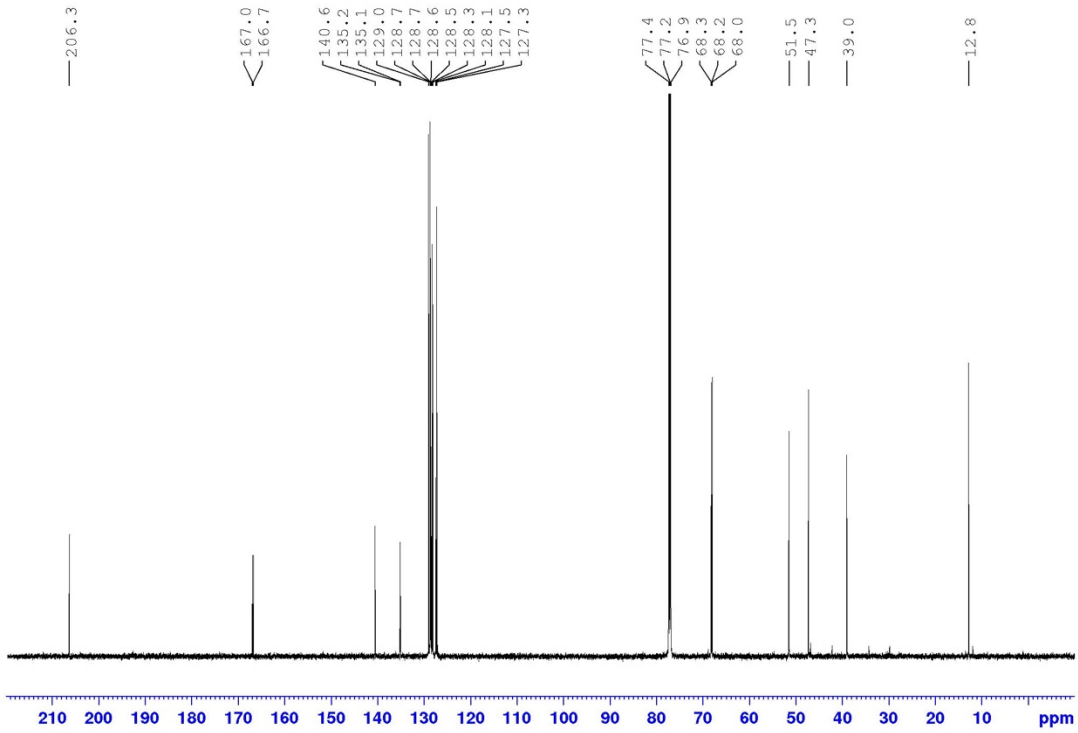




```
Current Data Parameters
NAME                  Dec13-2021
EXPNO                        100
PROCNO                         1

F2 - Acquisition Parameters
Date_               20211213
Time                     20.27 h
INSTRUM                  spect
PROBHD     Z847801_0071 (
PULPROG                zgpg30
TD                      65536
SOLVENT                  CDCl3
NS                        4096
DS                           4
SWH                 36057.691 Hz
FIDRES                1.100393 Hz
AQ                    0.9087659 sec
RG                        2050
DW                     13.867 usec
DE                      6.50 usec
TE                     295.2 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                          1
SFO1               150.9664335 MHz
NUC1                        13C
P0                     3.10 usec
P1                     9.30 usec
PLW1               80.00000000 W
SFO2               600.3254013 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                  70.00 usec
PLW2               23.39999962 W
PLW12               0.57783997 W
PLW13               0.29065001 W

F2 - Processing parameters
SI                          32768
SF                 150.9513390 MHz
WDW                          EM
SSB                0
LB                     1.00 Hz
GB                 0
PC                     1.40
```

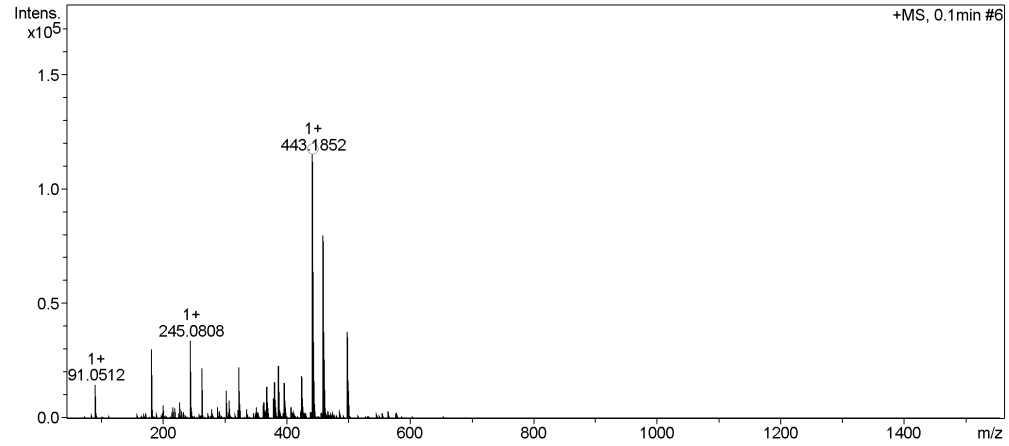
Dibenzyl (3R,4S)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate





Trinity College Dublin
School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-127_RB5_01_27734.d	Acquisition Date	06/10/2021 13:03:09
Sample Description			

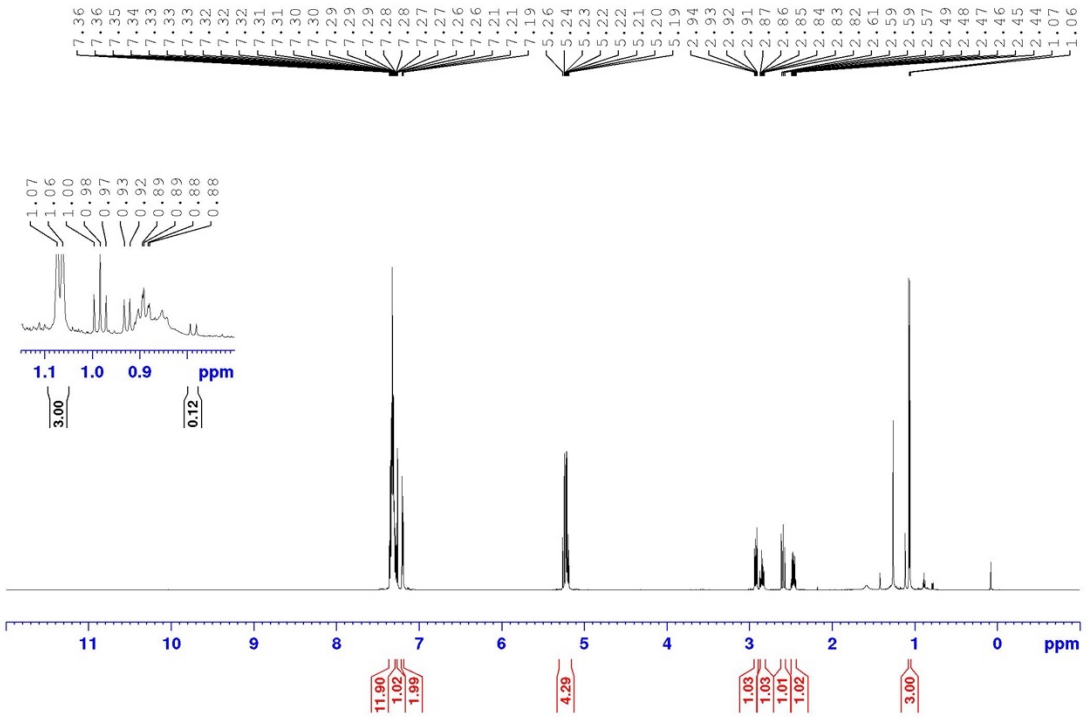


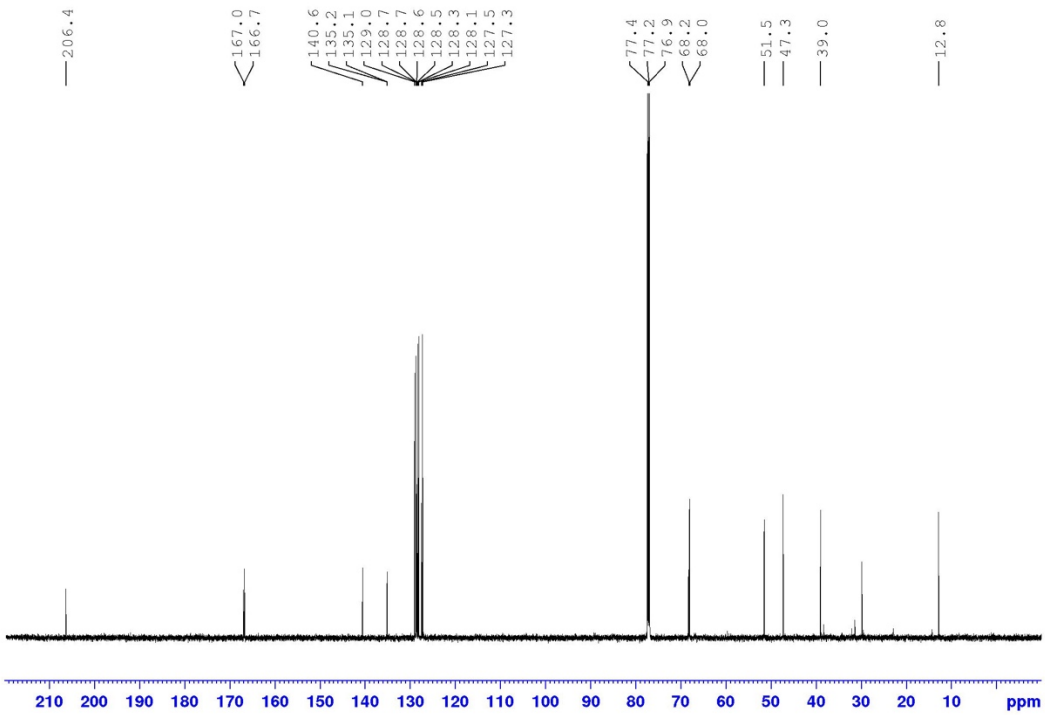
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
443.185186	1	C28H27O5	443.185300	-0.1	-0.3	15.5	ok	even	3.8

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

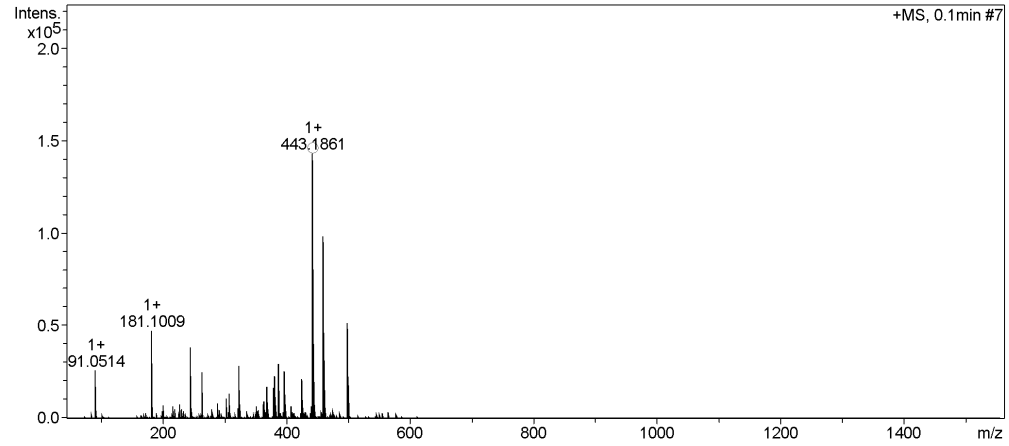
Dibenzyl (3S,4R)-3-methyl-2-oxo-4-phenylcyclopentane-1,1-dicarboxylate




206.4
167.0
166.7
140.6
135.2
135.1
129.0
128.7
128.7
128.6
128.5
128.3
128.1
127.5
127.3
77.4
77.2
76.9
68.2
68.0
51.5
47.3
39.0
12.8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Trinity College Dublin
School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-111_RB2_01_27731.d	Acquisition Date	06/10/2021 12:53:20
Sample Description			

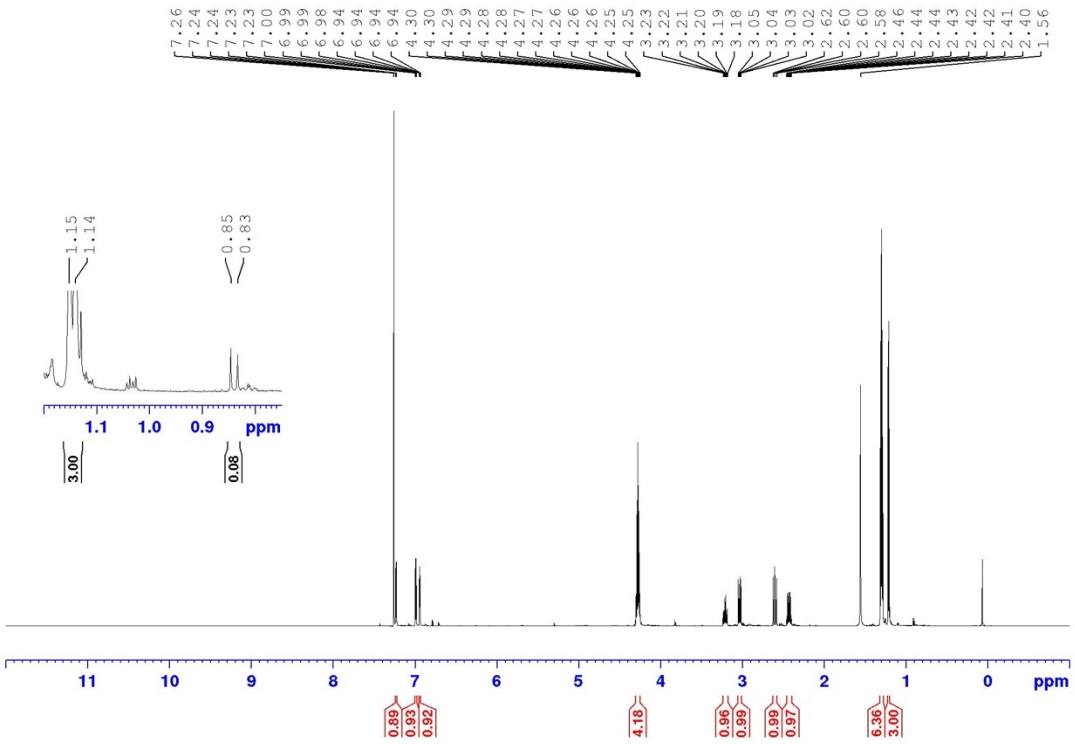


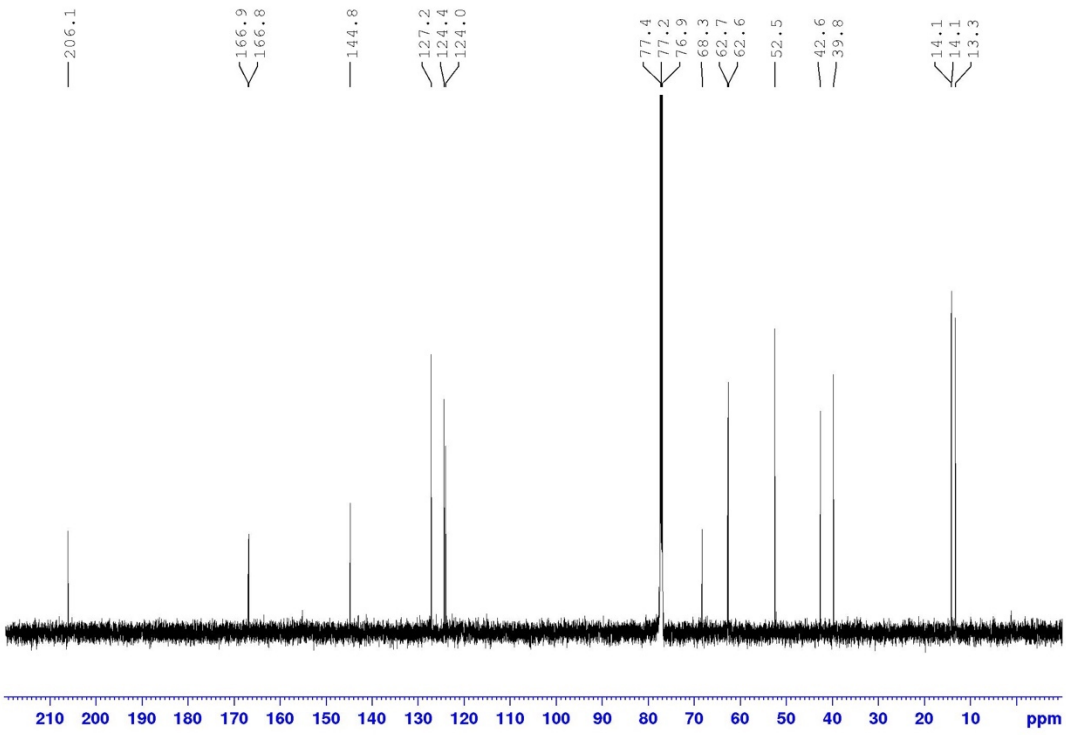
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
443.186071	1	C28H27O5	443.185300	0.8	1.7	15.5	ok	even	7.8

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

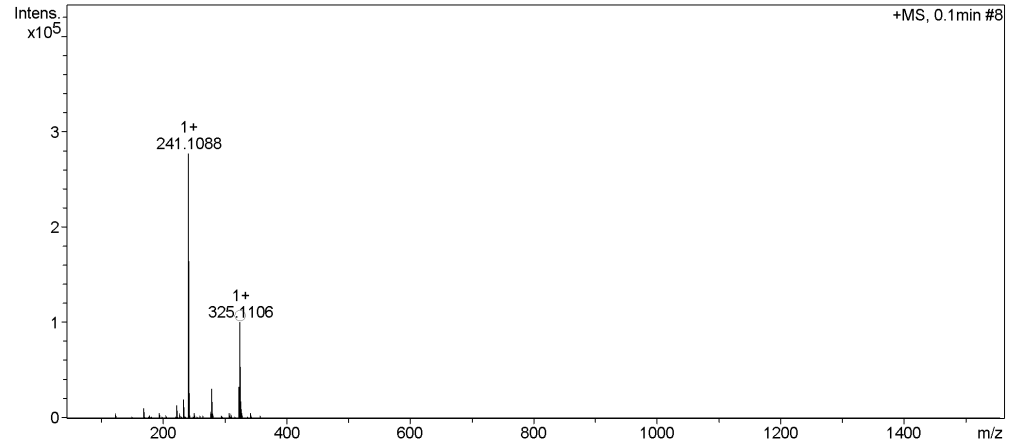
Diethyl (3S,4R)-3-methyl-2-oxo-4-(thiophen-2-yl)cyclopentane-1,1-dicarboxylate




206.1
166.9
166.8
144.8
127.2
124.4
124.0
77.4
77.2
76.9
68.3
62.7
62.6
52.5
42.6
39.8
14.1
14.1
13.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Trinity College Dublin
School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SC2-08_RA8_01_27729.d	Acquisition Date	06/10/2021 12:46:48
Sample Description			

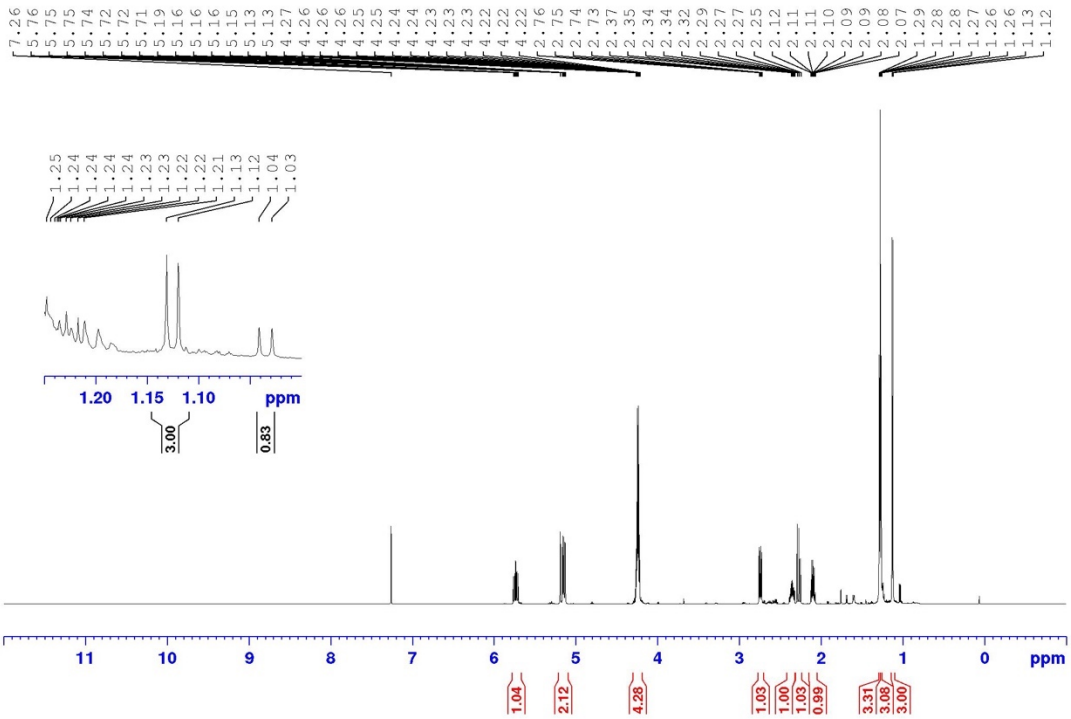


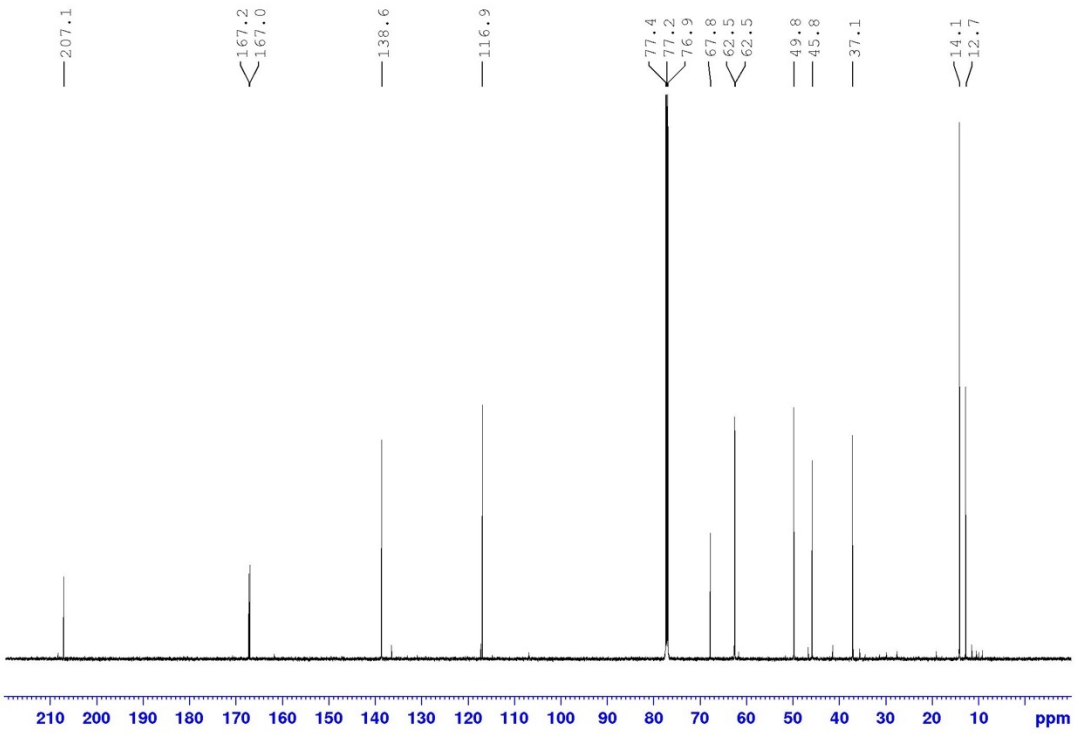
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
325.110621	1	C16H21O5S	325.110421	-0.2	-0.6	6.5	ok	even	9.2

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Diethyl (3S,4S)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate




207.1
167.2
167.0
138.6
116.9
77.4
77.2
76.9
67.8
62.5
62.5
49.8
45.8
37.1
14.1
12.7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

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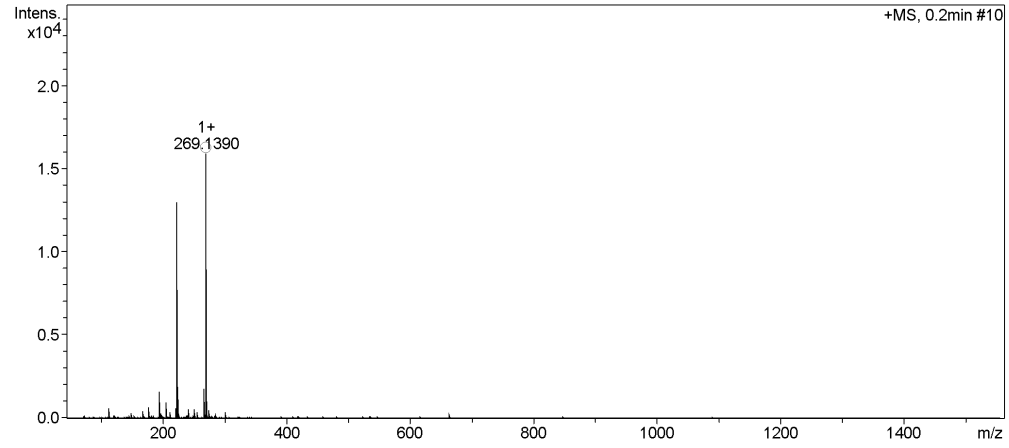
School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-137_RB8_01_27737.d	Acquisition Date	06/10/2021 13:13:01
Sample Description			

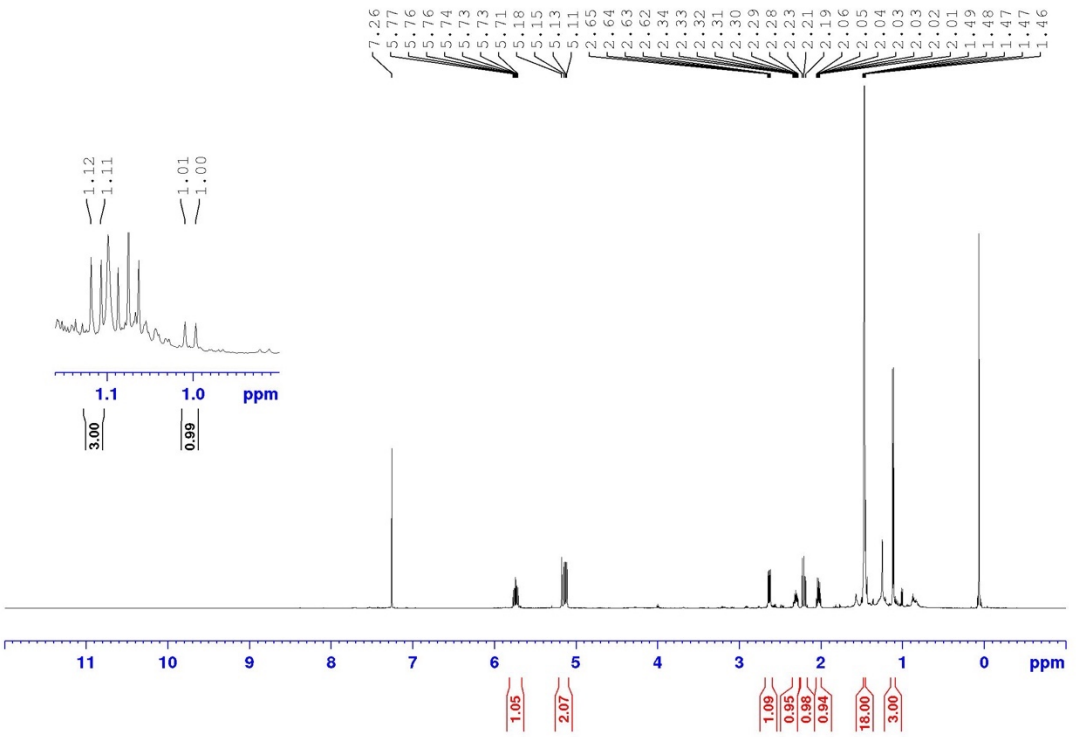


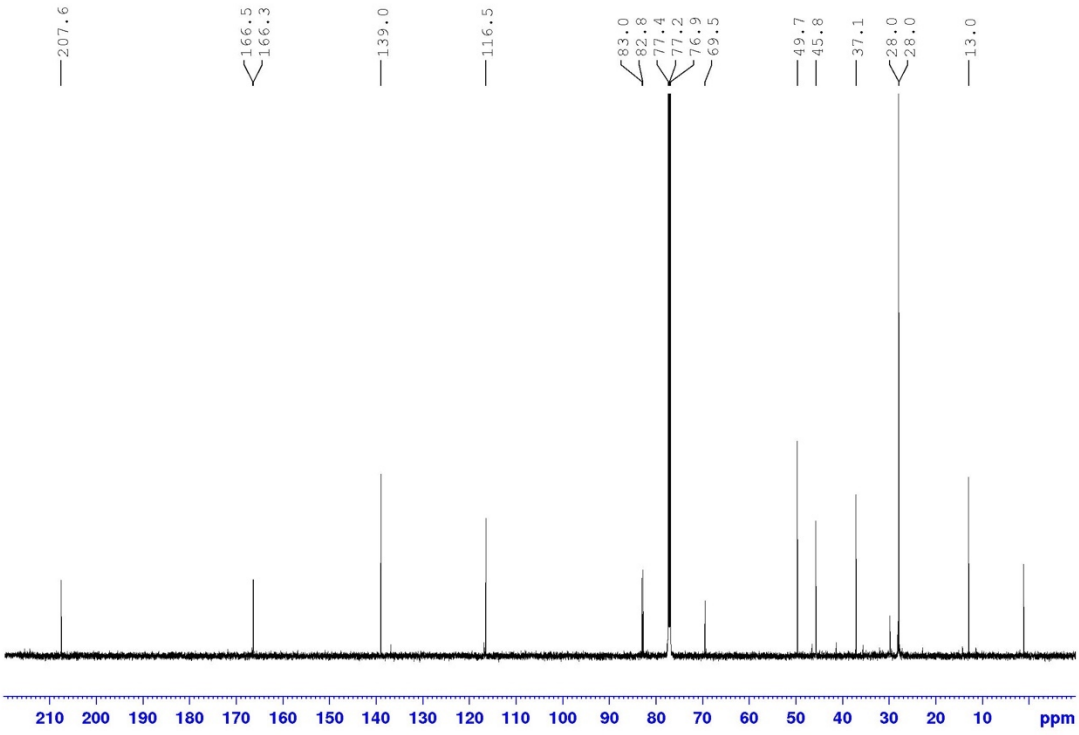
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
269.138977	1	C14H21O5	269.138350	-0.6	-2.3	4.5	ok	even	20.4

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Di-tert-butyl (3S,4S)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate





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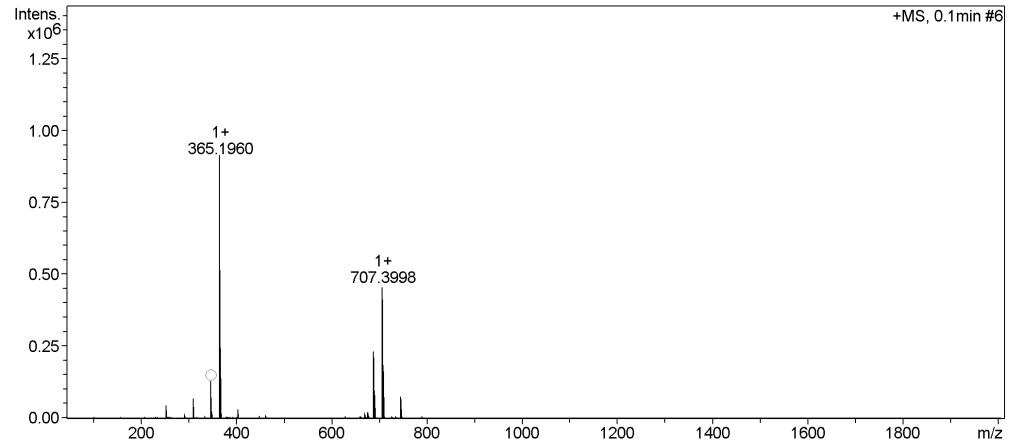
School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-116_RA8_01_28636.d	Acquisition Date	03/12/2021 11:31:13
Sample Description			

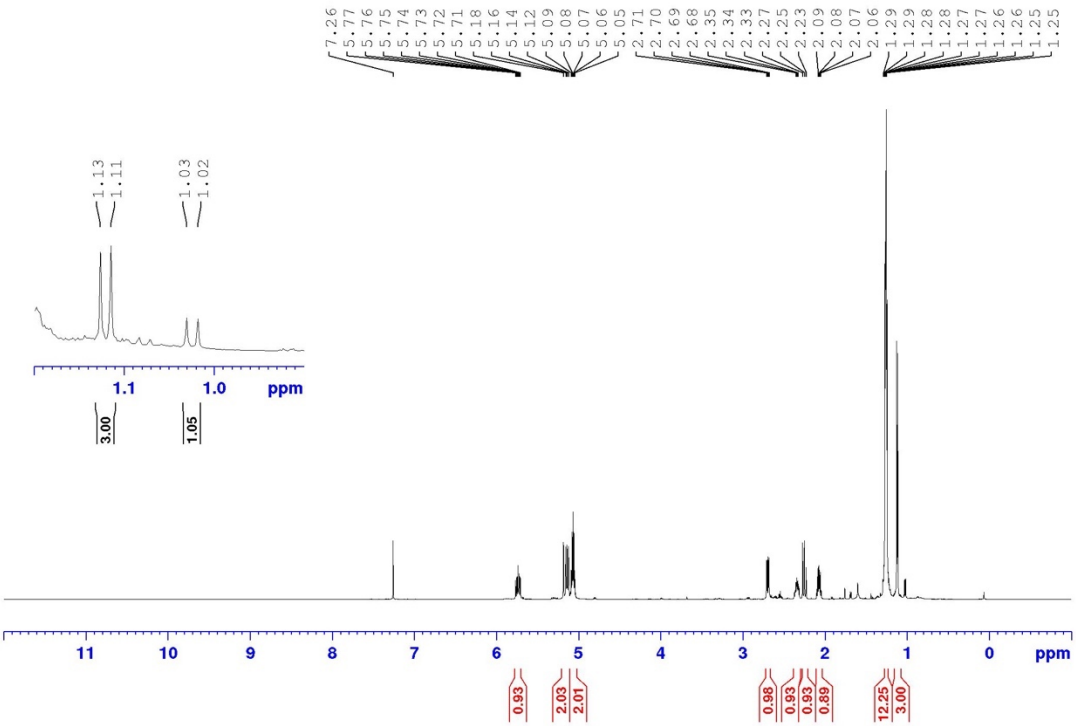


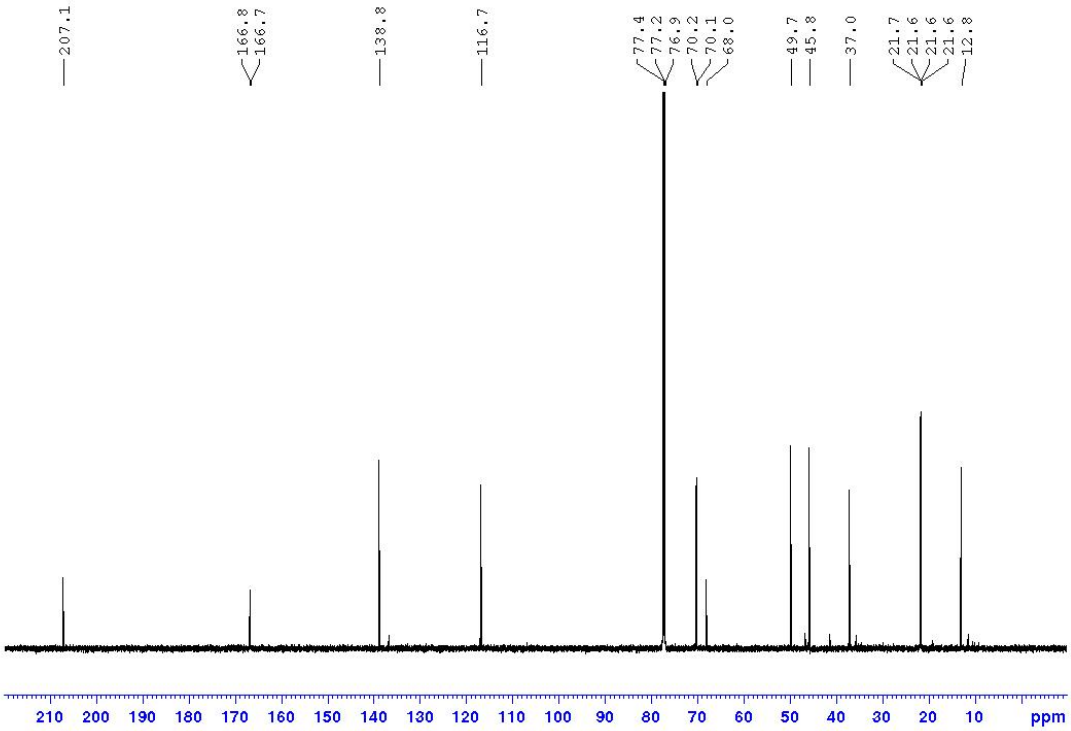
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
347.181764	1	C18H28NaO5	347.182895	-1.1	-3.3	4.5	ok	even	10.4

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Diisopropyl (3S,4S)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate





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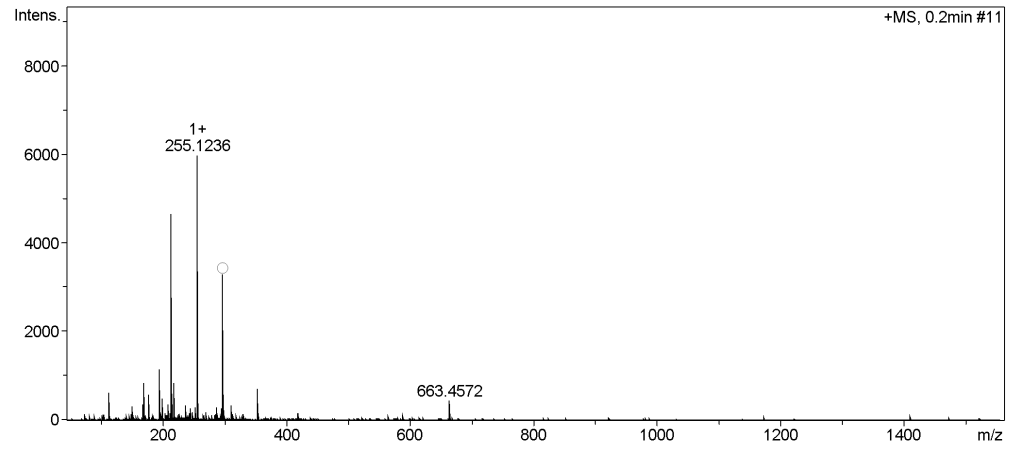
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-138_RC1_01_27738.d	Acquisition Date	06/10/2021 13:16:17
Sample Description			

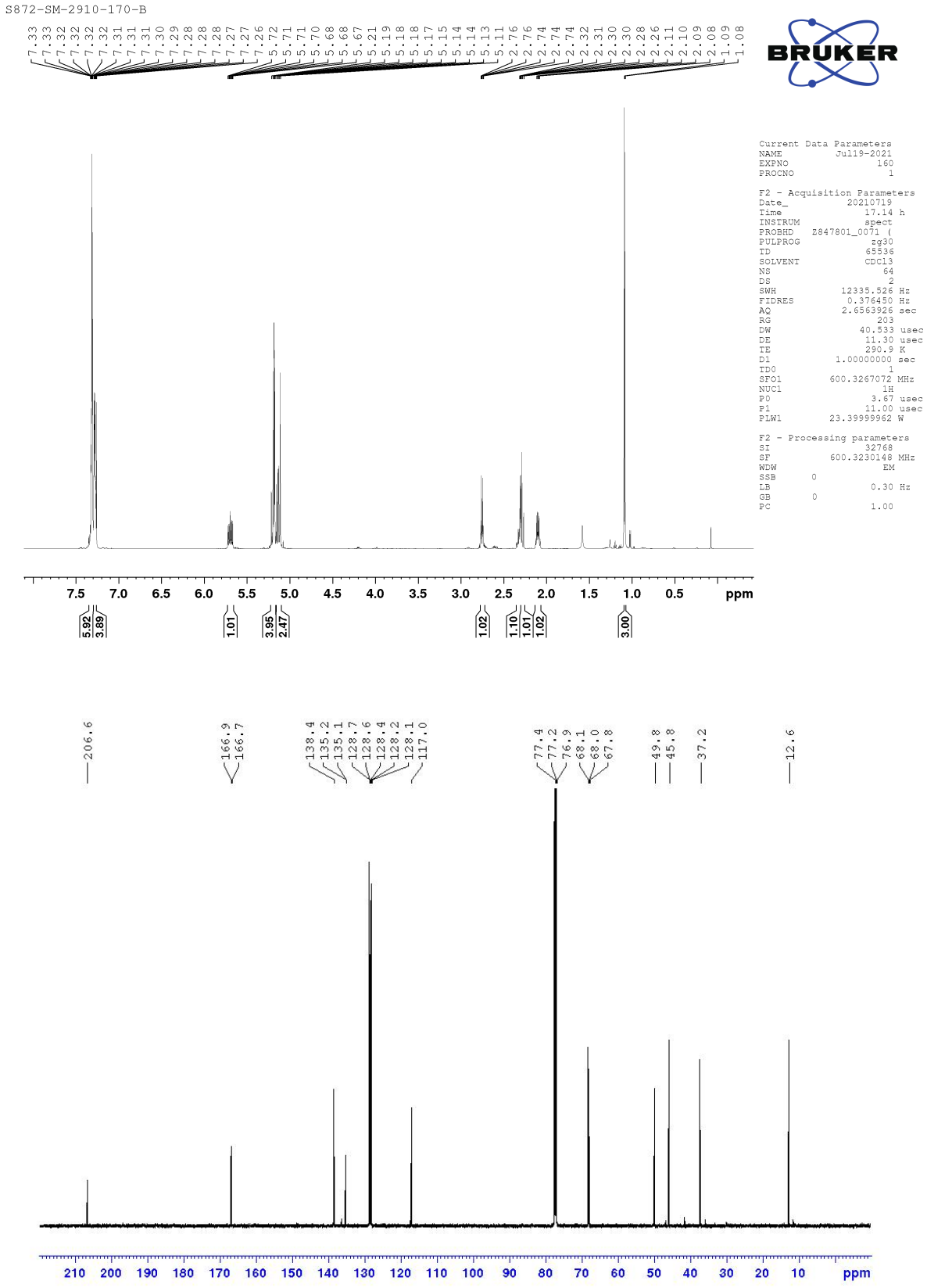


Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
297.169752	1	C16H25O5	297.169650	-0.1	-0.3	4.5	ok	even	31.9

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Dibenzyl (3S,4S)-3-methyl-2-oxo-4-vinylcyclopentane-1,1-dicarboxylate



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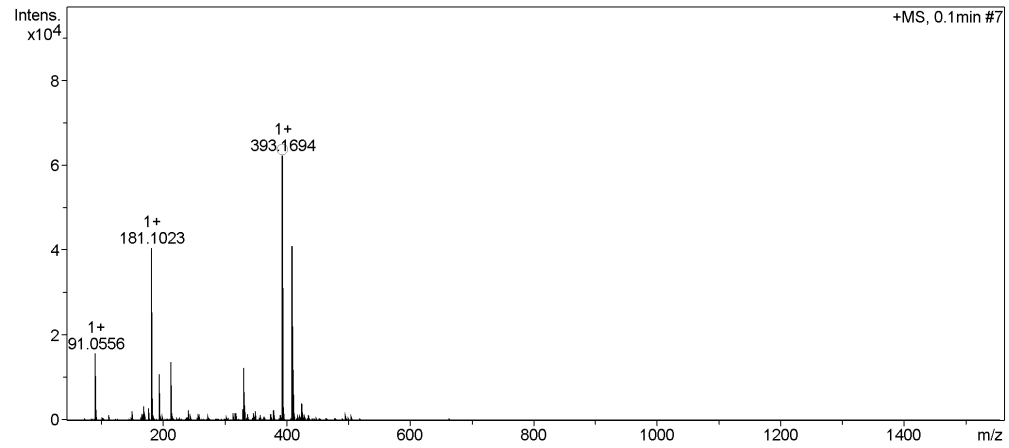
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-170_RC3_01_27740.d	Acquisition Date	06/10/2021 13:22:50
Sample Description			

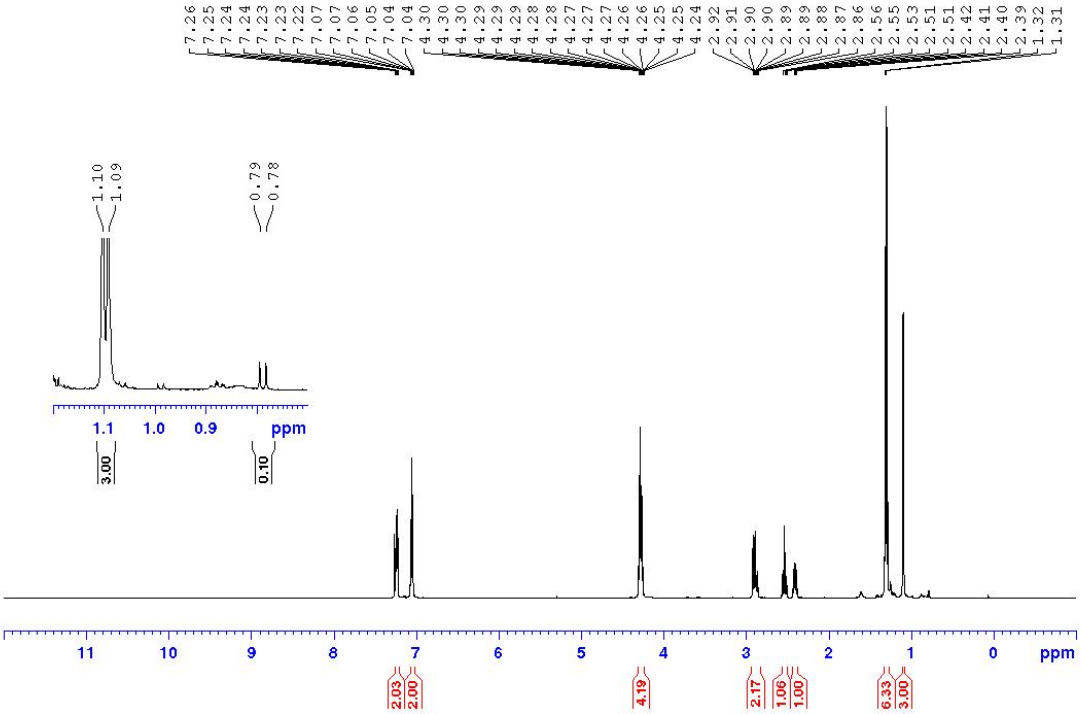


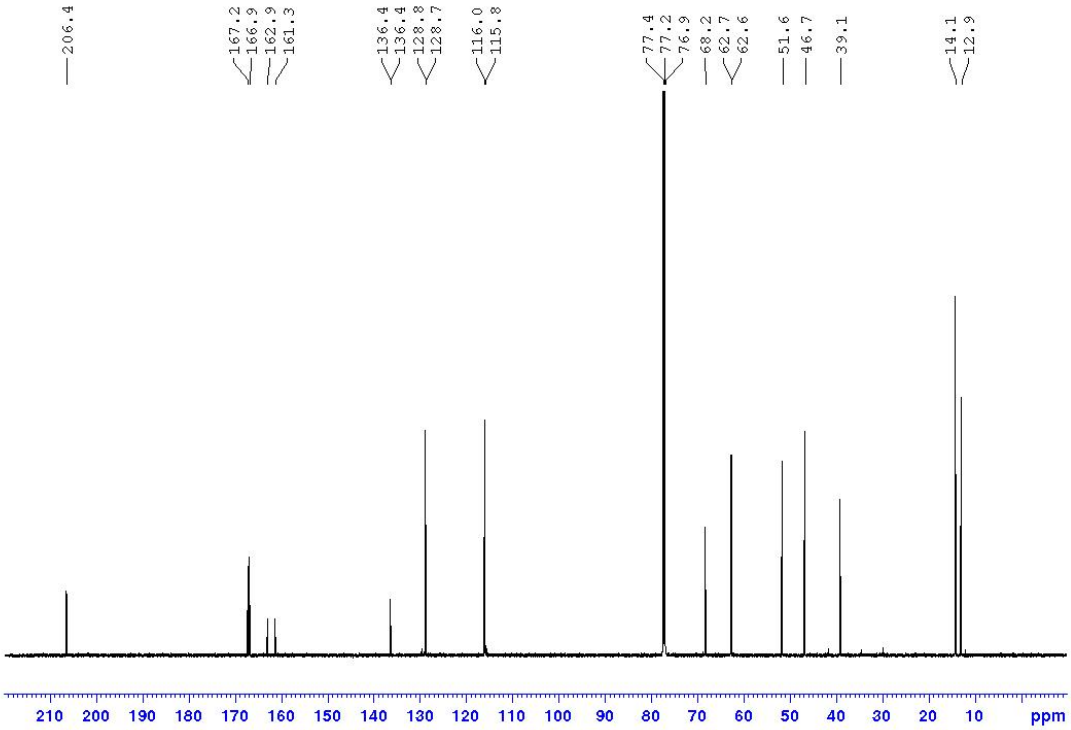
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
393.169414	1	C24H25O5	393.169650	-0.2	-0.6	12.5	ok	even	13.1

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Diethyl (3S,4R)-4-(4-fluorophenyl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate





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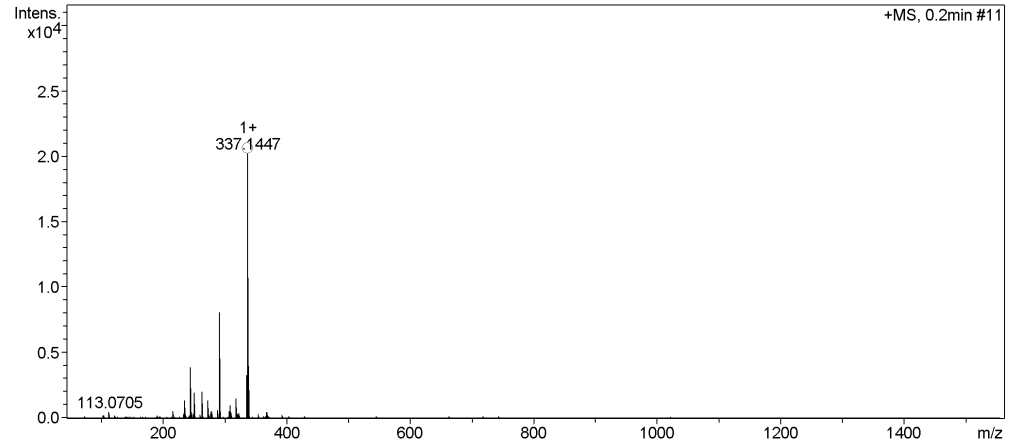
School of Chemistry Mass Spectrometry Unit

Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-180_RC5_01_27742.d	Acquisition Date	06/10/2021 13:29:25
Sample Description			

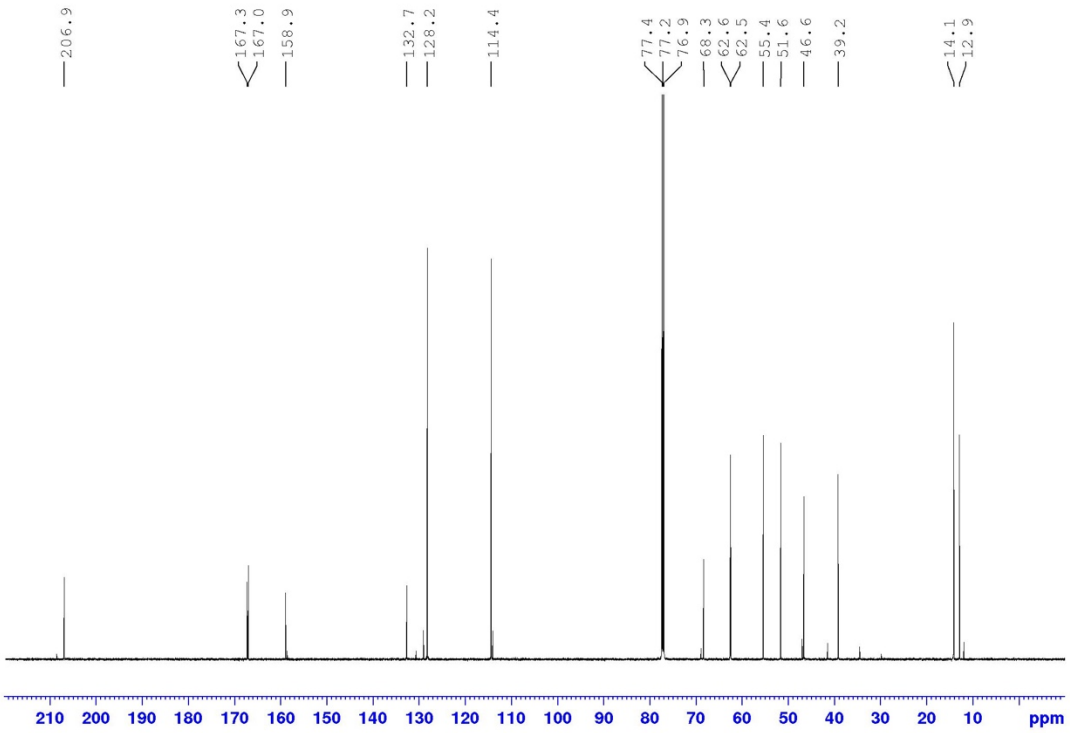


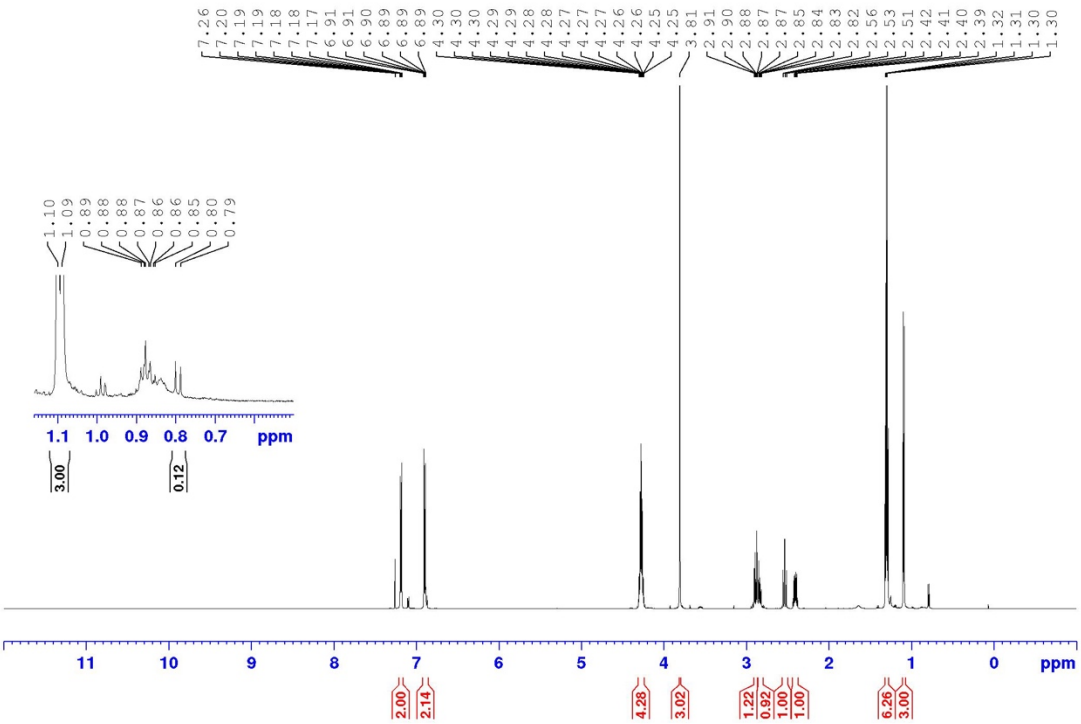
Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
337.144680	1	C18H22FO5	337.144578	0.1	0.3	7.5	ok	even	1.2

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match

Diethyl (3S,4R)-4-(4-methoxyphenyl)-3-methyl-2-oxocyclopentane-1,1-dicarboxylate





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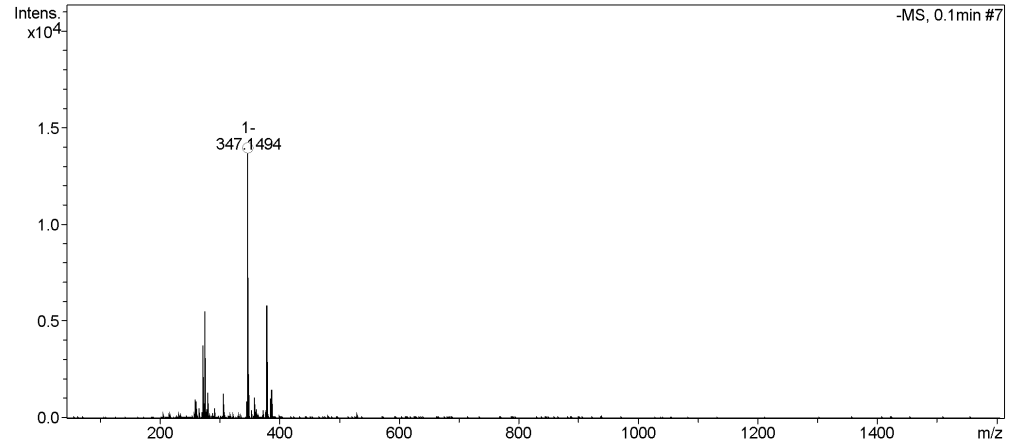
Sample-ID		Station	
Submitter		Supervisor	
Analysis Name	SM-179_RC4_01_27766.d	Acquisition Date	06/10/2021 14:48:42
Sample Description			



Meas. m/z	#	Ion Formula	m/z	err [mDa]	err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma
347.149418	1	C19H23O6	347.150012	0.6	1.7	8.5	ok	even	23.6

SmartFormula Settings

Low value of mSigma indicates good isotopic pattern match