Synthesis and reactivity of Cyclopropanes and Cyclopropenes

by

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ABSTRACT

Activated cyclopropanes have been extensively used in synthetic chemistry as precursors for cycloaddition reactions. The rationale behind this is their ability to undergo ring-opening when activated by a Lewis acid, this can be enhanced further by the presence of a carbocation stabilising group like electron-rich aromatics. The stabilised dipole formed after ring opening can be trapped with suitable electrophiles such as imines and aldehydes *via* a [3+2] cycloaddition reaction. This results in the synthesis of pyrrolidines and tetrahydrofurans in excellent yields but moderate diastereoselectivity. Similarly, 6-membered heterocycles can be formed *via* a [3+3] cycloaddition reaction of activated cyclopropanes with nitrones. Now to extend the scope of the methodology, a [3+3] dipolar cycloaddition has been developed using activated 2,3 disubstituted cyclopropane diesters to access a range of highly functionalised oxazines in moderate to good yields (50-75%) and with reasonable diastereoselectivity. The use of activated symmetrical disubstituted cyclopropanes afforded the desired oxazines in a regio- and diastereocontrolled manner, while the use of unsymmetrical cyclopropanes significantly reduced the diastereoselectivity of the reaction. The stereochemistry outcome of the reaction developed was determined by nOe analyses and X-ray diffraction structures could be recorded in some examples. A new methodology has also been developed to gain access to novel *N*-heterocyclic- and phenol- substituted cyclopropanes in one step from the corresponding cyclopropene *via* a conjugated addition.

Key Words:

Cycloaddition, cyclopropane, cyclopropene, nucleophilic addition, oxazine, ring-opening

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TABLE OF CONTENT

ABBREVIATIONS

Ac	=	acetyl
BINAP	=	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bp	=	boiling point
Bn	=	benzyl group
nBuLi or BuLi	=	butyl lithium
°C	=	degrees Celcius
cat	=	catalytic
CH_2Cl_2	=	dichloromethane
cm^{-1}	=	wave number
CuCN	=	copper(I) cyanide
δ	=	chemical shift
d	=	doublet
1,2-DCE	=	1,2-dichloroethane
dd	=	doublet of double
d.e.	=	diastereoisomeric excess
DMS	=	dimethylsulfide
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	dimethylsulfoxide
d.r.	=	diastereoisomeric ratio
e^-	=	electron
e.e.	=	enantiomeric excess
EI	=	electron impact ionisation
eq	=	equivalent(s)
ESI	=	electronspray ionisation
Et	=	ethyl
EtOH	=	ethanol
Et_2O	=	diethyl ether
FAB	=	fast atom bombardment
$FeCl_3$	=	iron(III) chloride
g	=	gram

h	=	hour
Hz	=	hertz
IR	=	infra-red
K_2CO_3	=	potassium carbonate
KOH	=	potassium hydroxide
$LiAlH_4$	=	lithium aluminium hydride
m	=	multiplet
Me	=	methyl
MeI	=	methyl iodide
MEM	=	β-methoxyethoxymethyl ether
MeOH	=	methanol
MeCN	=	acetonitrile
MHz	=	megahertz
min	=	minutes
mL	=	millilitre
mmol	=	millimole
MOM	=	methoxymethyl ether
MO	=	molecular orbital
mp	=	melting point
ms	=	4 Å molecular sieves
Ms	=	mesyl
MS	=	mass spectroscopy
m/z	=	mass to charge ratio
NH_4Cl	=	ammonium chloride
NMR	=	nuclear magnetic resonance
nOe	=	nuclear Overhauser effect
Nu	=	Nucleophile
OTf	=	trifluoromethanesulfonyl
P	=	protecting goup
p-	=	para-substituted
Ph	=	phenyl
ppm	=	parts per million
^{i}Pr	=	iso-propyl
r.t.	=	room temperature

$Rh_2(OAc)_4$	=	rhodium(II) acetate dimer
$Pd(OAc)_2$	=	palladium(II) acetate
s	=	singlet
SEM	=	[2-(trimethylsilyl)ethoxy]methyl
SM	=	starting material
t	=	triplet, time
T	=	temperature
^{t}Bu	=	tertiary-butyl
Tf	=	trifluoromethanesulfonyl
THF	=	tetrahydrofuran
THP	=	tetrahydropyran
TLC	=	thin layer chromatography
TMEDA	=	tetramethylethylenediamine
TMS	=	trimethylsilyl
μL	=	microlitre

1. Introduction

1.1. Background on three-membered rings

1.1.1. Bonding Properties of Cyclopropanes

Three-membered ring systems are very important building blocks in organic chemistry due to their versatility, along with their unique structural and electronic properties. The cyclopropyl sub-unit consists of three C-C bonds, which exhibit considerable ring strain as a result of the internal bond angles being 60°, which is significantly lower than the expected 109.5° for sp^3 hybridised orbitals. In addition to ring strain, there is also torsional strain due to the co-planar arrangement of the carbon atoms, which forces the C-H bonds to be eclipsed.[1] It is the relief of ring strain associated with ring-opening which helps to explain the lower thermodynamic stability and high reactivity of the cyclopropane ring.[2] Bonding within cyclopropanes has been described by two well known models: the Coulson-Moffit and Walsh models. [3,4] These represent equivalent descriptions of how the cyclopropane ring has been constructed. The Coulson-Moffit model suggests the cyclopropane is made from 3 sp^3 hybridised CH_2 groups, where the sp^3 hybridised orbitals deviate approximately 22° away from the imaginary line connecting the nuclei (Figure 1).[3]

Figure 1

As a result the overlap of the C-C bonds is poor, which is why the bonds are described as ''bent''. The increased *p*-character in the C-C σ-bond reduces the inter-orbital angle and improves the overlap of the p-orbitals.[5] However the Walsh model describes the cyclopropane ring as being formed from 3 sp^2 hybridised methylene groups.[4] The carbon-carbon bonds in the plane of the ring are then considered to be derived from six-

unhybridised carbon 2*p* orbitals, which leads to a delocalised molecular orbital (MO) with a maximum overlap inside the ring.[1](Figure 2)

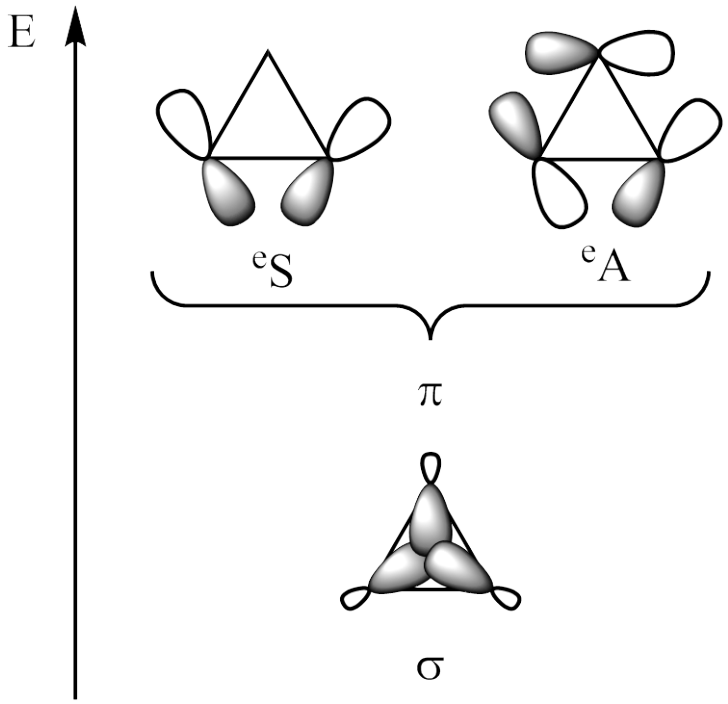


Figure 2

The molecular orbital of the lowest energy (σ) is shown by a linear combination of three sp^2 hybrid atomic orbitals, while the other two molecular orbitals (π) are shown by equal-energy linear combinations of three p-atomic orbitals.[2] In relation to the previous model, angular strain also occurs as a result of poor overlap.

1.1.2. The chemistry of cyclopropenes

Cyclopropenes have been described as important precursors in organic synthesis due to their ability to produce complex cyclopropanes. The rationale behind this is that the reduction of a cyclopropene into a cyclopropane is a highly exothermic process, which has proven to be useful in the more complex cases of cyclopropane synthesis in overcoming the difficulties that would arise with the use of unstrained precursors.[6] The physical properties of cyclopropenes are similar to that of the cyclopropane ring, where both are highly strained molecules.

The bonding within the cyclopropene ring has been explained by the Walsh model shown in Figure 3. The cyclopropene consists of two *sp*-hybridized vinylic carbon atoms where

one *p*-orbital on each is used in the formation of the double bond, while the other contributes to the ring.[7]

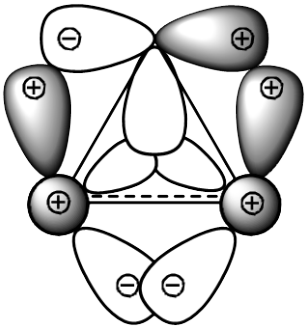


Figure 3

The remaining carbon atom is sp^2 hybridised as seen in the cyclopropane model.[1] The hybridisation of the alkene carbons are closer to that of an alkyne rather than an alkene, which helps explain the unusual reactivity of the cyclopropene ring.

Throughout the thesis the numbering of the cyclopropenes will start from the most substituted alkene carbon as illustrated in Figure 4.

Figure 4

1.1.3. Synthesis of Cyclopropenes

Initially cyclopropenes were synthesised from their corresponding cyclopropane precursors through elimination reactions, which has been extensively reviewed by Baird.[8] However more recently Doyle, Davies and Fox have reported the synthesis of racemic (Scheme 1) and enantioselective cyclopropenes **1** and **2** (Scheme 2) through catalytic cyclopropenation of alkynes with diazo compounds in the presence of a rhodium catalyst. [9,10,11]

R^1	R^2	R^3	Product	Yield (%)
H	Et	Me	$\mathbf{1}_a$	80
Ph	Me	Ph	$\mathbf{1}_b$	72
Ph	Me	butyl	$\mathbf{1}_c$	72
CO_2Me	Me	Ph	$\mathbf{1}_d$	69

Scheme 1

Scheme 2

The cyclopropenation reaction takes place *via* a rhodium carbenoid intermediate, which is followed by an electrophilic attack of the alkyne to afford the cyclopropene.

The conversion of cyclopropenes into cyclopropanes has been successfully achieved through a multitude of reactions, for example substitutions and hydrogenations.[12-13] However the work herein will focus on the metal-mediated and heteroatom nucleophilic additions of cyclopropenes.

1.2. Reactions of cyclopropenes

1.2.1. Carbometalation of cyclopropenes

The first metal mediated addition reaction was reported in 1967 by Welch and Magid, who demonstrated the ability of an unsubstituted cyclopropene **3** to undergo a *syn* selective addition reaction with phenyllithium, which was subsequently trapped with carbon dioxide

to afford the *cis*-2-phenylcyclopropene carboxylic acid **4** with an extremely low yield of less than 2.5% (Scheme 3).[14]

Scheme 3

The discovery that cyclopropenes undergo carbometalation reactions was a revelation and has since led to the synthesis of many cyclopropanes possessing an all-carbon quaternary centre with excellent regioselectivity. To date there has been many examples reported in the literature, however only a few have been selected to explain and show the progression of the chemistry in this area.

In the 1970s Nesmeyanova and Rudavshevskaya were the first to report the addition of Grignard reagents to cyclopropenes in a regiospecific manner, which was used in the synthesis of *cis*-Chrysanthemic acid **5**. (Scheme 4)[15]

Scheme 4

Many advances have been made in the carbometalation reaction of cyclopropenes, especially the work reported by Nakamura *et al*, which showed that cyclopropenone acetals were able to undergo enantioselective addition reactions with Grignard reagents and dialkyl zinc reagents when catalysed by iron (III) chloride.[16]

The initial work focused on the synthesis of cyclopropanones **7** by addition of a Grignard or dialkyl zinc reagent to a cyclopropenone precursor **6**. Di-substituted cyclopropanones were obtained in a diastereoselective manner, where the *cis*-isomer was exclusively formed. (Scheme 5)

Scheme 5

Nakamura *et al* researched the use of chiral ligands to extend the scope of their methodology using dialkyl zinc reagents, where they found (*R*)-*p*-Tol-BINAP to be the most effective chiral phosphine ligand affording the corresponding cyclopropanes in good yields with up to 92% *ee.* (Scheme 6)[16] It was found the addition of TMEDA slowed the reaction, but without it a racemic mixture was obtained. The results also showed that when the reaction was performed in THF rather than THP the enantioselectivity diminished significantly. (Scheme 6)

Entry	R_2Zn	Co solvent	R	Yield (%)	*ee* (%)
1	Pr_2Zn	THP	Pr	62	92
2	Et_2Zn	THP	Et	64	90
3	Et_2Zn	THF	Et	73	85

Scheme 6

Also within the Nakamura group they investigated the use of chiral Ligands in the synthesis of quaternary chiral centres *via* addition of an allylic zinc reagent attached to a chiral bisoxazoline ligand. (Scheme 7)[17] A test reaction was performed first with allylic zinc bromide, which successfully afforded product **9** within a regioselective manner.

Entry	R	Allyl Zinc	Conditions	Time (h)	Ratio (9:10)	Yield (%)	*ee* (%)
1$_a$	C_2H_5	Allyl ligand	25°C, 1 atm	200	100:0	64	>99
2$_b$	C_6H_5	Allyl ligand	25°C, 1 atm	70	100:0	51	>99.6
3$_c$	C_2H_5	Allyl ligand	25°C, 1 GPa	12	100:0	95	>98
4$_d$	C_6H_5	Allyl ligand	25°C, 1 GPa	12	100:0	98	>98
5$_e$	$(CH_3)_3Sn$	Allyl bromide	0°C, 1 atm	1	5:95	94	n/a
6$_f$	$(CH_3)_3Sn$	Allyl ligand	0°C, 1 atm	1	94:6	83	99.8

Scheme 7

The ligand possessing the allylic zinc reagent was prepared *in situ* starting from the bisoxazoline, which was treated with butyl lithium, followed by addition of the allyl zinc bromide. The reaction was first performed under ambient conditions, which afforded product **9** regioselectively but very slowly as indicated by entry 1 and 2. However when the reaction was performed under a pressure of 10 kbar the reaction took place cleanly to afford the allylation product in excellent yields and with > 99.6% *ee.* When the phenyl substituent in the bisoxazoline ligand was replaced with an alkyl chain the enantioselectivity and yield of the reaction was dramatically reduced. An interesting point to note is when the R^1 substituent on the cyclopropene was a group 14 metal derivative, the addition reaction performed with allylic zinc bromide resulted in a reversed regioselectivity favouring product **10** over product **9** with a ratio of 5:95(Scheme 7, entry 5). However the regioselectivity of the reaction could be reversed when in the presence of the ligand as shown by entry 6.

1.2.2. Facially selective and Hydroxyl directed carbometalation of Cyclopropenes

In the 1980s Richey and Bension were one of the first to address the regioselectivity for the addition of carbon nucleophiles to cyclopropenes. They discovered that the use of a hydroxyl group as a directing group afforded the *cis*-adduct predominately upon addition with an allylic Grignard reagent (Scheme 8).[18]

Scheme 8

However the reaction was very limited and only preceded with allylic Grignard reagents. The reaction was attempted with PhMgBr, *t*-BuMgCl and MeMgI without any success, where only the starting material was recovered. An interesting observation was made when the 3-hydroxylmethyl cyclopropene **11** was reacted with crotyl and cinnamyl magnesium chloride **12** and **13**. (Scheme 9)

Scheme 9

As shown in Scheme 9 the reaction with crotyl magnesium chloride **12** yielded two products, where the allylic transposition adduct **15** was favoured. In a similar way, the allylic transposition product **16** was only observed when the reaction was performed using cinnamyl magnesium chloride **13**. Although the work conducted by Richey and Bension was a valuable method of introducing allyl derivatives to hindered cyclopropenes, it lacked substrate scope due to the limited use of specific Grignard reagents.

The scope of introducing allyl derivatives to cyclopropenes was expanded by Araki and co-workers in 1998 through the use of allylindium reagents.[19a-b] They observed similar regioselective results as Richey and Bension 18 years before, confirming that the

mechanistic pathway must introduce the allyl group to the most substituted sp^2 carbon while the metal is transferred to the least-hindered carbon of the alkene bond, favouring formation of the *cis* cyclopropanes **17**$_{a\text{-}b}$. (Scheme 8)[19a]

R	Temp (°C)	Product	Yield (%)	*cis*:*trans*
CH_2OH	0-5	**17**$_a$	85	95:5
CO_2H	66	**17**$_b$	81	100:0

Scheme 10

The *cis*:*trans* ratio refers to the relationship between the R group at C3 and the introduction of the allyl group to C1 of the cyclopropane.

The formation of the *cis* adducts could be explained by chelation of the hydroxyl group to the indium atom of the allylindium reagent. This was further confirmed as the regioselectivity was reversed when the hydroxyl group of the starting material was protected with an acetate group or similarly when the carboxylic acid was converted into an ethyl ester. This resulted in formation of the *trans* allyl cyclopropanes **18**$_{a\text{-}b}$ as the preferential product in a regioselective manner. (Scheme 11)

R	Solvent	Temp (°C)	Product	Yield (%)	*cis*:*trans*
CH_2OAc	THF	25	**18**$_a$	66	0:100
CO_2Et	DMF	100	**18**$_b$	50	3:97

Scheme 11

Work by Araki also demonstrated that the regioselectivity of the reaction could be reversed when the hexyl chain was replaced with a hydroxyl carbon chain as illustrated in (Scheme 12).[19b]

Scheme 12

Treatment of the cyclopropene **19** with the tri-allyl, sesqui iodine-indium reagent and 1M HCl resulted in the formation of the cyclopropylindium complex **20**, where a small amount of the *trans* adduct **21** was also observed. The structure of complex was confirmed by X-ray diffraction analysis, which indicated that both the hydroxyl and carbonyl groups were chelated to the indium atom. Although the reaction mixture was treated with a 1M HCl solution, the cyclopropane/indium complex remained stable due to chelation, however a subsequent treatment with a more acidic 10M HCL solution afforded the corresponding C^2 allylated *cis*-adduct **22**. It was also noted that the length of the alkyl chain attached to the hydroxyl group directed the allylindation to the most substituted C-atom where only the *cis*-adduct **23** was observed.

Araki also showed the stereoselectivity of the reaction could be controlled by the polarity of the solvent, which suppressed the influence of the hydroxyl alkyl chain present at the C^1 position as shown in Scheme 13.

Entry	Solvent	Product	Yield (%)	*cis:trans*
1	THF	**25**	72	72:28
2	DMF	**25**	56	26:74
3	H_2O	**25**	75	6:94

Scheme 13

When the reaction was performed in THF, the *cis*-1,2-adduct was favoured due to chelation of both hydroxyl groups to the indium atom. However in the presence of water, the diastereoselectivity was reversed, affording the *trans*-adduct preferentially. This could be explained by water acting as a ligand, which prevented chelation of the hydroxyl groups to the indium complex. The work carried out to this point has shown the potential of using hydroxyl groups as directing groups to afford *cis* cyclopropanes selectively in a regio and

setereocontrolled manner. However the scope of this methodology was limited to the facially selective addition of allyl reagents to cyclopropenes.

Work by Fox and Liao expanded the scope of this reaction by demonstrating the ability of 3-hydroxymethyl cyclopropenes to undergo addition reactions with an array of Grignard reagents, which Bension was unable to achieve, to afford a range of facially selective cyclopropanes.[18,20] This was achieved by converting the hydroxyl group into a MOMO ether, as this protecting group is known for facilitating the *syn*-addition of Grignard reagents (Scheme 14).[20]

Entry	R	E^+	Conditions	*syn*:*anti*	Product	Yield (%)
1		H	1h, -20°C	96:4	**27**$_a$	81
2		MeI	1h, -20°C	97:3	**27**$_b$	83
3		H	1.5h, -40°C	96:4	**27**$_c$	81
4		H	1h, r.t.	75:25	**27**$_d$	67

Scheme 14

As can be seen in Scheme 15 the research group has shown that the cyclopropyl metal can also be trapped with an electrophile affording tetra-substituted cyclopropanes with a high degree of diastereoselective control. It was originally thought that the MOM group was required to direct the *syn* addition of the Grignard reagents, although this was not the case as the reaction proceeded with a similar diastereoselectivity when the reaction was performed with the corresponding hydroxyl deprotected cyclopropenes. A few examples are shown in Scheme 15.

Scheme 15

In the examples shown in Scheme 15 the reaction mixtures were quenched with water, apart from compound **28**$_d$ which was subjected to a CO_2 atmosphere, prior to the acidic work-up. The work presented by Fox and Liao clearly shows advancement in the addition of other types of carbanions to afford a range of functionalised cyclopropanes with quaternary centres.

The methodology was further improved by Fox and Liu in 2005, when they confirmed the ability of unsubstituted hydroxymethyl cyclopropenes to undergo enantio- and facially selective addition with MeMgCl as shown in Scheme 16.[21]

Scheme 16

In contrast to previous work with 3-hydroxylmethyl cyclopropenes, an additional substituent was placed at the C^1 position, which had been briefly investigated by Fox in earlier work. A range of ligands were screened and *N*-methylprolinol was found to afford the cyclopropanes in good yields with *ee* ranging from 91 to 98%. To achieve a high enantioselectivity, the cyclopropene was added to a pre-reacted mixture of MeMgCl and

N-methylprolinoate in a 1:1 ratio. This step was found to be critical to allow the formation of a chiral '*N*-methylprolinoate- MgMe' complex which was subsequently allowed to react with the cyclopropenes in an enantioselective manner.

During this research it was observed that old bottles of MeMgCl afforded the cyclopropane **29**$_a$ with a 93% *ee*, however the same reaction performed with a newly ordered reagent bottle afforded the desired cyclopropane **29**$_a$ with only 67% *ee*. It was later discovered that these surprising results were due to the presence of methoxide ions formed in the older reagent bottles. This restriction was overcome by the addition of MeOH to the reaction mixture.

In contrast to previous reactions performed with 3-hydroxylmethyl cyclopropenes, Fox *et al* showed that a cyclopropene tethered with a SEM/MEM protected pendant hydroxyl group **30** favoured the formation of the methylenecyclopropane **32** rather than the expected *syn* directed cyclopropane **31** as illustrated in Scheme 17.[22]

Scheme 17

The group discovered that the methylenecyclopropane could be isolated exclusively in using magnesium bromide Grignard reagents instead of their chloride equivalents. The reaction proceeded successfully using alkyl, allyl and methyl magnesium bromides affording the corresponding methylene cyclopropanes **33**$_{a-d}$ in a regio- and diastereoselective manner without any addition of copper iodide. A few examples are shown in Figure 5.

Figure 5

It was postulated from previous studies that chelation of the metal with the protected pendant hydroxyl group influenced the regioselectivity of the reaction. Replacement of the MOM ether group with a bulky trityl ether group prevented chelation to the metal centre and reversed the regioselectivity to favour product **35** over **36** as shown in Scheme 18.

Scheme 18

1.2.3. Use of Ester functionalities as *syn*-directing groups in Carbometalation reactions

The directed carbometalation reaction of cyclopropenes has been well documented using a hydroxyl group as the preferred *syn*-directing group as other functionalities such as the ester substituent have prevented the carbometalation reaction from taking place. However work by Rubin and Gevorgyan in the hydroboration of cyclopropenes have shown that the use of an ester group at the C^1 position also directed *syn*-addition of the metal complex to afford the cyclopropane boronates in an enantioselective fashion.[23] (Scheme 19)

Entry	R^1	R^2	R^3	Product	Ligand	*cis*/*trans*	Yield (%)	*ee* (%)
1	Me	CO_2Me	H	**38**$_a$	(*R*)-BINAP	>99:1	94	94
2	TMS	CO_2Et	H	**38**$_b$	(*R*)-BINAP	>99:1	99	97
3	Ph	CO_2Me	H	**38**$_c$	(*R*)-BINAP	>99:1	99	92
4	CO_2Me	CO_2Me	H	**38**$_d$	(*S*)-Tol-BINAP	n/a	99	98
5	Me	CH_2OMe	H	**38**$_e$	(*R*,*R*)-Et-BPE	>99:1	98	87
6	CO_2Me	CO_2Me	^{n}Bu	**n/a**	(*R*)-BINAP	n/a	0	n/a

Scheme 19

It can be seen from the results that the cyclopropanes were afforded in a high degree of diastereo- and enantioselective control achieving enantiomeric excesses of up to 98%. It was also shown that the methoxy substituent **37**$_e$ served as an excellent directing group affording the *cis*-adduct **38**$_e$ predominately. In all cases the *cis*-isomer was obtained exclusively apart from entry 6, where the corresponding furan derivative was observed.

A more recent example by Tarwade *et al* demonstrated the selective addition of organozinc reagents to ester and oxazolidine directed cyclopropenes to exclusively afford the *syn*-selective adduct as shown in Scheme 20. [24]

Scheme 20

It was found that the addition of organozinc reagents was successfully catalyzed by either CuI or CuCN affording the *syn*-selective cyclopropanes in a regio- and diastereoselective fashion. The solvent used was also found to be an important factor in the diastereoselectivity of the reaction, where the use of THF rather than toluene resulted in a decrease in diastereoselective control. Ester substituted cyclopropanes known to be unstable were converted into their corresponding acyloxazolidine from their carboxylic acid parent. These new amide-cyclopropenes were then subjected to the carbozincation conditions, successfully affording the *syn*-selective cyclopropanes in good yields and with excellent diastereoselectivity.[24]

1.2.4. Organolithium Carbometalation

In 1962 Breslow was one of the first to report the addition of a metal hydride to 2,3-diphenylcyclopropene carboxylic acid **39** to afford 1,2-α,α-diphenyl-3-β-hydroxylmethyl cyclopropane **40** as a single diastereoisomer.[25] (Scheme 21)

Scheme 21

Many years later further work was completed by Vidal and Domnin, which proved the reaction proceeded with a high degree of regio and diastereoselective control by means of deuterium labelling.[26] Since this, a vast improvement has been made in the hydroalumination reaction of the cyclopropenyl ring. Work by Marek and Zohar have shown the feasibility of cyclopropenylcarbinols **41**$_{a\text{-}e}$ to be reduced *trans*-selectively which had been difficult to achieve in the past as illustrated in Scheme 22.[27]

Entry	SM	R^1	R^2	R^3	Product	d.r.	Yield (%)
1	**41**$_a$	H	CH_3	Et	**42**$_a$	80:20	50
2	**41**$_b$	CH_3	CH_3	Et	**42**$_b$	>98:2	86
3	**41**$_c$	CH_3	H	Et	**42**$_c$	>98:2	80
4	**41**$_d$	CH_3	CH_3	$CH_2CH{=}CHEt$	**42**$_d$	>98:2	80
5	**41**$_e$	CH_3	$SiMe_3$	Et	**42**$_e$	>98:2	64

Scheme 22

The first reaction performed, entry 1 showed the *trans*-adduct **42**$_a$ was predominately formed but with only a moderate *trans*-selectivity. The selectivity was significantly enhanced as shown in entries 2-5 with geminal dialkyl cyclopropenes, where only a single diastereoisomer was afforded. The reduction of the cyclopropylcarbinols was dependent on the solvent as the use of a more polar solvent such as THF instead of diethyl ether afforded the product with only a 6:1 diastereomeric excess. Further investigations on the use of cyclopropene carbinols showed that the reaction did not proceed when the hydroxyl group was protected with *tert*butyldimethylsilyl ether.

1.2.5. Organocopper mediated carbometalation

To extend the scope of the methodology, Simaan and Marek varied the type of organometallic reagent used in the reduction of the alkene. They found that the selectivity of the carbometalation could be controlled by the type of organometallic reagent used to favour the *syn*- or *anti*- cyclopropane selectively.

Entry	SM	R	Product	*anti*:*syn*	Yield (%)
1	**43**$_a$	CH_2CH_2Ph	**44**$_a$	75:25	76
2	**43**$_b$	*i*-Pr	**44**$_b$	>95:5	82
3	**43**$_c$	*t*-Bu	**44**$_c$	>95:5	73
4	**43**$_d$	Ph	**44**$_d$	85:15	70

Scheme 23

It has been shown that when the cyclopropenes **43**$_{a-d}$ were treated with butyl magnesium chloride the *anti*-cyclopropanes **44**$_{a-d}$ (Scheme 23) were afforded selectively, whereas the use of dibutyl cuprate afforded the *syn*-cycloproplycarbinols **45**$_{a-d}$ predominately.[28] (Scheme 24)

Entry	SM	R	Product	*anti*:*syn*	Yield (%)
1	**43**$_a$	CH_2CH_2Ph	**45**$_a$	5:95	78
2	**43**$_b$	*i*-Pr	**45**$_b$	10:90	87
3	**43**$_c$	*t*-Bu	**45**$_c$	5:95	83
4	**43**$_d$	Ph	**45**$_d$	10:90	75

Scheme 24

During their investigations, Simaan and Marek noted that the R group in α position to the hydroxyl group had an effect on the diastereoselectivity of the carbometalation. When the cyclopropene **43**$_c$, bearing a bulky *tert*-butyl group was reacted with BuMgCl the cyclopropane **44**$_c$ (Scheme 23, entry 1) was afforded in 76% yield with a *d.r.* >95:5. However when the substituent was replaced with a phenyl group, the cyclopropane **44**$_d$ (Scheme 23, entry 4) was isolated in a similar yield but with a diminished *d.r.* of 85:15.

1.2.6. Tin mediated hydrometallation onto Cyclopropenes

In 2002 Rubina, Rubin and Gevorgyan reported for the first time a stereo- and regioselective transition-metal catalyzed hydro, sila- and stannation reaction of cyclopropenes.[29] A variety of disubstituted cyclopropenes were reacted with either a tri alkyl or aryl tin hydride in the presence of $Pd(PPh_3)_4$ to afford tri- and tetra-substituted cyclopropylstannanes with a high degree of selectivity as illustrated in Scheme 25.

Entry	SM	R^1	R^2	R^3	R^4	R^5	Product	Yield (%)
1	**46**$_a$	Me	Ph	H	H	Me	**47**$_a$	91
2	**46**$_b$	Me	Ph	H	H	Ph	**47**$_b$	92
3	**46**$_c$	Me	CO_2Me	H	H	Bu	**47**$_c$	85
4	**46**$_d$	Me	Me	CH_2OTBS	H	Bu	**47**$_e$	68
5	**46**$_e$	Me	Me	TMS	CO_2Me	Bu	**47**$_f$	82
6	**37**$_e$	CH_2OMe	Me	H	H	Bu	**47**$_d$	67[*]

[*] *d.r. 4:1*

Scheme 25

The tin hydride source was delivered to the least hindered face of the cyclopropenes no matter what substituents were attached to the metal. The hydrometallation afforded the adduct as a single regio- and diastereoisomer, however the cyclopropene **37**$_e$ possessing an alkoxylmethyl substituent (entry 6) led to a mixture of diastereoisomers with a *d.r.* of 4:1.

This was thought to occur due to a possible coordination of the palladium species to the oxygen heteroatom, which promoted addition to the most hindered face. During the investigation it was also discovered that the substituted cyclopropenes could undergo silastannation and distannation reactions when catalysed with palladium acetate and Walborsky's ligand to afford the corresponding tetra-substituted cyclopropanes as a single diastereoisomer (Scheme 26).[29]

Entry	SM	R^1	R^2	Tin species	Product	Yield (%)
1	**46**$_a$	Me	Ph	$Me_3SnSnMe_3$	**48**$_a$	83
2	**46**$_a$	Me	Ph	$Bu_3SnSiMe_3$	**48**$_b$	94
3	**46**$_g$	CO_2Et	TMS	$Bu_3SnSiMe_3$	**48**$_c$	85

Scheme 26

In 2004 Gevorgyan *et al* devised an enantioselective route for the hydrostannation of di-substituted cyclopropenes in the presence of a diphenylphosphinobenzoic acid derived ligand as illustrated in Scheme 27.[30]

Scheme 27

The reaction was mediated using a rhodium catalyst and the selective outcome of the reaction was controlled by the steric effect of groups at C^3 of the cyclopropenes to afford the cyclopropanes as single diastereoisomers. It was observed during the investigation that tri- and tetra-substituted cyclopropenes were unable to undergo hydrostannation under the present conditions. The research group have also shown the ability of di-, tri- and tetra-substituted cyclopropenes to undergo selective addition with other transition metal hydrides such as germanes and bimetallic species such as ditins and silyltins.[31]

More recently Rubin *et al* have shown that cyclopropenes can also undergo hydrophosphorylation and hydrophosphinylation when catalyzed by palladium to afford the corresponding phosphorous substituted cyclopropanes $\mathbf{49}_{a\text{-}d}$ in a diastereoselective manner (Scheme 28).[32] Again the results showed that the diastereoselectivity of the reaction was controlled by steric factors associated with the substituent at R^1, where a methyl group favoured the *trans*-isomer. However when the methyl group was replaced with a phenyl group, the diastereoselectivity of the reaction was significantly reduced. Replacement with a more sterically demanding group such as TMS reversed the diasteroselectively of the reaction affording the *cis*-isomer $\mathbf{49}_{d}$ exclusively as shown in Scheme 28.

Scheme 28

1.2.7. Selective addition of Heteroatoms to Cyclopropenes

To date in the literature nucleophilic additions onto cyclopropenes have been reported mainly utilising organometallic processes and less emphasis has been made on

conventional organic nucleophilic additions. Padwa and Wannamaker found during a study that a sulfonyl substituted cyclopropene **50** underwent an addition reaction in the presence of methanol as illustrated in Scheme 29. [33]

Scheme 29

The reaction was thought to take place *via* attack of the alkoxide onto the silyl group. This resulted in the formation of the protonated cyclopropene intermediate **51**. This was followed by the addition of the remaining alkoxide ion onto the activated cyclopropene to exclusively afford the *trans*-cyclopropane **52**.

The methodology was further expanded by Martínez-Grau and Vaquero who reported the diastereoselective addition of thioalkoxides and selenides to non activated cyclopropenes as shown in Scheme 30.[34]

Entry	X	R	Solvent	Yield (%)	Ratio 54:55
1$_a$	S	Me	CH_3CN	54	80:20
2$_b$	S	Et	CH_3CN	50	92:8
3$_c$	S	Ph	CH_3CN	37	5:95
4$_d$	Se	Me	DMF	48	22:78
5$_e$	Se	Ph	DMF	58	5:95

Scheme 30

When thioalkoxides were used as nucleophiles (Scheme 30, entries 1 and 2), the addition onto cyclopropene **53** afforded the corresponding *trans*- cyclopropanes **54**$_{a,b}$ as the nucelophile was delivered to the least hindered side. However in the presence of a larger R

group such as phenyl, the diastereoselectivity was reversed to afford the *cis*-cyclopropane **55**$_c$ as the major isomer (entry 3). The use of selenides as nucleophiles also reversed the diastereoselectivity of the reaction, favouring formation if the *cis*-isomers **55**$_{d,e}$ in the presence of either a small or large R group (entries 4, 5).

1.2.8. Addition to conjugated alkynylcyclopropenes

Alkynylcyclopropenes are of particular interest due to the presence of an extremely reactive triple bond combined with an unsaturated three-membered ring, which are prone to nucleophilic additions.

Shavrin *et al* inadvertantly discovered that alkynyl aminocyclopropanes could be synthesised from their corresponding alkynyl halocyclopropanes (Scheme 32).[35] Their initial work focused on the synthesis of 1-alkynylcyclopropenes by treatment of 1-(alk-1-ynyl)-1-chlorocyclopropane **56**$_{a,b}$ with an excess of lithium *N*,*N*-dialkylamide in THF to afford the desired alkynylcyclopropenes **57**$_{a,b}$ (Scheme 31).[35]

Entry	SM	R	Product
1	**56**$_a$	^{t}Bu	**57**$_a$
2	**56**$_b$	adamantyl	**57**$_b$

Scheme 31

The cyclopropenes were found to be unstable and therefore were expected to undergo addition with either lithium diethyl- or diisopropylamide, however this was not observed under the present conditions. In contrast, the alkynylchlorocyclopropanes were converted directly into the corresponding alkynyl aminocyclopropanes **58**$_{a-f}$ when treated with lithium derivatives of dimethylamine and cyclic amines in 40-78% yields as illustrated in Scheme 32.

Entry	SM	R^1	R^2	Product
1	**56**$_a$	^{t}Bu	pyrrolidine	**58**$_a$
2	**56**$_a$	^{t}Bu	morpholine	**58**$_b$
3	**56**$_b$	adamantyl	morpholine	**58**$_c$
4	**56**$_c$	Ph	morpholine	**58**$_d$
5	**56**$_c$	Ph	Me	**58**$_e$
6	**56**$_c$	Ph	piperazine	**58**$_f$

Scheme 32

In examples **56**$_{a\text{-}c}$, where the R^1substituent was a bulky *tert*-butyl or adamantyl group and in the presence of either lithium morpholide or pyrrolidide, the corresponding *trans* cyclopropane was afforded exclusively. Although in examples **58**$_{d\text{-}f}$, where the R^1 substituent was a phenyl group a mixture of *trans* and *cis* isomers of the cyclopropanes were afforded in ratios of 2.2:1 to 3:1. The stereoselectivity of the reaction was shown to be dependent on the substituents in both the starting alkynylhalocyclopropanes and in the lithium dialkylamides.

Further studies proved the reaction took place *via* the formation of an alkynylcyclopropene intermediate resulting from a dehydrochlorination of the starting halocyclopropane. A further nucleophilic addition of lithium dialkylamide onto the newly formed alkene afforded the alkynyl aminocyclopropane.[35]

The methodology was further expanded by Shavrin *et al* in 2008, where they reported the addition of alcohols and phenols to 1-alkynylhalocyclopropanes *via* their respective alkynylcyclopropene intermediate[35] The alkynylhalocyclopropanes were added to a mixture of the alcohol in alkaline DMSO to afford the corresponding alkoxy-substituted alkynylcyclopropanes in 37-80% yields with *trans*:*cis* ratios of 4:1 to 2:1 as shown in Scheme 33.

Scheme 33

A point to note is the R^1 substituent on the alkyne was shown to have a significant effect on the reaction. For example when the substituent was a phenyl, the reaction proceeded smoothly with all the alcohols listed, however when replaced with the *tert*-butyl group only methanol was able to undergo addition cleanly. This was thought to be associated with the stronger electron-withdrawing properties of the phenyl ring, which in turn would polarize the double bond in the cyclopropene to a greater extent and consequently facilitate the addition of the relative nucleophiles. However the presence of the *tert*-butyl group was shown to increase the stereoselectivity of the reaction, where only the *trans*-isomer was observed.

More recently the research group have also shown that pyrazole and imidazole are also able to react with the alkynylhalocyclopropanes. Using the same reaction conditions, the alkynyl-diazolylcyclopropanes **59**/**60** were synthesised in 23-69% yields (Scheme 34).[36]

Entry	R	SM	Diazole (XH)	Time (h)	Yield (%)	Ratio: 59:60
1$_a$	Ph	**56**$_c$	imidazole	1	52	3.2:1
2$_b$	Ph	**56**$_c$	pyrazole	1	69	4.5:1
3$_c$	^{t}Bu	**56**$_a$	pyrazole	6	38	100:0
4$_d$	^{t}Bu	**56**$_a$	2-methyl-imidazole	6	23	100:0

Scheme 34

1.2.9. Nucleophilic substitutions of bromocyclopropanes

In relation to the work described by Sharvin *et al*, Rubin and co-workers have recently reported the nucleophilic substitution of bromocyclopropanes with Oxygen – and Sulfur based nucleophiles.[37] They discovered that treatment of the bromocyclopropylcarboxamide with 18-crown-6 ether , powdered KOH, and an oxygen based nucleophile afford the *trans* cyclopropanes predominately. (Scheme 35)

Entry	R^1R^2	RO	Product	Yield (%)	d.r.
1	^{t}Bu, H	*n*-PrO	**63**$_a$	71	39:1
2	Et, Et	$MeOCH_2CH_2O$	**63**$_b$	87	16:1
3	^{t}Bu, H	$H_2C{=}CH(CH_2)_3O$	**63**$_c$	85	7:1
4	Me, MeO	$PhCH_2O$	**63**$_d$	44	>25:1
5	^{t}Bu, H	PhO	**63**$_e$	79	>50:1
6	^{t}Bu, H	*p*-MeO-C_6H_4O	**63**$_f$	75	7:1
7	Et, Et	*o*-F-C_6H_4O	**63**$_g$	82	12:1
8	^{t}Bu, H	*p*-I-C_6H_4O	**63**$_h$	80	10:1

Scheme 35

The reaction proceeded well with a wide range of alkoxides and phenoxides as outlined in Scheme 35 to afford cyclopropanes **63**$_{a\text{-}h}$ in excellent yields and a high degree diastereoselectivity. The reaction took place *via* dehydrobromination to afford the cyclopropene intermediate **62** which rapidly underwent addition with the nucleophile to afford the corresepponding cyclopropane. The research group proved that the diastereoselectivity of the reaction was controlled by epimerization of the tertiary carbon atom adjacent to the amide functionality rather than the reversible addition of the nucleophilic species. The group also showed that the cyclopropenes were able to undergo addition with thiolates, but the diastereoselectivity of the reaction was significantly reduced with most examples achieving a 2:1 mixture of diastereoisomers.

1.2.10. Ring-opening of cyclopropropenes

In the literature there are many examples of carbometalation reactions of cyclopropenes, where direct addition to the carbon-carbon double bond has resulted in preservation of the cyclopropane ring as explained previously.[21-24, 29-32] However there are a few examples of metal catalyzed addition to cyclopropenes, which have undergone ring-opening to afford a range of allylated compounds.

Work by Nakamura *et al* in 2003 successfully reported the palladium-catalyzed addition of carbon and nitrogen pronucleophiles to dihexylcyclopropenes **64** to afford the corresponding allylated products **65**$_{a\text{-}d}$ in 40-85% yields as shown in Scheme 36.[38]

Scheme 36

Deuterium labelling experiments were performed, which gave evidence to support the proposed mechanism shown in Scheme 37, where the nucleophile and its hydrogen were transferred onto the same carbon. However, more investigations would be required to confirm the mechanistic pathway as two routes A or B are plausible.[38] The route A describes the oxidative insertion of palladium (0) into the C-C bond of the cyclopropene to afford the palladacyclobutene intermediate **66**a, which would subsequently react with the pronucleophile to afford a π-allylpalladium complex **68**, followed by a reductive elimination to obtain the allylated product **69**. Whereas route B described the oxidative insertion of palladium (0) into either H-C or H-N bond to afford the intermediate hydride species **66**b, followed by hydropalladation of the alkene to afford the cyclopropylpalladium

intermediate **67**b. Subsequent cleavage of the C-C double bond would lead to the formation of the π-allylpalladium complex **68**.

Scheme 37

In addition to this work, Lam *et al* have developed the method further by illustrating the stereoselective synthesis of tri- and tetrasubstituted alkenes *via* iron-catalyzed carbometalation of cyclopropenes, followed by subsequent cleavage of the C-C sigma bond. (Scheme 38)[39]

Entry	SM	R^1	R^2	R^3	EWG	Product	Yield (%)
1	**70**$_a$	Bn	Ph	Me	CO_2Bn	**71**$_a$	66
2	**70**$_b$	Me	Benzyl	Et	CO_2Me	**71**$_b$	72
3	**70**$_c$	Me	*p*-Tolyl	^{n}Pr	CO_2Me	**71**$_c$	72
4	**70**$_d$	Me	Ph	Me	SO_2Ph	**71**$_d$	61

Scheme 38

To allow the ring-opening to take place, two electron withdrawing groups positioned at C^3 of the cyclopropene ring were required in addition to $Fe(acac)_3$ catalyst to promote the

carbometalation reaction. The reaction proceeded in a smooth manner, affording a range of trisubstituted alkenes **71**$_{a\text{-}d}$ with a stereoselectivity greater than 19:1. Functionalities of the substituents at R^1, R^2 and R^3 of the corresponding ester group, cyclopropene and trialkylaluminium moieties were well tolerated as shown in Scheme 38. The regioselectivity obtained for this reaction was in line with the results observed for previous carbometalation of cyclopropenes, where the alkyl nucleophile was delivered to the most substituted carbon of the alkene.

The group also synthesised a range of tetrasubstituted alkenes, with an additional TMS group attached to the cyclopropene ring **72**, where a high degree of regioselectivity was also obtained. Although the regioselectivity observed was different to the trisubstituted alkenes as the alkyl group was delivered to the least hindered carbon as illustrated in Scheme 39.

Scheme 39

1.3. Cycloaddition reactions onto cyclopropanes

1.3.1. Discovery and application

In the early 1980s the first dipolar cycloaddition of cyclopropanes was discovered by Schuchardt, Trost and Tsuji.[40a-c] Initial studies showed ring-opening of the methylenecyclopropane **74** in the presence of a nickel catalyst was trapped with electron-deficient olefins to afford the corresponding cyclopentane derivatives **75** and **76** as a mixture of regioisomers. However it was soon discovered that the same reaction performed with palladium (0) afforded the cyclopentane adduct **76** as a single regioisomer, where ring-opening of the cyclopropane took place between C^2 and C^3 as shown in Scheme 40

Scheme 40

In order for the cycloaddition reaction to take place, ring opening is essential, revealing a dipolar species. There are two main requirements for the ring opening to occur: the strength of the electron-withdrawing group to stabilise an adjacent negative charge combined with the ability of an electron-rich group such as an aryl to stabilise the positive charge. In later years, work by Tsuji developed this idea further by demonstrating the first palladium-catalyzed [3+2] cycloaddition reaction of vinylcyclopropanes with α, β-unsaturated esters and ketones (Scheme 41).[41]

Scheme 41

The success of the reaction depended on the formation of the zwitterionic π-allylpalladium complex **78**, which was subsequently trapped with the electron-poor olefins to afford the desired vinylcyclopentane **80**. This was achieved through a nucleophilic addition of the Pd^0 onto the vinyl group **77**, which resulted in an opening of the cyclopropane ring, revealing the zwitterionic π-allylpalladium complex **78**. The presence of the ester moieties stabilised the carbanion, while the carbocation was stabilised by the π-allylpalladium complex. This was followed by a Michael addition of the electron poor olefins onto the carbanion to form the second intermediate **79**, which rapidly cyclised to afford the vinylcyclopentanes **80** in 77-84% yields.

1.3.2. [3+2] dipolar cycloaddition reactions

While investigating the Michael addition of indoles onto activated 1,1-cyclopropanediesters, Kerr *et al* inadvertently discovered the [3+2] annulation of alkylindoles with cyclopropanes affording a new tricyclic indole derivative.[42,43] As depicted in Scheme 43, **84** was formed along with the desired Michael product **83**. It soon became apparent that the introduction of a substituent at C^3 of the indole $\mathbf{82}_{c,d}$ favoured formation of the tricyclic product $\mathbf{84}_{c,d}$. A few examples have been shown in Scheme 42.

Entry	R^1	R^2	R^3	R^4	Yield (%) 83	Yield (%) 84
$\mathbf{1}_a$	Me	H	H	Et	75	n/a
$\mathbf{2}_b$	Me	H	Ph	Me	97	n/a
$\mathbf{3}_c$	Me	Me	H	Et	5	41
$\mathbf{4}_d$	Bn	Me	diphenyl	Et	n/a	45

Scheme 42

The formation of the product shown in Scheme 43 is thought to have occurred *via* an attack of the malonate anion onto the iminium ion **85** indicated by path **b**, which must be in competition with the deprotonation and rearomatisation of the benzopyrrole to afford the expected indole **83** as shown by path **a** in Scheme 43.

Scheme 43

1.3.3. Use of [3+2] dipolar cycloadditions in the synthesis of oxazine derivatives

The [3+2] cycloaddition reaction with indoles developed by Kerr led to the belief that cyclopropanes had a very similar reactivity to α,β-unsaturated carbonyl moieties in their ability to react with nucleophiles in a homo-Michael type addition. Hence the use of substituted cyclopropanes as precursors for cycloaddition reactions has become very popular due to their ability to undergo ring-opening while in the presence of a Lewis acid.

Kerr postulated that the presence of a Lewis acid coordinating to the ester groups combined with the substitution of the cyclopropane with an electron donating group such as an electron rich aryl would considerably enhance the degree of charge separation between the cyclopropane carbons. This would result in a weakness of the cyclopropane, hence a higher reactivity. With this in mind Kerr was the first to demonstrate the homo [3+2] dipolar cycloaddition of cyclopropane diesters with a range of nitrones to afford the corresponding tetrahydro-1,2-oxazines **87**$_{a\text{-}f}$ in excellent yields as illustrated in Scheme 44.[44]

Entry	SM	Nitrone	R^1	R^2	R^3	R^4	t (h)	Product	Yield (%)
1	**81**$_a$	**86**$_a$	Ph	*p*-tolyl	H	Et	18	**87**$_a$	77
2	**81**$_a$	**86**$_b$	Ph	Me	H	Et	18	**87**$_b$	76
3	**81**$_b$	**86**$_a$	Ph	*p*-tolyl	Ph	Me	18	**87**$_c$	94
4	**81**$_e$	**86**$_a$	Ph	*p*-tolyl	styryl	Me	5	**87**$_d$	95
5	**81**$_f$	**86**$_b$	Ph	Me	styryl	Me	36	**87**$_e$	74
6	**81**$_g$	**86**$_b$	Ph	Me	vinyl	Et	18	**87**$_f$	52

Scheme 44

The results appeared to be consistent with what was suggested previously, in the fact that the presence of either a phenyl or a styryl group vicinal to the diester substituent on the cyclopropane ring improved yields. These results, as well as the *cis* regioselectivity observed can be explained by the presence of a π system vicinal to the diester moiety, which further enhances the charge separation undergone by the cyclopropane when in the presence of ytterbium triflate as shown in Figure 6.[44]

Figure 6

In all cases the oxazines were obtained as single diastereoisomers, where substituents at C^3 and C^6 favoured a *cis*-relationship. The mechanism for the reaction is believed to occur in a stepwise manner, involving an initial attack of the nitrone oxygen atom onto the cyclopropane followed by attack of the malonate anion onto the carbocation of the iminium ion **88**(Scheme 45).

Scheme 45

During their investigations, Kerr *et al* found that in some instances the nitrones were unstable under the present Lewis acid conditions, making the reaction substrate specific.[44] Kerr addressed this in developing a one-pot synthesis, where nitrones were prepared *in situ*, and subsequently reacted with the cyclopropane in the presence of the Lewis acid to afford the tetrahydro 1,2 oxazines as the *cis* diastereoisomer exclusively, in yields ranging from 66 to 93%. An example of this is shown in Scheme 46.[45a-b]

Scheme 46

The success of this methodology was then applied to the synthesis of FR900482 congeners as illustrated in Scheme 47.[45a] First part of the synthesis involved the formation of the oxazine core as previously described, whereby the following adduct was treated under Heck conditions to afford the corresponding tricyclic product. A variety of analogues were then synthesised and one of the examples has been shown in Scheme 47.

Scheme 47

$Yb(OTf)_3$ was initially found to be the most efficient Lewis acid in promoting the ring-opening of the cyclopropyl subunit to afford the oxazines in excellent yields and with a

high degree of diastereocontrol. However it soon became apparent to Kerr that the use of magnesium iodide (MgI_2) significantly increased the overall yielding of the products, but a small proportion of the *trans* cycloadduct was obtained,[46] which had not been observed in the presence of $Yb(OTf)_3$. It was observed while utilising MgI_2 as the Lewis acid that a nitrone derived from formaldehyde and a N-oxide could be used in the cycloaddition reaction while this was not permitted when $Yb(OTf)_3$was used. This observation was of importance as it enabled the synthesis of an unsubstituted oxazine ring which played a crucial part towards the total synthesis of FR900482.[47]

Sibi and co-workers took the method developed by *Kerr et al* and devised an enantioselective route to afford a range of oxazines with enantiomeric excesses of up to 99%.[48] This was achieved by the use of a chiral Lewis acid catalyst, where two types of ligands were tested; PyBox and bisoxazoline ligands as shown in Figure 7. The use of PyBox ligands resulted in very low enantioselectivities, but the bisoxaline ligand $\mathbf{91}_g$ combined with nickel perchlorate as the Lewis acid afforded the oxazines with a high degree of enantiocontrol. Although when the reaction was performed with a mono-substituted cyclopropane diester, a mixture of *cis*/*trans* diastereoisomers was observed as illustrated in Scheme 48. On a positive note, the enantioselectivity for both isomers were good where the *trans*-isomers were particularly remarkable with ≥95% *ee*. In all cases a complete degree of regioselectivity was observed, with the oxygen of the nitrone adding to the most substituted carbon of the cyclopropane ring.

Figure 7

Entry	R^1	R^2	product	yield (%)	*trans:cis*	*ee (%)* *trans* (*cis*)
1	Me	*p*-Br-C_6H_4	**92**$_a$	99	0.8:1	96 (90)
2	Ph	*p*-Br-C_6H_4	**92**$_b$	99	1.4:1	95 (90)
3	Ph	Ph	**92**$_c$	99	1.4:1	96 (90)

Scheme 48

In 2007 Tang *et al* improved the method conducted by Sibi and co-workers by maintaining the diastereoselectivity of the reaction of which Kerr had originally reported, as well as maintaining excellent enantioselectivity with mono-substituted cyclopropane diesters. [49] This was achieved with the trisoxazoline ligand as shown in Scheme 49.

Entry	R^1	R^2	Time (days)	Yield (%)	d.r. (*cis:trans)*	*ee* (%)
1	Et	Ph	4	99	99:1	57
2	Et	Me	4	88	11:1	95
3	Me	Me	3	82	13:1	90

Scheme 49

The reaction proceeded well with a range of electron-rich and electron-deficient aryl nitrones. However when the substituent on the nitrogen atom of the nitrone was a phenyl group a dramatic increase in the diastereoselectivity of the reaction was observed with a *cis*:*trans* ratio of 99:1, but the enantioselectivity of the reaction was reduced with an *ee* of only 57% (entry 1 Scheme 49). Replacement of the phenyl group with a methyl group significantly increased the enantioselectivity of the reaction with an *ee* of up to 95% (entry 2), but this in turn diminished the diastereoselectivity of the reaction, although ratios from 4:1 to 13:1 were sufficiently afforded.

In relation to this, Kerr *et al* also showed that the use of a chiral cyclopropane in both enantiomers was able to undergo the cycloaddition reaction catalyzed by the original $Yb(OTf)_3$ Lewis acid. This resulted in the formation of both enantiomers of the oxazines with a high degree of diastereocontrol and excellent enantioselectivity with *ee* up to 95% was observed.[50] It was also noted that, as the reaction progressed, a racemisation of the chiral cyclopropane took place and the *ee* of the oxazine diminished with time.

Through the progression of the cycloaddition reaction of cyclopropane diesters with nitrones, Kerr *et al* thought it wise to investigate the mechanism of the homo [3+2] dipolar cycloaddition.

Scheme 50

They found that the reaction of nitrones with the 2,3-*cis*-disubstituted cyclopropane $\mathbf{93}_a$ resulted in 5,6-*trans*-oxazines $\mathbf{94}_{a\text{-}c}$ (Scheme 50) and the 2,3-*trans*-disubstituted cyclopropane $\mathbf{93}_b$ results in 5,6-*cis*-oxazines $\mathbf{94}_{d,e}$ (Scheme 51).[51]

Scheme 51

These results showed that the yield of the cycloaddition diminished significantly when performed with the *trans*-disubstituted cyclopropane. It also proved their original theory that the reaction took place through a stepwise mechanism as shown in Scheme 52 with inversion of configuration which takes place in S_N2 nucleophilic additions.[51]

Scheme 52

The methodology used by Kerr in the synthesis of oxazines has been applied towards the synthesis of two complex natural products: (+)-phyllantidine and Nakadomarin A.[52,53] In the total synthesis of (+) phyllantidine, the oxazine core was afforded through a three-component coupling of the cyclopropane diester, hydroxylamine and aldehyde in the presence of ytterbium triflate[52] (Scheme 53). The oxazine **95** was afforded as a 12:1 mixture of diastereoisomers, where the major isomer showed the required *cis*-relationship

between C^3 and C^6 of the oxazine. The natural product **96** was afforded in 11 steps starting from the oxazine core in an overall yield of 6%.

Scheme 53

Within a similar time span Kerr *et al* reported the synthesis of the tetracyclic core of Nakadomarin A.[53] The synthesis commenced with the same 3-component coupling as shown previously to afford the corresponding tetrahydro 1,2-oxazine **97** exclusively as the *cis*-isomer in 74% yield. A subsequent 9 steps led to the formation of the tetracyclic core **98** within Nakadomarin A. (Scheme 54)

Scheme 54

For interest into the total synthesis of Nakadomarin A using the methodology described refer to the relevant review by Kerr.[54]

1.3.4. Intramolecular [3+2] cycloaddition reactions

Cycloadditions reported so far have not demonstrated an intramolecular cyclisation, until recently, where Kerr *et al* have reported the successful synthesis of bridged bicyclic tetrahydro-1,2-oxazines *via* an intramolecular cyclisation as illustrated in Scheme 55.[55]

Aldehyde-tethered cyclopropane	R	Time (h)	Product	Yield (%)
	PMB	15	**101**$_a$	63
	Bn	16.5	**101**$_b$	80
	Me	17	**101**$_c$	83
	PMB	48	**101**$_d$	91
	PMB	72	**101**$_e$	89

Scheme 55

The bridged oxazines **101**$_{a\text{-}e}$ were afforded *via* a nitrone-tethered cyclopropane **100**, which was formed *in situ* from a condensation reaction between an aldehyde-tethered cyclopropane **99** and a hydroxylamine. This was followed by an intramolecular cyclisation upon addition of $Yb(OTf)_3$. It was noted that the presence of an electron-withdrawing or donating group on the cyclopropane tethered aldehydes did not affect the efficiency of the reaction, producing adducts **101**$_d$ and **101**$_e$ in excellent yields. The mechanism of the reaction was thought to take place *via* an attack of the malonate ion onto the iminium species **102** to yield the cycloadduct **101** as shown in Scheme 56.[55]

Scheme 56

Treatment of the bridged bicyclic oxazines with zinc dust in glacial acetic acid resulted in a reductive N-O bond cleavage to successfully yield the *cis*-selective 1,4-aminocyclohexanols **103** in high yields (Scheme 57). These compounds are of significant importance as they resemble a motif in the natural product pancratistatin.[56]

Scheme 57

1.3.5. Synthesis of tetrahydrofuran derivatives *via* the [3+2] cycloaddition reaction

In light of the successful methodology used by Kerr in the ability of activated cyclopropanes to undergo nucleophilic ring-opening/cycloaddition reactions with indoles and nitrones,[44] Johnson *et al* reported the synthesis of tetrahydrofurans *via* an adaptation of this method.[57a-c] This was achieved *via* a cycloaddition reaction with donor-acceptor cyclopropane diesters and conjugated aldehydes catalysed by $Sn(OTf)_3$ (Scheme 58).

Entry	R^1	R^2	Time (h)	Product	Yield (%)	*cis*/*trans*
1	Ph	Ph	2.5	**104**$_a$	100	>100:1
2	Ph	*p*-MeO-C_6H_4	3.5	**104**$_b$	98	>86:1
3	Ph	*p*-O_2N-C_6H_4	15	**104**$_c$	89	>19:1
4	2-thienyl	Ph	0.45	**104**$_d$	97	20:1
5	styrenyl	Ph	1	**104**$_e$	94	2.4:1

Scheme 58

The 2,5-disubstiututed tetrahydrofurans **104**$_{a\text{-}e}$ were obtained in a high degree of diastereoselective control, where the *cis*-isomers were predominately formed. The reaction proceeded well with both electron-rich and electron poor aldehydes; however, 2-pyridinecarboxaldehyde was unreactive due to the potential coordination of tin triflate with the nitrogen of pyridine.

In 2009 Johnson and Parsons reported the synthesis of enantio enriched tetrahydrofurans *via* a dynamic kinetic asymmetric cycloaddition of racemic cyclopropanes with aldehydes under the influence of a chiral Lewis acid as illustrated in Scheme 59.[58]

Entry	R^1	R^2	Yield (%)	*ee* (%)
1	*p*-MeO-Ph	*p*-MeO-C_6H_4	88	90
2	*p*-MeO-Ph	*p*-F_3C-C_6H_4	48	83
3	*p*-MeO-Ph	2-thienyl	84	91
4	2-thienyl	styrenyl	91	94
5	2-thienyl	Ph	64	93
6	styrenyl	*p*-MeO-C_6H_4	75	90

Scheme 59

The tetrahydrofurans were obtained in a diastereoselective manner, where the *cis*-isomer was predominately formed and the *R,R* enantiomer was the most favoured with *ee* up to 94%.

1.3.6. Applications of [3+2] cycloaddition reaction to Natural Products

The methodology developed by Johnson *et al* was applied to the asymmetric synthesis of (+) polyanthellin A.[59a-b] It was established from the retrosynthesis shown in Scheme 60 that the hydroisobenzofuran **107** could be achieved through a [3+2] cycloaddition of the complex cyclopropane **105** with the β-silyloxy aldehyde **106**.

Scheme 60

The synthesis of the bicyclo heptanone synthon **105** was achieved in five steps from isovaleraldehyde. The silyloxy aldehyde synthon **106** was synthesised from the readily available isobutenol. The cycloaddition was first attempted using standard Lewis acid conditions, with either tin chloride or tin triflate, however this led to competitive elimination and the cyclic adduct was not obtained. It was later discovered that the use of the hindered catalyst MADNTf$_2$ [(ArO)$_2$AlNTf$_2$] resulted in the cycloaddition, affording the hydroisobenzofuran **107** in a 76% yield with a high degree of diastereocontrol. It was proposed that the cycloaddition took place through a cationic aluminium complex, which activated the bicyclo heptanone *via* chelation.[59a]

More recently Kerr *et al* have applied the successful cyclopropane/aldehyde cycloaddition reaction in the asymmetric synthesis of (+) isatisine A starting from the homochiral (S)-vinylcyclopropane diester.[60a-b] A close examination of isatisine A (Figure 8) revealed the stereochemistry between C^2 and C^5 of the tetrahydrofuran could be achieved through a cycloaddition reaction starting from the *S* cyclopropane.

Figure 8 - isatisine A

The synthesis of isatisine A **113** started with the formation of the tetrahydrofuran ring through a Lewis acid-catalyzed cycloaddition reaction of the chiral (S)-vinyl cyclopropane diester **110** and *N*-tosyl indole-2-carboxaldehyde **111**.[60a] (Scheme 61)

Scheme 61

The tetrahydrofuran **112** was afforded in 89% yield as an 11:1 mixture of diastereoisomers, where formation of the 2,5-*cis* isomer was favoured. With the correct stereochemistry in place, an additional 13 steps afforded the natural product **113** in an overall yield of 5.6%.

1.3.7. Synthesis of Pyrrolidines and Pyrazolines derivatives *via* the cycloaddition reaction

The original methodology reported by Kerr and co-workers for the cycloaddition reaction of activated cyclopropanes with nitrones has also been reported with imines in the synthesis of pyrrolidines.[61] Originally the imines were prepared and reacted by addition to the cyclopropane diesters, however it was noted that some imines were unstable and as a result a significant reduction in yields were obtained. This led to a one-pot procedure being applied, where the imine was formed *in situ* before addition of the cyclopropane diester as illustrated in Scheme 62.[61]

Entry	R^1	R^2	R^3	Product (*cis*)	Yield (%)	(*cis*:*trans*)
1	Ph	Bn	Ph	**114_a**	96%	93:7
2	Furan	Bn	Ph	**114_b**	93%	55:45
3	*p*-MeO-C_6H_4	Bn	Ph	**114_c**	95%	99:1
4	thiophene	Ph	H	**114_d**	95%	100:0
5	*p*-MeO-C_6H_4	Bn	styryl	**114_e**	76%	85:15

Scheme 62

The pyrrolidines were obtained with excellent diastereoselectivity, where the *cis*-isomer was predominately formed. This was further enhanced by the presence of an electron rich aryl group (entry 3). In an attempt to explain the *cis* outcome of the reaction, Kerr proposed two mechanistic pathways which are outlined in Scheme 63.

Scheme 63

As a result of the *cis*/trans geometry of the imines, either **114-*cis*** or **114-*trans*** could be afforded, with **114-*cis*** being at a higher energy state. Intermediate **115_a** would afford the *cis*-isomer by a Mannich ring closure and similarly intermediate **115_b** would afford the *trans*-isomer. The positioning of the geminal diester should enable the retro-Mannich

process to take place, which would leave a reasonable pathway for the less stable *trans* isomer to be converted to the more stable *cis* isomer.

Kerr reported that $Yb(OTf)_3$ was the most efficient Lewis acid to catalyze the cycloaddition reaction. Although reports by Tang and co-workers showed that scandium triflate was able to catalyze the reaction with an increase in diastereoselectivity and a lower catalyst loading.[62] A few examples are shown in Figure 9.

Figure 9

In these examples the imines were synthesised prior to the reaction *via* a condensation between amines and aldehydes. The results showed that both electron-rich and poor imines were successful in the cycloaddition reaction. The position of the substituent on the aryl groups affected the yield obtained, where the *para*-substituted imines were favoured over the *ortho*-substituted imines as a result of steric interactions.

The discovery of imines to undergo a cycloaddition reaction with activated cyclopropane diesters to afford 2,5-disubstituted pyrrolidines was a significant development on previous methods. However the substrate scopes of the imines used were limited to aryl substituents, where no reaction was observed with aliphatic imines. Kerr and co-workers originally thought that the substrate scope could be improved by the use of oxime ethers, as they envisioned this would increase the nucleophilicity of the nitrogen towards ring-opening as illustrated in Scheme 64.[63] Although it was soon discovered that the reaction

was limited to a few substrates, with diminished yields and could only be performed in neat conditions.

Scheme 64

To overcome this problem the group created an intramolecular variant in the form of an oxime ether-tethered cyclopropane, which underwent ring-opening in the presence of $Yb(OTf)_3$ to afford a wide range of 2,5-trans-pyrrolo-isoxazolidines *via* an oxy-iminium intermediate (Scheme 65).

Entry	Parent aldehyde/ketone	Product	Yield (%)	(*trans:cis*)
1	*p*-bromo-benzaldehyde	**118**$_a$	99	100:0
2	*p*-methoxy-benzaldehyde	**118**$_b$	99	100:0
3	*trans*-cinnamaldehyde	**118**$_c$	81	10:1
4	isobutyraldehyde	**118**$_d$	82	8:1
5	Pyridine-2,6-dicarboxaldehyde	**118**$_e$	70	100:0
6	Methyl benzoylformate	**118**$_f$	98	100:0

Scheme 65

The examples shown in entries 1, 5 and 6 were afforded from the enantiopure (S)-cyclopropylalkoxylamine as a single diastereoisomer with *ee* greater than 99%. The reaction proceeded well with a broad range of substrates; including electron rich and deficient aryl groups, aliphatic, dialdehydes and ketones with excellent diastereoselectivity. The research group discovered that the stereochemical outcome of the reaction was dependant on the geometry of the starting oxime ether. For example the minor *Z*-oxime **117**$_Z$ afforded the *cis*-isomer exclusively, whereas the major *E*-oxime **117**$_E$ afforded the

trans-isomer exclusively. It was envisioned by the group that in order to gain access to the 2,5-*cis*-isomer, the *Z*-oxy-iminium species $\mathbf{119}_Z$ would need to be favoured over the *E*-oxy-iminium species $\mathbf{119}_E$ as illustrated in Scheme 66.

Scheme 66

It was thought this could be achieved by treatment of the alkoxylamine **116** with $Yb(OTf)_3$ first to generate the isoxazolidine **120** before addition of the aldehyde. (Scheme 67) This would most likely result in the *Z*-oxy-iminium species as the most favoured conformation to afford the *cis*-adduct.[63] The hypothesis was tested and resulted in the successful synthesis of 2,5-*cis*-pyrrolo-isoxazolidines with excellent yields and diastereoselectivity. An example is shown in Scheme 67.

Scheme 67

The group has also demonstrated the ability of pyrrolo-isoxazolidines to be converted into highly substituted pyrrolidines *via* N-O bond cleavage. This was achieved through hydrogenation in methanolic HCl to suppress the isomerisation, which was observed under standard conditions to afford the pyrrolidine salt **121** in a high degree of diastereocontrol as represented by the example shown in Scheme 68.

Scheme 68

Kerr *et al* applied the same methodology in the synthesis of fused bicyclopyrazolidines **124**$_{a\text{-}f}$, where the oxime ether tethered cyclopropane **116** was replaced with a hydrazinoethyl 1,1-cyclopropanediester **122** as illustrated in Scheme 69.[64]

Entry	R/aldehyde	Product	Yield (%)	(*trans:cis*)
1	*p*-methoxy-benzaldehyde	**124**$_a$	83	100:0
2	*p*-nitro-benzaldehyde	**124**$_b$	90	100:0
3	*trans*-cinnamaldehyde	**124**$_c$	83	100:0
4	2-napthaldehyde	**124**$_d$	97	5:1
5	1-tosyl-1*H*-indole-carboxyaldehyde	**124**$_e$	82	2.7:1
6	pivaldehyde	**124**$_f$	70	100:0

Scheme 69

Treatment of the hydrazinoethyl 1,1-cyclopropanediesters **122** with a range of aldehydes in the presence of $Yb(OTf)_3$ initiated the formation of the hydrazone intermediate **123**, which subsequently cyclised to afford the 2,5-*trans*-pyrazolidines **124**$_{a\text{-}f}$ as the dominant product. In some cases as shown by entries 4 and 5 some of the *cis*-isomer was observed. The reaction took place with a diverse range of aldehydes as shown in Scheme 69, where

electron rich and poor aryl aldehydes, heteroaromatic aldehydes and sterically demanding aldehydes such as pivaldehyde afforded the cycloadducts in excellent yields and diastereoselectivities.

The diastereoselectivity of the reaction was in agreement with Kerr's previous work regarding oxime ethers,[63] which implied the reaction occurred through the same mechanistic pathway as described earlier in Scheme 66.

This encouraged the group to apply the same conditions used in earlier work to afford the 2,5-*cis*-isomer as the dominant product. In order to achieve this, the cyclopropane was first treated with $Yb(OTf)_3$ in refluxing dichloromethane to generate the pyrazolidine **125**, followed by addition of the aldehyde to afford the 2,5-*cis* cycloadducts preferentially (Scheme 70).

Entry	R/aldehyde	Product	Yield (%)	(*cis:trans*)
1	*p*-methoxy-benzaldehyde	**124**$_a$	72	2:1
2	*p*-nitro-benzaldehyde	**124**$_b$	84	3.7:1
3	*trans*-cinnamaldehyde	**124**$_c$	83	2.1:1
4	2-napthaldehyde	**124**$_d$	75	3.4:1
5	benzaldehyde	**124**$_g$	81	3:1
6	isobutyraldehyde	**124**$_h$	65	1:3

Scheme 70

However the diastereoselectivity of the reaction for the formation of the 2,5-*cis* cycloadducts were poor compared to the diastereoselectivity observed with the oxime ether cyclopropane diesters.[63] It was thought this happened due to a decrease in selectivity for formation of the *Z*-aza-iminium intermediate. To overcome this issue the Boc-protecting group was replaced with a less hindered methyl carbamate **126** to afford the 2,5-*cis*-isomers preferentially, where a significant increase in diastereoselectivity was observed in most cases as reflected by the results shown in Scheme 71. The only exception was

isobutyraldehyde (entry 6), which under the new conditions still afforded the 2,5-*trans*-isomer as the major product **127**$_f$.

Entry	R/aldehyde	Product	Yield (%)	(*cis:trans*)
1	benzaldehyde	**127**$_a$	83	6.5:1
2	*p*-methoxy-benzaldehyde	**127**$_b$	92	9.2:1
3	*p*-nitro-benzaldehyde	**127**$_c$	89	3.7:1
4	*trans*-cinnamaldehyde	**127**$_d$	85	3.3:1
5	2-napthaldehyde	**127**$_e$	86	6.8:1
6	isobutyraldehyde	**127**$_f$	64	1:1.66

Scheme 71

It became apparent that formation of the *cis*-isomer was dependant on the reaction time, where experiments showed that over a period of 27 hours the *cis*-isomer isomerised to the corresponding 2,5 *trans*-isomer with a ratio of 3.4:1.

1.3.8. Use of di-cobalt complexes in the [3+2] cycloaddition reaction with cyclopropanes

Within the Christie group we envisioned that an alkynyl substituent on a cyclopropane could be complexed as a cobalt hexacarbonyl derivative,[65] which would enable activation of the cyclopropane towards ring opening in order to undergo subsequent cycloadditions This is explained by the ring-opening of a cobalt complexed cyclopropanediester **128** under the influence of a Lewis acid to form the Nicholas carbocation **129** as illustrated in Scheme 72.

Scheme 72

The Scheme above shows that the cobalt alkyne unit stabilises the carbocation, while the ester moieties stabilises the carbanion.

The cobalt complexed cyclopropane was synthesised first as shown in Scheme 73.

Scheme 73

This was prepared in four steps, starting with formation of the vinyl cyclopropane **77**, upon reaction with dimethylmalonate and 1,4-dibromobut-2-ene **130**. Ozonolysis of the vinyl cyclopropane afforded the aldehyde **131**, which was reacted with the Bestmann reagent to afford the alkyne substituted cyclopropane **132**. The cyclopropane was complexed with cobalt to afford the cobalt hexacarbonyl cyclopropane **128** in 85% yield.

The cobalt complexed cyclopropane diesters **128** were then reacted with a variety of aldehydes in the presence of boron trifluoride etherate in dichloromethane to afford the desired tetrahydrofurans **133**$_{a\text{-}e}$ in high yields with poor diastereoselective control (Scheme 74). The cycloaddition reaction was limited to electron deficient aromatic, aliphatic and functionalised aldehydes, where no reaction was observed with electron rich aromatic aldehydes. The tetrahydrofurans were obtained as a 1:1 mixture of *cis*- and *trans*-isomers, where the best diastereomeric ratio obtained was 2:1 (entry 3) in favour of the *trans*-isomer.

Entry	R	Product	Temp (°C)	Yield (%)	*cis:trans*
1	Ph	**133**$_a$	40	83	1:1
2	4-$MeOC_6H_4$	**133**$_b$	0	0	n/a
3	4-$NO_2C_6H_4$	**133**$_c$	40	71	1:2
4	C_5H_{11}	**133**$_d$	40	83	1:1
5	$CO_2C_2H_5$	**133**$_e$	40	85	1:1.6

Scheme 74

The same conditions were applied using imines as the trapping reagent to afford the substituted pyrrolidines **134**$_{a-e}$ in relatively high yields[66] (Scheme 75).

Entry	R	R^1	Product	T(°C)	Yield (%)	*trans:cis*
1	4-$MeOC_6H_4$	CO_2Et	**134**$_a$	40	91	1:1
2	2,4-$(MeO)_2C_6H_4$	CO_2Et	**134**$_b$	40	80	2:1
3	4-Me-C_6H_4	CO_2Et	**134**$_c$	40	85	1:1
4	2-NC-C_6H_4	CO_2Et	**134**$_d$	25	72	1:3
5	C_6H_5	2-O_2N-C_6H_4	**134**$_e$	40	30	2:1

Scheme 75

Generally electron-withdrawing groups present on the imine carbon and electron donating groups on the nitrogen resulted in high yielding products. The results showed that the

diastereoselectivity increased to a maximum ratio of 3:1 compared to 2:1 ratio, which was obtained in the synthesis of the tetrahydrofurans. This only took place in the presence of an *ortho*-substituted aryl group such as *ortho*-nitrile, which gave a 3:1 ratio, preferentially as the *cis*-isomer **132**$_d$. When this was replaced with a nitro group a 2:1 ratio was observed in favour of the *trans*-isomer **134**$_e$ but a reduction in yield was obtained (entry 5 Scheme 75).

Kerr *et al* have also successfully reported the use of cobalt hexacarbonyl cyclopropanes **128** in [3+2] cycloadditions with nitrones *via* a Nicholas-type reaction in the presence of scandium triflate ($Sc(OTf)_3$) to afford a variety of oxazines **135**$_{a-e}$ in high yields (Scheme 76).[67]

Entry	R^1	R^2	Time (h)	Product	Yield (%)
1	Ph	Ph	3	**135**$_a$	90
2	Ph	4-$NO_2C_6H_4$	2	**135**$_a$	67
3	Ph	Thiophene	1	**135**$_a$	93
4	benzyl	4-MeO-C_6H_4	48	**135**$_a$	72
5	hexyl	Ph	21	**135**$_a$	56

Scheme 76

As stated, the majority of reactions were performed using 10 mol% $Sc(OTf)_3$, apart from entry 4 which required 20 mol% $Sc(OTf)_3$ to drive the reaction to completion. All oxazines were obtained as a single diastereoisomer, where substituents at C^3 and C^6 expressed a *cis*-relationship.

1.3.9. A radical approach towards the cycloaddition of activated cyclopropane diesters

An alternative method to the commonly used [3+2] cycloaddition reaction was reported by Oshima *et al*, where they demonstrated the synthesis of cyclopentane derivatives *via* a radical mediated cyclisation.[68] This was achieved through the generation of a benzenethiyl radical, which subsequently led to the formation of substituted cyclopentanes *via* ring-opening of the vinyl substituted cyclopropanediester, followed by the addition of electron rich and poor olefins. (Scheme 77)

Entry	R^1	R^2	Time (h)	Product	Yield	Isomeric Ratio (*cis*:*trans*)
1	H	O-Bu	0.7	**136**$_a$	82	65:35
2	Me	O-Me	16	**136**$_a$	71	100:00
3	Me	$OCOCH_3$	3	**136**$_a$	74	80:20
4	H	CO_2Me	48	**136**$_a$	38	76:24
5	H	CN	22	**136**$_a$	21	64:36

Scheme 77

The electron rich olefins afforded the cyclopentanes **136**$_{a\text{-}e}$ in high yields; however olefins possessing electron withdrawing groups resulted in poor yields (entry 4 and 5). Also for entries 4 and 5 the reaction was performed in benzene to prevent polymerisation of the olefin. The diastereoselectivity of the reaction was extremely low, apart from entry 2, where the *cis*-isomer was formed exclusively.

The group also demonstrated that the cycloaddition could take place with a vinylcyclopropane possessing only one ester moiety with both electron rich and poor olefins in 54-77% yields. The reaction was thought to take place through a step-wise mechanism, where the benzenethiyl radical attacks the vinyl group of the VCP **77** to form radical **137** on ring opening of the cyclopropane. This was followed by coupling of the radical **137** to the corresponding olefin to afford the second radical intermediate **138**,

which underwent cyclisation to afford the desired vinylcyclopentane **136** plus the regenerated thiyl radical. (Scheme 78)

Scheme 78

More recently Goff *et al* have shown the ability of 2-ethynylcyclopropane-1,1-dicarboxylates to undergo cycloadditions with electron rich olefins *via* radical addition[69] (Scheme 79).

Entry	Alkene	Product	Yield (%)	(*cis*:*trans*)
1$_a$	Butyl vinyl ether (R= OBu)		55	4.2:1
2$_b$	Allyl phenyl ether (R= CH_2OPh)		29	2.1:1
3$_c$	Allyl benzoate (R= CH_2O_2CPh)		30	2.5:1

Scheme 79

The initiator for the reaction was the phenylseleno radical, which was generated from PhSeSePh. The cyclopentane derivatives **139**$_{a\text{-}c}$ was achieved in relatively low yields through photolysis of a benzene solution containing the alkyne, olefin and PhSeSePh in a 1:10:0.2 molar ratio. In an attempt to increase the yield of the cycloadduct, 50 equivalents of the butyl vinyl ether were used but this only resulted in a 10% increase.

The mechanistic pathway for the reaction is shown in Scheme 80, where the generated phenylseleno radical attacks the terminal alkyne **132**, followed by ring-opening to afford the malonate radical substituted with a phenylselenoalkene **141**. The malonate radical then adds to the alkene generating a radical that cyclises back onto the allene to afford **143**, which is subsequently followed by the loss of the phenylseleno radical to afford the cyclopentane derivative **139**.

Scheme 80

2. Results and discussion

Activated cyclopropanes have been extensively used in synthetic chemistry as precursors in cycloaddition reactions. The main reason for this is their ability to undergo ring-opening when activated by Lewis acids which is further enhanced by the presence of a substituting aryl carbocation stabilising group such as phenyl.[44] This has led to the synthesis of many 5/6 membered heterocycles such as pyrrolidines,[61,62] oxazines and methylenecyclopropanes in excellent yields and diastereoselectivities.[45a, 48,53,70] To extend the scope of this methodology, we took the opportunity to examine the synthesis of activated cyclopropanes, di-substituted with various stabilising groups such as aromatics and *N*-heterocycles, to act as potential precursors in cycloaddition reactions. It was believed these features would lead to an increase in the regio- and diastereocontrol of the reaction.

The initial aim of the research project was to synthesise highly substituted heterocycles *via* 2,3-disubstituted cyclopropanes **146**. It was envisioned that this could be achieved through an array of Suzuki cross coupling reactions with the corresponding boron substituted cyclopropanes **145** to afford a diverse range of cycloadducts as illustrated in Scheme 81.

Scheme 81

2.1. Attempted synthesis of cyclopropyl boronates

2.1.1. First attempt-starting from vinyl boronic acid

Carboni, Maas and Pietruszka have successfully reported the synthesis of cyclopropylboronic acid esters. This was achieved *via* a carbene transfer to 1-alkenylboronic acid esters in good yields.[71,72] (Scheme 82)

Scheme 82

The methodology reported by Carboni and Maas was used in an attempt to allow the cyclopropanation of vinyl boronic pinacol ester **149** onto diazo dimethylmalonate **150**$_a$ *via* an acyl carbene transfer as depicted in Scheme 83.

Scheme 83

The starting material dimethyl diazomalonate **150**$_a$ was afforded in two steps as shown in Scheme 84. The mesyl azide **153** was obtained from the addition of sodium azide **152** to methansulfonyl chloride **151**, which was subsequently reacted with dimethylmalonate **154** in the presence of triethylamine to afford the dimethyl diazomalonate **150**$_a$ in 97% yield. (Scheme 84)

Scheme 84

A variety of conditions was tried and tested (Table 1), but unfortunately none of the desired product was afforded. In most cases either the vinyl boronic ester **149** was retained or a complex mixture was observed. It is believed the presence of two electron withdrawing groups attached to the diazomalonate **150**$_a$ attributed to this. As it was thought these would have lowered the reactivity of the acyl carbene transfer onto the vinylboronate. In an attempt to increase the reactivity of the carbene, ethyl diazoacetate **150**$_b$ was reacted with vinyl boronic ester (entry 3) utilising the same conditions reported in the literature, however only the ethyl diazoacetate dimer was observed even after careful addition.

Entry	R^1	R^2	Eq **150**$_{a,b}$	Product
1	CO_2Me	Me	2.5	**149**+ complex mixture
2	CO_2Me	Me	7.0	**149**+ complex mixture
3	H	Et	7.0	Dimer + complex mixture
4	H	Et	2.5	**149**+ complex mixture
5[1]	H	Et	7.0	complex mixture

[1]reaction performed in THF at 66°C

Table 1

^{1}H NMR analyses of the crude reaction indicated trace amounts of the desired product (entry 3), however degradation of the starting materials may have formed during the reaction as the majority of the signals were hidden under the dimer peaks. The latter could

unfortunately not be separated from the rest of the crude material. The catalyst used was palladium acetate (5 mol%) and no other catalysts were employed as the literature stated that the use of rhodium and copper catalysts were unsuccessful as both led to the formation of the carbene dimer. To explore the reactivity of the vinyl boronic acid in the cyclopropanation reaction, it was added with styrene to the reaction flask containing the diazo dimethylmalonate in the presence of rhodium acetate. This was performed to see if the reaction conditions were adequate for the reaction to proceed as styrene is known to undergo a [2+1] cycloaddition with diazo dimethylmalonate (Scheme 85).

Scheme 85

The reaction was performed with 0.5 eq of styrene **155** and the vinyl boronic acid **149** with 1 eq of the diazo dimethylmalonate **150**$_a$. The results showed that only the phenyl substituted cyclopropane diester was afforded, which implied that the diazo dimethylmalonate was less reactive towards the terminal bond of the boronic acid and further explains why the reaction may not have taken place.

2.1.2. Second attempt – Hydroboration of cyclopropenes

Hydroboration of olefins has been well documented and the reaction occurs with a *syn* addition of borane to the alkene. This borane is known to add preferentially to the least hindered carbon to form the anti-Markovnikov product. Hydroboration of cyclopropenes has been reported by Gevorgyan,[23] however only with mono substituted cyclopropenes. (Scheme 19) It was believed there was scope to address this by applying the reaction conditions he utilised to the hydroboration of a phenyl-substituted cyclopropene outlined in Scheme 86.

Scheme 86

The first part of synthesis involved the formation of the phenyl substituted cyclopropene $\mathbf{1}_d$. This was prepared using the method described by Fox *et al.*[73] A solution of the diazo dimethylmalonate $\mathbf{150}_a$ in dichloromethane was added slowly to a stirred solution of phenylacetylene **158** and rhodium (II) acetate dimer to afford the desired cyclopropene in 54% yield (Scheme 87).

Scheme 87

It was noted that the diazo compound must be added slowly to prevent formation of the carbene dimer. This was important as the nucleophilic attack of the diazomalonate with the catalyst to form the rhodium carbenoid intermediate has been proposed as the rate-limiting step of the catalytic cycle.

Pinacol borane was chosen as an alternative to the commonly used catecholborane as the hydroborating agent in the following reactions, due to its increased reactivity.[74] It is a stable hydroborating agent and adds to alkenes and alkynes at elevated temperatures; however it is known to decompose thermally resulting in a number of boron-containing products. The use of rhodium complexes enabled the pinacol borane to be used under milder conditions. Taking into consideration the above facts a variety of conditions were tried as illustrated in Table 2.

Entry	Catalyst	Reactant (eq)	Solvent	Temp (°C)	Time (h)	Product
1	$[Rh(COD)Cl]_2$ (3 mol %)	1.1	THF	25	2	$\mathbf{1}_d$
2	$Rh(PPh_3)_3Cl$ (6 mol %)	1.1	THF	25	4	$\mathbf{1}_d$+ complex mixture
3	$Rh(PPh_3)_3Cl$ (6 mol %)	1.1	THF	25	24	$\mathbf{1}_d$ + complex mixture
4	$[Rh(COD)Cl]_2$ (3 mol %)	1.5	CH_2Cl_2	25	24	Furan derivative
5	$[Rh(COD)Cl]_2$ (3 mol %)	1.5	Tol	110	24	$\mathbf{1}_d$+ uncharacterised product

Table 2

It can be seen that in all examples the boron-complex did not add across the cyclopropene. In the majority of cases the cyclopropene was retained, apart from one example when $[Rh(COD)Cl]_2$ was used in dichloromethane (entry 4) where the furan derivative was observed.[75] This was believed to be associated with the presence of two electron-withdrawing groups and a stabilising group adjacent to the alkene. It was assumed that the extra electron-withdrawing group destabilises the metallocarbene resulting in the formation of the furan derivative **158**. The scheme below illustrates a plausible mechanism which could explain the outcome of the reaction (Scheme 88).

Scheme 88

As the reactive substrate is a highly substituted olefin it was thought that employing a less bulky borane complex such as $H_3B.THF$, which in turn could be treated with ethylene glycol to afford the boronate ester $\mathbf{157}_b$ (Scheme 89).

Scheme 89

The synthesis of **157**$_b$ started from the phenyl cyclopropene **1**$_d$ which was treated with H_3B.THF in THF at 0°C prior to the addition of ethylene glycol. The resulting mixture was allowed stir at room temperature for a further 3 hours. Boron NMR analyses were performed on the mixture which unfortunately showed that none of the desired product was formed. This indicated that the BH_3 complex was not inserting into the relative alkene. The reaction was attempted utilising catechol and pinacol as alternatives to ethylene glycol, however this returned no results.

2.2. Third attempt-starting from 1-alkynyldiisopropoxyboranes

An alternative route was employed to synthesise cyclopropane **162** which involved cyclopropenation of 1-alkynyldiisopropoxyboranes **160** onto dimethyl diazomalonate **150**$_a$**.** The resulting cyclopropene **161** would then be subjected to hydrogenation to afford the corresponding cyclopropyl diisopropoxyborane **162** as outlined in Scheme 90.

Scheme 90

The first part of the synthesis involved formation of the phenyl-alkynyldiisopropoxyborane **160**. This was prepared utilising the procedure described by Brown *et al.*, where ^{n}butyl lithium was added to a solution of phenylacetylene **158** in Et_2O at -78^{o}C to afford the lithium acetylide **163**. The resulting mixture was subsequently added *via* a canula to a solution of triisopropylborane in Et_2O. A final addition of aqueous hydrochloric acid afforded the desired alkyne borane **160** in a moderate 46% yield. (Scheme 91) This was confirmed by proton and boron NMR which was in agreement with the literature values stated.[76]

Scheme 91

The prepared alkyne substituted borane **160** was subsequently reacted with the diazo dimethylmalonate **150**$_a$ in the presence of rhodium(II) acetate dimer (Scheme 90). The mixture was analysed by ^{1}H NMR which showed the methyl ester groups of the diazo dimethylmalonate were no longer seen as one chemical shift but as two with respective chemical shifts at 3.75 and 3.82 ppm. This implied that the two methyl groups were in different chemical environments. Additional analyses of the worked up mixture by ^{11}B NMR showed a significant chemical shift in the boron peak from 21.5 to 25.4 ppm. Upon purification by flash chromatography, the isolated product was identified as the mono-substituted phenyl cyclopropene derivative **1**$_d$ (Scheme 92).

Scheme 92

It was suspected that the isopropyl groups were hydrolysed due to the acidity of the silica. In an attempt to isolate the desired product, the reaction was repeated and the resulting crude mixture was distilled under a vacuum distillation apparatus, however this resulted in a complex mixture. It was then decided to adopt another approach using palladium acetate as the catalyst. This catalyst was chosen as the chemistry of Pd^{II} has been used and described in the literature as an efficient catalyst in cyclopropenations with boron substituted compounds. Unfortunately in this case only a complex mixture was obtained. Although there was enough evidence in our primary analyses to suggest the di-substituted cyclopropene had been obtained, however we were unable to isolate the desired product from the crude and no further attempts were conducted using this route. Instead, another

synthesis was designed to overcome the use of the capricious boronate substituted intermediates. The reason behind synthesising the cyclopropyl boronates was to obtain a cyclopropane precursor where the substituents could be varied using an efficient and quick methodology such as Suzuki cross coupling reactions.

2.3. Synthesis of 2,3 disubstituted cyclopropane diesters

Due to the unsuccessful synthesis of the cyclopropyl boronates another route was explored to afford the di-substituted cyclopropanes. Previously our research group primarily investigated the reactivity of mono-substituted 1,1-diester cyclopropanes. These were synthesised from various precursors such as alkyne-dicobalt hexacarbonyl complexes or cinnamaldehyde. These were shown to undergo [3+2] cycloaddition reactions with aldehydes or imines to afford their respective tetrahydrofurans and pyrrolidines in reasonable yields but with limited diastereoselectivity.[77] (Scheme 73 and Scheme 74)

A further development was made recently within the group, where a 2,3 disubstituted 1,1 cyclopropane diester was synthesised[78] (Scheme 93). The synthesis of disubstituted cyclopropane was achieved using a three step methodology. Treatment of the α/β unsaturated *trans*-cinnamaldehyde **164** with dimethyl bromomalonate **165** in the presence of diethyl amine afforded the aldehyde **166**. Subsequent addition of the Bestmann reagent to the aldehyde **166** afforded the alkyne **167** which underwent complexation with dicobalt octacarbonyl to afford the cyclopropane **168** in 36% yield over 3 steps.[78]

Scheme 93

However the cyclopropane **168** did not undergo cycloaddition reactions with aldehydes or imines upon treatment with Lewis acid. A new route was then explored to synthesise 2,3 disubstituted cyclopropane diesters possessing different stabilising groups such as substituted aromatics with the aim to overcome the issues associated with cyclopropane **168**.

To become familiar with the chemistry and the conditions best suited to synthesise these substituted cyclopropanes, an attempt was made to synthesise the 2,3-diphenyl cyclopropane diester **170**$_a$ outlined in Scheme 94. The reaction conditions used were reported by Doyle *et al* in the successful synthesis of the phenyl substituted 1,1 cyclopropane diester as described previously[79] (Scheme 85).

Scheme 94

Diazo dimethylmalonate and rhodium (II) acetate dimer were added to a stirred solution of *cis*-stilbene **169** in toluene, however after 2 days no reaction was observed. It was believed the presence of an extra stabilising group decreased the reactivity of the alkene to undergo cyclopropanation with the diazomalonate. The use of diazo ethylacetate could have been more successful as it is more reactive towards cyclopropanation. However, the presence of only one ester group to stabilise the negative charge during ring opening may diminish the reactivity of the cyclopropane towards ring opening. The presence of an extra chiral centre at the C^3 position would also increase the diastereomeric ratio of the reaction. A new route was explored, based on the work reported by Gevorgyan in the synthesis of di-substituted cyclopropenes.[13] Gevorgyan had shown that cyclopropenes underwent a Heck-type arylation reaction upon treatment with aryl iodides in the presence of palladium acetate and potassium carbonate. These conditions were utilised in the synthesis of the *cis* 2,3-disubstituted cyclopropanes **170**$_{a\text{-}g}$ outlined in Scheme 95.

Entry	R^1	R^2	Product	Yield (%)	Product	Yield (%)
1	Ph	Ph	**171**$_a$	51	**170**$_a$	80
2	Ph	4-MeO-C_6H_4	**171**$_b$	45	**170**$_b$	92
3	Ph	4-NO_2-C_6H_4	**171**$_c$	40	**170**$_c$	trace amount
4	Ph	4-F-C_6H_4	**171**$_d$	50	**170**$_d$	100
5	Ph	4-CF_3-C_6H_4	**171**$_e$	55	**170**$_e$	100
6	^{n}Bu	Ph	**171**$_f$	43	**170**$_f$	51
7	^{n}Bu	4-F-C_6H_4	**171**$_g$	42	**170**$_g$	50

Scheme 95

The phenyl and butyl substituted cyclopropene diesters were shown to undergo the Heck-type arylation reaction with both electron rich and poor aryl iodides in moderate yields. It was discovered that under these conditions the reaction was limited to only *p*-substituted

aryl/heteroaryl iodides as when 2-iodoanisole, 2-bromobenzaldehyde and 1-iodo-2-nitrobenzene was reacted with the phenyl cyclopropene none of the desired products were obtained. A range of palladium catalysts with different ligands were screened and the results are shown in Table 3.

Entry	catalyst	Product
1	5 mol % $Pd(OAc)_2$	Traces of product identified
2	10 mol% $Pd(OAc)_2$	$\mathbf{1}_d$
3	10 mol % $Pd(PPh_3)_3$	$\mathbf{1}_d$
4	10 mol% $Pd_2(dba)_3$	$\mathbf{1}_d$
5	10 mol% $PdCl_2$	Complex mixture

Table 3

However it can be seen from the results that changing the ligand of the palladium catalyst had no effect on the outcome of the product obtained. This implied the Heck reaction was dependent on the positioning of the iodo group attached to the aromatic ring. Gevorgyan proposed that arylation of the cyclopropene proceeded *via* a cationic pathway, (Scheme 96) whereby an electrophilic addition of the $ArPd^+$ species across the cyclopropene afforded the cyclopropyl cation **172**. The benzylic cation was additionally stabilised through interaction with the d orbitals of the Pd. This may explain the slight increase in yields when electron-deficient iodo-aromatic reagents were used (Scheme 95, entry 4 and 5). Gevorgyan postulated that the mechanistic pathway finishes with either a 1,3 shift of the aryl group or more likely by a reductive elimination of the co-ordinated nucleophile.

Scheme 96

The di-substituted cyclopropene diesters were then subjected to the hydrogenation conditions outlined in Scheme 95, where entries 1-2, 4-5 and 7-8 successfully afforded the

cyclopropanes in moderate to excellent yields. The fluoro and trifluoromethyl substituted phenyls (entry 4 and 5) underwent the hydrogenation in quantitative yields and no purification was required. When the *p*-nitrophenyl substituted cyclopropene was subjected to the hydrogenation conditions, (entry 3) it was observed that the nitro group may have been reduced to the amine during this process. However only a tentative assignment of the crude product by NMR was obtained as attempts at purification of the product failed when subjected to column chromatography.

2.4. Cycloadditions with di-substituted cyclopropanes

Reports by Kerr *et al.* successfully demonstrated the feasibility of the [3+3] dipolar cycloaddition of nitrones with cyclopropanes; however this was reported using mono-substituted cyclopropanes primarily.[61,62,70] Therefore we decided to focus our research on the reactivity of disubstituted cyclopropanes in the [3+3] cycloaddition reaction. The rationale in using disubstituted cyclopropanes is that they are known to have strained bonds showing significant π character. Within the cyclopropane diester the bond can be polarised and weakened by co-ordination of a Lewis acid to one or both of the ester substituents as shown in Figure 10.[61] The charge separation can be further enhanced by the presence of a carbocation-stabilising substituent (R^1 and R^2) such as phenyls, vinyls or organometallic complexes enabling them to be useful precursors in cycloaddition reactions.

Figure 10

Nitrones were preferentially chosen over imines or aldehydes to perform the [3+3] instead of the [3+2] dipolar cycloadditions as there had been extensive literature reported in this field resulting in high yielding products.

2.4.1. Synthesis of nitrones

Several nitrones were prepared in relatively high yields *via* a condensation reaction between the hydroxylamine hydrochlorides and aldehydes, heated to reflux in anhydrous dichloromethane in the presence of a desiccant (Scheme 97).

A variety of nitrones were prepared from *N*-benzyl hydroxylamine **173**$_a$ or *N*-methyl hydroxylamine **173**$_b$ and various aldehydes. Results of their respective synthesis are outlined in Scheme 97. In most cases, the use of electron rich aldehydes afforded the corresponding nitrones in higher yields compared to the use of electron deficient aldehydes (entries 4,8,9). However when *p*-nitrobenzaldehyde **174**$_b$ was allowed to react with *N*-benzyl hydroxylamine, the corresponding nitrone **175**$_b$ was surprisingly afforded in a respectable 61% yield (entry 2).

Entry	R^1	Amine	R^2	Aldehyde	Product	Yield (%)
1	benzyl	**173**$_a$	MeO-C_6H_4	**174**$_a$	**175**$_a$	72
2	benzyl	**173**$_a$	NO_2-C_6H_4	**174**$_b$	**175**$_b$	61
3	methyl	**173**$_b$	MeO-C_6H_4	**174**$_a$	**175**$_c$	63
4	methyl	**173**$_b$	O_2N-C_6H_4	**174**$_b$	**175**$_d$	52
5	benzyl	**173**$_b$	C_5H_4OS	**174**$_c$	**175**$_e$	57
6	methyl	**173**$_b$	C_5H_4OS	**174**$_c$	**175**$_f$	54
7	methyl	**173**$_b$	Me-C_6H_4	**174**$_d$	**175**$_g$	54
8	methyl	**173**$_b$	F_3C-C_6H_4	**174**$_e$	**175**$_h$	32
9	benzyl	**173**$_a$	F_3C-C_6H_4	**174**$_e$	**175**$_i$	46

Scheme 97

2.4.2. [3+3] cycloadditions

The cycloaddition reaction was performed with the diphenyl cyclopropane diester initially to investigate the feasibility of the reaction. Results are summarised in Scheme 98. We initially utilised the reaction conditions described in the literature by Kerr *et al.* to perform the [3+3] dipolar cycloaddition reaction of nitrones with the disubstituted cyclopropanes (entry 1). The majority of the reactions were performed at room temperature for a period of 24 hours, however the reaction time was extended when magnesium iodide was utilised as the Lewis acid (entry 5). The reaction time was also extended to 72 hours when nitrone **175**$_e$ was allowed to react with the diphenyl cyclopropane **170**$_a$ in dichloromethane at room temperature (entry 8).

Entry	Nitrone	Nitrone (eq)	Lewis acid	Solvent	Product	Yield (%)
1	**175**$_a$	1.2	$Yb(OTf)_3$ 5 mol %	CH_2Cl_2	**176**$_a$	23
2[1]	**175**$_a$	1.2	$Yb(OTf)_3$ 10 mol %	CH_2Cl_2	**176**$_a$	25
3[2]	**175**$_a$	1.2	$Yb(OTf)_3$ 5 mol %	CH_2Cl_2	**176**$_a$	30
4[1]	**175**$_a$	2.5	$Yb(OTf)_3$ 5 mol %	CH_2Cl_2	**176**$_a$	32
5[3]	**175**$_a$	2.5	MgI_2 5 mol %	CH_2Cl_2	**170**$_a$	>90
6	**175**$_d$	2.5	$Yb(OTf)_3$ 5 mol %	CH_2Cl_2	**176**$_b$	23
7	**175**$_d$	5.0	$Yb(OTf)_3$ 5 mol %	CH_2Cl_2	**170**$_a$	>90
8[3]	**175**$_e$	2.5	$Yb(OTf)_3$ 5 mol %	CH_2Cl_2	**176**$_c$	24
9	**175**$_b$	2.5	$Yb(OTf)_3$ 5 mol %	CH_2Cl_2	**176**$_d$	33
10[1]	**175**$_e$	2.5	$Yb(OTf)_3$ 5 mol %	DCE	**176**$_c$	57
11[1]	**175**$_a$	2.5	$Yb(OTf)_3$ 5 mol %	DMF	**170**$_a$	>90
12[1]	**175**$_b$	2.5	$Yb(OTf)_3$ 5 mol %	Tol	**176**$_d$	24

[1] reaction performed at reflux

[2] Microwave conditions performed at 110^{o}C for 30 min

[3] reaction time extended to 72 hours

Scheme 98

Cyclopropane **170**$_a$ was allowed to stir for ten minutes in anhydrous dichloromethane with 5 mol % $Yb(OTf)_3$ prior to the addition of nitrone **175**$_a$. The desired 1,2 oxazine **176**$_a$ was afforded in a very low 23% yield (entry 1) and 43% of the cyclopropane was recovered. This implied the reaction was not going to completion and therefore a variety of reaction conditions were implemented in an attempt to improve the yields of the cycloadduct. Hence the cycloaddition reaction was repeated under reflux, but this led to no improvement of the yield. (entry 2) To stress the reaction further, the reaction was performed under microwave conditions but only a slight increase in yield was observed. (entry 3) The cyclopropane **170**$_a$ was able to be recovered when conventional heating was utilised, however this was not observed when microwave irradiation was used due to decomposition. The amount of nitrone used in the reaction was increased, however only a slight improvement was observed (entry 4). An alternative Lewis acid MgI_2 was employed as Kerr had demonstrated this to be an efficient catalyst, but in our case only the cyclopropane was recovered after 24 hours (entry 5). To assess the effect of the nitrone on the cycloaddition reaction, a more electron rich nitrone **175**$_d$ was used, but this only afforded the oxazine **176**$_b$ in 23% yield (entry 6). In an attempt to drive the reaction further, 5 equivalents of nitrone were employed; however this only returned the cyclopropane **170**$_a$ (entry 7). This could be explained by saturation of the reaction mixture with the nitrone which may have prevented the Lewis acid from co-ordinating to the ester moieties of the cyclopropane. This would have resulted in a reduced weakening of the bond within the cyclopropane to undergo ring-opening. An electron deficient nitrone was also used as previous investigations in our research group showed that mono-substituted cyclopropanes were more reactive with electron deficient aldehydes, but again no significant increases in the yield was observed (entry 9). A higher boiling solvent, 1,2 dichloroethane was utilised increasing the temperature of the reaction to 88°C which was shown to significantly increase the yield from 33% to 57% (entry 10). With this in mind DMF was employed as it was thought a more polar solvent would favour ring-opening of the cyclopropane, however only the cyclopropane was retained (entry 11). Lastly a less polar solvent with a higher boiling point was used, but this had no effect on the yield of the oxazine obtained. In all cases the oxazines were obtained as single diastereoisomers, where C^3 and C^6 expressed a *cis* relationship while the two phenyls expressed a *trans* relationship. The relative stereochemistry was confirmed by nOe experiments and an X-ray diffraction structure of **176**$_a$ as illustrated in Figure 11.

Figure 11

The reactions were repeated with the optimised conditions detailed above and a significant increase in yields was obtained. (Scheme 99) In addition to this, the reaction was performed with the unsymmetrical 2,3-disubstituted cyclopropanes possessing two different stabilising groups, however a notable difference was observed in the results obtained.

Entry	R^1	SM	Nitrone	Time (h)	Yield (%)	Oxazine	176 d.r. *cis*:*trans*	176/178 ratio
1	Ph	**170**$_a$	**175**$_a$	24	70	**176**$_a$	100:0	n/a
2	Ph	**170**$_a$	**175**$_d$	24	60	**176**$_b$	100:0	n/a
3	Ph	**170**$_a$	**175**$_e$	24	57	**176**$_c$	100:0	n/a
4	Ph	**170**$_a$	**175**$_b$	19	55	**176**$_d$	100:0	n/a
5	*p*-F-C_6H_4	**170**$_d$	**175**$_e$	24	50	**176**$_e$	100:0	1:1
6	*p*-F-C_6H_4	**170**$_d$	**175**$_c$	48	51	**176**$_f$	0:100	1:1.5
7	*p*-MeO-C_6H_4	**170**$_b$	**175**$_f$	36	45	**176**$_g$	0:100	n/a
8	*p*-CF_3-C_6H_4	**170**$_e$	**175**$_g$	30	60	**176**$_h$	2:1	n/a
9	*p*-CF_3-C_6H_4	**170**$_e$	**175**$_f$	24	45	**176**$_i$	100:0	n/a
10	*p*-MeO-C_6H_4	**170**$_b$	**175**$_g$	24	49	**176**$_j$	100:0	n/a
11	*p*-CF_3-C_6H_4	**170**$_e$	**175**$_b$	24	45	**176**$_k$	100:0	n/a
12	^{n}Bu	**170**$_f$	**175**$_a$	18	SM	**n/a**	n/a	n/a
13	alkyne $Co_2(CO)_6$ complex	**177**	**175**$_e$	24	SM	**n/a**	n/a	n/a

Scheme 99

It can be seen from the results that in the majority of cases the 1,2 oxazines were afforded as a single diastereoisomer where the *cis*-isomer was predominately formed. However the introduction of a substituent to one of the aromatic rings resulted in the *trans* isomer **176**$_f$ and **176**$_g$ also being observed. (entries 6-8) Although in all the oxazines isolated, the

substituents at positions C^5 and C^6 of the ring expressed a *trans* relationship which implied that ring-opening of the cyclopropane most probably occurred with inversion of stereochemistry. These results further support the mechanistic pathway postulated by Kerr.[51] The cycloaddition performed with the di-phenyl cyclopropanes resulted in higher yielding products (**176a-d**) compared to that of the cyclopropanes possessing two different stabilising groups (**176e-k**). The introduction of a substituent to one of the aromatic rings significantly reduced the diastereo- and regioselectivity of the reaction and as a result a reduction in yields was observed. This was also reported by Kerr where he performed the cycloaddition reaction with a *cis* disubstituted cyclopropane which only possessed one carbocation stabilising group. It was envisioned that the presence of a different stabilising group would help to control the regioselectivity of the reaction. This was observed in some cases as shown by entries 7-11 where the *trans* oxazine and the *cis*-oxazine were obtained and in the case of entry 8 a separable mixture of *cis* and *trans*-isomers were afforded with a diastereomeric ratio of 2:1. These results reflect that the cycloaddition is able to take place with both electron rich and deficient nitrones. The formation of *cis* or *trans* isomers may be attributed to the reaction times where racemisation could have taken place under prolonged heating. This has been illustrated in entries 6-8 where the *trans* isomer was obtained when the reaction had been heated for longer than 24 hours. When trifluoromethyl phenyl substituted cyclopropane $\mathbf{170}_g$ was utilised, a 2:1 mixture of diastereoisomers were obtained as the reaction was heated for 30 hours leading to a small amount of racemisation. (entry 8) In all reactions performed, only the fluoro substituted phenyl cyclopropane $\mathbf{170}_d$ resulted in a mixture of regioisomers; with one as the *cis* isomer (entry 5) and the other as the *trans* isomer (entry 6). In this example the substituent was electron withdrawing and therefore would have expected to see only one regioisomer. The rationale behind this is the electron-withdrawing group is pulling electron density away from the ring making the carbon less nucleophilic. As a result the oxygen of the nitrone is more likely to attack the substituted phenyl over the unsubstituted phenyl resulting in one regioisomer, however this was not observed. This could be attributed to the fact that fluoro phenyl is not a strong enough electron deficient group to significantly alter the electron density between the two carbons within the cyclopropane ring. A recrystallisation of the product was performed in anticipation that one regioisomer would crystallise while the second one would remain soluble. An X-ray structure of $\mathbf{176}_e$ was obtained which unfortunately showed a mixture of the two regioisomers. (Figure 12)

Figure 12

The regioisomers of the oxazines were unable to be separated by flash chromatography, and our attempts to separate the two cycloadducts by preparative HPLC remained unsuccessful.

The cycloaddition was also attempted with the butyl substituted cyclopropane **170**$_f$ (entry 12) but unfortunately only a trace amount of the desired product was obtained with mainly starting material retained. The reaction may have been suppressed due to the presence of the slightly bulky butyl group as Kerr had reported that the cycloaddition took place with the methyl substituent. Finally, the hexacarbonyl cobalt complex disubstituted cyclopropane diester (entry 13) prepared previously within the research group was also used in an attempt to perform the cycloaddition reaction. However as observed with imines and aldehydes the cyclopropane **177** was not able to afford the cycloadduct where only starting material was obtained.[78] The rationale behind the cyclopropane not opening could be associated with the presence of a strong stabilising group which may override the cationic charge once the ring is opened. This would lead to a reduction in the charge separation between the ester moieties and the stabilising groups resulting in the opened ring to revert back to the closed ring which is more favoured.

The results obtained further support Kerr's theory that the cycloaddition reaction proceeds mainly through a stepwise mechanism. The reaction starts with an initial attack of the nitrone oxygen onto the cyclopropane which is subsequently followed by an attack of the anionic charged malonate onto the iminium species **179** to afford the *cis* isomer as the predominant product **176** (Scheme 100).

Scheme 100

It also implies that the reaction goes *via* a S_N2 addition as inversion of stereochemistry is observed between C^1 and C^2 of the cyclopropane which is expressed as a *trans* relationship between substituents at C^5 and C^6 within the oxazine ring. This stereochemistry was observed in all the compounds obtained. An alternative mechanism is coordination of the Lewis acid to one or two of the ester moieties to afford the ring-opened adduct (Scheme 101).

Scheme 101

This would be followed by an attack of the nitrone oxygen onto the carbocation of the cyclopropane and subsequent attack of the malonate anion onto the iminium species would afford the cycloadduct. However in this example no inversion of stereochemistry would be observed and therefore confirms this mechanism is less likely.

2.5. Synthesis of *N*-heterocycle substituted cyclopropane diesters

To extend the substrate scope of the 2,3 diaryl substituted cyclopropane diesters and in turn the products afforded *via* the [3+3] cycloaddition reaction, the replacement of aryl halides with heteroaromatic halides were investigated.

The phenyl cyclopropene diester $\mathbf{1}_d$ was treated with iodo-pyrazole **180** in presence of palladium acetate and potassium carbonate expecting to afford the Heck product **181**. (Scheme 102)

Scheme 102

However it soon became apparent from the NMR spectrum that the expected Heck product **181** had not been obtained. A split in the chemical shifts for the methyl ester peaks at 3.5 and 3.6 ppm combined with an additional two doublets at 4.2 and 5.0 ppm suggested the presence of a saturated cyclopropane ring. This was further confirmed by mass spectrometry and a crystal structure of product $\mathbf{182}_a$ was obtained by X-ray diffraction as illustrated in Figure 13.

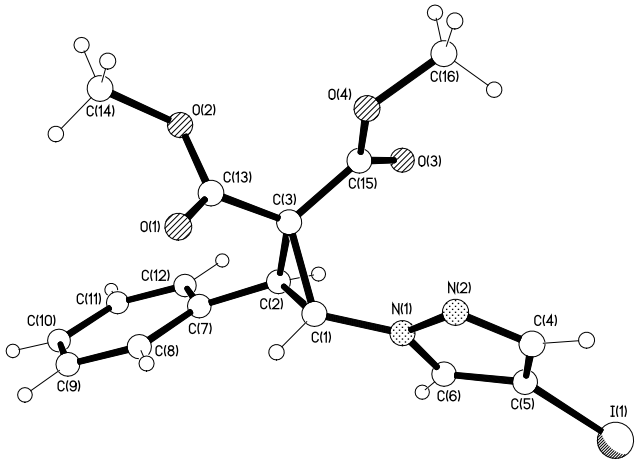


Figure 13

This implied that a hydroamination type reaction might have taken place as this reaction often occurs when catalysed by palladium (II) complexes. However this type of palladium mediated hydroamination is typically facilitated using a co-oxidant. In our case, the hydroamination of the cyclopropene was observed while no oxidant was used, and additionally the reaction was performed under anaerobic conditions. To identify whether the palladium source was responsible for the formation of product **182**$_a$, the reaction was performed with a palladium (0) source, $Pd_2(dba)_3$. This returned the same *trans* 2,3 disubstituted cyclopropane **182**$_a$ which was afforded with a similar yield despite the palladium source used.

The reaction was attempted with a further three heteroaromatic halides; bromo-pyrazole, imidazole and 3,6 dibromocarbazole. (Scheme 103) The corresponding *trans* 2,3 disubstituted cyclopropanes **182**$_{b\text{-}d}$ were isolated again in respectable yields and none of the Heck products were observed.

Entry	substrate	Product	Yield (%)
1		**182**$_b$	**80**
2		**182**$_c$	**60**
3		**182**$_d$	**50**

Scheme 103

In light of these results, the presence of the palladium catalyst was not thought to be essential as the palladium source had no detrimental effect on the yields. Further investigations were carried out using iodopyrazole as the initial reagent in an attempt to optimise the reaction conditions. (Scheme 104)

Entry	Solvent	Base	Temp (°C)	Time (h)	Product	Yield (%)
1	DMF	K_2CO_3	90	20	**182**$_a$	90
2	DMF	K_2CO_3	r.t.	24	**182**$_a$	67
3	DMF	n/a	90	72	**182**$_a$	SM
4	toluene	K_2CO_3	110	20	**182**$_a$	18
5	DMF	NMM	90	48	**182**$_a$	SM
6	CH_3CN	K_2CO_3	80	48	**182**$_a$	86
7	CH_3CN	K_2CO_3	r.t.	21	**182**$_a$	SM

Scheme 104

The first reaction was performed utilising potassium carbonate as the base in DMF at 90°C without the presence of palladium which successfully afforded the desired product **182**$_a$ in 90% yield. (entry 1) This proved the presence of palladium was not required within the reaction and as a result a significant increase in the yield was observed from 61 to 90%. To investigate further, a range of solvents, temperatures and bases was explored to see whether these had an adverse effect on the reaction. When the reaction was performed at room temperature (entry 2) a decrease in the yield was observed. It was thought this could be attributed to solubility issues with the potassium carbonate in DMF. A background reaction was performed without the base (entry 3), but no reaction was observed which proved the presence of base was required for the reaction to proceed. Replacement of DMF with a less polar solvent toluene (entry 4) resulted in a diminished yield of only 18% with 50% of the SM retained. This suggested a polar aprotic solvent was complementary to the reaction. To improve the solubility and reactivity of the base in the reaction, N-methylmorpholine was chosen as an alternative to potassium carbonate. However it can be seen from the results that no reaction was observed (entry 5), suggesting the base may have been too strong. This could have resulted in a stabilised anion unable to undergo addition with the cyclopropene. Finally, the reaction was attempted using acetonitrile as the solvent. The results observed were quite interesting as the cyclopropane was afforded in an excellent yield of 86% while heated to reflux (entry 6), although no reaction was observed when the reaction was performed at room temperature (entry 7). This is thought to be associated with the solubility of potassium carbonate in acetonitrile at room temperature and also implied the thermodynamic product was favoured over the kinetic product (entries 1 and 6).

The optimised conditions were applied to a range of nitrogen heterocycles and amines to test the substrate specificity of the reaction. (Scheme 105) With great success, a variety of halogenated and non-halogenated *N*-heterocycle substituted cyclopropanes were synthesised in a selective manner in respectable yields as depicted in Scheme 105.

Entry	Heterocycle	Product	Yield (%)
1	4-iodopyazole	**182**$_a$	90[1]
2	4-bromoimidazole	**182**$_b$	85
3	4-bromopyrazole	**182**$_c$	62
4	3,6 dibromocarbazole	**182**$_d$	68
5	pyrazole	**182**$_e$	53
6	1,2,4 triazole	**182**$_f$	50
7	imidazole	**182**$_g$	62
8	benzotriazole	**182**$_h$	60
9	4-nitropyrazole	**182**$_i$	50
10	3-trifluoromethylpyrazole	**182**$_j$	82[1]
11	tetrazole	**182**$_k$	trace amount
12	phthalimide	**n/a**	decomposition
13	*N*-boc amine	**1**$_d$	>99
14	di *N*-boc amine	**1**$_d$	>99
15	*N*-boc ethyl oxamate	**1**$_d$	>99

[1] No purification was required

Scheme 105

In the majority of cases the cyclopropanes were afforded within a high degree of diastereoselective control where the amine was added to the least hindered side to exclusively afford the *trans* isomer. (entries 1 to 10) However it can be seen from the results that the reaction was limited to mainly azoles where little or no reaction was

observed with primary and secondary amines. (entries 13-15) *N*-boc amine was used in an attempt to form the amino cyclopropane to enable further functionalisation of the ring, but unfortunately no reaction took place. To increase the acidity of the amine the di boc protected amine and *N*- boc ethyl oxamate were tested, however in both cases the starting cyclopropene was retained. The reason for di boc amine to not undergo addition could be associated with steric hindrance as a result of the bulky *t*-butyl group.

As mentioned previously it is believed that the pK_a of the amine combined with the stability of the ammonium intermediate formed *in situ* had a significant influence on the yield of the cyclopropane obtained. This was evident in the results shown in Scheme 105 where amines with a lower pK_a value (entries 1-3, 10) afforded the cyclopropane in a higher yield compared to amines with a higher pK_a value. (entries 5 and 7) A list of pK_a values of the azoles used is shown in Table 4.

Substrate	**pK_a H_2O (DMSO)**
imidazole	14.4 (18.9)[80]
pyrazole	14.2 (20.4)[80]
4-bromopyrazole	12.7[80]
4-iodopyrazole	12.9[81]
4-nitropyrazole	9.6[80]
3-trifluoromethylpyrazole	10.6[81]
4-bromoimidazole	12.2[81]
1,2,4 triazole	10.0 (13.9)[80]
benzotriazole	8.2 (11.9)[81]
carbazole	(19.9)[81]
phthalimide	8.3[81]
primary amine	(24.8)[81]

Table 4

However there was some anomalies with this explanation as 1,2,4 triazole, benzotriazole and 4-nitropyrazole (entry 6, 8, 9) afforded the cyclopropane in 50%, 60% and 50% yield respectively. It is believed in these examples that the diazole anion is stabilised by its mesomer form and in turn has limited its reactivity to undergo a conjugate addition with the cyclopropene. (Scheme 106)

Scheme 106

As with these amines the potassium carbonate is strong enough to abstract the proton to afford the stabilised anion which is therefore less likely to add to the cyclopropene. However the amines with a pK_a value higher than 10 are too basic to have their protons abstracted by potassium carbonate and therefore the amine acts as a nucleophile to undergo addition with the cyclopropene. This was further confirmed by the result obtained for tetrazole (entry 11) where only trace amounts of the desired product were observed. This was associated with the stability of the tetrazolate anion which has pronounced aromatic character. The diastereoselectivity observed for the cyclopropanes were confirmed by nOe experiments where no direct couplings were observed between the CH protons of the cyclopropane.

The results obtained for this reaction led us to believe that the addition reaction would take place with a conjugated alkene (e.g. styrene) as well as with the strained cyclopropene. Thus the addition reaction was attempted using styrene **155** which was allowed to react with iodopyrazole **180** in the presence of potassium carbonate in DMF at 90°C (Scheme 107).

Scheme 107

Unfortunately no reaction was observed and the alkene was retained which suggested that the combination of a strained cyclopropene with an activating group like phenyl was essential for the addition reaction to take place.

2.6. Synthesis of N-heterocycle substituted cyclopropane monoesters

Within the synthesis of the cyclopropane diesters, potassium carbonate was replaced with the slightly more reactive caesium carbonate in the knowledge that the latter base is more soluble in DMF. A test reaction was performed where the addition of Cs_2CO_3 to a stirred solution of 4-nitropyrazole and phenyl cyclopropene afforded the unexpected decarboxylated cyclopropane as a mixture of isomers in 60% yield (Scheme 108).

Scheme 108

The isomers were separated by column chromatography to afford a 1:2 (**184**$_a$:**185**$_a$) mixture of diastereoisomers. In both products, a *trans* relationship was observed between H^1 and H^2 which was also observed in the previous results. The stereochemistry of the products was confirmed by nOe analysis and the observed $^3J_{HH}$ couplings between the CH protons as illustrated in Figure 14.

Figure 14

To determine whether the reaction was reproducible, a further three substrates were reacted under the same conditions to afford the monoester cyclopropanes as a 2:1 mixture of diastereoisomers in moderate yields (Scheme 109).

Entry	XH	Yield (%)	184:185
1$_b$		60	1:2.5
2$_c$		60	1:2
3$_d$		55	1:2

Scheme 109

It was observed during the reaction that addition of the azole to the cyclopropene took place first, hence leading to the formation of the *trans* isomer followed by decarboxylation. This observation was made during addition of 3-trifluoromethylpyrazole where after 24 hrs a mixture of the diester and the two isomers of the monoester were obtained. After a further 20 h, only a mixture of the decarboxylated cyclopropanes was observed. It is known for activated esters to undergo decarboxylation when in the presence of caesium carbonate which has been observed in this reaction.

2.7. Use of electron rich and deficient cyclopropenes in the addition reaction

To extend the scope of the methodology and to explore the reaction further the addition reaction with azoles was performed with an electron deficient cyclopropene **186**$_a$ (Scheme 110).

Scheme 110

It was postulated that the electron withdrawing nature of the nitro group would provide greater stabilisation of the anion formed during addition of the azole to the cyclopropene. This in turn would increase the reactivity of the reaction resulting in higher yielding

products. It can be seen from Scheme 110 that under the revised conditions the desired cyclopropane was not obtained and instead the ring-opened product **187**$_a$ was afforded as a single diastereoisomer in 60% yield. The stereochemistry and characterisation of the product was further confirmed by X-ray crystallography as shown in Figure 15.

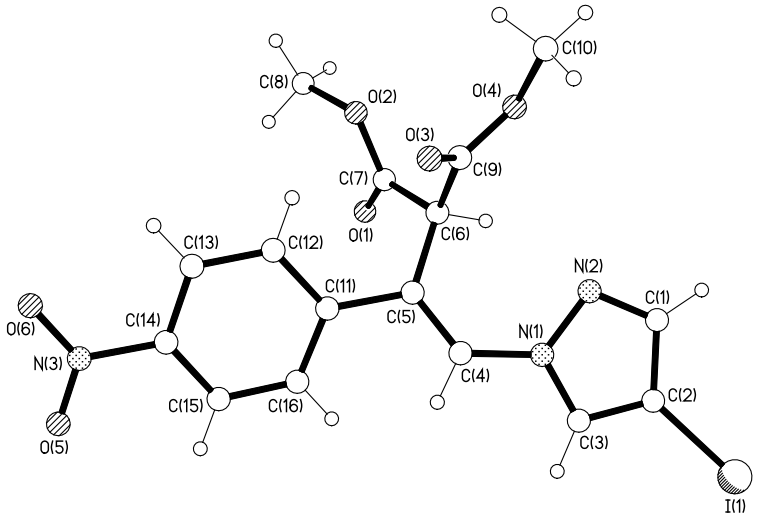


Figure 15

It is believed the presence of the nitro substituent has increased the strained energy within the cyclopropane ring which has resulted in ring-opening to afford the alkene as the most stable product. This has been observed by Lam in some carbometalation reactions of cyclopropenes where tri and tetra substituted alkenes have been afforded in the presence of an iron catalyst, followed by subsequent cleavage of the C-C sigma bond.[39] (Scheme 111)

Scheme 111

However in our case no metal was required and the nucleophiles were delivered to the least substituted carbon, whereas in this example the alkyl group has been delivered to the most substituted carbon.

In an attempt to obtain the cyclopropane rather than the alkene the reaction was performed at room temperature to see whether the ring-opened product was favoured as result of its thermodynamic stability. The results showed that 60% of the alkene was still obtained but 30% of the desired cyclopropane was also afforded. This result indicated that the formation of the cyclopropane was dependant on temperature which further illustrated that the alkene was the most thermodynamically stable product. To investigate further, a variety of reactions were performed as demonstrated in Scheme 112. This was to demonstrate that the reaction was reproducible with other substrates and whether the addition was able to take place with electron rich cyclopropenes.

Entry	R	XH	Temp (°C)	Time (h)	Product	Yield (%) 188:187
1	NO_2	4-bromoimidazole	r.t.	18	**188**$_a$	54:0
2	NO_2	4-bromoimidazole	90	24	**187**$_b$	0:54
4	MeO	4-iodopyrazole	90	48	**n/a**	0
5	MeO	4-bromopyrazole	90	48	**n/a**	0

Scheme 112

It can be seen from the results that the reaction took place with other azoles in a similar fashion to what was observed initially. (entries 1-3) The addition with 4-bromoimidiazole at room temperature (entry 1) afforded the *trans* cyclopropane **188**$_a$ exclusively where none of the alkene was observed. However when the reaction was performed at 90°C (entry 2) the contrary was observed and the alkene **187**$_b$ was afforded as the sole product. This further confirmed that the temperature had a significant influence on the product afforded. The introduction of an electron rich cyclopropene was not successful and no addition was observed. It was believed the electron-donating effect of the methoxy group destabilised the *in situ* anion which would reduce the reactivity of the cyclopropene to undergo addition.

Optimisation studies were performed in an attempt to improve the yield of the reaction and to suppress the formation of the ring-opened product. (Scheme 113) The two main variables investigated were solvent and temperature.

Entry	solvent	Temp (°C)	Time (h)	186_a (%)	188_b (%)	187_a (%)
1	CH_2Cl_2	r.t	30	>99	0	0
2	MeOH	r.t	24	70	0	0
3	THF	r.t.	20	45	55	0
4	DMF	0	20	0	45	23
5	MeCN	r.t	5.2	0	98	0

Scheme 113

It can be seen from the results that a range of solvents of varying degrees of polarity were employed where dichloromethane and methanol (entry 1 and 2) retained the starting cyclopropene. A small improvement was made with THF (entry 3) where only the *trans* cyclopropane was afforded in 55% yield, the remainder was recovered cyclopropene. The temperature of the reaction was lowered to 0°C (entry 4) in an attempt to avoid the formation of the alkene; however 23% of the alkene was still observed. We were pleased to observe that when the reaction was performed in acetonitrile (entry 5) the cyclopropane was afforded in 98% yield and no further purification was required. This was an

unexpected result as it was previously shown that the addition reaction performed with phenyl cyclopropene in acetonitrile at room temperature retained the cyclopropene. (Scheme 104) This illustrated that the electron deficient cyclopropene was more strained and more likely to undergo conjugate additions with selective nucleophiles.

To further understand the mechanism of the reaction, the cyclopropane **188**$_b$ was subjected again to the reaction conditions as shown in Scheme 114 as this would help to determine which of the two products were formed first during the reaction.

Scheme 114

Within two hours a full conversion of the cyclopropane **188**$_b$ into the alkene **187**$_a$ was observed in a quantitative yield. This illustrated that the addition of the azole to the cyclopropene took place first to afford the cyclopropane which was followed by ring-opening under thermodynamic conditions to afford the corresponding alkene. The alkene **187**$_a$ was subjected to the same reaction conditions however this returned no results and recovery of the alkene **187**$_a$ confirmed the reaction was irreversible. In an attempt to avoid the formation of the ring opened product, the reaction described in Scheme 113 was performed without the addition of potassium carbonate however this only returned the cyclopropene.

The optimised conditions to afford the cyclopropane diester were applied to a variety of substrates; mainly azoles and the results of these have been outlined in Scheme 115.

Entry	R	XH	Time (h)	Product	Yield (%)
1	NO_2		4	**188**$_a$	90*
2	NO_2		6	**188**$_b$	98*
3	NO_2		4	**188**$_c$	56
4	NO_2		22	**188**$_d$	75
5	NO_2		23	**188**$_e$	87*
6	NO_2		1	**188**$_f$	99*
7	CF_3		24	**188**$_g$	50
8	CF_3		30	**188**$_h$	60

*No purification required

Scheme 115

The cyclopropanes were afforded in moderate to excellent yields where the nitro substituent was shown to enhance the reactivity of the reaction. In all cases the cyclopropane was afforded as a single diastereoisomer and in some cases no purification was required (entries 1 2, 5 and 6). The unsubstituted azoles required a longer reaction time compared to the substituted azoles as a result of their basic nature (entries 4 and 5). It can be seen that the trifluoromethyl substituted phenyl cyclopropene **186**$_c$ was not as successful (entries 7 and 8) and required the reaction to be performed at 50°C to ensure consumption of the starting material.

It has been shown that the electron deficient cyclopropene was considerably more reactive to undergo addition than its electron rich analogue. With this in mind the addition of *N*-boc ethyl oxamate to the electron deficient cyclopropene **186**$_a$ was attempted. (Scheme 116)

Scheme 116

The desired product **189** was observed in the crude NMR and purification by column chromatography was attempted, however a significant amount of the amine was shown to co-elute with the product. In an attempt to consume the amine the reaction was performed with a stoichiometric amount of the protected amine, although residues were still present after purification. The crude product was then treated with TFA in an effort to deprotect the Boc group which would enable separation from the reaction product. Cleavage of the Boc group was observed, however impurities were still present in substantial amounts. Thus our investigations were abandoned.

It is proposed that the reaction occurs in a stepwise manner where the amine acts as a nucleophile and adds to the least substituted side of the cyclopropene to form an ammonium intermediate **190**. This is followed by abstraction of the amine proton with base which is abstracted by the anion to afford the corresponding cyclopropane diester **188**$_d$ (Scheme 117).

Scheme 117

The ring-opened product is afforded *via* a similar pathway where formation of the ammonium intermediate **190** results in activation of the cyclopropane ring and the formed anion kicks back in to afford a new C-C double bond between C^1 and C^2. This is followed by subsequent cleavage of the C-C sigma bond to afford the corresponding alkene **187**. (Scheme 118)

Scheme 118

The mechanism proposed is based on the evidence that electron deficient cyclopropenes which would provide greater stabilisation of an anion have resulted in higher yields (e.g. with the nitro group) and have driven the reaction to completion. Further evidence of this is the electron rich cyclopropenes (e.g. with the methoxy group) were unable to undergo nucleophilic addition. This also explains why selective amines within a narrow pK_a range are able to undergo nucleophilic addition with the cyclopropene. For example the pK_a of a quaternalised imidazole amine is around 6.95 and therefore the potassium carbonate is able to abstract the proton from the amine to afford the cyclopropane. Whereas a quaternalised ammonium complex with a pK_a greater than 10 would remain as the stable ammonium intermediate as potassium carbonate would not be strong enough to abstract the amine proton. In regards to the amines with pK_a values less than 10 the base is able to abstract the amine proton to afford the stable anion which is less prone to undergo addition with the cyclopropene as confirmed by the results in Scheme 105.

2.8. Addition of Phenols to activated cyclopropenes

Following our initial investigations, it was believed that the outcome of the reaction was influenced by the acidity of the heteroatom proton of the azoles used to develop the methodology. To widen the scope of the reaction, our interest focused on utilising phenols as an alternative to the *N*-heterocycles for its proton lability. The initial reaction involved treatment of the electron deficient cyclopropene with phenol under the standard conditions developed previously which successfully afforded the corresponding *trans* cyclopropane **191**$_a$ with excellent diastereocontrol. (Scheme 119)

Scheme 119

Subsequently, the electron deficient cyclopropene **186**$_a$ underwent addition with a range of electron rich and deficient *p*-substituted phenols to exclusively afford the *trans* selective cyclopropanes **191**$_{a\text{-}g}$ in moderate to excellent yields. (Scheme 120)

Entry	R	Equivalents	Time (h)	Product	Yield (%)
1	H	1.1	3	**191**$_a$	74
2	OMe	1.0	21	**191**$_b$	57
3	NO_2	1.0	5	**191**$_c$	50
4	NO_2	2.0	7	**191**$_d$	67
5	NH_2	2.0	7	**191**$_e$	45
6	CF_3	2.0	3	**191**$_f$	83
7	F	2.0	4	**191**$_g$	90

Scheme 120

It can be seen from the results that the use of the phenols substituted with electron withdrawing groups and neutral (entries 3-4, 6 and 7) afforded the corresponding cyclopropanes in significantly higher yields compared to those substituted with electron donating groups (entry 2 and 5). The proposed reaction mechanism for the addition of phenols to the cyclopropene has been outlined in Scheme 121.

Scheme 121

The main difference in the addition of phenols compared to the nitrogen azoles is that the base is strong enough to abstract the hydroxyl proton to afford the phenoxide anion which subsequently attacks the cyclopropene to afford the *trans* selective cyclopropane. This also

suggests that the addition of phenols was governed by the acidity of the heteroatom rather than its nucleophilicity (entry 5). Electron withdrawing groups such as CF_3 and NO_2 tend to increase the polarisation of the O-H bond of phenol by lowering its ground state energy. This in turn makes the phenol more acidic by delocalising the negative charge and hence stabilisation of the phenoxide anion. Whereas electron donating groups such as OMe and NH_2 tend to enrich the O-H bond of the phenol. This then leads to a decrease in the lability of the proton which in turn destabilises the phenoxide anion.

It was also discovered that by increasing the equivalents of the phenol, an increase in yield was also observed. An interesting result was the addition of 4-aminophenol (entry 5) as by NMR analysis it was not clear whether the reaction onto the cyclopropene proceeded via the *O* or *N*-alkylation. Fortunately an X-ray crystal structure was obtained as shown in Figure 16, which confirmed the presence of the *O*-alkylation product.

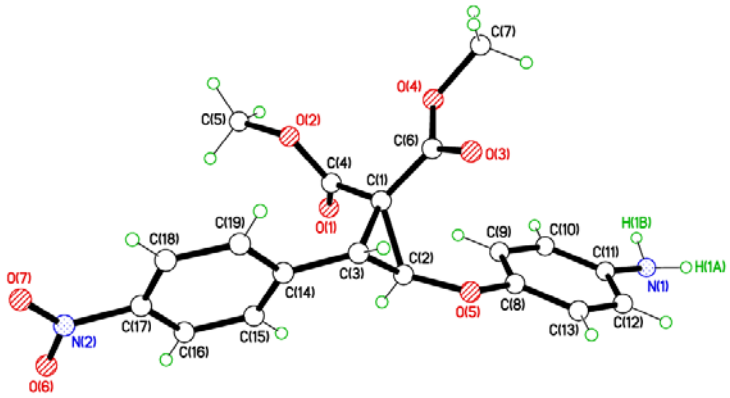


Figure 16

It was also shown from X-ray studies that H-bonding was observed between the NH_2 of the phenyl, carbonyl and the methoxy of the ester group. (Figure 17)

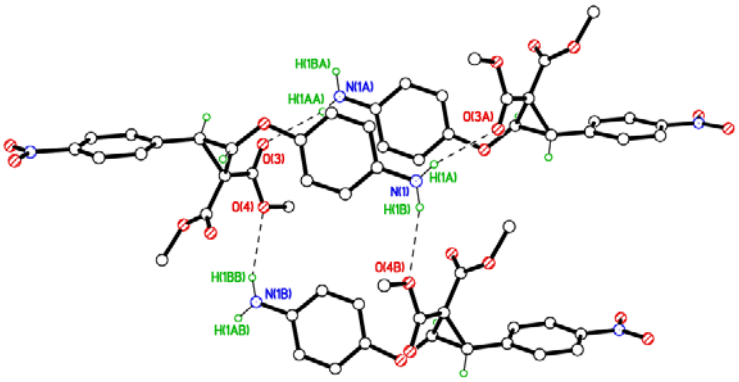


Figure 17

The addition of phenol to the CF_3 substituted phenyl cyclopropene was also performed which afforded the cyclopropane in a moderate 60% yield but the temperature of the reaction was raised to 80°C (Scheme 122).

Scheme 122

It is worthwhile to note that no ring-opening of the cyclopropane was observed in the addition of phenols to the electron-deficient cyclopropene even at elevated temperatures. This implied that the addition must take place *via* the mechanism outlined in Scheme 121. As the addition of the oxygen onto the cyclopropene would result in no charge and therefore there would be no resulting anion to allow the three-membered ring to open. However in the mechanism for the addition of the azoles (Scheme 118) an anion is formed after addition which has the opportunity to kick back in and ring-open the cyclopropane.

The same reaction was performed with the phenyl cyclopropene surrogate $\mathbf{1}_d$ in DMF at 90°C which afforded the corresponding cyclopropanes $\mathbf{193}_{a\text{-}e}$ in moderate yields with a high degree of diastereocontrol (Scheme 123).

Entry	R	Time (h)	Product	Yield (%)
1	H	20	$\mathbf{193}_a$	45
2	OMe	24	$\mathbf{193}_a$	50
3	NO_2	5	$\mathbf{193}_a$	30
4*	F	24	$\mathbf{193}_a$	40
5	NH_2	24	$\mathbf{193}_a$	40

Scheme 123

These results reflect that the addition of electron rich and deficient phenols to phenyl cyclopropene was less successful compared to its electron deficient analogue. The yields obtained were significantly lower ranging from 30-50% compared to the 45-90% observed in early investigations using the electron deficient cyclopropene $\mathbf{186}_a$. (Scheme 120) It was noted that the addition was favoured by electron rich phenols over electron deficient phenols but by only a small margin, however in terms of the electron rich cyclopropene the electron deficient phenols were favoured as expected. The addition of 4-fluorophenol (entry 4) was improved by the replacement of potassium carbonate with caesium carbonate, however this was not observed with the other phenols. Interestingly no decarboxylation was observed when caesium carbonate was employed in the reaction of which had been observed in the addition of *N*-heterocycles (Scheme 109).

An attempt was made to gain a greater understanding of the factors that influenced the reaction and hence improve the yields through the use of a factorial experimental design (FED) analysis. This is a tool used in the pharmaceutical industry which enables the chemist to discover which factors have an influence on the reaction and helps to improve

yields. Due to time constraints and limited material, not all the factor levels were explored (e.g. base, phenol and solvent used) and therefore there was a risk that some good reaction conditions may be missed. In our investigations, two types of solvent, two bases, and two types of phenol, base charge and temperature were explored as outlined in (Table 5). The results for electron rich phenol (e.g. *p*-methoxy substituted) have only been shown as the results obtained for the electron deficient phenol (e.g. *p*-nitro substituted) was not conclusive.

Solvent	Base	Temperature (°C)	Base charge (eq.)	In-solution yield (%)
DMF	K_2CO_3	80	2.5	48.0
DMF	K_2CO_3	80	1	35.4
MeCN	K_2CO_3	80	2.5	20.7
DMF	Et_3N	80	2.5	3.9
DMF	K_2CO_3	40	2.5	3.0
DMF	K_2CO_3	80	2.5	2.2
MeCN	K_2CO_3	40	1	0.0
MeCN	Et_3N	40	2.5	0.0
DMF	Et_3N	40	1	0.0
MeCN	Et_3N	80	1	0.0

Table 5

The solvents DMF and MeCN were chosen as previous studies suggested these were the most desirable. The temperature was lowered to 40°C as the cyclopropene was shown to decompose at temperatures greater than 50°C. As the initial reaction was performed at 90°C this meant that only a small proportion of the starting cyclopropene was available to

undergo addition. This partially explains why a significant reduction in yields was obtained. The base charge was varied to assess the actual requirements of the reaction.

The reaction was performed in 5 mL of solvent and samples were taken at four time points; 1h, 6h, 12h and 24h. The reaction was stopped after 24h as consumption of starting material was observed at this time point. The "in solution yield" was measured by HPLC (FAZ ACN) based on an external standard of the authentic product. It can be seen from the results that the original conditions were the most desirable for the factors explored. However it is important to note that these results are not conclusive as not all the factor levels have been investigated. The results showed that the right combination of temperature, solvent and base were essential for the reaction to take place. This was confirmed by the fact that no reaction was observed for DMF/MeCN in the presence of Et_3N at 40°C and in MeCN, K_2CO_3 at 40°C. The latter condition was also unsuccessful when employed in the addition of iodopyrazole to phenyl cyclopropene (Scheme 104, entry 7).

2.9. Attempted cycloadditions with N-heterocycle substituted cyclopropanes

It has been established in earlier work that di-aryl substituted cyclopropane diesters could undergo a [3+3] dipolar cycloaddition reaction with both electron rich and deficient nitrones. The oxazines were afforded in moderate yields with a high degree of diastereo- and regiocontrol, favouring formation of the *cis* isomer. The same reaction conditions were then applied in attempt to perform the cycloaddition with *N*-heterocyclic substituted cyclopropane diesters outlined in Scheme 124.

Entry	R	Conditions[1]	*N*-heterocycle	Catalyst	Product	Yield (%)
1	Me-C_6H_4	DCE, reflux	benzotriazole	$Yb(OTf)_3$	**182**$_h$	>99
2	Me-C_6H_4	DCE, reflux	3,6-dibromo carbazole	$Yb(OTf)_3$	**194**	50
3	Me-C_6H_4	DCE, reflux	4-iodo pyrazole	$Yb(OTf)_3$	**182**$_a$ + aldehyde	n/a
4	Me-C_6H_4	CH_2Cl_2, r.t.	4-iodo pyrazole	$Sc(OTf)_3$	**182**$_a$	>99
5	Me-C_6H_4	DCE, reflux[2]	4-iodo pyrazole	$AlCl_3$	**182**$_a$ + aldehyde	n/a
6	MeO-C_6H_4	DCE, reflux[2]	4-iodo pyrazole	$BF_3.OEt_2$	aldehyde	n/a
7	Me-C_6H_4	DCE, reflux	4-bromo pyrazole	$Yb(OTf)_3$	**182**$_c$+ aldehyde	n/a
8	O_2N-C_6H_4	DCE, reflux[3]	4-bromo pyrazole	$Yb(OTf)_3$	**182**$_c$	>99
9	O_2N-C_6H_4	DCE, reflux[3]	imidazole	$Yb(OTf)_3$	**182**$_g$+ aldehyde	n/a

[1] reaction time: 24 hours except for [1] and [2]

[2] reaction time: 72 hours

[3] reaction time: 48 hours

Scheme 124

The first reaction was performed with a benzotriazole substituted cyclopropane where only the starting cyclopropane was retained (entry 1). The reaction with 3,6-dibromocarbazole substituent (entry 2) was attempted which successfully afforded the oxazine **194** in a moderate 50% yield as a single diastereoisomer, where C^3 and C^6 expressed a *cis*-relationship, while C^5 and C^6 expressed a *trans* relationship. The NMR spectrum initially showed the presence of rotamers indicating rotation around the C^6-N bond. The stereochemistry of the product was confirmed by nOe analysis and X-ray crystallography (Figure 18).

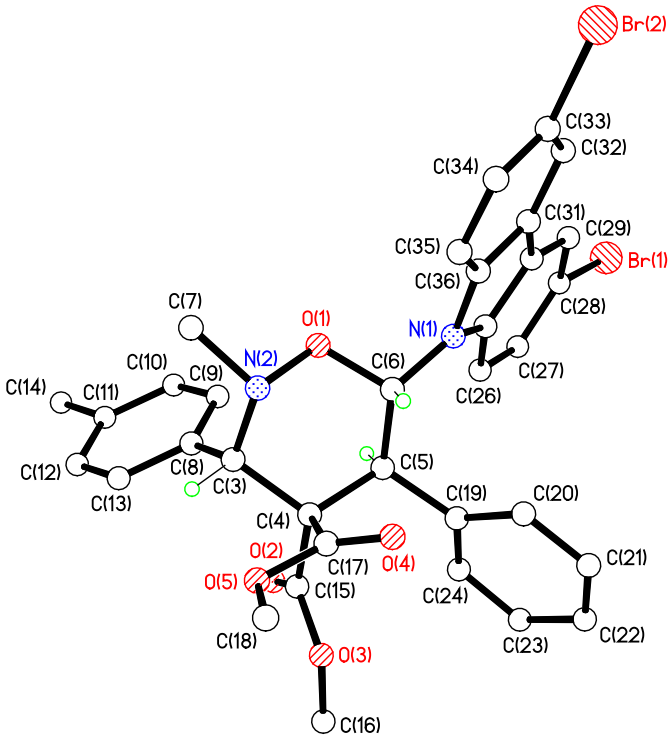


Figure 18

This illustrated that ring-opening of the cyclopropane did not occur with inversion of configuration as the stereochemistry between the groups on C^5 and C^6 was retained in the final product. This is in contrast to the results obtained in the cycloaddition reaction utilising the *cis* diaryl substituted cyclopropane diesters where inversion of stereochemistry was observed. This implied that in the example shown the reaction did not take place *via* the stepwise mechanism postulated by Kerr for both *cis* and *trans* disubstituted cyclopropanes. The reasons for this could be attributed to the steric hindrance of the carbazole reactant which may have prevented the initial attack of the nitrone oxygen, thus favouring the ring opening to afford a concerted rather than stepwise product.

It can be seen from the results that other substrates were tested under varying conditions however none of these afforded the cycloadduct. In most cases the cyclopropane was retained and decomposition of the nitrone into its corresponding aldehyde was also isolated. This may have occurred as a result of no reaction between the nitrone and the cyclopropane in the same way as aldehydes were unable to undergo cycloaddition reactions with the diaryl substituted cyclopropanes in our initial investigations. The

reaction was also attempted with electron deficient nitrones but again none of the desired product was afforded.

2.10. Replacement of the diester with a mono trifluoromethyl group

Similar work by Martínez-Grau and Vaquero had shown that non-activated cyclopropenes with a mono ester at C^3 of the cyclopropene **53** were able to undergo addition with a range of thioalkoxides and selenides.[34] An example has been outlined in Scheme 125 where formation of the *cis* isomer was favoured in the presence of a large group.

Scheme 125

This illustrated that a geminal diester at C^3 of the cyclopropene was not essential for the addition reaction to take place, however this was shown to reduce the diastereoselectivity of the reaction. In an attempt to adapt this methodology to aryl substituted cyclopropene mono-esters, our investigations started with the synthesis of the monoester phenyl cyclopropene **194** by using the same method described in the synthesis of the phenylcyclopropene diester.[73] (Scheme 126)

Scheme 126

However when this reaction was performed none of the desired product was obtained which could be associated with the reactivity of the ethyl diazoacetate towards carbene addition. It is also worthy to note that this exact example has not been reported in the literature, but many other alkyne substrates have.[39] This suggests that the reaction cannot be performed under these conditions and no further analysis was carried out.

An alternative to the geminal diester cyclopropene led us to replace one of the esters with a CF_3 group using the known diazo compound of methyl trifluoroacetate.[82] A solution of the diazo methyl trifluoroacetate **196** in CH_2Cl_2 was added slowly to a stirred solution of phenylacetylene **158** in CH_2Cl_2 with 5 mol % of rhodium acetate dimer to afford the cyclopropene **197** in 45% yield. (Scheme 127)

Scheme 127

The literature stated that 10 eq of the starting alkyne was required due to the high reactivity of the diazo compound to undergo dimerisation. The cyclopropene **197** was shown to undergo addition with a few azoles, mainly pyrazole derivatives as outlined in Scheme 128.

Entry	XH	Time	Temp (°C)	Solvent	Product	Yield (%)	d.r.	
							A	B
1		7	90	DMF	**198**$_{A/B}$	20	1	1
2		24	90	DMF	**198**$_{A/B}$	65	1	1.1
3		24	50	DMF	**199**$_{A/B}$	67	1	3
4		48	r.t	DMF	**197**	>99	n/a	n/a
5		48	80	CH_3CN	**197**	>99	n/a	n/a
6		24	50	DMF	**200**$_{A/B}$	50	1	2

Scheme 128

Removal of the geminal diester has however led to the introduction of a new stereo centre within the starting substrate which has resulted in a separable mixture of diastereoisomers as shown in Scheme 128. The initial reaction was performed with 1 eq of the 4-bromopyrazole in DMF at 90°C, however only a 1:1 mixture of diastereoisomers were obtained in a combined 20% yield with a significant amount of the cyclopropene being recovered at the end of the reaction. Subsequently, the reaction was performed with a slight excess of the azole and an increase in reaction time to afford a 1:1.1 mixture of diastereoisomers in a combined 65% yield. The stereochemistry of the isomers has been tentatively assigned from NMR analysis and also X-ray crystallography as illustrated in Figure 19.

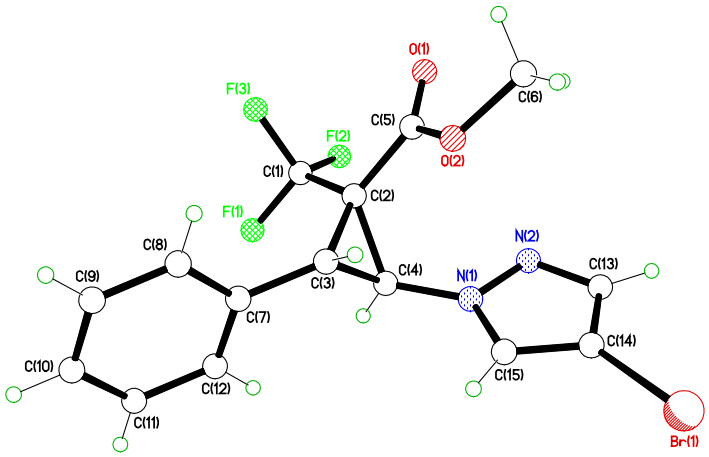


Figure 19

The X-ray structure shown in Figure 19 is of **198**$_A$ (entry 2) where it confirms that there is a *trans* relationship between the phenyl and azole as well as the CF_3 group and the proton attached to C^3. Unfortunately a crystal structure was not obtained for isomer B as the product afforded was an oil. The cyclopropene also underwent addition with 3-trifluromethylpyrazole (entry 3) where a decrease in temperature improved the diastereoselectivity of the reaction from 1:1 to 1:3 in favour of **199**$_B$. In an attempt to control the diastereoselectivity further, the reaction was performed at room temperature however this only retained the cyclopropene. For comparison with the other addition reactions, the reaction was performed in acetonitrile at reflux however mainly starting material was obtained with only trace amounts of product observed. Lastly the reaction was performed with an unsubstituted pyrazole at the lower temperature of 50°C which afforded the cyclopropane as 1:2 mixture of diastereoisomers in a 50% yield. This has expanded the scope of our methodology and showed that the reaction is not dependant on

the diester substituent. In addition to this, the functionality of the cyclopropane had been increased by the introduction of a CF_3 group of which are known to have biological significance.

2.11. Attempted cycloadditions reactions with nitro substituted cyclopropanes

An attempt was made to extend the scope of the cycloaddition reaction by deviating away from the typical cyclopropane diester and replacing it with a nitro substituent. There is limited literature reported on the synthesis and use of nitrocyclopropanes in organic chemistry. We believed that the synthesis of nitro substituted cyclopropanes would be of great interest as the introduction of a nitro group would enable further functionalisation of the ring which may prove to be useful as precursors for natural product synthesis.

It was envisioned that the introduction of a nitro group would act in the same way as the ester moieties in stabilising the anion formed during the cyclopropane ring-opening. In the case of the cyclopropane diesters the Lewis acid coordinates to the ester moiety which induces a polarisation of the cyclopropane C-C bonds resulting in ring-opening. It is known from the literature that Lewis acids are also able to coordinate to the nitro group.[83] With this in mind, we predicted the nitrocyclopropane **201** would have a similar reactivity to that of the diester cyclopropanes used previously. During the ring-opening, the nitro groups would stabilise the negative charge formed from the C-C bond cleavage while a π electron donor such as an aryl group would stabilise the carbocation **202**. This in turn would be trapped with either an aldehyde or a nitrone to afford the 5/6 membered ring systems **203** and **204**. (Scheme 129)

Scheme 129

2.12. Synthesis of nitrocyclopropanes

For the synthesis of the nitrocyclopropane, a limited number of publications were reported in the literature. Asunskis and Shechterin were the first to report the synthesis of nitrocyclopropanes in 1967.[84] However more recently Ciaccio and Aman have reported the preparation of the cyclopropanes using a different approach known as the "Instant Methylide modified Corey-Chaykovsky Cyclopropanation Reaction".[85] The methylide is synthesised *in situ* from trimethylsulfoxonium iodide ($Me_3S(O)I$) and a base which is subsequently reacted with the nitro olefin to afford the cyclopropane. The method developed by Ciaccio and Aman was explored first to synthesis the *trans*-2-phenyl-1-nitrocyclopropane **201** (Scheme 130).

Scheme 130

A solution of *trans*-β-nitrostyrene **205** in dimethyl sulfoxide (DMSO) was added to a dry equimolar mixture of $Me_3S(O)I/KO^tBu$ to afford the nitrocyclopropane **201** in a non-purified 60% yield. This was confirmed by ^1H NMR spectroscopy and was in agreement with what was previously reported in the literature. An attempt was made to purify the product by distillation, though only a small amount of the purified product was obtained as light yellow oil. The reaction was repeated and purified by flash chromatography, however only a 5% yield of the pure product was obtained. The low yield of product could be attributed to the amount of ylide formed from the dry mixture of $Me_3S(O)I/KO^tBu$ prior to the addition of the nitroalkene solution. In an attempt to increase yields, the original method reported by Asunskis and Shechter was utilised where a solution of trimethylsulfoxonium iodide in DMSO was added dropwise to a stirred suspension of KO^tBu in DMSO at room temperature. This ensured that the ylide had been formed prior to the addition of the *trans*-nitrosytrene which was added dropwise to prevent polymerisation. The mixture was heated to 50°C for four hours and subsequently allowed to stir at room temperature for an additional 12 hours to afford the pure product in an improved 18% yield. It can be seen that there was only a slight increase in the yield of the

cyclopropane obtained, however the maximum yield reported in the literature was only 44%.

We considered attempting the cycloaddition reaction using the crude mixture as yields obtained for the nitrocyclopropane were much higher, but giving the novelty of the chemistry and the presence of impurities it was decided to use pure samples of the nitrocyclopropane as it would best suit interpretation of the results. The synthetic method was also applied to a substituted phenyl nitro alkene; *trans*-β-nitro-4-fluro-phenylalkene **206** which afforded its corresponding *trans*-2-fluro-phenyl-1-nitrocyclopropane **207** in an acceptable 42% yield. (Scheme 131)

Scheme 131

2.13. Attempted intramolecular cycloadditions with nitrocyclopropanes

The next step of the synthesis was to perform the cycloaddition reaction where the nitrocyclopropane **201** would be activated upon coordination with a Lewis acid. This in turn would be trapped with either a nitrone to afford the oxazine **203** or an aldehyde to afford the tetrahydrofuran derivative **204**. (Scheme 129)

The nitrocyclopropane **201** prepared previously was reacted with a range of nitrones and aldehydes under various reaction conditions, however unfortunately none of the desired products were obtained. The results have been detailed in Table 6.

Entry	Reactant	Conditions	Results
1		$Yb(OTf)_3$, DCE, Reflux, 2 h	cyclopropane +*p*-nitrobenzaldehyde
2		DCE, reflux, 4.5 h	No reaction
3		DCE, reflux, organocatalyst	No reaction
4		$TiCl_4$, DCE, reflux, 3 h	cyclopropane + *p*-methyl benzaldehyde
5		$BF_3.OEt_2$, DCE, 24 h	No reaction
6		BCl_3, DCE, reflux, 24 h	cyclopropane + *p*-nitro benzaldehyde
7		Zr(IV)Cl, DCE, reflux, 24 h	No reaction
8		$AlCl_3$, DCM 0°C-r.t., 20 h	No reaction
9		$AlCl_3$, DCM 0°C-r.t., 24 h	complex mixture
10		$AlMe_3$ (2 eq), DCM, 0°C-r.t., 24 h	complex mixture
11		$SnCl_4$ (2 eq), DCM, 0°C-r.t., 24 h	No reaction
12*		$AlCl_3$, DCM 0°C-r.t., 24 h	No reaction
13*		$AlMe_3$ (2 eq), DCM, 0°C-r.t., 24 h	80% p-methoxy benzaldehyde +cyclopropane
14		$AlCl_3$, DCM 0°C-r.t., 24 h	Analyses of the crude mixture showed mainly aldehyde
15		LDA, THF, -78°C-r.t., 20 h.	Complex mixture
16	Me-I	LDA, THF, -78°C-r.t., 48 h.	Complex mixture

Table 6

All the reactions were performed with *trans*-2-phenyl-1-nitrocyclopropane **201** where 1 eq of reactant was used in entries 1-7, 3 eq of reactant was used in entries 8-10, 12-16 and 2 eq of reactant was used in entry 11. The first set of conditions tried were the same as previously used for the diaryl substituted cyclopropane cycloadditions. The nitrocyclopropane **201** in a solution of DCE was treated with $Yb(OTf)_3$ (5 mol%) and 1eq of nitrone $\mathbf{175}_d$ (entry 1) which was heated under reflux for 2 hours affording 30% of the cyclopropane starting material along with 9% of *p*-nitrobenzaldehyde indicating decomposition of the nitrone. Entry 2 is of reasonable interest as no Lewis acid was used but none of the starting cyclopropane was recovered and 100% of the nitrone was also recovered. The result of this indicated that the nitrocyclopropane may have undergone thermal decomposition. To weaken the bond further in an attempt to open the nitrocyclopropane, the Lewis acid was replaced with an organocatalyst which are known to form complexes with the nitro group and hence weaken the bond. However no reaction took place and both the cyclopropane and organocatalyst was recovered (entry 3). As no reaction was obtained with the organocatalyst, a range of Lewis acids were screened with various degrees of reactivity. The Lewis acids chosen were based on a report by Horng *et al* which reported that,[83] when *trans*-2-phenyl-1-nitrocyclopropane was treated with aluminium chloride ($AlCl_3$) at 0°C, a mixture of products were obtained in the form of a cyclohydroxamic ester **208** and a chlorohydroxamic acid **209** in 48% and 23% yield respectively. In the presence of a weaker Lewis acid like tin (IV) chloride ($SnCl_4$), a respectable 78% yield of the cyclohydroxamic ester **208** was obtained where no traces of the chlorohydroxamic acid was isolated (Scheme 132).

Scheme 132

The hydroxamic derivatives obtained proved that the Lewis acids have the ability to open the nitrocyclopropane ring, where the involvement of the nitro group in an intramolecular cyclisation afforded the cyclohydroxamic ester **208**. The hydroxamic acid **209** was afforded from an intermolecular chloride ion transfer from $AlCl_3$ to the ring-opened intermediate. It was believed that this posed well for the cycloaddition reaction to take place, as this proved that the Lewis acids are capable of inducing ring opening of the nitrocyclopropane. This in turn could be subsequently trapped with either an aldehyde or a nitrone to afford the cycloadduct. If the ring opens first, as shown by the previous results, to form the carbocation **202** then the aldehyde would be more favoured as the trapping reagent than the nitrone as the carbonyl carbon is more electrophilic than the nitrone carbon (Scheme 133).

Scheme 133

However it can be seen from the results that this was not the case even though a variety of Lewis acids were tested with varying degrees of reactivity in different conditions. The only Lewis acid which showed some signs of reactivity was trimethylaluminium ($AlMe_3$) (entries 10 and 13), where an uncharacterised by-product was observed. Although the result obtained suggested that the aldehyde was not reacting with the nitrocyclopropane but with itself.

As the use of Lewis acids were not able to afford the cycloadduct, a new approach was investigated into ring opening of the nitrocyclopropane *via* an aza-Henry type reaction. It was believed that treatment of the nitrocyclopropane **201** with a strong base would remove the proton in α position to the nitro group leaving a carbanion **210**. This would subsequently attack the carbonyl of the aldehyde and induce an intramolecular cyclisation to afford the desired tetrahydrofuran derivative **204** illustrated in Scheme 134.

Scheme 134

The methodology described by Wade *et al.* was employed in the reaction as they had shown the ability of a dinitrospiropentane to undergo a nitroaldol reaction with benzaldehyde.[86] However it can be seen from the results in Table 6 (entry 15) that only a complex mixture was obtained and neither of the starting materials was recovered. In order to show the proton in α position to the nitro group was abstracted under treatment with a base, the reaction was performed again utilising methyl iodide (entry 16). However no methyl peak was observed which demonstrated that the base was not strong enough to abstract the proton.

In conclusion, the nitro cyclopropane was unable to perform the cycloaddition reaction with either aldehydes or nitrones. It is believed the nitro substituent is not strong enough to stabilise the anion formed during ring opening due to a weak interaction with the Lewis acid. This would suppress weakening of the bond within the cyclopropane and consequently diminish the reactivity of the cyclopropane towards cycloaddition. Although, there is evidence in the literature that reports the introduction of an ester moiety to the nitro carbon **211** leads to ring opening of the cyclopropane when attacked by an amine nucleophile as outlined in Scheme 135 to afford **212**.[87]

Scheme 135

This suggested that two electron-withdrawing groups were essential to enable weakening of the bond within the cyclopropane ring. The literature stated that the reactivity of the Lewis acid had an influence on the amount of ring-opened product obtained where a reactive Lewis acid like $AlCl_3$ resulted in smaller amounts of the rearranged product shown in Figure 20.

Figure 20

With this in mind, a gem-diester nitro cyclopropane was synthesised in an attempt to assess the reactivity of the cyclopropane to undergo cycloaddition with either nitrones or aldehydes. The treatment of dimethyl bromomalonate **165** and *trans* nitro-styrene **205** in DMF with triethylamine afforded the cyclopropane **213** in 92% yield (Scheme 136).

Scheme 136

The nitro substituted cyclopropane diester **213** was then subjected to a range of reaction conditions as outlined in Scheme 137, but unfortunately none of the desired products were afforded.

Entry	R^1	R^2	Lewis acid	Solvent	Time (h)	Product
1	n/a	*p*-OMe	$Yb(OTf)_3$	DCE	24	**213**
2	CO_2Et	n/a	$Yb(OTf)_3$	DCE	24	**213**
3	n/a	*p*-NO_2	$Yb(OTf)_3$	DCE	72	**213**
4	n/a	*p*-NO_2	$TiCl_4$	DCE	24	**213**
5	*p*-OMe-C_6H_4	n/a	$BF_3.(OEt)_2$	CH_2Cl_2	72	**213**
6	Ph	n/a	$Sc(OTf)_3$	CH_2Cl_2	72	**213**
7	Ph	n/a	$Zn(OTf)_3$	CH_2Cl_2	72	**213**

Scheme 137

The initial conditions utilised earlier for the cycloaddition reactions with the diaryl substituted cyclopropanes were employed in a first attempt, however this led back to the starting material. To increase the reactivity of the trapping reagent, ethyl glyoxlate was used as it is known to have a high reactivity towards cycloaddition reactions due to its great electrophilic nature but this returned no results. (entry 2) An electron deficient nitrone was employed but again only the cyclopropane was retained. A range of Lewis acids were also employed (entries 4-7), but again no reaction was observed. Due to time constraints and little reactivity observed our investigations towards the use of nitro substituted cyclopropanes were not resumed.

3. Conclusion

The initial aim of the research project was to develop an efficient and robust method to access a wide range of activated 2,3 disubstituted cyclopropane diesters to serve as precursors in [3+2] and [3+3] cycloaddition reactions.

The disubstituted cyclopropylboronate esters could not be prepared *via* the palladium and rhodium catalysed cyclopropanation or cyclopropenation and the hydroboration of a mono-substituted cyclopropene diester also failed to produce the desire boron substituted cyclopropanes (Scheme 138).

Scheme 138

In most examples the starting material was retained or a complex mixture was observed. The use of the diester in all three routes has been suggested as the limiting factor in these reactions not taking place as there have been no examples reported in the literature possessing an ester moiety.

A variety of 2,3-disubstituted cyclopropane diesters bearing two stabilising groups have been prepared in moderate yields *via* a Heck-type arylation and subsequent hydrogenation of the cyclopropene. These cyclopropanes were then used towards [3+3] dipolar cycloaddition reactions with nitrones to afford the highly functionalised oxazines in moderate yields with good to excellent diastereoselectivity (Scheme 139).

Scheme 139

In most examples, the oxazines were afforded as a single diastereoisomer where C^3 and C^6 expressed a *cis* relationship, however the *trans* isomer was also observed. The inversion of stereochemistry between C^5 and C^6 illustrates that the cycloaddition may go through a stepwise process instead of a concerted process. The *trans* relationship between C^5 and C^6 was expressed in all the oxazines formed. The next step would be to synthesise a enantiomerically pure cyclopropane to gain a better understanding of the reaction mechanism proposed.

An extension of the methodology in the synthesis of the 2,3 disubstituted cyclopropane diesters led us to investigate the influence of *N*-heterocycles as substituents of the cyclopropane on the [3+3] cycloaddition reaction. Following the same protocol shown in Scheme 139, it was inadvertently discovered that the Heck-coupling reaction conditions afforded the corresponding cyclopropane in one step, with the nitrogen directly bonded to the cyclopropane. Further work indicated that the presence of palladium was not required within the reaction, where a range of halogenated and non-halogenated *N*-heterocycles were successfully coupled to electron rich and deficient cyclopropenes in good to excellent yields (**182/188)**. The reaction was also shown to take place with electron rich and deficient phenols, where the electron deficient cyclopropenes afforded the cyclopropanes in significantly higher yields (Scheme 140).

Scheme 140

The cyclopropanes were afforded in a diastereoselective manner, where the amine was delivered to the least hindered to afford the *trans*-isomer selectively. The yield of the cyclopropane obtained was dependant on the cyclopropene employed and the pKa of the heteroaromatic proton. It is believed the electron deficient cyclopropene provides a greater stabilisation of the anion formed once the amine has attacked the cyclopropene, hence an increase in reactivity. To extend the scope of this methodology addition with thiols, carbamates and sulphonamides could be explored to test the substrate specificity of the conjugate addition and the influence of pK_a.

Unfortunately there was limited success in the use of *trans*-*N*-heterocyclic cyclopropane diesters as precursors in the cycloaddition reaction with nitrones, where only one of the cyclopropanes afforded the oxazine in a moderate yield. (Scheme 141)

Scheme 141

An interesting point to note is that when the *trans*-*N*-heterocyclic cyclopropane **182**$_d$ was employed we would have expected to see a *cis* relationship between C^5 and C^6. However the stereochemistry was maintained within the oxazine ring expressing a *trans* relationship between C^5 and C^6. This implies that no inversion of stereochemistry took place when ring-opening of the cyclopropane took place suggesting the cyclopropane ring opened first and reaction took place *via* a concerted mechanism. However as only one example has been obtained there is insufficient evidence to confirm this hypothesis.

4. Experimental

General information

All reactions herein were carried out in one of the following solvents, which were dried and purified, or purchased by the following procedures.

Acetone Stirred over anhydrous potassium carbonate, followed by distillation over anhydrous calcium sulfate.

Acetonitrile Purchased from Aldrich (99.8%), Sure/seal^{TM} anhydrous quality.

Chloroform Purchased from Aldrich (99+%) and used without further purification.

Dichloromethane For general use, CH_2Cl_2 was distilled over boiling chips or CaH_2 for anhydrous reactions.

Diethyl ether Purchased from Fischer Scientific (99+%) used without purification for general use or distilled over sodium and benzophenone for anhydrous reactions.

Ethyl acetate Distilled over $CaCl_2$ for general use.

Light petroleum Distilled over boiling chips for general use, collecting the fraction distilling below 60°C.

Tetrahydrofuran Distilled over sodium and benzophenone.

Palladium(II) acetate (reagent grade 98%) was purchased from Sigma-Aldrich and rhodium(II) acetate dimer (98+%) was purchased from Alfa Aesar and used without further purification.

Anhydrous reactions were carried out in oven-dried glassware and under an atmosphere of nitrogen.

Analysis of the compounds created herein was made using a number of the following instruments and procedures.

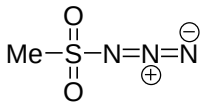
High-resolution mass spectroscopy was carried out on three different instruments: (1) a Jeol SX 102 machine, used for both electron ionisation (EI) and fast atom bombardment (FAB) ionisation techniques. For FAB spectroscopy a matrix of 1,3-nitrobenzylalcohol was used to dissolve the compounds under investigation prior to ionisation. (2) A Thermo Exactive (Orbi) machine, where the spectra was recorded in positive ion mode using electrospray ionisation (ES) from methanol or methanol/acetic (1% v/v) solution. The samples were delivered to the instrument using an Advion Triversa NanoMate. (3) A Bruker MicrOTOFQ, AC113, where the spectra was recorded in positive ion mode using electrospray ionisation. The MS method used was GEN MA-M34-01 HPLC Method "Fast Zorbax ACN" and formic acid (4% of 250Mm in gradient) was used for the mobile phase additive.

Nuclear magnetic resonance spectroscopy was carried out using a Bruker DPX 400 instrument. The spectra were calibrated where possible to the signals of tetramethylsilane or the small quantity of $CHCl_3$ present in $CDCl_3$. Where possible, coupling constants (*J*) are shown denoting the multiplicity as a singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or broad signal (br). The size of the coupling constant is given in hertz (Hz).

Fourier transform Infra Red spectroscopy was recorded using a Paragon 1000 Perkin Elmer FT-IR spectrophotometer in the range of 600-3800 cm^{-1} following a standard background correction.

Flash silica column chromatography was used as a standard purification procedure using Fluka Kiesel gel 60, 0.04-0.063 mm particle size. Thin layer chromatography was used where possible as a standard procedure for monitoring the course and rate of a given reaction. TLC plates used were Merck aluminium backed sheets with Kiesel gel 60 F_{254} silica coating.

Methanesulfonyl azide (153)[88]



Sodium azide (10.14g, 156 mmol, 1.2 eq) was added slowly to a solution of methanesulfonyl chloride (10.14 mL, 15g, 130 mmol) in acetone (100 mL) and the resulting mixture was stirred at r.t. under a nitrogen atmosphere for 4 hours. On completion the reaction mixture was quenched with water (100 mL) and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The ethereal extracts were combined and dried over anhydrous $MgSO_4$. The excess solvents were removed under reduced pressure to afford the *title compound* as a colourless liquid in >99% yield (15.57 g, 120 mmol), IR ν_{max} (neat)/cm^{-1} 2359.7 (N=N=N), 668.0, δ_H(400 MHz; $CDCl_3$) 3.27 (3H, s, C*H*$_3$), δ_C(100 MHz; $CDCl_3$) 42.9 (CH_3). The above data is in agreement with the literature values stated.

Diazo Dimethylmalonate (150_a)[13]

Triethylamine (11.5 mL, 8.36 g, 82.6 mmol, 2 eq) was added dropwise to a stirred solution of dimethylmalonate (4.3 mL, 4.96 g, 37.6 mmol) and methanesulfonyl azide **153** (5 g, 41.4 mmol, 1.1 eq) in anhydrous acetonitrile (60 mL) at 0°C. Once addition was complete the reaction mixture was stirred at ambient temperature for 24 hours under a nitrogen atmosphere. The solution was concentrated *in vacuo* and the residue was dissolved in a 1:1 solution of petrol/chloroform (40 mL). The solids were removed by filtration on a Büchner funnel and the filtrate was concentrated *in vacuo* to afford the *title compound* as a yellow oil in 97% yield (5.74 g, 36.3 mmol), IR ν_{max} (film)/cm^{-1} 2137 (C=N) and 1761(C=O); δ_H(400 MHz; $CDCl_3$) 3.85 (6H, s, 2 CO_2CH_3); δ_C(100 MHz; $CDCl_3$) 52.4 (2 CO_2CH_3), 65.5 (CN), 161.3 (2 C=O). The above data is in agreement with the literature values stated.

Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (81_b)[57a,b]

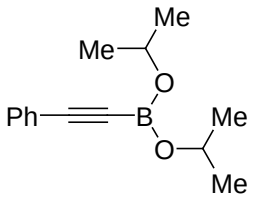
In a 50 ml round-bottom flask, styrene (2.2 ml, 2 g, 19 mmol) was dissolved in anhydrous toluene (25ml). Diazomalonate **150_a** (5.04 g, 32mmol, 1.66 eq) and a catalytic amount of rhodium acetate dimer (50 mg) was added. The reaction mixture was heated to reflux under a nitrogen atmosphere for 19 hours. Once complete the reaction mixture was cooled to room temperature and filtered through a pad of celite and silica and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:9) to afford the *title compound* as straw yellow oil in 55% yield (2.45 g, 10.47 mmol). R_f (EtOAc/petrol 1:9) 0.44; IR ν_{max} (neat)/cm^{-1} 3028 (sp CH), 2951(sp^2 CH), 1732 (C=O) 1279 (C-O); δ_H(400 MHz; $CDCl_3$) 1.73 (1H, dd, *J* 9.4, 5.2 Hz, CHC*H*$_2$C), 2.20 (1H, dd, *J* 8.0, 5.2 Hz, CHC*H*$_2$C), 3.22 (1H, t, *J* 8.5 Hz, CH$_2$C*H*C), 3.32 (3H, s, CO_2CH_3), 3.74 (3H, s, CO_2CH_3), 7.16-7.22 (2H, m, ArC*H*), 7.23-7.26 (3H, m, ArC*H*), δ_C(100 MHz; $CDCl_3$) 19.0 (CH*C*H$_2$C), 32.5 (C*H*CH$_2$C), 37.2 (*C*(CO$_2$CH$_3$)$_2$), 52.3 (CO$_2$*C*H$_3$), 52.7 (CO$_2$*C*H$_3$), 127.4 (Ar*C*H), 128.2 (2 Ar*C*H), 128.4 (2 Ar*C*H), 134.6 (Ar*C*), 166.9 (C=O), 170.2 (C=O). The above data is in agreement with the literature values stated.

Phenyl cyclopropene-1,1-dicarboxylic acid dimethyl ester (1_d)[73]

A solution of diazo dimethylmalonate **150_a** (5 g, 32 mmol) in anhydrous dichloromethane (60 mL) was added via a syringe (1.0 mL/ph) to a stirred solution of phenylacetylene (10.4 mL, 9.7 g, 95 mmol, 3 eq) and rhodium acetate dimer (140 mg, 0.32 mmol) under a nitrogen atmosphere. Once addition was complete the reaction mixture was stirred for an additional six hours at room temperature. The mixture was filtered through a pad of celite and silica and the excess solvents were removed under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (EtOAc/petrol 1:5) to afford the *title compound* as a pale yellow solid in 54 % yield (4.01g, 17.28 mmol). R_f (EtOAc/Petrol 1:5) 0.33; mp 69.1-72.4°C; Lit mp 73-74°C ;IR ν_{max} (film)/cm^{-1} 2951 (sp^2

C-H), 1726 (C=O), 1487, 1288 (C-O), 1064; δ_H(400 MHz; $CDCl_3$) 3.73 (6H, s, 2 CO_2CH_3), 6.89 (1H, s, C*H*), 7.46-7.44 (3H, m, ArC*H*), 7.62 (2H, dd, *J* 4.0, 2.0 Hz, ArC*H*); δ_C(100 MHz; $CDCl_3$) 52.5 (2 CO_2CH_3), 62.5 ($C(CO_2CH_3)_2$), 76. 7 (C=C), 95. 2 (*C*H), 123.9 (Ar*C*), 128.9 (2 Ar*C*H), 130.4 (3 Ar*C*H), 171.2 (2 C=O). The above data is in agreement with the literature values stated.

2-Phenyl-1-ethynyldiisopropoxyborane (160)[76]



^{n}Butyllithium (2.5M solution in hexane) (3.9 mL, 9.79 mmol) was slowly added to a stirred solution of phenylacetylene (1.07 mL, 1 g, 9.79 mmol) in diethyl ether (10mL) at -78°C under a nitrogen atmosphere. The formed lithium acetylide was added to a separate solution of triisopropylborane (1.34 mL, 1.84 g, 9.79 mmol) in diethyl ether (10 mL) at -78°C *via* a canula. The reaction was maintained at -78^{o}C for two hours, prior to the addition of anhydrous HCl in dioxane (2.4 mL, 0.35 g, 9.79 mmol). The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature. The precipitated lithium chloride was removed by filtration and excess solvents were removed under reduced pressure to afford the *title compound* as an orange oil in 46% yield (1.03 g, 4.48 mmol), IR ν_{max} (film)/cm^{-1} 2245 (C≡C), 1445 (B-O), 1194 (B-C); δ_H(400 MHz; $CDCl_3$) 1.23 (12H, d, *J* 6.3 Hz, 4 CH_3), 4.66 (2H, q, *J* 6.4 Hz, 2 C*H*$(CH_3)_2$), 7.30-7.35 (3H, m, ArC*H*), 7.48-7.52 (2H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 24.4 (4 *C*H_3), 65.3 (2 *C*H), 83.66 (C-B), 101.84 (C≡C), 122.3 (ArC), 129.1 (3 Ar*C*H), 132.3 (2 Ar*C*H); δ_B (100 MHz; $CDCl_3$) 21.5 (B). The above data is in agreement with the literature values stated.

2,3-Diphenylcyclopropene-1,1-dicarboxylic acid dimethyl ester (171_a)[13]

An oven-dried round bottom flask was charged with palladium (II) acetate (18 mg, 0.08 mmol, 5 mol %), iodobenzene (0.09 mL, 0.16 g, 0.81 mmol), substituted cyclopropene $\mathbf{1}_d$

(0.19 g, 0.81 mmol) and anhydrous potassium carbonate (0.28 g, 2.0 mmol, 2.5 eq) under a nitrogen atmosphere. *N*,*N*-dimethylformamide (0.70 mL) was added and the reaction mixture was stirred at 30°C for 48 hours. Once the reaction was complete the reaction mixture was filtered through a short column of celite and silica gel (eluent: diethyl ether). The ethereal solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), brine (2 x20 mL) and dried over anhydrous sodium sulphate and the excess solvents were removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc/ petrol 1:10) to afford the *title compound* as a light yellow solid 51% yield (0.13 g, 0.41 mmol). R_f (EtOAc/ petrol 1:10) 0.50; mp 121-122°C; IR ν_{max} (film)/cm^{-1} 1643 (C=O), 1280 (C-O); δ_H(400 MHz; $CDCl_3$) 3.72 (6H, d, *J* 7.2 Hz, 2 CO_2CH_3), 7.43-7.51 (6H, m, ArC*H*), 7.74-7.76 (4H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 51.2 (2 CO_2CH_3), 62.4 ($C(CO_2Me)_2$), 126.2 (4 ArCH), 126.8 (C=C), 127.7 (2 ArCH), 128.4 (4 ArCH), 134.9 (2 ArC), 171.0 (C=O).

2,3-Diphenyl cyclopropane diester (170$_a$)

5% Palladium/calcium carbonate (68 mg, 0.0097 mmol) was added to a solution of the substituted cyclopropene **171**$_a$ (0.3 g, 0.97 mmol) in ethyl acetate (4 mL). The reaction was stirred vigorously under a H_2 atmosphere with the aid of a hydrogen balloon for 6 hours (monitored by TLC). The crude product was filtered through a pad of celite and silica and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EtOAc/ petrol 1:10) to afford the *title compound* as an off-white solid in 80% yield (240 mg, 0.78 mmol). R_f (EtOAc/ petrol 1:10) 0.41; mp 134.4-136.4°C, IR ν_{max} (film)/cm^{-1} 2955 (CH), 1732 (C=O), 1643 (C=O), 1253 (C-O); δ_H(400 MHz; $CDCl_3$) 3.33 (2H, s, 2 C*H*), 3.45 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 7.03-7.05 (4H, m, ArC*H*), 7.17-7.20 (6H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 35.7 (2 CH), 40.9 ($C(CO_2Me)_2$), 52.1 (CO_2CH_3), 53.3 (CO_2CH_3), 127.2 (6 ArCH), 130.6 (4 ArCH), 132.7 (2 ArC), 166.3 (C=O), 171.0 (C=O), FTMS (ES) ($M+Na^+$), calculated for $C_{19}H_{18}O_4Na$ 333.109, found 333.109 (+0.235 ppm).

2-(4'-Fluorophenyl)-3-phenyl cyclopropene diester (171$_d$)

N,*N*-dimethylformamide (3 mL) was added to an oven-dried round bottom flask charged with palladium (II) acetate (48 mg, 0.2 mmol, 5 mol %), 1-iodo-4-fluorobenzene (0.50 mL, 0.95 g, 4.30 mmol), substituted cyclopropene **1**$_d$ (0.8 g, 4.30 mmol) and anhydrous potassium carbonate (1.48 g, 11.0 mmol, 2.5 eq) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 48 hours (monitored by TLC). Once complete the reaction mixture was cooled to room temperature and filtered through a short column of celite and silica gel (eluent diethyl ether). The ethereal solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), brine (2 x20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:10) to obtain the *title compound* as a rusty orange solid in a 50% yield (0.70 g, 2.14 mmol). R_f (EtOAc/ Petrol 1:10) 0.35; mp 116.2-118.2°C; IR ν_{max} (film)/cm^{-1} 2951 (sp^3 C-H), 1730 (C=O), 1601(ArC=C), 1506(ArC=C), 1284(C-O), 1154 (Ar-F); δ_H(400 MHz; $CDCl_3$) 3.73 (6H, s, 2 CO_2CH_3), 7.17-7.21 (2H, m, ArF-C*H*), 7.45-7.51 (3H, m, ArC*H*), 7.71-7.75 (4 H, m, 2 ArC*H*, 2 ArF-C*H*); δ_C(100 MHz; $CDCl_3$) 35.0 ($C(CO_2CH_3)_2$), 52.4 (2 CO_2CH_3), 116.3 (ArF-*C*H), 116.5 (ArF-*C*H), 122.3 (C=C), 125.1 (C=C), 129.0 (2 Ar*C*H), 130.0 (ArF-*C*H), 130.1 (ArF-*C*H), 132.0 (2 ArC*H*), 132.1 (ArC*H*), 163.4 (1C, d, *J* 250 Hz, CF), 170.7 (2 C=O); HRMS (FAB) ($M+H^+$), calculated for $C_{19}H_{16}FO_4$ 327.1031, found 327.1032; *m/z* 327 (49%), 326 (38%) and 267 (100%).

(±) 2-(4'-Fluorophenyl)-3-phenyl cyclopropane diester (170$_d$)

5% Palladium/calcium carbonate (34 mg, 0.0046 mmol) was added to a solution of the substituted cyclopropene **171**$_d$ (0.15 g, 0.46 mmol) in ethyl acetate (4 mL). The reaction mixture was stirred vigorously under a H_2 atmosphere with the aid of a hydrogen balloon

for 3 hours (monitored by TLC). The crude product was filtered through a pad of celite and silica and the filtrate was concentrated *in vacuo* to afford the *title compound* without further purification as a light yellow viscous oil in 99% yield (0.15g, 0.45 mmol); IR ν_{max} (film)/cm^{-1} 2952 (sp^3C-H), 1728 (C=O), 1635, 1604 (ArC=C), 1511 (ArC=C), 1255 (C-O), 1156 (Ar-F); δ_H(400 MHz; $CDCl_3$) 3.29 (1H, d, *J* 10.1 Hz, C*H*CAr), 3.31 (1H, d, *J* 10.1 Hz, C*H*CAr), 3.46 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 6.86-6.90 (2H, m, ArF-C*H*), 6.97-6.99 (2H, m, ArF-C*H*), 7.02-7.06 (2H, m, ArC*H*), 7.16-7.20 (3H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 34.4 (2 *C*HCAr), 42.4 ($C(CO_2CH_3)_2$), 52.1 (2 CO_2CH_3), 114.9 (2 ArF-*C*H), 124.9 (Ar*C*H), 125.2 (2 Ar*C*H), 126.8 (2 ArF-*C*H), 127.9 (2 Ar*C*H), 138.6 (CH*C*ArF), 144.2 (Ar*C*), 163.4 (1C, d, *J* 250 Hz, CF), 171.3 (2 C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{19}H_{18}FO_4$ 329.1110, found 329.1192; *m/z* 329 (37%), 296 (48%), 265 (100%), 209 (88%), 196 (30%) and 91 (38%).

2-(4'-Methoxyphenyl)-3-phenyl cyclopropene diester (171$_b$)

N,*N*-dimethylformamide (1.5 mL) was added to an oven-dried round bottom flask charged with palladium (II) acetate (25 mg, 0.11 mmol, 5 mol %), 4-iodo-anisole (0.50 g, 2.2 mmol), substituted cyclopropene **1**$_d$ (0.5 g, 2.2 mmol) and anhydrous potassium carbonate (0.74 g, 5.0 mmol, 2.5 eq) under a nitrogen atmosphere. The resulting mixture was stirred at 90^{o}C for 48 hours and once complete was cooled to room temperature and filtered through a short column of celite and silica gel (eluent diethyl ether). The obtained ethereal solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), brine (2 x20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:10) to obtain the *title compound* as an orange/brown solid in 45% yield (0.33 g, 0.99 mmol). R_f (EtOAc/ Petrol 1:10) 0.71; mp 116.1-118.6°C; IR ν_{max} (film)/cm^{-1} 2950 (sp^3CH), 1730 (C=O), 1604 (ArC=C), 1509 (ArC=C), 1434 (ArC=C), 1283 (C-O), 1128(C-O); δ_H(400 MHz; $CDCl_3$) 3.72 (6H, s, 2 CO_2CH_3), 3.86 (3H, s, OCH_3), 7.01 (2H, d, *J* 8.8 Hz, ArOMe-C*H*), 7.39 (1 H, t, *J* 7.2, Hz, ArC*H*), 7.47 (2H, t, *J* 7.2 Hz, ArC*H*), 7.68 (2H, d, *J* 8.8 Hz, ArOMe-C*H*), 7.71 (2H, d, *J* 1.2 Hz, ArC*H*); δ_C(100 MHz; $CDCl_3$) 35.4 ($C(CO_2CH_3)_2$), 52.3 (CO_2CH_3), 55.5 (OCH_3), 103.9 (C=C), 106.2

(C=C), 114.7 (ArOMe-*C*H), 117.8 (Ar*C*), 125.6 (Ar*C*), 128.9 (2 Ar*C*H), 129.4 (Ar*C*H), 129.8 (ArOMe-*C*H), 131.9 (2 Ar*C*H), 161.1 (Ar*C*-OCH_3), 171.0 (C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{20}H_{19}O_5$ 339.1154, found 339.1233; *m/z* 339 (39%), 329 (28%), 279 (35%), 162 (56%) and 148 (100%).

(±) 2-(4'-Methoxyphenyl)-3-phenyl cyclopropane diester (**170**$_b$)

5% Palladium/calcium carbonate (54 mg, 0.0080 mmol) was added to a stirred solution of the substituted cyclopropene **171**$_b$ (0.28 g, 0.80 mmol) in ethyl acetate (10 mL). The resulting mixture was stirred vigorously under a H_2 atmosphere with the aid of a hydrogen balloon for 19 hours (monitored by TLC). The crude product was filtered through a pad of celite and silica, prior to purification by flash chromatography on silica gel (EtOAc/ Petrol 1:10) to afford the *title compound* as an orange oil in 92% yield (0.26g, 0.76 mmol). R_f (EtOAc/ Petrol 1:10) 0.54; IR ν_{max} (film)/cm^{-1} 2948 (sp^3CH), 1728 (C=O), 1608 (ArC=C), 1249 (C-O), 1179; δ_H(400 MHz; $CDCl_3$) 3.20 (2H, d, *J* 7.2 Hz, ArC*H*C*H*Ar), 3.39 (3H, s, CO_2CH_3), 3.69 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 6.65 (2H, dd, *J* 6.8, 2.0 Hz, ArOMe-C*H*), 6.91 (2H, dd, *J* 3.6 , 6.4 Hz, ArOMe-C*H*), 6.94-6.96 (2H, m, ArC*H*), 7.10-7.13 (3H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 35.2 (CH), 35.6 (CH), 42.3 ($C(CO_2CH_3)_2$), 52.1 (CO_2CH_3), 53.2 (OCH_3), 55.1 (CO_2CH_3), 113.0 (ArOMe-*C*H), 126.8 (ArOMe-*C*H), 127.5 (Ar*C*H), 130.6 (2 Ar*C*H), 131.8 (2 Ar*C*H), 158.5 (Ar*C*-OMe), 171.0 (C=O); HRMS (FAB) (M^+) calculated for $C_{20}H_{20}O_5$ 340.1310, found 340.1316; *m/z* 340 (55%), 309 (48%), 280 (52%), 277 (100%), 249 (37%), 221 (84%), 178 (30%), 135 (37%) and 121 (44%). Due to a weak sample not all the quaternary carbons have been accounted for.

2-Phenyl-3-(4'-trifluoromethylphenyl) cyclopropene diester (**171**$_e$)

N,*N*-dimethylformamide (4 mL) was added to an oven-dried round bottom flask charged with palladium (II) acetate (48 mg, 0.21 mmol, 5 mol %), 1-Iodo-4-(trifluoromethyl)benzene (0.63 mL, 1.17 g, 4.3 mmol), substituted cyclopropene **1**$_d$ (1.0 g, 4.3 mmol) and anhydrous potassium carbonate (1.48 g, 10.0 mmol, 2.5 eq) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 48 hours and once complete was cooled to room temperature and was filtered through a short column of celite and silica gel (eluent diethyl ether). The obtained ethereal solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), brine (2 x20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/ petrol 1:10) to afford the *title compound* as a pale yellow solid in 55% yield (0.89 g, 2.37 mmol). R_f (EtOAc/ petrol 1:10) 0.30; mp 160.8-161.7°C, IR ν_{max} (film)/cm^{-1} 1748 (C=O), 1720 (C=O), 1188 (C-F), 1158 (C-F); δ_H(400 MHz; $CDCl_3$) 3.74 (6H, s, 2 CO_2CH_3), 7.50-7.56 (3H, m, ArC*H*), 7.67-7.73 (4H, m, 2 ArC*H*-CF_3, 2 ArC*H*), 7.87 (2H, d, *J* 8.8 Hz, ArC*H*-CF_3); δ_C(100 MHz; $CDCl_3$) 35.0 ($C(CO_2CH_3)_2$), 52.5 (CO_2CH_3), 105.2 (C=C), 109.2 (C=C), 124.7 (1C, q, *J* 271 Hz, CF_3), 125.2 (Ar*C*H-CF_3), 126.0 (Ar*C*H-CF_3), 129.2 (3 Ar*C*H), 130.2 (Ar*C*-CF_3), 130.5 (Ar*C*H), 130.7 (Ar*C*H), 139.2 (Ar*C*), 142.7 (Ar*C*) 170.4 (C=O); δ_F(376 MHz; $CDCl_3$) 99.4 (3F, s, CF_3); HRMS (FAB) ($M+H^+$) calculated for $C_{20}H_{15}F_3O_4$ 377.1007, found 377.1007; *m/z* 377 (65%), 376 (51%), 317 (100%), 289 (32%), 154 (50%) and 136 (43%).

(±) 2-Phenyl-3-(4'-trifluoromethyl) phenyl cyclopropane diester (170$_e$)

5% Palladium/calcium carbonate (68 mg, 0.0082 mmol) was added to a solution of the substituted cyclopropene **171**$_e$ (310 mg, 0.82 mmol) in ethyl acetate (10 mL). The resulting mixture was stirred vigorously under a H_2 atmosphere with the aid of a hydrogen balloon for 3 hours (monitored by TLC). The crude product was filtered through a pad of celite and silica and the filtrate was concentrated *in vacuo* to afford the *title compound* without further purification as a yellow oil in 99% yield (310 mg, 0.82 mmol); IR ν_{max} (film)/cm^{-1} 2953 (sp^3CH), 1736 (C=O), 1617 (ArC=C), 1495 (ArC=C), 1325 (C-O), 1256 (C-O), 1163 (C-F), 1122 (C-F); δ_H(400 MHz; $CDCl_3$) 2.82 (1H, dd, *J* 4.0, 13.2 Hz, C*H*), 3.11 (1H, dd, *J*

4.0, 13.2 Hz, C*H*), 3.47 (3H, s, CO_2CH_3), 3.79 (3H, s, CO_2CH_3), 6.91 (2H, d, *J* 8.0 Hz, ArC*H*-CF_3), 7.11-7.18 (5H, m, ArC*H*), 7.45 (2H, d, *J* 8.0 Hz, ArC*H*-CF_3); δ_C(100 MHz; $CDCl_3$) 35.1 (CH), 35.6 (CH), 41.1 ($C(CO_2CH_3)_2$), 52.3 (CO_2CH_3), 53.5 (CO_2CH_3), 124.4 (1C, q, *J* 271 Hz, CF_3), 125.1 (Ar*C*H-CF_3), 127.8 (Ar*C*H), 128.2 (Ar*C*H), 128.6 (Ar*C*-CF_3), 130.2 (Ar*C*H-CF_3), 131.1 (Ar*C*H), 132.2 (Ar*C*), 136.9 (Ar*C*), 166.1 (C=O), 170.6 (C=O); FTMS (ES) ($M+H^+$), calculated for $C_{20}H_{18}F_3O_4$ 379.110, found 379.123.

2-Phenyl,3-(4'-nitrophenyl) cyclopropane diester (171_c)[13]

N,*N*-dimethylformamide (3 mL) was added to an oven-dried round bottom flask charged with palladium (II) acetate (25 mg, 0.11 mmol, 5 mol %),4- iodo-nitrobenzene (0.54 g, 2.2 mmol), substituted cyclopropene $\mathbf{1}_d$ (0.5 g, 2.2 mmol) and anhydrous potassium carbonate (0.74 g, 5.5 mmol, 2.5 eq) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 48 hours and once complete was cooled to room temperature and was filtered through a short column of celite and silica gel (eluent diethyl ether). The obtained ethereal solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), brine (2 x20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/ petrol 1:10) to afford the *title compound* as a yellow oil in 40% yield. (0.31 g, 0.88 mmol); IR ν_{max} (film)/cm^{-1} 2952 (sp^3CH), 1729 (C=O), 1591 (ArC=C), 1517 (NO_2), 1341 (NO_2), 838 (*p*-disubstituted benzene ring); δ_H(400 MHz; $CDCl_3$) 3.87 (6H, s, 2 CO_2CH_3), 7.51-7.55 (3H, m, 3 ArC*H*), 7.78-7.80 (2H, m, 3 ArC*H*), 7.90 (2H, dd, *J* 2.0, 6.8 Hz, 2 ArC*H*-NO_2), 8.34 (2H, dd, *J* 2.0, 6.2 Hz, 2 ArC*H*-NO_2); δ_C(100 MHz; $CDCl_3$) 35.2 ($C(CO_2CH_3)_2$), 52.7 (2 CO_2CH_3), 104.6 (C=C), 111.6 (C=C), 124.4 (2 Ar*C*H-NO_2), 127.4 (Ar*C*), 129.3 (3 Ar*C*H), 130.6 (Ar*C*H-NO_2), 130.8 (Ar*C*H-NO_2), 131.2 (Ar*C*H), 131.5 (Ar*C*), 147.9 (*C*-NO_2), 170.1 (2 C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{19}H_{16}NO_6$ 354.0894, found 354.0975. The above data is in agreement with the literature values stated.

2-Butylcyclopropene-1,1-dicarboxylic acid dimethyl ester (37_f)[73]

A solution of diazo dimethylmalonate **150**$_a$ (1.58 g, 10 mmol) in anhydrous dichloromethane (5ml) was added *via* a syringe pump over a period of 18 hours to a stirred solution of 1-hexyne (3.58 ml, 2.56 g, 31 mmol, 3.1 eq) and rhodium acetate dimer (22 mg, 0.05 mmol, 1 mol%) in anhydrous dichloromethane (10 ml) under a nitrogen atmosphere. Once addition was complete the reaction mixture was stirred for additional 6 hours at room temperature. The mixture was filtered through a pad of silica and celite and excess solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/ petrol 1:8) to afford the *title compound* as colourless oil in 46% yield. (0.95 g, 4.5 mmol); IR ν_{max} (film)/cm^{-1} 2955 (sp^3CH), 1732 (C=O), 1280 (C-O); δ_H(400 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.28-1.35 (2H, m, CH_2), 1.48-1.56 (2H, m, CH_2), 2.48 (2H, t, *J* 7.6 Hz, CH_2), 3.65 (6H, s, 2 CO_2CH_3), 6.28 (1H, t, *J* 1.4 Hz, $CHC{=}CCH_2$); δ_C(100 MHz; $CDCl_3$) 13.4 (CH_3), 21.9 (CH_2), 24.1 (CH_2), 29.1 (CH_2), 52.1 (2 CO_2CH_3), 60.4 ($C(CO_2CH_3)_2$), 95.6 (CH), 108.7 (C=C), 171.3 (2 C=O). The above data is in agreement with the literature values stated.

2-Butyl-3-phenyl-cyclopropene-1,1-dicarboxylic acid dimethyl ester (171_f)[13]

N,*N*-dimethylformamide (3 mL) was added to an oven dried flask loaded with palladium (II) acetate (53 mg, 0.24 mmol, 5 mol %), iodobenzene (0.53 ml, 0.96 g, 4.7 mmol), substituted cyclopropene **37**$_f$ (1.0g, 4.7 mmol) and anhydrous potassium carbonate (1.62 g, 12.0 mmol, 2.5 eq) under a nitrogen atmosphere. The resulting mixture was stirred at 60^{o}C for 48 hours and once complete was cooled to room temperature and filtered through a pad of silica and celite and washed with diethyl ether (10 mL). The obtained ethereal solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), brine (2 x20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel

(EtOAc/ petrol 1:10) to afford the *title compound* as a clear oil in 43% yield. (0.58g, 2.0 mmol); IR ν_{max} (film)/cm^{-1} 2954 (CH_2), 1731 (C=O), δ_H(400 MHz; $CDCl_3$) 0.84 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.44-1.36 (2H, m, C*H*$_2$), 1.69-1.64 (2H, m, C*H*$_2$), 2.65 (2H, t, *J* 7.6 Hz, C*H*$_2$), 3.64 (6H, s, 2 CO_2CH_3), 7.36-7.29 (3H, m, ArC*H*), 7.51-7.53 (2H, m, ArC*H*), δ_C(100 MHz; $CDCl_3$) 13.7 (*C*H_3), 22.4 (*C*H_2), 24.2 (*C*H_2), 29.2 (*C*H_2), 52.1 (CO_2CH_3), 104.4 (*C*(CO_2CH_3), 109.2 (2 Ar*C*=*C*CH_2), 125.1 (Ar*C*), 128.8 (3 Ar*C*H), 129.3 (Ar*C*H), 129.6 (Ar*C*H), 171.5 (C=O). The above data is in agreement with the literature values stated.

(±) 2-Butyl-3-phenyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (170$_f$)

5% Palladium/calcium carbonate (44 mg, 1 mol%) was added to a solution of the substituted cyclopropene **171**$_f$ (0.24 g, 0.83 mmol) in ethyl acetate (4 ml). The resulting mixture was stirred vigorously under a H_2 atmosphere with the aid of a balloon for 19 hours (monitored by TLC). The crude product was filtered through a pad of celite and silica prior to purification by flash chromatography on silica gel (EtOAc/ petrol 1:10) to afford the *title compound* as a colourless oil in 67% yield. (0.16g, 0.55 mmol); IR ν_{max} (neat)/cm^{-1} 2952 (sp^3 CH), 2858 (CH), 1730 (C=O), 1602 (ArC=C), 1498 (ArC=C); δ_H(400 MHz; $CDCl_3$) 0.80 (3H, t, *J* 7.2 Hz, C*H*$_3$), 1.22-1.30 (2H, m, C*H*$_2$), 1.32-1.41 (2H, m, C*H*$_2$), 1.65-1.71 (2H, m, C*H*$_2$), 1.89 (1H, d, *J* 10 Hz, C*H*CH_2), 3.04 (1H, d, *J* 10 Hz, C*H*Ar), 3.54 (3H, s, CO_2CH_3), 3.71 (3H, s, CO_2CH_3), 7.13-7.17 (2H, m, ArC*H*), 7.19-7.22 (3H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 14.0 (*C*H_3), 22.7 (*C*H_2), 24.7 (*C*H_2), 31.7 (*C*H_2), 33.5 (*C*H), 34.9 (*C*H), 37.6(*C*(CO_2CH_3)), 52.0 (CO_2CH_3), 52.9 (CO_2CH_3), 126.9 (Ar*C*H), 128.0 (Ar*C*H), 128.6 (Ar*C*H), 129.1 (Ar*C*H), 129.6 (Ar*C*H), 134.1 (Ar*C*), 167.3 (C=O), 171.4 (C=O); FTMS (ES) ($M+H^+$), calculated for $C_{17}H_{23}O_4$ 291.150, found 291.670.

2-Butyl-3-(4'-fluorophenyl) cyclopropene diester (171$_g$)

N,N-dimethylformamide (3.1 mL) was added to an oven-dried round bottom flask charged with palladium (II) acetate (53 mg, 0.23 mmol, 5 mol %), 1-Fluoro-4-iodobenzene (0.55 mL, 1.05 g, 4.7 mmol), substituted cyclopropene **37**$_f$ (1.0 g, 4.7 mmol) and anhydrous potassium carbonate (1.62 g, 12.0 mmol, 2.5 eq) under a nitrogen atmosphere. The resulting mixture was stirred at 90^{o}C for 48 hours and once complete was cooled to room temperature and filtered through a short column of celite and silica gel (eluent diethyl ether). The obtained ethereal solution was washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), brine (2 x20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/ petrol 1:10) to afford the *title compound* as a light yellow oil in 42% yield (0.60 g, 1.97 mmol). R_f ; (EtOAc/ petrol 1:10) 0.29; IR ν_{max} (film)/cm^{-1} 2963 (sp^{3}C-H), 1730 (C=O), 1128 (Ar-F); δ_H(400 MHz; $CDCl_3$) 0.96 (3H, t, *J* 7.6 Hz, C*H*$_3$), 1.45 (2H, dd, *J* 7.6, 7.2 Hz, C*H*$_2$), 1.70-1.75 (2H, m, C*H*$_2$), 2.70 (2H, t, *J* 7.2 Hz, C*H*$_2$), 3.71 (6H, s, 2 CO_2CH_3), 7.09-7.13 (2H, m, ArF-C*H*), 7.52-7.49 (2H, m, ArF-C*H*); δ_C(100 MHz; $CDCl_3$) 13.7 (*C*H$_3$), 22.4 (*C*H$_2$), 24.1 (*C*H$_2$), 29.2 (*C*H$_2$), 42.4 (*C*(CO$_2$CH$_3$)$_2$), 52.2 (2 CO$_2$*C*H$_3$), 106.3 (C=C), 108.4 (C=C), 116.0 (Ar*C*H), 116.2 (Ar*C*H), 131.4 (Ar*C*H), 131.5 (Ar*C*H), 171.4 (2 C=O); δ_F(376 MHz; $CDCl_3$) 51.9 (1F, sept, *J* 4.7 Hz); HRMS (FAB) (M+H$^+$) calculated for $C_{17}H_{19}O_4F$ 307.1267, found 307.1345; *m/z* 307 (84%), 306 (26%) and 247 (100%). Due to a weak sample not all the quaternary carbons have been accounted for.

(±) 2-Butyl-3-(4'-fluorophenyl) cyclopropane diester (**170**$_g$)

5% Palladium/calcium carbonate (69 mg, 0.0065 mmol) was added to a solution of the substituted cyclopropene **171**$_g$ (0.20 g, 0.65 mmol) in ethyl acetate (10 mL). The reaction mixture was stirred vigorously under a H_2 atmosphere with the aid of a hydrogen balloon for 20 hours (monitored by TLC). The crude product was filtered through a pad of celite and silica prior to purification by flash chromatography on silica gel (EtOAc/ petrol 1:10) to afford the *title compound* as a yellow viscous oil in 50% yield (100 mg, 0.32 mmol); IR ν_{max} (film)/cm^{-1} 2953(sp^{3}CH), 1728 (C=O), 1605 (ArC=C), 1101(Ar-F); δ_H(400 MHz;

$CDCl_3$) 0.88 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$CH$_2$CH$_2$), 1.30-1.35 (2H, m, C*H*$_2$), 1.40-1.48 (2H, m, C*H*$_2$), 1.71 (2H, t, *J* 7.2 Hz, C*H*$_2$), 1.96 (1H, d, *J* 10.0 Hz, C*H*CH$_2$), 3.06 (1H, d, *J* 10.0 Hz, C*H*Ar), 3.62 (3H, s, CO_2CH_3), 3.79 (3H, s, CO_2CH_3), 6.95-6.99 (2H, m, ArF-C*H*), 7.18-7.21 (2H, m, ArF-C*H*); δ_C(100 MHz; $CDCl_3$) 14.0 (*C*H$_3$CH$_2$CH$_2$CH$_2$), 22.6 (*C*H$_2$), 24.7 (*C*H$_2$), 31.7 (*C*H$_2$), 33.3 (*C*H), 34.0 (*C*H), 37.5 (*C*(CO$_2$CH$_3$)$_2$), 52.0 (CO_2CH_3), 53.0 (CO_2CH_3), 114.9 (Ar*C*H), 115.0 (Ar*C*H), 131.3 (2 Ar*C*H), 161.8 (1C, d, *J* 244 Hz, CF), 167.2 (Ar*C*), 171.2 (2 C=O).;FTMS (ES) ($M+H^+$), calculated for $C_{17}H_{22}O_4$ 309.14, found 309.457.

N-Benzyl-(4'-methoxy-benzylidene)-amine-*N*-oxide (175$_a$)

N-Benzylhydroxylamine hydrochloride (0.8 g, 5.0 mmol) and *p*-anisaldehyde (0.61 mL, 0.68 g, 5.0 mmol, 1.0 eq) was added to a stirred suspension of $MgSO_4$ (0.97 g, 8.0 mmol, 1.6 eq) and $NaHCO_3$ (0.55 g, 6.5 mmol, 1.3 eq) in anhydrous dichloromethane (40 mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. Once complete the solution was cooled to room temperature and the solids removed. The filtrate was concentrated *in vacuo* to afford a white powder. The crude product was triturated from diethyl ether to afford the *title compound* as a white crystalline solid in 72% yield. (0.86g, 3.5 mmol); mp 106.6-108.4°C; IR ν_{max} (film)/cm^{-1} 2973 (sp^3CH), 1602 (ArC=C), 1565 (ArC=C), 1506.(ArC=C), 1253 (N-O); δ_H(400 MHz; $CDCl_3$) 3.84 (3H, s, OC*H*$_3$), 5.03 (2H, s, C*H*$_2$Ar), 6.91 (2H, dd, *J* 2.8, 2.8 Hz, ArOMe-C*H*), 7.31 (1H, s, CH), 7.38-7.43 (3H, m, ArC*H*), 7.47 (2H, dd, *J* 2.0, 2.4 Hz, ArC*H*), 8.21 (2H, dd, *J* 2.0, 2.8 Hz, ArOMe-C*H*); δ_C(100 MHz; $CDCl_3$) 55.4 (O*C*H$_3$) 72.3 (*C*H$_2$Ar), 113.8 (ArOMe-*C*H), 114.0 (ArOMe-*C*H), 129.3 (2 Ar*C*H) 129.6 (2 Ar*C*H), 130.2 (*C*H), 132.8 (Ar*C*), 135.6 (Ar*C*), 146.8 (Ar*C*-OMe); HRMS (FAB) (M^+) calculated for $C_{15}H_{16}NO_2$ 241.110, found 241.112; *m/z* 241 (70%), 154 (25%) and 91 (70%).

N-Benzyl-(4'-nitro-benzylidene)-amine-*N*-oxide (175_b)

N-Benzylhydroxylamine hydrochloride (0.8 g, 5.0 mmol) and *p*-nitrobenzaldehyde (0.76 g, 5.0 mmol) were added to a stirred suspension of $MgSO_4$ (0.96 g, 8.0 mmol, 1.6 eq) and $NaHCO_3$ (0.55 g, 6.5 mmol, 1.3 eq) in anhydrous dichloromethane (40mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids removed. The filtrate was concentrated *in vacuo* to afford a yellow powder. The crude product was triturated from diethyl ether to afford the *title compound* as a yellow crystalline solid in 61% yield (0.78 g, 3.0 mmol); mp 116.6-118.4°C; IR ν_{max} (film)/cm^{-1} 2989 (sp^3 CH), 1595 (ArC=C), 1562 (NO_2), 1347 (NO_2); δ_H(400 MHz; $CDCl_3$) 5.0 (2H, s, ArCH_2), 7.36-7.42 (5H, m, ArC*H*), 7.45 (1H, s, C*H*), 8.16 (2H, dd, *J* 7.2, 7.2 Hz, $ArNO_2$-C*H*), 8.28 (2H, dd, *J* 7.2, 7.2 Hz, $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 72.1 (Ar*C*H_2), 123.8 (2 $ArNO_2$-*C*H), 128.8 (2 $ArNO_2$-*C*H), 129.2 (2 Ar*C*H) 129.4 (3 Ar*C*H), 132.1 (*C*H), 132.5 (Ar*C*), 135.9 (Ar*C*), 147.8 (Ar*C*-NO_2); HRMS (FAB) (M^+) calculated for $C_{14}H_{13}N_2O_3$ 256.082, found 256.084; *m/z* 256 (100%), 176 (24%) 154 (79%) 136 (56%) and 91 (66%).

N-Benzyl-N-thiophen-2-yl-methyleneamine-*N*-oxide (175_d)

N-Benzylhydroxylamine hydrochloride (0.5 g, 3.1 mmol) and thiophene-2-carboxaldehyde (0.35 g, 0.29 mL, 3.1 mmol) were added to a stirred suspension of $MgSO_4$ (0.6 g, 5.0 mmol, 1.6 eq) and $NaHCO_3$ (0.34 g, 4.1 mmol, 1.3 eq) in anhydrous dichloromethane (25mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids were removed. The filtrate was concentrated *in vacuo* to afford a dark yellow powder. The crude product was triturated from diethyl ether to afford the *title compound* as a white solid in 57% yield (0.38 g, 1.8 mmol); mp 112.4-114.8°C; IR ν_{max} (film)/cm^{-1} 3060 (ArC-H), 1560 (C=N), 1135 (C-S); δ_H(400 MHz; $CDCl_3$) 5.0 (2H, s, ArCH_2), 7.12 (2H, dd, *J* 4.0, 3.6 Hz,

CC*H*C*H*C), 7.39-7.45 (5H, m, ArC*H*), 7.46 (1H, s, C*H*), 7.8 (1H, d, *J* 0.4 Hz, C*H*S); δ_C(100 MHz; $CDCl_3$) 68.6 (Ar*C*H_2), 126.4 (2 C*C*H*C*HC), 129.1 (2 Ar*C*H), 129.5 (3 Ar*C*H), 129.8 (*C*HS), 132.4 (*C*H), 132.7 (Ar*C*), 137.2 (Ar*C*); FTMS (ES) ($M+H^+$), calculated for $C_{12}H_{12}NOS$ 218.29, found 218.06 (+0.215 ppm).

N-Methyl-(4'-Methoxy-benzylidene)-amine-*N*-oxide (175$_c$)

N-Methylhydroxylamine hydrochloride (1.0 g, 12 mmol) and *p*-anisaldehyde (1.46 mL, 1.63 g, 12 mmol, 1.0 eq) were added to a stirred suspension of $MgSO_4$ (2.29 g, 19 mmol, 1.6 eq) and $NaHCO_3$ (1.34 g, 16 mmol, 1.3 eq) in anhydrous dichloromethane (40 mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids were removed. The filtrate was concentrated *in vacuo* to afford an off-white solid. The crude product was triturated from diethyl ether to afford the *title compound* as a cream crystalline solid in 63% yield (1.16g, 7.5 mmol); mp 99.8-102.4°C; IR ν_{max} (film)/cm^{-1} 2839 (sp^3 CH), 1603 (ArC=C), 1508 (C=N); δ_H(400 MHz; $CDCl_3$) 3.84 (3H, s, OC*H*$_3$), 3.85 (3H, s, C*H*$_3$N), 6.94 (2H, dd *J* 2.0, 6.8 Hz, ArMeO-C*H*), 7.28 (1H, s, CH), 8.21 (2H, dd, *J* 2.0, 6.8 Hz, ArMeO-C*H*); δ_C(100 MHz; $CDCl_3$) 53.9 (*C*H_3N), 55.3 (O*C*H_3), 113.84 (2 ArMeO-*C*H), 123.5 (ArC), 130.4 (2 ArMeO-*C*H), 134.8 (*C*H), 161.1 (Ar*C*); HRMS (FAB) ($M+H^+$) calculated for $C_9H_{12}NO_2$ 166.08, found 166.084; *m/z* 166 (100%), 165 (55%).

N-Methyl-N-thiophen-2-yl-methyleneamine-*N*-oxide (175$_e$)

N-Methylhydroxylamine hydrochloride (1.0 g, 12 mmol) and thiophene-2-carboxaldeyhe (1.1 mL, 1.34 g, 12 mmol, 1.0 eq) were added to a stirred suspension of $MgSO_4$ (2.29 g, 19 mmol, 1.6 eq) and $NaHCO_3$ (1.34 g, 16 mmol, 1.3 eq) in anhydrous dichloromethane (40 mL) under nitrogen atmosphere. The resulting mixture was stirred and refluxed under

nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids were removed. The filtrate was concentrated *in vacuo* to afford a light orange solid. The crude product was triturated from diethyl ether to afford the *title compound* as a light orange crystalline solid in 54% yield (0.91g, 6.5 mmol); mp 122.6-124.7°C; IR ν_{max} (film)/cm^{-1} 2109 (sp^3 CH), 1643 (C=N), 1161 (C-S), 1092; δ_H(400 MHz; $CDCl_3$) 3.87 (3H, s, C*H*$_3$), 7.14 (1H, dd, *J* 3.6, 4.0 Hz, CHC*H*CH), 7.43 (1H, d, *J* 4.0 Hz, C*H*), 7.48 (1H, d, *J* 4.8 Hz, C*H*), 7.86 (1H, s, *H*C=N); δ_C(100 MHz; $CDCl_3$) 51.7 (CH_3), 126.5 (CH), 129.1(CH), 129.3 (CH), 130.9 (H*C*=N), 132.4 (Ar*C*); FTMS (ES) ($M+Na^+$) calculated for C_6H_7NNaO 164.014, found 164.014 (+0.266 ppm).

N-Methyl-(4'-methylbenzylidene)-amine-*N*-oxide (175$_f$)

N-Methylhydroxylamine hydrochloride (1.0 g, 11.9 mmol) and *p*-tolualdehyde (1.41 mL, 1.44 g, 11.9 mmol, 1.0 eq) were added to a stirred suspension of $MgSO_4$ (2.29 g, 19.0 mmol, 1.6 eq) and $NaHCO_3$ (1.30 g, 15.5 mmol, 1.3 eq) in anhydrous dichloromethane (50 mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids were removed. The filtrate was concentrated *in vacuo* to afford a white powder. The crude product was triturated from diethyl ether to afford the *title compound* as a white crystalline solid in 54% yield (0.95g, 6.4 mmol); mp 127.6-129.4°C; IR ν_{max} (film)/cm^{-1} 2941 (sp^3 CH), 1585 (ArC=C), 1504 (C=N), 838 (*p*-substituted aromatic, CH); δ_H(400 MHz; $CDCl_3$) 2.39 (3H, s, ArC*H*$_3$), 3.87 (3H, s, NC*H*$_3$), 7.23 (2H, d, *J* 8.4 Hz, ArCH$_3$-C*H*), 7.34 (1H, s, CH), 8.11 (2H, d, *J* 8.4 Hz, ArCH$_3$-C*H*); δ_C(100 MHz; $CDCl_3$) 21.7 (Ar*C*H$_3$), 54.2 (N*C*H$_3$), 127.8 (Ar*C*), 128.5 (2 Ar*C*H), 129.2 (2 Ar*C*H), 135.3 (CH), 140.9 (Ar*C*), HRMS (FAB) ($M+H^+$) calculated for $C_9H_{12}NO$ 150.084, found 150.092; *m/z* 150 (100%) and 132 (16%).

N-Methyl-(4'-trifluoromethyl benzylidene)-amine-*N*-oxide (175$_g$)

N-Methylhydroxylamine hydrochloride (1.0 g, 11.9 mmol) and 4-trifluromethylbenzaldehyde (1.63 mL, 2.08 g, 11.9 mmol, 1.0 eq) were added to a stirred suspension of $MgSO_4$ (2.29 g, 19.1 mmol, 1.6 eq) and $NaHCO_3$ (1.30 g, 15.6 mmol, 1.3 eq) in anhydrous dichloromethane (50 mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids were removed. The filtrate was concentrated *in vacuo* to afford a white powder. The crude product was triturated from diethyl ether to afford the *title compound* as a white crystalline solid in 32% yield. (0.77g, 3.8 mmol); mp 133.4-134.6°C; IR ν_{max} (film)/cm^{-1} 2943 (sp^3 CH), 1604 (ArC=C), 1184 (C-F); δ_H(400 MHz; $CDCl_3$) 3.92 (3H, s, C*H*$_3$), 7.46 (1H, s, CH), 7.66 (2H, d, *J* 8.4 Hz, 2 ArC*H*), 8.32 (2H, d, *J* 8.4 Hz, 2 ArC*H*), δ_C(100 MHz; $CDCl_3$) 54.8 (CH_3), 124.2 (1C q, *J* 270 Hz, CF_3), 125.5 (2 Ar*C*H), 128.3 (2 Ar*C*H), 131.4 (1C, q, 32.5 Hz, Ar*C*-CF_3), 132.5 (Ar*C*), 133.8 (CH); FTMS (ES) ($M+H^+$) calculated for $C_9H_9F_3NO$ 204.055, found 204.063 (-0.59 ppm).

N-Methyl-(4'-nitrobenzylidene)-amine-*N*-oxide (175$_h$)

N-Methylhydroxylamine hydrochloride (1.0 g, 11.9 mmol) and *p*-nitrobenzaldehyde (1.70 g, 11.9 mmol, 1.0 eq) were added to a stirred suspension of $MgSO_4$ (2.29 g, 19.0 mmol, 1.6 eq) and $NaHCO_3$ (1.31 g, 8.1 mmol, 1.3 eq) in anhydrous dichloromethane (50 mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids were removed. The filtrate was concentrated *in vacuo* to afford a dark yellow powder. The crude product was triturated from diethyl ether to afford the *title compound* as a bright yellow crystalline solid in 52% yield. (1.09g, 6.1 mmol); mp 134.6-135.4°C; IR ν_{max} (film)/cm^{-1} 1597 (ArC=C), 1576 (NO_2), 1342 (NO_2); δ_H(400 MHz; $CDCl_3$) 3.96 (3H, s, C*H*$_3$), 7.54 (1H, s,

CH), 8.27 (2H, dd, *J* 7.2, 7.2 Hz, ArC*H*), 8.38 (2H, dd, *J* 7.2, 7.2 Hz, ArC*H*), δ_C(100 MHz; $CDCl_3$) 55.2 (CH_3), 123.8 (2 ArC*H*), 128.7 (2 Ar*C*H), 133.2 (CH), 136.0 (Ar*C*), 147.8 (Ar*C*NO_2), HRMS (FAB) ($M+H^+$) calculated for $C_8H_9N_2O_3$ 181.0534, found 181.0613; *m/z* 181 (100%), 154 (100%), 136 (80%), 107 (25%), 89 (25%).

***N*-Benzyl-(4'-trifluromethylbenzylidene)-amine-*N*-oxide (175$_i$)**

N-Benzylhydroxylamine hydrochloride (1.0 g, 6.2 mmol) and *p*-trifluromethylbenzaldehyde (1.0 g, 6.2 mmol, 1.0 eq) were added to a stirred suspension of $MgSO_4$ (1.19 g, 9.9 mmol, 1.6 eq) and $NaHCO_3$ (0.68 g, 8.1 mmol, 1.3 eq) in anhydrous dichloromethane (50 mL) under a nitrogen atmosphere. The resulting mixture was stirred and refluxed under nitrogen for 72 hrs. On completion the reaction mixture was left to cool and the solids were removed. The filtrate was concentrated *in vacuo* to afford a white powder. The crude product was triturated from diethyl ether to afford the *title compound* as a white crystalline solid in 46% yield. (0.75g, 2.7 mmol); mp 134.6-136.4°C, IR ν_{max} (film)/cm^{-1} 3068 (ArCH), 1580 (ArC=C), 1459 (sp^2 CH); δ_H(400 MHz; $CDCl_3$) 5.09 (2H, s, ArCH_2), 7.40-7.44 (3H, m, ArC*H*), 7.46 (1H, s, CH), 7.47-7.50 (2H, m, ArC*H*), 7.64 (2H, d, *J* 8.4 Hz, ArC*H*-CF_3), 8.31 (2H, d, *J* 8.4 Hz, ArC*H*-CF_3); δ_C(100 MHz; $CDCl_3$) 71.7 (Ar*C*H_2), 124.1 (1C, q, *J* 270 Hz, *C*F_3) 125.4 (Ar*C*H-CF_3), 128.5 (Ar*C*H-CF_3), 129.2-129.3 (3 Ar*C*H), 131.3 (Ar*C*), 131.5 (1C, q, *J* 32.4 Hz, Ar*C*-CF_3), 132.8 (*C*H), 133.5 (Ar*C*), HRMS (FAB) ($M+H^+$) calculated for $C_{15}H_{13}F_3NO$ 280.0875, found 280.0952; *m/z* 280 (100%) and 91 (85%).

(±) 2-Benzyl-3-(4-methoxyphenyl)-5,6-diphenyl-oxazine-4,4-dimethyl ester (176$_a$)

$Yb(OTf)_3$ (9 mg, 0.016 mmol, 10 mol %) was added to a stirred solution of nitrone **175**$_a$ (97 mg, 0.40 mmol, 2.5 eq) and di-substituted cyclopropane **170**$_a$ (50 mg, 0.16 mmol) in 1,2-dichloroethane (3 mL) under a nitrogen atmosphere. The resulting mixture was heated under reflux overnight and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:8) to afford the *title compound* as a white crystalline solid in 70% yield (60 mg, 0.10 mmol) as a single diastereoisomer; mp 190.9-192.2°C, IR ν_{max} (film)/cm^{-1} 3029 (ArCH), 2922 (sp^3 CH), 2851 (sp^3 CH), 1732 (C=O), 1606 (ArC=C), 1509 (ArC=C), 1253 (C-O), 1175 (C-O); δ_H(400 MHz; $CDCl_3$) 3.11 (3H, s, OCH_3), 3.36 (3H, s, CO_2CH_3), 3.50 (1H, d, *J* 13.6 Hz, ArCH_2), 3.77 (3H, s, CO_2CH_3), 3.87 (1H, d, *J* 13.6 Hz, ArCH_2), 4.41 (1H, d, *J* 11.6 Hz, C*H*), 4.51 (1H, s, C*H*N), 5.52 (1H, d, *J* 12 Hz, C*H*ON), 6.85 (2H, d, *J* 8.4 Hz, ArC*H*-OMe), 7.02-7.09 (6H, m, Ar*C*H), 7.17-7.21 (9H, m, ArC*H*), 7.22 (2H, d, *J* 8.4 Hz, ArC*H*-OMe); δ_C(100 MHz; $CDCl_3$) 46.1 (CH), 51.7 (CO_2CH_3), 51.8 (CO_2CH_3), 55.2 (OCH_3), 59.3 (ArCH_2), 62.6 ($C(CO_2CH_3)_2$), 63.0 (*C*HN), 82.0 (*C*HON), 113.2 (Ar*C*H-OMe), 127.0 (2 Ar*C*H), 127.5 (2 Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 129.0 (2 Ar*C*H), 130.1 (2 Ar*C*H), 132.6 (Ar*C*H-OMe), 136.9 (Ar*C*), 137.3 (Ar*C*), 138.3 (Ar*C*), 159.4 (Ar*C*-OMe), 169.3 (C=O), 170.3 (C=O); HRMS (FAB) (M^+) calculated for $C_{34}H_{33}NO_6$ 551.20, found 551.23; *m/z* 551 (25%), 307 (23%), 176 (30%), 154 (100%), 136 (75%) and 91 (37%).

(±) 2-Benzyl-5,6-diphenyl-3-thiophen-2-yl-oxazine-4,4 dimethyl ester (176$_b$)

$Yb(OTf)_3$ (4 mg, 0.008 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_d$ (33 mg, 0.15 mmol, 1.2 eq) and di-substituted cyclopropane **170**$_a$ (40 mg, 0.13 mmol) in 1,2-dichloroethane (3 mL) under a nitrogen atmosphere. The resulting mixture was refluxed overnight and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:8) to afford the *title compound* as a white

crystalline solid in 60% yield (44 mg, 0.078 mmol); mp 178.4-180.2°C; IR ν_{max} (film)/cm^{-1} 3032 (ArCH), 3009 (sp^2 CH), 2947 (sp^3 CH), 2924 (sp^3 CH), 1735 (C=O), 1257 (C-O); δ_H(400 MHz; $CDCl_3$) 3.32 (3H, s, CO_2CH_3), 3.47 (3H, s, CO_2CH_3), 3.60 (1H, d, *J* 13.2 Hz, $ArCH_2$), 4.10 (1H, d, *J* 13.2 Hz, $ArCH_2$), 4.40 (1H, d, *J* 11.6 Hz, $CHCCO_2CH_3$), 5.06 (1H, s, CHN), 5.59 (1H, d, *J* 11.6 Hz, CHON), 6.87 (2H, dd, *J* 0.8, 1.2 Hz, CH, thiophene), 7.03-7.08 (4H, m, ArCH), 7.11-7.23 (5H, m, ArCH), 7.27-7.39 (6H, m, ArCH), 7.45 (1H, d, *J* 5.2 Hz, CHS); δ_C(100 MHz; $CDCl_3$) 46.8 ($CHCCO_2CH_3$), 51.1 (CO_2CH_3), 51.8 (CO_2CH_3), 59.2 ($ArCH_2$), 62.2 ($C(CO_2CH_3)_2$), 63.9 (CHN), 82.2 (CHON), 125.6 (2 CH, thiophene), 125.7 (ArCH), 126.5 (ArCH), 126.7 (CHS), 127.1 (ArCH), 127.4 (ArCH) 127.9 (ArCH), 128.1 (ArCH), 128.2 (ArCH), 128.4 (ArCH), 129.2 (ArCH), 130.4 (ArCH), 137.5 (HC=CS), 140.2 (2 ArC), 142.4 (ArC), 174.5 (C=O), HRMS (FAB) ($M+H^+$) calculated for $C_{31}H_{30}NO_5S$ 528.63, found 528.45; *m/z* 528 (50%), 91 (65%).

(±) 2-Benzyl,3(4-nitrophenyl)5,6-diphenyl-oxazine-4,4 dimethyl ester (176_d)

$Yb(OTf)_3$ (5 mg, 0.008 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_b$ (97 mg, 0.40 mmol, 2.5 eq) and di-substituted cyclopropane **170**$_a$ (50 mg, 0.16 mmol) in 1,2-dichloroethane (4 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 19 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:8) to afford the *title compound* as a white powder in 55% yield (50 mg, 0.08 mmol). R_f (EtOAc/ petrol 1:8) 0.40; mp 214.2-215.5°C; IR ν_{max} (film)/cm^{-1} 1734 (C=O), 1603 (ArC=C), 1549 (NO_2), 1347 (NO_2), 1260 (C-O); δ_H(400 MHz; $CDCl_3$) 3.11 (3H, s, CO_2CH_3), 3.39 (3H, s, CO_2CH_3), 3.44 (1H, d, *J* 13.2 Hz, $ArCH_2$), 3.92 (1H, d, *J* 13.2 Hz, $ArCH_2$), 4.36 (1H, d, *J* 11.6 Hz, $CHCCO_2CH_3$), 4.70 (1H, s, CHN), 5.58 (1H, d, *J* 11.6 Hz, CHON), 6.99-7.11 (6H, m, ArCH), 7.12-7.18 (5H, m, ArCH), 7.18-7.27 (4H, m, ArCH), 7.56 (2H, d, *J* 9.0 Hz, $ArNO_2$-CH), 8.20 (2H, d, *J* 8.8 Hz, $ArNO_2$-CH); δ_C(100 MHz; $CDCl_3$) 45.1 ($CHCCO_2CH_3$), 50.9 (2 CO_2CH_3), 58.4

(Ar*C*H_2), 61.6 (*C*(CO_2CH_3)$_2$), 65.3 (*C*HN), 81.1 (*C*HON), 121.9 (ArNO_2-*C*H), 126.2 (ArNO_2-*C*H), 126.5 (Ar*C*H), 126.7 (Ar*C*H), 127.0 (Ar*C*H), 127.3 (Ar*C*H), 127.8 (Ar*C*H), 129.1 (Ar*C*H), 131.2 (Ar*C*H), 134.9 (Ar*C*), 135.6 (Ar*C*), 136.6 (Ar*C*), 142.0 (Ar*C*), 146.7 (Ar*C*), 167.7 (C=O), 168.6 (C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{33}H_{31}N_2O_7$ 567.2053, found 567.2131; m/z 567 (22%), 278 (41%), 246 (26%), 176 (30%), 154 (97%), 136 (78%), 107 (26%), 91 (100%) and 77 (26%).

(±) 2-Methyl-5,6-diphenyl-3-(thiophen-2-yl)oxazine-4,4-dimethyl ester (176$_c$)

$Yb(OTf)_3$ (5 mg, 0.008 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_e$ (52 mg, 0.4 mmol, 2.5 eq) and di-substituted cyclopropane **170**$_a$ (50 mg, 0.16 mmol) in 1,2-dichloroethane (3 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 24 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:8) to afford the *title compound* as a white powder in 57% yield. (40mg, 0.08 mmol). R_f (EtOAc/ petrol 1:8) 0.31 mp 175.4-177.2°C; IR ν_{max} (film)/cm^{-1} 3029 (ArCH), 2948 (sp^3 CH), 1732 (C=O), 1602 (ArC=C), 1495 (ArC=C), 1257 (C-O), 1202 (C-O); δ_H(400 MHz; $CDCl_3$) 2.53 (3H, s, C*H*$_3$N), 3.31 (3H, s, CO_2C*H*$_3$), 3.40 (3H, s, CO_2C*H*$_3$), 4.30 (1H, d, *J* 11.6 Hz, C*H*CCO_2CH_3), 5.00 (1H, s, C*H*N), 5.39 (1H, d, *J* 11.6 Hz, C*H*ON), 7.01-7.11 (5H, m, Ar*C*H), 7.14-7.19 (5H, m, Ar*C*H), 7.38 (2H, d, *J* 6.8 Hz, C=C*H*C*H*=CH), 7.41 (1H, d, *J* 4.8 Hz, HC=C*H*S); δ_C(100 MHz; $CDCl_3$) 43.2 (*C*H_3N), 46.3 (*C*HCCO_2CH_3), 51.8 (CO_2*C*H_3), 52.1 (CO_2*C*H_3), 62.7 (*C*(CO_2CH_3)$_2$), 66.1 (*C*HN), 82.6 (*C*HON), 125.3 (2 Ar*C*H), 126.9 (Ar*C*H), 127.4 (Ar*C*H), 127.8 (C=CH*C*H=C), 128.2 (ArCH), 128.3 (C=*C*HCH=C*H*S), 130.3 (Ar*C*H), 130.4 (Ar*C*H), 134.0 (HC=*CS*), 136.7 (Ar*C*), 137.9 (Ar*C*), 168.7 (C=O), 170.1 (C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{25}H_{26}NO_5S$ 452.144, found 452.153 (-1.4 ppm); m/z 452 (100%), 451 (45%), 309 (22%), 257 (22%), 176 (39%), 142 (61%), 136 (38%), 125 (31%) and 69 (30%).

(±) 2-Methyl-3(4-trifluoromethylphenyl),5-phenyl,6(4-trifluoromethylphenyl)-oxazine-4,4 dimethyl ester (176$_h$)

$Yb(OTf)_3$ (15 mg, 0.002 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_g$ (220mg, 1.2 mmol, 2.5 eq) and di-substituted cyclopropane **170**$_e$ (180 mg, 0.47 mmol) in 1,2 dichloroethane (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 30 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:9) to afford the *title compound* as a white crystalline solid in a combined 60% yield (163 mg, 0.28 mmol) in a 1: 2.26 d.r. (*trans:cis*), (i) first eluted *trans* isomer; mp 194.7-196.1°C; IR ν_{max} (film)/cm^{-1} 1719 (C=O), 1618 (ArC=C), 1324 (C-O), 1249 (C-O), 1166 (C-F); δ_H(400 MHz; $CDCl_3$) 2.53 (3H, s, C*H*$_3$N), 3.42 (3H, s, CO_2CH_3), 3.48 (3H, s, CO_2CH_3), 3.63 (1H, d, *J* 10.4 Hz, C*H*CCO_2CH_3), 4.63 (1H, s, C*H*N), 6.24 (1H, d, *J* 10.8 Hz, C*H*ON), 7.07-7.13 (3H, m, ArC*H*), 7.17-7.21 (4H, m, 2 $ArCF_3$-C*H*), 7.26 (2H, d, *J* 8.4 Hz, $ArCF_3$-C*H*), 7.34-7.45 (2H, m, Ar*C*H), 7.50 (2H, d, *J* 8.8 Hz, $ArCF_3$-C*H*); δ_C(100 MHz; $CDCl_3$) 45.7 (*C*H_3N), 51.6 (CO_2CH_3), 51.9 (CO_2CH_3), 55.6 (CH), 64.7 (*C*$(CO_2CH_3)_2$), 75.0 (*C*HN), 80.2 (*C*HON), 124.5-124.6 (Ar*C*H), 125.3 (2C, q, $^1J_{CF}$ 271 Hz, CF_3), 127.9 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 129.1 (Ar*C*H), 129.4 (Ar*C*), 130.3 (Ar*C*), 130.6 (Ar*C*H), 137.5 (Ar*C*), 140.9 (Ar*C*), 167.9 (C=O), 169.5 (C=O), (ii) second eluted *cis* isomer; mp 157.5-159.1°C; δ_H(400 MHz; $CDCl_3$) 2.55 (3H, s, C*H*$_3$N), 3.23 (3H, s, CO_2CH_3), 3.48 (3H, s, CO_2CH_3), 4.53 (1H, d, *J* 12 Hz, C*H*CO_2CH_3), 4.74 (1H, s, C*H*N), 5.54 (1H, d, *J* 11.6 Hz, C*H*ON), 7.21-7.28 (3H, m, Ar*C*H), 7.30-7.32 (2H, m, ArC*H*), 7.41 (4H, s, 2 $ArCF_3$-C*H*), 7.70 (2H, d, *J* 8.4 Hz, $ArCF_3$-CH), 7.78 (2H, bs, $ArCF_3$-C*H*); δ_C(100 MHz; $CDCl_3$) 43.4 (*C*H_3N), 45.9 (*C*HCCO_2CH_3), 52.0 (CO_2CH_3), 52.1 (CO_2CH_3), 60.4 (*C*$(CO_2CH_3)_2$), 69.3 (*C*HN),

81.9 (*C*HON), 124.4-124.5 (ArCF$_3$-*C*H), 124.9-125.0 (ArCF$_3$-*C*H), 125.3 (2C, q, $^1J_{CF}$ 271 Hz, CF$_3$), 127.9 (Ar*C*H), 128.5-128.6 (2 Ar*C*H), 129.2 (1C, q, $^4J_{CF}$ 32 Hz, C$_6$H$_4$), 130.5 (1C, q, $^4J_{CF}$ 32 Hz, C$_6$H$_4$), 130.6 (Ar*C*H), 137.5 (Ar*C*), 139.1 (Ar*C*), 141.2 (Ar*C*), 168.6 (C=O), 169.9 (C=O); δ_F(376 MHz; CDCl$_3$) 99.4 (3F, s, CF$_3$), 99.5 (3F, s, CF$_3$); HRMS (FAB) (M+H$^+$), calculated for $C_{29}H_{26}F_6NO_5$ 582.1715, found 582.1637 (-1.6 ppm); *m/z* 582 (33%), 346 (25%), 127 (100%) and 105 (43%). Due to a weak sample not all the quaternary carbons have been accounted for.

(±) 2-Methyl, 3(4-methylphenyl),5-phenyl,6(4-trifluoromethylphenyl)-oxazine-4,4 dimethyl ester (176$_i$)

Yb(OTf)$_3$ (17 mg, 0.003 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_f$ (210mg, 1.4 mmol, 2.5 eq) and di-substituted cyclopropane **170**$_e$ (210 mg, 0.55 mmol) in 1,2 dichloroethane (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 24 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:6) to afford the *cis* isomer as a white crystalline solid in 60 % yield. (174 mg, 0.33 mmol). R$_f$ (EtOAc/ petrol 1:8) 0.19; mp 110.4-112.2°C, IR ν_{max} (film)/cm^{-1} 2950 (sp^3 CH), 1732 (C=O), 1617 (ArC=C), 1325 (C-O), 1259 (C-O), 1165 (C-F); δ_H(400 MHz; CDCl$_3$) 2.37 (3H, s, C*H*$_3$Ar), 2.53 (3H, s, C*H*$_3$N), 3.22 (3H, s, CO$_2$C*H*$_3$), 3.44 (3H, s, CO$_2$*C*H$_3$), 4.53 (1H, d, *J* 12 Hz, C*H*CCO$_2$CH$_3$), 4.59 (1H, s, C*H*N), 5.49 (1H, d, *J* 12 Hz, C*H*ON), 7.16-7.19 (5H, m, ArC*H*), 7.31 (2 H, dd, *J* 0.8, 1.6 Hz, ArC*H*), 7.35-7.41 (4H, m, ArC*H*), 7.45-7.52 (2H, m, ArC*H*); δ_C(100 MHz; CDCl$_3$) 21.1 (*C*H$_3$Ar), 43.4 (*C*H$_3$N), 45.8 (*C*HCCO$_2$CH$_3$), 51.9 (CO$_2$*C*H$_3$), 52.0 (CO$_2$*C*H$_3$), 62.7 (*C*(CO$_2$CH$_3$)$_2$), 69.4 (*C*HN), 81.9 (*C*HON), 124.3 (ArCH), 125.4 (1C, q, $^1J_{CF}$ 271 Hz, CF$_3$), 128.0 (Ar*C*H), 128.5 (Ar*C*H), 128.8 (Ar*C*H),

130.6 (Ar*C*H), 131.1 (Ar*C*H), 131.7 (Ar*C*), 137.7 (Ar*C*), 138.1 (Ar*C*), 141.6 (Ar*C*), 168.9 (C=O), 170.2 (C=O); δ_F(376 MHz; $CDCl_3$) 99.6 (3F, s, CF_3), HRMS (FAB) ($M+H^+$), calculated for $C_{29}H_{29}F_3NO_5$ 528.1919, found 528.2002 (+0.8 ppm); *m/z* 528 (86%), 315 (28%), 150 (100%) and 133 (80%). Due to a weak sample not all of the quaternary carbons have been accounted for.

(±) 2-Methyl,3(4-trifluoromethylphenyl),5-phenyl,6(4-methoxyphenyl)-oxazine-4,4 dimethyl ester (176$_j$)

$Yb(OTf)_3$ (9 mg, 0.0016 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_g$ (150mg, 0.81 mmol, 2.5 eq) and di-substituted cyclopropane **170**$_b$ (110 mg, 0.32 mmol) in 1,2-dichloroethane (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 24 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:8) to afford the *cis* isomer as a pale yellow solid in 49 % yield (80 mg, 0.16 mmol). R_f (EtOAc/ petrol 1:8) 0.17; mp 157.7-160.3°C, ν_{max} IR (film)/cm^{-1} 2949 (sp^3 CH), 1734 (C=O), 1612 (ArC=C), 1514 (ArC=C), 1325 (C-O), 1249 (C-O), 1175 (C-F); δ_H(400 MHz; $CDCl_3$) 2.50 (3H, s, C*H*$_3$N), 3.20 (3H, s, CO_2CH_3), 3.42 (3H, s, CO_2CH_3), 3.72 (3H, s, OC*H*$_3$), 4.42 (1H, d, *J* 12 Hz, C*H*CCO_2CH_3), 4.67 (1H, s, C*H*N), 5.48 (1H, d, *J* 12 Hz, C*H*ON), 6.74 (2H, d, *J* 8.4 Hz, ArOMe-C*H*), 7.06-7.09 (1H, m, ArC*H*), 7.13 (2H, d, *J* 8.4 Hz, ArOMe-C*H*), 7.25 (4H, dd, *J* 3.6, 6.8 Hz, ArCH), 7.66 (2H, d, *J* 8.0 Hz, ArCF_3-C*H*), 7.78 (2H, bs, ArCF_3-C*H*); δ_C(100 MHz; $CDCl_3$) 43.4 (*C*H$_3$N), 45.8 (*C*HCCO_2CH_3), 52.0 (2 CO_2*C*H$_3$), 55.1 (O*C*H$_3$), 62.5 (C(CO_2CH_3)$_2$), 69.3 (*C*HN), 81.6 (*C*HON), 113.7 (ArOMe-*C*H), 124.8 (ArCF_3-*C*H), 127.0 (ArCF_3-*C*H), 127.6 (ArCH), 129.2 (ArOMe-*C*H), 130-130.2 (Ar*C*H), 131.0 (Ar*C*H), 137.0 (Ar*C*), 159.3 (Ar*C*-OMe), 168.9 (C=O), 170.3 (C=O); δ_F(376 MHz; $CDCl_3$) 99.5 (3F, s,

CF_3) FTMS (ES) ($M+Na^+$), calculated for $C_{29}H_{28}F_3NO_6Na$ 566.183, found 566.176 (+0.60 ppm). Due to a weak sample not all of the quaternary carbons have been accounted for.

(±)2-Methyl,3(4-methylphenyl),5-phenyl,6(4-methoxyphenyl)-oxazine-4,4 dimethyl ester (176_g)

$Yb(OTf)_3$ (9 mg, 0.0016 mmol, 5 mol %) was added to a stirred solution of nitrone $\mathbf{175}_f$ (110mg, 0.73 mmol, 2.5 eq) and di-substituted cyclopropane $\mathbf{170}_b$ (100 mg, 0.29 mmol) in 1,2-dichloroethane (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 36 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:10) to afford the *trans* isomer as a white solid in 45 % yield (64 mg, 0.13 mmol). R_f (EtOAc/ petrol 1:8) 0.36; mp 154.3-156.7°C, ν_{max} (film)/cm^{-1} 2922 (sp^3 CH), 1717 (C=O), 1611 (ArC=C), 1514 (ArC=C), 1250 (C-O), 1093, δ_H(400 MHz; $CDCl_3$) 2.32 (3H, s, *C*H_3Ar), 2.50 (3H, s, *C*H_3N), 3.42 (3H, s, CO_2*C*H_3), 3.47 (3H, s, CO_2*C*H_3), 3.58 (1H, d, *J* 10.8 Hz, CH), 3.68 (3H, s, O*C*H_3), 4.47 (1H, s, *C*HN), 6.18 (1H, d, *J* 10.8 Hz, C*H*ON), 6.68 (2H, d, *J* 8.2 Hz, ArOMe-C*H*), 7.02-7-05 (2H, m, ArCH_3- C*H*), 7.06-7.12 (6H, m, 4 ArC*H*, 2 ArCH_3-C*H*), 7.19-7.22 (1H, m, ArC*H*), 7.24 (2H, d, *J* 8.4 Hz, ArOMe-C*H*); δ_C(100 MHz; $CDCl_3$) 21.1 (Ar*C*H_3), 45.7 (*C*H_3N), 51.4 (CO_2*C*H_3), 51.7 (CO_2*C*H_3), 55.1 (O*C*H_3), 55.5 (CH), 65.3 (*C*(CO_2CH_3)$_2$), 75.6 (*C*HN), 79.7 (*C*HON), 113.5 (2 ArOMe-*C*H), 126.9 (2 ArCH_3- *C*H), 127.7 (2 ArOMe-*C*H), 128.1 (Ar*C*H), 128.5 (2 ArCH_3- *C*H), 129.3 (2 Ar*C*H), 130.1 (2 Ar*C*H), 130.5 (Ar*C*), 133.9 (Ar*C*), 137.1 (Ar*C*), 137.9 (Ar*C*), 159.2 (Ar*C*-OMe), 168.4 (C=O), 170.0 (C=O), LCMS-IT-TOF ($M+H^+$), calculated for $C_{29}H_{32}NO_6$, 490.21, found 490.22 (+1.84 ppm).

2-Methyl,3(2-thienyl),5(6)-phenyl,6(5)(4-fluorophenyl)-oxazine-4,4-dimethyl ester. (176_e)

$Yb(OTf)_3$ (14 mg, 0.022 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_e$ (148mg, 1.15 mmol, 2.5 eq) and di-substituted cyclopropane **170**$_d$ (150 mg, 0.46 mmol) in 1,2 dichloroethane (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 24 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:9) to afford the *cis* isomer as an inseparable mixture of regioisomers (1.1:1) as a white solid in 50 % yield (100 mg, 0.21 mmol); mp 165.2-167.7°C, Major isomer; IR ν_{max} (film)/cm^{-1} 2948 (sp^3 CH), 1733 (C=O), 1604 (ArC=C), 1510 (ArC=C), 1259 (C-O), 1107 (C-F); δ_H(400 MHz; $CDCl_3$) 2.61 (3H, s, C*H*$_3$N), 3.40 (3H, s, CO_2C*H*$_3$), 3.48 (3H, s, CO_2C*H*$_3$), 4.34 (1H, d, *J* 11.6 Hz, C*H*CCO_2CH_3), 5.08 (1H, s, C*H*N), 5.47 (1H, d, *J* 11.6 Hz, C*H*ON), 6.88 (2H, d, *J* 8.8 Hz, ArF-C*H*), 7.03-7.05 (2H, m, C=C*H*C*H*=CHS), 7.10 (3H, t, *J* 6.4 Hz, ArC*H*), 7.19 (2H, d, *J* 7.2 Hz, ArC*H*), 7.38 (2H, dd, *J* 8.8, 14.0 Hz, ArF-C*H*), 7.42 (1H s, C*H*S); δ_C(100 MHz; $CDCl_3$) 43.2 (*C*H_3N), 46.5 (*C*HCCO_2CH_3), 52.1 (CO_2*C*H_3), 52.2 (CO_2*C*H_3), 62.7 (*C*(CO_2CH_3)$_2$), 66.2 (*C*HN), 81.8 (*C*HON), 115.0 (ArF-*C*H), 115.2 (ArF-*C*H), 125.4 (C=CH*C*H=CHS), 127.5 (3 Ar*C*H), 127.8 (2 CH, C=*C*HCH=*C*HS), 128.3 (2 Ar*C*H), 129.9 (ArF-*C*H), 130.0 (ArF-*C*H), 134.0 (HC=*C*S), 136 5 (Ar*C*), 138.9 (Ar*C*) 161.1 (Ar*C*-F), 168.6 (C=O), 170.0 (C=O), δ_F(376 MHz; $CDCl_3$) 46.7 (1F, sept, *J* 5.4 Hz) Minor isomer; δ_H(400 MHz; $CDCl_3$) 2.60 (3H, s, *C*H_3N), 3.39 (3H, s, CO_2C*H*$_3$), 3.52 (3H, s, CO_2C*H*$_3$), 4.39 (1H, d, *J* 11.6 Hz, CH), 5.09 (1H, s, C*H*N), 5.43 (1H, d, *J* 11.6 Hz, C*H*ON), 6.80 (2H, d, *J* 8.8 Hz, ArF-C*H*),7.06 (2H, dd, *J* 5.2, 6.0 Hz, C=C*H*C*H*=CHS), 7.19 (2H, dd, *J* 8.8, 14.0 Hz, ArF-C*H*), 7.21 (3H, t, *J* 5.6 Hz, ArC*H*), 7.41 (2H, d, *J* 6.0 Hz, ArC*H*), 7.43 (1H, s, C*H*S); δ_C(100 MHz; $CDCl_3$) 43.2 (*C*H_3N), 45.7 (*C*HCCO_2CH_3), 51.8 (CO_2*C*H_3), 51.9 (CO_2*C*H_3), 62.7 (*C*(CO_2CH_3)$_2$), 66.2 (*C*HN), 82.6 (*C*HON), 114.2 (ArF-*C*H), 114.4 (ArF-*C*H), 125.4 (C=CH*C*H=CHS), 127.0 (2 C=*C*HCH=*C*HS), 130.3 (2 CH, Ar*C*H), 130.5 (3 Ar*C*H), 131.8 (ArF-*C*H), 131.9 (ArF-*C*H), 132.5 (HC=*C*S), 137.7 (Ar*C*),

138.6 (Ar*C*), 162.8 (Ar*C*-F), 168.5 (C=O), 169.9 (C=O), δ_F(376 MHz; $CDCl_3$) 48.5 (1F, sept, *J* 5.3 Hz); HRMS (FAB) ($M+H^+$) calculated for $C_{25}H_{25}FNO_5S$ 470.13, found 470.14; *m/z* 470 (14%), 198 (15%) and 176 (23%).

(±) 2-Benzyl,3(4-nitrophenyl),5-phenyl,6(4-trifluoromethylphenyl)-oxazine-4,4 dimethyl ester (176_h)

$Yb(OTf)_3$ (9 mg, 0.015 mmol, 5 mol %) was added to a stirred solution of nitrone (176mg, 0.73 mmol, 2.5 eq) and di-substituted cyclopropane (110 mg, 0.29 mmol) in 1,2 dichloroethane (4 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 30 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:9) to afford an inseparable mixture of diastereoisomers in a d.r. of 2:1 (*cis*:*trans*) as a yellow solid in 50 % yield (100 mg, 0.21 mmol); mp 176.4-178.4°C, IR ν_{max} (film)/cm^{-1} 3031 (ArCH), 1733 (C=O), 1604 (ArC=C), 1453 (ArC=C), 1522 (NO_2), 1346 (N-O), 1166 (CF_3), 1120 (C-O), 853 (*p*-substituted aromatic), Major *cis*-isomer; δ_H(400 MHz; $CDCl_3$) 3.21 (3H, s, CO_2CH_3), 3.48 (3H, s, CO_2CH_3), 3.52 (1H, d, *J* 13.6 Hz, CH_2Ar), 4.01(1H, d, *J* 13.2 Hz, CH_2Ar), 4.49 (1H, d, *J* 11.6 Hz, $CHCCO_2CH_3$), 4.79 (1H, s, CHN), 5.66 (1H, d, *J* 11.6 Hz, CHON), 7.17-7.19 (2H, m, ArCH), 7.25-7.21 (3H, m, ArCH), 7.31 (5H, ddd, *J* 1.6, 7.2, 12.0 Hz, ArCH), 7.59 (4H, d, *J* 8.8 Hz, 2 $ArCF_3$-CH, 2 $ArNO_2$-CH), 7.80 (2H, bs, $ArCF_3$-CH), 8.29 (2H, d, *J* 8.8 Hz, $ArNO_2$-CH); δ_C(100 MHz; $CDCl_3$) 46.1 (CH), 52.1 (CO_2CH_3), 52.2 (CO_2CH_3), 59.4 (CH_2Ar), 62.7 ($C(CO_2CH_3)_2$), 66.2 (CHN), 81.9 (CHON), 123.1 (2 ArNO2-CH), 124.5 (2 ArNO2-CH), 125.6 (q, ^1J 246 Hz, CF_3), 127.6 ($ArCF_3$-CH), 127.9 ($ArCF_3$-CH), 128.0 (ArCH), 128.2 (ArCH), 128.3 (2 ArCH), 128.6 (2 ArCH), 128.7 (ArCH), 128.8 (2 ArCH),

128.9 (Ar*C*H), 130.0 (2 Ar*C*H), 135.6 (Ar*C*), 137.0 (Ar*C*), 140.9 (Ar*C*), 142.8 (Ar*C*), 147.8 (Ar*C*-NO_2), 168.5 (C=O), 169.5 (C=O), δ_F(376 MHz; $CDCl_3$) 99.6 (3F, s, CF_3), Minor *trans*-isomer; δ_H(400 MHz; $CDCl_3$) 3.38 (3H, s, CO_2CH_3), 3.43 (3H, s, CO_2CH_3), 3.56 (1H, d, *J* 10.8 Hz. C*H*N), 3.67 (1H, d, *J* 3.6 CH_2Ar), 3.72 (1H, d, *J* 3.6 CH_2Ar), 4.91 (1H, s, C*H*), 6.22 (1H, d, *J* 10.4 Hz, C*H*ON), 7.20-7.26 (5H, m, ArC*H*), 7.27-7.30 (5H, m, ArC*H*), 7.47 (2H, d, *J* 6.8 Hz, $ArCF_3$-C*H*), 7.56 (2H, d, *J* 7.2 Hz, $ArNO_2$-*C*H), 7.94 (2H, d, *J* 6.8 Hz, $ArCF_3$-C*H*), 8.17 (2H, d, *J* 7.2 Hz, $ArNO_2$-*C*H); δ_C(100 MHz; $CDCl_3$), 51.6 (CO_2CH_3), 51.9 (CO_2CH_3), 55.7 (CH), 59.7 (CH_2Ar), 62.7 ($C(CO_2CH_3)_2$), 71.4 (*C*HN), 80.0 (*C*HON), 123.1 (2 ArNO2-*C*H), 124.5 (2 ArNO2-*C*H), 125.6 (CF_3), 127.6 ($ArCF_3$-*C*H), 127.9 ($ArCF_3$-*C*H), 128.0 (ArCH), 128.2 (ArCH), 128.3 (2 ArCH), 128.6 (2 ArCH), 128.7 (Ar*C*H), 128.8 (2 Ar*C*H), 128.9 (Ar*C*H), 130.0 (2 Ar*C*H), 135.6 (Ar*C*), 137.0 (Ar*C*), 140.9 (Ar*C*), 142.8 (Ar*C*), 147.8 (Ar*C*-NO_2), 168.5 (C=O), 169.3 (C=O), δ_F(376 MHz; $CDCl_3$) 99.0 (3F, s, CF_3); FTMS (ES) ($M+H^+$) calculated for $C_{34}H_{30}F_3N_2O_7$ 635.19, found 635.20 (+0.23 ppm). Due to a weak sample not all the quaternary carbons have been accounted for.

(±)2-Methyl,3(4-fluorophenyl),5(6)phenyl,6(5)(4-methoxyphenyl)-oxazine-4,4 dimethyl ester (176_f)

$Yb(OTf)_3$ (12 mg, 0.020 mmol, 5 mol %) was added to a stirred solution of nitrone $\mathbf{175}_c$ (240mg, 0.99 mmol, 2.5 eq) and di-substituted cyclopropane $\mathbf{170}_d$ (130 mg, 0.40 mmol) in 1,2 dichloroethane (5 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 48 hours and once complete the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:6) to afford the *trans*-isomer as an inseparable mixture of regioisomers (1:1.5) as a white solid in 51% yield. (99

mg, 0.20 mmol); mp 180.4-181.7°C; IR ν_{max} (film)/cm^{-1} 2950 (sp^3 CH), 1739 (C=O), 1717 (C=O), 1608 (ArC=C), 1581 (ArC=C), 1511 (ArC=C), 1249 (C-O), 1178 (C-F), 1160 (C-F), (i) Major isomer; δ_H(400 MHz; $CDCl_3$) 2.5 (3H, s, C*H*$_3$N), 3.41 (3H, s, CO_2C*H*$_3$), 3.48 (3H, s, CO_2C*H*$_3$), 3.51 (1H, d, *J* 10.8 Hz, CH), 3.79 (3H, s, OC*H*$_3$), 4.47 (1H, s, C*H*N), 6.18 (1H, d, *J* 10.8 Hz, C*H*ON), 6.76 (2 H, d, *J* 8.8 Hz, ArC*H*), 6.82 (3H, d, *J* 15.6 Hz, ArC*H*), 7.05-7.09 (2H, m, ArC*H*), 7.11-7.19 (2H, m, ArC*H*), 7.24-7.29 (4H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 45.7 (*C*H$_3$N), 51.5 (CO_2*C*H$_3$), 51.8 (CO_2*C*H$_3$), 55.2 (O*C*H$_3$), 55.9 (CH), 65.1 (*C*(CO$_2$CH$_3$)$_2$), 75.2 (*C*HN), 79.6 (*C*HON), 115.0 (ArCH, d, $^2J_{CF}$ 21.3 Hz), 127.1 (Ar*C*H), 127.8 (Ar*C*H), 128.0 (Ar*C*H), 128.2 (Ar*C*H), 128.8 (Ar*C*), 129.7 (ArCH, d, $^3J_{CF}$ 8.3 Hz), 130.1 (Ar*C*H), 134.2 (Ar*C*), 136.8 (Ar*C*), 138.1 (Ar*C*), 162.3 (1C, d, $^1J_{CF}$ 245 Hz), 168.3 (C=O), 169.9 (C=O); Minor isomer, δ_H(400 MHz; $CDCl_3$) 2.50 (3 H, s, *CH*$_3$N), 3.43 (3H, s, CO_2C*H*$_3$), 3.50 (3H, s, CO_2C*H*$_3$), 3.56 (1H, d, *J* 10.4 Hz, CH), 3.80 (3H, s, OC*H*$_3$), 4.48 (1H, s, C*H*N), 6.18 (1H, d, *J* 10.8 Hz, C*H*ON), 6.76 (2H, d, *J* 8.8 Hz, Ar*C*H), 6.82 (3H, d, *J* 15.6 Hz, Ar*C*H), 7.05-7.09 (2H, m, Ar*C*H), 7.11-7.19 (2H, m, ArC*H*), 7.24-7.29 (4H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 45.7 (*C*H$_3$N), 51.5 (CO_2*C*H$_3$), 51.8 (CO_2*C*H$_3$), 55.0 (CH), 55.2 (O*C*H$_3$), 65.2 (*C*(CO$_2$CH$_3$)$_2$), 75.1 (*C*HN), 80.4 (*C*HON), 113.2 (Ar*C*H), 114.6 (Ar*C*H, d, $^2J_{CF}$ 21.3 Hz), 127.1 (Ar*C*H), 128.0 (Ar*C*H), 128.2 (Ar*C*H), 128.8 (Ar*C*), 130.1 (Ar*C*H), 131.6 (Ar*C*H, d, $^3J_{CF}$ 8.3 Hz), 134.2 (Ar*C*), 136.8 (Ar*C*), 138.1 (Ar*C*), 161.0 (1C, d, $^1J_{CF}$ 245 Hz), 168.4 (C=O), 170.0 (C=O), HRMS (FAB) (M^+), calculated for $C_{28}H_{29}FNO_6$ 494.19, found 494.1969 (-1.8 ppm); *m/z* 494 (25%), 95 (33%), 81 (30%), 69 (35%) and 55 (53%).

(±) 2(4-Iodo-1*H*-pyrazol-1-yl)-1-phenylcyclopropane dimethyl ester (182$_a$)

Anhydrous potassium carbonate (759 mg, 5.5 mmol, 2.5 eq) was added to a stirred solution of 4-iodopyrazole (418 mg, 2.2 mmol) and the substituted cyclopropene **1**$_d$ (500 mg, 2.2 mmol) in *N*,*N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 20 hours (monitored by TLC). On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was

washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford a yellow viscous oil. The residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:9) to afford the *title compound* as a pale yellow solid in 90% yield (840 mg, 1.97 mmol). R_f (EtOAc/ petrol 1:9) 0.39; mp 81.7-83.9°C, IR ν_{max} (film)/cm^{-1} 2950 (sp^3 CH), 1731 (C=O), 1500 (ArC=C); δ_H(400 MHz; $CDCl_3$) 3.50 (3H, s, CO_2CH_3), 3.63 (3H, s, CO_2CH_3), 4.21 (1H, d, *J* 6.4 Hz, C*H*Ar), 5.04 (1H, d, *J* 6.4 Hz, C*H*N), 7.28-7.35 (5H, m, ArC*H*), 7.35 (1H, s, N=C*H*CI), 7.61 (1H, s, IC=C*H*N); δ_C(100 MHz; $CDCl_3$) 35.6 (*C*HAr), 44.3 ($C(CO_2CH_3)_2$), 47.1 (*C*HN), 52.8 (CO_2CH_3), 53.3 (CO_2CH_3), 57.1 (C-I), 128.1 (Ar*C*H), 128.4 (2 Ar*C*H), 128.7 (2 Ar*C*H), 131.8 (Ar*C*), 134.7 (IC=*C*HN), 145.4 (N=*C*HCI), 165.1 (C=O), 165.3 (C=O), HRMS (FAB) ($M+H^+$) calculated for $C_{16}H_{16}IN_2O_4$ 427.00, found 427.02.

(±) 2-(4 (5)-Bromo-1H-imidazol-1-yl)-1-phenylcyclopropane dimethyl ester (182_b)

Anhydrous potassium carbonate (0.75 g, 5.4 mmol, 2.5 eq) was added to a solution of 4-bromo-imidazole (0.32 g, 2.2 mmol) and the substituted cyclopropene $\mathbf{1}_d$ (0.5 g, 2.2 mmol) in *N,N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford the *title compound* without further purification as an orange/brown viscous oil in 85%. (0.58 g, 1.5 mmol), IR ν_{max} (film)/cm^{-1} 3140 (ArCH), 2952 (sp^3 CH), 1732 (C=O), 1254 (C-O); δ_H(400 MHz; $CDCl_3$) 3.48 (3H, s, CO_2CH_3), 3.63 (3H, s, CO_2CH_3), 4.04 (1H, d, *J* 6.4 Hz, C*H*), 4.79 (1H, d, *J* 6.4 Hz, C*H*), 6.99 (1H, d, *J* 1.6 Hz, $C_2H_2N_2Br$), 7.25-7.37 (5H, m, ArC*H*), 7.45 (1H, d, *J* 1.6 Hz, $C_2H_2N_2Br$); δ_C(100 MHz; $CDCl_3$) 35.2 (*C*HAr), 42.6 (*C*HN), 44.2 ($C(CO_2CH_3)_2$), 53.0 (CO_2CH_3), 53.6 (CO_2CH_3), 115.8 (C-Br), 118.8 ($C_2H_2N_2Br$), 128.0 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 131.1 (Ar*C*), 137.2 ($C_2H_2N_2Br$), 164.9 (C=O), 168.0 (C=O); HRMS (FAB) ($M+H^+$) calculated

for $C_{16}H_{16}{}^{79/81}BrN_2O_4$ 379.02 and 381.02, found 379.02 and 381.02; *m/z* 379 (99%), 233 (24%), 145 (22%), 136 (21%), 115 (25%).

(±) 2-(1*H*-Pyrazol-1-yl)-1-phenylcyclopropane dimethyl ester (182_e)

Anhydrous potassium carbonate (297 mg, 2.2 mmol, 2.5 eq) was added to a solution of pyrazole (60 mg, 0.86 mmol) and the substituted cyclopropene $\mathbf{1}_d$ (200 mg, 0.86 mmol) in *N*, *N*-dimethylformamide (2.5 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 20 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford a yellow viscous oil. The residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:9) to afford the *title compound* as a pale yellow solid in 53% yield (136 mg, 0.46 mmol). R_f (EtOAc/ petrol 1:9) 0.40; mp 72.4-74.6°C, IR ν_{max} (film)/cm^{-1} 3123 (ArCH), 2953 (sp^3 CH), 1789 (C=O), 1736 (C=O), 1519 (C=N), 1500 (ArC=C), 1397 (C-O), 1277 (C-O); δ_H(400 MHz; $CDCl_3$) 3.48 (3H, s, CO_2CH_3), 3.60 (3H, s, CO_2CH_3), 4.26 (1H, d, *J* 6.8 Hz, C*H*), 5.07 (1H, d, *J* 6.4 Hz, C*H*), 6.27 (1H, t, *J* 2.0 Hz, $C_3H_3N_2$), 7.27-7.32 (5H, m, Ar*C*H), 7.52 (1H, d, *J* 1.6 Hz, $C_3H_3N_2$), 7.55 (1H, d, *J* 2.0 Hz, $C_3H_3N_2$); δ_C(100 MHz; $CDCl_3$) 35.6 (*C*HAr), 44.2 ($C(CO_2CH_3)_2$), 47.1 (*C*HN), 52.6 (CO_2CH_3), 53.1 (CO_2CH_3), 106.3 ($C_3H_3N_2$), 127.5-127.9 (Ar*C*H), 128.0-128.2 (Ar*C*H), 128.5 (Ar*C*H), 130.2 ($C_3H_3N_2$), 132.2 (Ar*C*), 140.4 ($C_3H_3N_2$), 165.4 (C=O), 165.5 (C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{16}H_{17}N_2O_4$ 301.11, found 301.11; *m/z* 301 (23%), 255 (58%), 233 (100%), 173 (99%), 154 (54%), 136 (45%) and 115 (20%).

(±) 2-(1*H*-Benzo[1,2,3]triazol-1-yl)-1-phenylcyclopropane dimethyl ester (182_h)

Anhydrous potassium carbonate (0.75 g, 5.4 mmol, 2.5 eq) was added to a solution of benzotriazole (0.26 g, 2.2 mmol) and the substituted cyclopropene **1**$_d$ (0.5 g, 2.2 mmol) in *N*,*N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford dark oil. The residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:1) to afford the *title compound* as yellow viscous oil in 60% yield. (463 mg, 1.37 mmol); IR ν_{max} (film)/cm^{-1} 3029 (ArCH), 2951 (sp^3 CH), 1734 (C=O), 1613 (ArC=C), 1499 (C=N), 1302 (C-O), 1281 (C-O); δ_H(400 MHz; $CDCl_3$) 3.40 (3H, s, CO_2CH_3), 3.56 (3H, s, CO_2CH_3), 4.53 (1H, d, *J* 6.4 Hz, C*H*), 5.23 (1H, d, *J* 6.4 Hz, C*H*), 7.31-7.42 (6H, m, 5 Ar*C*H, 1 Ar*C*H), 7.49 (1H, t, *J* 7.9 Hz, ArC*H*), 7.62 (1H, d, *J* 8.2 Hz, ArC*H*), 8.04 (1H, d, *J* 8.4 Hz, ArC*H*); δ_C(100 MHz; $CDCl_3$) 34.2 (*C*HAr), 43.1 (*C*HN), 43.9 (*C*$(CO_2CH_3)_2$), 52.9 (CO_2CH_3), 53.1 (CO_2CH_3), 109.2-109.3 (Ar*C*H), 120.1 (Ar*C*H), 124.1 (Ar*C*H), 127.0 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 131.7 (Ar*C*), 133.7 (Ar*C*), 145.9 (Ar*C*), 165.1 (C=O), 168.0 (C=O); HRMS (FAB) (M+H$^+$) calculated for $C_{19}H_{18}N_3O_4$ 352.12, found 352.12; *m/z* 352 (100%), 173 (34%), 154 (21%) and 115 (18%).

(±) 2-(3,6-dibromocarbazole),1-phenylcyclopropane dimethyl ester (182$_d$)

Anhydrous potassium carbonate (442 mg, 3.2 mmol, 2.5 eq) was added to a solution of 3,6-dibromo-carbazole (423 mg, 1.3 mmol) and the substituted cyclopropene **1**$_d$ (300 mg, 1.3 mmol) in *N*,*N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and

concentrated *in vacuo* to afford brown solid. The residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:9) to afford the *title compound* as a yellow solid in 68% yield. (490 mg, 0.88 mmol); mp 192.4-194.7°C; IR ν_{max} (film)/cm^{-1} 3417 (ArCH), 1729 (C=O), 1300 (C-O), 1283(C-O), 1059 (C-Br); δ_H(400 MHz; $CDCl_3$) 3.27 (3H, s, CO_2CH_3), 3.58 (3H, s, CO_2CH_3), 4.24 (1H, d, *J* 6.8 Hz, C*H*), 4.86 (1H, d, *J* 6.4 Hz, C*H*), 7.31-7.55 (9H, m, 5 ArC*H*, 4 ArC*H*, carbazole), 8.10 (2H, s, ArC*H*, carbazole); δ_C(100 MHz; $CDCl_3$) 37.3 (*C*H), 41.3 (*C*HN), 44.9 ($C(CO_2CH_3)_2$), 52.9 (CO_2CH_3), 53.0 (CO_2CH_3), 111.4 (2 Ar*C*H, carbazole), 124.0 (2 Ar*C*H, carbazole), 124.2 (2 C-Br), 128.4 (3 Ar*C*H), 128.5 (2 Ar*C*H), 130.0 (2 Ar*C*H, carbazole), 132.1 (Ar*C*), 165.5 (C=O), 165.9 (C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{25}H_{20}{}^{79/81}Br_2N_2O_4$ 555.97 and 557.97, found 555.98 and 557.98; m/z 555 (100%), 307 (33%), 233 (88%), 154 (100%), 136 (65%). Due to a weak sample not all the quaternary carbons have been accounted for.

(±) Phenyl, 2(1*H*-imidazol-1-yl) cyclopropane dimethyl ester (182_g)

Anhydrous potassium carbonate (297 mg, 2.2 mmol, 2.5 eq) was added to a solution of imidazole (59 mg, 0.86 mmol), substituted cyclopropene $\mathbf{1}_d$ (200 mg, 0.86 mmol) in *N*, *N*-dimethylformamide (2.5 mL), under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 19 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford a dark orange semi solid. The residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:3) to afford the *title compound* as a rusty orange solid in 62% yield. (160 mg, 0.53 mmol); mp 103.1-104.9°C; IR ν_{max} (film)/cm^{-1} 3116 (Ar-CH), 3029 (Ar-CH), 2953 (sp^3CH), 1731 (C=O), 1503 (ArC=C), 1359 (C-O); δ_H(400 MHz; $CDCl_3$) 3.41 (3H, s, CO_2CH_3), 3.52 (3H, s, CO_2CH_3), 4.01 (1H, d, *J* 6.4 Hz, C*H*), 4.75 (1H, d, *J* 6.4 Hz, C*H*N), 6.93 (2H, d, *J* 13.2 Hz, NC*H*C*H*NCH), 7.19-7.25 (5H, m, ArC*H*), 7.51 (1H, s, NCHCHN=C*H*); δ_C(100 MHz; $CDCl_3$) 32.5 (CH), 40.9 ($C(CO_2CH_3)_2$), 42.5 (*C*HN), 52.9 (CO_2CH_3), 53.4 (CO_2CH_3), 119.4 (N*C*HCHNCH), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 129.0 (Ar*C*H), 129.8 (NCH*C*HNCH), 131.6 (ArC), 136.0

(NCHCHN=*C*H), 165.1 (C=O), 165.3 (C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{16}H_{17}N_2O_4$ 301.112, found 301.114 (+1.6 ppm).

(±) 2-(4-Bromopyrazole)-1-phenyl cyclopropane dimethyl ester (182_c)

Anhydrous potassium carbonate (0.75 g, 5.4 mmol, 2.5 eq) was added to a solution of 4-bromopyrazole (0.83 g, 4.3 mmol), substituted cyclopropene $\mathbf{1}_d$ (0.5 g, 2.2 mmol) in *N*, *N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford yellow oil. The residue was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:8) to afford the *title compound* as a clear viscous oil in 62% yield (520 g, 1.37 mmol); IR ν_{max} (film)/cm^{-1} 3131 (ArCH), 2951 (sp^3CH), 1732 (C=O), 1500 (ArC=C), 1301 (C-O); δ_H(400 MHz; $CDCl_3$) 3.50 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 4.22 (1H, d, *J* 6.4 Hz, C*H*), 5.02 (1H, d, 6.4 Hz, C*H*N), 7.28-7.36 (5H, m, ArC*H*), 7.48 (1H, s, NC*H*CBr), 7.58 (1H, s, N=C*H*CBr); δ_C(100 MHz; $CDCl_3$) 35.6 (CH), 44.3 ($C(CO_2CH_3)_2$), 47.3 (*C*HN), 52.8 (CO_2CH_3), 53.3 (CO_2CH_3), 94.0 (C-Br), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 130.4 (N*C*HCBr), 131.8 (Ar*C*), 141.0 (N=*C*HCBr), 165.1 (C=O), 165.3 (C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{16}H_{16}{}^{79/81}BrN_2O_4$ 379.028 and 381.028, found 379.028 and 381.028 (-0.22 ppm).

(±) 2-(4-Nitropyrazole) phenylcyclopropane dimethyl ester (182_i)

Anhydrous potassium carbonate (297 mg, 2.16 mmol, 2.5 eq) was added to a solution of 4-nitropyrazole (97 mg, 0.86 mmol) and the substituted cyclopropene **1**$_d$ (200 mg, 0.86 mmol) in *N*, *N*-dimethylformamide (3 mL), under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford brown oil. The crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:3) to afford the *title compound* as a yellow oil in 50% yield (149 mg, 0.43 mmol); IR, ν_{max} (film)/cm^{-1} 3130 (sp^2 ArC-H), 2955 (sp^3 C-H), 1733 (C=O), 1537 (C-NO_2), 1514 (C=N), 1316 (C-NO_2); δ_H(400 MHz; $CDCl_3$) 3.52 (3H, s, CO_2CH_3), 3.69 (3H, s, CO_2CH_3), 4.21 (1H, d, *J* 6.4 Hz, C*H*), 5.10 (1H, d, *J* 6.4 Hz, C*H*N), 7.25-7.34 (5H, m, ArC*H*), 8.08 (1H, s, N=C*H*CNO_2), 8.34 (1H, s, NC*H*CNO_2); δ_C(100 MHz; $CDCl_3$) 35.8 (C*C*HC), 44.2 (*C*(CO_2CH_3)$_2$), 47.6 (*C*HN), 53.0 (CO_2CH_3), 53.6 (CO_2CH_3), 128.3-129.1 (3 Ar*C*H), 129.8 (N*C*H=C), 131.4 (Ar*C*), 136.4 (N=*C*HC), 164.6 (2 C=O); FTMS (ES) ($M+H^+$) calculated for $C_{16}H_{16}N_3O_6$ 346.0955, found 346.1023 (-3.02 ppm). Due to a weak sample not all the quaternary carbons have been accounted for.

(±) 2-(3(4)-Trifluoromethylpyrazole) phenylcyclopropane 3,3-dimethyl ester (182$_j$)

Anhydrous potassium carbonate (297 mg, 2.16 mmol, 2.5 eq) was added to a solution of 3-trifluoromethylpyrazole (117 mg, 0.86 mmol) and the substituted cyclopropene **1**$_d$ (200 mg, 0.86 mmol) in *N*, *N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The reaction mixture stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford *title compound* without further purification as a yellow oil in 82% yield (260 mg, 0.70 mmol); IR, ν_{max} (film)/cm^{-1} 3130 (sp^2 ArC-H), 2957 (sp^3 C-H), 1733 (C=O), 1488 (C=N), 1134 (C-F); δ_H(400 MHz; $CDCl_3$) 3.48 (3H, s,

CO_2CH_3), 3.62 (3H, s, CO_2CH_3), 4.24 (1H, d, *J* 6.4 Hz, C*H*), 5.10 (1H, d, *J* 6.4 Hz, C*H*N), 6.54 (1H, d, *J* 2.8 Hz, C*H*CCF_3), 7.27-7.36 (5H, m, ArC*H*), 7.62 (1H, d, *J* 2.8 Hz, NC*H*CH); δ_C(100 MHz; $CDCl_3$) 35.8 (CH), 44.1 (*C*$(CO_2CH_3)_2$), 47.2 (*C*HN), 52.8 (CO_2CH_3), 53.3 (CO_2CH_3), 105.0 (N*C*HCHC), 128.3 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.7 (Ar*C*H), 128.8 (Ar*C*H), 131.5 (Ar*C*), 131.1 (NCH*C*HCCF_3), 143.4 (Ar*C*-CF_3), 165.0 (C=O), 165.2 (C=O), FTMS (ES) ($M+H^+$) calculated for $C_{17}H_{16}F_3N_2O_4$ 369.1057, found 369.1057 (+0.014 ppm).

(±) 2-(1*H*-1,2,4-Triazol-1-yl) phenylcyclopropane 3,3-dimethyl ester (182_f)

Anhydrous potassium carbonate (149 mg, 1.08 mmol, 2.5 eq) was added to a solution of 1,2,4 triazole (30 mg, 0.43 mmol) and the substituted cyclopropene $\mathbf{1}_d$ (100 mg, 0.43 mmol) in *N*,*N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford a brown viscous oil. The crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:3) to afford the *title compound* as a yellow oil in 50% yield (65 mg, 0.22 mmol); IR ν_{max} (film)/cm^{-1} 3123 (sp^2 ArC-H), 2951(sp^3 C-H), 1730 (C=O), 1507 (ArC=C), 1437(C=N), 1277(C-O), 1056 (C-O); δ_H(400 MHz; $CDCl_3$) 3.52 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 4.23 (1H, d, *J* 6.0 Hz, CC*H*C), 5.07 (1H, d, *J* 6.4 Hz, C*H*CN), 7.24-7.36 (5H, m, Ar*C*H), 7.95 (1H, s, $N_3C_2H_2$), 8.24 (1H, s, $N_3C_2H_2$); δ_C(100 MHz; $CDCl_3$) 35.4 (CH), 43.8 (C*C*HC), 44.4 (*C*$(CO_2CH_3)_2$), 52.9 (CO_2CH_3), 53.4 (CO_2CH_3), 126.8 (Ar*C*H), 126.9 (Ar*C*H), 127.7 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 131.4 (Ar*C*), 143.6 ($N_3C_2H_2$), 152.3 ($N_3C_2H_2$), 164.9 (C=O), 165.0 (C=O); FTMS (ES) ($M+H^+$) calculated for $C_{15}H_{16}N_3O_4$ 302.106, actually found 302.114 (-0.116 ppm).

(±) Phenyl 2-(4-nitro-1H-pyrazol-1-yl)-3-methyl cyclopropane diester (184/185$_a$)

Cesium carbonate (351 mg, 1.0 mmol) was added to a stirred solution of 4-nitropyrazole (73 mg, 0.65 mmol, 1.5 eq) and substituted cyclopropene **1**$_d$ (100 mg, 0.43 mmol) in *N*, *N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford dark yellow oil. The residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a separable mixture of diastereoisomers in a combined 60% yield as a yellow oil in a d.r. 1:2 (**184**:**185**); IR, ν_{max} (film)/cm^{-1} 3131 (sp^2 Ar-CH), 2954 (sp^3 C-H), 1732 (C=O), 1606 (ArC=C), 1534 (C-NO_2), 1318 (C-NO_2); (i) first eluted isomer **184**$_a$, R_f (EtOAc/petrol 1:3) 0.65 δ_H(400 MHz; $CDCl_3$) 2.95 (1H, dd, *J* 3.9, 10.8 Hz, C*H*^{3}), 3.50 (1H, dd, *J* 5.5, 10.8 Hz, C*H*^{2}), 3.57 (3H, s, CO_2CH_3), 4.70 (1H, dd, *J* 3.9, 5.4 Hz, C*H*^{1}), 7.31-7.33 (5H, m, ArC*H*), 8.08 (1H, s, N=C*H*CNO_2), 8.35 (1H, s, NC*H*CNO_2); δ_C (100 MHz; $CDCl_3$) 29.6 (C*H*^{3}), 32.3 (C*H*^{2}), 44.5 (C*H*^{1}), 52.3 (CO_2CH_3), 127.9 (2 Ar*C*H), 128.6 (3 Ar*C*H), 129.0 (N*C*HCNO_2), 132.5 (Ar*C*), 135.9 (N=*C*HCNO_2), 167.9 (C=O), (i) second eluted isomer **185**$_a$, R_f (EtOAc/petrol 1:3) 0.47 δ_H(400 MHz; $CDCl_3$) 2.62 (1H, dd, *J* 6.2, 7.9 Hz, C*H*^{3}), 3.55 (1H, dd, *J* 6.2, 7.6 Hz, C*H*^{2}), 3.66 (3H, s, CO_2CH_3), 4.28 (1H, dd, *J* 5.3, 7.9 Hz, C*H*^{1}), 7.22-7.25 (2H, m, ArC*H*), 7.32-7.38 (3H, m, ArC*H*), 8.08 (1H, s, N=C*H*CNO_2), 8.32 (1H, s, NC*H*CNO_2); δ_C (100 MHz; $CDCl_3$) 29.7 (*C*H^3), 30.7 (*C*H^2), 46.2 (*C*H^1), 52.7 (CO_2CH_3), 126.8 (Ar*C*H), 128.1 (Ar*C*H), 128.6 (Ar*C*H), 130.0 (N*C*HCNO_2), 135.0 (Ar*C*), 136.4 (N=*C*HCNO_2), 168.2 (C=O); FTMS (ES) (M+Na$^+$) calculated for $C_{14}H_{13}N_3O_4Na$, 310.080, actually found 310.080 (-1.179 ppm).

(±) Phenyl-2-(3-trifluoromethyl-1H-pyrazol-1-yl) 3-methyl cyclopropane ester (184/185$_b$)

Cesium carbonate (351 mg, 1.0 mmol) was added to a stirred solution of 4-trifluoromethyl-pyrazole (59 mg, 0.43 mmol) and the substituted cyclopropene **1**$_d$ (100 mg, 0.43 mmol) in *N*, *N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 48 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford yellow oil. The crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as an inseparable mixture of diastereoisomers as a clear oil in 60% yield (80 mg, 0.26 mmol) in a d.r. 1:2.5 (**184**:**185**); IR, ν_{max} (film)/cm^{-1} 2955 (sp^3 C-H), 1735 (C=O), 1606 (ArC=C), 1489 (C=N), 1260 (C-F), 1135 (C-F); Assigned from a combined spectrum (i) Isomer **184**$_b$; δ_H(400 MHz; $CDCl_3$) 2.90 (1H, dd, *J* 4.0, 10.8 Hz, C*H*^{3}), 3.48 (1H, dd, *J* 5.6, 10.8 Hz, C*H*^{2}), 3.54 (3H, s, CO_2CH_3), 4.70 (1H, dd, *J* 4.0, 5.2 Hz, C*H*^{1}), 6.56 (1H, d, *J* 2.4 Hz, NC*H*=CH), 7.25-7.31 (2H, m, ArC*H*), 7.33-7.40 (3H, m, ArC*H*), 7.67 (1H, d, *J* 1.6 Hz, NCH=C*H*CCF$_3$); δ_C (100 MHz; $CDCl_3$) 29.9 (*C*H^3), 32.5 (*C*H^2), 44.1 (*C*H^1), 52.1 (CO_2CH_3), 105.0 (N*C*H=CH), 122.3 (q, $^1J_{CF}$ 266 Hz, CF3), 126.8 (Ar*C*H), 127.7 (Ar*C*H), 128.5 (Ar*C*H), 128.7 (Ar*C*H), 131.2 (NCH=*C*HCCF$_3$), 133.1 (Ar*C*), 143.4 (Ar*C*-CF$_3$), 168.3 (C=O); δ_F (376 MHz; $CDCl_3$) 100.2 (3F); (ii) Isomer **185**$_b$, δ_H(400 MHz; $CDCl_3$) 2.58 (1H, dd, *J* 6.0, 7.6 Hz, C*H*^{3}), 3.56 (1H, dd, *J* 5.5, 5.5 Hz, C*H*^{2}), 3.61 (3H, s, CO_2CH_3), 4.30 (1H, dd, *J* 5.2, 7.6 Hz, CH^1), 6.52 (1H, d, *J* 2.4 Hz, NC*H*=CH), 7.25-7.31 (2H, m, ArC*H*), 7.33-7.40 (3H, m, ArC*H*), 7.65 (1H, d, *J* 1.6 Hz, NCH=C*H*CCF$_3$); δ_C (100 MHz; $CDCl_3$) 30.0 (*C*H^3), 30.4 (*C*H^2), 45.8 (*C*H^1), 52.5 (CO_2CH_3), 104.3 (N*C*H=CH), 122.3 (q, $^1J_{CF}$ 266 Hz, CF3), 126.8 (Ar*C*H), 127.7 (Ar*C*H), 128.5 (Ar*C*H), 128.7 (Ar*C*H), 131.9 (NCH=*C*HCCF$_3$), 135.7 (Ar*C*), 143.5 (ArC-CF$_3$) 168.4 (C=O), δ_F (376 MHz; $CDCl_3$) 100.1 (3F); FTMS, (ES), (M+Na$^+$) calculated for $C_{15}H_{13}F_3N_2O_2Na$ 333.090, found 333.082 (-0.672 ppm).

(±) Phenyl 2-(1*H*-imidazol-1-yl)-3-methyl cyclopropane diester (184/185$_c$)

Cesium carbonate (351 mg, 1.0 mmol) was added to a stirred solution of imidazole (59 mg, 0.86 mmol, 2.0 eq) and substituted cyclopropene **1**$_d$ (100 mg, 0.43 mmol) in *N*,*N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 26 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford an orange/brown oil. The crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:3) to afford the *title compound* as an inseparable mixture of diastereoisomers as a yellow oil in 60% yield (62 mg, 0.26 mmol) in a d.r. 1:2 (**184**:**185**); IR, ν_{max} (film)/cm^{-1} 2952 (sp^3 C-H), 1732 (C=O), 1605 (ArC=C), 1500 (C=N), 1199 (C-O), 1176 (C-O). Assigned from combined spectrum, Isomer **184**$_c$; δ_H(400 MHz; $CDCl_3$) 2.65 (1H, dd, *J* 4.0, 10.8 Hz, C*H*^{3}), 3.20 (1H, dd, *J* 5.6, 10.4 Hz, C*H*^{2}), 3.56 (3H, s, CO_2CH_3), 4.46 (1H, dd, *J* 4.0, 5.6 Hz, C*H*^{1}), 7.04 (1H, s, NC*H*=CH), 7.08 (1H, s, NCH=C*H*), 7.28-7.33 (5H, m, ArC*H*), 7.64 (1H, s, NC*H*NCH); δ_C (100 MHz; $CDCl_3$) 29.8 (*C*H^3), 32.5 (*C*H^2), 38.7 (*C*H^1), 52.2 (CO_2CH_3), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.4-128.6 (Ar*C*H), 129.4 (N*C*HCH), 129.9 (NCH*C*H), 133.0 (Ar*C*), 137.1 (N*C*HNCH), 168.4 (C=O), Isomer **185**$_c$; δ_H(400 MHz; $CDCl_3$) 2.50 (1H, dd, *J* 6.0, 8.0 Hz, C*H*^{3}), 3.46 (1H, dd, *J* 6.0, 7.6 Hz, C*H*^{2}), 3.61 (3H, s, CO_2CH_3), 3.99 (1H, dd, *J* 5.2, 7.6 Hz, C*H*^{1}), 7.00 (1H, s, NC*H*=CH), 7.04 (NCHC*H*), 7.22 (2H, d, *J* 8.8 Hz, ArC*H*), 7.34-7.39 (3H, m, ArC*H*), 7.60 (1H, s, NC*H*NCH); δ_C (100 MHz; $CDCl_3$) 29.5 (*C*H^2), 29.9 (*C*H^3), 40.9 (*C*H^1), 53.4 (3H, s, CO_2CH_3), 119.2 (N*C*HCH), 119.7 (NCH*C*H), 126.8 (Ar*C*H), 128.8-130.0 (2 Ar*C*H), 136.0 (Ar*C*), 137.7 (N*C*HNCH), 168.2 (C=O); FTMS (ES) (M+H$^+$) calculated for $C_{14}H_{15}N_2O_2$ 243.094, found 243.113 (-0.643 ppm).

(±) Phenyl-2-(1*H*-1,2,4-triazol-1-yl) 3-methyl cyclopropane ester (184/185$_d$)

Cesium carbonate (351 mg, 1.1 mmol) was added to a stirred solution of 1,2,4-triazole (59 mg, 2.0 eq) and substituted cyclopropane in *N*,*N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 21 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and partitioned with saturated aqueous ammonium chloride (20 mL). The ethereal solution was washed with water (15 mL), brine (15 mL) and the organic layer was dried over anhydrous sodium sulphate and concentrated *in vacuo* to afford a brown oil. The crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:3) to afford the *title compound* as an inseparable mixture of diastereoisomers as a yellow oil in 55% yield (57 mg, 0.24 mmol) in a d.r. 1:2 (**184**:**185**); IR, ν_{max} (film)/cm^{-1} 2924 (sp^3 C-H), 1732 (C=O), 1506 (C=N), 1441 (C-O). Assigned from a combined spectrum, isomer **184**$_d$; δ_H(400 MHz; $CDCl_3$) 2.90 (1H, dd, *J* 4.0, 10.8 Hz, C*H*^{3}), 3.45 (1H, dd, *J* 5.2, 10.8 Hz, C*H*^{2}), 3.60 (3H, s, CO_2CH_3), 4.71 (1H, dd, *J* 4.0, 5.6 Hz, C*H*^{1}), 7.23-7.27 (2H, m, ArC*H*), 7.36-7.40 (3H, m, ArC*H*), 7.95 (1H, s, NC*H*NCHN), 8.30 (1H, s, NCHNC*H*N); δ_C (100 MHz; $CDCl_3$) 29.5 (*C*H^3), 32.2 (*C*H^2), 41.3 (*C*H^1), 52.2 (CO_2CH_3), 127.8 (2 Ar*C*H), 127.9 (Ar*C*H), 128.5 (2 Ar*C*H), 132.8 (Ar*C*), 143.5 (N*C*HNCHN), 151.9 (NCHN*C*HN), 168.2 (C=O); isomer **185**$_d$, δ_H(400 MHz; $CDCl_3$) 2.60 (1H, dd, *J* 6.4, 8.0 Hz, C*H*^{3}), 3.56 (1H, dd, *J* 5.6, 7.6 Hz, C*H*^{2}), 3.62 (3H, s, CO_2CH_3), 4.22 (1H, dd, *J* 5.2, 8.0 Hz, C*H*^{1}), 7.28-7.36 (5H, m, ArC*H*), 7.94 (1H, s, NC*H*NCHN), 8.25 (1H, s, NCHNC*H*N); δ_C (100 MHz; $CDCl_3$) 29.4 (*C*H^3), 30.1 (*C*H^2), 42.9 (*C*H^3), 52.5 (CO_2CH_3), 126.9 (2 Ar*C*H), 128.7-129.0 (3 Ar*C*H), 135.5 (Ar*C*), 144.3 (N*C*HNCHN), 152.2 (NCHN*C*HN), 168.1 (C=O); FTMS (ES) (M+H$^+$) calculated for $C_{13}H_{14}N_3O_2$ 244.108, found 244.108 (0.115 ppm).

4-Nitrophenyl cyclopropene dimethyl ester (186$_a$)

A solution of diazo dimethylmalonate **150**$_a$ (2 g, 12.6 mmol) in anhydrous dichloromethane (5 mL) was added *via* a syringe (1.0 mL/ph) to a stirred solution of 1-ethynyl-4-nitrobenzene (4.63 g, 31.5 mmol, 2.5 eq) and rhodium acetate dimer (0.12 mmol) in dichloromethane (17 mL) under a nitrogen atmosphere. Once addition was complete the reaction mixture was stirred for an additional six hours. The reaction mixture was filtered through a pad of celite and silica and excess solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:5) to afford the *title compound* as a light orange solid in 50 % yield (1.75 g, 6.3 mmol); mp 108.2-109.5°C; IR, ν_{max} (film)/cm^{-1} 1727 (C=O), 1522 (C-NO_2), 1345 (C-NO_2); δ_H(400 MHz; $CDCl_3$) 3.77 (6H, s, 2 CO_2CH_3), 7.22 (1H, s, *H*=C-Ar), 7.81 (2H, d, *J* 8.4 Hz, $ArNO_2$-C*H*), 8.31 (2H, d, *J* 8.4 Hz, $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 33.2 ($C(CO_2CH_3)_2$), 52.7 (2 CO_2CH_3), 100.6 (HCC-Ar), 111.1 (HCC-Ar), 124.2 ($ArNO_2$-CH), 130.1 (ArC), 131.1 ($ArNO_2$-CH), 148.7 (C-NO_2), 170.4 (2 C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{13}H_{12}NO_6$ 278.0659, found 278.0658 (-0.41 ppm).

4-Methoxyphenyl cyclopropene dimethyl ester (186$_b$)

A solution of diazo dimethylmalonate **150**$_a$ (2 g, 12.6 mmol) in anhydrous dichloromethane (5 mL) was added *via* syringe (1.0 mL/ph) to a stirred solution of 1-ethynyl-4-methoxybenzene (4.18 g, 4.1 mL, 31.6 mmol, 2.5 eq) and rhodium acetate dimer (0.12 mmol) in dichloromethane (17 mL) under a nitrogen atmosphere. Once addition was complete the reaction mixture was stirred for an additional six hours. The reaction mixture was filtered through a pad of celite and silica and excess solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:5) to afford the *title compound* as a light yellow solid in 45% yield (1.49g, 5.67 mmol); mp 97.2-98.4°C, IR, ν_{max} (film)/cm^{-1} 1713 (C=O), 1604 (ArC=C), 1250, 1095 (C-O); δ_H(400 MHz; $CDCl_3$) 3.83 (6H, s, 2 CO_2CH_3), 4.20 (3H, s, OCH_3), 6.71 (1H, s, *H*CC-Ar), 6.91 (2H, d, *J* 8.8 Hz, ArOMe-C*H*), 7.46 (2H, d, *J* 8.8 Hz, ArOMe-C*H*), δ_C(100 MHz; $CDCl_3$) 33.9 ($C(CO_2CH_3)_2$), 54.3 (2 CO_2CH_3), 58.2 (OCH_3), 107.4 (CH=C-Ar), 116.8 (ArCH), 127.3 (ArCH), 130.2 (ArC), 136.8 (HCC-Ar), 146.6 (ArC-OCH_3),

166.5 (2 C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{14}H_{15}O_5$ 263.0912, found 263.0912 (-0.65 ppm).

4-Trifluoromethylphenyl cyclopropene dimethyl ester (186$_c$)

A solution of diazo dimethylmalonate **150**$_a$ (2 g, 12.6 mmol) in anhydrous dichloromethane (5 mL) was added *via* syringe (1.0 mL/ph) to a stirred solution of 1-ethynyl-4-trifluoromethylbenzene (4.18 g, 4.1 mL, 31.6 mmol, 2.5 eq) and a rhodium acetate dimer (0.12 mmol) in dichloromethane (17 mL) under a nitrogen atmosphere. Once addition was complete the reaction mixture was stirred for an additional six hours. The reaction mixture was filtered through a pad of celite and silica and excess solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/ Petrol 1:5) to afford the *title compound* as a light yellow oil in 45% yield (1.71g, 5.67 mmol); IR, ν_{max} (film)/cm^{-1} 2954 (sp^3 CH), 1732 (C=O), 1604 (ArC=C), 1168 (C-F), 1124 (C-F); δ_H(400 MHz; $CDCl_3$), 3.75 (6H, s, CO_2CH_3), 7.06 (1H, s, *H*C=C-Ar), 7.74 (4H, dd, *J* 4.4, 8.4 Hz, $ArCF_3$-C*H*); δ_C(100 MHz; $CDCl_3$) 32.5 (*C*$(CO_2CH_3)_2$), 52.6 (2 CO_2CH_3), 102.3 (H*C*=C-Ar), 125.9 (Ar*C*H), 127.4 (Ar*C*H), 130.6 (Ar*C*), 170.7 (2 C=O); FTMS (ES) ($M+Na^+$) calculated for $C_{14}H_{11}F_3O_4Na$ 323.050, found 323.049 (-1.857 ppm). Due to a weak sample not all the quaternary carbons have been accounted for.

(±) Dimethyl 2-(2-(4-iodo-1H-pyrazol-1-yl)-1-(4-nitrophenyl vinyl) malonate (187$_a$)

Potassium carbonate (124 mg, 0.90 mmol, 2.5 eq) was added to a solution of 4-iodopyrazole (70 mg, 0.36 mmol) and the substituted cyclopropene **186**$_a$ (100 mg, 3.6 mmol) in *N*,*N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 19 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and washed with saturated aqueous

ammonium chloride (20 mL). The layers were separated and the ethereal solution was subsequently washed with water (15 mL), brine (15 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the unexpected ring-opened product as a yellow solid in 60% yield (102 mg, 0.21 mmol); mp 153.7-154.2°C; IR, ν_{max} (film)/cm^{-1} 2951(sp^3C-H), 1737 (C=O), 1518 (C-NO_2), 1346 (C-NO_2); δ_H(400 MHz; $CDCl_3$) 3.66 (6H, s, 2 CO_2CH_3), 6.11 (1H, s, $CHCO_2CH_3$), 7.08 (1H, s, *H*C=C-Ar), 7.64 (2H, d, *J* 8.8 Hz, 2 $ArNO_2$-C*H*), 7.65 (1H, s, N=C*H*Cl), 7.67 (1H, s, IC=C*H*N), 8.20 (2H, d, *J* 8.8 Hz, 2 $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 53.0 (2 CO_2CH_3), 54.0 ($CHCO_2CH_3$), 60.4 (*C*-I), 122.1 (HC=*C*-Ar), 123.6 ($ArNO_2$-*C*H), 128.0 (H*C*=C), 128.9 ($ArNO_2$-*C*H), 136.0 (IC=*C*HN), 145.1 (Ar*C*), 146.0 (N=*C*HCl), 147.3 (Ar*C*-NO_2), 168 (2 C=O); HRMS (FAB) ($M+H^+$) calculated for $C_{16}H_{15}IN_3O_6$ 471.9998, found 471.9998 (-0.47 ppm).

Dimethyl 2-(2-(4(5)-bromo-1H-imidazol-1-yl)-1-(4-nitrophenyl vinyl) malonate (**187**$_b$)

Potassium carbonate (124 mg, 0.90 mmol, 2.5 eq) was added to a solution of 4-bromo-1*H*-imidazole (53 mg, 0.36 mmol) and the substituted cyclopropene **186**$_a$ (100 mg, 0.36 mmol) in *N*,*N*-dimethylformamide (3 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 24 hours. On completion the reaction mixture was cooled to room temperature, diluted with diethyl ether (20 mL) and washed with saturated aqueous ammonium chloride (20 mL). The layers were separated and the ethereal solution was subsequently washed with water (15 mL), brine (15 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:4) to afford the unexpected ring-opened product as a yellow/orange viscous oil in 54% yield (80 mg, 0.19 mmol); IR, ν_{max} (film)/cm^{-1} 1737(C=O), 1520 (C-NO_2), 1348 (C-NO_2), 855(C-Br); δ_H(400 MHz; $CDCl_3$) 3.71 (6H, s, 2 CO_2CH_3), 4.73 (1H, s, $CHCO_2CH_3$), 7.04 (1H, s, *H*CC-Ar), 7.08 (1H, s, $C_3H_2N_2Br$), 7.57 (1H, s, $C_3H_2N_2Br$), 7.63 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*), 8.25 (2H,

d, *J* 8.8 Hz, $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 53.2 (*C*HCO_2CH_3), 53.5 (2 CO_2*C*H_3), 118.5 (H*C*C-Ar), 123.9 ($ArNO_2$-C*H*), 127.4 (*C*$_3H_2N_2Br$), 129.1 (Ar-NO_2-*C*H), 132.6 (HC*C*-Ar), 137.1 (*C*$_3H_2N_2Br$), 142.9 (ArC), 148.1 (Ar*C*-NO_2), 166.7 (2 C=O), HRMS (FAB) ($M+H^+$) calculated for $C_{16}H_{15}{}^{79/81}BrN_3O_6$ 424.0137 and 426.0317, found 424.0127 and 426.0126 (-2.878 ppm).

(±) Dimethyl 2-(4-bromo-1H-imidazol-1-yl)-3-4-nitrophenylcyclopropane-1,1-dicarboxylate (188$_a$)

Potassium carbonate (124 mg, 0.90 mmol, 2.5 eq) was added to a solution of 4-bromo-1*H*-imidazole (53 mg, 0.36 mmol) and the substituted cyclopropene **186**$_a$ (100 mg, 0.36 mmol) in acetonitrile (3 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 hours. Once complete the resulting mixture was diluted with diethyl ether (10 mL) and subsequently washed with saturated aqueous ammonium chloride (15 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure to afford the *title compound* without further purification as brown solid in 90% yield (137 mg, 0.32 mmol); mp 101.4-102.9°C; IR, ν_{max} (film)/cm^{-1} 2954 (sp^3 CH), 1730 (C=O), 1603 (ArC=C), 1520 (NO_2), 1348 (NO_2); δ_H(400 MHz; $CDCl_3$) 3.57 (3H, s, CO_2C*H*$_3$), 3.71 (3H, s, CO_2C*H*$_3$), 4.12 (1H, d, *J* 6.8 Hz, C*H*-Ar), 4.87 (1H, d, *J* 6.8 Hz, C*H*N), 7.02 (1H, s, NC*H*N), 7.48 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*), 7.50 (1H, s, NC*H*CBr), 8.22 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 34.5 (CH), 42.6 (*C*HN), 44.5 (*C*(CO_2CH_3)$_2$), 116.3 (C-Br), 118.7 (N*C*HN), 124.0 (2 $ArNO_2$-*C*H), 129.5 (2 $ArNO_2$-*C*H), 137.0 (N*C*HCBr), 138.6 (Ar*C*-NO_2), 147.9 (Ar*C*), 164.3 (C=O), 164.6 (C=O); FTMS (ES) ($M+H^+$) calculated for $C_{16}H_{15}{}^{79/81}BrN_3O_6$ 424.0137 and 426.0137, found 424.0137 and 426.0115 (-0.455ppm).

(±) Dimethyl 2-(4-iodo-1H-pyrazol-1-yl)-3-4-nitrophenylcyclopropane-1,1-dicarboxylate (188$_b$)

Potassium carbonate (63 mg, 0.45 mmol, 2.5 eq) was added to a solution of 4-iodopyrazole (35 mg, 0.18 mmol) and the substituted cyclopropene **186**$_a$ (50 mg, 0.18 mmol) in acetonitrile (3 mL). The reaction mixture was stirred at room temperature for 6 hours. Once complete the resulting mixture was diluted with diethyl ether (10 mL) and subsequently washed with saturated aqueous ammonium chloride (15 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure to afford the *title compound* without further purification as a yellow solid in 98% yield (83 mg, 0.17 mmol); mp 141.1-142.4°C; IR, ν_{max} (film)/cm^1 2953(sp^{3}C-H), 1732 (C=O), 1603(ArC=C), 1521 (C-NO_2), 1347 (C-NO_2), 1437(C=N); δ_H(400 MHz; $CDCl_3$) 3.56 (3H, s, CH_3, CO_2CH_3), 3.67 (3H, s, CH_3, CO_2CH_3), 4.34 (1H, d, *J* 6.4 Hz, C*H*), 5.07 (1H, d, *J* 6.4 Hz, C*H*N), 7.51 (2H, d, *J* 8.4 Hz, $ArNO_2$-C*H*), 7.53 (1H, s, NC*H*CICH), 7.64 (1H, s, NCHCIC*H*), 8.21 (2H, d, *J* 8.4 Hz, $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 34.7 (CH), 44.6 (*C*(CO_2CH_3)$_2$), 47.1 (C*H*N), 53.2 (CO_2CH_3), 53.6 (CO_2CH_3), 57.7 (C-I), 123.9 ($ArNO_2$-*C*H), 129.6 ($ArNO_2$-*C*H), 134.8 (NCHCI*C*H), 139.4 (ArC-NO_2), 145.4 (N*C*HCICH), 147.7 (Ar*C*), 164.7 (C=O), 164.8 (C=O); FTMS (ES) ($M+H^+$) calculated for $C_{16}H_{15}IN_3O_6$ 471.9922, found 471.9987 (-2.838ppm).

(±) Dimethyl 2-(3,6-dibromocarbazole)- 3-4-nitrophenylcyclopropane-1,1-dicarboxylate (188$_c$)

Potassium carbonate (63 mg, 0.45 mmol, 2.5 eq) was added to a solution of di-bromocarbazole (59 mg, 0.18 mmol) and the substituted cyclopropene **186**$_a$ (50 mg, 0.18

mmol) in acetonitrile (3 mL) at room temperature. The reaction mixture was stirred for 4 hours and upon completion diluted with diethyl ether (10 mL). The ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a white solid in 56% yield (60 mg, 0.10 mmol); mp 218.4-219.6°C; IR, ν_{max} (film)/cm^{-1} 2956 (sp^3 *C*-H), 1737 (C=O), 1606 (ArC=C) 1524 (C-NO_2), 1436 (C-N), 1347 (C-NO_2), 1260 C-O), 740 (C-Br); δ_H(400 MHz; $CDCl_3$) 3.24 (3H, s, CO_2CH_3), 3.56 (3H, s, CO_2CH_3), 4.24 (1H, d, *J* 6.7 Hz, CC*H*-Ar), 4.82 (1H, d, *J* 6.7 Hz, CC*H*N), 7.19 (2H, s, 2 CC*H*CBr), 7.45 (2H, d, *J* 8.6 Hz, 2 NCC*H*), 7.54 (2H, d, *J* 8.8 Hz, 2 $ArNO_2$-C*H*), 8.04 (2H, d, *J* 2.0 Hz, 2 C*H*CBr), 8.23 (2H, d, *J* 8.8 Hz, 2 $ArNO_2$-C*H*); δ_C (100 MHz; $CDCl_3$) 35.5 (CH), 40.5 (C*C*HN), 44.3 (*C*(CO_2CH_3)$_2$), 52.3 (2 CO_2CH_3), 78.4 (2 CH, carbazole) 110.2 (2 Ar*C*), 111.2 (2 Ar*C*), 116.8 (2 Ar*C*), 121.7 (2 CH, carbazole), 122.4 ($ArNO_2$-*C*H), 128.4 ($ArNO_2$-*C*H), 129.7 (2 CH, carbazole), 138.4 (Ar*C*-NO_2), 147.0 (Ar*C*), 163.9 (C=O), 164.4 (C=O); FTMS (EI) ($M-H^+$) calculated for $C_{25}H_{17}{}^{79}Br_2N_2O_6$ 598.946, actually found 598.946 (+0.675 ppm).

(±) Dimethyl 2-(4-nitrophenyl)-3-1H-pyrazol-1-yl-cyclopropane-1,1-dicarboxylate (188_d)

Potassium carbonate (63 mg, 0.45 mmol, 2.5 eq) was added to a solution of prazole (25 mg, 0.36 mmol, 2.0 eq) and the substituted cyclopropene **186**$_a$ (50 mg, 0.18 mmol) in acetonitrile (3 mL) at room temperature. The reaction mixture was stirred for 22 hours and upon completion diluted with diethyl ether (10 mL). The ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as yellow solid in 65% yield (40 mg, 0.12 mmol); mp 67.2°C; IR, ν_{max} (film)/cm^{-1} 2955 (sp^3 *C*-H) , 1733 (C=O), 1604 (ArC=C), 1522 (NO_2), 1349 (NO_2), 1300 (C-O), 1125 (C-O); δ_H(400 MHz; $CDCl_3$) 3.56 (3H, s, CO_2CH_3), 3.63 (3H, s, CO_2CH_3), 4.40 (1H, d, *J* 6.4 Hz, CC*H*C),

5.09 (1H, d, *J* 6.4 Hz, CC*H*N), 6.32 (1H, t, *J* 2.0 Hz, NCHC*H*CHN), 7.52 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*), 7.53 (1H, d, *J* 2.0 Hz, NC*H*CHCHN), 7.56 (1H, d, *J* 2.0 Hz, NCHCHC*H*N), 8.21 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*); δ_C (100 MHz; $CDCl_3$) 34.9 (C*C*HC), 44.6 (*C*$(CO_2CH_3)_2$), 47.1 (C*C*HN), 53.1 (CO_2CH_3), 53.4 (CO_2CH_3), 107.0 (NCH*C*HCHN), 123.8 ($ArNO_2$-*C*H), 129.7 ($ArNO_2$-*C*H), 130.3 (N*C*HCHCHN), 139.8 (Ar*C*-NO_2), 140.7 (NCHCH*C*HN), 147.7 (Ar*C*), 164.9 (C=O), 165.1 (C=O); FTMS (ES) ($M+Na^+$) calculated for $C_{16}H_{15}N_3O_6Na$ 368.085, found 368.085 (-1.521 ppm).

(±) Dimethyl 2-(1*H*-imidazol-1-yl)-3-(4-nitrophenyl) cyclopropane-1,1-dicarboxylate (188_e)

Potassium carbonate (63 mg, 0.45 mmol, 2.5 eq) was added to a stirred solution of imidazole (25 mg, 0.36 mmol, 2.0 eq) and the substituted cyclopropene **188**$_a$ (50 mg, 0.18 mmol) in acetonitrile (3 mL) at room temperature. The reaction mixture was stirred for 23 hours and upon completion diluted with diethyl ether (10 mL). The ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure to afford the *title compound* without further purification as a brown oil in 87% yield (54 mg, 0.16 mmol); IR, ν_{max} (film)/cm^{-1} 2955 (sp^3 C-H), 1732 (C=O), 1603 (ArC=C), 1520 (C-NO_2), 1349 (C-NO_2); δ_H(400 MHz; $CDCl_3$) 3.58 (3H, s, CO_2CH_3), 3.66 (3H, s, CO_2CH_3), 4.15 (1H, d, *J* 6.8 Hz, CC*H*C), 4.89 (1H, d, *J* 6.8 Hz, CC*H*N), 7.01 (1H, s, NC*H*CHN), 7.08 (1H, s, NCHC*H*N), 7.50 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*), 7.61 (1H, s, NC*H*NCH), 8.23 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*); δ_C (100 MHz; $CDCl_3$) 34.6 (C*C*HC), 42.6 (C*C*HN), 44.6 (*C*$(CO_2CH_3)_2$), 53.3 (CO_2CH_3), 53.7 (CO_2CH_3), 119.3 (N*C*HCHN), 123.9 (2 $ArNO_2$-*C*H), 129.5 (2 $ArNO_2$-*C*H), 130.2 (NCH*C*HN), 137.3 (N*C*HNCH), 139.1 (Ar*C*), 147.8 (Ar*C*), 164.5 (C=O), 164.8 (C=O); FTMS (ES) ($M+H^+$) calculated for $C_{16}H_{16}N_3O_6$ 346.096, found 346.102 (-3.719 ppm).

(±) Dimethyl 2-(4-nitrophenyl)-3-(3(4)-(trifluoromethyl)-1H-pyrazol-1-yl) cyclopropane-1,1-dicarboxylate (188_f)

Potassium carbonate (63 mg, 0.45 mmol, 2.5 eq) was added to a stirred solution of pyrazole-trifluoromethyl (25 mg, 0.18 mmol) and the substituted cyclopropene **186**$_a$ (50 mg, 0.18 mmol) in acetonitrile (3 mL) at room temperature. The reaction mixture was stirred for 1 hour and upon completion diluted with diethyl ether (10 mL). The ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure to afford the *title compound* without further purification as a yellow solid in 99% yield (60 mg, 0.18 mmol); mp: 121.2-121.6°C; IR, ν_{max} (film)/cm^{-1} 2957 (sp^3 C-H), 1734 (C=O), 1605 (ArC=C), 1524 (C-NO_2), 1438 (C=N), 1350 (C-NO_2), 1132 (C-F); δ_H(400 MHz; $CDCl_3$) 3.57 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 4.38 (1H, d, *J* 6.4 Hz, CC*H*C), 5.13 (1H, d, *J* 6.4 Hz, CC*H*N), 6.59 (1H, d, *J* 2.4 Hz, NC*H*CHCCF$_3$), 7.52 (2H, d, *J* 8.8 Hz, 2 ArNO_2-C*H*), 7.66 (1H, d, *J* 2.0 Hz, NCHC*H*CCF$_3$), 8.21 (2H, d, *J* 8.8 Hz, 2 ArNO_2-C*H*); δ_C (100 MHz; $CDCl_3$) 34.9 (C*C*HC), 44.5 (*C*(CO_2CH_3)$_2$), 47.2 (C*C*HN), 53.3 (CO_2CH_3), 53.5 (CO_2CH_3), 105.52 (N*C*HCHC), 123.9 (2 Ar-CH), 124.8 (CF_3), 130.0 (2 Ar-CH), 132.1 (NCH*C*HCCF$_3$), 139.2 (Ar*C*), 143.2 (N*C*-CF_3), 147.7 (Ar*C*), 164.6 (C=O), 164.7 (C=O); δ_F(376 MHz; $CDCl_3$) 100.0 (C_6F_6); FTMS (ES) ($M+Na^+$) calculated for $C_{17}H_{14}F_3N_3O_6Na$ 436.072, found 436.072 (-1.484 ppm).

Dimethyl 2-(4-iodo-1H-pyrazol-1-yl)-3-4-trifluoromethylphenyl cyclopropane-1,1-dicarboxylate (188_g)

Potassium carbonate (114 mg, 0.83 mmol, 2.5 eq) was added to a stirred solution of 4-iodopyrazole (64 mg, 0.33 mmol) and the substituted cyclopropene **188**$_g$ (100 mg, 0.33

mmol) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred initially for 19 hours but no reaction had taken place. The reaction was heated to 50°C for additional 5 hours and upon completion the reaction mixture was cooled to room temperature and diluted with diethyl ether (10 mL). The ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a yellow viscous oil in 50% yield (81 mg, 0.17 mmol); IR, ν_{max} (film)/cm^{-1} 3129 (sp^{2}ArC-H), 2955 (sp^3 C-H), 1622 (ArC=C), 1325 (C-O), 1167 (C-F), 1125 (C-F), 1068 (C-O); δ_H(400 MHz; $CDCl_3$) 3.54 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 4.28 (1H, d, *J* 6.4 Hz, CC*H*C), 5.05 (1H, d, *J* 6.8 Hz, CC*H*N), 7.43 (2H, d, *J* 8.4 Hz, 2 $ArCF_3$-C*H*), 7.52 (NC*H*CI), 7.60 (2H, d, *J* 8.4 Hz, 2 $ArCF_3$-C*H*), 7.62 (1H, s, NC*H*CI); δ_C (100 MHz; $CDCl_3$) 34.9 (C*C*HC), 44.4 (*C*$(CO_2CH_3)_2$), 47.0 (C*C*HN), 53.0 (CO_2CH_3), 53.4 (CO_2CH_3), 57.1 (C-I), 125.6 (q, $^1J_{CF}$ 251 Hz, CF_3), 125.7 ($ArCF_3$-*C*H), 129.0 ($ArCF_3$-*C*H), 130.6 (Ar*C*), 134.8 (N*C*HCI), 136.0 (Ar*C*), 145.4 (N*C*HCI), 164.9 (2 C=O); δ_F(376 MHz; $CDCl_3$) 99.5 (C_6F_6), FTMS (ES) ($M+H^+$) calculated for $C_{16}H_{15}F_3IN_3O_4$ 482.999, found 483.001 (-2.194 ppm).

(±) Dimethyl 2-4-(5)-bromo-1H-imidazol-1-yl-3-4-trifluoromethyl phenyl cyclopropane-1,1-dicarboxylate (188$_h$)

Potassium carbonate (104 mg, 0.75 mmol, 2.5 eq) was added to a stirred solution of 4-bromoimidazole (90 mg, 0.60 mmol, 2.0 eq) and substituted cyclopropene **186**$_a$ (100 mg, 0.30 mmol) in acetonitrile (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 hours. Once complete the crude mixture was diluted with diethyl ether (15 mL) and the ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/iso-hexane 1:3) to afford the *title compound* as a yellow solid in 60% yield (80 mg, 0.18 mmol); mp 74.4°C; IR, ν_{max} (film)/cm^{-1} 2954 (sp^3 C-H), 1605 (ArC=C), 1734 (C=O), 1501 (C=N), 1265 (C-F); δ_H(400 MHz; $CDCl_3$) 3.55 (3H, s, CO_2CH_3), 3.70 (3H, s,

CO_2CH_3), 4.08 (1H, d, *J* 6.4 Hz, CC*H*C), 4.81 (1H, d, *J* 6.5 Hz, CC*H*N), 6.99 (1H, s, NC*H*CBr), 7.40 (2H, d, *J* 8.2 Hz, 2 $ArCF_3$-C*H*), 7.50 (1H, s, NC*H*N),7.62 (2H, d, *J* 8.2 Hz, 2 $ArCF_3$-C*H*); δ_C (100 MHz; $CDCl_3$) 34.6 (C*C*HC), 42.5 (C*C*HN), 44.3 (*C*$(CO_2CH_3)_2$), 53.2 (CO_2CH_3), 53.7 (CO_2CH_3), 118.7 (N*C*HCBr), 125.8 ($ArCF_3$-*C*H), 128.8 ($ArCF_3$-*C*H), 135.3 (Ar*C*), 137.1 (N*C*HN), 164.5 (C=O), 164.7 (C=O); δ_F(376 MHz; $CDCl_3$) -62.8 ($CFCl_3$), FTMS (ES) ($M+H^+$) calculated for $C_{17}H_{15}{}^{79}BrF_3N_2O_4$ 447.016, found 447.016 (-1.175 ppm). Not all the quaternary carbons have been accounted for due to a weak sample.

(±) Dimethyl 2-(4-nitrophenyl)-3-phenoxycyclopropane-1,1-dicarboxylate (191_a)

Potassium carbonate (149 mg, 1.08 mmol, 2.5 eq) was added to a solution of phenol (34 mg, 0.36 mmol) and substituted cyclopropene **186**$_a$ (50 mg, 0.18 mmol) in acetonitrile (3 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 hours. Once complete the crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a yellow solid in 74% yield (48 mg, 0.13 mmol); mp 98.7-100.2°C; IR, ν_{max} (film)/cm^{-1} 2954 (sp^3C-H), 1732 (C=O), 1600 (ArC=C), 1522 (C-NO_2), 1347 (C-NO_2), 1296 (C-O), 1099 (C-O); δ_H(400 MHz; $CDCl_3$) 3.55 (3H, s, CO_2CH_3), 3.61 (3H, s, CO_2CH_3), 3.91 (1H, d, *J* 5.6 Hz, CH), 5.04 (1H, d, *J* 5.6 Hz, C*H*O-Ar), 7.04 (3H, d, *J* 8.0 Hz, C_6H_5-O), 7.31 (2H, t, 8.4 Hz, C_6H_5-O), 7.46 (2H, d, *J* 8.4 Hz, 2 $ArNO_2$-C*H*), 8.19 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 36.0 (CH), 45.0 (*C*$(CO_2CH_3)_2$), 52.9 (CO_2CH_3), 53.2 (CO_2CH_3), 63.1 (*C*HO-Ar), 115.1 (Ar*C*H), 122.5 (Ar*C*H), 123.8 ($ArNO_2$-*C*H), 129.4 ($ArNO_2$-*C*H), 129.6 (Ar*C*H), 140.2 (ArC), 147.5 (Ar*C*), 157.0 (Ar*C*-O), 165.0 (C=O), 165.6 (C=0); FTMS (ES) ($M+Na^+$) calculated for $C_{19}H_{17}NO_7Na$ 394.089, found 394.089 (-1.018ppm).

(±) Dimethyl 2-(4-methoxyphenoxy)-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate (191$_b$)

Potassium carbonate (62 mg, 0.45 mmol, 2.5 eq) was added to a solution of 4-methoxyphenol (22 mg, 0.18 mmol) and the substituted cyclopropene **186**$_a$ (50 mg, 0.18 mmol) in acetonitrile (3 mL) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 21 hours. Once complete the crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/iso-hexane 1:3) to afford the *title compound* as a yellow oil in 57% yield (41 mg, 1.0 mmol); IR, ν_{max} (film)/cm^{-1} 1734 (C=O), 1525 (NO_2), 1348 (NO_2), 1200 (C-O); δ_H(400 MHz; $CDCl_3$) 3.54 (3H, s, CO_2CH_3), 3.64 (3H, s, CO_2CH_3), 3.78 (3H, s, OCH_3), 3.89 (1H, d, *J* 5.5 Hz, CH), 4.98 (1H, d, *J* 5.6 Hz, C*H*O-Ar), 6.84 (2H, d, *J* 9.0 Hz, 2 ArOMe-C*H*), 6.97 (2H, d, *J* 9.1 Hz, 2 ArOMe-C*H*), 7.44 (2H, d, *J* 8.4 Hz, 2 $ArNO_2$-C*H*), 8.18 (2H, d, *J* 8.7 Hz, 2 $ArNO_2$-C*H*); δ_C (100 MHz; $CDCl_3$) 36.0 (CH), 45.0 ($C(CO_2CH_3)_2$), 52.9 (CO_2CH_3), 53.1 (CO_2CH_3), 55.7 (OCH_3), 63.7 (*C*HO-Ar), 114.7 (ArOMe-*C*H), 116.0 (ArOMe-*C*H), 123.7 ($ArNO_2$-*C*H), 129.4 ($ArNO_2$-*C*H), 140.3 (Ar*C*), 147.5 (Ar*C*), 151.0 (Ar*C*), 155.0 (Ar*C*), 165.0 (C=O), 165.6 (C=O); FTMS (ES) ($M+Na^+$) calculated for $C_{20}H_{19}NO_8Na$ 424.099, found 424.099 (-1.887 ppm).

(±) Dimethyl 2-(4-nitrophenoxy)-3-(4-nitrophenyl) cyclopropane-1,1-dicarboxylate (191$_c$)

Potassium carbonate (124 mg, 0.90 mmol, 2.5 eq) was added to a solution of 4-nitrophenol (100 mg, 0.72 mmol, 2.0 eq) and substituted cyclopropene **186**$_a$ (100 mg, 0.36 mmol) in acetonitrile (5 mL) under a nitrogen atmosphere. The resulting mixture was stirred at room

temperature for 7 hours. Once complete the crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* to afford the *title compound* without further purification as yellow solid in 67% yield (100 mg, 0.24 mmol); mp 157.1°C; IR, ν_{max} (film)/cm^{-1} 1732 (C=O), 1520 (NO), 1346 (NO), 1270 (C-O); δ_H(400 MHz; $CDCl_3$) 3.58 (3H, s, CO_2CH_3), 3.61 (3H, s, CO_2CH_3), 3.95 (1H, d, *J* 5.5 Hz, C*H*), 5.07 (1H, d, *J* 5.5 Hz, C*H*O-Ar), 7.17 (2H, d, *J* 9.2 Hz, $OArNO_2$-C*H*), 7.46 (2H, d, *J* 8.5 Hz, $ArNO_2$-C*H*), 8.23 (4H, t, *J* 9.4 Hz, 4 $ArNO_2$-C*H*); δ_C (100 MHz; $CDCl_3$) 35.8 (CH), 44.9 ($C(CO_2CH_3)_2$), 53.2 (CO_2CH_3), 53.4 (CO_2CH_3), 63.2 (C*H*O-Ar), 115.4 (Ar*C*H), 123.9 (Ar*C*H), 125.9 (Ar*C*H), 129.4 (Ar*C*H), 139.3 (Ar*C*), 143.0 (Ar*C*), 147.7 (Ar*C*), 161.8 (Ar*C*), 164.5 (C=O), 165.2 (C=O); FTMS (ES); ($M+Na^+$) calculated for $C_{19}H_{16}N_2O_9Na$ 439.074, found 439.074 (+2.30 ppm).

(±) Dimethyl 2-(4-aminophenoxy)-3-(4-nitrophenyl) cyclopropane-1,1-dicarboxylate (191$_d$)

Potassium carbonate (100 mg, 0.73 mmol, 2.5 eq) was added to a solution of 4-aminophenol (63 mg, 0.58 mmol, 2.0 eq) and substituted cyclopropene **186**$_a$ (80 mg, 0.29 mmol) in acetonitrile (4 mL) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 7 hours. Once complete the crude solution was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a yellow/brown oil in 45% yield (45 mg, 0.12 mmol); IR, ν_{max} (film)/cm^{-1} 3380 (NH), 2925 (sp^3 C-H), 1730 (C=O), 1604 (ArC=C), 1511 (C-NO_2), 1347 (C-NO_2), 1297 (C-O), 1228 (C-O); δ_H(400 MHz; $CDCl_3$) 3.53 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 3.87 (1H, d, *J* 5.6 Hz, CC*H*C), 4.95 (1H, d, *J* 5.6 Hz, CC*H*O-Ar), 6.63 (2H, d, *J* 8.8 Hz, 2 $ArNH_2$-C*H*), 6.86 (2H, d, *J* 8.8 Hz, $ArNH_2$-C*H*), 7.43 (2H, d, *J* 8.4 Hz, 2 $ArNO_2$-C*H*), 8.17 (2H, d, *J* 8.4 Hz, 2 $ArNO_2$-C*H*); δ_C(100 MHz; $CDCl_3$) 36.0 (C*C*HC), 45.1 ($C(CO_2CH_3)_2$), 52.9 (CO_2CH_3), 53.2 (CO_2CH_3),

63.8 (C*C*HO), 116.2 (2 Ar*C*H), 123.9 (Ar*C*H), 129.5 (Ar*C*H), 132.7 (Ar*C*), 141.2 (Ar*C*), 147.5 (Ar*C*), 150.1 (Ar*C*), 165.1 (C=O), 165.5 (C=O); FTMS (ES) ($M+Na^+$) calculated for $C_{19}H_{18}N_2O_7Na$ 409.056, found 409.100 (-1.194 ppm).

(±) Dimethyl 2-(4-nitrophenyl)-3-(4-(trifluoromethyl phenoxy) cyclopropane-1,1-dicarboxylate (191_e)

Potassium carbonate (124 mg, 0.90 mmol, 2.5 eq) was added to a solution of 4-trifluoromethyl-phenol (83 mg, 0.51 mmol, 2.0 eq) and substituted cyclopropene **186**$_a$ (70 mg, 0.26 mmol) in acetonitrile (4 mL) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 3 hours. Once complete the crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/iso-hexane 1:5) to afford the *title compound* as a colourless oil in 83% yield (94 mg, 0.22 mmol); IR, ν_{max} (film)/cm^{-1} 2957(sp^3 C-H), 1732 (C=O), 1617 (C=C), 1523 (NO), 1349 (NO), 1329 (C-F), 1270 (C-O), 1112 (C-F); δ_H(400 MHz; $CDCl_3$) 3.57 (3H, s, CO_2CH_3), 3.61 (3H, s, CO_2CH_3), 3.92 (1H, d, *J* 5.5 Hz, CH), 5.06 (1H, d, *J* 5.6 Hz, C*H*O-Ar), 7.14 (2H, d, *J* 8.5 Hz, $OArCF_3$-C*H*), 7.46 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*), 7.58 (2H, d, *J* 8.5 Hz, $OArCF_3$-C*H*), 8.20 (2H, d, *J* 8.8 Hz, $ArNO_2$-C*H*); δ_C (100 MHz; $CDCl_3$) 35.8 (CH), 44.9 ($C(CO_2CH_3)_2$), 53.1 (CO_2CH_3), 53.3 (CO_2CH_3), 115.2 (Ar*C*H), 123.8 (Ar*C*H), 127.1-127.2 (Ar*C*H), 129.4 (Ar*C*H), 139.7 (Ar*C*), 147.6 (Ar*C*), 159.4 (Ar*C*), 164.7 (C=O), 165.4 (C=O); δ_F(376 MHz; $CDCl_3$) -61.8 ($CFCl_3$), FTMS (ES) ($M+Na^+$) calculated for $C_{20}H_{16}F_3NO_7Na$ 462.076, found 462.076 (-1.827 ppm). Not all quaternary carbons have been accounted for due to a weak sample.

(±) Dimethyl 2-(4-fluorophenoxy)-3-(4-nitrophenyl) cyclopropane-1,1-dicarboxylate (191$_e$)

Potassium carbonate (100 mg, 0.73 mmol, 2.5 eq) was added to a solution of 4-fluorophenol (65 mg, 0.58 mmol, 2.0 eq) and substituted cyclopropene **186**$_a$ (80 mg, 0.29 mmol) in acetonitrile (4 mL) under a nitrogen atmosphere. The resulting mixture was stirred at room temperature for 4 hours. Once complete the crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* to afford the *title compound* without further purification as a yellow solid in 90% yield (94 mg, 0.23 mmol); mp 88.6°C IR, ν_{max} (film)/cm^{-1} 2956 (sp^{3}C-H), 1732 (C=O), 1605 (ArC=C), 1525 (C-NO_2), 1349 (C-NO_2), 1298 (C-O), 1125 (C-F); δ_H(400 MHz; $CDCl_3$) 3.55 (3H, s, CO_2CH_3), 3.62 (3H, s, CO_2CH_3), 3.90 (1H, d, *J* 5.6 Hz, CC*H*C), 4.98 (1H, d, *J* 5.6 Hz, CC*H*O), 6.99 (4H, d, *J* 6.8 Hz, ArF-C*H*), 7.45 (2H, d, *J* 8.4 Hz, 2 ArNO_2-C*H*), 8.18 (2H, d, *J* 8.4 Hz, 2 ArNO_2-C*H*); δ_C(100 MHz; $CDCl_3$) 35.9 (C*C*HC), 45.0 (*C*(CO_2CH_3)$_2$), 53.1 (CO_2CH_3), 53.3 (CO_2CH_3), 63.5 (C*C*HO), 115.9-116.3 (4 Ar*C*H), 123.8 (2 Ar*C*H), 129.4 (2 Ar*C*H), 140.1 (Ar*C*), 147.5 (Ar*C*), 153.0 (Ar*C*), 159.4 (Ar*C*), 164.8 (C=O), 165.5 (C=O); δ_F(376 MHz; $CDCl_3$) 40.5 (1F, sept, *J* 4.7 Hz); FTMS (ES) (M+Na$^+$) calculated for $C_{19}H_{16}FNO_7Na$ 412.080, found 412.080 (-0.720 ppm).

(±) Dimethyl 2-phenoxy-3-(4-trifluoromethylphenyl) cyclopropane-1,1-dicarboxylate (192)

Potassium carbonate (138 mg, 0.83 mmol, 2.5 eq) was added to a stirred solution of phenol (56 mg, 0.66 mmol, 2.0 eq) and the substituted cyclopropene **186**$_a$ (100 mg, 0.33 mmol) in acetonitrile (5 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 80°C for 19 hours and once complete was cooled to room temperature. The crude mixture was

diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a clear oil in 60% yield (76 mg, 0.19 mmol); IR, ν_{max} (film)/cm^{-1} 2956 (sp^{3}C-H), 1732 (C=O), 1602 (ArC=C), 1326 (C-O), 1125 (C-F); δ_H(400 MHz; $CDCl_3$) 3.52 (3H, s, CO_2CH_3), 3.60 (3H, s, CO_2CH_3), 3.87 (1H, d, *J* 5.6 Hz, CC*H*Ar), 5.01 (1H, d, *J* 5.6 Hz, CC*H*O), 7.00-7.08 (3H, m, ArC*H*), 7.28-7.32 (2H, m, ArC*H*), 7.40 (2H, d, *J* 8.4 Hz, $ArCF_3$-C*H*), 7.58 (2H, d, *J* 8.4 Hz, $ArCF_3$-C*H*); δ_C (100 MHz; $CDCl_3$) 36.1 (C*C*HC), 44.7 (*C*$(CO_2CH_3)_2$), 52.8 (CO_2CH_3), 53.0 (CO_2CH_3), 63.0 (C*C*HO), 115.1 (Ar*C*H), 122.3 (Ar*C*H), 125.1 (Ar*C*H), 128.9 (2 Ar*C*H), 129.6 (2 Ar*C*H), 130.2 (Ar*C*), 136.8 (Ar*C*), 157.1 (ArC), 165.2 (C=O), 165.8 (C=O); δ_F(376 MHz; $CDCl_3$) 99.6 (C_6F_6), FTMS (ES) (M+Na$^+$) calculated for $C_{20}H_{17}F_3O_5Na$ 417.092, found 417.092 (-1.025 ppm). Due to a weak sample not all the quaternary carbons have been accounted for.

(±) Dimethyl phenoxy-3-phenylcyclopropane-1,1-dicarboxylate (193$_a$)

Potassium carbonate (149 mg, 1.08 mmol, 2.5 eq) was added to a solution of phenol (41 mg, 0.43 mmol) and substituted cyclopropene **1**$_d$ (100 mg, 0.43 mmol) in *N*,*N*-dimethylformamide (5 mL), under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 20 hours and once complete was cooled to room temperature. The crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a yellow oil in 45% yield (63 mg, 0.19 mmol); IR, ν_{max} (film)/cm^{-1} 3033(sp^2 ArC-H), 2953 (sp^3 C-H), 1732 (C=O), 1595 (ArC=C), 1435; δ_H(400 MHz; $CDCl_3$) 3.49 (3H, s, CO_2CH_3), 3.59 (3H, s, CO_2CH_3), 3.86 (1H, d, *J* 5.6 Hz, CC*H*Ar), 5.01 (1H, d, *J* 5.6 Hz, CC*H*O), 7.01 (1H, t, *J* 7.2 Hz, ArC*H*), 7.07 (2H, d, *J* 7.6 Hz, ArC*H*), 7.31-7.25 (7H, m, 7 ArC*H*); δ_C(100 MHz; $CDCl_3$) 36.7 (C*C*HC), 44.5 (*C*$(CO_2CH_3)_2$), 52.6 (CO_2CH_3), 52.9 (CO_2CH_3), 63.2 (C*C*HO), 115.2 (2 Ar*C*H), 122.1

(Ar*C*H), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.9 (Ar*C*H), 129.5 (Ar*C*H), 132.6 (Ar*C*), 157.3 (Ar*C*), 165.6 (C=O), 166.1 (C=O); FTMS (ES) ($M+H^+$) calculated for $C_{19}H_{19}O_5$ 327.1149, found 327.1217 (-2.953 ppm).

(±) Dimethyl 2-(4-methoxyphenoxy)-3-phenylcyclopropane-1,1-dicarboxylate (193_b)

Potassium carbonate (149 mg, 1.1 mmol, 2.5 eq) was added to a solution of 4-methoxyphenol (53 mg, 0.43 mmol) and substituted cyclopropene $\mathbf{1}_d$ (100 mg, 0.43 mmol) in *N*,*N*-dimethylformamide (5 mL), under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 24 hours and once complete was cooled to room temperature. The crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/iso-hexane 1:6) to afford the *title compound* as a white solid in 50% yield (77 mg, 0.21 mmol); mp 97.0°C; IR, ν_{max} (film)/cm^{-1} 1730 (C=O), 1642 (C-O); δ_H(400 MHz; $CDCl_3$) 3.48 (3H, s, CO_2CH_3), 3.62 (3H, s, CO_2CH_3), 3.77 (3H, s, OCH_3), 3.84 (1H, d, *J* 5.5 Hz, CC*H*Ar), 4.95 (1H, d, *J* 5.6 Hz, CC*H*O), 6.83 (2H, d, *J* 9.2 Hz, ArOMe-C*H*), 6.99 (2H, d, *J* 9.2 Hz, ArOMe-C*H*), 7.28-7.25 (5H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 35.8 (C*C*HAr), 43.5 ($C(CO_2CH_3)_2$), 51.5 (CO_2CH_3), 51.9 (CO_2CH_3), 54.6 (OCH_3), 62.8 (C*C*HO), 113.6 (Ar*C*H), 115.0 (Ar*C*H), 126.7 (Ar*C*H), 127.50-127.39 (2 Ar*C*H), 131.7 (Ar*C*), 150.3 (Ar*C*), 153.7 (Ar*C*), 164.6 (C=O), 165.1 (C=O); FTMS (ES) ($M+Na^+$) calculated for $C_{20}H_{20}O_6Na$ 379.115, found 379.115 (-0.31 ppm).

(±) Dimethyl 2-(4-nitrophenoxy)-3-phenylcyclopropane-1,1-dicarboxylate (193_c)

Potassium carbonate (138 mg, 0.83 mmol, 2.5 eq) was added to a stirred solution of 4-nitrophenol (120 mg, 0.86 mmol, 2.0 eq) and the substituted cyclopropene **1**$_d$ (100 mg, 0.43 mmol) in *N, N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 5 hours and once complete was cooled to room temperature. The crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/iso-hexane 1:6) to afford the *title compound* as yellow oil in 30% yield. (46 mg, 0.13 mmol); IR, ν_{max} (film)/cm^{-1} 2954 (sp^{3}C-H), 1735 (C=O), 1605 (ArC=C), 1524 (C-NO_2), 1345 (C-NO_2); δ_H(400 MHz; $CDCl_3$) 3.54 (3H, s, CO_2CH_3), 3.85 (3H, s, CO_2CH_3), 4.98 (1H, d, *J* 8.7 Hz, CC*H*Ar), 5.01 (1H, d, *J* 8.7 Hz, CC*H*O), 7.35 (2H, d, *J* 9.2 Hz, ArNO_2-C*H*), 7.36-7.38 (3H, m, ArC*H*), 7.48-7.50 (2H, m, Ar*C*H), 8.28 (2H, d, *J* 9.2 Hz, ArNO_2-C*H*); δ_C (100 MHz; $CDCl_3$) 36.6 (C*C*HAr), 44.5 (*C*(CO_2CH_3)$_2$), 52.5 (CO_2CH_3), 52.8 (CO_2CH_3), 63.4 (C*C*HO), 115.4 (Ar*C*H), 125.7 (Ar*C*H), 127.2 (Ar*C*H), 127.4 (Ar*C*H), 127.8 (Ar*C*H), 132.6 (Ar*C*), 139.3 (Ar*C*), 161.7 (Ar*C*), 165.3 (C=O), 166.0 (C=O); FTMS (ES) (M+Na$^+$) calculated for $C_{19}H_{17}NO_7$ 371.10, found 371.10 (-1.254 ppm).

(±) Dimethyl 2-(4-fluorophenoxy)-3-phenylcyclopropane-1,1-dicarboxylate (193$_d$)

Cesium carbonate (350 mg, 1.1 mmol, 2.5 eq) was added to a solution of 4-fluorophenol (73 mg, 0.65 mmol, 2.0 eq) and the substituted cyclopropene **1**$_d$ (100 mg, 0.43 mmol) in *N,N*-dimethylformamide (5 mL), under a nitrogen atmosphere. The resulting mixture was stirred at 90°C for 24 hours and once complete was cooled to room temperature. The crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/iso-hexane 1:3) to afford the *title compound* as a clear oil in 50% yield (74 mg, 0.22 mmol); IR, ν_{max} (film)/cm^{-1} 3031(sp^{2}Ar-CH), 2954(sp^{3}C-H), 1729 (C=O), 1602 (ArC=C), 1505 (ArC=C), 1100 (C-F); δ_H(400

MHz; $CDCl_3$) 3.49 (3H, s, CO_2CH_3), 3.60 (3H, s, CO_2CH_3), 3.84 (1H, d, *J* 5.5 Hz, CC*H*Ar), 4.95 (1H, d, *J* 5.5 Hz, CC*H*O), 7.00 (4H, dd, *J* 2.8, 7.4 Hz, 4 ArF-C*H*), 7.25-7.30 (5H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 36.7 (C*C*HAr), 44.5 ($C(CO_2CH_3)_2$), 52.6 (CO_2CH_3), 52.9 (CO_2CH_3), 63.6 (C*C*HO), 115.9 (Ar*C*H), 116.1 (Ar*C*H,), 116.2 (Ar*C*H), 116.3 (Ar*C*H), 127.9-128.6 (5 Ar*C*H), 132.5 (Ar*C*), 156.9 (Ar*C*), 159.3 (Ar*C*), 165.5 (C=O), 166.0 (C=O); δ_F(376 MHz; $CDCl_3$) -122.24 (1F, sept, *J* 4.7 Hz); FTMS (ES) ($M+Na^+$) calculated for $C_{19}H_{17}FO_5Na$ 367.095, found 367.096 (-2.017 ppm).

(±) Dimethyl 2-(4-aminophenoxy)-3-phenylcyclopropane-1,1-dicarboxylate (193$_e$)

Potassium carbonate (149 mg, 1.08 mmol, 2.5 eq) was added to a solution of 4-aminophenol (94 mg, 0.86 mmol, 2.0 eq) and substituted cyclopropene **1**$_d$ (100 mg, 0.43 mmol) in *N*,*N*-dimethylformamide (5 mL), under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 24 hours and once complete was cooled to room temperature. The crude mixture was diluted with diethyl ether (10 mL) and subsequently washed with aqueous potassium carbonate (2 x 20 mL), water (20 mL) and brine (20 mL) and dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as an orange/yellow viscous oil in 40% yield (57 mg, 0.17 mmol); IR, ν_{max} (film)/cm^{-1} 3371 (NH_2), 2953 (sp^3 C-H), 1729 (C=O), 1297 (C-O); δ_H(400 MHz; $CDCl_3$) 3.47 (3H, s, CO_2CH_3), 3.68 (3H, s, CO_2CH_3), 3.83 (1H, d, *J* 5.6 Hz, CC*H*C), 4.93 (1H, d, *J* 5.6 Hz, CC*H*O), 6.63 (2H, d, *J* 8.8 Hz, $ArNH_2$-C*H*), 6.89 (2H, d, *J* 8.8 Hz, $ArNH_2$-C*H*), 7.28-7.32 (5H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 36.8 (C*C*HC), 44.6 ($C(CO_2CH_3)_2$), 52.5 (CO_2CH_3), 52.7 (CO_2CH_3), 63.9 (C*C*HO), 116.0-116.3 (2 Ar*C*H), 127.0 (Ar*C*H), 127.7 (Ar*C*H), 128.5 (Ar*C*H), 132.8 (Ar*C*), 141.1 (Ar*C*), 150.3 (C-O), 165.7 (C=O), 166.2 (C=O); FTMS (ES), ($M+H^+$) calculated for $C_{19}H_{20}NO_5$ 342.126, found 342.133 (-2.656 ppm).

(±) 2-Methyl-5-phenyl-6-(3,6-dibromo-9*H*-carbazol-9-yl)-3-(4-tolyl)-oxazine-4,4-dimethyl ester (194)

$Yb(OTf)_3$ (6 mg, 0.009 mmol, 5 mol %) was added to a stirred solution of nitrone **175**$_f$ (53mg, 0.36 mmol, 2.0 eq) and di-substituted cyclopropane **182**$_d$ (100 mg, 0.18 mmol) in 1,2 dichloroethane (4 mL) under a nitrogen atmosphere. The resulting mixture was refluxed for 24 hours and once complete was cooled to room temperature, diluted with dichloromethane (10 mL) and filtered through a pad of celite and silica. The excess solvents were removed under reduced pressure and the crude residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:9) to afford the *title compound* as a white crystalline solid in 50% yield (64 mg, 0.90 mmol), mp: 216.4-217.8°C; IR, ν_{max} (film)/cm^1 2954 (sp^3 CH), 1734 (C=O), 1603 (ArC=C), 1586 (ArC=C), 1302 (C-O), 1282 (C-O), 1057 (C-Br); δ_H(400 MHz; $CDCl_3$) 2.38 (3H, s, C*H*$_3$N), 2.60 (3H, s, ArC*H*$_3$), 3.11 (3H, s, CO_2C*H*$_3$), 3.69 (3H, s, CO_2C*H*$_3$), 4.18 (1H, s, NC*H*Ar), 5.35 (1H, d, *J* 11.2 Hz, CC*H*Ar), 6.79 (1H, d, *J* 11.2 Hz, C*H*O), 6.92 (3H, t, *J* 3.6 Hz, ArC*H*), 7.13-7.15 (2H, m, ArC*H*), 7.27 (2H, d, *J* 4.0 Hz, ArC*H*), 7.52 (2H, d, *J* 7.6 Hz, ArC*H*), 7.56 (2H, d, *J* 8.4 Hz, ArC*H*), 7.84-7.91 (2H, m, ArC*H*), 7.98 (2H, s, ArC*H*); δ_C(100 MHz; $CDCl_3$) 21.1 (C*H*$_3$N), 43.2 (C*H*$_3$Ar), 44.3 (N*C*HAr), 51.7 (CO_2*C*H$_3$), 52.1 (CO_2*C*H$_3$), 65.1 (*C*(CO_2CH_3)$_2$), 75.4 (C*C*HAr), 85.1 (*C*HO), 113.1 (Ar*C*), 122.9 (Ar*C*H), 127.4 (Ar*C*H), 127.5 (Ar*C*H), 129.0 (4 Ar*C*H), 129.1 (2 Ar*C*H), 129.7 (3 Ar*C*H), 129.9 (Ar*C*H), 134.3 (Ar*C*), 138.5 (Ar*C*), 168.3 (C=O), 170.5 (C=O); FTMS (ES), ($M+H^+$) calculated for $C_{34}H_{30}{}^{79}Br_2N_2O_5$ 704.05, found 704.15 (+2.345 ppm). Not all the quaternary carbons have been accounted for due to a weak sample.

Methyl 2-phenyl-1-trifluoromethyl cyclopropene methyl ester (197)[82]

A solution of methyl 2-diazo-3,3,3-trifluoropropanoate (1.0 g, 5.95 mmol) in anhydrous dichloromethane (45 mL) was added via a syringe (1.5 mL/hr) to a stirred solution of phenylacetylene (6.53 mL, 59.5 mmol) and a catalytic amount of rhodium acetate dimer in anhydrous dichloromethane (60 mL) under a nitrogen atmosphere. Once addition was complete the reaction mixture was stirred for an additional six hours. The mixture was filtered through a pad of celite and silica and the filtrate was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (EtOAc/ iso-hexane 1:8) to afford the *title compound* as a yellow/brown oil in 45% yield (648 mg, 2.68 mmol). R_f (EtOAc/ iso-hexane 1:8) 0.27; IR, ν_{max} (film)/cm^{-1} 3154 (sp^2 ArC-H), 3029 (sp^2 ArC-H), 2956 (sp^3 C-H), 1736 (C=O), 1598 (ArC=C), 1489 (ArC=C), 1279 (C-F), 1147 (C-F); δ_H(400 MHz; $CDCl_3$) 3.75 (3H, s, CO_2CH_3), 6.82 (1H, s, C=C*H*), 7.47 (3H, bs, ArC*H*), 7.58-7.61 (2H, m, ArC*H*); δ_C (100 MHz; $CDCl_3$) 52.6 (CO_2CH_3), 61.4 ($F_3CCCO_2CH_3$) 93.0 (C=*C*H), 129.1 (Ar*C*H), 130.3 (Ar*C*H), 131.1 (Ar*C*H), 169.7 (C=O); δ_F(376 MHz; $CDCl_3$) -64.7 ($CFCl_3$); TOFMS (ES) ($M+H^+$) calculated for $C_{12}H_{10}F_3O_2$ 243.063, found 243.063 (-1.60 ppm). The data is in agreement with the literature values stated.

(±) Methyl 2-(4-bromo-1*H*-pyrazol-1-yl)-3-phenyl trifluoromethyl cyclopropane methyl ester ($198_{a/b}$)

Potassium carbonate (138 mg, 1.0 mmol, 2.5 eq) was added to a stirred solution of 4-bromopyrazole (90 mg, 0.62 mmol, 1.5 eq) and the substituted cyclopropene **182_c** (100 mg, 0.41 mmol) in *N*, *N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 90°C for 24 hours and once complete was cooled to room temperature and diluted with diethyl ether (20 mL). The ethereal solution was washed with

water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:5) to afford the *title compound* as a separable mixture of isomers in a combined 65% yield (103 mg, 0.27 mmol) with a 1:1.1 d.r., (i) first eluted isomer **A** as an orange solid; mp 107.5°C; IR, ν_{max} (film)/cm^{-1} 3032 (sp^2 ArC-H), 2954 (sp^3 C-H), 1740 (C=O), 1501 (ArC=C), 1438 (C=N), 1361 (C-F), 1317 (C-F), 1278 (C-O), 1154 (C-F), 1099 (C-O), 697 (C-Br); δ_H(400 MHz; $CDCl_3$) 3.71 (3H, s, CO_2CH_3), 4.32 (1H, d, *J* 7.0 Hz, CC*H*C), 4.76 (1H, d, *J* 7.0 Hz, CC*H*N), 7.36-7.38 (5H, m, ArC*H*), 7.52 (1H, s, NC*H*CBrN), 7.59 (1H, s, NC*H*NCBr); δ_C (100 MHz; $CDCl_3$) 35.9 (C*C*HC), 45.8 (CC*H*N), 53.6 (CO_2CH_3), 94.1 (C-Br), 128.4-128.9 (3 Ar*C*H), 130.4 (N*C*HCBrCHN), 130.9 (Ar*C*), 141.4 (NCHCBr*C*HN), 163.9 (C=O); δ_F(376 MHz; $CDCl_3$) -61.04 ($CFCl_3$); TOFMS (EI) ($M+H^+$) calculated for $C_{15}H_{13}{}^{79,81}BrF_3N_2O_2$ 389.010 and 391.009, found 389.010 and 391.009 (-1.50 ppm), (ii) second eluted isomer **B** as a yellow oil; IR, ν_{max} (film)/cm^{-1} 3133 (sp^2 ArC-H), 3032 (sp^2 C-H), 2956 (sp^3 C-H), 1741 (C=O), 1502 (ArC=C), 1364 (C-F), 1307 (C-F), 1152 (C-F), 1096 (C-O), 697 (C-Br); δ_H(400 MHz; $CDCl_3$) 3.57 (3H, s, CO_2CH_3), 4.05 (1H, d, *J* 6.90 Hz, CC*H*C), 5.08 (1H, dd, *J* 1.8, 6.90 Hz, CC*H*N), 7.30-7.38 (5H, m, ArC*H*), 7.53 (1H, s, NC*H*CBrN), 7.60 (1H, s, NC*H*NCBr); δ_C (100 MHz; $CDCl_3$) 34.3 (C*C*HC), 47.2 (CC*H*N), 53.0 (CO_2CH_3), 94.7 (C-Br), 128.4-128.7 (3 Ar*C*H), 130.4 (N*C*HCBrCHN), 131.0 (Ar*C*), 141.1 (NCHCBr*C*HN), 163.7 (C=O); δ_F(376 MHz; $CDCl_3$) -62.87 ($CFCl_3$).

(±) Methyl 2-phenyl-1-(trifluoromethyl)-3-(3-(trifluoromethyl)-1H-pyrazol-1-yl cyclopropane carboxylate ($199_{a/b}$)

Potassium carbonate (138 mg, 1.0 mmol, 2.5 eq) was added to a stirred solution of 4-trifluoromethyl-pyrazole (84 mg, 0.62 mmol, 1.5 eq) and the substituted cyclopropene **182**$_j$ (100 mg, 0.41 mmol) in *N*, *N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 50°C for 24 hours and once complete was cooled to room temperature and diluted with diethyl ether (20 mL). The ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess

solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/*iso*-hexane 1:6) to afford the *title compound* as a separable mixture of isomers in a combined 67% yield (103 mg, 0.27 mmol) in a 1:3 d.r., (i) first eluted isomer **A** as a yellow solid; mp 108.3-110.6°C; IR, ν_{max} (film)/cm^{-1} 1742 (C=O), 1488 (C=N), 1363 (C-F), 1310 (C-F); δ_H(400 MHz; $CDCl_3$) 3.68 (3H, s, CO_2CH_3), 4.36 (1H, d, *J* 6.9 Hz, CC*H*C), 4.84 (1H, d, *J* 7.0 Hz, CC*H*N), 6.56 (1H, d, *J* 2.4 Hz, NCF_3CHCHN), 7.39-7.37 (5H, m, ArC*H*), 7.62 (1H, d, *J* 1.5 Hz, NCF_3CHCHN); δ_C (100 MHz; $CDCl_3$) 35.8 (C*C*HC), 45.7 (C*C*HN), 53.5 (CO_2CH_3), 105.1 (NCF_3CHCHN), 119.5 (CF_3), 121.5 (q, $^1J_{CF}$ 274 Hz, CF_3), 128.5-128.9 (3 Ar*C*H), 130.6 (Ar*C*), 131.8 (NCF_3CHCHN), 143.6 (N*C*CF_3), 163.9 (C=O): δ_F(376 MHz; $CDCl_3$) -61.1 (CF_3), -62.25 ($NCCF_3$,) ($CFCl_3$), ii) second eluted isomer **B** as a yellow oil; δ_H(400 MHz; $CDCl_3$) 3.58 (3H, s, CO_2CH_3), 4.11 (1H, d, *J* 6.9 Hz, CC*H*C), 5.16 (1H, d, *J* 6.9 Hz, CC*H*N), 6.61 (1H, d, *J* 2.5 Hz, NCF_3CHCHN), 7.34-7.36 (5H, m, ArC*H*), 7.63 (1H, d, *J* 1.4 Hz, NCF_3CHCHN); δ_C (100 MHz; $CDCl_3$) 34.3 (C*C*HC), 47.1 (C*C*HN), 53.1 (CO_2CH_3), 105.7 (NCF_3CHCHN), 128.2-129.0 (3 Ar*C*H), 130.8 (Ar*C*), 131.8 (NCF_3CHCHN), δ_F(376 MHz; $CDCl_3$) -63.0 (CF_3), -62.25 ($NCCF_3$) ($CFCl_3$); TOFMS (EI) ($M+Na^+$) calculated for $C_{16}H_{12}F_6N_2O_2Na$ 401.069, found 401.069 (-1.443 ppm). Not all quaternary carbons have been accounted for due to a high signal to noise ratio.

(±) Methyl 2-phenyl-3-(1H-pyrazol-1-yl)-1-trifluoromethyl cyclopropane carboxylate ($200_{a/b}$)

Potassium carbonate (141 mg, 1.0 mmol, 2.5 eq) was added to a stirred solution of pyrazole (42 mg, 0.62 mmol, 1.5 eq) and the substituted cyclopropene $\mathbf{182}_e$ (100 mg, 0.41 mmol) in *N, N*-dimethylformamide (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 50°C for 24 hours and once complete was cooled to room temperature and diluted with diethyl ether (20 mL). The ethereal solution was washed with water (20 mL), brine (20 mL) and dried over sodium sulphate. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:8) to afford the *title compound* as an

inseparable mixture of isomers as a yellow oil in a combined 50% yield (64mg, 0.21 mmol) in a d.r. of 1:2 (**A**:**B**); IR, ν_{max} (film)/cm^{-1} 3031 (sp^2 ArC-H), 2957 (sp^3C-H), 1741 (C=O), 1607 (ArC=C), 1520 (C=N), 1365 (C-F), 1151 (C-F), 1099 (C-O), isomer **A** δ_H(400 MHz; $CDCl_3$) 3.67 (CO_2CH_3), 4.38 (1H, d, *J* 7.2 Hz, CC*H*C), 4.81 (1H, d, *J* 7.2 Hz, CC*H*N), 6.31 (1H, t, *J* 2.4 Hz, NCHC*H*CHN), 7.34-7.40 (5H, m, ArC*H*), 7.56 (2H, d, *J* 2.0 Hz, NC*H*CHC*H*N); δ_C (100 MHz; $CDCl_3$) 35.9 (C*C*HC), 39.7 ($F_3CCCO_2CH_3$), 45.6 (C*C*HN), 53.4 (CO_2CH_3), 106.4 (NCH*C*HCHN), 128.2-128.7 (3 ArC*H*), 130.2 (NCHCH*C*HN), 131.4 (Ar*C*), 140.9 (N*C*HCHCHN), 164.2 (C=O) , isomer **B**, δ_H(400 MHz; $CDCl_3$) 3.56 (CO_2CH_3), 4.08 (1H, d, *J* 7.2 Hz, CC*H*C), 5.13 (1H, d, *J* 7.2 Hz, CC*H*N), 6.35 (1H, t, *J* 2.4 Hz, NCHC*H*CHN), 7.32-7.34 (5H, m, ArC*H*), 7.58 (2H, d, *J* 2.0 Hz, (NC*H*CHC*H*N); δ_C (100 MHz; $CDCl_3$) 34.6 (C*C*HC) 39.4 ($F_3CCCO_2CH_3$), 47.1 (C*C*HN), 52.9 (CO_2CH_3), 107.1 (NCH*C*HCHN),128.2-128.7 (3 Ar*C*H), 130.2 (NCHCH*C*HN), 131.3 (Ar*C*), 140.5 (N*C*HCHCHN), 164.0 (C=O); FTMS (ES) ($M+H^+$) calculated for $C_{15}H_{14}F_3N_2O_2$ 311.090, found 311.098 (-1.605 ppm).

2-Nitrocyclopropylbenzene (201)[85]

A solution of trimethylsulfoxonium iodide (8.8g, 40 mmol, 1.2 eq) in DMSO (156 mL) was added dropwise *via* a canula to a stirred suspension of potassium *t*-butoxide (4.49 g, 40 mmol, 1.2 eq) in DMSO (31 mL) under a nitrogen atmosphere. Once the reaction had been stirred for additional two hours, the solution was cooled to 10°C and a solution of the *trans* nitro-styrene (5g, 34.0 mmol) in DMSO (15 mL) was added dropwise. The reaction mixture was heated to 50°C for four hours and stirred for a further twelve hours at room temperature. Once the reaction was complete, the solution was poured onto ice, extracted with diethyl ether (3 x 100 mL), washed with water (3 x 50 mL) and dried over $MgSO_4$. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:15) to afford the *title compound* as a light yellow oil in 18% yield (1.0 g, 6.1 mmol); IR ν_{max} (film)/cm^{-1} 1603 (ArC=C), 1541, (N-O), 1498 (ArC=C), 1362 (N-O); δ_H(400 MHz; $CDCl_3$) 1.67 (1H, q, *J* 7.6 Hz, CH_2), 2.24 (1H, ddd, *J* 4.0, 6.4, 10.4 Hz, CH_2), 3.14 (1H, ddd, *J* 2.8, 8.0, 10.8 Hz, C*H*NO_2), 4.42 (1H, ddd, *J* 2.8, 3.6, 6.8 Hz, C*H*), 7.12 (2H, d, *J* 8.4 Hz, ArC*H*), 7.27-7.34

(3H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 17.2-17.8 (*C*H_2), 28.4 (*C*H), 60.6 (*C*H), 125.6 (Ar*C*H), 127.5 (Ar*C*H), 129.1 (Ar*C*H), 135.3 (ArC). The above data is in agreement with the literature values stated.

1-Fluorophenyl,2-nitrocyclopropane (207)[85]

A solution of trimethylsulfoxonium iodide (3.16g, 14 mmol, 1.2 eq) in DMSO (35 mL) was added dropwise *via* a canula to a stirred suspension of potassium *t*-butoxide (1.57g, 14 mmol, 1.2 eq) in DMSO (11 mL) under a nitrogen atmosphere. Once the reaction had been stirred for additional two hours, the solution was cooled to 10°C and a solution of the *trans* 4-fluorophenyl-nitro-styrene (2g, 12 mmol), in DMSO (5 mL) was added dropwise. The reaction mixture was heated at 50°C for four hours and stirred for a further twelve hours at room temperature. The resulting mixture was poured onto ice, extracted with diethyl ether (3 x 100 mL), washed with water (3 x 50 mL) and dried over $MgSO_4$. The excess solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (EtOAc/Petrol 1:15) to afford the *title compound* as a light yellow oil in 42% yield (0.91 g, 5.0 mmol); IR ν_{max} (film)/cm^{-1} 1605 (ArC=C), 1543 (N-O), 1496 (ArC=C), 1363 (N-O), 1156 (C-F); δ_H(400 MHz; $CDCl_3$) 1.65 (1H, q, *J* 6.4 Hz, C*H*$_2$), 2.24 (1H, ddd, *J* 4.0, 6.4, 10.4 Hz, C*H*$_2$), 3.13 (1H, ddd, *J* 3.2, 8.0, 10.8 Hz, C*H*), 4.37 (1H, ddd, *J* 3.2, 4.0, 7.2 Hz, C*H*), 6.99-7.05 (2H, m, C*H*, ArF), 7.08-7.16 (2H, m, C*H*, ArF); δ_C(100 MHz; $CDCl_3$) 18.7 (*C*H_2), 28.6 (*C*H), 61.4 (*C*H), 115.7 (Ar*C*H), 115.9 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 131.9 (Ar*C*), 161.0 (Ar*C*-F). The above data is in agreement with the literature values stated.

(±) Dimethyl 2-nitro-3-phenylcyclopropane-1,1-dimethyl ester (213)[89]

Dimethyl bromomalonate (1.71 mL, 2.70g, 13 mmol) was added to a stirred solution of *trans* nitro styrene (2.0g, 13 mmol) in *N*,*N*-dimethylformamide (52 mL) at room temperature. The resulting mixture was stirred for 5 minutes prior to the addition of

triethylamine (1.09 mL 1.52g, 15 mmol). The resulting mixture was left to stir at room temperature overnight. On completion the reaction mixture was diluted with EtOAc (50 mL) and subsequently washed with 1M HCl and water, dried over anhydrous magnesium sulphate. The excess solvents were concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (EtOAc/Petrol 1:12) to afford the *title compound* as a yellow oil in 92% yield. (2.30g, 11.3 mmol), IR ν_{max} (film)/cm^{-1} 2954 (sp^3CH), 1731 (C=O), 1603 (ArC=C), 1542 (NO_2), 1347 (NO_2); δ_H(400 MHz; $CDCl_3$) 3.57 (3H, s, CO_2CH_3), 3.87 (3H, s, CO_2CH_3), 4.22 (1H, d, *J* 6.0 Hz, C*H*-Ar), 5.42 (1H, d, *J* 6.0 Hz, $CHNO_2$), 7.27-7.30 (2H, m, ArC*H*), 7.33-7.36 (3H, m, ArC*H*); δ_C(100 MHz; $CDCl_3$) 37.7 (*C*H-Ar), 46.1 ($C(CO_2CH_3)_2$), 53.4 (CO_2CH_3), 53.9 (CO_2CH_3), 66.2 ($CHNO_2$), 128.2 (2 ArC*H*), 128.6 (Ar*C*H), 128.8 (2 Ar*C*H), 130.1 (Ar*C*), 163.6 (C=O), 163.8 (C=O). The above data is in agreement with the literature values stated.

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6. Appendices

6.1. Appendix I: X-Ray crystallographic data for 176_a

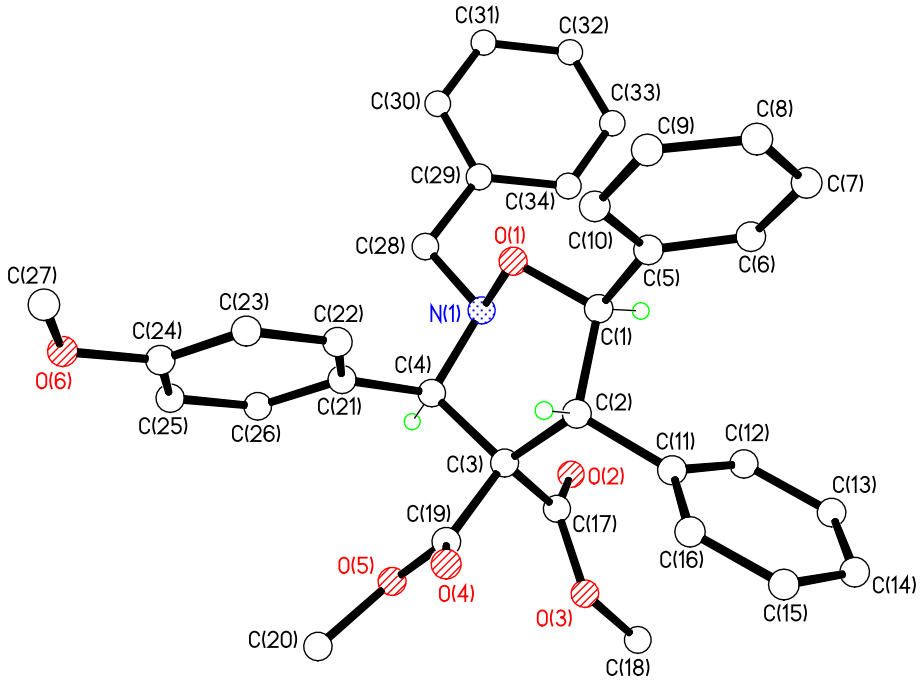


Table 1. Crystal data and structure refinement for sdrc22.

Identification code	sdrc22	
Chemical formula	$C_{34}H_{33}NO_6$	
Formula weight	551.61	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	a = 15.4723(6) Å	□ = 90°
	b = 10.2737(4) Å	□ = 109.7472(6)°
	c = 18.7483(8) Å	□ = 90°
Cell volume	2804.9(2) $Å^3$	

Z	4
Calculated density	1.306 g/cm^3
Absorption coefficient □	0.089 mm^{-1}
F(000)	1168
Crystal colour and size	colourless, 0.69 × 0.56 × 0.18 mm^3
Reflections for cell refinement	7656 (□ range 2.29 to 30.76°)
Data collection method	Bruker APEX 2 CCD diffractometer
	□ rotation with narrow frames
□ range for data collection	2.26 to 30.92°
Index ranges	h −22 to 22, k −14 to 14, l −26 to 26
Completeness to □ = 29.00°	99.9 %
Intensity decay	0%
Reflections collected	32518
Independent reflections	8731 (R_{int} = 0.0324)
Reflections with F^2>2□	6475
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.941 and 0.984
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0655, 0.6338
Data / restraints / parameters	8731 / 0 / 372
Final R indices [F^2>2□]	R1 = 0.0479, wR2 = 0.1251
R indices (all data)	R1 = 0.0665, wR2 = 0.1365
Goodness-of-fit on F^2	1.064

Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.395 and –0.317 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sdrc22. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.11953(6)	0.16271(10)	0.09190(6)	0.0218(2)
O(1)	0.19921(5)	0.22122(8)	0.14850(5)	0.02154(17)
C(1)	0.24979(8)	0.28235(11)	0.10661(6)	0.0203(2)
C(2)	0.28898(7)	0.17888(11)	0.06541(6)	0.0205(2)
C(3)	0.21753(7)	0.07063(11)	0.02534(6)	0.0203(2)
C(4)	0.14982(7)	0.03853(11)	0.06946(6)	0.0208(2)
C(5)	0.32642(8)	0.36006(12)	0.16173(7)	0.0240(2)
C(6)	0.34769(12)	0.48223(16)	0.14139(9)	0.0431(4)
C(7)	0.42068(14)	0.55310(19)	0.18919(11)	0.0546(5)
C(8)	0.47311(11)	0.50230(19)	0.25775(11)	0.0509(5)
C(9)	0.45152(12)	0.38265(18)	0.27987(11)	0.0540(5)
C(10)	0.37814(11)	0.31132(15)	0.23236(9)	0.0410(4)
C(11)	0.33356(8)	0.24547(13)	0.01398(7)	0.0244(2)
C(12)	0.28994(9)	0.34629(13)	–0.03480(7)	0.0295(3)
C(13)	0.33233(11)	0.40920(16)	–0.07951(9)	0.0393(3)
C(14)	0.42001(12)	0.3725(2)	–0.07567(10)	0.0508(4)
C(15)	0.46360(11)	0.2715(2)	–0.02898(10)	0.0505(4)

C(16)	0.42112(9)	0.20795(16)	0.01597(8)	0.0356(3)
C(17)	0.16278(8)	0.11052(12)	–0.05658(7)	0.0227(2)
O(2)	0.08955(6)	0.16441(10)	–0.07681(5)	0.0351(2)
O(3)	0.20973(6)	0.07910(9)	–0.10221(5)	0.0279(2)
C(18)	0.16995(11)	0.11804(15)	–0.18106(7)	0.0371(3)
C(19)	0.26718(8)	–0.05733(12)	0.02176(6)	0.0225(2)
O(4)	0.34804(6)	–0.07770(9)	0.04980(5)	0.0302(2)
O(5)	0.20452(6)	–0.14579(8)	–0.01564(5)	0.02563(19)
C(20)	0.23537(10)	–0.27861(13)	–0.01299(10)	0.0381(3)
C(21)	0.18603(8)	–0.06364(11)	0.13139(7)	0.0221(2)
C(22)	0.26659(8)	–0.04916(12)	0.19343(7)	0.0251(2)
C(23)	0.29860(9)	–0.14608(12)	0.24780(7)	0.0265(2)
C(24)	0.24954(9)	–0.26111(13)	0.24079(7)	0.0280(3)
C(25)	0.16936(9)	–0.27850(13)	0.17888(8)	0.0312(3)
C(26)	0.13821(9)	–0.18140(12)	0.12555(7)	0.0269(2)
O(6)	0.27328(7)	–0.36164(10)	0.29126(6)	0.0404(3)
C(27)	0.35289(12)	–0.34522(16)	0.35646(8)	0.0424(4)
C(28)	0.05160(8)	0.14764(12)	0.12960(7)	0.0245(2)
C(29)	0.00803(8)	0.27565(12)	0.13811(7)	0.0220(2)
C(30)	–0.04056(9)	0.28427(13)	0.18837(7)	0.0269(2)
C(31)	–0.08134(9)	0.40054(14)	0.19773(8)	0.0313(3)
C(32)	–0.07396(9)	0.50987(13)	0.15683(8)	0.0310(3)

C(33)	–0.02713(9)	0.50203(13)	0.10566(8)	0.0303(3)
C(34)	0.01365(8)	0.38574(13)	0.09637(7)	0.0268(2)

Table 3. Bond lengths [Å] and angles [°] for sdrc22.

N(1)–O(1)	1.4571(12)	N(1)–C(28)	1.4595(15)
N(1)–C(4)	1.4688(15)	O(1)–C(1)	1.4279(13)
C(1)–C(5)	1.5110(16)	C(1)–C(2)	1.5528(16)
C(2)–C(11)	1.5241(16)	C(2)–C(3)	1.5691(16)
C(3)–C(19)	1.5355(16)	C(3)–C(17)	1.5379(16)
C(3)–C(4)	1.5734(16)	C(4)–C(21)	1.5246(16)
C(5)–C(6)	1.3834(19)	C(5)–C(10)	1.389(2)
C(6)–C(7)	1.387(2)	C(7)–C(8)	1.370(3)
C(8)–C(9)	1.374(3)	C(9)–C(10)	1.392(2)
C(11)–C(12)	1.3957(18)	C(11)–C(16)	1.3969(18)
C(12)–C(13)	1.3864(19)	C(13)–C(14)	1.386(2)
C(14)–C(15)	1.378(3)	C(15)–C(16)	1.394(2)
C(17)–O(2)	1.2016(14)	C(17)–O(3)	1.3355(14)
O(3)–C(18)	1.4525(15)	C(19)–O(4)	1.2004(14)
C(19)–O(5)	1.3410(14)	O(5)–C(20)	1.4409(15)
C(21)–C(22)	1.3961(16)	C(21)–C(26)	1.4029(17)
C(22)–C(23)	1.3910(17)	C(23)–C(24)	1.3866(18)
C(24)–O(6)	1.3646(16)	C(24)–C(25)	1.3946(19)

C(25)–C(26)	1.3789(19)	O(6)–C(27)	1.4220(19)
C(28)–C(29)	1.5106(16)	C(29)–C(30)	1.3927(16)
C(29)–C(34)	1.3947(17)	C(30)–C(31)	1.3895(18)
C(31)–C(32)	1.386(2)	C(32)–C(33)	1.3862(19)
C(33)–C(34)	1.3893(18)		

O(1)–N(1)–C(28)	105.16(9)	O(1)–N(1)–C(4)	107.08(8)
C(28)–N(1)–C(4)	113.47(9)	C(1)–O(1)–N(1)	105.48(8)
O(1)–C(1)–C(5)	107.79(9)	O(1)–C(1)–C(2)	110.57(9)
C(5)–C(1)–C(2)	110.72(9)	C(11)–C(2)–C(1)	110.10(10)
C(11)–C(2)–C(3)	114.31(9)	C(1)–C(2)–C(3)	113.13(9)
C(19)–C(3)–C(17)	107.42(9)	C(19)–C(3)–C(2)	110.22(9)
C(17)–C(3)–C(2)	110.51(9)	C(19)–C(3)–C(4)	105.98(9)
C(17)–C(3)–C(4)	109.94(9)	C(2)–C(3)–C(4)	112.55(9)
N(1)–C(4)–C(21)	116.78(9)	N(1)–C(4)–C(3)	107.58(9)
C(21)–C(4)–C(3)	113.96(9)	C(6)–C(5)–C(10)	118.41(13)
C(6)–C(5)–C(1)	119.72(12)	C(10)–C(5)–C(1)	121.86(12)
C(5)–C(6)–C(7)	121.05(16)	C(8)–C(7)–C(6)	120.04(16)
C(7)–C(8)–C(9)	119.78(14)	C(8)–C(9)–C(10)	120.45(17)
C(5)–C(10)–C(9)	120.21(16)	C(12)–C(11)–C(16)	118.18(12)
C(12)–C(11)–C(2)	121.72(11)	C(16)–C(11)–C(2)	120.09(12)
C(13)–C(12)–C(11)	121.29(13)	C(14)–C(13)–C(12)	119.76(15)
C(15)–C(14)–C(13)	119.88(14)	C(14)–C(15)–C(16)	120.49(15)

C(15)–C(16)–C(11)	120.38(15)	O(2)–C(17)–O(3)	124.62(11)
O(2)–C(17)–C(3)	125.48(11)	O(3)–C(17)–C(3)	109.88(9)
C(17)–O(3)–C(18)	116.76(10)	O(4)–C(19)–O(5)	124.97(11)
O(4)–C(19)–C(3)	126.37(11)	O(5)–C(19)–C(3)	108.61(9)
C(19)–O(5)–C(20)	116.83(10)	C(22)–C(21)–C(26)	117.12(11)
C(22)–C(21)–C(4)	123.78(10)	C(26)–C(21)–C(4)	119.07(10)
C(23)–C(22)–C(21)	122.06(11)	C(24)–C(23)–C(22)	119.51(12)
O(6)–C(24)–C(23)	124.67(12)	O(6)–C(24)–C(25)	115.82(12)
C(23)–C(24)–C(25)	119.51(12)	C(26)–C(25)–C(24)	120.36(12)
C(25)–C(26)–C(21)	121.42(12)	C(24)–O(6)–C(27)	117.28(11)
N(1)–C(28)–C(29)	112.26(10)	C(30)–C(29)–C(34)	118.57(11)
C(30)–C(29)–C(28)	119.28(11)	C(34)–C(29)–C(28)	122.15(11)
C(31)–C(30)–C(29)	120.81(12)	C(32)–C(31)–C(30)	120.05(12)
C(33)–C(32)–C(31)	119.72(12)	C(32)–C(33)–C(34)	120.16(12)
C(33)–C(34)–C(29)	120.67(11)		

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sdrc22.

	x	y	z	U
H(1)	0.2083	0.3426	0.0683	0.024
H(2)	0.3397	0.1338	0.1057	0.025
H(4)	0.0941	–0.0007	0.0313	0.025
H(6)	0.3118	0.5182	0.0939	0.052
H(7)	0.4343	0.6369	0.1744	0.066

H(8)	0.5242	0.5496	0.2899	0.061
H(9)	0.4869	0.3484	0.3279	0.065
H(10)	0.3634	0.2290	0.2483	0.049
H(12)	0.2300	0.3723	–0.0374	0.035
H(13)	0.3014	0.4772	–0.1127	0.047
H(14)	0.4500	0.4169	–0.1052	0.061
H(15)	0.5230	0.2450	–0.0274	0.061
H(16)	0.4519	0.1387	0.0481	0.043
H(18A)	0.1084	0.0803	–0.2029	0.056
H(18B)	0.2089	0.0869	–0.2093	0.056
H(18C)	0.1657	0.2132	–0.1842	0.056
H(20A)	0.3026	–0.2806	0.0041	0.057
H(20B)	0.2106	–0.3172	–0.0637	0.057
H(20C)	0.2139	–0.3284	0.0224	0.057
H(22)	0.3006	0.0294	0.1987	0.030
H(23)	0.3537	–0.1336	0.2894	0.032
H(25)	0.1360	–0.3577	0.1734	0.037
H(26)	0.0832	–0.1945	0.0840	0.032
H(27A)	0.4067	–0.3332	0.3407	0.064
H(27B)	0.3617	–0.4226	0.3887	0.064
H(27C)	0.3452	–0.2686	0.3848	0.064
H(28A)	0.0816	0.1090	0.1804	0.029

H(28B)	0.0031	0.0868	0.0999	0.029
H(30)	–0.0459	0.2098	0.2166	0.032
H(31)	–0.1143	0.4051	0.2322	0.038
H(32)	–0.1009	0.5898	0.1638	0.037
H(33)	–0.0229	0.5764	0.0769	0.036
H(34)	0.0457	0.3812	0.0612	0.032

Table 5. Torsion angles [°] for sdrc22.

C(28)–N(1)–O(1)–C(1)	−157.82(9)	C(4)–N(1)–O(1)–C(1)	81.19(10)
N(1)–O(1)–C(1)–C(5)	172.50(8)	N(1)–O(1)–C(1)–C(2)	−66.35(10)
O(1)–C(1)–C(2)–C(11)	173.70(9)	C(5)–C(1)–C(2)–C(11)	−66.91(12)
O(1)–C(1)–C(2)–C(3)	44.42(12)	C(5)–C(1)–C(2)–C(3)	163.82(10)
C(11)–C(2)–C(3)–C(19)	81.55(12)	C(1)–C(2)–C(3)–C(19)	−151.36(9)
C(11)–C(2)–C(3)–C(17)	−37.03(13)	C(1)–C(2)–C(3)–C(17)	90.06(11)
C(11)–C(2)–C(3)–C(4)	−160.37(9)	C(1)–C(2)–C(3)–C(4)	−33.28(13)
O(1)–N(1)–C(4)–C(21)	61.61(11)	C(28)–N(1)–C(4)–C(21)	−53.96(13)
O(1)–N(1)–C(4)–C(3)	−67.95(10)	C(28)–N(1)–C(4)–C(3)	176.47(9)
C(19)–C(3)–C(4)–N(1)	165.13(9)	C(17)–C(3)–C(4)–N(1)	−79.08(11)
C(2)–C(3)–C(4)–N(1)	44.57(12)	C(19)–C(3)–C(4)–C(21)	33.98(12)
C(17)–C(3)–C(4)–C(21)	149.77(10)	C(2)–C(3)–C(4)–C(21)	−86.57(11)
O(1)–C(1)–C(5)–C(6)	−139.07(12)	C(2)–C(1)–C(5)–C(6)	99.87(14)
O(1)–C(1)–C(5)–C(10)	42.33(15)	C(2)–C(1)–C(5)–C(10)	−78.72(15)

C(10)–C(5)–C(6)–C(7)	2.0(2)	C(1)–C(5)–C(6)–C(7)	–176.67(14)
C(5)–C(6)–C(7)–C(8)	0.1(3)	C(6)–C(7)–C(8)–C(9)	–1.9(3)
C(7)–C(8)–C(9)–C(10)	1.6(3)	C(6)–C(5)–C(10)–C(9)	–2.3(2)
C(1)–C(5)–C(10)–C(9)	176.34(14)	C(8)–C(9)–C(10)–C(5)	0.5(3)
C(1)–C(2)–C(11)–C(12)	–46.84(15)	C(3)–C(2)–C(11)–C(12)	81.79(14)
C(1)–C(2)–C(11)–C(16)	131.81(12)	C(3)–C(2)–C(11)–C(16)	–99.56(13)
C(16)–C(11)–C(12)–C(13)	–0.9(2)	C(2)–C(11)–C(12)–C(13)	177.81(12)
C(11)–C(12)–C(13)–C(14)	–0.4(2)	C(12)–C(13)–C(14)–C(15)	1.7(3)
C(13)–C(14)–C(15)–C(16)	–1.6(3)	C(14)–C(15)–C(16)–C(11)	0.3(3)
C(12)–C(11)–C(16)–C(15)	0.9(2)	C(2)–C(11)–C(16)–C(15)	–177.75(14)
C(19)–C(3)–C(17)–O(2)	145.36(12)	C(2)–C(3)–C(17)–O(2)	–94.36(14)
C(4)–C(3)–C(17)–O(2)	30.48(16)	C(19)–C(3)–C(17)–O(3)	–36.08(13)
C(2)–C(3)–C(17)–O(3)	84.20(11)	C(4)–C(3)–C(17)–O(3)	–150.96(10)
O(2)–C(17)–O(3)–C(18)	2.44(19)	C(3)–C(17)–O(3)–C(18)	–176.14(11)
C(17)–C(3)–C(19)–O(4)	125.59(13)	C(2)–C(3)–C(19)–O(4)	5.13(17)
C(4)–C(3)–C(19)–O(4)	–116.92(13)	C(17)–C(3)–C(19)–O(5)	–56.89(12)
C(2)–C(3)–C(19)–O(5)	–177.35(9)	C(4)–C(3)–C(19)–O(5)	60.60(11)
O(4)–C(19)–O(5)–C(20)	8.61(18)	C(3)–C(19)–O(5)–C(20)	–168.95(11)
N(1)–C(4)–C(21)–C(22)	–66.14(14)	C(3)–C(4)–C(21)–C(22)	60.34(15)
N(1)–C(4)–C(21)–C(26)	115.97(12)	C(3)–C(4)–C(21)–C(26)	–117.56(12)
C(26)–C(21)–C(22)–C(23)	–0.41(18)	C(4)–C(21)–C(22)–C(23)	–178.35(11)
C(21)–C(22)–C(23)–C(24)	–0.01(19)	C(22)–C(23)–C(24)–O(6)	–178.67(12)

C(22)–C(23)–C(24)–C(25)	0.70(19)	O(6)–C(24)–C(25)–C(26)	178.46(12)
C(23)–C(24)–C(25)–C(26)	−1.0(2)	C(24)–C(25)–C(26)–C(21)	0.5(2)
C(22)–C(21)–C(26)–C(25)	0.14(18)	C(4)–C(21)–C(26)–C(25)	178.18(11)
C(23)–C(24)–O(6)–C(27)	1.6(2)	C(25)–C(24)–O(6)–C(27)	−177.82(13)
O(1)–N(1)–C(28)–C(29)	74.60(11)	C(4)–N(1)–C(28)–C(29)	−168.70(9)
N(1)–C(28)–C(29)–C(30)	−164.34(11)	N(1)–C(28)–C(29)–C(34)	16.59(16)
C(34)–C(29)–C(30)–C(31)	−1.04(19)	C(28)–C(29)–C(30)–C(31)	179.86(12)
C(29)–C(30)–C(31)–C(32)	0.0(2)	C(30)–C(31)–C(32)–C(33)	1.1(2)
C(31)–C(32)–C(33)–C(34)	−1.1(2)	C(32)–C(33)–C(34)–C(29)	0.07(19)
C(30)–C(29)–C(34)–C(33)	1.01(18)	C(28)–C(29)–C(34)–C(33)	−179.92(11)

6.2. **Appendix II:** X-Ray crystallographic data for **176$_e$**

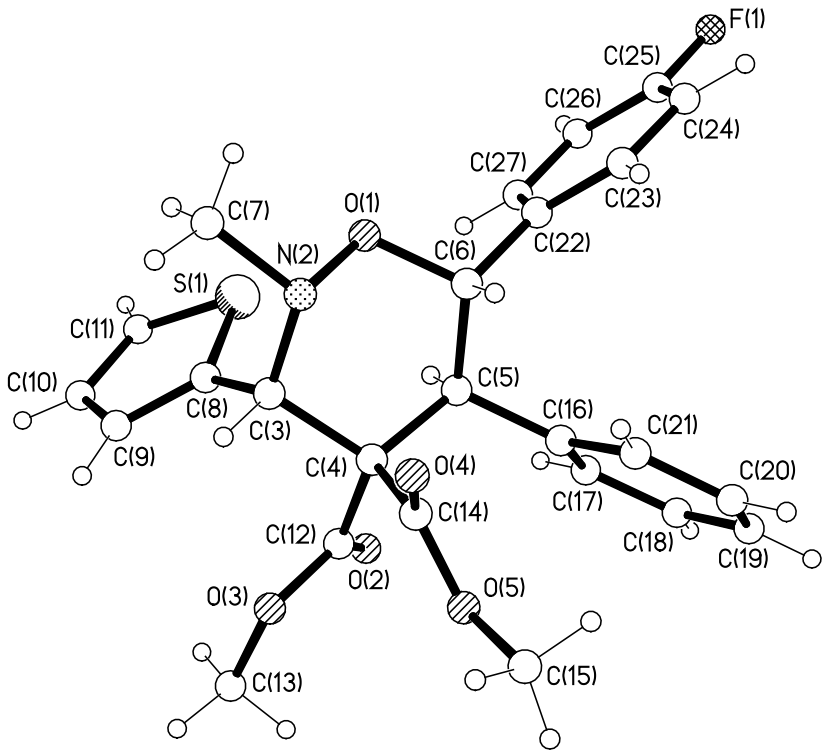


Table 1. Crystal data and structure refinement for sdrc25.

Identification code	sdrc25	
Chemical formula	$C_{25}H_{24}FNO_5S$	
Formula weight	469.51	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	triclinic, P $\bar{1}$	
Unit cell parameters	a = 9.5110(8) Å	□ = 77.6318(12)°
	b = 14.9284(12) Å	□ = 84.1856(13)°
	c = 17.3054(14) Å	□ = 78.8426(13)°
Cell volume	2350.1(3) $Å^3$	
Z	4	
Calculated density	1.327 g/cm^3	
Absorption coefficient □	0.182 mm^{-1}	
F(000)	984	
Crystal colour and size	colourless, 0.51 × 0.16 × 0.16 mm^3	
Reflections for cell refinement	7034 (□ range 2.39 to 29.99°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	1.67 to 31.70°	
Index ranges	h –13 to 13, k –21 to 21, l –24 to 24	
Completeness to □ = 29.00°	99.1 %	
Intensity decay	0%	
Reflections collected	28290	
Independent reflections	14416 (R_{int} = 0.0274)	
Reflections with F^2>2□	10392	

Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.913 and 0.972
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0636, 0.2917
Data / restraints / parameters	14416 / 0 / 621
Final R indices [F^2>2□]	R1 = 0.0492, wR2 = 0.1228
R indices (all data)	R1 = 0.0720, wR2 = 0.1353
Goodness-of-fit on F^2	1.064
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.412 and −0.468 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sdrc25. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	0.23202(10)	0.46643(7)	0.34258(6)	0.0230(2)
N(2)	0.29843(13)	0.50009(8)	0.40048(7)	0.0229(2)
C(3)	0.38143(15)	0.41780(10)	0.44941(8)	0.0222(3)
C(4)	0.50791(14)	0.37460(9)	0.39490(8)	0.0209(3)
C(5)	0.45134(14)	0.36159(9)	0.31700(8)	0.0205(3)
C(6)	0.34387(14)	0.44867(10)	0.28242(8)	0.0212(3)
C(7)	0.17960(17)	0.54788(11)	0.44500(9)	0.0292(3)
C(8)	0.29529(16)	0.34671(10)	0.49688(8)	0.0253(3)
C(9)	0.30163(19)	0.31081(11)	0.57644(9)	0.0330(3)
C(10)	0.2083(2)	0.24575(12)	0.60496(10)	0.0396(4)
C(11)	0.13280(19)	0.23281(12)	0.54760(10)	0.0387(4)

S(1)	0.17192(4)	0.30047(3)	0.45775(2)	0.03307(10)
C(12)	0.57484(15)	0.27991(10)	0.44357(8)	0.0253(3)
O(2)	0.57404(13)	0.20509(8)	0.42897(7)	0.0352(3)
O(3)	0.63091(12)	0.29378(8)	0.50712(6)	0.0328(2)
C(13)	0.6933(3)	0.21081(15)	0.56105(12)	0.0558(6)
C(14)	0.62210(15)	0.43719(10)	0.37497(8)	0.0243(3)
O(4)	0.59830(13)	0.52032(8)	0.36606(8)	0.0404(3)
O(5)	0.75255(11)	0.38699(8)	0.36572(6)	0.0315(2)
C(15)	0.86659(18)	0.44047(15)	0.33741(11)	0.0417(4)
C(16)	0.56704(15)	0.33480(10)	0.25428(8)	0.0231(3)
C(17)	0.59489(17)	0.24399(11)	0.24127(9)	0.0298(3)
C(18)	0.69864(18)	0.21829(12)	0.18340(10)	0.0367(4)
C(19)	0.77452(18)	0.28321(14)	0.13857(10)	0.0377(4)
C(20)	0.74778(17)	0.37405(13)	0.14978(9)	0.0334(3)
C(21)	0.64264(16)	0.39955(11)	0.20696(8)	0.0267(3)
F(1X)	0.8823(4)	0.2626(3)	0.0850(2)	0.0491(12)
C(22)	0.27308(15)	0.43620(10)	0.21228(8)	0.0235(3)
C(23)	0.27746(18)	0.50003(12)	0.14113(9)	0.0328(3)
C(24)	0.2120(2)	0.49013(14)	0.07596(10)	0.0426(4)
C(25)	0.14175(19)	0.41635(14)	0.08380(11)	0.0420(4)
C(26)	0.13483(18)	0.35229(13)	0.15323(11)	0.0395(4)
C(27)	0.20104(17)	0.36260(11)	0.21781(10)	0.0319(3)
F(1)	0.07512(19)	0.40513(13)	0.02275(10)	0.0583(6)
O(1')	0.34396(11)	0.96897(7)	0.10612(6)	0.0258(2)
N(2')	0.23795(13)	1.05487(8)	0.09696(7)	0.0262(3)
C(3')	0.15648(16)	1.05448(10)	0.17372(8)	0.0251(3)
C(4')	0.06625(15)	0.97392(10)	0.18858(8)	0.0224(3)
C(5')	0.16273(14)	0.88051(9)	0.17492(8)	0.0210(3)

C(6')	0.26633(15)	0.89697(10)	0.10085(8)	0.0234(3)
C(7')	0.32154(18)	1.12990(11)	0.07441(10)	0.0334(3)
C(8')	0.24227(17)	1.05295(10)	0.24349(9)	0.0287(3)
C(9')	0.20423(19)	1.11159(11)	0.29906(10)	0.0341(3)
C(10')	0.3054(2)	1.09176(14)	0.35724(12)	0.0494(5)
C(11')	0.4156(2)	1.02274(14)	0.34704(11)	0.0452(4)
S(1')	0.40138(5)	0.97889(3)	0.26590(3)	0.03813(11)
C(12')	0.00709(15)	0.96277(10)	0.27546(8)	0.0238(3)
O(2')	0.04450(11)	0.89829(7)	0.32796(6)	0.0289(2)
O(3')	–0.08908(12)	1.03856(8)	0.28513(6)	0.0320(2)
C(13')	–0.1487(2)	1.04028(14)	0.36534(10)	0.0431(4)
C(14')	–0.06177(15)	1.00294(10)	0.13583(8)	0.0244(3)
O(4')	–0.07095(12)	1.06253(8)	0.07667(7)	0.0363(3)
O(5')	–0.16410(11)	0.95285(7)	0.16478(6)	0.0287(2)
C(15')	–0.28255(17)	0.96469(13)	0.11469(10)	0.0356(4)
C(16')	0.08481(14)	0.80165(9)	0.17144(8)	0.0218(3)
C(17')	0.08513(16)	0.72698(10)	0.23512(9)	0.0263(3)
C(18')	0.02195(17)	0.65157(11)	0.23205(10)	0.0312(3)
C(19')	–0.04194(16)	0.65161(10)	0.16417(10)	0.0295(3)
C(20')	–0.04449(16)	0.72417(11)	0.09956(9)	0.0291(3)
C(21')	0.01940(16)	0.79911(10)	0.10340(9)	0.0262(3)
F(1')	–0.10229(16)	0.57657(10)	0.16015(9)	0.0376(5)
C(22')	0.37653(15)	0.81071(10)	0.09448(9)	0.0258(3)
C(23')	0.38538(17)	0.77101(11)	0.02803(9)	0.0310(3)
C(24')	0.4861(2)	0.69152(12)	0.02112(11)	0.0384(4)
C(25')	0.57787(19)	0.65263(12)	0.08105(12)	0.0416(4)
C(26')	0.56993(18)	0.69003(12)	0.14761(12)	0.0403(4)

C(27')	0.46981(17)	0.76962(12)	0.15421(10)	0.0333(3)
F(1X')	0.6690(4)	0.5776(2)	0.0793(2)	0.0656(13)

Table 3. Bond lengths [Å] and angles [°] for sdrc25.

O(1)–C(6)	1.4389(16)	O(1)–N(2)	1.4568(15)
N(2)–C(7)	1.4584(18)	N(2)–C(3)	1.4709(18)
C(3)–C(8)	1.5161(19)	C(3)–C(4)	1.5758(19)
C(4)–C(14)	1.5330(19)	C(4)–C(12)	1.5372(19)
C(4)–C(5)	1.5634(18)	C(5)–C(16)	1.5240(18)
C(5)–C(6)	1.5392(19)	C(6)–C(22)	1.5073(19)
C(8)–C(9)	1.369(2)	C(8)–S(1)	1.7282(15)
C(9)–C(10)	1.419(2)	C(10)–C(11)	1.349(3)
C(11)–S(1)	1.7123(17)	C(12)–O(2)	1.1983(18)
C(12)–O(3)	1.3402(18)	O(3)–C(13)	1.446(2)
C(14)–O(4)	1.1965(19)	C(14)–O(5)	1.3334(18)
O(5)–C(15)	1.4538(19)	C(16)–C(21)	1.390(2)
C(16)–C(17)	1.392(2)	C(17)–C(18)	1.393(2)
C(18)–C(19)	1.377(3)	C(19)–F(1X)	1.346(3)
C(19)–C(20)	1.382(3)	C(20)–C(21)	1.392(2)
C(22)–C(27)	1.385(2)	C(22)–C(23)	1.389(2)
C(23)–C(24)	1.389(2)	C(24)–C(25)	1.371(3)
C(25)–F(1)	1.341(2)	C(25)–C(26)	1.371(3)
C(26)–C(27)	1.387(2)	O(1')–C(6')	1.4392(16)
O(1')–N(2')	1.4598(16)	N(2')–C(7')	1.4607(19)
N(2')–C(3')	1.4679(18)	C(3')–C(8')	1.518(2)
C(3')–C(4')	1.5720(19)	C(4')–C(14')	1.535(2)
C(4')–C(12')	1.5370(19)	C(4')–C(5')	1.5635(19)

C(5')–C(16')	1.5217(19)	C(5')–C(6')	1.5418(19)
C(6')–C(22')	1.511(2)	C(8')–C(9')	1.411(2)
C(8')–S(1')	1.7177(17)	C(9')–C(10')	1.409(3)
C(10')–C(11')	1.347(3)	C(11')–S(1')	1.6986(19)
C(12')–O(2')	1.1988(17)	C(12')–O(3')	1.3396(17)
O(3')–C(13')	1.4488(19)	C(14')–O(4')	1.2021(17)
C(14')–O(5')	1.3341(17)	O(5')–C(15')	1.4515(18)
C(16')–C(17')	1.3893(19)	C(16')–C(21')	1.397(2)
C(17')–C(18')	1.388(2)	C(18')–C(19')	1.376(2)
C(19')–F(1')	1.3710(19)	C(19')–C(20')	1.379(2)
C(20')–C(21')	1.389(2)	C(22')–C(23')	1.391(2)
C(22')–C(27')	1.391(2)	C(23')–C(24')	1.392(2)
C(24')–C(25')	1.380(3)	C(25')–F(1X')	1.280(3)
C(25')–C(26')	1.373(3)	C(26')–C(27')	1.389(2)

C(6)–O(1)–N(2)	105.53(9)	O(1)–N(2)–C(7)	105.41(10)
O(1)–N(2)–C(3)	106.77(10)	C(7)–N(2)–C(3)	113.27(11)
N(2)–C(3)–C(8)	115.84(12)	N(2)–C(3)–C(4)	108.04(11)
C(8)–C(3)–C(4)	113.21(11)	C(14)–C(4)–C(12)	108.78(11)
C(14)–C(4)–C(5)	110.11(11)	C(12)–C(4)–C(5)	110.45(11)
C(14)–C(4)–C(3)	109.96(11)	C(12)–C(4)–C(3)	106.44(11)
C(5)–C(4)–C(3)	111.03(11)	C(16)–C(5)–C(6)	111.10(11)
C(16)–C(5)–C(4)	115.31(11)	C(6)–C(5)–C(4)	110.16(11)
O(1)–C(6)–C(22)	107.26(10)	O(1)–C(6)–C(5)	108.46(10)
C(22)–C(6)–C(5)	112.63(11)	C(9)–C(8)–C(3)	125.53(14)
C(9)–C(8)–S(1)	110.09(11)	C(3)–C(8)–S(1)	124.37(11)
C(8)–C(9)–C(10)	113.14(15)	C(11)–C(10)–C(9)	112.84(15)
C(10)–C(11)–S(1)	111.65(13)	C(11)–S(1)–C(8)	92.27(8)

O(2)–C(12)–O(3)	124.84(14)	O(2)–C(12)–C(4)	126.05(13)
O(3)–C(12)–C(4)	109.07(12)	C(12)–O(3)–C(13)	115.98(14)
O(4)–C(14)–O(5)	123.86(14)	O(4)–C(14)–C(4)	125.12(13)
O(5)–C(14)–C(4)	110.98(12)	C(14)–O(5)–C(15)	115.43(13)
C(21)–C(16)–C(17)	118.44(13)	C(21)–C(16)–C(5)	121.88(13)
C(17)–C(16)–C(5)	119.64(13)	C(16)–C(17)–C(18)	120.63(15)
C(19)–C(18)–C(17)	119.80(16)	F(1X)–C(19)–C(18)	123.4(2)
F(1X)–C(19)–C(20)	115.9(2)	C(18)–C(19)–C(20)	120.66(15)
C(19)–C(20)–C(21)	119.23(16)	C(16)–C(21)–C(20)	121.20(15)
C(27)–C(22)–C(23)	119.03(14)	C(27)–C(22)–C(6)	121.05(13)
C(23)–C(22)–C(6)	119.91(13)	C(22)–C(23)–C(24)	120.79(16
C(25)–C(24)–C(23)	118.42(17)	F(1)–C(25)–C(26)	117.37(19)
F(1)–C(25)–C(24)	120.32(19)	C(26)–C(25)–C(24)	122.31(15)
C(25)–C(26)–C(27)	118.80(17)	C(22)–C(27)–C(26)	120.65(16)
C(6')–O(1')–N(2')	105.47(10)	O(1')–N(2')–C(7')	105.15(11)
O(1')–N(2')–C(3')	106.65(10)	C(7')–N(2')–C(3')	113.44(12)
N(2')–C(3')–C(8')	116.12(12)	N(2')–C(3')–C(4')	108.10(11)
C(8')–C(3')–C(4')	113.31(11)	C(14')–C(4')–C(12')	107.99(11)
C(14')–C(4')–C(5')	112.17(11)	C(12')–C(4')–C(5')	109.57(11)
C(14')–C(4')–C(3')	109.54(11)	C(12')–C(4')–C(3')	106.51(11)
C(5')–C(4')–C(3')	110.87(11)	C(16')–C(5')–C(6')	109.72(11)
C(16')–C(5')–C(4')	116.36(11)	C(6')–C(5')–C(4')	111.15(11)
O(1')–C(6')–C(22')	106.98(11)	O(1')–C(6')–C(5')	109.42(11)
C(22')–C(6')–C(5')	111.72(11)	C(9')–C(8')–C(3')	125.47(15)
C(9')–C(8')–S(1')	110.04(12)	C(3')–C(8')–S(1')	124.48(11)
C(10')–C(9')–C(8')	111.53(16)	C(11')–C(10')–C(9')	113.69(17)
C(10')–C(11')–S(1')	112.15(15)	C(11')–S(1')–C(8')	92.57(9)
O(2')–C(12')–O(3')	124.37(13)	O(2')–C(12')–C(4')	125.86(13)

O(3')–C(12')–C(4')	109.70(11)	C(12')–O(3')–C(13')	116.00(12)
O(4')–C(14')–O(5')	123.79(14)	O(4')–C(14')–C(4')	125.64(13)
O(5')–C(14')–C(4')	110.57(11)	C(14')–O(5')–C(15')	115.90(12)
C(17')–C(16')–C(21')	118.32(13)	C(17')–C(16')–C(5')	119.99(13)
C(21')–C(16')–C(5')	121.58(12)	C(18')–C(17')–C(16')	121.37(14)
C(19')–C(18')–C(17')	118.71(14)	F(1')–C(19')–C(18')	119.04(15)
F(1')–C(19')–C(20')	119.11(15)	C(18')–C(19')–C(20')	121.84(14)
C(19')–C(20')–C(21')	118.84(14)	C(20')–C(21')–C(16')	120.93(13)
C(23')–C(22')–C(27')	118.96(14)	C(23')–C(22')–C(6')	119.82(14)
C(27')–C(22')–C(6')	121.22(14)	C(22')–C(23')–C(24')	120.65(16)
C(25')–C(24')–C(23')	119.11(17)	F(1X')–C(25')–C(26')	116.8(3)
F(1X')–C(25')–C(24')	121.9(3)	C(26')–C(25')–C(24')	121.22(16)
C(25')–C(26')–C(27')	119.58(17)	C(26')–C(27')–C(22')	120.47(16)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sdrc25.

	x	y	z	U
H(3)	0.4271	0.4414	0.4888	0.027
H(5)	0.3962	0.3092	0.3325	0.025
H(6)	0.3943	0.5033	0.2664	0.025
H(7A)	0.1266	0.6006	0.4090	0.044
H(7B)	0.2172	0.5707	0.4864	0.044
H(7C)	0.1151	0.5044	0.4695	0.044
H(9)	0.3623	0.3277	0.6092	0.040
H(10)	0.2000	0.2146	0.6587	0.047
H(11)	0.0661	0.1913	0.5560	0.046
H(13A)	0.6210	0.1710	0.5794	0.084

H(13B)	0.7264	0.2284	0.6066	0.084
H(13C)	0.7749	0.1768	0.5337	0.084
H(15A)	0.8505	0.4746	0.2831	0.063
H(15B)	0.9593	0.3981	0.3383	0.063
H(15C)	0.8668	0.4848	0.3718	0.063
H(17)	0.5427	0.1991	0.2721	0.036
H(18)	0.7170	0.1562	0.1749	0.044
H(19)	0.8460	0.2654	0.0995	0.045
H(20)	0.8005	0.4186	0.1188	0.040
H(21)	0.6222	0.4623	0.2138	0.032
H(23)	0.3258	0.5511	0.1370	0.039
H(24)	0.2158	0.5335	0.0271	0.051
H(25)	0.0963	0.4094	0.0396	0.050
H(26)	0.0856	0.3017	0.1570	0.047
H(27)	0.1969	0.3188	0.2663	0.038
H(3')	0.0854	1.1140	0.1673	0.030
H(5')	0.2241	0.8578	0.2212	0.025
H(6')	0.2104	0.9164	0.0523	0.028
H(7D)	0.3872	1.1254	0.1158	0.050
H(7E)	0.2565	1.1902	0.0681	0.050
H(7F)	0.3770	1.1245	0.0242	0.050
H(9')	0.1208	1.1586	0.2975	0.041
H(10')	0.2968	1.1241	0.3997	0.059
H(11')	0.4924	1.0011	0.3813	0.054
H(13D)	–0.1988	0.9874	0.3844	0.065
H(13E)	–0.2166	1.0986	0.3660	0.065
H(13F)	–0.0712	1.0360	0.3999	0.065
H(15D)	–0.3356	1.0287	0.1089	0.053

H(15E)	–0.3469	0.9211	0.1390	0.053
H(15F)	–0.2450	0.9523	0.0624	0.053
H(17')	0.1295	0.7276	0.2817	0.032
H(18')	0.0228	0.6009	0.2760	0.037
H(19')	–0.0855	0.6002	0.1618	0.035
H(20')	–0.0892	0.7229	0.0532	0.035
H(21')	0.0186	0.8494	0.0591	0.031
H(23')	0.3221	0.7984	–0.0131	0.037
H(24')	0.4916	0.6644	–0.0243	0.046
H(25')	0.6478	0.5990	0.0762	0.050
H(26')	0.6325	0.6617	0.1889	0.048
H(27')	0.4650	0.7962	0.1998	0.040

Table 6. Torsion angles [°] for sdrc25.

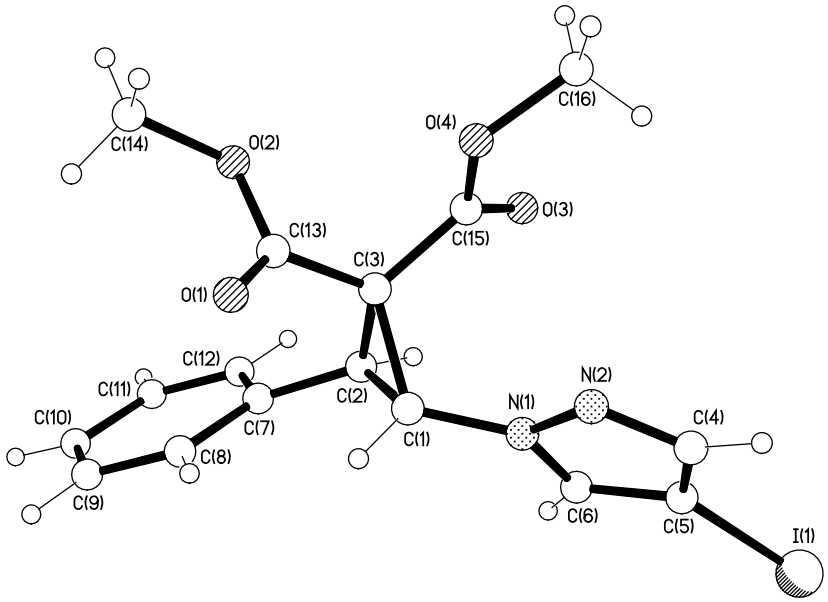
C(6)–O(1)–N(2)–C(7)	160.73(11)	C(6)–O(1)–N(2)–C(3)	–78.54(12)
O(1)–N(2)–C(3)–C(8)	–62.31(14)	C(7)–N(2)–C(3)–C(8)	53.26(16)
O(1)–N(2)–C(3)–C(4)	65.87(12)	C(7)–N(2)–C(3)–C(4)	–178.56(11)
N(2)–C(3)–C(4)–C(14)	72.37(13)	C(8)–C(3)–C(4)–C(14)	–157.96(12)
N(2)–C(3)–C(4)–C(12)	–169.98(11)	C(8)–C(3)–C(4)–C(12)	–40.31(15)
N(2)–C(3)–C(4)–C(5)	–49.73(14)	C(8)–C(3)–C(4)–C(5)	79.94(14)
C(14)–C(4)–C(5)–C(16)	48.72(15)	C(12)–C(4)–C(5)–C(16)	–71.43(14)
C(3)–C(4)–C(5)–C(16)	170.73(11)	C(14)–C(4)–C(5)–C(6)	–77.99(13)
C(12)–C(4)–C(5)–C(6)	161.86(11)	C(3)–C(4)–C(5)–C(6)	44.02(14)
N(2)–O(1)–C(6)–C(22)	–166.60(10)	N(2)–O(1)–C(6)–C(5)	71.49(12)
C(16)–C(5)–C(6)–O(1)	175.90(11)	C(4)–C(5)–C(6)–O(1)	–55.06(13)
C(16)–C(5)–C(6)–C(22)	57.34(15)	C(4)–C(5)–C(6)–C(22)	–173.62(11)
N(2)–C(3)–C(8)–C(9)	–128.65(16)	C(4)–C(3)–C(8)–C(9)	105.77(17)

N(2)–C(3)–C(8)–S(1)	50.35(17)	C(4)–C(3)–C(8)–S(1)	–75.24(15)
C(3)–C(8)–C(9)–C(10)	179.74(14)	S(1)–C(8)–C(9)–C(10)	0.63(18)
C(8)–C(9)–C(10)–C(11)	0.0(2)	C(9)–C(10)–C(11)–S(1)	–0.7(2)
C(10)–C(11)–S(1)–C(8)	0.89(15)	C(9)–C(8)–S(1)–C(11)	–0.85(13)
C(3)–C(8)–S(1)–C(11)	–179.98(13)	C(14)–C(4)–C(12)–O(2)	–127.11(16)
C(5)–C(4)–C(12)–O(2)	–6.2(2)	C(3)–C(4)–C(12)–O(2)	114.45(16)
C(14)–C(4)–C(12)–O(3)	54.92(15)	C(5)–C(4)–C(12)–O(3)	175.87(11)
C(3)–C(4)–C(12)–O(3)	–63.51(14)	O(2)–C(12)–O(3)–C(13)	–0.4(2)
C(4)–C(12)–O(3)–C(13)	177.59(14)	C(12)–C(4)–C(14)–O(4)	–149.85(15)
C(5)–C(4)–C(14)–O(4)	88.99(17)	C(3)–C(4)–C(14)–O(4)	–33.65(19)
C(12)–C(4)–C(14)–O(5)	32.54(15)	C(5)–C(4)–C(14)–O(5)	–88.62(13)
C(3)–C(4)–C(14)–O(5)	148.74(11)	O(4)–C(14)–O(5)–C(15)	–4.7(2)
C(4)–C(14)–O(5)–C(15)	172.96(12)	C(6)–C(5)–C(16)–C(21)	49.67(17)
C(4)–C(5)–C(16)–C(21)	–76.57(16)	C(6)–C(5)–C(16)–C(17)	–127.73(13)
C(4)–C(5)–C(16)–C(17)	106.03(15)	C(21)–C(16)–C(17)–C(18)	1.5(2)
C(5)–C(16)–C(17)–C(18)	179.01(13)	C(16)–C(17)–C(18)–C(19)	0.0(2)
C(17)–C(18)–C(19)–F(1X)	175.8(2)	C(17)–C(18)–C(19)–C(20)	–0.7(2)
F(1X)–C(19)–C(20)–C(21)	–176.9(2)	C(18)–C(19)–C(20)–C(21)	–0.2(2)
C(17)–C(16)–C(21)–C(20)	–2.4(2)	C(5)–C(16)–C(21)–C(20)	–179.84(13)
C(19)–C(20)–C(21)–C(16)	1.8(2)	O(1)–C(6)–C(22)–C(27)	–64.15(16)
C(5)–C(6)–C(22)–C(27)	55.12(17)	O(1)–C(6)–C(22)–C(23)	114.74(14)
C(5)–C(6)–C(22)–C(23)	–125.99(14)	C(27)–C(22)–C(23)–C(24)	–0.6(2)
C(6)–C(22)–C(23)–C(24)	–179.55(14)	C(22)–C(23)–C(24)–C(25)	0.6(3)
C(23)–C(24)–C(25)–F(1)	178.89(17)	C(23)–C(24)–C(25)–C(26)	–0.4(3)
F(1)–C(25)–C(26)–C(27)	–179.17(16)	C(24)–C(25)–C(26)–C(27)	0.1(3)
C(23)–C(22)–C(27)–C(26)	0.4(2)	C(6)–C(22)–C(27)–C(26)	179.26(14)
C(25)–C(26)–C(27)–C(22)	–0.1(2)	C(6')–O(1')–N(2')–C(7')	–160.58(11)
C(6')–O(1')–N(2')–C(3')	78.68(12)	O(1')–N(2')–C(3')–C(8')	61.15(15)

C(7')–N(2')–C(3')–C(8')	−54.13(17)	O(1')–N(2')–C(3')–C(4')	−67.45(13)
C(7')–N(2')–C(3')–C(4')	177.27(12)	N(2')–C(3')–C(4')–C(14')	−74.57(14)
C(8')–C(3')–C(4')–C(14')	155.25(12)	N(2')–C(3')–C(4')–C(12')	168.88(11)
C(8')–C(3')–C(4')–C(12')	38.70(16)	N(2')–C(3')–C(4')–C(5')	49.75(15)
C(8')–C(3')–C(4')–C(5')	−80.43(15)	C(14')–C(4')–C(5')–C(16')	−45.67(15)
C(12')–C(4')–C(5')–C(16')	74.25(15)	C(3')–C(4')–C(5')–C(16')	−168.48(11)
C(14')–C(4')–C(5')–C(6')	80.89(14)	C(12')–C(4')–C(5')–C(6')	−159.19(11)
C(3')–C(4')–C(5')–C(6')	−41.92(15)	N(2')–O(1')–C(6')–C(22')	169.51(11)
N(2')–O(1')–C(6')–C(5')	−69.29(13)	C(16')–C(5')–C(6')–O(1')	−177.63(11)
C(4')–C(5')–C(6')–O(1')	52.24(15)	C(16')–C(5')–C(6')–C(22')	−59.35(15)
C(4')–C(5')–C(6')–C(22')	170.52(11)	N(2')–C(3')–C(8')–C(9')	132.17(15)
C(4')–C(3')–C(8')–C(9')	−101.82(17)	N(2')–C(3')–C(8')–S(1')	−47.64(17)
C(4')–C(3')–C(8')–S(1')	78.37(15)	C(3')–C(8')–C(9')–C(10')	179.19(14)
S(1')–C(8')–C(9')–C(10')	−0.97(17)	C(8')–C(9')–C(10')–C(11')	0.5(2)
C(9')–C(10')–C(11')–S(1')	0.2(2)	C(10')–C(11')–S(1')–C(8')	−0.62(15)
C(9')–C(8')–S(1')–C(11')	0.91(12)	C(3')–C(8')–S(1')–C(11')	−179.25(13)
C(14')–C(4')–C(12')–O(2')	132.76(15)	C(5')–C(4')–C(12')–O(2')	10.3(2)
C(3')–C(4')–C(12')–O(2')	−109.65(16)	C(14')–C(4')–C(12')–O(3')	−50.13(15)
C(5')–C(4')–C(12')–O(3')	−172.57(11)	C(3')–C(4')–C(12')–O(3')	67.46(14)
O(2')–C(12')–O(3')–C(13')	0.3(2)	C(4')–C(12')–O(3')–C(13')	−176.82(13)
C(12')–C(4')–C(14')–O(4')	136.25(15)	C(5')–C(4')–C(14')–O(4')	−102.91(17)
C(3')–C(4')–C(14')–O(4')	20.6(2)	C(12')–C(4')–C(14')–O(5')	−43.47(15)
C(5')–C(4')–C(14')–O(5')	77.36(14)	C(3')–C(4')–C(14')–O(5')	−159.08(12)
O(4')–C(14')–O(5')–C(15')	8.3(2)	C(4')–C(14')–O(5')–C(15')	−171.97(12)
C(6')–C(5')–C(16')–C(17')	127.41(14)	C(4')–C(5')–C(16')–C(17')	−105.33(15)
C(6')–C(5')–C(16')–C(21')	−48.59(17)	C(4')–C(5')–C(16')–C(21')	78.67(17)
C(21')–C(16')–C(17')–C(18')	−0.2(2)	C(5')–C(16')–C(17')–C(18')	−176.37(13)
C(16')–C(17')–C(18')–C(19')	0.0(2)	C(17')–C(18')–C(19')–F(1')	178.83(15)

C(17')–C(18')–C(19')–C(20')	0.1(2)	F(1')–C(19')–C(20')–C(21')	−178.70(14)
C(18')–C(19')–C(20')–C(21')	0.0(2)	C(19')–C(20')–C(21')–C(16')	−0.3(2)
C(17')–C(16')–C(21')–C(20')	0.4(2)	C(5')–C(16')–C(21')–C(20')	176.43(13)
O(1')–C(6')–C(22')–C(23')	−119.50(14)	C(5')–C(6')–C(22')–C(23')	120.77(14)
O(1')–C(6')–C(22')–C(27')	60.70(17)	C(5')–C(6')–C(22')–C(27')	−59.03(18)
C(27')–C(22')–C(23')–C(24')	−0.2(2)	C(6')–C(22')–C(23')–C(24')	−179.96(14)
C(22')–C(23')–C(24')–C(25')	−0.3(2)	C(23')–C(24')–C(25')–F(1X')	177.4(2)
C(23')–C(24')–C(25')–C(26')	1.0(3)	F(1X')–C(25')–C(26')–C(27')	−177.9(2)
C(24')–C(25')–C(26')–C(27')	−1.3(3)	C(25')–C(26')–C(27')–C(22')	0.9(3)
C(23')–C(22')–C(27')–C(26')	−0.2(2)	C(6')–C(22')–C(27')–C(26')	179.64(14)

6.3. **Appendix III:** X-Ray crystallographic data for **182$_a$**



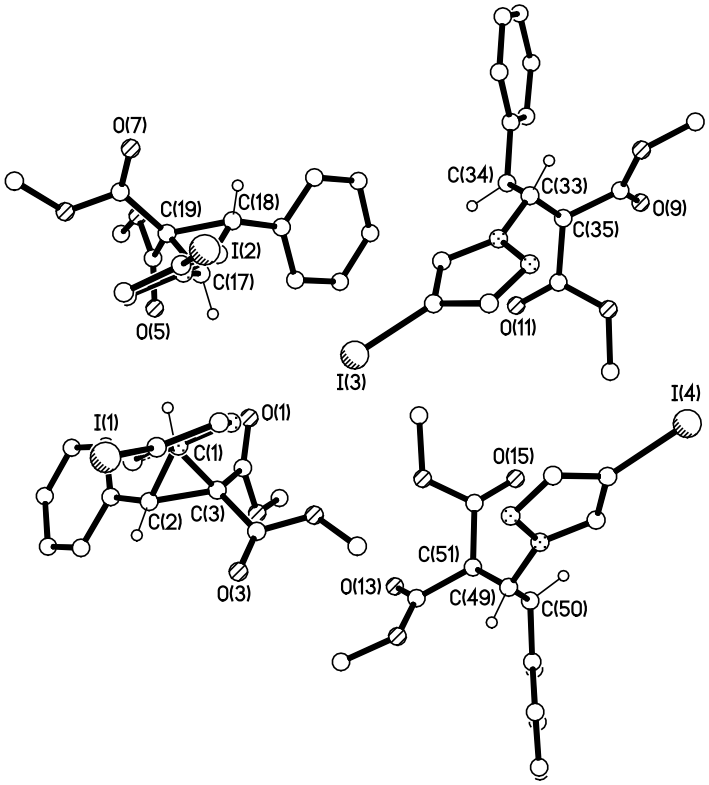


Table 1. Crystal data and structure refinement for sdrc27.

Identification code	sdrc27	
Chemical formula	$C_{16}H_{15}IN_2O_4$	
Formula weight	426.20	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	a = 14.6567(19) Å	□ = 90°
	b = 24.633(3) Å	□ = 94.084(2)°
	c = 19.004(3) Å	□ = 90°
Cell volume	6843.7(15) $Å^3$	
Z	16	

Calculated density	1.655 g/cm^3
Absorption coefficient □	1.892 mm^{-1}
F(000)	3360
Crystal colour and size	colourless, 0.36 × 0.28 × 0.02 mm^3
Reflections for cell refinement	9554 (□ range 2.30 to 26.43°)
Data collection method	Bruker APEX 2 CCD diffractometer
	□ rotation with narrow frames
□ range for data collection	1.65 to 25.00°
Index ranges	h –17 to 17, k –29 to 29, l –22 to 22
Completeness to □ = 25.00°	99.9 %
Intensity decay	0%
Reflections collected	53066
Independent reflections	12060 (R_{int} = 0.0750)
Reflections with F^2>2□	8303
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.549 and 0.963
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.1158, 41.5664
Data / restraints / parameters	12060 / 34 / 847
Final R indices [F^2>2□]	R1 = 0.0707, wR2 = 0.1764
R indices (all data)	R1 = 0.1003, wR2 = 0.2056
Goodness-of-fit on F^2	1.031
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	7.306 and –1.100 e Å^{-3}

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å^2) for sdrc27. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.1766(5)	0.2097(3)	0.5028(4)	0.0249(18)
C(2)	0.1459(5)	0.1861(3)	0.5696(4)	0.0184(16)
C(3)	0.2442(5)	0.1768(3)	0.5496(4)	0.0179(16)
N(1)	0.1909(4)	0.2669(3)	0.4989(4)	0.0251(15)
N(2)	0.2648(5)	0.2865(3)	0.4675(4)	0.0301(17)
C(4)	0.2555(6)	0.3392(4)	0.4677(5)	0.033(2)
C(5)	0.1764(6)	0.3545(3)	0.5001(4)	0.0261(18)
C(6)	0.1362(6)	0.3073(3)	0.5191(4)	0.0264(18)
I(1)	0.12486(5)	0.43220(3)	0.51285(4)	0.0425(2)
C(7)	0.0773(5)	0.1414(3)	0.5709(4)	0.0169(16)
C(8)	0.0502(6)	0.1101(3)	0.5124(4)	0.0254(18)
C(9)	–0.0131(6)	0.0682(3)	0.5192(5)	0.0287(19)
C(10)	–0.0468(6)	0.0562(3)	0.5823(5)	0.032(2)
C(11)	–0.0206(5)	0.0876(3)	0.6415(5)	0.0272(19)
C(12)	0.0413(5)	0.1298(3)	0.6357(4)	0.0242(18)
C(13)	0.2703(6)	0.1220(3)	0.5231(4)	0.0265(18)
O(1)	0.2660(5)	0.1081(3)	0.4628(3)	0.0423(17)
O(2)	0.3000(5)	0.0907(2)	0.5776(3)	0.0357(15)
C(14)	0.3255(9)	0.0361(4)	0.5599(7)	0.059(3)
C(15)	0.3175(5)	0.2084(3)	0.5913(4)	0.0189(16)
O(3)	0.3037(4)	0.2400(2)	0.6370(3)	0.0272(13)
O(4)	0.3982(4)	0.1980(2)	0.5675(3)	0.0273(13)
C(16)	0.4712(6)	0.2328(4)	0.5964(5)	0.036(2)
O(15)	0.6950(4)	0.0817(3)	0.5083(3)	0.0395(16)
O(16)	0.5500(4)	0.1084(3)	0.5172(3)	0.0365(15)

C(17)	0.1718(5)	0.2033(3)	0.2994(4)	0.0221(17)
C(18)	0.2022(5)	0.1788(3)	0.2327(4)	0.0201(17)
C(19)	0.1045(5)	0.1696(3)	0.2534(4)	0.0197(16)
N(3)	0.1564(4)	0.2601(3)	0.3034(3)	0.0214(14)
N(4)	0.0838(5)	0.2787(3)	0.3361(3)	0.0264(16)
C(20)	0.0906(6)	0.3316(4)	0.3347(4)	0.0295(19)
C(21)	0.1685(6)	0.3482(3)	0.3008(4)	0.0245(18)
C(22)	0.2094(5)	0.3011(3)	0.2818(4)	0.0225(17)
I(2)	0.21238(4)	0.42749(2)	0.28763(4)	0.03989(19)
C(23)	0.2723(5)	0.1356(3)	0.2316(4)	0.0154(15)
C(24)	0.3091(5)	0.1241(3)	0.1675(4)	0.0228(17)
C(25)	0.3744(6)	0.0836(4)	0.1627(5)	0.029(2)
C(26)	0.4039(6)	0.0539(4)	0.2223(5)	0.033(2)
C(27)	0.3691(6)	0.0651(4)	0.2863(5)	0.030(2)
C(28)	0.3030(5)	0.1055(3)	0.2912(4)	0.0230(17)
C(29)	0.0777(5)	0.1156(3)	0.2803(4)	0.0227(17)
O(5)	0.0898(5)	0.1002(3)	0.3399(3)	0.0434(18)
O(6)	0.0370(4)	0.0871(2)	0.2285(3)	0.0321(14)
C(30)	0.0027(7)	0.0339(4)	0.2480(6)	0.043(2)
C(31)	0.0311(5)	0.2022(3)	0.2125(4)	0.0204(17)
O(7)	0.0437(4)	0.2321(2)	0.1646(3)	0.0294(13)
O(8)	−0.0487(4)	0.1947(2)	0.2402(3)	0.0258(13)
C(32)	−0.1208(6)	0.2318(4)	0.2133(5)	0.031(2)
C(33)	0.6442(5)	0.1643(3)	0.1721(4)	0.0195(16)
C(34)	0.6072(5)	0.1089(4)	0.1527(4)	0.0252(18)
C(35)	0.7025(5)	0.1143(3)	0.1900(4)	0.0223(17)
N(5)	0.6067(4)	0.1939(3)	0.2285(3)	0.0196(14)
N(6)	0.6578(5)	0.2355(3)	0.2581(4)	0.0311(17)

C(36)	0.6070(6)	0.2549(4)	0.3078(5)	0.032(2)
C(37)	0.5260(5)	0.2261(3)	0.3119(4)	0.0210(17)
C(38)	0.5270(5)	0.1873(3)	0.2595(4)	0.0221(17)
I(3)	0.42330(3)	0.24185(2)	0.37896(3)	0.02477(16)
C(39)	0.5983(6)	0.0916(3)	0.0765(4)	0.0261(18)
C(40)	0.5678(6)	0.1268(4)	0.0232(5)	0.034(2)
C(41)	0.5596(8)	0.1094(5)	–0.0471(5)	0.048(3)
C(42)	0.5848(9)	0.0576(5)	–0.0633(6)	0.064(4)
C(43)	0.6166(10)	0.0223(5)	–0.0101(7)	0.070(4)
C(44)	0.6219(8)	0.0385(4)	0.0596(6)	0.055(3)
C(45)	0.7845(5)	0.0999(4)	0.1492(4)	0.0249(18)
O(9)	0.8232(4)	0.0579(3)	0.1568(4)	0.0394(16)
O(10)	0.8035(4)	0.1379(3)	0.1035(3)	0.0315(14)
C(46)	0.8804(7)	0.1240(5)	0.0626(5)	0.049(3)
C(47)	0.7118(6)	0.0973(3)	0.2661(4)	0.0255(18)
O(11)	0.6528(4)	0.0761(3)	0.2973(3)	0.0450(18)
O(12)	0.7946(4)	0.1098(3)	0.2944(3)	0.0362(15)
C(48)	0.8143(8)	0.0963(5)	0.3684(5)	0.054(3)
C(49)	0.7063(5)	0.1670(3)	0.6333(4)	0.0222(17)
C(50)	0.7459(5)	0.1128(3)	0.6520(4)	0.0205(16)
C(51)	0.6493(5)	0.1163(3)	0.6177(4)	0.0211(17)
N(7)	0.7404(4)	0.1966(3)	0.5754(3)	0.0200(14)
N(8)	0.6885(5)	0.2369(3)	0.5459(4)	0.0319(18)
C(52)	0.7392(6)	0.2564(4)	0.4954(5)	0.033(2)
C(53)	0.8212(5)	0.2281(3)	0.4918(4)	0.0193(16)
C(54)	0.8189(5)	0.1898(3)	0.5443(4)	0.0200(16)
I(4)	0.92303(3)	0.24147(2)	0.42360(3)	0.02406(16)
C(55)	0.7656(5)	0.0956(3)	0.7270(4)	0.0239(18)

C(56)	0.7792(6)	0.1329(4)	0.7816(5)	0.031(2)
C(57)	0.8004(8)	0.1150(4)	0.8499(5)	0.045(3)
C(58)	0.8079(8)	0.0608(4)	0.8645(6)	0.048(3)
C(59)	0.7956(7)	0.0234(4)	0.8103(5)	0.036(2)
C(60)	0.7749(6)	0.0415(4)	0.7425(5)	0.031(2)
C(61)	0.5700(6)	0.1024(3)	0.6622(5)	0.0336(18)
O(13)	0.5328(4)	0.0579(3)	0.6546(4)	0.0423(16)
O(14)	0.5502(4)	0.1382(3)	0.7061(4)	0.0445(17)
C(62)	0.4697(10)	0.1225(6)	0.7446(7)	0.053(4)
C(62X)	0.4556(19)	0.0554(15)	0.7047(15)	0.032(8)
C(63)	0.6362(6)	0.0996(3)	0.5415(4)	0.0281(19)
C(64)	0.5284(8)	0.0968(5)	0.4418(5)	0.052(3)

Table 3. Bond lengths [Å] and angles [°] for sdrc27.

C(1)–N(1)	1.426(11)	C(1)–C(2)	1.494(11)
C(1)–C(3)	1.518(11)	C(2)–C(7)	1.493(10)
C(2)–C(3)	1.533(10)	C(3)–C(13)	1.499(11)
C(3)–C(15)	1.506(11)	N(1)–C(6)	1.352(11)
N(1)–N(2)	1.363(9)	N(2)–C(4)	1.305(12)
C(4)–C(5)	1.402(12)	C(5)–C(6)	1.364(12)
C(5)–I(1)	2.077(8)	C(7)–C(8)	1.387(11)
C(7)–C(12)	1.404(11)	C(8)–C(9)	1.399(12)
C(9)–C(10)	1.361(13)	C(10)–C(11)	1.396(13)
C(11)–C(12)	1.389(12)	C(13)–O(1)	1.194(10)
C(13)–O(2)	1.339(11)	O(2)–C(14)	1.443(11)
C(15)–O(3)	1.192(9)	C(15)–O(4)	1.322(9)
O(4)–C(16)	1.448(10)	O(15)–C(63)	1.188(11)
O(16)–C(63)	1.332(11)	O(16)–C(64)	1.475(11)

C(17)–N(3)	1.419(11)	C(17)–C(18)	1.501(11)
C(17)–C(19)	1.518(11)	C(18)–C(23)	1.480(11)
C(18)–C(19)	1.530(10)	C(19)–C(29)	1.488(11)
C(19)–C(31)	1.513(11)	N(3)–N(4)	1.351(9)
N(3)–C(22)	1.355(10)	N(4)–C(20)	1.308(11)
C(20)–C(21)	1.411(12)	C(21)–C(22)	1.366(12)
C(21)–I(2)	2.076(8)	C(23)–C(24)	1.396(10)
C(23)–C(28)	1.401(11)	C(24)–C(25)	1.388(12)
C(25)–C(26)	1.393(13)	C(26)–C(27)	1.378(13)
C(27)–C(28)	1.397(12)	C(29)–O(5)	1.195(10)
C(29)–O(6)	1.315(10)	O(6)–C(30)	1.463(10)
C(31)–O(7)	1.194(10)	C(31)–O(8)	1.330(9)
O(8)–C(32)	1.462(10)	C(33)–N(5)	1.437(9)
C(33)–C(34)	1.506(11)	C(33)–C(35)	1.524(11)
C(34)–C(39)	1.506(11)	C(34)–C(35)	1.526(11)
C(35)–C(47)	1.503(12)	C(35)–C(45)	1.518(11)
N(5)–C(38)	1.354(10)	N(5)–N(6)	1.367(9)
N(6)–C(36)	1.333(11)	C(36)–C(37)	1.391(11)
C(37)–C(38)	1.381(11)	C(37)–I(3)	2.077(8)
C(39)–C(40)	1.383(13)	C(39)–C(44)	1.396(13)
C(40)–C(41)	1.399(13)	C(41)–C(42)	1.370(16)
C(42)–C(43)	1.386(18)	C(43)–C(44)	1.381(16)
C(45)–O(9)	1.185(10)	C(45)–O(10)	1.319(11)
O(10)–C(46)	1.455(10)	C(47)–O(11)	1.203(10)
C(47)–O(12)	1.327(10)	O(12)–C(48)	1.454(11)
C(49)–N(7)	1.439(10)	C(49)–C(50)	1.487(11)
C(49)–C(51)	1.519(11)	C(50)–C(55)	1.496(11)
C(50)–C(51)	1.519(10)	C(51)–C(63)	1.503(12)

C(51)–C(61)	1.525(11)	N(7)–C(54)	1.341(10)
N(7)–N(8)	1.349(9)	N(8)–C(52)	1.345(11)
C(52)–C(53)	1.395(11)	C(53)–C(54)	1.377(11)
C(53)–I(4)	2.071(7)	C(55)–C(60)	1.371(12)
C(55)–C(56)	1.389(12)	C(56)–C(57)	1.385(13)
C(57)–C(58)	1.366(14)	C(58)–C(59)	1.384(14)
C(59)–C(60)	1.376(12)	C(61)–O(13)	1.228(9)
C(61)–O(14)	1.264(9)	O(13)–C(62X)	1.53(2)
O(14)–C(62)	1.484(12)		

N(1)–C(1)–C(2)	118.8(7)	N(1)–C(1)–C(3)	117.8(7)
C(2)–C(1)–C(3)	61.2(5)	C(7)–C(2)–C(1)	123.0(7)
C(7)–C(2)–C(3)	122.6(6)	C(1)–C(2)–C(3)	60.2(5)
C(13)–C(3)–C(15)	117.0(7)	C(13)–C(3)–C(1)	117.1(7)
C(15)–C(3)–C(1)	116.3(7)	C(13)–C(3)–C(2)	119.0(7)
C(15)–C(3)–C(2)	116.0(6)	C(1)–C(3)–C(2)	58.6(5)
C(6)–N(1)–N(2)	111.6(7)	C(6)–N(1)–C(1)	128.4(7)
N(2)–N(1)–C(1)	119.8(7)	C(4)–N(2)–N(1)	105.3(7)
N(2)–C(4)–C(5)	111.1(8)	C(6)–C(5)–C(4)	105.9(8)
C(6)–C(5)–I(1)	125.9(6)	C(4)–C(5)–I(1)	128.2(7)
N(1)–C(6)–C(5)	106.1(7)	C(8)–C(7)–C(12)	119.0(7)
C(8)–C(7)–C(2)	123.5(7)	C(12)–C(7)–C(2)	117.4(7)
C(7)–C(8)–C(9)	119.4(8)	C(10)–C(9)–C(8)	121.7(8)
C(9)–C(10)–C(11)	119.6(8)	C(12)–C(11)–C(10)	119.5(8)
C(11)–C(12)–C(7)	120.8(8)	O(1)–C(13)–O(2)	124.8(8)
O(1)–C(13)–C(3)	125.7(8)	O(2)–C(13)–C(3)	109.5(7)
C(13)–O(2)–C(14)	115.5(8)	O(3)–C(15)–O(4)	125.3(7)
O(3)–C(15)–C(3)	124.7(7)	O(4)–C(15)–C(3)	110.0(6)

C(15)–O(4)–C(16)	114.2(6)	C(63)–O(16)–C(64)	116.0(7)
N(3)–C(17)–C(18)	119.9(7)	N(3)–C(17)–C(19)	118.1(7)
C(18)–C(17)–C(19)	60.9(5)	C(23)–C(18)–C(17)	123.3(7)
C(23)–C(18)–C(19)	124.0(7)	C(17)–C(18)–C(19)	60.1(5)
C(29)–C(19)–C(31)	117.2(6)	C(29)–C(19)–C(17)	118.0(6)
C(31)–C(19)–C(17)	114.5(7)	C(29)–C(19)–C(18)	119.8(7)
C(31)–C(19)–C(18)	115.6(6)	C(17)–C(19)–C(18)	59.0(5)
N(4)–N(3)–C(22)	111.9(7)	N(4)–N(3)–C(17)	119.5(6)
C(22)–N(3)–C(17)	128.5(7)	C(20)–N(4)–N(3)	105.4(7)
N(4)–C(20)–C(21)	111.3(7)	C(22)–C(21)–C(20)	105.0(7)
C(22)–C(21)–I(2)	128.4(6)	C(20)–C(21)–I(2)	126.5(6)
N(3)–C(22)–C(21)	106.4(7)	C(24)–C(23)–C(28)	118.4(7)
C(24)–C(23)–C(18)	118.1(7)	C(28)–C(23)–C(18)	123.5(7)
C(25)–C(24)–C(23)	121.0(8)	C(24)–C(25)–C(26)	119.9(8)
C(27)–C(26)–C(25)	119.9(8)	C(26)–C(27)–C(28)	120.2(8)
C(27)–C(28)–C(23)	120.5(8)	O(5)–C(29)–O(6)	124.7(8)
O(5)–C(29)–C(19)	125.7(8)	O(6)–C(29)–C(19)	109.6(6)
C(29)–O(6)–C(30)	115.7(7)	O(7)–C(31)–O(8)	125.1(7)
O(7)–C(31)–C(19)	125.2(7)	O(8)–C(31)–C(19)	109.6(7)
C(31)–O(8)–C(32)	114.1(6)	N(5)–C(33)–C(34)	119.4(7)
N(5)–C(33)–C(35)	118.8(6)	C(34)–C(33)–C(35)	60.5(5)
C(33)–C(34)–C(39)	119.7(7)	C(33)–C(34)–C(35)	60.3(5)
C(39)–C(34)–C(35)	119.0(7)	C(47)–C(35)–C(45)	113.9(7)
C(47)–C(35)–C(33)	116.8(6)	C(45)–C(35)–C(33)	121.7(7)
C(47)–C(35)–C(34)	116.1(7)	C(45)–C(35)–C(34)	118.4(7)
C(33)–C(35)–C(34)	59.2(5)	C(38)–N(5)–N(6)	112.0(6)
C(38)–N(5)–C(33)	130.7(7)	N(6)–N(5)–C(33)	117.3(6)
C(36)–N(6)–N(5)	104.1(7)	N(6)–C(36)–C(37)	112.2(8)

C(38)–C(37)–C(36)	105.1(7)	C(38)–C(37)–I(3)	128.1(6)
C(36)–C(37)–I(3)	126.7(6)	N(5)–C(38)–C(37)	106.6(7)
C(40)–C(39)–C(44)	119.4(8)	C(40)–C(39)–C(34)	121.9(8)
C(44)–C(39)–C(34)	118.6(8)	C(39)–C(40)–C(41)	120.6(9)
C(42)–C(41)–C(40)	119.5(10)	C(41)–C(42)–C(43)	120.1(10)
C(44)–C(43)–C(42)	120.8(11)	C(43)–C(44)–C(39)	119.5(11)
O(9)–C(45)–O(10)	125.3(8)	O(9)–C(45)–C(35)	122.1(8)
O(10)–C(45)–C(35)	112.5(7)	C(45)–O(10)–C(46)	113.1(7)
O(11)–C(47)–O(12)	124.8(8)	O(11)–C(47)–C(35)	125.2(8)
O(12)–C(47)–C(35)	110.0(7)	C(47)–O(12)–C(48)	116.8(7)
N(7)–C(49)–C(50)	119.1(7)	N(7)–C(49)–C(51)	118.9(7)
C(50)–C(49)–C(51)	60.7(5)	C(49)–C(50)–C(55)	121.8(7)
C(49)–C(50)–C(51)	60.7(5)	C(55)–C(50)–C(51)	122.4(7)
C(63)–C(51)–C(49)	116.4(7)	C(63)–C(51)–C(50)	116.6(7)
C(49)–C(51)–C(50)	58.6(5)	C(63)–C(51)–C(61)	115.0(7)
C(49)–C(51)–C(61)	120.5(7)	C(50)–C(51)–C(61)	118.2(7)
C(54)–N(7)–N(8)	112.6(6)	C(54)–N(7)–C(49)	129.0(7)
N(8)–N(7)–C(49)	118.4(6)	C(52)–N(8)–N(7)	103.6(7)
N(8)–C(52)–C(53)	112.3(7)	C(54)–C(53)–C(52)	103.9(7)
C(54)–C(53)–I(4)	128.2(6)	C(52)–C(53)–I(4)	127.8(6)
N(7)–C(54)–C(53)	107.5(7)	C(60)–C(55)–C(56)	118.5(8)
C(60)–C(55)–C(50)	119.3(8)	C(56)–C(55)–C(50)	122.1(7)
C(57)–C(56)–C(55)	120.0(8)	C(58)–C(57)–C(56)	120.7(9)
C(57)–C(58)–C(59)	119.7(9)	C(60)–C(59)–C(58)	119.4(9)
C(55)–C(60)–C(59)	121.8(9)	O(13)–C(61)–O(14)	125.6(8)
O(13)–C(61)–C(51)	119.0(7)	O(14)–C(61)–C(51)	115.4(7)
C(61)–O(13)–C(62X)	107.6(15)	C(61)–O(14)–C(62)	111.8(8)
O(15)–C(63)–O(16)	125.6(8)	O(15)–C(63)–C(51)	124.5(8)

O(16)–C(63)–C(51) 109.9(7)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sdrc27.

	x	y	z	U
H(1)	0.1524	0.1917	0.4582	0.030
H(2)	0.1409	0.2135	0.6081	0.022
H(4)	0.2969	0.3639	0.4485	0.040
H(6)	0.0809	0.3037	0.5419	0.032
H(8)	0.0743	0.1171	0.4682	0.031
H(9)	–0.0330	0.0476	0.4787	0.034
H(10)	–0.0878	0.0267	0.5860	0.038
H(11)	–0.0451	0.0802	0.6855	0.033
H(12)	0.0596	0.1509	0.6761	0.029
H(14A)	0.2746	0.0187	0.5322	0.089
H(14B)	0.3399	0.0153	0.6032	0.089
H(14C)	0.3793	0.0372	0.5321	0.089
H(16A)	0.4514	0.2708	0.5932	0.054
H(16B)	0.5253	0.2279	0.5696	0.054
H(16C)	0.4864	0.2233	0.6459	0.054
H(17)	0.1965	0.1857	0.3442	0.027
H(18)	0.2061	0.2059	0.1937	0.024
H(20)	0.0485	0.3558	0.3541	0.035
H(22)	0.2641	0.2978	0.2583	0.027
H(24)	0.2893	0.1442	0.1266	0.027
H(25)	0.3989	0.0763	0.1187	0.035
H(26)	0.4479	0.0259	0.2190	0.040

H(27)	0.3903	0.0454	0.3271	0.036
H(28)	0.2786	0.1126	0.3353	0.028
H(30A)	0.0512	0.0139	0.2751	0.065
H(30B)	–0.0165	0.0134	0.2052	0.065
H(30C)	–0.0497	0.0385	0.2768	0.065
H(32A)	–0.1031	0.2692	0.2254	0.047
H(32B)	–0.1779	0.2229	0.2346	0.047
H(32C)	–0.1297	0.2282	0.1619	0.047
H(33)	0.6636	0.1868	0.1320	0.023
H(34)	0.5587	0.0949	0.1825	0.030
H(36)	0.6241	0.2851	0.3370	0.039
H(38)	0.4809	0.1611	0.2475	0.026
H(40)	0.5522	0.1631	0.0343	0.040
H(41)	0.5367	0.1334	–0.0833	0.058
H(42)	0.5805	0.0457	–0.1110	0.077
H(43)	0.6349	–0.0134	–0.0218	0.084
H(44)	0.6415	0.0137	0.0958	0.066
H(46A)	0.9349	0.1179	0.0945	0.074
H(46B)	0.8920	0.1538	0.0303	0.074
H(46C)	0.8661	0.0909	0.0354	0.074
H(48A)	0.7686	0.1133	0.3965	0.080
H(48B)	0.8753	0.1097	0.3842	0.080
H(48C)	0.8124	0.0568	0.3744	0.080
H(49)	0.6882	0.1894	0.6738	0.027
H(50)	0.7922	0.1000	0.6195	0.025
H(52)	0.7213	0.2860	0.4655	0.039
H(54)	0.8646	0.1634	0.5564	0.024
H(56)	0.7739	0.1707	0.7720	0.037

H(57)	0.8099	0.1407	0.8869	0.053
H(58)	0.8216	0.0489	0.9116	0.057
H(59)	0.8013	–0.0143	0.8198	0.043
H(60)	0.7668	0.0157	0.7054	0.037
H(62A)	0.4186	0.1133	0.7107	0.080
H(62B)	0.4520	0.1530	0.7740	0.080
H(62C)	0.4852	0.0910	0.7747	0.080
H(62D)	0.4245	0.0203	0.6997	0.049
H(62E)	0.4117	0.0847	0.6931	0.049
H(62F)	0.4813	0.0598	0.7534	0.049
H(64A)	0.5579	0.1240	0.4132	0.079
H(64B)	0.4620	0.0982	0.4312	0.079
H(64C)	0.5509	0.0606	0.4307	0.079

Table 5. Torsion angles [°] for sdrc27.

N(1)–C(1)–C(2)–C(7)	140.6(7)	C(3)–C(1)–C(2)–C(7)	−111.6(8)
N(1)–C(1)–C(2)–C(3)	−107.7(8)	N(1)–C(1)–C(3)–C(13)	−141.5(7)
C(2)–C(1)–C(3)–C(13)	109.1(8)	N(1)–C(1)–C(3)–C(15)	3.6(10)
C(2)–C(1)–C(3)–C(15)	−105.8(7)	N(1)–C(1)–C(3)–C(2)	109.4(8)
C(7)–C(2)–C(3)–C(13)	6.5(11)	C(1)–C(2)–C(3)–C(13)	−105.7(8)
C(7)–C(2)–C(3)–C(15)	−141.6(7)	C(1)–C(2)–C(3)–C(15)	106.2(7)
C(7)–C(2)–C(3)–C(1)	112.2(8)	C(2)–C(1)–N(1)–C(6)	−46.3(11)
C(3)–C(1)–N(1)–C(6)	−116.9(9)	C(2)–C(1)–N(1)–N(2)	138.4(7)
C(3)–C(1)–N(1)–N(2)	67.8(9)	C(6)–N(1)–N(2)–C(4)	–0.4(9)
C(1)–N(1)–N(2)–C(4)	175.6(7)	N(1)–N(2)–C(4)–C(5)	0.8(10)
N(2)–C(4)–C(5)–C(6)	–0.9(10)	N(2)–C(4)–C(5)–I(1)	−178.0(6)
N(2)–N(1)–C(6)–C(5)	–0.1(9)	C(1)–N(1)–C(6)–C(5)	−175.8(8)

C(4)–C(5)–C(6)–N(1)	0.6(9)	I(1)–C(5)–C(6)–N(1)	177.8(6)
C(1)–C(2)–C(7)–C(8)	14.0(11)	C(3)–C(2)–C(7)–C(8)	−59.2(10)
C(1)–C(2)–C(7)–C(12)	−168.3(7)	C(3)–C(2)–C(7)–C(12)	118.4(8)
C(12)–C(7)–C(8)–C(9)	0.8(11)	C(2)–C(7)–C(8)–C(9)	178.5(7)
C(7)–C(8)–C(9)–C(10)	−2.0(13)	C(8)–C(9)–C(10)–C(11)	2.4(13)
C(9)–C(10)–C(11)–C(12)	−1.7(12)	C(10)–C(11)–C(12)–C(7)	0.6(12)
C(8)–C(7)–C(12)–C(11)	−0.2(11)	C(2)–C(7)–C(12)–C(11)	−177.9(7)
C(15)–C(3)–C(13)–O(1)	−121.3(9)	C(1)–C(3)–C(13)–O(1)	23.5(12)
C(2)–C(3)–C(13)–O(1)	90.9(10)	C(15)–C(3)–C(13)–O(2)	58.3(9)
C(1)–C(3)–C(13)–O(2)	−156.8(7)	C(2)–C(3)–C(13)–O(2)	−89.4(8)
O(1)–C(13)–O(2)–C(14)	−1.7(13)	C(3)–C(13)–O(2)–C(14)	178.6(8)
C(13)–C(3)–C(15)–O(3)	−149.8(8)	C(1)–C(3)–C(15)–O(3)	65.1(10)
C(2)–C(3)–C(15)–O(3)	−1.0(11)	C(13)–C(3)–C(15)–O(4)	33.3(9)
C(1)–C(3)–C(15)–O(4)	−111.8(7)	C(2)–C(3)–C(15)–O(4)	−178.0(6)
O(3)–C(15)–O(4)–C(16)	−6.2(12)	C(3)–C(15)–O(4)–C(16)	170.7(7)
N(3)–C(17)–C(18)–C(23)	139.2(7)	C(19)–C(17)–C(18)–C(23)	−113.3(8)
N(3)–C(17)–C(18)–C(19)	−107.5(8)	N(3)–C(17)–C(19)–C(29)	−139.8(7)
C(18)–C(17)–C(19)–C(29)	109.7(8)	N(3)–C(17)–C(19)–C(31)	4.2(9)
C(18)–C(17)–C(19)–C(31)	−106.3(7)	N(3)–C(17)–C(19)–C(18)	110.5(7)
C(23)–C(18)–C(19)–C(29)	5.5(11)	C(17)–C(18)–C(19)–C(29)	−106.6(8)
C(23)–C(18)–C(19)–C(31)	−143.6(7)	C(17)–C(18)–C(19)–C(31)	104.3(8)
C(23)–C(18)–C(19)–C(17)	112.1(8)	C(18)–C(17)–N(3)–N(4)	139.2(7)
C(19)–C(17)–N(3)–N(4)	68.5(9)	C(18)–C(17)–N(3)–C(22)	−45.3(11)
C(19)–C(17)–N(3)–C(22)	−116.1(8)	C(22)–N(3)–N(4)–C(20)	0.5(9)
C(17)–N(3)–N(4)–C(20)	176.6(7)	N(3)–N(4)–C(20)–C(21)	0.0(9)
N(4)–C(20)–C(21)–C(22)	−0.4(10)	N(4)–C(20)–C(21)–I(2)	−177.9(6)
N(4)–N(3)–C(22)–C(21)	−0.8(9)	C(17)–N(3)–C(22)–C(21)	−176.5(7)
C(20)–C(21)–C(22)–N(3)	0.7(9)	I(2)–C(21)–C(22)–N(3)	178.1(6)

C(17)–C(18)–C(23)–C(24)	−166.6(7)	C(19)–C(18)–C(23)–C(24)	119.4(8)
C(17)–C(18)–C(23)–C(28)	13.8(11)	C(19)–C(18)–C(23)–C(28)	−60.2(10)
C(28)–C(23)–C(24)–C(25)	0.3(11)	C(18)–C(23)–C(24)–C(25)	−179.4(7)
C(23)–C(24)–C(25)–C(26)	0.1(12)	C(24)–C(25)–C(26)–C(27)	−0.9(13)
C(25)–C(26)–C(27)–C(28)	1.4(13)	C(26)–C(27)–C(28)–C(23)	−1.0(12)
C(24)–C(23)–C(28)–C(27)	0.2(11)	C(18)–C(23)–C(28)–C(27)	179.8(7)
C(31)–C(19)–C(29)–O(5)	−127.6(9)	C(17)–C(19)–C(29)–O(5)	15.4(12)
C(18)–C(19)–C(29)–O(5)	83.8(11)	C(31)–C(19)–C(29)–O(6)	51.4(9)
C(17)–C(19)–C(29)–O(6)	−165.6(7)	C(18)–C(19)–C(29)–O(6)	−97.2(8)
O(5)–C(29)–O(6)–C(30)	1.9(12)	C(19)–C(29)–O(6)–C(30)	−177.1(7)
C(29)–C(19)–C(31)–O(7)	−146.7(8)	C(17)–C(19)–C(31)–O(7)	69.0(10)
C(18)–C(19)–C(31)–O(7)	3.2(11)	C(29)–C(19)–C(31)–O(8)	36.4(9)
C(17)–C(19)–C(31)–O(8)	−107.9(7)	C(18)–C(19)–C(31)–O(8)	−173.7(6)
O(7)–C(31)–O(8)–C(32)	−7.6(11)	C(19)–C(31)–O(8)–C(32)	169.3(6)
N(5)–C(33)–C(34)–C(39)	143.1(7)	C(35)–C(33)–C(34)–C(39)	−108.5(8)
N(5)–C(33)–C(34)–C(35)	−108.4(8)	N(5)–C(33)–C(35)–C(47)	3.6(10)
C(34)–C(33)–C(35)–C(47)	−105.8(8)	N(5)–C(33)–C(35)–C(45)	−144.2(7)
C(34)–C(33)–C(35)–C(45)	106.3(8)	N(5)–C(33)–C(35)–C(34)	109.5(8)
C(33)–C(34)–C(35)–C(47)	107.0(8)	C(39)–C(34)–C(35)–C(47)	−143.3(8)
C(33)–C(34)–C(35)–C(45)	−111.9(8)	C(39)–C(34)–C(35)–C(45)	−2.2(12)
C(39)–C(34)–C(35)–C(33)	109.7(8)	C(34)–C(33)–N(5)–C(38)	−17.8(12)
C(35)–C(33)–N(5)–C(38)	−88.2(10)	C(34)–C(33)–N(5)–N(6)	161.2(7)
C(35)–C(33)–N(5)–N(6)	90.8(9)	C(38)–N(5)–N(6)–C(36)	−0.8(10)
C(33)–N(5)–N(6)–C(36)	−180.0(7)	N(5)–N(6)–C(36)–C(37)	1.6(10)
N(6)–C(36)–C(37)–C(38)	−1.7(11)	N(6)–C(36)–C(37)–I(3)	−178.4(6)
N(6)–N(5)–C(38)–C(37)	−0.2(9)	C(33)–N(5)–C(38)–C(37)	178.8(7)
C(36)–C(37)–C(38)–N(5)	1.1(9)	I(3)–C(37)–C(38)–N(5)	177.8(5)
C(33)–C(34)–C(39)–C(40)	−40.6(11)	C(35)–C(34)–C(39)–C(40)	−111.0(10)

C(33)–C(34)–C(39)–C(44)	139.3(9)	C(35)–C(34)–C(39)–C(44)	68.8(12)
C(44)–C(39)–C(40)–C(41)	0.7(14)	C(34)–C(39)–C(40)–C(41)	−179.5(9)
C(39)–C(40)–C(41)–C(42)	−2.1(16)	C(40)–C(41)–C(42)–C(43)	1.2(19)
C(41)–C(42)–C(43)–C(44)	1(2)	C(42)–C(43)–C(44)–C(39)	−2(2)
C(40)–C(39)–C(44)–C(43)	1.6(17)	C(34)–C(39)–C(44)–C(43)	−178.3(11)
C(47)–C(35)–C(45)–O(9)	40.9(11)	C(33)–C(35)–C(45)–O(9)	−170.4(8)
C(34)–C(35)–C(45)–O(9)	−101.0(10)	C(47)–C(35)–C(45)–O(10)	−142.1(7)
C(33)–C(35)–C(45)–O(10)	6.5(10)	C(34)–C(35)–C(45)–O(10)	76.0(9)
O(9)–C(45)–O(10)–C(46)	−1.5(12)	C(35)–C(45)–O(10)–C(46)	−178.3(7)
C(45)–C(35)–C(47)–O(11)	−136.3(9)	C(33)–C(35)–C(47)–O(11)	73.4(11)
C(34)–C(35)–C(47)–O(11)	6.5(12)	C(45)–C(35)–C(47)–O(12)	44.3(9)
C(33)–C(35)–C(47)–O(12)	−105.9(8)	C(34)–C(35)–C(47)–O(12)	−172.9(7)
O(11)–C(47)–O(12)–C(48)	0.2(14)	C(35)–C(47)–O(12)–C(48)	179.5(8)
N(7)–C(49)–C(50)–C(55)	139.2(7)	C(51)–C(49)–C(50)–C(55)	−112.0(8)
N(7)–C(49)–C(50)–C(51)	−108.7(8)	N(7)–C(49)–C(51)–C(63)	2.7(10)
C(50)–C(49)–C(51)–C(63)	−106.5(8)	N(7)–C(49)–C(51)–C(50)	109.1(8)
N(7)–C(49)–C(51)–C(61)	−144.4(7)	C(50)–C(49)–C(51)–C(61)	106.5(8)
C(49)–C(50)–C(51)–C(63)	106.0(8)	C(55)–C(50)–C(51)–C(63)	−142.9(8)
C(55)–C(50)–C(51)–C(49)	111.0(8)	C(49)–C(50)–C(51)–C(61)	−110.3(8)
C(55)–C(50)–C(51)–C(61)	0.7(11)	C(50)–C(49)–N(7)–C(54)	−18.2(12)
C(51)–C(49)–N(7)–C(54)	−88.8(10)	C(50)–C(49)–N(7)–N(8)	161.2(7)
C(51)–C(49)–N(7)–N(8)	90.6(9)	C(54)–N(7)–N(8)–C(52)	−1.4(10)
C(49)–N(7)–N(8)–C(52)	179.1(7)	N(7)–N(8)–C(52)–C(53)	1.2(11)
N(8)–C(52)–C(53)–C(54)	−0.6(11)	N(8)–C(52)–C(53)–I(4)	179.8(6)
N(8)–N(7)–C(54)–C(53)	1.0(9)	C(49)–N(7)–C(54)–C(53)	−179.5(7)
C(52)–C(53)–C(54)–N(7)	−0.2(9)	I(4)–C(53)–C(54)–N(7)	179.3(5)
C(49)–C(50)–C(55)–C(60)	160.1(7)	C(51)–C(50)–C(55)–C(60)	86.9(10)
C(49)–C(50)–C(55)–C(56)	−23.0(11)	C(51)–C(50)–C(55)–C(56)	−96.2(10)

C(60)–C(55)–C(56)–C(57)	−0.8(13)	C(50)–C(55)–C(56)–C(57)	−177.7(8)
C(55)–C(56)–C(57)–C(58)	−0.2(16)	C(56)–C(57)–C(58)–C(59)	1.0(17)
C(57)–C(58)–C(59)–C(60)	−0.7(16)	C(56)–C(55)–C(60)–C(59)	1.1(13)
C(50)–C(55)–C(60)–C(59)	178.1(8)	C(58)–C(59)–C(60)–C(55)	−0.4(14)
C(63)–C(51)–C(61)–O(13)	42.0(11)	C(49)–C(51)–C(61)–O(13)	−170.5(8)
C(50)–C(51)–C(61)–O(13)	−102.2(10)	C(63)–C(51)–C(61)–O(14)	−140.0(8)
C(49)–C(51)–C(61)–O(14)	7.5(12)	C(50)–C(51)–C(61)–O(14)	75.8(10)
O(14)–C(61)–O(13)–C(62X)	3.1(18)	C(51)–C(61)–O(13)–C(62X)	179.2(15)
O(13)–C(61)–O(14)–C(62)	−5.0(15)	C(51)–C(61)–O(14)–C(62)	177.2(9)
C(64)–O(16)–C(63)–O(15)	−2.7(13)	C(64)–O(16)–C(63)–C(51)	176.6(8)
C(49)–C(51)–C(63)–O(15)	70.0(11)	C(50)–C(51)–C(63)–O(15)	3.7(12)
C(61)–C(51)–C(63)–O(15)	−141.1(9)	C(49)–C(51)–C(63)–O(16)	−109.2(8)
C(50)–C(51)–C(63)–O(16)	−175.6(7)	C(61)–C(51)–C(63)–O(16)	39.6(10)

6.4. **Appendix IV:** X-Ray crystallographic data for **187$_a$**

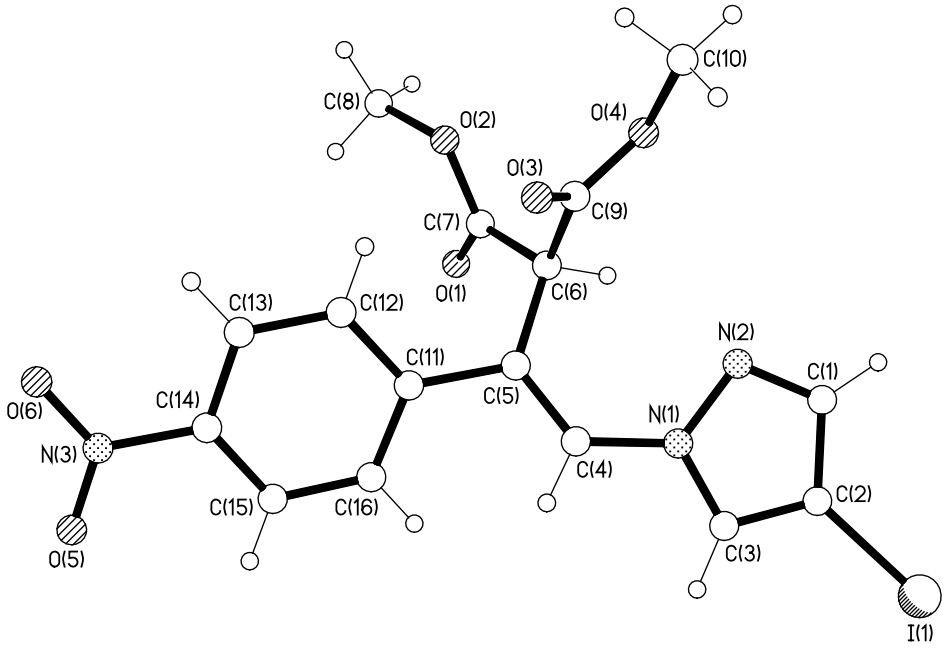


Table 1. Crystal data and structure refinement for sdrc29.

Identification code	sdrc29	
Chemical formula	$C_{16}H_{14}IN_3O_6$	
Formula weight	471.20	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	monoclinic, I2/a	
Unit cell parameters	a = 20.177(10) Å	□ = 90°
	b = 7.744(4) Å	□ = 93.667(4)°
	c = 22.960(17) Å	□ = 90°
Cell volume	3580(4) $Å^3$	
Z	8	
Calculated density	1.748 g/cm^3	
Absorption coefficient □	1.827 mm^{-1}	
F(000)	1856	
Crystal colour and size	colourless, 0.26 × 0.25 × 0.13 mm^3	
Reflections for cell refinement	2779 (□ range 2.60 to 26.18°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	1.78 to 25.00°	
Index ranges	h –23 to 23, k –8 to 9, l –27 to 26	
Completeness to □ = 25.00°	97.1 %	
Intensity decay	0%	
Reflections collected	7713	
Independent reflections	3058 (R_{int} = 0.0454)	
Reflections with F^2>2□	2335	

Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.648 and 0.797
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0913, 188.9837
Data / restraints / parameters	3058 / 0 / 237
Final R indices [F^2>2□]	R1 = 0.0955, wR2 = 0.2297
R indices (all data)	R1 = 0.1158, wR2 = 0.2419
Goodness-of-fit on F^2	1.097
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	5.287 and −2.201 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sdrc29. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.4221(5)	0.8163(13)	0.4617(4)	0.030(2)
N(2)	0.3643(6)	0.8606(16)	0.4857(5)	0.041(3)
C(1)	0.3208(7)	0.876(2)	0.4404(6)	0.045(4)
C(2)	0.3501(7)	0.8395(17)	0.3873(5)	0.032(3)
I(1)	0.31074(5)	0.84474(13)	0.30275(4)	0.0428(4)
C(3)	0.4155(6)	0.8049(16)	0.4036(5)	0.030(3)
C(4)	0.4830(6)	0.7792(15)	0.4936(6)	0.029(3)
C(5)	0.4925(6)	0.7379(16)	0.5494(5)	0.025(3)
C(6)	0.4381(6)	0.7248(15)	0.5912(5)	0.023(2)
C(7)	0.4462(6)	0.5720(16)	0.6309(5)	0.026(3)
O(1)	0.4552(4)	0.4278(11)	0.6144(4)	0.031(2)

O(2)	0.4499(5)	0.6168(11)	0.6873(4)	0.038(2)
C(8)	0.4624(10)	0.475(2)	0.7282(6)	0.058(5)
C(9)	0.4265(6)	0.8972(16)	0.6218(5)	0.029(3)
O(3)	0.4678(5)	0.9969(11)	0.6334(5)	0.042(2)
O(4)	0.3642(5)	0.9134(13)	0.6342(5)	0.052(3)
C(10)	0.3480(10)	1.076(2)	0.6611(12)	0.087(8)
C(11)	0.5622(6)	0.6981(16)	0.5706(5)	0.025(3)
C(12)	0.5860(6)	0.7247(17)	0.6284(5)	0.029(3)
C(13)	0.6499(7)	0.6817(16)	0.6471(6)	0.034(3)
C(14)	0.6907(6)	0.6042(16)	0.6072(6)	0.029(3)
C(15)	0.6690(6)	0.5752(17)	0.5503(6)	0.031(3)
C(16)	0.6049(6)	0.6176(16)	0.5324(6)	0.030(3)
N(3)	0.7582(5)	0.5541(16)	0.6278(6)	0.039(3)
O(5)	0.7936(5)	0.4876(15)	0.5928(5)	0.053(3)
O(6)	0.7768(5)	0.5811(14)	0.6788(4)	0.046(3)

Table 3. Bond lengths [Å] and angles [°] for sdrc29.

N(1)–C(3)	1.335(16)	N(1)–N(2)	1.364(15)
N(1)–C(4)	1.419(16)	N(2)–C(1)	1.323(18)
C(1)–C(2)	1.42(2)	C(2)–C(3)	1.375(18)
C(2)–I(1)	2.051(13)	C(4)–C(5)	1.322(18)
C(5)–C(11)	1.490(16)	C(5)–C(6)	1.507(16)
C(6)–C(7)	1.497(16)	C(6)–C(9)	1.534(17)
C(7)–O(1)	1.197(15)	C(7)–O(2)	1.337(14)
O(2)–C(8)	1.455(16)	C(9)–O(3)	1.154(15)
C(9)–O(4)	1.314(16)	O(4)–C(10)	1.450(18)
C(11)–C(12)	1.397(17)	C(11)–C(16)	1.413(18)

C(12)–C(13)	1.374(18)	C(13)–C(14)	1.404(19)
C(14)–C(15)	1.369(18)	C(14)–N(3)	1.465(16)
C(15)–C(16)	1.371(17)	N(3)–O(5)	1.223(16)
N(3)–O(6)	1.224(15)		

C(3)–N(1)–N(2)	112.8(10)	C(3)–N(1)–C(4)	121.9(11)
N(2)–N(1)–C(4)	125.3(11)	C(1)–N(2)–N(1)	104.3(11)
N(2)–C(1)–C(2)	111.5(13)	C(3)–C(2)–C(1)	104.6(11)
C(3)–C(2)–I(1)	124.6(10)	C(1)–C(2)–I(1)	130.7(10)
N(1)–C(3)–C(2)	106.9(11)	C(5)–C(4)–N(1)	128.0(12)
C(4)–C(5)–C(11)	116.3(11)	C(4)–C(5)–C(6)	124.5(11)
C(11)–C(5)–C(6)	119.2(10)	C(7)–C(6)–C(5)	112.8(10)
C(7)–C(6)–C(9)	115.0(10)	C(5)–C(6)–C(9)	111.9(10)
O(1)–C(7)–O(2)	123.2(11)	O(1)–C(7)–C(6)	123.9(10)
O(2)–C(7)–C(6)	112.5(11)	C(7)–O(2)–C(8)	115.2(10)
O(3)–C(9)–O(4)	124.9(12)	O(3)–C(9)–C(6)	124.0(12)
O(4)–C(9)–C(6)	111.1(11)	C(9)–O(4)–C(10)	114.8(12)
C(12)–C(11)–C(16)	117.9(11)	C(12)–C(11)–C(5)	122.7(11)
C(16)–C(11)–C(5)	119.3(11)	C(13)–C(12)–C(11)	121.3(12)
C(12)–C(13)–C(14)	118.6(12)	C(15)–C(14)–C(13)	121.8(12)
C(15)–C(14)–N(3)	119.9(12)	C(13)–C(14)–N(3)	118.3(12)
C(14)–C(15)–C(16)	119.0(12)	C(15)–C(16)–C(11)	121.4(12)
O(5)–N(3)–O(6)	123.0(11)	O(5)–N(3)–C(14)	118.0(12)
O(6)–N(3)–C(14)	119.0(12)		

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sdrc29.

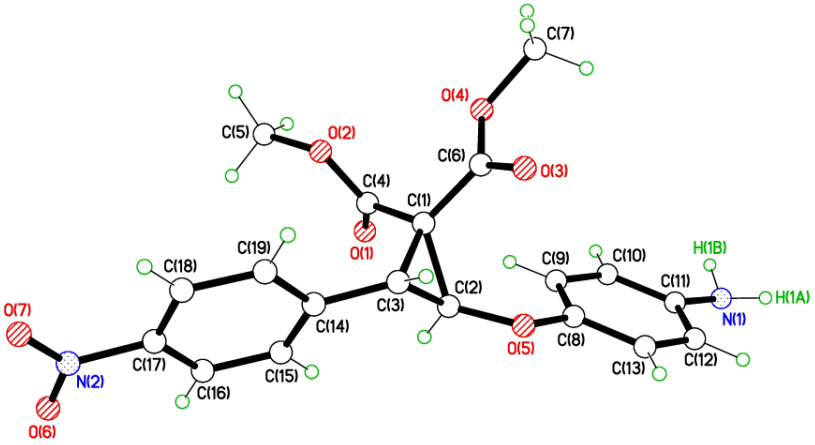
	x	y	z	U
H(1)	0.2755	0.9067	0.4431	0.054
H(3)	0.4495	0.7781	0.3784	0.036
H(4)	0.5217	0.7848	0.4722	0.035
H(6)	0.3966	0.7023	0.5662	0.028
H(8A)	0.4985	0.4031	0.7151	0.087
H(8B)	0.4221	0.4055	0.7300	0.087
H(8C)	0.4750	0.5219	0.7670	0.087
H(10A)	0.3565	1.1712	0.6344	0.131
H(10B)	0.3756	1.0909	0.6974	0.131
H(10C)	0.3011	1.0764	0.6697	0.131
H(12)	0.5574	0.7735	0.6553	0.035
H(13)	0.6661	0.7039	0.6861	0.040
H(15)	0.6979	0.5264	0.5237	0.037
H(16)	0.5889	0.5923	0.4936	0.036

Table 6. Torsion angles [°] for sdrc29.

C(3)–N(1)–N(2)–C(1)	0.4(15)	C(4)–N(1)–N(2)–C(1)	–177.4(12)
N(1)–N(2)–C(1)–C(2)	0.6(17)	N(2)–C(1)–C(2)–C(3)	–1.3(17)
N(2)–C(1)–C(2)–I(1)	–178.5(10)	N(2)–N(1)–C(3)–C(2)	–1.3(15)
C(4)–N(1)–C(3)–C(2)	176.7(11)	C(1)–C(2)–C(3)–N(1)	1.5(15)
I(1)–C(2)–C(3)–N(1)	178.9(9)	C(3)–N(1)–C(4)–C(5)	–159.2(13)
N(2)–N(1)–C(4)–C(5)	18(2)	N(1)–C(4)–C(5)–C(11)	177.4(11)
N(1)–C(4)–C(5)–C(6)	–1(2)	C(4)–C(5)–C(6)–C(7)	138.2(12)
C(11)–C(5)–C(6)–C(7)	–40.2(15)	C(4)–C(5)–C(6)–C(9)	–90.4(14)
C(11)–C(5)–C(6)–C(9)	91.2(13)	C(5)–C(6)–C(7)–O(1)	–50.6(16)
C(9)–C(6)–C(7)–O(1)	179.5(12)	C(5)–C(6)–C(7)–O(2)	122.1(11)
C(9)–C(6)–C(7)–O(2)	–7.8(15)	O(1)–C(7)–O(2)–C(8)	–3.2(19)

C(6)–C(7)–O(2)–C(8)	–175.9(12)	C(7)–C(6)–C(9)–O(3)	97.9(15)
C(5)–C(6)–C(9)–O(3)	–32.4(17)	C(7)–C(6)–C(9)–O(4)	–80.4(13)
C(5)–C(6)–C(9)–O(4)	149.3(11)	O(3)–C(9)–O(4)–C(10)	4(2)
C(6)–C(9)–O(4)–C(10)	–177.6(15)	C(4)–C(5)–C(11)–C(12)	151.7(12)
C(6)–C(5)–C(11)–C(12)	–29.7(17)	C(4)–C(5)–C(11)–C(16)	–33.4(17)
C(6)–C(5)–C(11)–C(16)	145.2(11)	C(16)–C(11)–C(12)–C(13)	3.0(19)
C(5)–C(11)–C(12)–C(13)	178.0(12)	C(11)–C(12)–C(13)–C(14)	–2.2(19)
C(12)–C(13)–C(14)–C(15)	1.8(19)	C(12)–C(13)–C(14)–N(3)	–178.3(12)
C(13)–C(14)–C(15)–C(16)	–2.3(19)	N(3)–C(14)–C(15)–C(16)	177.8(11)
C(14)–C(15)–C(16)–C(11)	3.2(19)	C(12)–C(11)–C(16)–C(15)	–3.5(18)
C(5)–C(11)–C(16)–C(15)	–178.7(11)	C(15)–C(14)–N(3)–O(5)	0.4(19)
C(13)–C(14)–N(3)–O(5)	–179.6(12)	C(15)–C(14)–N(3)–O(6)	180.0(12)
C(13)–C(14)–N(3)–O(6)	0.0(18)		

6.5. **Appendix V:** X-Ray crystallographic data for **191$_e$**



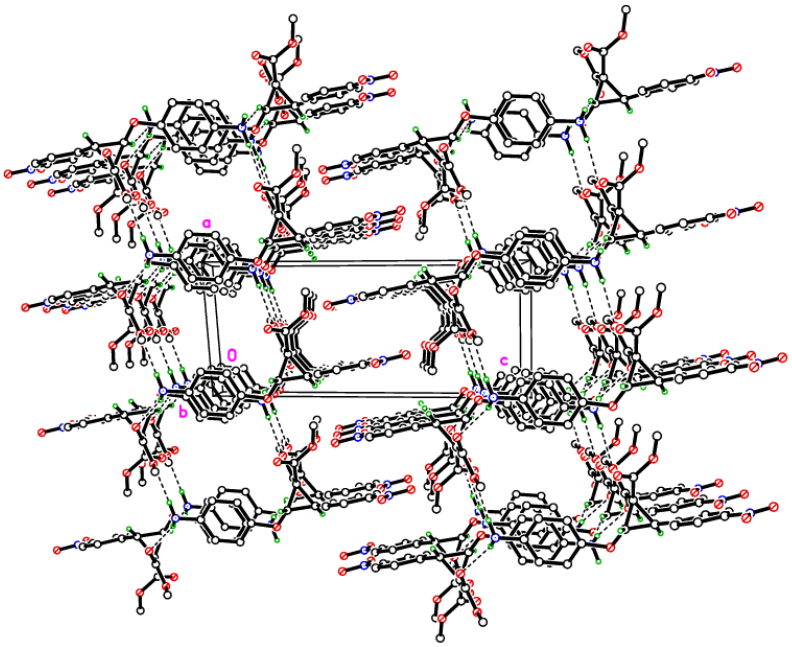


Table 1. Crystal data and structure refinement for sdrc37.

Identification code	sdrc37	
Chemical formula	$C_{19}H_{18}N_2O_7$	
Formula weight	386.35	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	triclinic, P $\bar{1}$	
Unit cell parameters	a = 7.9396(4) Å	□ = 78.8916(8)°
	b = 8.0836(4) Å	□ = 86.8382(8)°
	c = 16.8025(9) Å	□ = 60.6970(7)°
Cell volume	921.82(8) Å^3	
Z	2	
Calculated density	1.392 g/cm^3	
Absorption coefficient □	0.108 mm^{-1}	
F(000)	404	
Crystal colour and size	orange, 0.95 × 0.43 × 0.23 mm^3	
Reflections for cell refinement	6027 (□ range 2.47 to 29.65°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	□ rotation with narrow frames	
□ range for data collection	2.47 to 29.65°	
Index ranges	h –11 to 11, k –11 to 11, l –23 to 23	
Completeness to □ = 29.65°	99.0 %	
Intensity decay	0%	
Reflections collected	13713	
Independent reflections	5164 (R_{int} = 0.0193)	
Reflections with F^2>2□	4248	

Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.905 and 0.976
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0758, 0.2359
Data / restraints / parameters	5164 / 0 / 261
Final R indices [F^2>2□]	R1 = 0.0467, wR2 = 0.1266
R indices (all data)	R1 = 0.0565, wR2 = 0.1349
Goodness-of-fit on F^2	1.036
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.409 and −0.169 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sdrc37. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.32157(16)	0.09858(16)	0.25058(7)	0.0217(2)
C(2)	0.12835(17)	0.27601(17)	0.21913(7)	0.0244(2)
C(3)	0.15939(16)	0.19961(17)	0.30806(7)	0.0236(2)
C(4)	0.49115(17)	0.13391(16)	0.24781(7)	0.0234(2)
O(1)	0.50771(16)	0.25212(16)	0.19778(6)	0.0402(3)
O(2)	0.61662(13)	0.02262(14)	0.30981(6)	0.0326(2)
C(5)	0.7783(2)	0.0564(2)	0.31643(9)	0.0368(3)
C(6)	0.35513(17)	−0.09286(16)	0.23845(7)	0.0238(2)
O(3)	0.23954(14)	−0.14975(13)	0.25334(6)	0.0318(2)
O(4)	0.52547(13)	−0.19034(12)	0.20684(6)	0.0292(2)
C(7)	0.5713(2)	−0.38115(19)	0.19481(9)	0.0373(3)

O(5)	–0.00764(12)	0.25421(13)	0.18023(5)	0.02768(19)
C(8)	0.01585(17)	0.24737(17)	0.09776(7)	0.0251(2)
C(9)	0.17887(19)	0.2294(2)	0.05716(8)	0.0306(3)
C(10)	0.1894(2)	0.2174(2)	–0.02492(8)	0.0333(3)
C(11)	0.0372(2)	0.22738(18)	–0.06697(8)	0.0299(3)
C(12)	–0.1258(2)	0.2474(2)	–0.02445(8)	0.0331(3)
C(13)	–0.13726(19)	0.25662(19)	0.05715(8)	0.0296(3)
N(1)	0.0441(2)	0.2251(2)	–0.15036(7)	0.0376(3)
C(14)	0.19059(16)	0.29727(17)	0.36781(7)	0.0235(2)
C(15)	0.1830(2)	0.47546(19)	0.34543(8)	0.0309(3)
C(16)	0.2158(2)	0.56046(19)	0.40291(8)	0.0324(3)
C(17)	0.25430(19)	0.4651(2)	0.48245(8)	0.0298(3)
C(18)	0.2658(2)	0.2865(2)	0.50712(8)	0.0344(3)
C(19)	0.2329(2)	0.20356(19)	0.44898(8)	0.0312(3)
N(2)	0.2838(2)	0.5583(2)	0.54326(8)	0.0404(3)
O(6)	0.2663(2)	0.7184(2)	0.52128(8)	0.0609(4)
O(7)	0.3239(2)	0.4712(2)	0.61339(7)	0.0649(4)

Table 3. Bond lengths [Å] and angles [°] for sdrc37.

C(1)–C(6)	1.4898(15)	C(1)–C(4)	1.5036(15)
C(1)–C(2)	1.5275(16)	C(1)–C(3)	1.5476(16)
C(2)–O(5)	1.3902(14)	C(2)–C(3)	1.4869(16)
C(3)–C(14)	1.4889(16)	C(4)–O(1)	1.1993(15)
C(4)–O(2)	1.3277(15)	O(2)–C(5)	1.4509(15)
C(6)–O(3)	1.2083(15)	C(6)–O(4)	1.3307(15)
O(4)–C(7)	1.4542(15)	O(5)–C(8)	1.3960(14)
C(8)–C(9)	1.3851(18)	C(8)–C(13)	1.3899(17)

C(9)–C(10)	1.3961(18)	C(10)–C(11)	1.3940(19)
C(11)–C(12)	1.396(2)	C(11)–N(1)	1.4025(17)
C(12)–C(13)	1.3829(18)	C(14)–C(15)	1.3889(17)
C(14)–C(19)	1.3965(17)	C(15)–C(16)	1.3897(18)
C(16)–C(17)	1.3751(19)	C(17)–C(18)	1.3815(19)
C(17)–N(2)	1.4706(17)	C(18)–C(19)	1.3874(18)
N(2)–O(6)	1.2150(18)	N(2)–O(7)	1.2198(18)

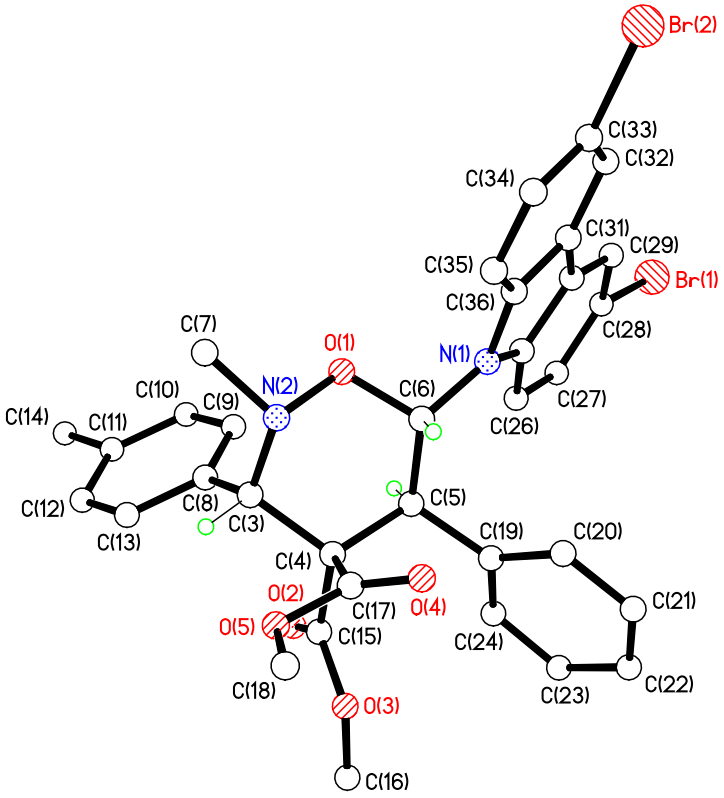
C(6)–C(1)–C(4)	118.52(10)	C(6)–C(1)–C(2)	117.79(10)
C(4)–C(1)–C(2)	115.20(9)	C(6)–C(1)–C(3)	116.07(9)
C(4)–C(1)–C(3)	117.27(9)	C(2)–C(1)–C(3)	57.83(7)
O(5)–C(2)–C(3)	115.80(10)	O(5)–C(2)–C(1)	119.56(10)
C(3)–C(2)–C(1)	61.77(8)	C(2)–C(3)–C(14)	123.94(10)
C(2)–C(3)–C(1)	60.41(7)	C(14)–C(3)–C(1)	119.76(9)
O(1)–C(4)–O(2)	124.31(11)	O(1)–C(4)–C(1)	124.42(11)
O(2)–C(4)–C(1)	111.22(10)	C(4)–O(2)–C(5)	115.60(10)
O(3)–C(6)–O(4)	124.36(11)	O(3)–C(6)–C(1)	124.09(11)
O(4)–C(6)–C(1)	111.52(10)	C(6)–O(4)–C(7)	114.96(10)
C(2)–O(5)–C(8)	116.21(9)	C(9)–C(8)–C(13)	120.55(11)
C(9)–C(8)–O(5)	124.19(11)	C(13)–C(8)–O(5)	115.25(11)
C(8)–C(9)–C(10)	119.27(12)	C(11)–C(10)–C(9)	121.15(13)
C(10)–C(11)–C(12)	118.11(12)	C(10)–C(11)–N(1)	120.99(13)
C(12)–C(11)–N(1)	120.85(12)	C(13)–C(12)–C(11)	121.44(12)
C(12)–C(13)–C(8)	119.47(12)	C(15)–C(14)–C(19)	119.09(11)
C(15)–C(14)–C(3)	122.44(11)	C(19)–C(14)–C(3)	118.46(11)
C(14)–C(15)–C(16)	120.65(12)	C(17)–C(16)–C(15)	118.58(12)
C(16)–C(17)–C(18)	122.64(12)	C(16)–C(17)–N(2)	118.27(12)
C(18)–C(17)–N(2)	119.09(12)	C(17)–C(18)–C(19)	118.05(12)

C(18)–C(19)–C(14)	120.97(12)	O(6)–N(2)–O(7)	123.30(13)
O(6)–N(2)–C(17)	118.43(13)	O(7)–N(2)–C(17)	118.28(13)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sdrc37.

	x	y	z	U
H(2)	0.1308	0.3998	0.2000	0.029
H(3)	0.0886	0.1277	0.3295	0.028
H(5A)	0.8428	0.0495	0.2648	0.055
H(5B)	0.8702	–0.0422	0.3596	0.055
H(5C)	0.7310	0.1847	0.3294	0.055
H(7A)	0.5589	–0.4558	0.2459	0.056
H(7B)	0.7042	–0.4480	0.1773	0.056
H(7C)	0.4819	–0.3683	0.1531	0.056
H(9)	0.2824	0.2252	0.0849	0.037
H(10)	0.3022	0.2023	–0.0526	0.040
H(12)	–0.2311	0.2549	–0.0522	0.040
H(13)	–0.2489	0.2692	0.0852	0.036
H(1A)	–0.026(3)	0.174(3)	–0.1629(12)	0.045
H(1B)	0.166(3)	0.173(3)	–0.1682(12)	0.045
H(15)	0.1552	0.5399	0.2903	0.037
H(16)	0.2118	0.6818	0.3876	0.039
H(18)	0.2954	0.2224	0.5623	0.041
H(19)	0.2393	0.0812	0.4646	0.037

6.6. **Appendix VI:** X-Ray crystallographic data for **194**



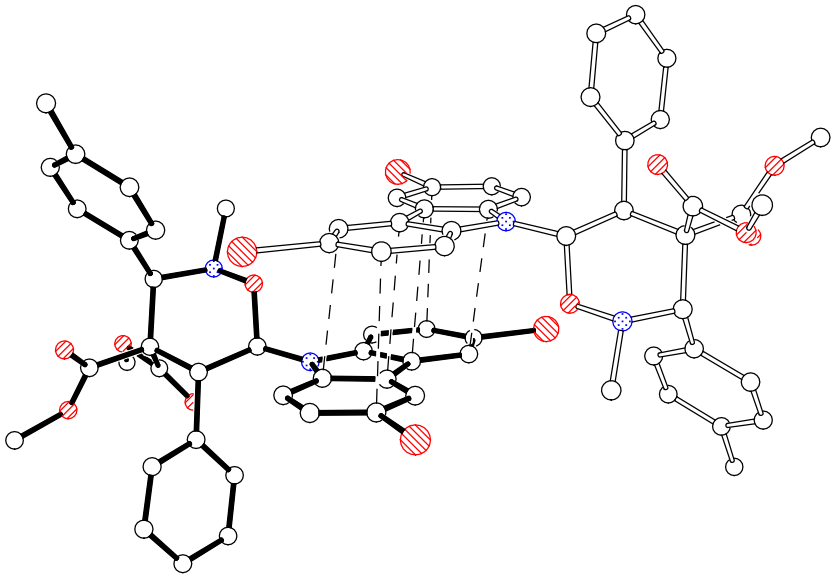


Table 1. Crystal data and structure refinement for sdrc28.

Identification code	sdrc28	
Chemical formula	$C_{34}H_{30}Br_2N_2O_5$	
Formula weight	706.42	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, P $\bar{1}$	
Unit cell parameters	a = 9.455(2) Å	α = 77.879(4)°
	b = 12.302(3) Å	β = 88.511(4)°
	c = 13.223(3) Å	γ = 86.870(4)°
Cell volume	1501.5(6) $Å^3$	
Z	2	
Calculated density	1.563 g/cm^3	
Absorption coefficient μ	2.745 mm^{-1}	
F(000)	716	
Crystal colour and size	colourless, 0.47 × 0.39 × 0.15 mm^3	
Reflections for cell refinement	4346 (θ range 2.65 to 26.37°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.70 to 26.41°	
Index ranges	h –11 to 11, k –15 to 15, l –16 to 16	
Completeness to θ = 26.41°	98.5 %	
Intensity decay	0%	
Reflections collected	12907	
Independent reflections	6078 (R_{int} = 0.0386)	
Reflections with $F^2>2\sigma$	4689	
Absorption correction	semi-empirical from equivalents	

Min. and max. transmission	0.359 and 0.684
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0878, 0.4234
Data / restraints / parameters	6078 / 0 / 392
Final R indices [$F^2>2\sigma$]	R1 = 0.0497, wR2 = 0.1335
R indices (all data)	R1 = 0.0684, wR2 = 0.1435
Goodness-of-fit on F^2	1.035
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	1.419 and –0.587 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sdrc28. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
O(1)	0.7187(2)	0.7561(2)	0.87816(19)	0.0260(5)
N(2)	0.8300(3)	0.8363(2)	0.8667(2)	0.0265(6)
C(3)	0.8290(3)	0.8990(3)	0.7585(3)	0.0232(7)
C(4)	0.6857(3)	0.9711(3)	0.7506(3)	0.0221(7)
C(5)	0.5560(3)	0.8940(3)	0.7807(3)	0.0215(7)
C(6)	0.5873(3)	0.8192(3)	0.8862(3)	0.0231(7)
C(7)	0.9606(4)	0.7673(4)	0.8942(3)	0.0371(9)
C(8)	0.8700(4)	0.8346(3)	0.6747(3)	0.0256(7)
C(9)	0.8108(4)	0.7373(3)	0.6603(3)	0.0329(8)
C(10)	0.8657(4)	0.6827(3)	0.5853(3)	0.0373(9)
C(11)	0.9786(4)	0.7216(3)	0.5207(3)	0.0344(9)
C(12)	1.0355(4)	0.8196(3)	0.5337(3)	0.0323(8)

C(13)	0.9825(4)	0.8742(3)	0.6089(3)	0.0306(8)
C(14)	1.0399(5)	0.6592(4)	0.4408(4)	0.0516(12)
C(15)	0.6601(3)	1.0376(3)	0.6403(3)	0.0239(7)
O(2)	0.6685(3)	0.9983(2)	0.5652(2)	0.0326(6)
O(3)	0.6202(3)	1.1443(2)	0.6398(2)	0.0330(6)
C(16)	0.5717(5)	1.2099(4)	0.5413(3)	0.0425(10)
C(17)	0.6967(4)	1.0514(3)	0.8248(3)	0.0238(7)
O(4)	0.6132(3)	1.0627(2)	0.89204(19)	0.0284(6)
O(5)	0.8140(3)	1.1098(2)	0.8036(2)	0.0301(6)
C(18)	0.8312(4)	1.1917(4)	0.8659(4)	0.0408(10)
C(19)	0.4133(3)	0.9597(3)	0.7722(3)	0.0233(7)
C(20)	0.3381(4)	0.9838(3)	0.8576(3)	0.0280(8)
C(21)	0.2124(4)	1.0488(3)	0.8437(3)	0.0353(9)
C(22)	0.1609(4)	1.0904(3)	0.7450(3)	0.0372(9)
C(23)	0.2330(4)	1.0637(3)	0.6600(3)	0.0328(8)
C(24)	0.3564(4)	0.9968(3)	0.6748(3)	0.0290(8)
N(1)	0.4849(3)	0.7378(2)	0.9281(2)	0.0248(6)
C(25)	0.3874(4)	0.6811(3)	0.8827(3)	0.0229(7)
C(26)	0.3396(4)	0.6973(3)	0.7819(3)	0.0289(8)
C(27)	0.2378(4)	0.6282(3)	0.7604(3)	0.0311(8)
C(28)	0.1859(4)	0.5453(3)	0.8384(3)	0.0298(8)
Br(1)	0.04449(5)	0.45408(3)	0.80477(4)	0.04394(15)
C(29)	0.2293(4)	0.5278(3)	0.9383(3)	0.0267(8)
C(30)	0.3309(3)	0.5971(3)	0.9617(3)	0.0223(7)
C(32)	0.3864(4)	0.5402(3)	1.1580(3)	0.0274(8)
C(33)	0.4686(4)	0.5688(3)	1.2318(3)	0.0289(8)
Br(2)	0.45607(5)	0.49046(4)	1.37185(3)	0.04289(15)
C(34)	0.5620(4)	0.6559(3)	1.2090(3)	0.0309(8)

C(35)	0.5762(4)	0.7155(3)	1.1089(3)	0.0280(8)
C(36)	0.4927(4)	0.6881(3)	1.0330(3)	0.0234(7)
C(31)	0.3983(3)	0.6012(3)	1.0566(3)	0.0229(7)

Table 3. Bond lengths [Å] and angles [°] for sdrc28.

O(1)–C(6)	1.443(4)	O(1)–N(2)	1.465(4)
N(2)–C(7)	1.469(5)	N(2)–C(3)	1.477(5)
C(3)–C(8)	1.523(5)	C(3)–C(4)	1.572(5)
C(4)–C(15)	1.534(5)	C(4)–C(17)	1.540(5)
C(4)–C(5)	1.582(4)	C(5)–C(6)	1.527(5)
C(5)–C(19)	1.528(5)	C(6)–N(1)	1.446(4)
C(8)–C(13)	1.398(5)	C(8)–C(9)	1.398(5)
C(9)–C(10)	1.385(6)	C(10)–C(11)	1.390(6)
C(11)–C(12)	1.391(6)	C(11)–C(14)	1.517(6)
C(12)–C(13)	1.382(5)	C(15)–O(2)	1.192(4)
C(15)–O(3)	1.345(4)	O(3)–C(16)	1.451(5)
C(17)–O(4)	1.199(4)	C(17)–O(5)	1.346(4)
O(5)–C(18)	1.447(5)	C(19)–C(24)	1.386(5)
C(19)–C(20)	1.395(5)	C(20)–C(21)	1.390(5)
C(21)–C(22)	1.388(6)	C(22)–C(23)	1.388(6)
C(23)–C(24)	1.384(5)	N(1)–C(36)	1.395(5)
N(1)–C(25)	1.404(5)	C(25)–C(26)	1.390(5)
C(25)–C(30)	1.421(5)	C(26)–C(27)	1.391(5)
C(27)–C(28)	1.390(5)	C(28)–C(29)	1.363(5)
C(28)–Br(1)	1.911(4)	C(29)–C(30)	1.401(5)
C(30)–C(31)	1.433(5)	C(32)–C(33)	1.376(6)
C(32)–C(31)	1.398(5)	C(33)–C(34)	1.405(5)

C(33)–Br(2)	1.904(3)	C(34)–C(35)	1.379(5)
C(35)–C(36)	1.399(5)	C(36)–C(31)	1.410(5)

C(6)–O(1)–N(2)	105.8(2)	O(1)–N(2)–C(7)	104.3(3)
O(1)–N(2)–C(3)	107.5(3)	C(7)–N(2)–C(3)	113.5(3)
N(2)–C(3)–C(8)	117.3(3)	N(2)–C(3)–C(4)	103.8(3)
C(8)–C(3)–C(4)	119.7(3)	C(15)–C(4)–C(17)	109.8(3)
C(15)–C(4)–C(3)	111.8(3)	C(17)–C(4)–C(3)	106.6(3)
C(15)–C(4)–C(5)	106.7(3)	C(17)–C(4)–C(5)	111.4(3)
C(3)–C(4)–C(5)	110.6(3)	C(6)–C(5)–C(19)	115.7(3)
C(6)–C(5)–C(4)	107.2(3)	C(19)–C(5)–C(4)	112.9(3)
O(1)–C(6)–N(1)	105.5(3)	O(1)–C(6)–C(5)	108.4(3)
N(1)–C(6)–C(5)	117.2(3)	C(13)–C(8)–C(9)	117.1(3)
C(13)–C(8)–C(3)	116.4(3)	C(9)–C(8)–C(3)	126.5(3)
C(10)–C(9)–C(8)	120.3(3)	C(9)–C(10)–C(11)	122.6(4)
C(10)–C(11)–C(12)	117.1(3)	C(10)–C(11)–C(14)	121.9(4)
C(12)–C(11)–C(14)	121.0(4)	C(13)–C(12)–C(11)	120.8(3)
C(12)–C(13)–C(8)	122.1(4)	O(2)–C(15)–O(3)	124.4(3)
O(2)–C(15)–C(4)	124.1(3)	O(3)–C(15)–C(4)	111.4(3)
C(15)–O(3)–C(16)	115.6(3)	O(4)–C(17)–O(5)	123.4(3)
O(4)–C(17)–C(4)	125.8(3)	O(5)–C(17)–C(4)	110.7(3)
C(17)–O(5)–C(18)	115.2(3)	C(24)–C(19)–C(20)	118.6(3)
C(24)–C(19)–C(5)	118.2(3)	C(20)–C(19)–C(5)	123.2(3)
C(21)–C(20)–C(19)	120.1(4)	C(22)–C(21)–C(20)	120.4(4)
C(23)–C(22)–C(21)	119.7(4)	C(24)–C(23)–C(22)	119.5(4)
C(23)–C(24)–C(19)	121.5(4)	C(36)–N(1)–C(25)	108.0(3)
C(36)–N(1)–C(6)	117.8(3)	C(25)–N(1)–C(6)	133.3(3)
C(26)–C(25)–N(1)	131.6(3)	C(26)–C(25)–C(30)	120.3(3)

N(1)–C(25)–C(30)	108.1(3)	C(25)–C(26)–C(27)	118.4(3)
C(28)–C(27)–C(26)	120.3(4)	C(29)–C(28)–C(27)	123.0(3)
C(29)–C(28)–Br(1)	118.6(3)	C(27)–C(28)–Br(1)	118.5(3)
C(28)–C(29)–C(30)	117.6(3)	C(29)–C(30)–C(25)	120.5(3)
C(29)–C(30)–C(31)	131.8(3)	C(25)–C(30)–C(31)	107.7(3)
C(33)–C(32)–C(31)	117.7(3)	C(32)–C(33)–C(34)	122.8(3)
C(32)–C(33)–Br(2)	119.9(3)	C(34)–C(33)–Br(2)	117.3(3)
C(35)–C(34)–C(33)	120.0(4)	C(34)–C(35)–C(36)	118.0(3)
N(1)–C(36)–C(35)	128.6(3)	N(1)–C(36)–C(31)	109.7(3)
C(35)–C(36)–C(31)	121.6(3)	C(32)–C(31)–C(36)	119.9(3)
C(32)–C(31)–C(30)	133.7(3)	C(36)–C(31)–C(30)	106.4(3)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sdrc28.

	x	y	z	U
H(3)	0.9043	0.9538	0.7547	0.028
H(5)	0.5557	0.8445	0.7297	0.026
H(6)	0.5994	0.8675	0.9372	0.028
H(7A)	0.9575	0.7323	0.9679	0.056
H(7B)	1.0424	0.8140	0.8798	0.056
H(7C)	0.9691	0.7094	0.8532	0.056
H(9)	0.7326	0.7086	0.7021	0.039
H(10)	0.8247	0.6162	0.5777	0.045
H(12)	1.1117	0.8494	0.4903	0.039
H(13)	1.0238	0.9407	0.6162	0.037
H(14A)	1.1032	0.5973	0.4747	0.077
H(14B)	1.0932	0.7099	0.3882	0.077

H(14C)	0.9628	0.6301	0.4078	0.077
H(16A)	0.6469	1.2096	0.4889	0.064
H(16B)	0.5482	1.2866	0.5483	0.064
H(16C)	0.4874	1.1778	0.5203	0.064
H(18A)	0.7577	1.2517	0.8486	0.061
H(18B)	0.9248	1.2227	0.8520	0.061
H(18C)	0.8227	1.1564	0.9393	0.061
H(20)	0.3728	0.9558	0.9254	0.034
H(21)	0.1613	1.0648	0.9021	0.042
H(22)	0.0768	1.1370	0.7357	0.045
H(23)	0.1980	1.0911	0.5923	0.039
H(24)	0.4031	0.9759	0.6168	0.035
H(26)	0.3756	0.7541	0.7289	0.035
H(27)	0.2035	0.6378	0.6920	0.037
H(29)	0.1920	0.4706	0.9902	0.032
H(32)	0.3238	0.4811	1.1754	0.033
H(34)	0.6154	0.6738	1.2626	0.037
H(35)	0.6407	0.7734	1.0920	0.034

Table 5. Torsion angles [°] for sdrc28.

C(6)–O(1)–N(2)–C(7)	161.3(3)	C(6)–O(1)–N(2)–C(3)	−77.9(3)
O(1)–N(2)–C(3)–C(8)	−65.7(3)	C(7)–N(2)–C(3)–C(8)	49.1(4)
O(1)–N(2)–C(3)–C(4)	68.8(3)	C(7)–N(2)–C(3)–C(4)	−176.3(3)
N(2)–C(3)–C(4)–C(15)	−176.3(3)	C(8)–C(3)–C(4)–C(15)	−43.0(4)
N(2)–C(3)–C(4)–C(17)	63.8(3)	C(8)–C(3)–C(4)–C(17)	−163.0(3)
N(2)–C(3)–C(4)–C(5)	−57.5(3)	C(8)–C(3)–C(4)–C(5)	75.8(4)
C(15)–C(4)–C(5)–C(6)	174.6(3)	C(17)–C(4)–C(5)–C(6)	−65.6(3)

C(3)–C(4)–C(5)–C(6)	52.7(3)	C(15)–C(4)–C(5)–C(19)	–56.9(3)
C(17)–C(4)–C(5)–C(19)	62.9(4)	C(3)–C(4)–C(5)–C(19)	–178.7(3)
N(2)–O(1)–C(6)–N(1)	–163.1(3)	N(2)–O(1)–C(6)–C(5)	70.5(3)
C(19)–C(5)–C(6)–O(1)	174.7(3)	C(4)–C(5)–C(6)–O(1)	–58.4(3)
C(19)–C(5)–C(6)–N(1)	55.4(4)	C(4)–C(5)–C(6)–N(1)	–177.7(3)
N(2)–C(3)–C(8)–C(13)	–123.5(3)	C(4)–C(3)–C(8)–C(13)	109.3(4)
N(2)–C(3)–C(8)–C(9)	53.3(5)	C(4)–C(3)–C(8)–C(9)	–73.9(5)
C(13)–C(8)–C(9)–C(10)	1.6(6)	C(3)–C(8)–C(9)–C(10)	–175.2(4)
C(8)–C(9)–C(10)–C(11)	–1.0(7)	C(9)–C(10)–C(11)–C(12)	–0.3(6)
C(9)–C(10)–C(11)–C(14)	178.4(4)	C(10)–C(11)–C(12)–C(13)	1.0(6)
C(14)–C(11)–C(12)–C(13)	–177.8(4)	C(11)–C(12)–C(13)–C(8)	–0.3(6)
C(9)–C(8)–C(13)–C(12)	–1.0(6)	C(3)–C(8)–C(13)–C(12)	176.1(3)
C(17)–C(4)–C(15)–O(2)	168.2(3)	C(3)–C(4)–C(15)–O(2)	50.1(4)
C(5)–C(4)–C(15)–O(2)	–70.9(4)	C(17)–C(4)–C(15)–O(3)	–14.9(4)
C(3)–C(4)–C(15)–O(3)	–133.0(3)	C(5)–C(4)–C(15)–O(3)	105.9(3)
O(2)–C(15)–O(3)–C(16)	6.2(5)	C(4)–C(15)–O(3)–C(16)	–170.6(3)
C(15)–C(4)–C(17)–O(4)	112.2(4)	C(3)–C(4)–C(17)–O(4)	–126.5(4)
C(5)–C(4)–C(17)–O(4)	–5.8(5)	C(15)–C(4)–C(17)–O(5)	–67.1(4)
C(3)–C(4)–C(17)–O(5)	54.2(4)	C(5)–C(4)–C(17)–O(5)	174.9(3)
O(4)–C(17)–O(5)–C(18)	–2.1(5)	C(4)–C(17)–O(5)–C(18)	177.3(3)
C(6)–C(5)–C(19)–C(24)	–157.7(3)	C(4)–C(5)–C(19)–C(24)	78.3(4)
C(6)–C(5)–C(19)–C(20)	22.3(5)	C(4)–C(5)–C(19)–C(20)	–101.7(4)
C(24)–C(19)–C(20)–C(21)	–3.3(5)	C(5)–C(19)–C(20)–C(21)	176.7(3)
C(19)–C(20)–C(21)–C(22)	–0.2(6)	C(20)–C(21)–C(22)–C(23)	2.3(6)
C(21)–C(22)–C(23)–C(24)	–0.8(6)	C(22)–C(23)–C(24)–C(19)	–2.9(6)
C(20)–C(19)–C(24)–C(23)	4.9(5)	C(5)–C(19)–C(24)–C(23)	–175.1(3)
O(1)–C(6)–N(1)–C(36)	74.5(4)	C(5)–C(6)–N(1)–C(36)	–164.7(3)

O(1)–C(6)–N(1)–C(25)	–93.2(4)	C(5)–C(6)–N(1)–C(25)	27.6(5)
C(36)–N(1)–C(25)–C(26)	179.2(4)	C(6)–N(1)–C(25)–C(26)	–12.2(6)
C(36)–N(1)–C(25)–C(30)	1.8(4)	C(6)–N(1)–C(25)–C(30)	170.4(3)
N(1)–C(25)–C(26)–C(27)	–178.3(3)	C(30)–C(25)–C(26)–C(27)	–1.1(5)
C(25)–C(26)–C(27)–C(28)	0.0(5)	C(26)–C(27)–C(28)–C(29)	0.7(6)
C(26)–C(27)–C(28)–Br(1)	179.3(3)	C(27)–C(28)–C(29)–C(30)	–0.1(5)
Br(1)–C(28)–C(29)–C(30)	–178.7(2)	C(28)–C(29)–C(30)–C(25)	–1.1(5)
C(28)–C(29)–C(30)–C(31)	–179.9(3)	C(26)–C(25)–C(30)–C(29)	1.7(5)
N(1)–C(25)–C(30)–C(29)	179.5(3)	C(26)–C(25)–C(30)–C(31)	–179.2(3)
N(1)–C(25)–C(30)–C(31)	–1.4(4)	C(31)–C(32)–C(33)–C(34)	0.2(5)
C(31)–C(32)–C(33)–Br(2)	179.2(2)	C(32)–C(33)–C(34)–C(35)	–1.2(6)
Br(2)–C(33)–C(34)–C(35)	179.7(3)	C(33)–C(34)–C(35)–C(36)	1.6(5)
C(25)–N(1)–C(36)–C(35)	179.4(3)	C(6)–N(1)–C(36)–C(35)	8.8(5)
C(25)–N(1)–C(36)–C(31)	–1.4(4)	C(6)–N(1)–C(36)–C(31)	–172.1(3)
C(34)–C(35)–C(36)–N(1)	177.9(3)	C(34)–C(35)–C(36)–C(31)	–1.1(5)
C(33)–C(32)–C(31)–C(36)	0.3(5)	C(33)–C(32)–C(31)–C(30)	–179.2(3)
N(1)–C(36)–C(31)–C(32)	–179.1(3)	C(35)–C(36)–C(31)–C(32)	0.1(5)
N(1)–C(36)–C(31)–C(30)	0.5(4)	C(35)–C(36)–C(31)–C(30)	179.7(3)
C(29)–C(30)–C(31)–C(32)	–0.9(6)	C(25)–C(30)–C(31)–C(32)	–179.9(4)
C(29)–C(30)–C(31)–C(36)	179.5(3)	C(25)–C(30)–C(31)–C(36)	0.6(4)

6.7. **Appendix VII:** X-Ray crystallographic data for **198$_A$**

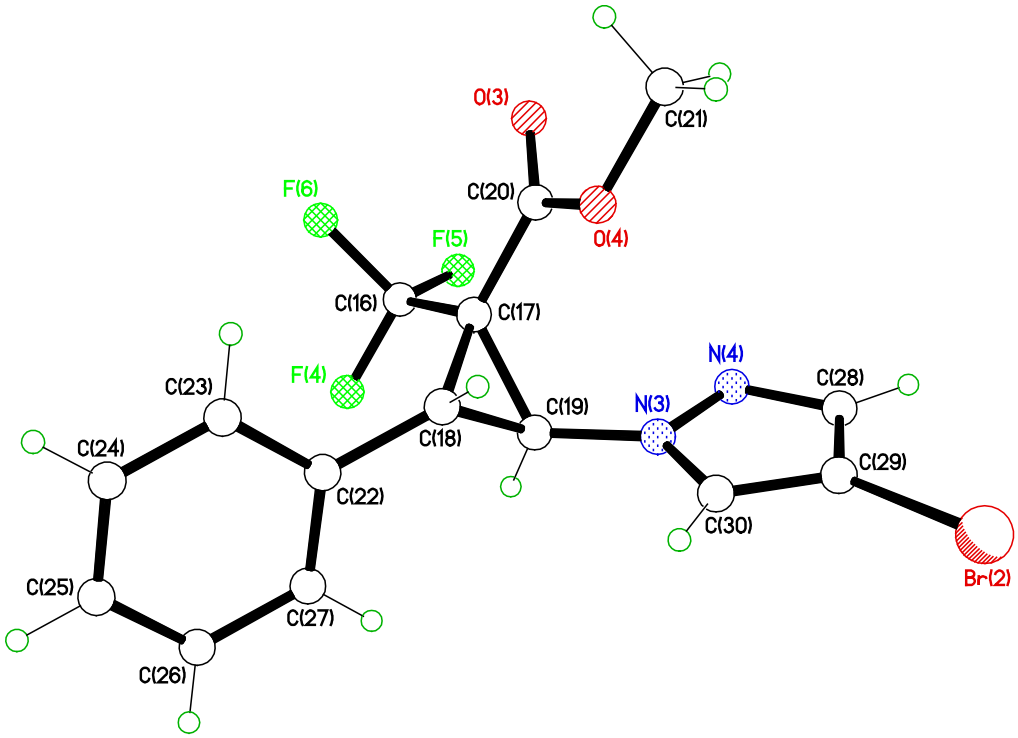


Table 1. Crystal data and structure refinement for sdrc36.

Identification code	sdrc36	
Chemical formula	$C_{15}H_{12}BrF_3N_2O_2$	
Formula weight	389.18	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1/c$	
Unit cell parameters	a = 10.4447(4) Å	α = 90°
	b = 36.3216(12) Å	β = 105.3551(5)°
	c = 8.6004(3) Å	γ = 90°
Cell volume	3146.25(19) $Å^3$	
Z	8	
Calculated density	1.643 g/cm^3	
Absorption coefficient μ	2.654 mm^{-1}	
F(000)	1552	
Crystal colour and size	colourless, 0.31 × 0.30 × 0.13 mm^3	
Reflections for cell refinement	9088 (θ range 2.31 to 28.01°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.02 to 27.50°	
Index ranges	h −13 to 13, k −47 to 47, l −11 to 11	
Completeness to θ = 27.50°	99.9 %	
Intensity decay	0%	
Reflections collected	30392	
Independent reflections	7215 (R_{int} = 0.0282)	
Reflections with $F^2>2\sigma$	5732	
Absorption correction	semi-empirical from equivalents	

Min. and max. transmission	0.493 and 0.724
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0405, 5.5534
Data / restraints / parameters	7215 / 6 / 435
Final R indices [$F^2>2\sigma$]	R1 = 0.0458, wR2 = 0.1031
R indices (all data)	R1 = 0.0607, wR2 = 0.1111
Goodness-of-fit on F^2	1.050
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	1.798 and –1.277 e $Å^{-3}$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for sdrc36. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
C(1)	0.6019(3)	0.31487(11)	0.7567(4)	0.0438(8)
F(1)	0.6174(2)	0.28747(6)	0.6603(3)	0.0493(5)
F(2)	0.4711(2)	0.31597(7)	0.7468(3)	0.0561(6)
F(3)	0.6632(2)	0.30476(7)	0.9077(3)	0.0612(6)
C(2)	0.6541(3)	0.35058(9)	0.7125(4)	0.0343(7)
C(3)	0.7686(3)	0.35113(8)	0.6310(4)	0.0331(7)
C(4)	0.6302(3)	0.35815(8)	0.5324(4)	0.0308(6)
C(5)	0.6367(4)	0.38109(11)	0.8220(4)	0.0469(9)
O(1)	0.5636(3)	0.38010(9)	0.9070(3)	0.0608(8)
O(2)	0.7101(2)	0.41026(7)	0.8072(3)	0.0495(7)
C(6)	0.6783(5)	0.44201(13)	0.8950(6)	0.0478(15)
C(6X)	0.5971(19)	0.4184(5)	0.993(2)	0.069(8)

C(7)	0.8514(3)	0.31890(8)	0.6078(4)	0.0326(7)
C(8)	0.9729(3)	0.31365(9)	0.7213(4)	0.0367(7)
C(9)	1.0569(4)	0.28533(10)	0.7018(5)	0.0454(9)
C(10)	1.0212(4)	0.26240(9)	0.5692(5)	0.0494(10)
C(11)	0.9023(4)	0.26784(10)	0.4558(6)	0.0534(10)
C(12)	0.8172(4)	0.29629(10)	0.4742(5)	0.0455(9)
N(1)	0.5964(2)	0.39494(7)	0.4758(3)	0.0322(5)
N(2)	0.4863(2)	0.41147(8)	0.4989(3)	0.0365(6)
C(13)	0.4855(3)	0.44452(9)	0.4353(4)	0.0370(7)
C(14)	0.5941(3)	0.44940(9)	0.3719(4)	0.0357(7)
C(15)	0.6637(3)	0.41719(9)	0.3997(4)	0.0373(7)
Br(1)	0.63404(4)	0.490915(10)	0.26377(5)	0.05171(12)
C(16)	1.0336(3)	0.63801(10)	0.8258(4)	0.0375(7)
F(4)	1.00766(19)	0.67386(5)	0.8068(2)	0.0422(4)
F(5)	1.15864(19)	0.63342(7)	0.8162(3)	0.0570(6)
F(6)	1.0327(2)	0.62964(6)	0.9773(2)	0.0570(6)
C(17)	0.9364(3)	0.61503(8)	0.7041(3)	0.0286(6)
C(18)	0.7933(3)	0.62796(8)	0.6336(3)	0.0255(6)
C(19)	0.8903(3)	0.63161(8)	0.5363(3)	0.0258(6)
C(20)	0.9611(4)	0.57448(10)	0.7281(4)	0.0446(8)
O(3)	1.0582(3)	0.56270(8)	0.8251(4)	0.0771(10)
O(4)	0.8686(3)	0.55368(6)	0.6382(3)	0.0411(5)
C(21)	0.8983(6)	0.51444(12)	0.6615(7)	0.0504(15)
C(21X)	1.043(2)	0.5216(4)	0.835(3)	0.093(10)
C(22)	0.7287(3)	0.65972(8)	0.6947(3)	0.0274(6)
C(23)	0.6702(4)	0.65305(10)	0.8195(4)	0.0469(9)
C(24)	0.5990(5)	0.68042(12)	0.8715(5)	0.0592(11)
C(25)	0.5870(4)	0.71461(11)	0.8014(4)	0.0493(9)

C(26)	0.6440(3)	0.72156(9)	0.6778(4)	0.0409(8)
C(27)	0.7145(3)	0.69407(8)	0.6236(4)	0.0329(6)
N(3)	0.8799(2)	0.60782(7)	0.3998(3)	0.0257(5)
N(4)	0.9926(2)	0.59335(7)	0.3759(3)	0.0316(5)
C(28)	0.9521(3)	0.57445(8)	0.2394(4)	0.0339(7)
C(29)	0.8148(3)	0.57690(8)	0.1777(3)	0.0299(6)
C(30)	0.7706(3)	0.59859(8)	0.2828(3)	0.0299(6)
Br(2)	0.71148(4)	0.554753(10)	–0.01111(4)	0.04902(12)

Table 3. Bond lengths [Å] and angles [°] for sdrc36.

C(1)–F(1)	1.332(4)	C(1)–F(3)	1.338(4)
C(1)–F(2)	1.347(4)	C(1)–C(2)	1.495(5)
C(2)–C(5)	1.496(5)	C(2)–C(4)	1.527(4)
C(2)–C(3)	1.538(4)	C(3)–C(4)	1.491(4)
C(3)–C(7)	1.500(4)	C(4)–N(1)	1.434(4)
C(5)–O(1)	1.190(5)	C(5)–O(2)	1.333(5)
O(1)–C(6X)	1.569(14)	O(2)–C(6)	1.463(4)
C(7)–C(12)	1.380(5)	C(7)–C(8)	1.394(5)
C(8)–C(9)	1.391(4)	C(9)–C(10)	1.381(6)
C(10)–C(11)	1.376(6)	C(11)–C(12)	1.399(5)
N(1)–C(15)	1.349(4)	N(1)–N(2)	1.357(3)
N(2)–C(13)	1.318(4)	C(13)–C(14)	1.393(5)
C(14)–C(15)	1.365(4)	C(14)–Br(1)	1.876(3)
C(16)–F(4)	1.331(4)	C(16)–F(5)	1.341(4)
C(16)–F(6)	1.341(4)	C(16)–C(17)	1.503(4)
C(17)–C(20)	1.500(4)	C(17)–C(19)	1.520(4)
C(17)–C(18)	1.530(4)	C(18)–C(19)	1.481(4)

C(18)–C(22)	1.500(4)	C(19)–N(3)	1.438(3)
C(20)–O(3)	1.208(5)	C(20)–O(4)	1.306(5)
O(3)–C(21X)	1.506(14)	O(4)–C(21)	1.461(5)
C(22)–C(27)	1.380(4)	C(22)–C(23)	1.390(4)
C(23)–C(24)	1.384(5)	C(24)–C(25)	1.371(6)
C(25)–C(26)	1.373(5)	C(26)–C(27)	1.392(4)
N(3)–C(30)	1.349(4)	N(3)–N(4)	1.354(3)
N(4)–C(28)	1.329(4)	C(28)–C(29)	1.394(4)
C(29)–C(30)	1.368(4)	C(29)–Br(2)	1.877(3)

F(1)–C(1)–F(3)	107.1(3)	F(1)–C(1)–F(2)	105.7(3)
F(3)–C(1)–F(2)	106.6(3)	F(1)–C(1)–C(2)	112.2(3)
F(3)–C(1)–C(2)	111.9(3)	F(2)–C(1)–C(2)	113.0(3)
C(1)–C(2)–C(5)	111.7(3)	C(1)–C(2)–C(4)	116.2(3)
C(5)–C(2)–C(4)	119.4(3)	C(1)–C(2)–C(3)	120.5(3)
C(5)–C(2)–C(3)	121.1(3)	C(4)–C(2)–C(3)	58.2(2)
C(4)–C(3)–C(7)	124.3(3)	C(4)–C(3)–C(2)	60.53(19)
C(7)–C(3)–C(2)	126.6(3)	N(1)–C(4)–C(3)	117.8(3)
N(1)–C(4)–C(2)	118.1(2)	C(3)–C(4)–C(2)	61.3(2)
O(1)–C(5)–O(2)	124.2(3)	O(1)–C(5)–C(2)	124.7(4)
O(2)–C(5)–C(2)	111.1(3)	C(5)–O(1)–C(6X)	99.4(8)
C(5)–O(2)–C(6)	111.3(3)	C(12)–C(7)–C(8)	119.3(3)
C(12)–C(7)–C(3)	123.0(3)	C(8)–C(7)–C(3)	117.6(3)
C(9)–C(8)–C(7)	120.2(3)	C(10)–C(9)–C(8)	120.3(4)
C(11)–C(10)–C(9)	119.6(3)	C(10)–C(11)–C(12)	120.5(4)
C(7)–C(12)–C(11)	120.1(4)	C(15)–N(1)–N(2)	112.1(3)
C(15)–N(1)–C(4)	127.6(3)	N(2)–N(1)–C(4)	120.3(2)
C(13)–N(2)–N(1)	104.7(3)	N(2)–C(13)–C(14)	111.2(3)

C(15)–C(14)–C(13)	105.9(3)	C(15)–C(14)–Br(1)	126.7(3)
C(13)–C(14)–Br(1)	127.4(2)	N(1)–C(15)–C(14)	106.1(3)
F(4)–C(16)–F(5)	106.5(3)	F(4)–C(16)–F(6)	106.7(3)
F(5)–C(16)–F(6)	106.8(3)	F(4)–C(16)–C(17)	112.3(3)
F(5)–C(16)–C(17)	112.2(3)	F(6)–C(16)–C(17)	111.9(3)
C(20)–C(17)–C(16)	112.9(3)	C(20)–C(17)–C(19)	121.3(3)
C(16)–C(17)–C(19)	115.3(3)	C(20)–C(17)–C(18)	118.1(3)
C(16)–C(17)–C(18)	120.9(3)	C(19)–C(17)–C(18)	58.10(18)
C(19)–C(18)–C(22)	124.6(2)	C(19)–C(18)–C(17)	60.62(18)
C(22)–C(18)–C(17)	125.5(2)	N(3)–C(19)–C(18)	119.5(2)
N(3)–C(19)–C(17)	118.3(2)	C(18)–C(19)–C(17)	61.28(18)
O(3)–C(20)–O(4)	123.9(3)	O(3)–C(20)–C(17)	121.7(4)
O(4)–C(20)–C(17)	114.4(3)	C(20)–O(3)–C(21X)	108.0(10)
C(20)–O(4)–C(21)	112.7(3)	C(27)–C(22)–C(23)	118.9(3)
C(27)–C(22)–C(18)	123.0(3)	C(23)–C(22)–C(18)	117.8(3)
C(24)–C(23)–C(22)	120.5(3)	C(25)–C(24)–C(23)	120.2(3)
C(24)–C(25)–C(26)	119.9(3)	C(25)–C(26)–C(27)	120.3(3)
C(22)–C(27)–C(26)	120.2(3)	C(30)–N(3)–N(4)	112.8(2)
C(30)–N(3)–C(19)	128.6(2)	N(4)–N(3)–C(19)	118.4(2)
C(28)–N(4)–N(3)	104.4(2)	N(4)–C(28)–C(29)	111.0(3)
C(30)–C(29)–C(28)	106.2(3)	C(30)–C(29)–Br(2)	127.0(2)
C(28)–C(29)–Br(2)	126.8(2)	N(3)–C(30)–C(29)	105.6(3)

Table 4. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for sdrc36.

	x	y	z	U
H(3)	0.8218	0.3743	0.6548	0.040

H(4)	0.5872	0.3379	0.4581	0.037
H(6A)	0.7341	0.4629	0.8826	0.072
H(6B)	0.6951	0.4358	1.0095	0.072
H(6C)	0.5846	0.4485	0.8515	0.072
H(6X1)	0.5432	0.4218	1.0693	0.104
H(6X2)	0.5775	0.4380	0.9120	0.104
H(6X3)	0.6914	0.4191	1.0508	0.104
H(8)	0.9983	0.3295	0.8123	0.044
H(9)	1.1392	0.2817	0.7800	0.054
H(10)	1.0785	0.2430	0.5564	0.059
H(11)	0.8777	0.2522	0.3643	0.064
H(12)	0.7358	0.3001	0.3947	0.055
H(13)	0.4195	0.4627	0.4331	0.044
H(15)	0.7434	0.4116	0.3713	0.045
H(18)	0.7307	0.6069	0.5971	0.031
H(19)	0.9219	0.6572	0.5247	0.031
H(21A)	0.8259	0.5001	0.5920	0.076
H(21B)	0.9076	0.5079	0.7745	0.076
H(21C)	0.9814	0.5090	0.6335	0.076
H(21D)	1.1212	0.5114	0.9131	0.140
H(21E)	1.0357	0.5106	0.7289	0.140
H(21F)	0.9633	0.5160	0.8697	0.140
H(23)	0.6791	0.6295	0.8696	0.056
H(24)	0.5584	0.6755	0.9559	0.071
H(25)	0.5393	0.7335	0.8384	0.059
H(26)	0.6353	0.7452	0.6290	0.049
H(27)	0.7531	0.6990	0.5373	0.039
H(28)	1.0091	0.5611	0.1903	0.041

H(30)	0.6815	0.6057	0.2750	0.036

Table 5. Torsion angles [°] for sdrc36.

F(1)–C(1)–C(2)–C(5)	−179.8(3)	F(3)–C(1)–C(2)–C(5)	−59.4(4)
F(2)–C(1)–C(2)–C(5)	60.9(4)	F(1)–C(1)–C(2)–C(4)	38.6(4)
F(3)–C(1)–C(2)–C(4)	158.9(3)	F(2)–C(1)–C(2)–C(4)	−80.8(3)
F(1)–C(1)–C(2)–C(3)	−28.4(4)	F(3)–C(1)–C(2)–C(3)	92.0(4)
F(2)–C(1)–C(2)–C(3)	−147.7(3)	C(1)–C(2)–C(3)–C(4)	103.8(3)
C(5)–C(2)–C(3)–C(4)	−107.5(3)	C(1)–C(2)–C(3)–C(7)	−9.0(5)
C(5)–C(2)–C(3)–C(7)	139.7(3)	C(4)–C(2)–C(3)–C(7)	−112.8(4)
C(7)–C(3)–C(4)–N(1)	−135.1(3)	C(2)–C(3)–C(4)–N(1)	108.6(3)
C(7)–C(3)–C(4)–C(2)	116.3(3)	C(1)–C(2)–C(4)–N(1)	140.8(3)
C(5)–C(2)–C(4)–N(1)	2.3(4)	C(3)–C(2)–C(4)–N(1)	−108.1(3)
C(1)–C(2)–C(4)–C(3)	−111.1(3)	C(5)–C(2)–C(4)–C(3)	110.4(3)
C(1)–C(2)–C(5)–O(1)	−17.2(5)	C(4)–C(2)–C(5)–O(1)	123.0(4)
C(3)–C(2)–C(5)–O(1)	−168.5(3)	C(1)–C(2)–C(5)–O(2)	165.3(3)
C(4)–C(2)–C(5)–O(2)	−54.5(4)	C(3)–C(2)–C(5)–O(2)	14.0(4)
O(2)–C(5)–O(1)–C(6X)	−5.5(9)	C(2)–C(5)–O(1)–C(6X)	177.3(8)
O(1)–C(5)–O(2)–C(6)	−6.2(5)	C(2)–C(5)–O(2)–C(6)	171.3(3)
C(4)–C(3)–C(7)–C(12)	12.5(5)	C(2)–C(3)–C(7)–C(12)	88.9(4)
C(4)–C(3)–C(7)–C(8)	−172.5(3)	C(2)–C(3)–C(7)–C(8)	−96.1(4)
C(12)–C(7)–C(8)–C(9)	−1.6(5)	C(3)–C(7)–C(8)–C(9)	−176.8(3)
C(7)–C(8)–C(9)–C(10)	0.5(5)	C(8)–C(9)–C(10)–C(11)	0.4(5)
C(9)–C(10)–C(11)–C(12)	−0.3(6)	C(8)–C(7)–C(12)–C(11)	1.7(5)
C(3)–C(7)–C(12)–C(11)	176.7(3)	C(10)–C(11)–C(12)–C(7)	−0.8(6)
C(3)–C(4)–N(1)–C(15)	49.2(4)	C(2)–C(4)–N(1)–C(15)	119.7(3)
C(3)–C(4)–N(1)–N(2)	−129.7(3)	C(2)–C(4)–N(1)–N(2)	−59.3(4)

C(15)–N(1)–N(2)–C(13)	0.2(3)	C(4)–N(1)–N(2)–C(13)	179.3(3)
N(1)–N(2)–C(13)–C(14)	–0.1(4)	N(2)–C(13)–C(14)–C(15)	0.0(4)
N(2)–C(13)–C(14)–Br(1)	178.0(2)	N(2)–N(1)–C(15)–C(14)	–0.2(4)
C(4)–N(1)–C(15)–C(14)	–179.2(3)	C(13)–C(14)–C(15)–N(1)	0.2(4)
Br(1)–C(14)–C(15)–N(1)	–177.9(2)	F(4)–C(16)–C(17)–C(20)	–177.7(3)
F(5)–C(16)–C(17)–C(20)	62.4(4)	F(6)–C(16)–C(17)–C(20)	–57.7(4)
F(4)–C(16)–C(17)–C(19)	36.9(4)	F(5)–C(16)–C(17)–C(19)	–83.0(3)
F(6)–C(16)–C(17)–C(19)	156.9(2)	F(4)–C(16)–C(17)–C(18)	–29.7(4)
F(5)–C(16)–C(17)–C(18)	–149.6(3)	F(6)–C(16)–C(17)–C(18)	90.4(3)
C(20)–C(17)–C(18)–C(19)	–111.2(3)	C(16)–C(17)–C(18)–C(19)	102.3(3)
C(20)–C(17)–C(18)–C(22)	135.3(3)	C(16)–C(17)–C(18)–C(22)	–11.2(4)
C(19)–C(17)–C(18)–C(22)	–113.5(3)	C(22)–C(18)–C(19)–N(3)	–137.1(3)
C(17)–C(18)–C(19)–N(3)	108.1(3)	C(22)–C(18)–C(19)–C(17)	114.9(3)
C(20)–C(17)–C(19)–N(3)	–4.4(4)	C(16)–C(17)–C(19)–N(3)	137.9(3)
C(18)–C(17)–C(19)–N(3)	–110.0(3)	C(20)–C(17)–C(19)–C(18)	105.7(3)
C(16)–C(17)–C(19)–C(18)	–112.1(3)	C(16)–C(17)–C(20)–O(3)	–7.4(5)
C(19)–C(17)–C(20)–O(3)	135.6(4)	C(18)–C(17)–C(20)–O(3)	–156.5(4)
C(16)–C(17)–C(20)–O(4)	171.5(3)	C(19)–C(17)–C(20)–O(4)	–45.4(4)
C(18)–C(17)–C(20)–O(4)	22.5(4)	O(4)–C(20)–O(3)–C(21X)	–6.5(11)
C(17)–C(20)–O(3)–C(21X)	172.3(10)	O(3)–C(20)–O(4)–C(21)	–2.8(5)
C(17)–C(20)–O(4)–C(21)	178.2(3)	C(19)–C(18)–C(22)–C(27)	23.7(4)
C(17)–C(18)–C(22)–C(27)	99.8(4)	C(19)–C(18)–C(22)–C(23)	–162.3(3)
C(17)–C(18)–C(22)–C(23)	–86.2(4)	C(27)–C(22)–C(23)–C(24)	0.0(6)
C(18)–C(22)–C(23)–C(24)	–174.3(4)	C(22)–C(23)–C(24)–C(25)	–0.8(7)
C(23)–C(24)–C(25)–C(26)	1.0(7)	C(24)–C(25)–C(26)–C(27)	–0.3(6)
C(23)–C(22)–C(27)–C(26)	0.7(5)	C(18)–C(22)–C(27)–C(26)	174.7(3)
C(25)–C(26)–C(27)–C(22)	–0.6(5)	C(18)–C(19)–N(3)–C(30)	45.4(4)

C(17)–C(19)–N(3)–C(30)	116.5(3)	C(18)–C(19)–N(3)–N(4)	−138.0(3)
C(17)–C(19)–N(3)–N(4)	−66.9(3)	C(30)–N(3)–N(4)–C(28)	−0.1(3)
C(19)–N(3)–N(4)–C(28)	−177.2(2)	N(3)–N(4)–C(28)–C(29)	−0.1(3)
N(4)–C(28)–C(29)–C(30)	0.2(4)	N(4)–C(28)–C(29)–Br(2)	−179.6(2)
N(4)–N(3)–C(30)–C(29)	0.2(3)	C(19)–N(3)–C(30)–C(29)	177.0(3)
C(28)–C(29)–C(30)–N(3)	−0.3(3)	Br(2)–C(29)–C(30)–N(3)	179.6(2)