Synthesis of *O*-Heterocycles:

The [2,3]-Sigmatropic Rearrangement of Transition Metal Carbenoid-Generated Allylic Oxonium Ylides

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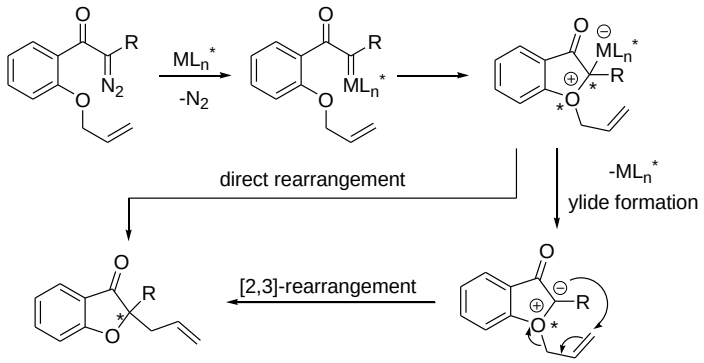
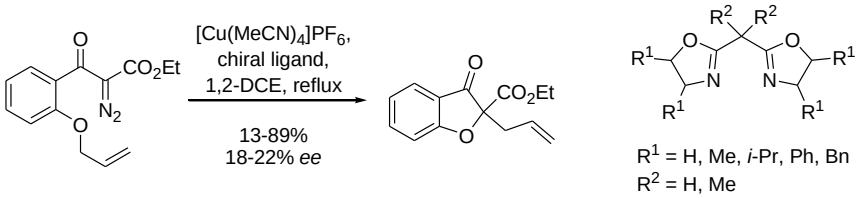
Abstract

In many natural products, heterocycles, such as cyclic ethers, are important features. While there are many different approaches to the formation of these ethers, there are only a few methods available for the synthesis of substituted cyclic ethers with good diastereoselectivity and even less so with good enantioselectivity. The rearrangement of oxonium ylides has proved to be a versatile method for the stereoselective synthesis of cyclic ethers. However, to date, there is no general efficient enantioselective method for the rearrangement of oxonium ylides. This project aimed to develop an enantioselective synthesis of *O*-heterocycles from chiral copper carbenoids.



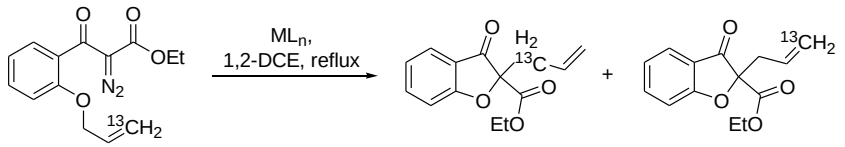
Screening of various catalysts generated *in situ* from [Cu(MeCN)$_4$]PF$_6$ and chiral ligands led us to identify a class of ligands, specifically chiral bisoxazoline ligands, that generally resulted in asymmetric induction during the [2,3]-sigmatropic rearrangement of oxonium ylides. Unfortunately, while asymmetric induction was obtained, generally the rearrangement reaction resulted in quite low enantiomeric excess.



During the course of this project, iridium-mediated reactions was also investigated. It was found that the catalyst $[Ir(COD)Cl]_2$ could be used for the same transformation as the copper catalysts, which to the best of our knowledge was the first example of the use of an iridium catalyst for the tandem oxonium ylide generation and subsequent [2,3]-sigmatropic rearrangement of diazoketones.

As only rather low asymmetric induction was obtained during this transformation, our attention turned towards achieving a greater mechanistic understanding of this reaction, as good mechanistic understanding is essential for enantioselective development. Isotopic labelling of the diazoketone starting materials provided information on the rearrangement products, from which conclusions could be drawn as to the rearrangement mechanism.

It was concluded that the rearrangement reactions in question, that take place *via* copper or iridium carbenoid-mediated reactions, either do not proceed through a free oxonium ylide, but rather through the metal-associated oxonium ylide derivative, or follow a major competing non-ylide route that delivers apparent [2,3]-sigmatropic rearrangement products of oxonium ylides. With regard to rhodium-catalysed reactions, firm conclusions could not be drawn, although there is some suggestion that this reaction also does not proceed solely through the free oxonium ylide pathway.



$Rh_2(OAc)_4$	>99:1
$Cu(acac)_2$	84:16
$[Ir(COD)Cl]_2$	45:55

Further investigations of the iridium-catalysed reaction through crossover experiments suggest that the metal-associated oxonium ylide derivative dissociates during the reaction to give an allylic cation and an iridium enolate, which then recombines to give the apparent [2,3]-rearrangement product.

Author's Declaration

I hereby declare that the work presented in this thesis is the result of my own investigations and that where the work of other investigators has been used, this has been fully acknowledged in the text.

I also declare that the substance of this thesis has not been submitted, nor is concurrently submitted, in candidature for any other degree.

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K. Emelie Hansen

Acknowledgements

It is fair to say that many people have played a substantial part in the success of this project, and in making the years spent in Glasgow such a memorable time. Therefore, I would now like to take this opportunity to thank all those who have made such a great impact and have been of tremendous support during the last few years.

Firstly, I would like to thank my supervisor, Prof. J. Stephen Clark, for giving me the opportunity to join his group and the chance to work with such a fascinating project. His help and support have been much appreciated.

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Finally, I would like to thank my parents, Irene and Kenth Hansen. Without their never-ending support, encouragement and belief in me this thesis would not exist.

Abbreviations

abs.	absolute
ABSA	4-acetamido-benzenesulfonyl azide
Ac	acetyl
acac	acetylacetonate
app.	apparent
Ar	aryl
BARF	tetra-aryl borate
Bn	benzyl
Bu	butyl
CI	chemical ionization
COD	1,5-cyclooctadienyl
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo-[5,4,0]-undec-7-ene
DCE	dichloroethane
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DMF	*N*,*N'*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide

DOSP	*N*-(*para*-dodecylphenylsulfonyl)prolinate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron-donating group
ee	enantiomeric excess
EI	electron ionization
Et	ethyl
EWG	electron-withdrawing group
FAB	fast atom bombardment
FOD	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate
h	hour(s)
hfacac	hexafluoroacetylacetonate
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
i	iso
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LRMS	low resolution mass spectrometry
MACIM	methyl 1-acetyl-2-oxoimidazolidine-4-carboxylate
MCHIM	methyl 1-cyclohexylethanoyl-2-oxoimidazolidine-4-carboxylate
Me	methyl
MEOX	methyl 2-oxooxazolidine-4-carboxylate
MEPY	methyl 2-oxopyrrolidine-5-carboxylate

min	minute(s)
ML_n	transition metal and associated ligands
mp	melting point
MPPIM	methyl 2-phenylpropanoyl-2-oxoimidazolidine-4-carboxylate
Ms	methanesulfonyl
n	normal
NaHMDS	sodium bis(trimethylsilyl)amide
naph	naphthyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
o	ortho
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
piv	pivalate
Pr	propyl
PTAD	(1-adamantyl)-(*N*-phthalimido)acetate
PTTL	*N*-phthaloyl-*tert*-leucinate
quant.	quantitative
R_f	retention factor
rt	room temperature
t	tert

TBAF	tetra-*normal*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
TBSP	*N*-(*para*-*tert*-butylbenzenesulfonyl)prolinate
t-Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
tfa	trifluoroacetate
tfacac	trifluoroacetylacetonate
TFPTTL	*N*-tetrafluorophthaloyl-*tert*-leucinate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	tetramethylsilane
TMS	trimethylsilyl
Tp	trispyrazolylborate
tpa	triphenylacetate
Ts	*para*-toluenesulfonyl

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Introduction

The development of enantioselective reactions is a major area of interest in organic chemistry. If a particular reaction that previously could only be performed to produce racemic products is adapted to be enantioselective, new possibilities open up. Many situations call for chiral non-racemic substrates; many natural products and biologically active substrates contain chiral centres. If a racemic substrate is used, then the enantiomers have to be separated, and half the material must be discarded. In contrast, if enantiomerically pure product could be obtained from a racemic or achiral starting material in a single step, this would be a highly useful transformation and of general interest to many synthetic chemists. While not an easy task, the development of asymmetric reactions is one well-deserving of the attention and the efforts required.

Heterocycles such as cyclic ethers are an important feature of many natural products. While there are many approaches to the formation of cyclic ethers, there relatively few methods for the synthesis of substituted cyclic ethers with good diastereoselectivity and even fewer that deliver high levels of enantiocontrol during ring formation from achiral acyclic starting materials. The generation and rearrangement of oxonium ylides or metal-bound ylide equivalents has proved to be a versatile method for the stereoselective synthesis of cyclic ethers. However, to date, there is no general, efficient and enantioselective variant of this reaction. This project aims to develop an enantioselective synthesis of *O*-heterocycles from chiral copper carbenoids. In addition, a greater mechanistic understanding of the reaction is required in order to enable the development of an enantioselective reaction.

1 Carbenes and Carbenoids

A carbene is defined as a neutral compound containing a carbon atom with only six valence electrons, of which two are nonbonding electrons. The reactive nature of the carbenes means that normally they cannot be isolated. Nevertheless, a few, very stable, carbenes have been isolated and stands as proof of the existence of the carbene species. In Figure 1 is shown a stable free carbene (**1**), where the stability can be explained by both steric effects, in addition to lone pair donation from the nitrogen substituents.

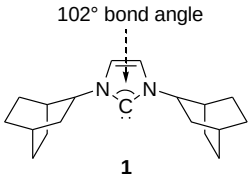

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Figure 1 Stable "free" carbene.

The term "carbenoid" refers to a metal-bound carbene, which results in a more stable species as compared to a "free" carbene. Even though a carbenoid is generally more stable than the corresponding carbene, it possesses some of the characteristics of a free carbene and is a reactive intermediate in its own right. The first metal-carbene complex, methoxyphenylmethylene tungsten(0), was reported by Fischer in 1964.[1] Ten years later, Schrock reported the synthesis of a tantalum alkylidene complex by α-hydrogen abstraction.[2] Many metal carbenoids, such as copper and rhodium carbenoids, are quite unstable and highly reactive molecules.

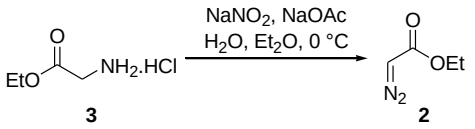
The high reactivity and low selectivity of carbenes can make them difficult to work with, because many different reactions can take place simultaneously and it can be difficult to control the reaction selectivity. In contrast, metal carbenoids are generally

more stable and are capable of highly selective reactions. This has led to metal carbenoids finding wide and varied use in modern organic chemistry.

A common method for generating metal carbenoids is by the reaction of diazo compounds with transition metal complexes and especially those of copper and rhodium. This method forms the basis for this research project.

2 The Chemistry of α-Diazocarbonyl Compounds

In 1883, Curtius synthesised the first example of an α-diazocarbonyl compound — ethyl diazoacetate **2** — upon reaction of glycine ester hydrochloride **3** with sodium nitrite (Scheme 1).[3] Since then, α-diazocarbonyl compounds have been shown to be very useful intermediates in organic synthesis.



Scheme 1 Synthesis of ethyl diazoacetate.

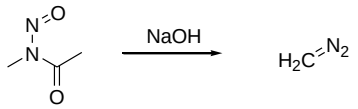
Although the method developed by Curtius is not commonly used any longer, the variety of alternative preparative procedures ensures the easy synthesis of a wide range of diazoketones. Furthermore, the facile decomposition of the diazoketones under various conditions, such as thermal, photochemical or transition metal catalysed conditions, results in useful and reactive carbenes or carbenoids.

2.1 Synthesis of α-Diazocarbonyl Compounds

While the Curtius method for the synthesis of ethyl diazoacetate is not widely used any longer, a wide variety of methods are available for the formation of α-diazocarbonyl compounds. Among the most common methods for preparation of α-diazocarbonyl substrates are acylation of diazomethane with an activated carboxylic acid and diazo transfer from an azide reagent to the α-carbon of a carbonyl group.

2.1.1 Acylation of diazomethane

One of the most common methods for the synthesis of α-diazocarbonyl compounds is the acylation of diazomethane. In 1894, von Pechman found that treating *N*-methyl-*N*-nitrosoacetamide **4** or *N*-methyl-*N*-nitrosourethane with sodium hydroxide resulted in the liberation of a yellow gas, which was later identified as diazomethane **5** (Scheme 2).

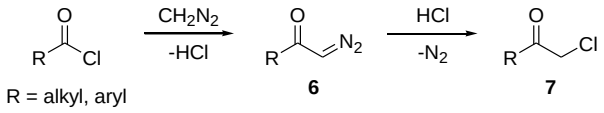


4 **5**

Scheme 2 Synthesis of diazomethane.

von Pechman found that diazomethane was useful in various reactions such as the formation of diiodomethane, C-H insertion of hydrogen cyanide to produce acetonitrile as well as methyl ester formation upon reaction with carboxylic acids.[4] Later, it was also found that reacting diazomethane with acid chlorides resulted in the formation of α-diazocarbonyl compounds.[5]

However, this reaction also produces hydrogen chloride, which could react with the resulting α-diazocarbonyl **6** to form an α-chlorocarbonyl compound **7**, diminishing the usefulness of the protocol (Scheme 3).



Scheme 3 Formation of an α-chlorocarbonyl compound.

In 1927 Arndt, Eistert and Partale published a modified procedure for the acylation of diazomethane with an acid chloride. In this procedure, the acid chloride was added to an excess of ethereal diazomethane, causing the hydrogen chloride to react with the excess diazomethane rather than the α-diazocarbonyl product.[6] The method was later tested using three substrates from which three α-diazoketones — diazoacetophenone, diazoacetone and 1-chloro-3-diazoacetone — were synthesised according to this protocol.[7] Shortly after Arndt, Eistert and Partale's publication, Bradley and Robinson also published similar observations.[8]

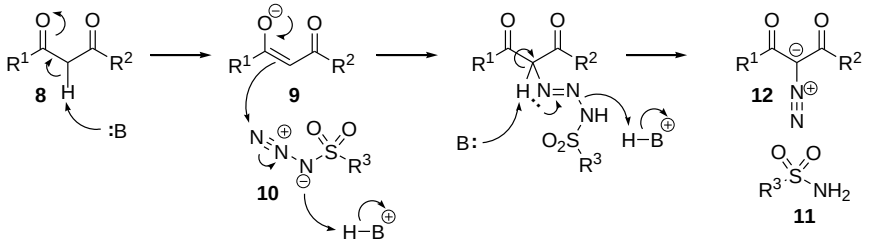
This protocol allowed the ready access to α-diazoketones for the first time and enhanced the utility for synthetic transformations of this substrate. To date, this is still one of the most commonly used methods for the preparation of α-diazocarbonyl compounds. In addition to acid chlorides, anhydrides can also be used as precursors for diazoketone preparation, particularly when acid-sensitive substrates are involved. Treatment of carboxylic acids with chloroformates, *e.g.* methyl, ethyl or isobutyl chloroformate, followed by treatment of the anhydride with diazomethane results in the synthesis of the corresponding diazoketone.

2.1.2 Diazotransfer reactions

Acylation of diazomethane has the disadvantage that only primary diazo ketones can be synthesised using this method. If, for example, a cyclic diazo ketone is required, it is necessary to use an alternative method of preparation. Dimroth[9] first described the concept of diazotransfer reactions, but Regitz was amongst the first to methodically develop procedures for a variety of diazotransfer reactions using arenesulfonyl azides in the presence of a base.[10,11]

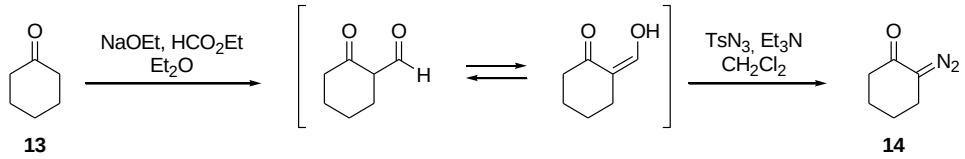
In diazotransfer reactions a diazo group is transferred from a donor molecule to an acceptor molecule in exchange for two protons. There are several commercially available diazotransfer reagents, such as tosyl azide, mesyl azide and 4-acetamido-benzenesulfonyl azide (ABSA). The acceptor is typically a 1,3-dicarbonyl compound **8**, such as a malonic ester, ß-keto ester, ß-diketone or ß-keto amide. For these types of

substrates, the protons at the α-position tend to be sufficiently acidic for the transfer reaction to take place. Removal of a proton at the α-position by base (:B) generates an enolate **9**, which undergoes a nucleophilic attack on the azide diazotransfer reagent **10**. Removal of the second proton at the α-position followed by loss of a sulfonyl amine **11** produces the diazoketone **12** (Scheme 4).



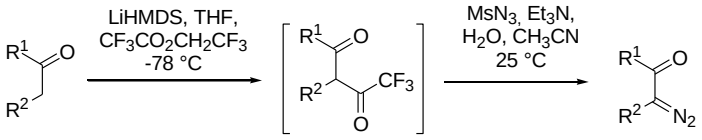
Scheme 4 Mechanism of diazotransfer reaction.

If the acceptor is not a 1,3-dicarbonyl compound, the compound does not usually react directly with the azide substrate because the protons at the α-position are not generally acidic enough to be removed by base. In these cases, additional activation might be necessary, using a temporary activating group. Regitz developed a procedure whereby formylation at the α-position of the carbonyl **13** activated the substrate to improve the reactivity (Scheme 5). After completion of the diazotransfer, deformylation during the work-up delivers the diazocarbonyl substrate **14**.[10,12,13]



Scheme 5 Activation for diazotransfer reactions according to Regitz' procedure.

There are other methods that can be deployed to activate carbonyl substrates. For example, Danheiser *et al*. developed a method based on Regitz' procedure, where a trifluoroacetyl group was used to activate the acceptor (Scheme 6).[14] This method proved to be efficient for various types of ketones, amongst them α,β-unsaturated ketones.



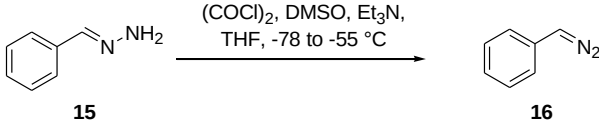
Scheme 6 Activation for diazotransfer reactions according to Danheiser's procedure.

Using a trifluoroacetyl group rather than an acetyl group facilitates the deacetylation reaction, and is particularly useful for sensitive substrates.[15]

2.1.3 Miscellaneous reactions

While acylation of diazomethane and diazotransfer reactions are by far the most common methods employed for the preparation of diazocarbonyl compounds, there are some alternative methods for diazo synthesis, although many are not commonly used today.

One method involves the dehydrogenation of hydrazones and various oxidants, such as manganese(II) oxide[16] or Swern-type reagents, can be used.[17] In Scheme 7 is shown how dehydrogenation of phenyl hydrazone **15** by Swern-type reagents results in formation of phenyldiazomethane **16**.

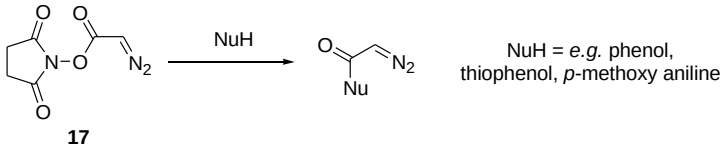


15 **16**

Scheme 7 The synthesis of phenyldiazomethane.

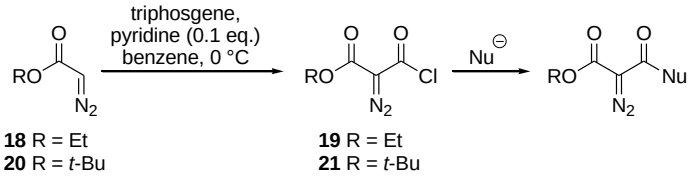
A related procedure for the synthesis of diazo compounds is the Bamford-Stevens reaction. In this reaction, cleavage of a tosyl hydrazone followed by reaction with base generates the corresponding diazocarbonyl compound.[18]

A different approach to the synthesis of diazocarbonyl compounds involves modification of already existing diazocarbonyl systems. For example, Badet *et al*. have reported that succinimidyl diazoacetate **17** can be used for direct diazo formation by nucleophilic substitution by phenols, thiophenols, peptides or aromatic or aliphatic amines under mild conditions (Scheme 8).[19]



Scheme 8 Modification of succinimidyl diazoacetate **17**.

Diazomalonate derivatives can be synthesised through modification of an existing diazocarbonyl system, an approach that has been promoted by, amongst others, Padwa *et al*. (Scheme 9). Treatment of the ethyl diazoacetate **18** with triphosgene affords ethyl 2-diazomalonyl chloride **19** (R = Et), which is an efficient diazoacylating reagent. Upon further reaction of this system with nucleophilic reagents, various α-diazo dicarbonyl compounds can be obtained. The *t*-butyl derivative **20** can be employed in a similar fashion.[20]

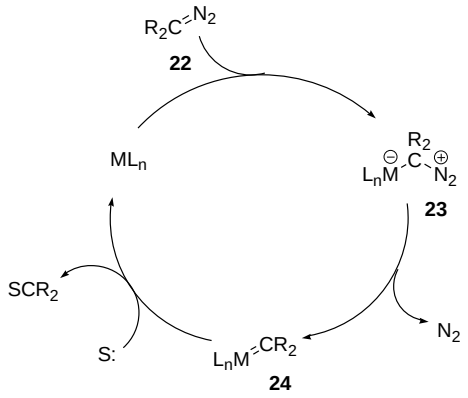


Scheme 9 Synthesis of diazomalonate derivatives.

2.2 Decomposition of α-diazocarbonyl compounds

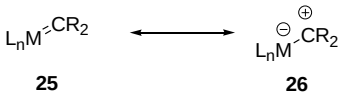
In order for a reaction to take place using diazocarbonyl compounds, the diazo substrate first needs to be activated. Heating or irradiation of α-diazocarbonyl compounds will cause the decomposition of the diazo group, resulting in formation of the corresponding carbene and liberation of nitrogen gas. Although the photochemical or thermal reactions do not require additional reagents and liberate only nitrogen gas, the resulting free carbenes are highly reactive and not particularly selective in their reactions. In contrast, metal carbenoids are still reactive but tend to display increased selectivity and are of great synthetic use. Metal carbenoids can easily be generated from diazocarbonyls upon treatment with transition metal catalysts. Lewis acid transition metal complexes are generally effective catalysts for this type of carbenoid generation. Coordinative unsaturation at their metal centre allows them to react as electrophiles with diazocompounds.

In the generally accepted reaction mechanism, the catalytic cycle commences with nucleophilic addition of the diazo compound **22** to the metal catalyst ML_n to form diazonium ion adduct **23** (Scheme 10). Subsequent loss of nitrogen gas results in formation of the corresponding metal carbenoid **24**. In the presence of an electron-rich substrate (S:), the carbene can react with the substrate, resulting in regeneration of the transition metal catalyst.[21,22,23,24] If this electron-rich substrate is an ether, then an oxonium ylide is generated. Reactions with amines or sulfides result in the generation of ammonium or sulfonium ylides. Spectroscopic evidence for the intermediacy of the diazonium ion adduct **23** has been obtained.[25] The first suggestion for the mechanism to account for the decomposition of a diazo compound with a transition metal catalyst was published in 1952 by Yates.[26]



Scheme 10 Catalytic cycle of the decomposition of diazo compounds.

The stability and the reactivity of a specific carbenoid depends on the degree of π-back donation from the metal atom to the carbonic carbon. Carbenoids generated from electrophilic transition metal complexes have two resonance forms; the metal carbenoid **25** and the metal stabilised carbocation **26** (Scheme 11).



Scheme 11 Resonance forms of carbenoids.

The first example of the use of a metal complex to perform decomposition of an α-diazocarbonyl compound to give a metal carbenoid was reported by Silberrad and Roy in 1906. They used copper dust to catalyse the decomposition of ethyl diazoacetate to give the corresponding copper carbenoid.[27] In early work in this area, copper(II) sulphate was also a common catalyst.[28] During the 1960's, soluble copper catalysts were developed as an alternative to the heterogeneous catalysts. Amongst these were copper(II) acetylacetonate [$Cu(acac)_2$] and its fluorinated analogues **27**, which are still widely in use today (Figure 2).[29,29]

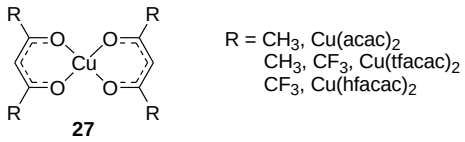
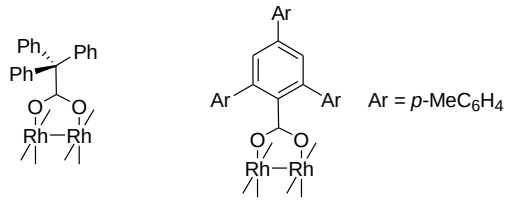


Figure 2 Copper(II) acetylacetonate and derivatives.

It was found that the active catalyst is not a copper(II) complex but copper(I) species, following the observation that diazo compounds are able to reduce copper(II) complexes such as copper(II) chloride and copper(II) triflate ($Cu(OTf)_2$) to their copper(I) equivalents.[30,31] Amongst the more common achiral copper catalysts are, in addition to the ones already mentioned, copper(I) hexafluorophosphate,[32] trialkyl or triaryl phosphite copper(I) chloride[33,34] and various salicylaldimine complexes of copper(II).[35] Chiral copper catalysts have also been utilised in asymmetric reactions and in these cases, bi- or tridentate ligands are commonly very effective. For example, copper complexes derived from bisoxazoline ligands and derivatives of these, have been found to be efficient catalysts for enantioselective cyclopropanation reactions.[36,37,38,39] The chiral catalysts can be generated *in situ* from either CuOTf or $[Cu(MeCN)_4]PF_6$.[32,34,40]

Until the late 1970's, copper complexes were usually the catalysts of choice for the metal-mediated decomposition reactions of diazo compounds. However, in 1973, Teyssié *et al*. discovered that dirhodium(II) tetraacetate $[Rh_2(OAc)_4]$ is a highly active transition metal complex for the decomposition of diazocarbonyl substrates.[41] This was the beginning of the era in which rhodium carboxylate complexes have enjoyed great popularity as efficient catalysts for the decomposition of diazocarbonyl compounds. Generally, rhodium carbenoid reactions proceed at lower temperatures than reactions involving copper carbenoids. A wide range of rhodium catalysts is readily available through ligand exchange reactions with simple rhodium halides or carboxylates.

A variety of rhodium dimers are commonly used as catalysts for metal carbenoid formation. The selectivity of the dirhodium complexes is highly dependent on the electronic properties of the bridging ligands present in the rhodium dimer. Varying the bridging acetate ligand with different carboxylate or carboxamidate ligands influences the physical and chemical properties of the catalyst, such as solubility or chirality. For example, dirhodium complexes containing chiral ligands are commonly used as catalysts for asymmetric carbenoid transformations.[42] The wide range of carboxylate ligands generally facilitates control of reactivity and selectivity. For example, dirhodium(II) tetratriphenylacetate $[Rh_2(tpa)_4]$ **28** has been found to be a highly efficient catalyst for C-H insertion reactions of α-diazo-ß-keto esters,[43] whereas dirhodium(II) tri-and tetrakis(tri-tolylbenzoate) **29** has been used to promote cyclopropanation reactions (Figure 3).[44]



28 **29**

Figure 3 Rhodium catalysts.

In addition to copper and rhodium complexes, other transition metal complexes have also been used to generate metal carbenoids. These include complexes of cobalt,[45,46] palladium,[47] ruthenium,[48,49] osmium,[50] iron,[51] platinum,[52] nickel[53] and tungsten, of which a tungsten carbenoid could be used as a procatalyst for the catalytic decomposition of diazocompounds.[54] Most of these transition metal carbenoids have been used to perform cyclopropanation reactions. Ruthenium complexes have also been used for ylide generation.[55] Very recently, iridium carbenoids have been used to perform enantioselective Si-H insertion.[56]

With the wide range of transition metal complexes available for carbenoid generation, it has been found that some specific metal-ligand combinations afford good chemoselectivity with regard to competing reactions of the intermediate carbenoids (such as ylide generation, cyclopropanation and C-H insertion) or afford good stereoselectivity during a given reaction. This issue will be discussed later in this chapter, mainly with respect to copper catalysis.

2.3 Common Metal Carbenoid Reactions

Metal carbenoids, obtained through metal-catalysed decomposition of α-diazoketones, participate in a wide range of various reactions. The more common transformations include cyclopropanation, X-H insertion (X = C, O, S, N, Si) and ylide generation followed by rearrangement. These reactions have all been used for the synthesis of complex targets.[21,22,57,58,59] The emphasis of this thesis is on the generation of oxonium ylides or ylide-like intermediates and their subsequent rearrangement; such transformations will be discussed in great detail (*vide infra*). However, alternative reactions such as cyclopropanation and C-H insertion will also be discussed because they

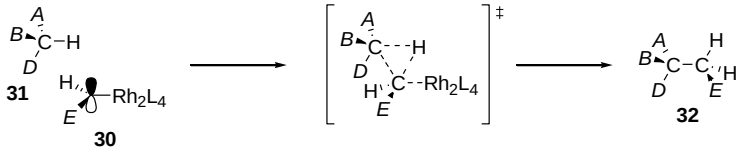
are of great importance in organic synthesis and are closely connected to the main topic of this thesis as they often compete with ylide generation.

2.3.1 Insertion reactions

X-H insertion reactions of metal carbenoids are well known for X = O, S, N, Si or C. The low bond polarity of C-H bonds in comparison with O-H, S-H or N-H bonds, combined with the formation of a carbon-carbon bond, make this a reaction of great interest.

In 1942, Meerwein, Rathjen and Werner first reported the discovery of insertion reactions of carbenes into C-H bonds.[60] Although insertion reactions can proceed both intermolecularly and intramolecularly, intermolecular C-H insertion reactions tend to be unselective and intramolecular reactions often compete. Multiple products are generally obtained from intermolecular C-H insertion reactions and a highly electrophilic catalyst is usually required to minimise competitive reactions. In comparison, intramolecular carbenoid insertion reactions tend to be selective, even when moderately electrophilic complexes are used to generate the carbenoid, and generally proceed relatively efficiently.[57,61,62,63] Therefore, intramolecular C-H insertion is considered to be a versatile tool in organic chemistry, despite the challenge of insertion selectivity control. In fact, the catalytic decomposition of diazocompounds has proved to be one of the very few methods where selective reaction at an unactivated C-H bond can be achieved.[21,22,24,53,64,65] Through intramolecular C-H insertion reactions, various carbocycles and heterocycles can be synthesised, in a regiocontrolled and stereoselective manner.

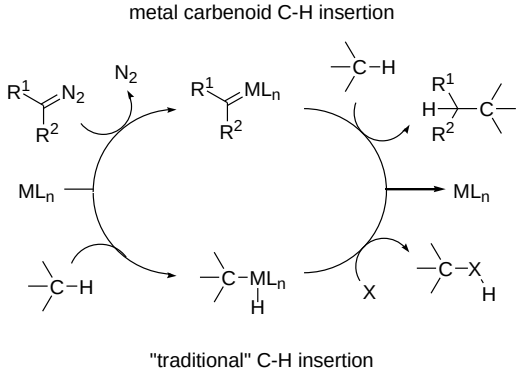
The mechanism of the C-H insertion reaction of an electrophilic carbenoid generated using a transition metal catalysis has been debated extensively.[21,22,24,53,57,61,62,63] It is believed that the reaction commences with overlap of the *p*-orbital of the metal carbenoid **30** with the σ-orbital of the reacting C-H bond **31**. Formation of C-C and C-H bonds occurs with dissociation of the transition metal as shown in Scheme 12. There is also substantial experimental evidence for retention of configuration at the carbon atom of the C-H bond undergoing insertion.[66]



Scheme 12 C-H insertion reaction mechanism.

The selectivity of the reaction does in some part depend on the ligands of the transition metal. By increasing the electron withdrawal of the ligand from the transition metal, the electrophilicity of the carbenoid carbon increases. This makes possible bond formation at a greater distance from the reacting C-H bond. As a consequence, the earlier transition state results in lower selectivity. By the same principle, decreasing the electron withdrawal leads to a later transition state which confers greater reaction selectivity.[67] Although both copper and rhodium catalysts can be used to facilitate C-H insertion, rhodium catalysts have become the most popular.

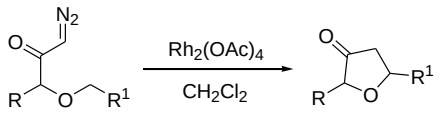
Metal-catalysed C-H activation and insertion that does not proceed through a metal carbenoid intermediate is also well known. The mechanism differs significantly from that involving a carbenoid intermediate. In the mechanism shown in Scheme 12 the metal does not interact directly with the C-H bond, however, for many metal-catalysed C-H reactions, the C-H activation is based on oxidative addition of the metal across the alkane C-H bond. This can take place either by insertion of a highly reactive metal complex into the C-H bond which then activates the system to further transformations, or by less reactive metal complexes being directed to the site of transformation by neighbouring functionalities (Scheme 13).[68,69,70]



Scheme 13 Different approaches to C-H insertion.

Various factors are influential in the C-H activation process, such as electronic and steric factors. The reactivity of the substrates is greatly influenced by the number of alkyl substituents; tertiary C-H bonds are more reactive than secondary C-H bonds, which in turn are more reactive than primary C-H bonds. In addition, for compounds containing heteroatoms, insertion tends to proceed regioselectively with insertion into the C-H bond α to the heteroatom. For example, it is known that the presence of an ether oxygen increases this type of selectivity.[71,72,73]

The most favoured intramolecular process is formation of a five-membered ring because the six-membered transition state is entropically favourable. Five-membered ring formation generally takes precedence over factors such as whether the C-H bond is secondary or tertiary, as is also shown in Scheme 14. Conformationally restricted structures facilitate intramolecular C-H insertion due to favourable entropic considerations. However, activation of a C-H bond by an adjacent heteroatom such as oxygen or nitrogen allows cyclic systems of differing ring-size to be obtained. Both 1,4- and 1,7-insertions have been reported when this type of activation is employed,[74,75,76,77] and 1,6-insertion reactions have been reported for structurally rigid systems.[78,79,80] Wang *et al*. have also reported a previously unprecedented intramolecular 1,3-insertion.[81]



33 **34**

Scheme 14 C-H insertion.

Although intermolecular C-H insertion was not commonly used in organic synthesis, initially due to low selectivity, further research has provided methods for performing intermolecular C-H insertion with improved selectivity. Dirhodium carboxylates, which are efficient catalysts for intramolecular C-H insertion reactions, caused low selectivity and carbenoid dimerisation when used to mediate the intermolecular counterpart. The discovery that placement of a donor substituent on the carbenic carbon generated a stabilised intermediate, for which highly regioselective C-H insertion reactions could be obtained, resulted in increasing use of the intermolecular C-H insertion reaction.[65] Carbenoid intermediates can be classified into three major groups, based on what substituents the carbenoid carbon possesses. An acceptor substituted carbenoid compound possesses one electron-withdrawing substituent, such as a carbonyl or an

ester group. An acceptor/acceptor substituted carbenoid in turn possesses two electron-withdrawing substituents, whereas an acceptor/donor substituted carbenoid compound possesses an electron-withdrawing group and an electron-donating group (Figure 4).

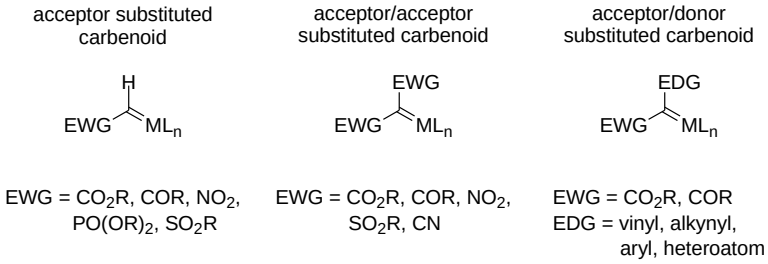
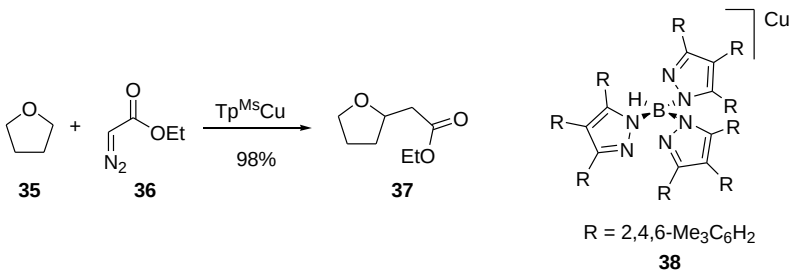


Figure 4 Different categories of substituted carbenoids.

An acceptor/donor substituted carbenoid, where both an electron-donating and electron-withdrawing group is present, is less prone to undergo dimerisation and displays an increased propensity to undergo intermolecular reactions. An alternative method for obtaining the selectivity of intermolecular reactions has been reported by Pérez *et al*. In this case, intermolecular C-H insertion reactions of carbenoids result in higher yields when the carbenoid is generated using a bulky copper catalyst such as $Tp^{Ms}Cu$ (Scheme 15). The bulky ligands **38** around the metal were found to suppress dimerisation effectively. With a similar catalyst as that in Scheme 15 (R = Br), good chemoselectivity could also be obtained.[82,83]

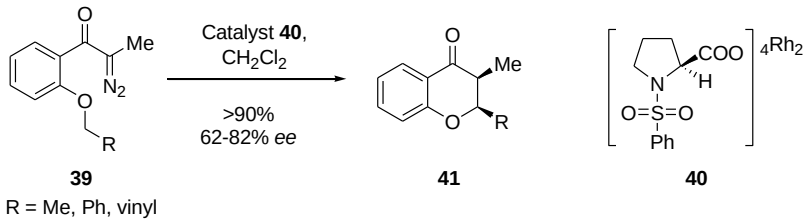


35 **36** **37** **38**

Scheme 15 Intermolecular C-H insertion with bulky copper catalyst.

Enantioselective C-H insertion reactions have been performed using chiral rhodium catalysts. The first example of an enantioselective C-H insertion reaction was reported in 1990.[84,85] Despite the relatively short time since the first report of enantioselective

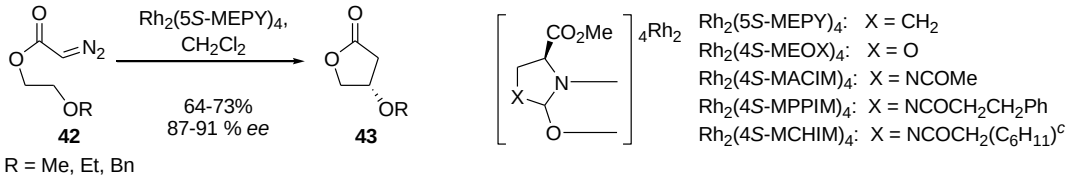
C-H insertion, many efficient chiral catalysts have been developed. Work towards the enantioselective reaction has mainly focused on intramolecular C-H insertion. The first chiral catalysts, dirhodium(II) carboxylates formed from *N*-protected amino acids, tend to be most efficient when diazoketones of the structure $RCOCN_2R'$ (where R' ≠ H) are employed as substrates (**39**) (Scheme 16).[86]



39 R = Me, Ph, vinyl **41** **40**

Scheme 16 Example of asymmetric reaction mediated by catalyst formed from *N*-protected amino acid.

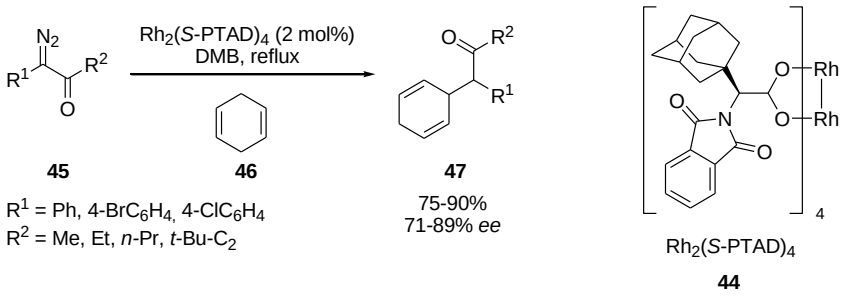
Also of note are the chiral dirhodium(II) carboxamidate catalysts, developed by Doyle *et al*. These are particularly efficient with diazoacetate substrates, and have proved to be highly efficient and very versatile catalysts.[87] An example of an asymmetric reaction employing this type of catalyst is shown in Scheme 17.



42 R = Me, Et, Bn **43**

Scheme 17 Dirhodium(II) carboxamidate catalysts, as developed by Doyle *et al*.

Recently, Davies *et al*. used chiral rhodium catalysts in both intermolecular asymmetric C-H insertion reactions as well as cyclopropanation reactions. The catalyst Rh_2(*S*-PTAD)$_4$ **44** delivered good levels of asymmetric induction during the C-H insertion reaction, and C-H insertion of diazoketone **45** with 1,4-cyclohexadiene **46** proceeded in good yield (75-90%) and with good enantioselectivity (71-89% *ee*) obtained (Scheme 18).[88]



45 **46** **47** **44**

R^1 = Ph, 4-BrC_6H_4, 4-ClC_6H_4
R^2 = Me, Et, *n*-Pr, *t*-Bu-C_2

75-90%
71-89% *ee*

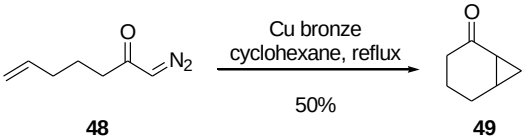
Rh_2(*S*-PTAD)$_4$

Scheme 18 Enantioselective intermolecular C-H insertion.

2.3.2 Cyclopropanation

A very common reaction involving carbenoids is cyclopropanation. During the cyclopropanation reaction, an olefin react with a carbenoid to form a cyclopropyl ring. Three-membered rings are very important building blocks, as they are structural sub-units in many biologically active natural products and are present in many synthetic intermediates. Therefore, the cyclopropanation reaction of diazoketones has received substantial attention during the last few decades.

While transition metal catalysed cyclopropanation first was reported in 1906,[27] it was not until during the late 1960's that the catalyst development began in earnest and the reaction gained in importance. Initially, catalytic cyclopropanation using diazocarbonyl compounds was focused on intermolecular reaction. As catalysts were limited to a few, often insoluble complexes, it was difficult to obtain selectivity during these intermolecular reactions.[89,90] Following the report of the first intramolecular cyclopropanation reaction by Stork and Ficini in 1961, interest in this procedure increased significantly.[91] In this case, the diazoketone **48** prepared from 5-hexenoic acid underwent intramolecular cyclopropanation in reasonable yield when treated with copper bronze (Scheme 19).

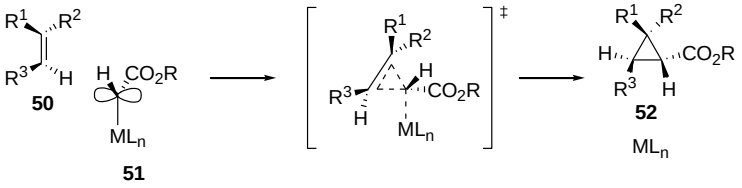


48 **49**

Scheme 19 The first intramolecular cyclopropanation reaction.

With the development of homogeneous transition metal complexes as catalysts, major advances were reported for cyclopropanation as well as other metal carbenoid transformations.[21,53] With catalysts that are soluble in organic solvents, reactions could take place at lower temperatures compared with the heterogeneous reactions. The ability to modify the catalyst ligands to a greater extent meant that it was possible to achieve a degree of reaction selectivity.[24] It is now possible to perform highly effective syntheses of functionalised cyclopropanes with high levels of diastereocontrol using catalysts based on copper and rhodium complexes.

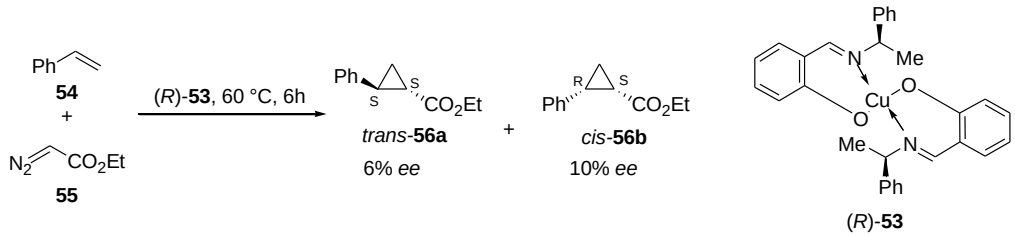
The mechanism of cyclopropanation has been debated, but is now generally assumed to proceed as described by Doyle *et al*.[92,93] as well as by Kodadek *et al*.[51,94] (Scheme 20). Here, the orientation of the alkene **50** relative to the carbenoid **51** provides the stereoselectivity. The carbenoid substituents and the ligands of the metal control the orientation of the reactive species. For example, large R-substituents at the ester group cause steric restrictions with respect to the alkene substituents, with larger substituents in the preferred placement of R^1.



Scheme 20 Cyclopropanation mechanism.

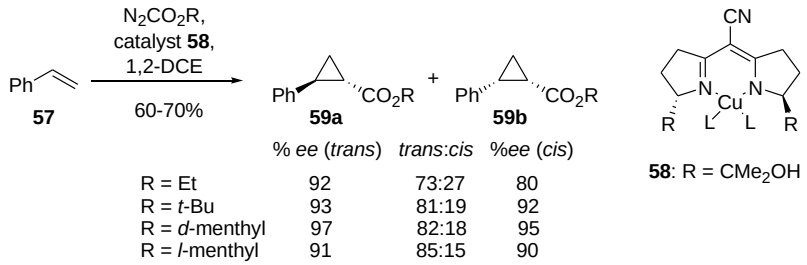
During the cyclopropanation reaction, up to three stereogenic centres are created in a single step. This feature of the reaction provides interesting opportunities but also presents challenges with regard to diastereoselectivity. Both stereoselective inter- and intramolecular cyclopropanation reactions have been studied extensively, from a diastereoselective as well as an enantioselective perspective. During intramolecular cyclopropanation reactions, formation of a bicyclic system in which the cyclopropane is fused to a five- or six-membered ring appears to be favoured.[95] However, syntheses of macrocycles possessing up to twenty-membered rings have been achieved.[32] A considerable advantage for intramolecular cyclopropanation is that under certain circumstances, such as during the formation of ring sizes <9, only one stereoisomer is obtained. In comparison, during the intermolecular reaction control of diastereoselectivity is a major consideration.

The first report concerning catalytic asymmetric cyclopropanation came in 1966, when Nozaki used a chiral Schiff base-copper(II) complex **53** to catalyse the cyclopropanation of styrene **54** with ethyl diazoacetate **55** to give *trans*- and *cis*-2-phenylcyclopropanecarboxylate (**56a**, **56b**) (Scheme 21).[29,96,97] The enantioselectivity of this reaction was very low, but further research has led to more efficient methods for asymmetric cyclopropanation (*vide infra*). This reaction has served as the bench-mark reaction for the development of almost every new chiral catalyst that has been developed subsequently.



Scheme 21 Asymmetric cyclopropanation according to Nozaki.

The area of enantioselective cyclopropanation has since attracted a great deal of interest, both with regard to the inter- and the intramolecular variants. Some classes of chiral catalysts have been found to be efficient for both types of reactions, such as copper complexes bearing semicorrin ligands. These were first reported by Pfaltz *et al.* in 1986.[98] High enantioselectivities were obtained in the bench-mark reaction involving reaction of styrene **57** with a diazoacetate (Scheme 22).[99] This was also found to be the case in the intramolecular reaction.[100]

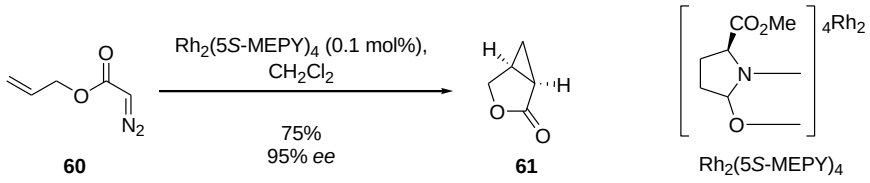


	% *ee* (*trans*)	*trans*:*cis*	%*ee* (*cis*)
R = Et	92	73:27	80
R = *t*-Bu	93	81:19	92
R = *d*-menthyl	97	82:18	95
R = *l*-menthyl	91	85:15	90

Scheme 22 Semicorrin based catalysts.

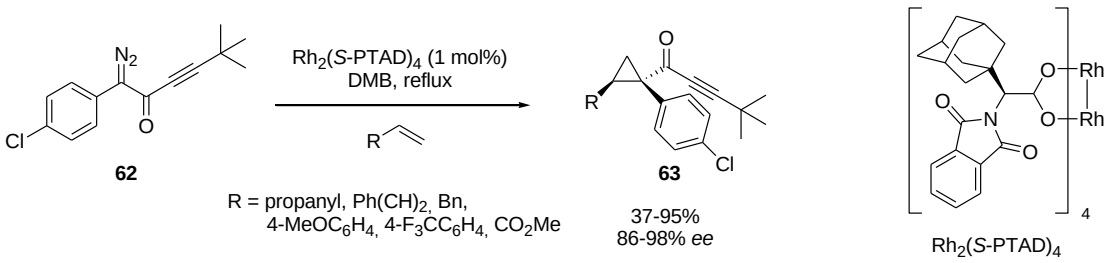
Catalysts complexed to derivatives of semicorrins, such as aza-semicorrins[101] and bisoxazolines,[37,38,102] have also been found to be highly efficient from an enantioselective point of view.

Chiral rhodium carboxamidates that are efficient in enantioselective C-H insertion, as previously mentioned, were also found to be applicable in enantioselective inter- and intramolecular cyclopropanation reactions and delivering high enantioselectivity, particularly in the intramolecular process. An example of this type of reaction is shown in Scheme 23.[103,104,105]



Scheme 23 Example of enantioselective intramolecular cyclopropanation.

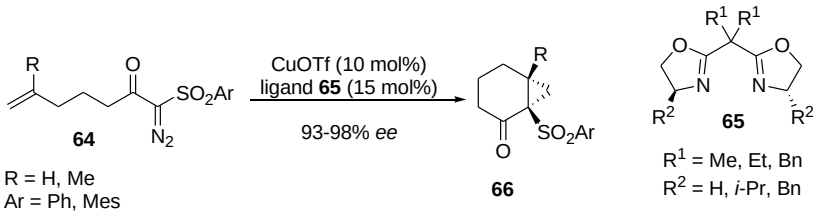
Davies *et al*. have also been investigating the use of chiral rhodium catalysts for various carbenoid reactions. As mentioned in the previous chapter, Rh_2(*S*-PTAD)$_4$ delivered good enantioselectivity when used to mediate asymmetric carbenoid C-H insertion reactions. However, this catalyst also proved to be efficient for asymmetric intermolecular cyclopropanation reactions, delivering good levels of enantioselectivity (86-98% *ee*) (Scheme 24).[88]



Scheme 24 Asymmetric intermolecular cyclopropanation.

In 2003, Nakada *et al*. reported that intramolecular cyclopropanation reactions of α-diazo-β-keto sulfones **64** could be performed with high enantioselectivity (Scheme 25).[106,107] Copper complexes, generated *in situ* from CuOTf and chiral bisoxazoline

ligands **65**, were employed for these reactions. It was found that while good enantioselectivity was obtained, yields could sometimes be modest due to competing C-H insertion reactions.

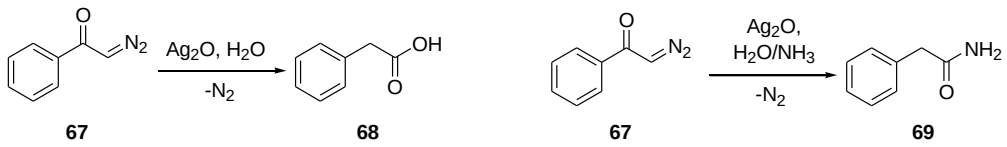


Scheme 25 Intramolecular cyclopropanation of α-diazo-β-keto sulfones.

2.3.3 Miscellaneous reactions

2.3.3.1 Wolff rearrangement

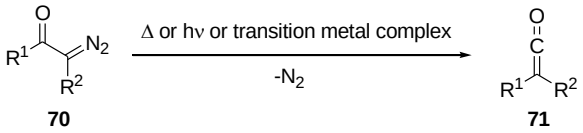
The Wolff rearrangement reaction was reported in 1902, following Wolff's observation that treatment of diazoacetophenone **67** with silver oxide and water resulted in rearrangement to form phenylacetic acid **68** (Scheme 26).[108] The presence of ammonia resulted in the formation of phenylacetamide **69** rather than the carboxylic acid.



Scheme 26 Rearrangements of diazoacetophenone.

Although other findings from similar reactions were published not long after,[109,110] it was not until several decades later that the reaction was examined in detail because of the lack of general methods for the preparation of the diazoketone precursors.

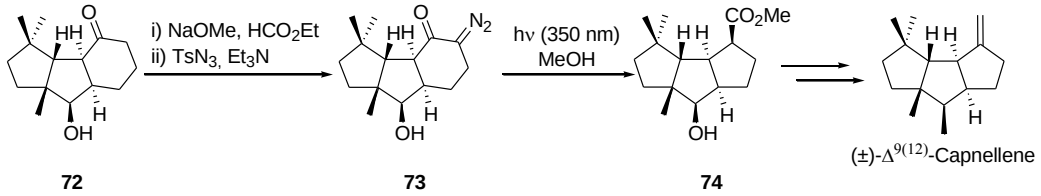
In the Wolff rearrangement reaction, the diazoketone **70** forms a ketene **71** upon loss of nitrogen gas (Scheme 27). The electrophilic ketene then undergoes nucleophilic attacks, [2+2] cycloaddition with an alkene, ring contraction (for a cyclic diazoketone) or rearrangement to γ,δ-unsaturated ester (for an α,β-unsaturated diazoketone).



70 **71**

Scheme 27 Ketene formation.

Wolff rearrangement reactions have been widely used for the total synthesis of natural products. Fukumoto *et al*. used the Wolff rearrangement for the total synthesis of (±)-$\Delta^{9(12)}$-capnellene. Here, a 5-5-6 tricyclic system obtained after an intramolecular Diels-Alder reaction was converted into the 5-5-5 tricyclic system of the target molecule (Scheme 28).[111]

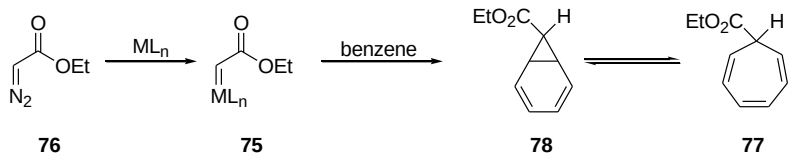


72 **73** **74**

Scheme 28 Wolff rearrangement for the total synthesis of (±)-Δ-capnellene.

2.3.3.2 Büchner reaction

Upon treatment of benzene with a metal carbenoid **75** generated from ethyl diazoacetate **76**, the ethyl ester of cycloheptatriene carboxylic acid **77** is formed, *via* arene cyclopropanation and subsequent electrocyclic ring opening (Scheme 29). This reaction was first reported by Büchner and Curtius in 1885.[112] As with many other diazo reactions, the advent of soluble copper- and rhodium-based catalysts brought increased reaction selectivity and the Büchner reaction became a convenient reaction for the synthesis of seven-membered carbocycles.



76 **75** **78** **77**

Scheme 29 The Büchner reaction.

Maguire *et al*. were the first to report that good enantioselectivity for the intramolecular Büchner reaction can be obtained when chiral copper bisoxazoline ligands are employed.[113] Furthermore, they also showed that the enantioselectivity of a given reaction was influenced by identity of the counterion. Non-coordinating BARF anions tended to enhance the enantioselectivity of the intramolecular carbenoid addition to aromatic rings.

2.3.4 Ylide generation

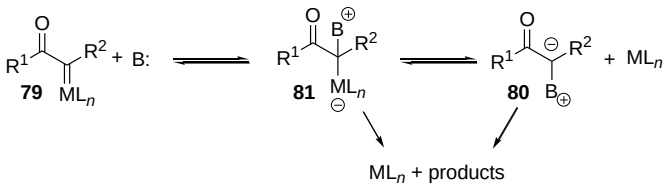
As mentioned before, ylide generation is one of the most important reactions of metal carbenoids, and the reaction forms the basis of this research project. Consequently, the chemistry of ylides will be discussed in greater detail in Chapter 3.

3 Chemistry of Ylides

Ylides can be viewed as species possessing positive and negative charges on adjacent atoms — generally a positively charged heteroatom connected to a carbon atom possessing an unshared pair of electrons. These readily react to undergo synthetically useful transformations.

3.1 Ylide generation

Upon the interaction of the electron-deficient carbon of a metal carbenoid intermediate **79** with a pair of non-bonding electrons from a Lewis base (B:), such as a heteroatom, an ylide is generated (Scheme 30). The ylide can either be in the shape of a "free" ylide **80** or the metal complex associated equivalent **81**.

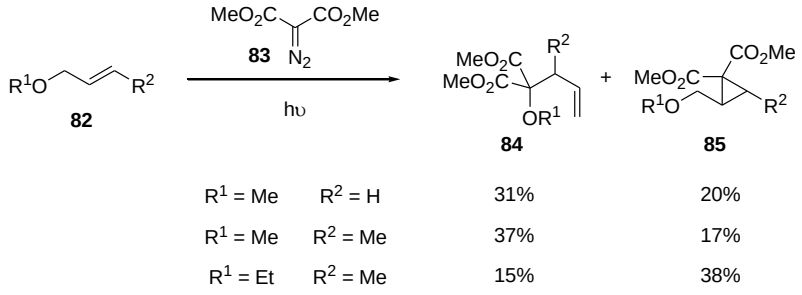


Scheme 30 Mechanism of ylide generation.

Common Lewis bases include ethers, to generate oxonium ylides, sulfides, to generate sulfonium ylides and amines, to generate ammonium ylides. The ylide is usually highly reactive and readily undergoes further reactions, but ylide stability can vary greatly. Some ylides are stable enough to isolate and characterise. For example, many sulfonium ylides are quite stable, due to d-orbital participation.[114] In contrast, some, in particular

oxonium ylides, are highly unstable as well as very reactive and can not be isolated, which makes them very difficult to characterise. Evidence of their existence therefore tends to be circumstantial, with isolation of the products expected from further reactions of these ylides.[114] This is most likely the reason that unlike ammonium or sulfonium ylides, the chemistry of oxonium ylides has until recently received little attention. However, due to their accessibility by the reaction of metal carbenoids with ethers, oxonium ylides have over the last few decades been found to be a very versatile intermediates in organic synthesis.[57,59,67,73,114,115]

Ylide formation can also proceed from free carbenes that have been generated thermally or photochemically. Unfortunately, as so often is the case with carbene intermediates, the selectivity is lower compared with the same reaction mediated by the carbenoid equivalent. This process has been explored by Ando *et al*. as well as Nozaki *et al*. Ando and co-workers explored the reactions of allylic ethers **82** with carbenes **83** generated photochemically from dimethyl diazomalonate (Scheme 31).[116] It was found that while the size of the alkyl groups influenced the selectivity, mixtures of ylide rearrangement products **84** and cyclopropanation products **85** were obtained.



R^1 = Me	R^2 = H	31%	20%
R^1 = Me	R^2 = Me	37%	17%
R^1 = Et	R^2 = Me	15%	38%

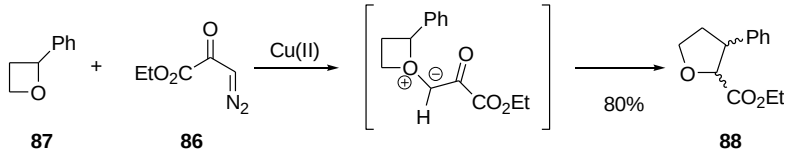
Scheme 31 Carbene-generated reaction selectivity.

Nozaki *et al*. investigated the thermal and photochemical reactions of ethyl diazoacetate with 2-phenyl-oxirane and 2-phenyloxetane. Again, several products were obtained from each reaction, some which appeared to be formed through rearrangements of oxonium ylides, such as ring-expanded Stevens shift products.[117,118]

To conclude, ylides produced from carbenes that have been generated by thermal or photochemical reactions, are not particularly selective. In contrast, ylide generation from metal carbenoid intermediates can proceed with much improved selectivity. Homogeneous copper complexes, as well as rhodium carboxylates, have proved to be highly efficient for generating metal-stabilised oxonium ylides. In addition, using

rhodium carboxylates as catalysts for carbenoid generation usually enables the reaction to proceed at lower temperatures compared with the copper-catalysed reactions.

One of the earliest examples of ylide generation from catalytically generated metal carbenoids was provided by Nozaki *et al*. in 1966. These workers discovered that the copper-catalysed reaction of ethyl diazoacetate **86** with 2-phenyloxetane **87** afforded 2-carboethoxy-3-phenyltetrahydrofuran **88** in 80% yield, which could be expected following the oxonium ylide generation and subsequent ring-expanding [1,2]-shift (Scheme 32).[117]



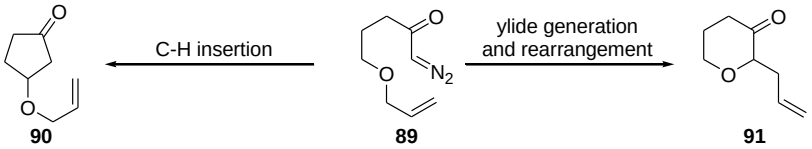
Scheme 32 One of the earliest examples of oxonium ylide generation.

In addition, Kirmse and Kapps reported in 1968 that reactions of allylic ethers with copper carbenoids, generated from diazomethane and copper salts, delivered the product expected from an oxonium ylide generation followed by [2,3]-rearrangement.[119]

In the catalytic intramolecular reaction of a diazocarbonyl ether, cyclic oxonium ylides can be generated. A subsequent [1,2]-shift or [2,3]-sigmatropic rearrangement reaction of the reactive ylide or ylide-like intermediate provides a versatile approach towards the construction of substituted cyclic ethers or carbocycles. The first examples were provided by Pirrung and Werner as well as Roskamp and Johnson, who independently reported intramolecular oxonium ylide generation *via* $Rh_2(OAc)_4$-catalysed carbenoid formation from diazocarbonyl compounds.[120,121]

Ylide generation is only one of several possible reactions that transition metal-generated carbenoids can undergo and this can result in selectivity problems. In fact, C-H insertion can be a major competitive reaction in intramolecular cyclic oxonium ylide generation. It has, however, been found that the nature of the catalyst greatly influences the reaction selectivity, and varying the catalyst enables switching between oxonium ylide generation and C-H insertion.[86,122] For example, Clark *et al*. have found that carbenoid generation by $Cu(acac)_2$ and its fluorinated analogues, $Cu(tfacac)_2$ and $Cu(hfacac)_2$, is usually more selective than $Rh_2(OAc)_4$ towards ylide generation and subsequent rearrangement in competition with C-H insertion (Scheme 33). Whereas

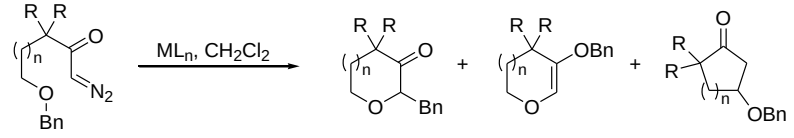
$Cu(acac)_2$ resulted in a greater ratio of rearrangement product **91** *vs*. the C-H insertion product **90** compared to $Rh_2(OAc)_4$, some C-H insertion product **90** was still obtained. However, the fluorinated catalysts only resulted in ylide generation and subsequent rearrangement, with the more heavily fluorinated catalyst resulting in the greater yield.



18%	$Rh_2(OAc)_4$	41%
12%	$Cu(acac)_2$	61%
0%	$Cu(tfacac)_2$	78%
0%	$Cu(hfacac)_2$	83%

Scheme 33 C-H insertion *vs*. ylide generation and rearrangement.

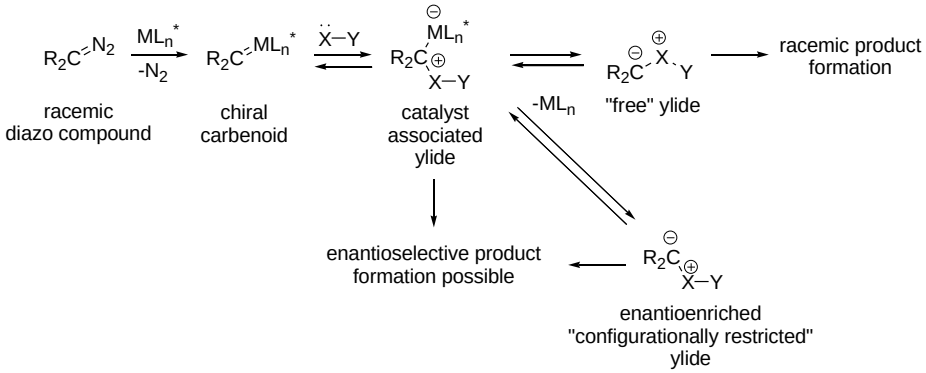
West *et al*. have also reported that the choice of catalyst greatly influences the outcome of the reaction with regard to competing C-H insertion.[123] Treatment of diazoketone **92** (R = Me, n = 0) with $Rh_2(OAc)_4$ afforded the [1,2]-shift product **93** in 65% yield (Scheme 34). Performing the same reaction with $Cu(hfacac)_2$ resulted in **93** with 24% yield and the [1,4]-shift product **94** in 6% yield. Increasing the tether length to n = 1 drastically altered the outcome of the reaction. The $Rh_2(OAc)_4$-mediated reaction afforded [1,2]-shift product **92** in 16% yield, whereas the C-H insertion product, **95**, was afforded as the major product with 47% yield. In comparison, the $Cu(hfacac)_2$-mediated reaction afforded the C-H insertion product **95** in very low yield, whereas the [1,2]-shift product **93** was obtained with 35% yield. However, a significant amount of [1,4]-shift product was also obtained, 24% from this reaction.



R = Me	n = 0	$Rh_2(OAc)_4$	rt	65%		
R = Me	n = 0	$Cu(hfacac)_2$	reflux	24%	6%	
R = H	n = 1	$Rh_2(OAc)_4$	rt	16%		47%
R = H	n = 1	$Cu(hfacac)_2$	reflux	35%	24%	6%

Scheme 34 Ylide generation and subsequent rearrangement *vs*. C-H insertion.

There are two possible scenarios for rearrangement following reaction of a metal carbenoid with an ether. The reaction can proceed *via* a "free" ylide as intermediate, that is, with an ylide that is not associated with the metal catalyst, or it can proceed with the metal-associated ylide equivalent as intermediate. Whether a free ylide would undergo rearrangement to give a non-racemic product in the event that a chiral catalyst was used, has been the issue of some debate. If a chiral catalyst is used for the carbenoid generation, the subsequent ylide formation could result in a chiral catalyst associated ylide (Scheme 35). From this complex, asymmetric rearrangements should be possible. If the ylide dissociates from the metal catalyst, two pathways are possible. Either the ylide racemises, and then racemic product will be formed, or the ylide retains its configurational integrity at the oxonium centre, in which case an asymmetric rearrangement is possible.[124]



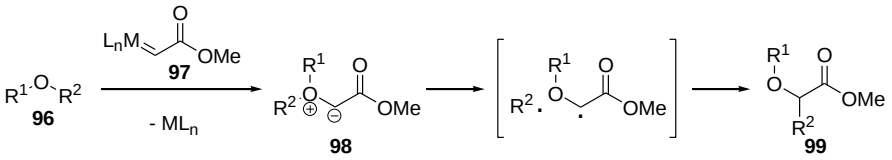
Scheme 35 Different pathways for subsequent ylide reactions.

3.2 Rearrangements and shift reactions

The most common reactions of catalytically generated ylides include [2,3]-sigmatropic rearrangement, [1,2]-shift reaction, X-H insertion and ß-hydride elimination. In the case of ylides generated from carbonyl compounds or imines, dipolar cycloaddition to suitable dipolarophiles is possible. In some cases, [1,4]-shift reactions have been observed. The following chapters discuss the more common reactions of catalytically generated oxonium ylides.

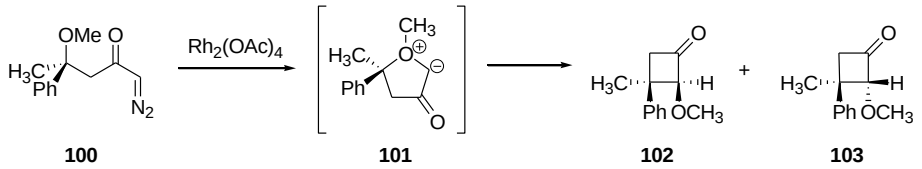
3.2.1 [1,2]-Shift

A concerted [1,2]-rearrangement is forbidden according to the Woodward-Hoffmann rules.[125] There is, however, evidence that oxonium ylides undergo homolytic cleavage resulting in a singlet radical pair, which then quickly recombine within the solvent-cage to produce the formal [1,2]-shift product.[126,127] Thus, [1,2]-shift reactions involve reactions of one of the lone pair electrons of an oxygen atom with the electrophilic carbene **97** to form an oxonium ylide **98**, which can then undergo a [1,2]-shift (Scheme 36).



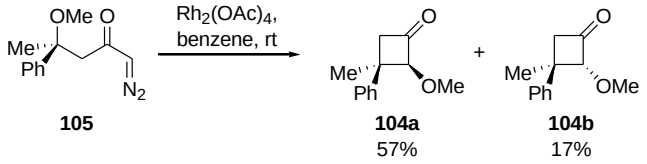
Scheme 36 [1,2]-Shift reaction mechanism.

For cyclic oxonium ylides **101**, the [1,2]-shift technique offers a new method for synthesising substituted carbocycles and cyclic ethers (Scheme 37).[121]



Scheme 37 Synthesis of substituted carbocycles.

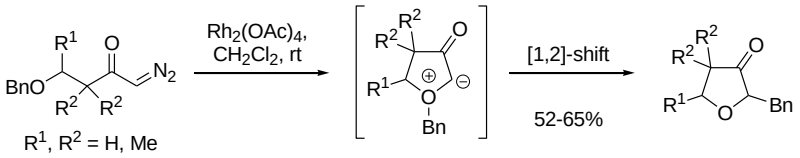
The first people to explore the intramolecular generation of oxonium ylides followed by [1,2]-shift reactions were Johnson and Roskamp, who reported the synthesis of substituted carbocycles in 1986.[121] They showed that, a mixture of cyclobutanones **104** was obtained in a good overall yield upon treatment of diazoketone **105** with $Rh_2(OAc)_4$.



105 **104a** 57% **104b** 17%

Scheme 38 The first example of an intramolecular [1,2]-shift reaction.

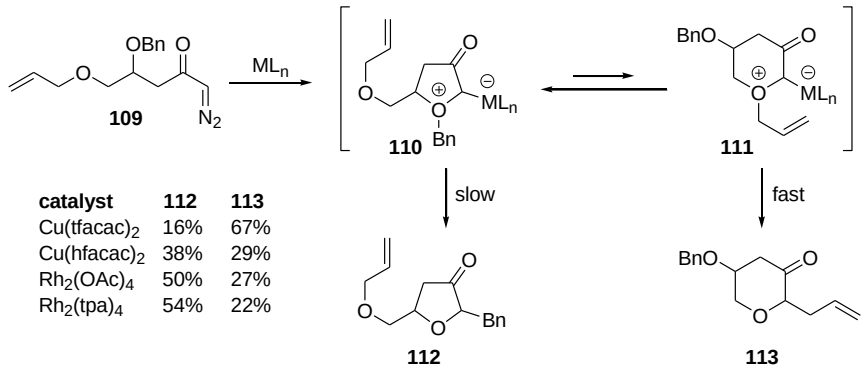
This intramolecular reaction sequence also enabled the synthesis of simple cyclic ethers, as illustrated by West *et al.*, who investigated the conversion of simple diazoketones **106** into functionalised tetrahydrofurans **107** and discovered that oxonium ylides **108** generated from benzylic ethers generally undergo [1,2]-shift with migration of the benzyl group (Scheme 39).[128] The tether of the benzyloxy group was found to be of importance for the selectivity of this reaction, as increasing the tether length tended to result in a lower yield of the ylide-derived product due to increased competitive C-H insertion. Substituents adjacent to the ether oxygen (R^1 in Scheme 39) delivered a diastereomeric mixture of cyclised products.



106 **108** **107**

Scheme 39 Intramolecular [1,2]-shift.

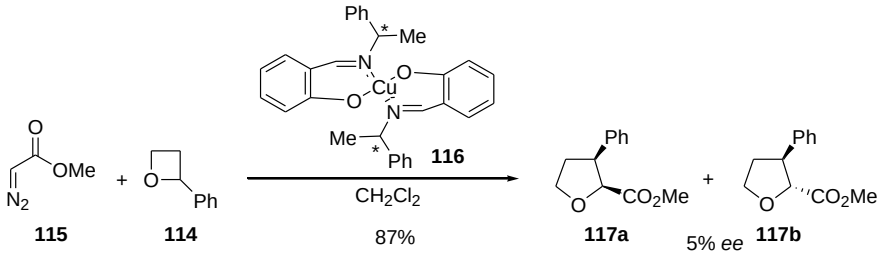
West *et al.* have also studied reactions of diazoketones in which the same carbenoid precursor **109** enables the competitive intramolecular formation of two discrete oxonium ylides, one five-membered (**110**) and one six-membered (**111**) (Scheme 40).[129] It was found that five-membered ylide generation was generally favoured but that certain factors influenced the selectivity and in some cases could override formation of a five-membered oxonium ylide. In principle, equilibration between the two oxonium ylides is possible and so the energy barrier for the subsequent rearrangement can potentially influence the selectivity. Properties of the migrating group for example could influence what subsequent reaction would take place after ylide formation. Additionally, the choice of catalyst was found to play a major influence on the selectivity of the reaction.



catalyst	112	113
$Cu(tfacac)_2$	16%	67%
$Cu(hfacac)_2$	38%	29%
$Rh_2(OAc)_4$	50%	27%
$Rh_2(tpa)_4$	54%	22%

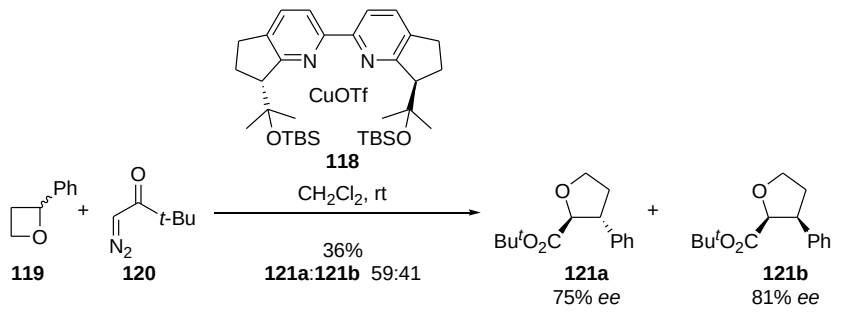
Scheme 40 Selectivity of five- and six-membered oxonium ylide formation.

In 1968, Nozaki *et al*. were the first to demonstrate that the oxonium ylide generation and rearrangement from a metal carbenoid can be rendered asymmetric by using a chiral metal catalyst. This fact was demonstrated by the preparation of non-racemic tetrahydrofurans from racemic oxetanes (Scheme 41).[96] Upon treatment of (±)-2-phenyl-oxetane **114** with the chiral copper carbenoid generated from methyl diazoacetate **115** and the chiral copper complex **116**, an apparent [1,2]-benzylic shift occurred, resulting in formation of a mixture of the diastereomeric tetrahydrofurans **117a** and **117b** in good yields. Although the level of asymmetric induction was very low, this was the first example of an asymmetric [1,2]-shift reaction.



Scheme 41 The first example of asymmetric [1,2]-shift

Katsuki *et al*. later improved enantioselectivity of the process by using the chiral bipyridine copper complex **118**. Upon treatment of racemic 2-phenyloxetane **119** and *t*-butyl diazoacetate **120** under copper-mediated conditions, the tetrahydrofuran diastereomers **121a** and **121b** were obtained with 75% and 81% *ee*, respectively (Scheme 42).[130,131,131a]



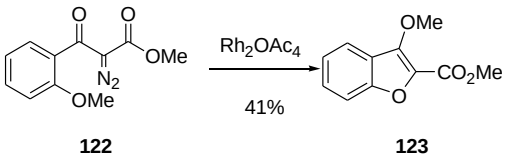
Scheme 42 Asymmetric [1,2]-shift according to Katsuki *et al*.

In addition to the above, Doyle *et al*. have reported highly enantioselective tandem oxonium ylide formation and [1,2]-shift through the use of chiral rhodium catalysts.[132]

3.2.2 [1,4]-Shift

When an ylide is generated from an appropriately functionalised precursor, a [2,3]-rearrangement or a [1,2]-shift reaction usually occurs. However, the formation of [1,4]-shift products from these reactions have been reported. West *et al*. reported the formation of oxonium ylide [1,4]-shift products during their studies using $Cu(hfacac)_2$ as the catalyst.[123] Additionally, Clark *et al*. more recently noticed the formation of similar products during the [2,3]-sigmatropic rearrangement of allylic oxonium ylides, generated using $Cu(acac)_2$ or fluorinated derivatives of the same catalyst.[133]

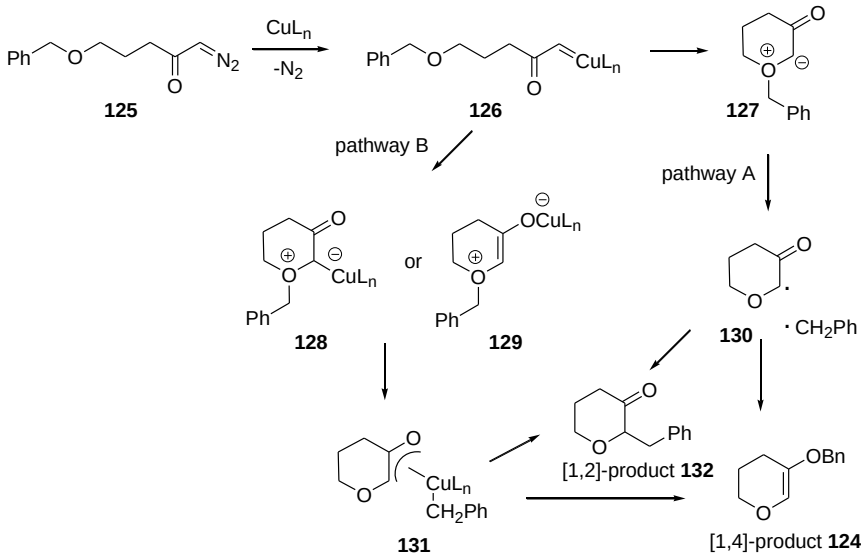
Pirrung *et al*. were the first to notice an example of [1,4]-migration in a rhodium(II)-mediated reaction during an investigation of the selectivity of ylide formation when several *O*-alkoxy groups are present in the diazocarbonyl starting material (Scheme 43).[134]



Scheme 43 The first example of rhodium-mediated [1,4]-migration.

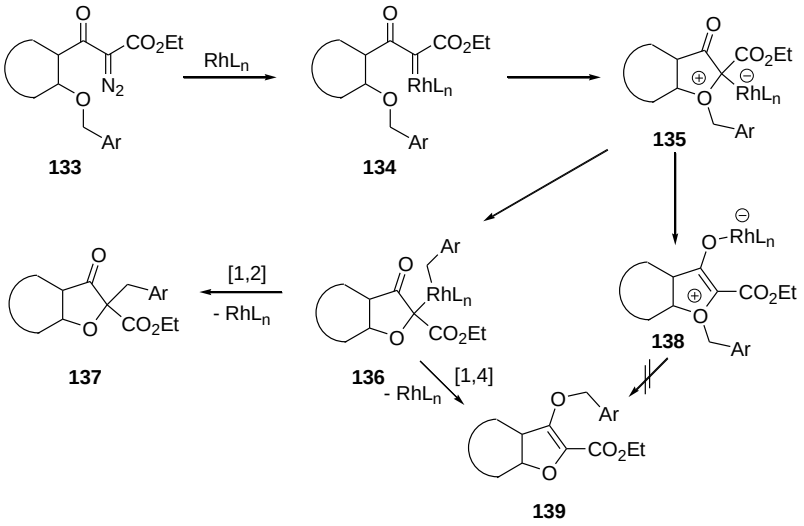
The mechanism by which these products are formed has not been determined, but it is believed to proceed either *via* ylide and radical intermediates, similar to those for the [1,2]-shifts, or possibly *via* a metal-assisted mechanism.

West *et al*. proposed a mechanism for the [1,4]-shift (Scheme 44).[123] First, it was assumed that the [1,4]-shift product **124** was the result of the same ylide and radical pair intermediates that are found in the [1,2]-shift reaction (pathway A), but with recombination at the ketone oxygen instead of the carbon. However, the products of radical dimerisation have not been observed and so it was suggested that an alternative mechanism involving a metal-complex intermediate (pathway B) is the more likely.



Scheme 44 The reaction mechanism according to West *et al.*

Although the [1,4]-shift is not as common a reaction as either a [1,2]- or [2,3]-rearrangement, there have been reports that in certain cases the rhodium(II)-catalysed reactions of α-diazo-β-keto esters proceed with a [1,4]-shift as the dominant pathway.[135,136] With different product ratios obtained for rhodium- and copper catalysed reactions, Dhavale *et al*. suggested an alternative mechanism for the rhodium mediated [1,4]-rearrangement (Scheme 45).[135] While their pathway is similar to that suggested by West *et al.*, they suggested that only one metal-associated oxonium ylide **135** can be considered for the subsequent shift reaction because the distance between metal and migrating group in oxonium ylide **138** is too large.



Scheme 45 The reaction mechanism according to Dhavale *et al*.

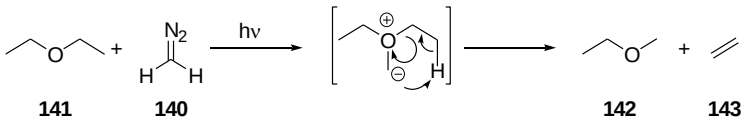
The selectivity regarding [1,2]- and [1,4]-shift reactions was found to be dependent on the nature of the migrating group; electron-poor substituents were found to provide a mixture of products whereas electron-rich substituents were found to deliver only the [1,4]-shift product.

3.2.3 [2,3]-Sigmatropic rearrangement

When the ylide is generated from an allylic ether substrate, the oxonium ylide or ylide-like intermediate may undergo a [2,3]-sigmatropic rearrangement. Chapter 4 discusses the details of this reaction pathway.

3.3 ß-Hydride elimination

On studying the irradiation of diazomethane **140** in diethyl ether **141**, Franzen and Fikentscher observed that not only was the methylene insertion product ethyl propyl ether obtained, but also methyl ethyl ether **142** and ethylene **143**. These observations were explained by intramolecular ß-hydride elimination of the putative free ylide intermediate (Scheme 46).[137,138,139]



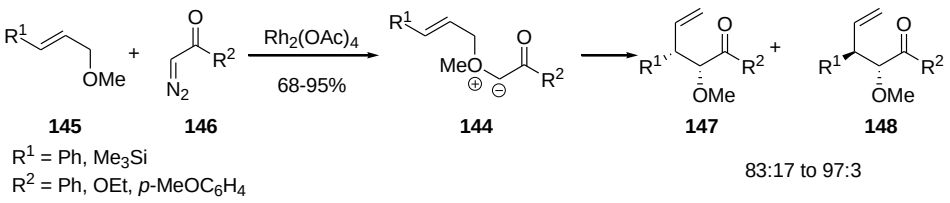
141 **140** **142** **143**

Scheme 46 ß-Hydride elimination of diethyl ether.

Oxonium ylides possessing a ß-hydrogen might undergo ß-hydride elimination, forming an ether and an alkene. It seems likely that this reaction proceeds through intramolecular abstraction of the ß-hydrogen by the negatively charged carbon atom of the ylide followed by loss of alkene and formation of the new ether product.

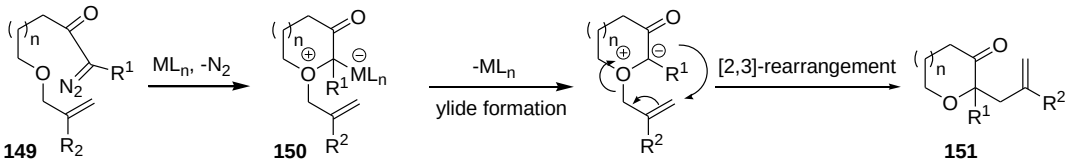
4 [2,3]-Sigmatropic Rearrangement

One of the earliest examples of intermolecular oxonium ylide generation with subsequent [2,3]-rearrangement was reported by Ando *et al*.[116] Upon treatment of dimethyl diazomalonate and an allylic ether with copper sulfate, the [2,3]-rearrangement products was obtained as the major product, although only modest yields were obtained in many cases. Doyle *et al*. later reported that $Rh_2(OAc)_4$ is a more efficient catalyst for the intermolecular generation and rearrangement of allylic oxonium ylides **144** (Scheme 47).[140]



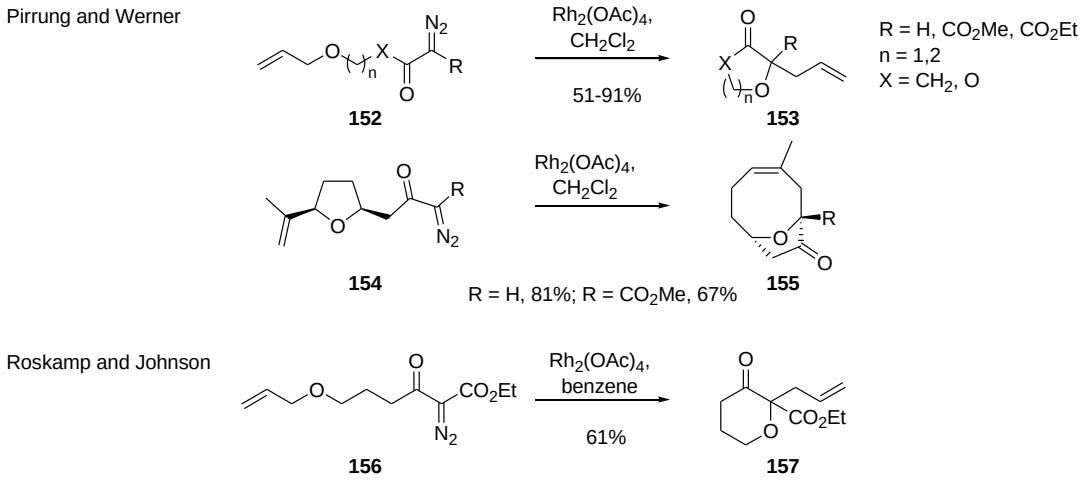
Scheme 47 Intramolecular [2,3]-rearrangement of allylic oxonium ylides.

It is now known that when ylides are generated from allylic ether **149**, the allylic oxonium ylide **150** that is generated readily undergoes a [2,3]-sigmatropic rearrangement reaction (Scheme 48). Unlike the [1,2]-shift reaction, [2,3]-sigmatropic rearrangements are symmetry-allowed according to the Woodward-Hoffmann rules. The [2,3]-sigmatropic rearrangement of ylides generated in both an inter- and an intramolecular fashion can occur. In the case of intramolecularly generated oxonium ylides, heterocyclic compounds bearing a new stereogenic centre are formed. Often highly substituted heterocycles can be obtained, which makes this one of the most versatile bond reorganisation reactions in organic chemistry.



Scheme 48 The mechanism of the [2,3]-sigmatropic rearrangement.

As mentioned previously, in 1986 the first examples of intramolecular [2,3]-rearrangements of oxonium ylides were reported (Scheme 49). Pirrung and Werner reported that upon treatment of diazoketones possessing an allylic ether substituent (**152**,**154**) with $Rh_2(OAc)_4$, five-, six- and eight-membered oxygen-heterocycles (**153**, **155**) could be obtained, through oxonium ylide generation with subsequent [2,3]-rearrangement.[120] Concurrently, Johnson and Roskamp were investigating the same phenomenon.[121] The reaction was shown to be useful for the synthesis of reduced *O*-heterocycles, and highly substituted ones in some cases. Thus, the intramolecular [2,3]-rearrangement of oxonium ylides has become a reaction of great interest to organic chemists.

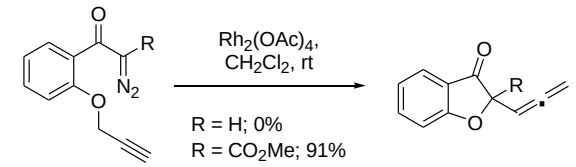


Scheme 49 The first examples of intramolecular [2,3]-rearrangement of oxonium ylides.

Although Doyle *et al*. have explored the intermolecular generation and [2,3]-rearrangement of allylic oxonium ylides from simple allylic ethers,[140] this process is of limited use in organic synthesis when compared to the more widely used intramolecular reaction sequences. One reason for this is that competitive cyclopropanation is usually a major problem, which is generally not the case in

intramolecular reactions. The selectivity between cyclopropanation and ylide generation followed by rearrangement, is highly dependent on factors such as the catalyst, the steric environment around the ether oxygen and the alkene substituents. Another problem with the intramolecular reaction is that it is generally necessary to use a large excess of the allylic ether compared to the diazo compound, in order to minimise dimerisation of the diazo compound, or further reactions of the diazo compound with the product formed initially.

With regards to the substrates for the reaction, not only allylic oxonium ylides undergo [2,3]-rearrangement. In fact, oxonium ylides generated from propargylic ethers are known to undergo apparent [2,3]-rearrangement, even though the oxonium ylide forms the correct transition state geometry with difficulty. Studies undertaken by Pirrung and Werner demonstrated that the success of the reaction depends on the starting substrate. Treatment of the α-diazo-ß-keto ester **158a** (R = CO_2Me) with $Rh_2(OAc)_4$ resulted in the formation of the corresponding allene, **159a** (Scheme 50).[120] Attempts to perform the same reaction with the corresponding α-diazoketone **159b** (R = H) resulted in no reaction.



158a: R = CO_2Me
158b: R = H

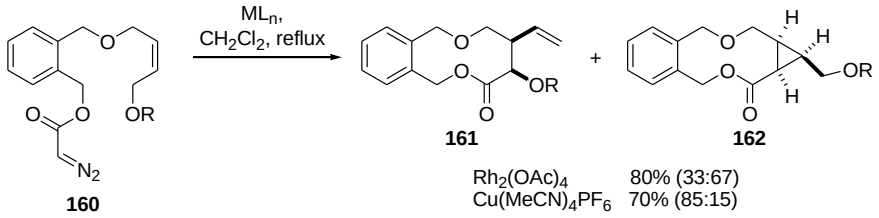
159a: R = CO_2Me
159b: R = H

Scheme 50 [2,3]-Rearrangement of propargylic oxonium ylides.

In addition to the use of the tandem ylide generation with subsequent [2,3]-rearrangement reaction to construct five- and six-membered rings, the reaction has also been employed to synthesise macrocycles with great success.

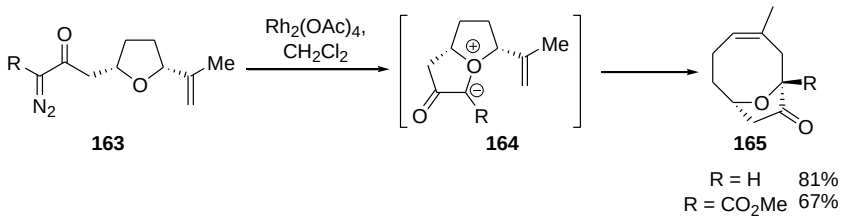
Doyle *et al*. reported that treatment of α-diazo esters, such as **160**, with a transition metal catalyst results in the generation of a 13-membered cyclic oxonium ylide, which upon subsequent [2,3]-rearrangement with a three-atom ring contraction delivers the ten-membered lactone **161** (Scheme 51).[141] Although competitive cyclopropanation was observed, this could to some extent be suppressed through the choice of catalyst. When the reaction was performed with $Rh_2(OAc)_4$, the cyclopropane was obtained as the major product. Carbenoid generation using a copper catalyst, such as $[Cu(MeCN)_4]PF_6$,

resulted in suppression of the cyclopropanation reaction pathway and the [2,3]-rearrangement product was formed as the major product.



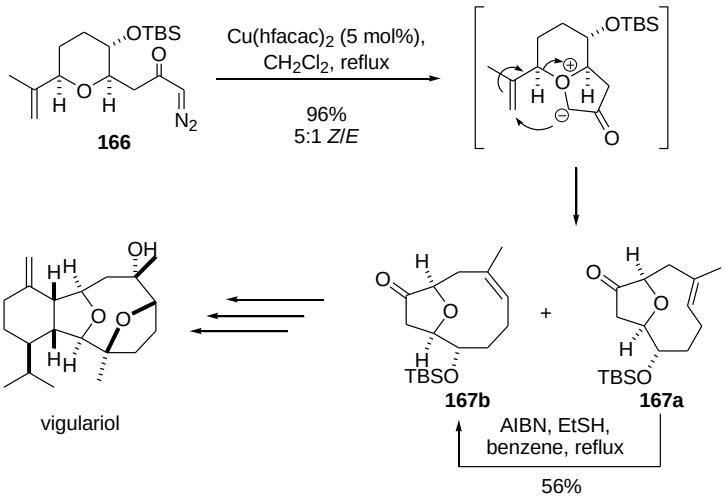
Scheme 51 Ten-membered lactone formation.

An alternative method or the synthesis of macrocycles was explored by Pirrung *et al*. in which a vinyl-substituted tetrahydrofuran precursor **163** was converted into the corresponding rhodium carbenoid which then underwent oxonium ylide formation and subsequent [2,3]-rearrangement (Scheme 52). In this example, the location of the allylic ether within an existing ring resulted in three-carbon ring expansion upon rearrangement to deliver an oxygen-bridged bicyclic compound **165**.[120]



Scheme 52 Ring-expansion of vinyl-substituted tetrahydrofuran.

This tandem sequence has been applied to the total synthesis of several natural products by Clark and co-workers. In 2007, Clark *et al*. reported the total synthesis of (±)-vigulariol, a member of the cladiellin family.[142] Here, oxonium ylide formation of tetrahydropyran **166** followed by [2,3]-rearrangement resulted in a 5:1 mixture of the *E*- and *Z*-isomers **167a** and **167b**. Subsequent steps afforded the natural product (±)-vigulariol.



Scheme 53 Key step of the total synthesis of (±)-vigulariol.

Other members of the cladiellin family were also synthesised by employing this rearrangement reaction as one of the key synthetic steps. Furthermore, it was found that the choice of catalyst was crucial for tuning this reaction towards either *E*- or *Z*-selectivity, with Cu(hfacac)$_2$ giving the *Z*-product predominantly, and rhodium carboxylates showing preference for the *E*-product.[143] This methodology was also employed in further syntheses of other cladiellin natural products.[144,145]

Clark and co-workers are not the only researchers to have utilised the oxonium ylide generation and subsequent [2,3]-rearrangement sequence for the total synthesis of natural products. For example, West *et al*. have developed a new route towards the synthesis of marine ladder toxins (e.g. gambierol, Figure 5) based on ylide generation and subsequent rearrangement.[146,147,148] This route is mediated by copper catalysis, more specifically by Cu(tfacac)$_2$, as this catalyst was found to be more selective towards ylide generation compared with C-H insertion.

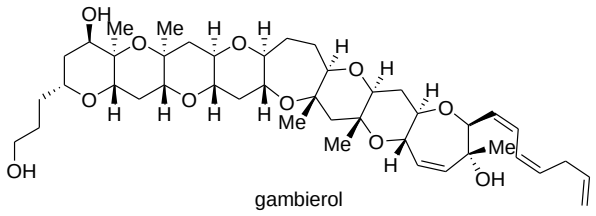
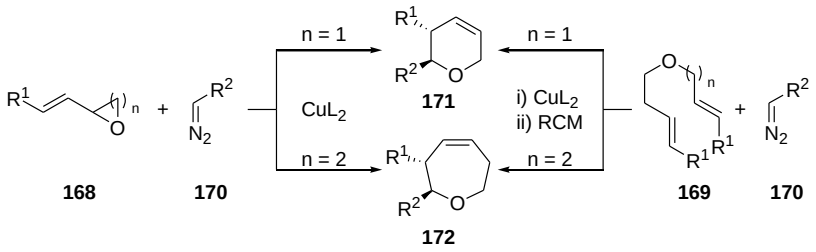


Figure 5 The *trans*-fused polycyclic ether gambierol.

Recently, Njardarson *et al*. reported a copper-catalysed chemoselective intermolecular [2,3]-rearrangement reaction of oxonium ylides generated from cyclic or acyclic allyl ethers.[149] Medium-sized ring systems could be obtained through either intermolecular three-carbon ring expansion of vinyl oxetanes and vinyl tetrahydrofurans (**168**) or through a one-pot synthesis of acyclic allyl ether precursors **169**, involving ylide generation, rearrangement and cyclisation through ring closing metathesis (Scheme 54).



Scheme 54 Synthesis of medium-sized ring systems according to Njardarson *et al*.

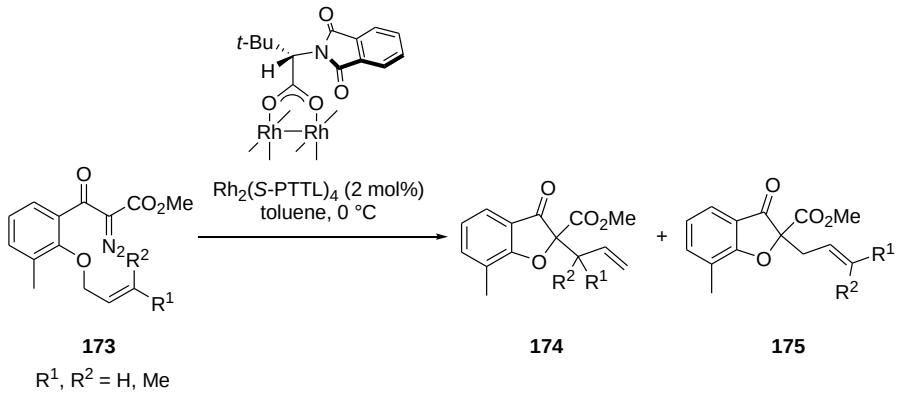
Furthermore, it was found that copper(II) catalysts, such as $Cu(tfacac)_2$ and $Cu(FOD)_2$, resulted in selective oxonium ylide generation, and that competing reactions such as a [1,2]-shift or cyclopropanation could be suppressed by the choice of catalyst. The previously mentioned catalysts $Cu(tfacac)_2$ and $Cu(FOD)_2$ were found to be superior also regarding diastereoselectivity.

4.1 Selectivity *vs*. Competing Reactions

It is not just oxonium ylide generation that suffers from competition by other reactions. Once generated, the highly reactive ylide can undergo several, often competing, reactions. Consequently, reaction selectivity after oxonium ylide generation also requires consideration. This issue has been under investigation by many groups.

Hashimoto *et al*. demonstrated that methyl substitution at the allylic group at either the *cis*- or the *trans*-position (or both) strongly influences the ratio of the [2,3]-sigmatropic rearrangement product and the apparent [1,2]-shift product.[150] Hashimoto *et al*. investigated the enantioselective [2,3]-sigmatropic rearrangement and [1,2]-Stevens shift using chiral rhodium catalysts (Scheme 55). It was found that if

diazoketone **173** was substituted with a methyl group in the *trans*-position (R^1), the ratio of the [2,3]-sigmatropic rearrangement product **174** and the [1,2]-Stevens shift product **175** was 92:8. A substitution with a methyl group in the *cis*-position (R^2) resulted in the ratio 82:18. If **173** was methyl-substituted at both the *trans*- and the *cis*-position, the reaction resulted in a 71:29 ratio of products. This suggests that substituents at the allyl group of an allylic oxonium ylide influence the type of reaction that takes place. Furthermore, it suggests that investigations of the mechanism of the rearrangement of allylic oxonium ylides by adding substituents will affect the rearrangement taking place.



173 **174** **175**

R^1, R^2 = H, Me

Scheme 55 Investigation of the rearrangement of an allylic oxonium ylide.

Hashimoto *et al*. also suggested that both the [2,3]-rearrangement reaction and the [1,2]-shift proceed through a common chiral rhodium(II)-associated oxonium ylide intermediate (Figure 6). The basis for this being that similar levels of asymmetric induction being observed in each product, as well as the retention of *cis*- and *trans*-configuration during the [1,2]-shift.

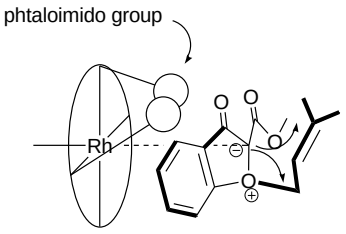
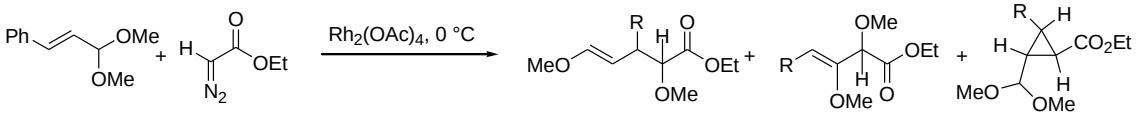


Figure 6 Common [2,3]- and [1,2]-shift intermediate according to Hashimoto *et al*.

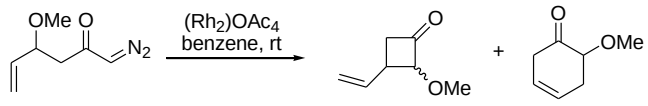
Other research groups have also reported the presence of both the [2,3]- and [1,2]-shift products. For example, Doyle *et al*. attempted to make ylide generation and rearrangement more favourable compared to cyclopropanation when a diazo compound was reacted with a more heavily substituted allylic substrate. They reported that under certain conditions, a reaction of an acetal with a diazoketones delivered the [1,2]-shift product. An example is shown in Scheme 56, where reaction of the ethylene acetal of cinnamaldehyde **176** with ethyl diazoacetate **177** results in product **178** by [2,3]-rearrangement, product **179** by a [1,2]-shift and product **180** by cyclopropanation. Doyle *et al*. suggest that two different reaction mechanisms take place, both a concerted [2,3]-sigmatropic rearrangement, leading to the enol **179**, and cleavage of the ylide followed by recombination giving both products **178** and **179**.[151]



176 **177** **178** 45% **179** 11% **180** 6%

Scheme 56 The reaction of the ethylene acetal of cinnamaldehyde with ethyl diazoacetate according to Doyle *et al*.

Roskamp and Johnson postulated that [2,3]-rearrangement of an allylic oxonium ylide generated from diazoketone **181** accounts for formation of the minor product **182**, whereas the cyclobutanone **183** was produced as the major product by a [1,2]-shift reaction (Scheme 57).[121]



181 **183** (45%) **182** (10%)

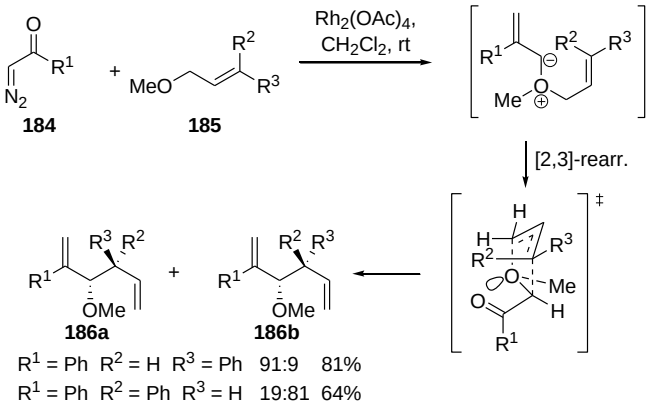
Scheme 57 Competing [2,3]- and [1,2]-shift reaction of **181**.

In contrast to the results described above, when the oxonium ylide was generated from a diazoketone containing an allyloxy group or a prop-2-ynyl ether group, only [2,3]-rearrangement was observed.[121] West *et al*. have investigated the mechanism by which allylic oxonium ylides undergo rearrangement, again with substituents adorning the allyl group in order to investigate which process takes place.[152]

Zercher *et al*. in turn have studied the synthesis of bicyclic structures through ylide generation and rearrangement. These workers demonstrated that intramolecular ylide formation fusing a ketal and rearrangement of the resulting bicyclic ylide is a facile process. They also found that larger ring precursors reacted to give more flexible ylides which then underwent [1,2]-shift more easily than smaller ring systems. The presence of radical-stabilizing groups directly attached to the ketal oxygens also promoted [1,2]-shifts.[153,154]

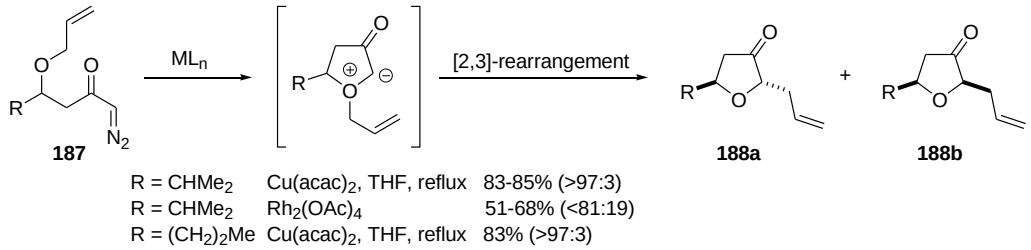
4.2 Diastereoselectivity

When substituted diazo compounds are used as precursors, an issue of diastereoselectivity arises. This issue was studied by Doyle *et al*. in the case of rhodium-catalysed intermolecular [2,3]-rearrangement reactions, and it was found that the alkene geometry generally controls the diastereoselectivity of the reaction (Scheme 58). Doyle *et al*. proposed that the oxonium ylide rearranges through an "envelope" transition state in which steric interactions between substituents are minimised.[140]



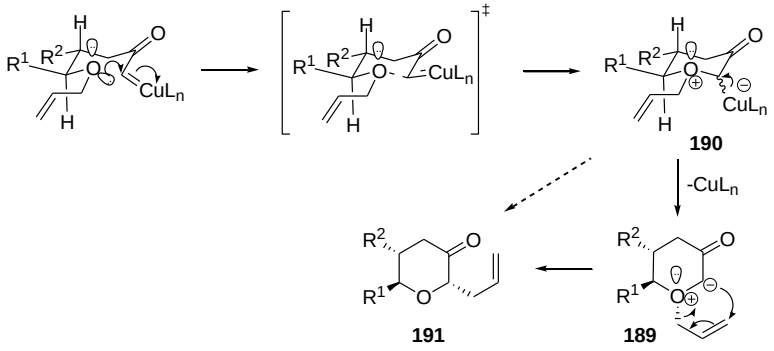
Scheme 58 Diastereoselective investigation by Doyle *et al*.

Clark *et al*. investigated the intramolecular generation and [2,3]-rearrangement of oxonium ylides with regard to the diastereoselective synthesis of 2,5-dialkyl tetrahydrofuran-3-ones. Through the copper- and rhodium mediated ylide generation and subsequent rearrangement from an α-diazoketone precursor **187**, a mixture of diastereoisomeric furanones **188a** and **188b** was afforded (Scheme 59). *Trans*-isomer **188a** was the major product, although in the rhodium-mediated reaction large amounts of the *cis*-isomer **188b** was also obtained. In general, $Cu(acac)_2$ afforded good yields and excellent levels of diastereocontrol.[155]



Scheme 59 Diastereoselective investigation.

The reaction mechanism is believed to involve a configurationally restricted ylide (Scheme 60). There are two possible pathways. In one, a free oxonium ylide **189** undergoes [2,3]-rearrangement in a classical fashion and in the other the metal-bound ylide equivalent **190** undergoes direct rearrangement. In the latter case, the allyl group is transferred from the oxygen to copper in the intermediate, followed by reductive elimination to afford C-C bond formation, resulting in **191**.[133] In the case of the free ylide, the lone pair electrons are diastereotopic, with one pair of the electrons favoured, this will control the stereochemical outcome of the reaction.

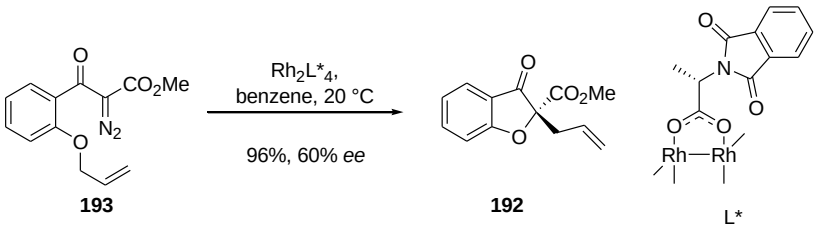


Scheme 60 A mechanistic explanation of diastereoselectivity.

4.3 Asymmetric Rearrangement

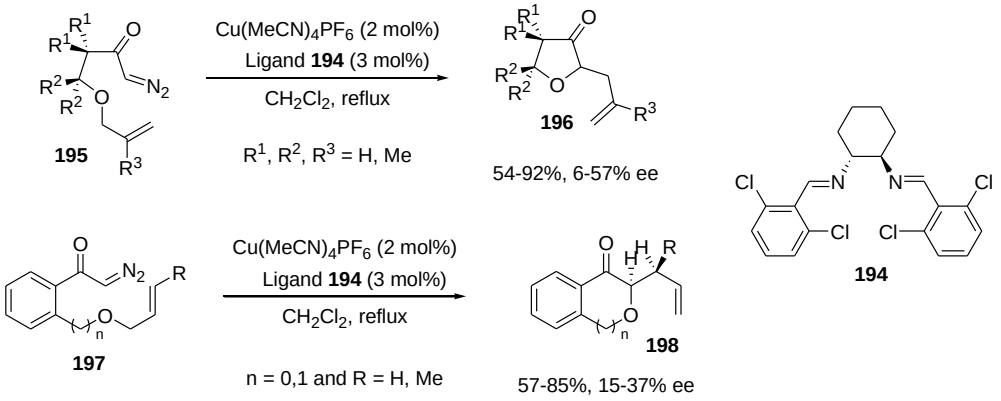
4.3.1 Chiral catalysis

In 1992, McKervey *et al*. were the first to report an asymmetric version of the carbenoid-mediated ylide generation and [2,3]-rearrangement sequence. When a chiral binol-phosphate dirhodium(II) complex was employed as catalyst, products with up to 30% *ee* were obtained.[156] Further improvement of enantioselectivity was obtained when a chiral rhodium carboxylate complex was used;[157] the benzofuranone **192** was obtained with 60% *ee* and in excellent yield.



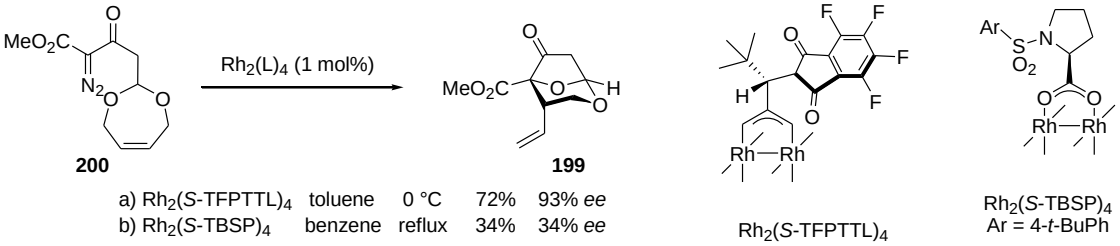
Scheme 61 Asymmetric [2,3]-rearrangement of oxonium ylide.

Following this initial study, Clark *et al*. investigated an intramolecular asymmetric tandem oxonium ylide generation and subsequent [2,3]-rearrangement sequence, catalysed by chiral copper(I) diimine complexes (Scheme 62). Various diazoketones, both aliphatic and aromatic, were employed. Catalyst complexes generated with C_2-symmetric ligand **194** were found to provide the highest levels of asymmetric induction, with the highest enantioselectivities obtained using aliphatic substrates.



Scheme 62 Asymmetric [2,3]-rearrangement of oxonium ylides, as described by Clark *et al*.

Hashimoto *et al*. have recently reported the use of chiral dirhodium(II) carboxylates, in particular Rh_2(*S*-TFPTTL)$_4$, to construct the 2,8-dioxabicyclo[3.2.1]octane ring system of zaragozic acid C **199** in an enantioselective fashion through [2,3]-sigmatropic rearrangement of an oxonium ylide (Scheme 63a).[158]

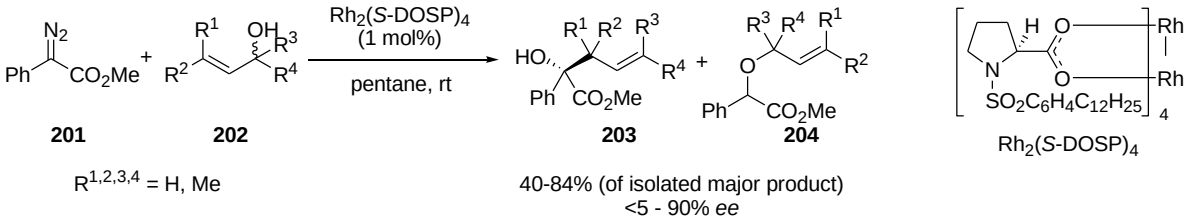


Scheme 63 Enantioselective synthesis of the ring system of zaragozic acid C.

This reaction sequence had previously been reported by Calter and Sugathapala, but only modest enantioselectivity was obtained in that case when Rh_2(*S*-TBSP)$_4$ was employed as catalyst (Scheme 63b).[159] Hashimoto *et al*. demonstrated that the product could be obtained in appreciable yield and with excellent enantioselectivity (93% *ee*) when Rh_2(*S*-TFPTTL)$_4$ was employed as the catalyst. This is the highest reported enantioselectivity for the [2,3]-sigmatropic rearrangement of a cyclic oxonium ylide that has been reported to date. It is important to point out that only this particular substrate appears to undergo ylide formation and rearrangement with such an excellent level of enantioselectivity.

Davies *et al*. have also investigated asymmetric oxonium ylide rearrangements and in particular, intermolecular enantioselective oxonium ylide formation and rearrangement

of racemic alcohols with diazoacetates (Scheme 64). Davies *et al*. make use of chiral rhodium catalysts, with the highest enantioselectivity obtained when the complex Rh_2(*S*-DOSP)$_4$ is employed as the catalyst. However, it was found that while highly substituted allyl alcohols generally favour formation of the [2,3]-rearrangement product **203**, reactions with less substituted allylic alcohols generally favoured formation of the O-H insertion product **204**.[160] It should be noted that enantioselectivity of <5% *ee* was achieved when the O-H insertion product was obtained as the major product (Scheme 64). In cases where [2,3]-rearrangement was the favoured reaction pathway, greatly improved enantioselectivity (65-90% *ee*) was obtained.

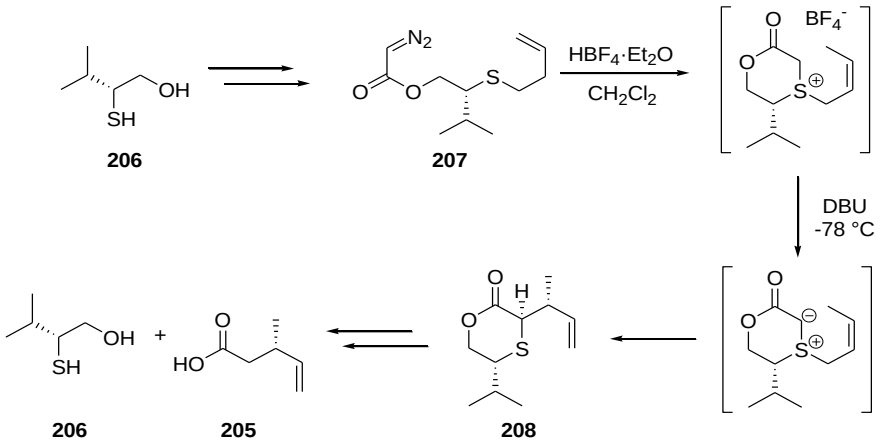


Scheme 64 Asymmetric diazoketone transformations, as described by Davies *et al*.

The development of reactions involving asymmetric formation and [2,3]-sigmatropic rearrangement of oxonium ylides promoted by chiral transition metal catalysis, has proven to be very challenging.[59,124] Many chiral complexes are available but, to the best of my knowledge, a general chiral catalyst that affords good yields and high enantioselectivities for a variety of substrates has yet to be developed. Nevertheless, these recent developments prove that asymmetric catalytic formation and [2,3]-rearrangement of oxonium ylides is a viable method for the synthesis of enantio-enriched reduced *O*-heterocycles.

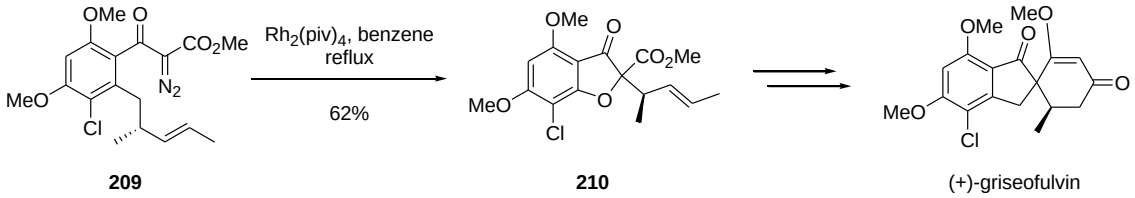
4.3.2 Alternative methods

An alternative general approach to the development of asymmetric [2,3]-rearrangement reactions involves the use of chiral auxiliaries. Kurth *et al*. have reported a thioxanone-based method for synthesising **205** with good selectivity (Scheme 65).[161] However, this method generally requires more steps than that involving the use of a chiral catalyst, because the auxiliary **206** needs to be introduced into the substrate and removed from the product.



Scheme 65 The use of a chiral auxiliary for asymmetric [2,3]-sigmatropic rearrangement.

In the course of their total synthesis of the natural product (+)-griseofulvin, Pirrung *et al*. employed the [2,3]-rearrangement reaction of a methylated allyl oxonium ylide generated from diazoketone **209** as one of the key steps.[134] Here, the benzofuranone **210** was obtained as the sole product; no other stereoisomers or regioisomers were detected (Scheme 66).

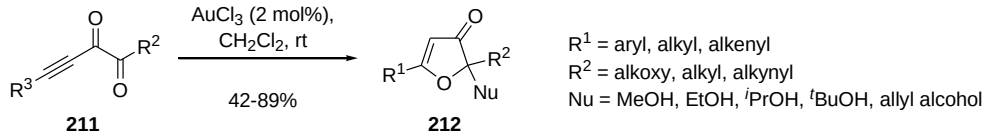


Scheme 66 The key step of the total synthesis of (+)-griseofulvin.

However, although a good result was obtained in this particular case, the entire methodology depends on the presence of an additional chiral centre. Not only might this cause difficulty when preparing the precursor, it is also possible that an additional substituent in the product is in fact not desirable. Ideally, an efficient chiral catalyst would be the one that provides the desired furanone compound from a simple racemic starting material with good control of the enantioselectivity and in a single step.

5 Alternative Methods for Furanone Synthesis

Transition metal catalysis has been employed in the synthesis of furanones through different types of reactions, not only through rearrangement reactions of oxonium ylides generated from transition metal carbenoids. In 2006, Liu *et al*. reported that 2-oxo-3-butynoic esters or disubstituted 1,2-diones (**211**) could undergo gold-catalysed cyclisation with various nucleophiles, forming substituted furanones (**212**) (Scheme 67).[162] Unfortunately the reaction proceeded without enantiocontrol, which resulted in the formation of racemic products. Furthermore, the choice of nucleophile was limited to various alcohols.



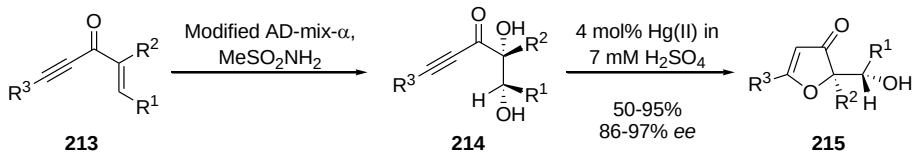
211 **212**

Scheme 67 Gold-catalysed furanone synthesis.

A similar catalytic protocol, employing NIS in addition to gold(III) chloride, could be used to synthesise 4-iodo furanones.[163] Other transition metals have also proved useful in furanone synthesis, such as palladium[164] and platinum.[165]

In addition to transition metal catalysed cyclisations, other methods of furanone synthesis includes an intramolecular Wadsworth-Emmons condensation variation of γ-(acyloxy)-ß-ketophosphonates,[166] conversions of furans to furanones,[167,168] acid-induced cyclisation-dehydration of substituted α'-hydroxy-1,3-diketones,[169,170,171] hydrogenolysis with subsequent acidic hydrolysis of isoxazoles[172] and cyclisations of dianion equivalents with α-chloroacetic acid chlorides.[173,174]

It has also been demonstrated that upon cyclisation of asymmetric starting materials, asymmetric furanones can be obtained. Marson *et al*. reported that asymmetric furanones can be synthesised from prochiral enynones (**213**) in two steps (Scheme 68).[175]



Scheme 68 Asymmetric furanone synthesis in two steps.

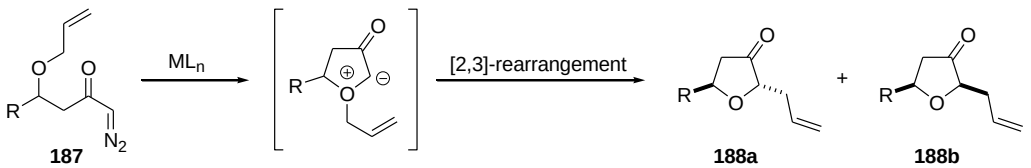
First, Sharpless asymmetric dihydroxylation of the enynone **213** using a modified AD-mix-α, containing 5 mol% $(DHQ)_2PHAL$ and 1 mol% potassium osmate, resulted in an asymmetric diol (**214**). The resulting diol was cyclised using mercury(II) in sulfuric acid, forming the asymmetric furanones **215** with yields of 50-95% and 86-97% *ee*. At present, the range of enynones that have undergone this transformation is rather limited.

6 Research Project Outline

6.1 Previous work within the Clark group

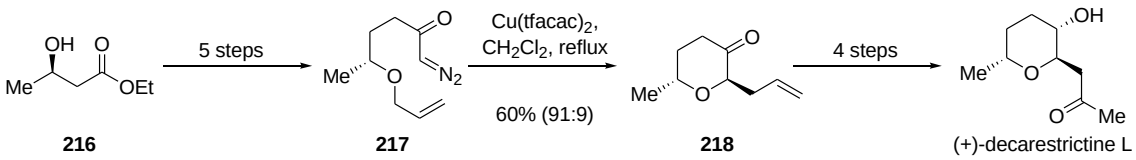
Diazo chemistry and ylide rearrangement reactions are important research themes in the Clark group. These reactions are being studied mainly with the aim of applying them in natural product synthesis.

Commencing with the study of the synthesis of cyclic ethers such as 2,5-dialkyl tetrahydropyran-3-ones, factors influencing the diastereoselectivity of the reaction were studied.[155] It was found that good diasterecontrol could be obtained, but also that the metal catalyst greatly influences the selectivity (Scheme 69). For reactions mediated by rhodium catalysts such as $Rh_2(OAc)_4$, modest yields and low diastereoselectivities were obtained and mixtures of the *trans*- and *cis*-isomers were produced. In contrast, copper-mediated ylide formation and rearrangement reactions provided high levels of diastereoselectivity. Although simple copper salts such as $Cu(OTf)_2$ can be employed as catalysts, it was found that both yields and the level of diastereoselectivity were increased when $Cu(acac)_2$ was employed as the catalyst. In addition, fluorinated derivatives, and $Cu(tfacac)_2$ in particular, were found to deliver good diastereoselectivities. Further investigations were undertaken to develop a better understanding of the factors influencing the diastereoselectivity.[133]



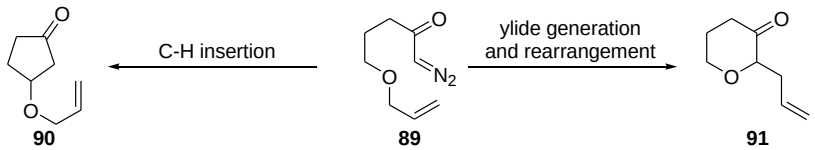
Scheme 69 Diastereoselective investigation.

The first example of the application of this reaction to the stereoselective synthesis of a 2,6-dialkyl tetrahydropyran-3-one as a step in a total synthesis was reported in 1994, with the total synthesis of (±)-decarestrictine L.[176] In 2006, the enantioselective synthesis of (+)-decarestrictine L was reported, in a ten-step procedure starting with commercially available ethyl (*R*)-3-hydroxybutyrate **216** (Scheme 70).[177] This methodology was further employed for the key step in the stereocontrolled synthesis of the A-ring fragment of gambieric acid A. In this case, two of the four stereocentres found in the natural products were introduced during the copper-mediated cyclisation reaction.[178] In addition, a fragment of the natural products amphidinolides T1-T5 have been synthesised diastereoselectively, using this methodology.[179]



Scheme 70 Synthesis of (+)-decarestrictine L.

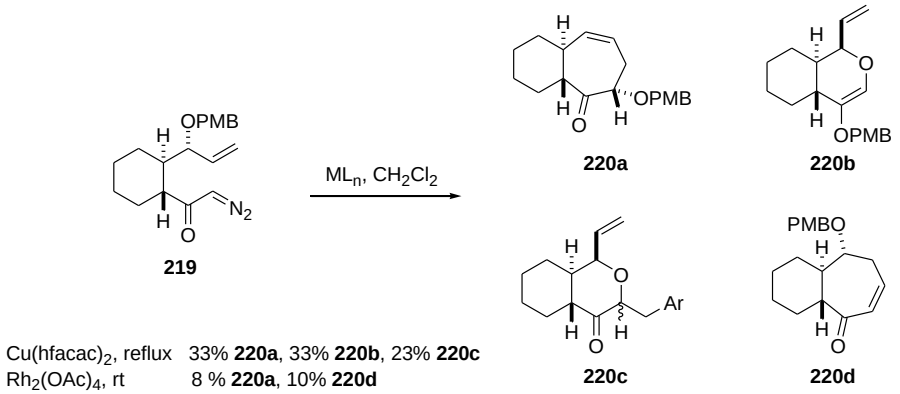
The nature of the catalyst was found to significantly influence the selectivity for ylide generation and subsequent rearrangement over C-H insertion (Scheme 71). Again, rhodium-based catalysts showed a greater affinity for C-H insertion reactions than copper-based catalysts. The selectivity towards ylide generation could further be improved by modifying the copper catalyst. It was found that while $Cu(acac)_2$ was more selective towards ylide generation than C-H insertion, the fluorinated derivatives, $Cu(tfacac)_2$, and particularly $Cu(hfacac)_2$, showed greater selectivity towards ylide generation.[180]



18%	$Rh_2(OAc)_4$	41%
12%	$Cu(acac)_2$	61%
0%	$Cu(tfacac)_2$	78%
0%	$Cu(hfacac)_2$	83%

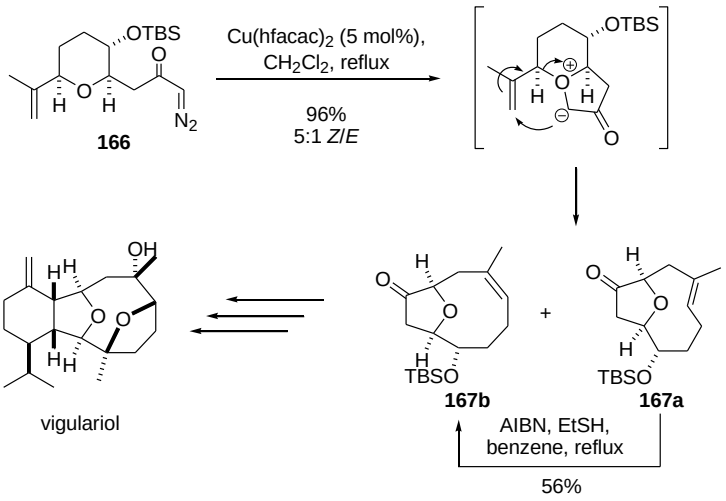
Scheme 71 Ylide generation and rearrangement *vs*. C-H insertion.

The selectivity for oxonium ylide generation and rearrangement has been investigated further. Upon synthesis of fused bicyclic systems **220a** containing a seven-membered ring through ylide generation and [2,3]-rearrangement, it was found that undesired [1,2]- and [1,4]-shift reactions could be suppressed if the optimal catalyst was employed. In general, copper- and rhodium-mediated reactions showed opposite preferences for the reaction pathway (Scheme 72).[181] Fused ring systems containing an eight-membered ring have successfully been synthesised; in addition to the [2,3]-ylide rearrangement products, [1,2]-shift products were also observed. Here again, the choice of catalyst is of the highest importance regarding the selectivity and success of this reaction.[182]



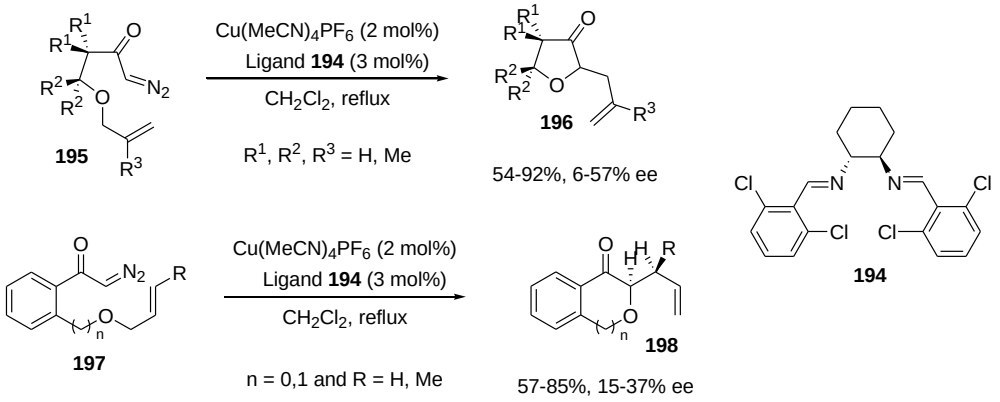
Scheme 72 Synthesis of fused bicyclic systems.

With regard to the synthesis of natural targets, members of the cladiellin family have been synthesised using tandem oxonium ylide generation and [2,3]-rearrangement as the key step (Scheme 73).[142,143] In this case, ring opening of an allylic tetrahydrofuran **166** during the rearrangement process led to the synthesis of the bridge ether core **167** found in the cladiellins in good yield and with high selectivity. Addionally, the syntheses of the tricyclic core of labiatin A and australin A employed the same tandem reaction sequence.[145] Oxonium ylide generation with subsequent [2,3]-rearrangement is also being employed for the synthesis of the natural product neoliacinic acid.[144,183,184]



Scheme 73 Key step of the total synthesis of (±)-vigulariol.

As mentioned previously, the Clark group has also investigated intramolecular asymmetric tandem oxonium ylide generation and [2,3]-rearrangement, catalysed by chiral copper(I) diimine complexes (Scheme 74).[185] Catalyst complexes generated with C_2-symmetric ligand **194** were found to provide the highest levels of asymmetric induction, with the highest enantioselectivity obtained for the aliphatic substrates.



Scheme 74 Initial study of the asymmetric [2,3]-rearrangement of oxonium ylides.

As shown, the Clark group has demonstrated the versatility of oxonium ylide generation from transition metal carbenoids and subsequent rearrangement over the past 20 years. This reaction sequence has been considered from a chemo-, diastereo- and an enantioselective point of view, for the synthesis of both oxygen-containing heterocycles

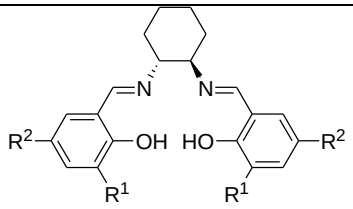
and medium ring carbocycles. During this time, this reaction sequence has also been employed towards the synthesis of several natural products, with excellent results.

6.2 Asymmetric [2,3]-Sigmatropic rearrangement of oxonium ylides — the Clark approach

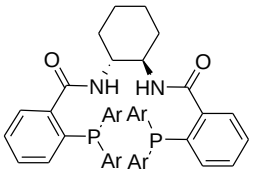
Although the intramolecular [2,3]-sigmatropic rearrangement of oxonium ylides is a well known reaction for generating substituted *O*-heterocycles, there is no general and efficient asymmetric variant of this process. While chiral catalysis has been shown to provide asymmetric induction during this reaction, in some specific situations with good enantioselectivity, to the best of our knowledge no general catalyst has been designed to date. Consequently, the aim of the project was the design of suitable catalyst systems and the creation of a robust and efficient asymmetric process. As copper-catalysed reactions had been shown to be more selective towards ylide generation and subsequent [2,3]-rearrangement compared with C-H insertion, the main focus of the project was, at the outset, the use of copper catalysis. As described above, preliminary studies of chiral copper catalysis had already been performed within our group. For the asymmetric rearrangement of oxonium ylides, chiral copper complexes can be generated *in situ* from $[Cu(MeCN)_4]PF_6$ and various chiral ligands. Initially, the chiral ligands selected for screening included classes such as salen,[186,185] Trost,[187] SEGPHOS,[188,189] DUPHOS,[190] bisoxazoline,[191,192,36] MonoPhos,[193] QuinoxP,[194] pyridine bisoxazoline[195] and phosphinooxazoline[196] (Chart 1). These ligands are representative of different types of chiral ligands that have previously been used in asymmetric copper-catalysed reactions, often with very good results. Many of these are also commercially available, or easily synthesised.

However, while the focus of the project was to be on the use of chiral copper catalysts, catalysts based on different transition metals were also to be considered.

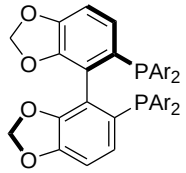
Chart 1 Chiral ligands for initial screening.



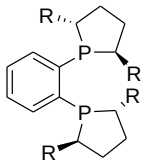
Salen-type



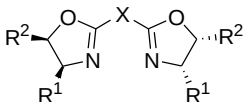
Trost-type



SEGPHOS-type



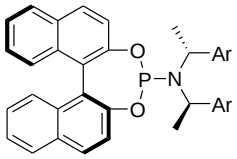
DUPHOS-type



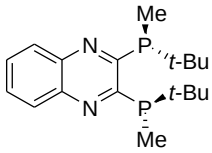
Bisoxazoline-type

($R = CH_2$, CMe_2)

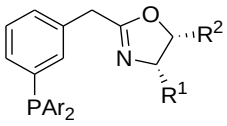
Pyridine bisoxazoline-type
(R = 2,6-pyridyl)



MonoPhos-type



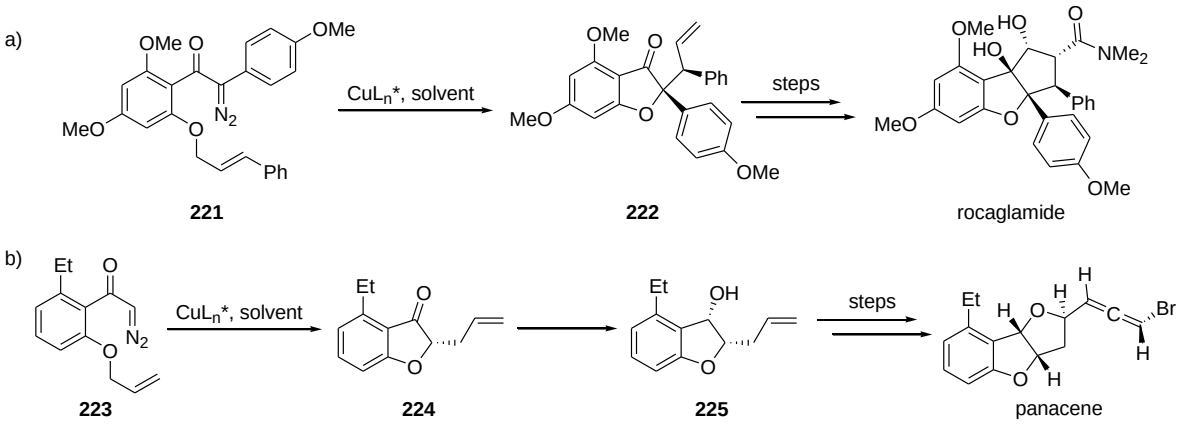
QuinoxP



Phosphinooxazoline-type

There was an interest in employing the rearrangement of oxonium ylides generated from chiral copper carbenoids in the synthesis of benzofuran natural systems. Therefore, a chiral catalyst for enantioselective ylide generation and subsequent [2,3]-sigmatropic rearrangement was initially to be developed for aromatic diazoketones, with the aspiration to later adapt the asymmetric conditions for aliphatic diazoketones.

Two examples of natural products of interest are shown in Scheme 75. In Scheme 75a, the enantioselective ylide generation and rearrangement of diazoketone **221** would give benzofuranone **222**, which upon further steps can be converted the natural product rocaglamide.[197] The natural product panacene is shown in Scheme 75b.[198] Here, in a similar fashion, enantioselective ylide generation and rearrangement of diazoketone **223** would give benzofuranone **224**, which can be stereoselectively reduced to give alcohol **225**. Further steps would deliver panacene.



Scheme 75 Enantioselective key steps in the total synthesis of rocaglamide and panacene.

The detailed reaction mechanism is still open to debate. While the mechanism is generally written as a free allylic oxonium ylide undergoing [2,3]-sigmatropic rearrangement, is this truly the case? The issue of whether the rearrangement reaction proceeds *via* a free ylide or the metal-associated equivalent has been the subject of debate in the past.[59,124] That chiral catalysis can provide some asymmetric induction has been considered to support the theory that the rearrangement proceeds *via* the metal-associated ylide intermediate. However, a comprehensive study regarding the reaction pathway(s) has yet to be undertaken, and so it is not possible to make firm conclusions at this time. Indeed, while the details of the reaction mechanism are unknown, the design of an enantioselective rearrangement methodology is very difficult and relies on trial and error. Therefore, we proposed to investigate the mechanism of the apparent ylide formation and rearrangement sequence. By employing isotopically labelled substrates, we believed that the structures of the rearrangement products would provide insights into the reaction mechanism, thus facilitating the work towards the development of an enantioselective reaction.

The following section comprises a discussion of the research carried out during the Ph.D. programme, along with strategy plans and detailed discussion of the results and data obtained. Following this, there is a brief summary of the work carried out and an outline of some proposed future work that further advance the research programme.

Results and Discussion

The aim of this project at the outset was the enantioselective synthesis of furanones and benzofuranones through asymmetric rearrangement of oxonium ylides, generated from copper carbenoids. During the course of the project, however, different aspects of this particular reaction also came into consideration. The following chapters outline and discuss the various results obtained during this project.

Chapter 7 — Towards the Asymmetric Synthesis of *O*-Heterocycles — concerns the original project. All aspects of this project are discussed herein. These involve areas such as the preparation of various diazoketone substrates and the development and optimisation of the oxonium ylide rearrangement reaction to deliver racemic products. Additionally, this chapter includes details concerning the preparation of chiral ligands and complexes thereof and their use for this transformation to provide furanone and benzofuranone products in an enantioenriched form.

Chapter 8 — Iridium-Catalysed Rearrangement — presents the results of studies to establish the feasibility of utilising a different metal, iridium, to generate iridium carbenoids. To my knowledge, iridium carbenoids had not previously been utilised for oxonium ylide generation and subsequent rearrangement, and it was anticipated that the use of this alternative metal would open up new possibilities in terms of catalyst design.

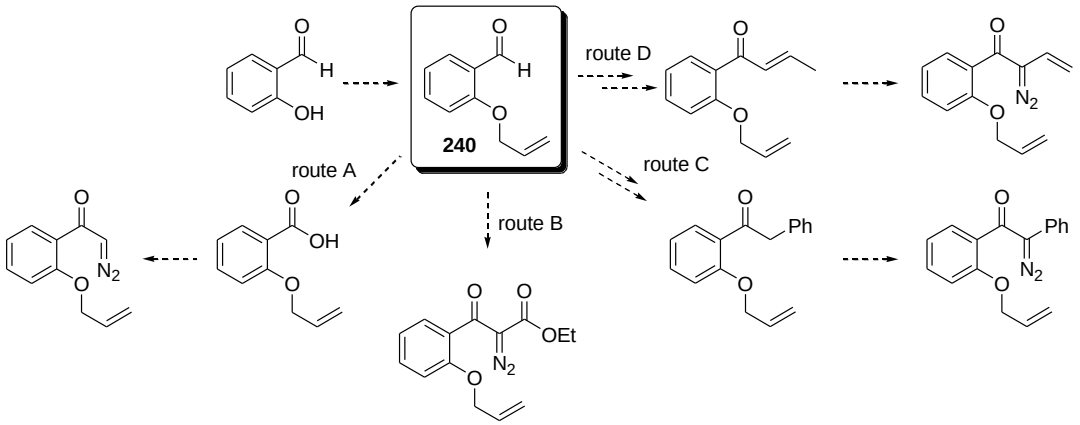
Chapter 9 — Mechanistic Study — describes our investigations into the detailed reaction mechanism. The fact that the mechanism of a reaction is not fully understood vastly complicates the process of designing a chiral catalyst for the particular transformation. Herein is discussed the synthesis of isotopically labelled substrates, possessing either ^{2}H- or ^{13}C-labels, as well as mechanistic studies in which the reactions of these isotopically labelled starting materials were investigated.

7 Towards the Asymmetric Synthesis of *O*-Heterocycles

7.1 Synthesis of diazoketones

7.1.1 Synthesis of aromatic diazoketones

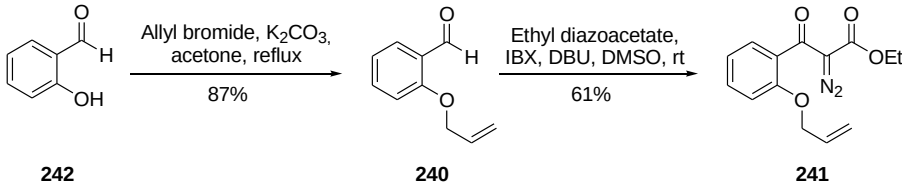
It was believed that a common intermediate, 2-allyloxybenzaldehyde **240**, could be used as precursor for the synthesis of a variety of aromatic diazoketones of interest as substrates in just a few steps (Scheme 76). For example, oxidation to the corresponding carboxylic acid followed by acylation of diazomethane would result in a terminal diazoketone (route A), whereas an aldol-type reaction with ethyl diazoacetate followed by oxidation would produce an α-diazo ß-keto ester (route B). The formation of various carbonyl compounds followed by diazo transfer could result in the formation of *e.g.* phenyl-substituted diazoketones (route C) or vinyl-substituted diazoketones (route D).



Scheme 76 Planned routes for the synthesis of various aromatic diazoketones.

7.1.1.1 Synthesis of α-diazo ß-keto ester **241**

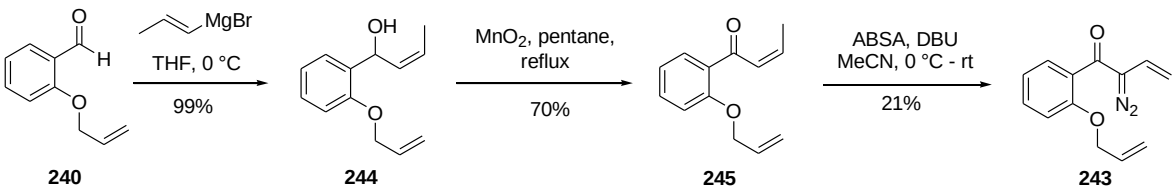
240 was easily synthesised directly from salicylaldehyde **242** by allylation with allyl bromide and potassium carbonate (Scheme 77). Despite containing an aldehyde, **240** proved to be stable enough to purify by flash column chromatography and the product was obtained in 87% yield.[199] α-Diazo ß-ketoester diazocarbonyl **241** was synthesised from **240** in 61% yield using a one-pot aldol-type reaction with ethyl diazoacetate and DBU followed by oxidation using IBX, in a procedure that was developed by Erhunmwunse and Steel.[200]



Scheme 77 Synthesis of diazocarbonyl **240**.

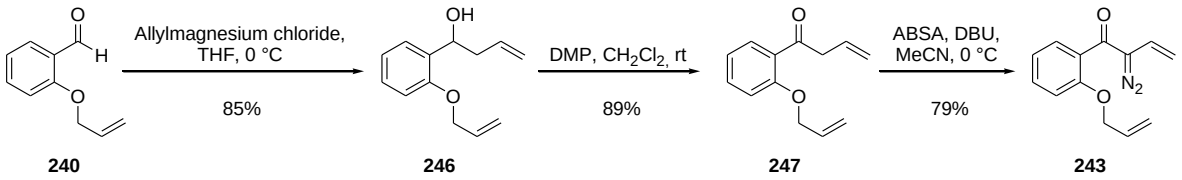
7.1.1.2 Synthesis of vinyl diazoketone **243**

The next diazo carbonyl substrate to be synthesised was the vinyl diazoketone **243**. The first route was based on Grignard addition to the aldehyde **240** followed by oxidation and diazotransfer (Scheme 78). Grignard reaction of **240** with propenylmagnesium bromide resulted in alcohol **244** in 99% yield.[201] According to ^{1}H-NMR analysis, only the *Z*-alkene was obtained. Oxidation of **244** using manganese dioxide afforded ketone **245** in 70% yield.[202] Davies *et al*. have developed a procedure for the formation of vinyl diazoketones from this type of substrate by diazotransfer using ABSA.[88] Applying these conditions to **245** resulted in the formation of **243** in just 21% yield. However, the low yield was not the only problem with this route. There were further considerable problems with reproducing the diazotransfer reaction and yields ranging from 0-21% were obtained. Consequently, a new, albeit similar, route was developed.



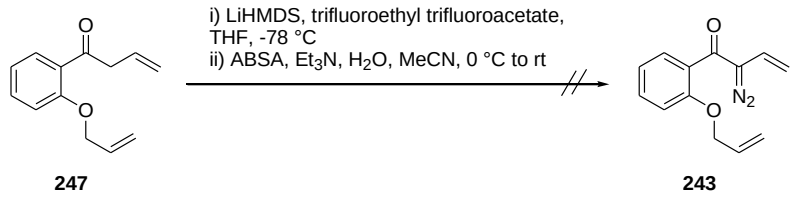
Scheme 78 Synthesis of vinyl diazoketone **243** – route one.

Here, rather than using propenylmagnesium chloride, the Grignard reaction was performed using allylmagnesium chloride (Scheme 79).[201] Alcohol **246** was obtained in 85% yield. Oxidation of **246** with Dess-Martin periodinane resulted in formation of the ketone **247** in 89% yield.[203] Again, diazotransfer with ABSA and DBU resulted in the formation of vinyl diazoketone **243**, although this time with a much improved yield of 79%. Not only was the yield significantly improved, there were no problems reproducing this reaction. Having said this, **243** was found to be quite unstable and started to polymerise when stored in a freezer for more than a day or two.



Scheme 79 Synthesis of vinyl diazoketone **243** – route two.

In addition to the above results, an alternative method for diazotransfer was also explored. Activation by the addition of a trifluoroacetyl group in the α-position followed by diazotransfer as described by Danheiser and McKervey would result in diazoketone **243** (Scheme 80).[14,86] Unfortunately, the required product was not obtained from this reaction.

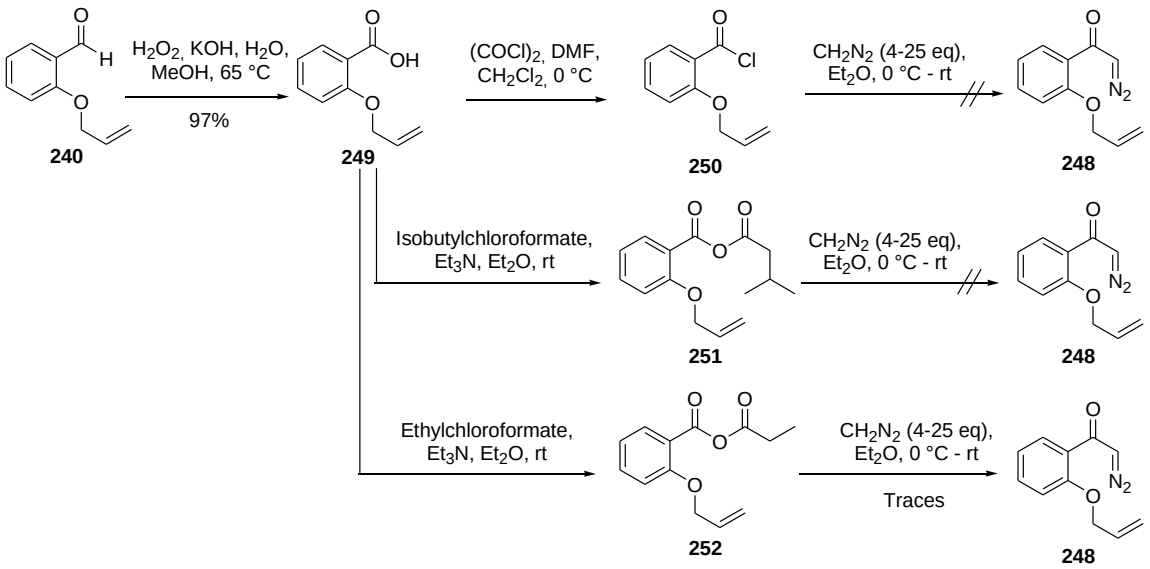


Scheme 80 Synthesis of vinyl diazoketone **243** – route three.

7.1.1.3 Synthesis of terminal diazoketone **248**

The synthesis of terminal diazoketone **248** proved to be more difficult than expected. It was believed that oxidation of the aldehyde **240** to the corresponding carboxylic acid **249** followed by activation of the acid as either the acid halide or an anhydride and subsequent acylation of diazomethane would deliver the terminal diazoketone (Scheme 81). Oxidation of **240** to 2-allyloxy benzoic acid **249** was easily carried out with aqueous

hydrogen peroxide (27.5%) to give **249** in 97% yield.[204] Reaction with oxalyl chloride in DMF resulted in the acid chloride **250**, which was used directly without further purification. However, reaction of the presumed intermediate acid chloride with diazomethane did not yield diazoketone **248**, and only a by-product, which was later isolated, was obtained from this reaction. Varying the number of equivalents of diazomethane used, from 4 to 25 equivalents, gave the same result. A diazo group gives a very strong peak at around 2200 cm^{-1} in the IR spectrum, but analysis of the crude product clearly showed the absence of diazoketone.

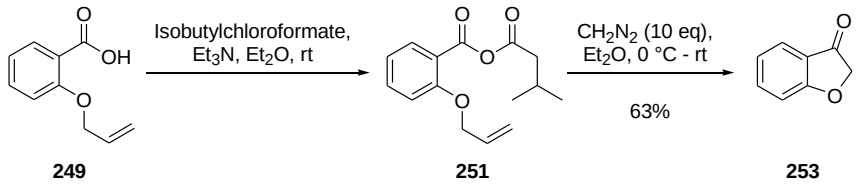


Scheme 81 Attempts to acylate diazomethane.

In addition to the preparation of an acid halide as an activated carboxylic acid, the formation of mixed anhydrides was investigated. First, **249** was reacted with isobutyl chloroformate to give isobutyl anhydride **251**. Again, acylation of diazomethane was attempted using various amounts of diazomethane, but without success. IR analysis of the crude product showed the absence of a diazoketone. The reaction was also attempted using ethyl chloroformate instead of isobutyl chloroformate, forming the anhydride **252**. Subsequent reaction with diazomethane did result in traces of diazoketone according to IR analysis when the reaction was quenched after two hours, but the reaction was incomplete. Moreover, attempts to isolate the diazoketone were unsuccessful. Further attempts to optimise the reaction were unsuccessful.

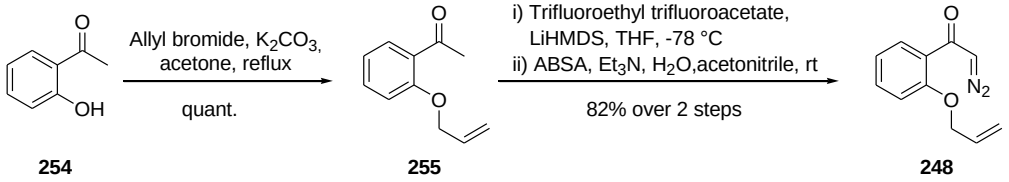
It appeared that the same by-product was obtained during all attempts to acylate diazomethane. The by-product was isolated from the reaction of **251** with ten

equivalents of diazomethane and identified as 3-benzofuranone **253** (Scheme 82). The isolation of the ketone **253** suggests that diazoketone **248** might have been formed, but decomposed and rearranged during the acylation process.



Scheme 82 Formation of by-product **253**.

Due to the difficulties encountered with acylation of diazomethane, a new route was investigated which proved to be more successful (Scheme 83). Allylation of 1-(2'-hydroxyphenyl) ethanone **254** resulted in formation of the ketone **255** in quantitative yield.[199] Activation by incorporation of a trifluoroacetyl group at the α-position followed by diazotransfer, a reaction that had been attempted previously for the synthesis of vinyl diazoketone **243** but with little success (*cf*. Scheme 80), resulted in formation of the terminal diazoketone **248** in 82% yield over two steps.[14,86] An added advantage of this procedure was that while ABSA is potentially explosive upon contact with metals, it is both safer and easier to handle than diazomethane, which is a highly toxic and explosive gas.

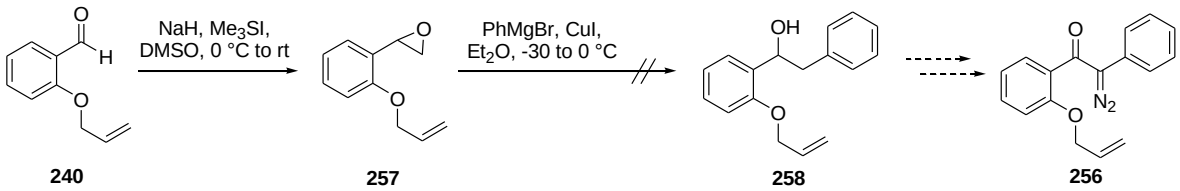


Scheme 83 Synthesis of **248** by diazotransfer.

7.1.1.4 Synthesis of phenyl diazoketone **256**

The attempted synthesis of phenyl-substituted diazoketone **256** also proved to be difficult. The first strategy involved epoxidation of **240** to generate epoxide **257** (Scheme 84). Grignard reaction with phenylmagnesium bromide should generate benzylic alcohol **258**, which upon oxidation and diazotransfer was anticipated to form **256**. The epoxidation of **240** using the Corey-Chaykovsky epoxidation reaction

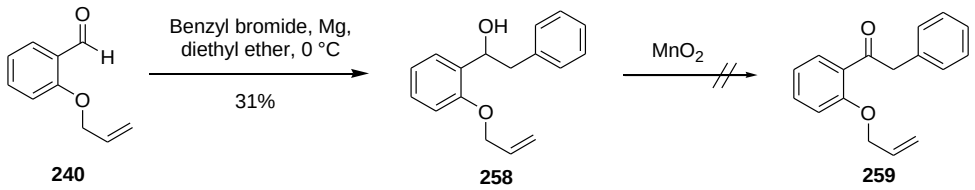
proceeded without problem.[205] Due to the unstable nature of the epoxide, attempted purification resulted in decomposition of the product. However, the ^{1}H-NMR spectrum of the crude product confirmed the formation of the epoxide and so the Grignard reaction was then attempted using the crude product. Unfortunately, Grignard reaction with phenylmagnesium bromide did not result in the formation of **258** and a complex mixture of products was obtained instead.[206]



240 **257** **258** **256**

Scheme 84 Attempt to synthesise phenyl diazoketone **256**.

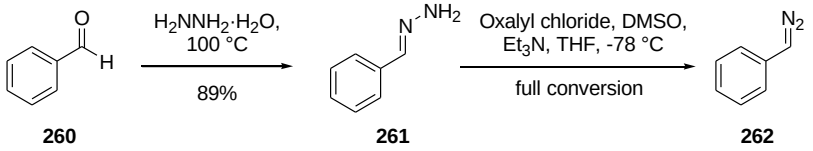
Despite the above result, alcohol **258** could be obtained from **240** in one step, through a Grignard reaction with benzylmagnesium bromide (Scheme 85). **258** was obtained in a modest yield of 31%. Unfortunately, attempts to oxidise **258** using manganese dioxide were unsuccessful. At this point, another member of our research team had attempted to oxidise **258** by screening an extensive variety of oxidants. Regrettably, all reactions were unsuccessful, including that in which PCC was used, which had been described in literature.[86] Consequently, alternative routes were investigated.



240 **258** **259**

Scheme 85 Attempt to synthesise ketone **259**.

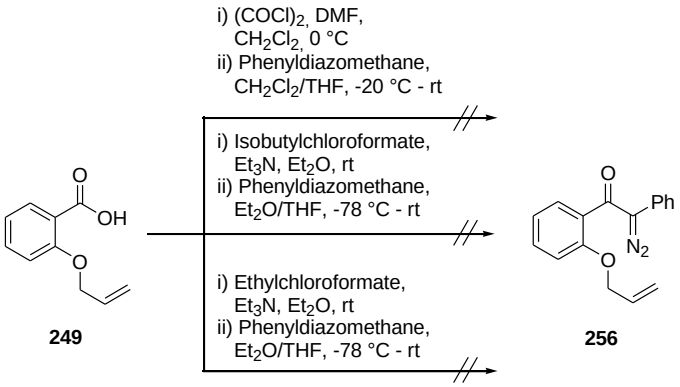
The next route involved the synthesis of phenyl diazomethane, in order to attempt a reaction analogous to the acylation reaction of diazomethane (Scheme 86). Starting from benzaldehyde **260**, treatment with hydrazine monohydrate afforded the hydrazone **261** in 89% yield.[207] Phenyl diazomethane **262** was obtained directly from the hydrazone.[208] Due to the sensitivity of this molecule, it was not isolated and the crude product was used immediately in the subsequent reaction.



260 **261** **262**

Scheme 86 Synthesis of phenyl diazomethane **262**.

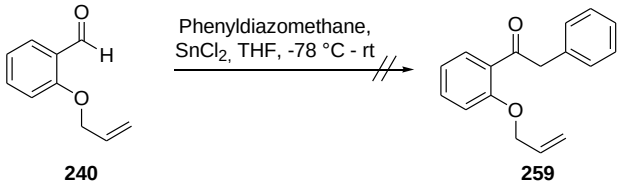
Attempts to acylate phenyl diazomethane were unsuccessful (Scheme 87). Various methods of activating the carboxylic acid **249** were explored, as earlier with acylation of diazomethane (*cf*. Scheme 81). However, when using an acid chloride, an isobutyl anhydride or an ethyl anhydride, none of the required diazoketone **256** was obtained and analysis of the reaction mixture showed that only starting material was present.



249 **256**

Scheme 87 Attempted acylation of phenyl diazomethane.

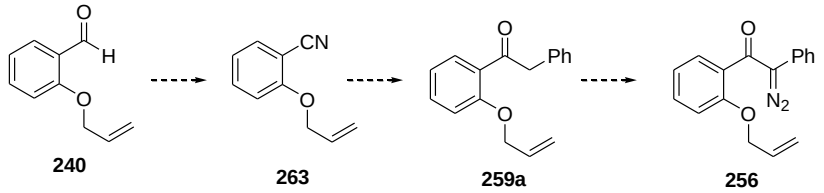
A coupling reaction of 2-allyloxybenzaldehyde **240** and phenyl diazomethane using tin dichloride as catalyst was attempted, but without success (Scheme 88).[209] The coupling reaction catalysed by scandium triflate as reported by Brewer *et al*. was also attempted in the group but without success.[208]



240 **259**

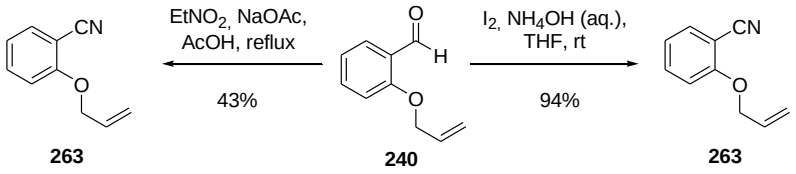
Scheme 88 Attempted coupling reaction with phenyl diazomethane.

The final route to the ketone **259** that was explored was based on a Grignard addition reaction to the nitrile **263** (Scheme 89). During a Grignard reaction to nitrile **263** an iminium species is formed, which upon aqueous work-up would undergo hydrolysis to give the corresponding ketone **259a**. This would hopefully by-pass the problematic oxidation of the alcohol **258**.



Scheme 89 The nitrile route to synthesise **256**.

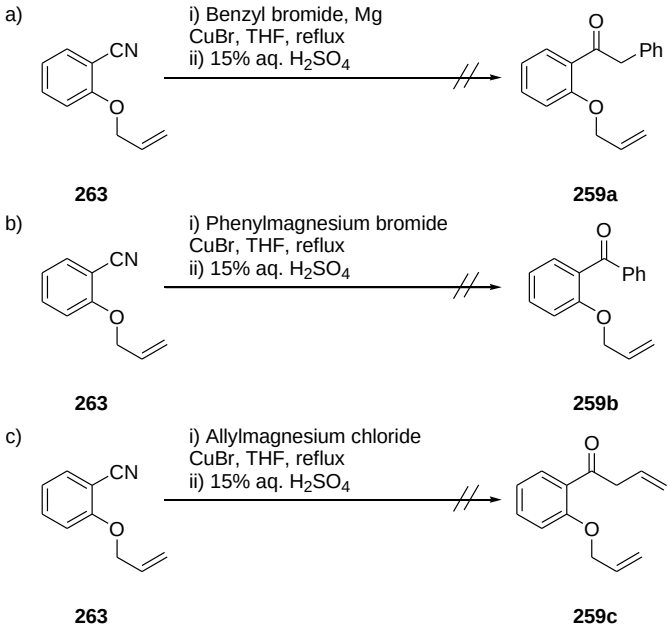
The route commenced with the synthesis of 2-allyloxybenzonitrile **263** (Scheme 90). Reaction of **240** with nitroethane and sodium acetate in refluxing glacial acetic acid did deliver the nitrile **263** in 43% yield.[210] However, reaction of **240** with iodine and aqueous ammonia in THF at room temperature provided **263** in an excellent 94% yield.[211]



Scheme 90 Synthesis of nitrile **263**.

Having synthesised nitrile **263**, Grignard addition was attempted with benzylmagnesium bromide (Scheme 91a).[212] The Grignard reagent was generated *in situ* by reaction of benzyl bromide with magnesium turnings. However, while the starting material was completely consumed, the product was not obtained. The same reaction was attempted with phenylmagnesium bromide rather than benzylmagnesium bromide (Scheme 91b).[212] In this case, the Grignard reagent was used as received by the supplier. Again, the required product was not obtained. Finally, this reaction was attempted with allylmagnesium chloride (Scheme 91c). This Grignard reagent had been used successfully with 2-allyloxybenzaldehyde to provide **246**, which was oxidised to ketone **247** (*cf*. Scheme 79). However, reaction with **263** did not provide **259c**.

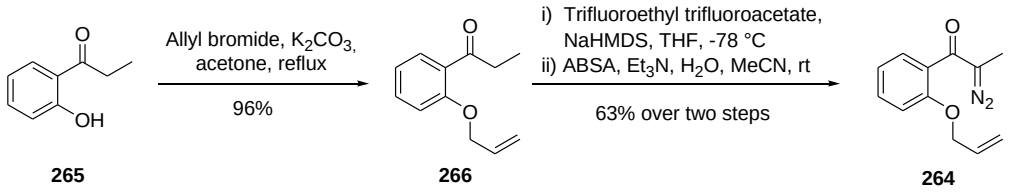
As this reaction was further investigated at the time by other members of our research team, the focus of this project was redirected.



Scheme 91 Reaction of nitrile **263** and Grignard reagents.

7.1.1.5 Synthesis of methyl diazoketone **264**

The synthesis of the final aromatic diazoketone target was performed using diazotransfer to an activated ketone (Scheme 92). Allylation of 1-(2'-hydroxyphenyl) propanone **265** using allyl bromide resulted in formation of the ketone **266** in 96% yield. Diazotransfer, as described by Danheiser and McKervey, resulted in methyl substituted diazoketone **264** in 63% yield over two steps.[14,86]



Scheme 92 Synthesis of diazoketone **264**.

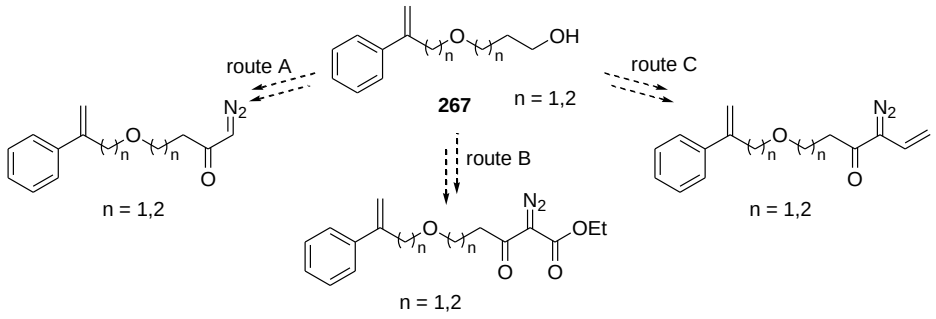
It is important to note that the choice of base has a direct impact on the yield of the diazotransfer reaction. When LiHMDS was used rather than NaHMDS the best yield

obtained was 51% over two steps; more commonly yields of around 30-40% were achieved.

A sufficient number of aromatic diazoketone substrates had now been synthesised in reasonable yield. Attention then focused on the preparation of a variety of aliphatic substrates.

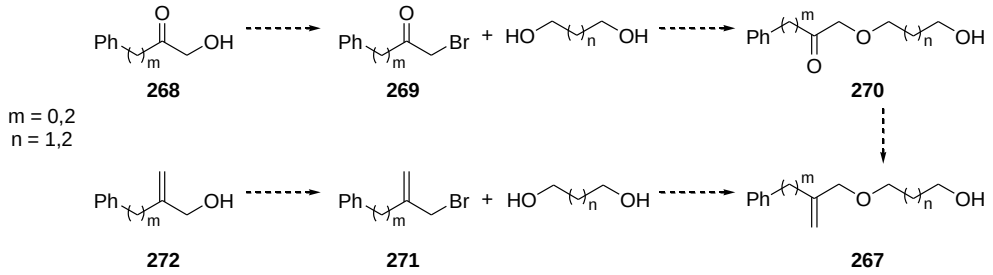
7.1.2 Synthesis of aliphatic diazoketones

To allow a complete survey of the proposed synthetic methodology, aliphatic diazoketone substrates were also prepared. A variety of aliphatic diazoketones can be synthesised from precursors such as **267** (Scheme 93). Oxidation of the alcohol to give the corresponding carboxylic acid followed by acylation of diazomethane (route A) should provide a terminal diazoketone. Oxidation to the aldehyde with a subsequent aldol-type reaction with ethyl diazoacetate followed by oxidation should result in formation of an α-diazo ß-keto ester (route B), whereas formation of an allyl carbonyl substrate with subsequent diazo transfer would result in a vinyl-substituted diazoketone (route C).



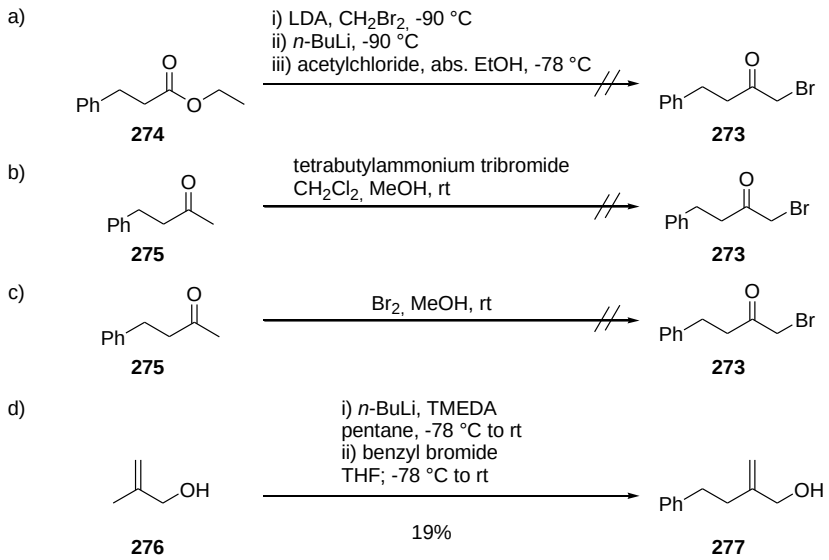
Scheme 93 Synthesis of various aliphatic diazoketones.

Provided the alcohol **268** could be synthesised, a substitution reaction would result in bromide **269**. **269** could be coupled with either 1,3-propanediol or 1,4-butanediol to give alcohol **270**, and a Wittig reaction or Tebbe reaction would give the alcohol **267** (Scheme 94). This would provide a starting point for the synthesis of aliphatic diazoketones. Alternatively, the bromide **271** could be formed from **272**, and subsequent coupling with either 1,3-propanediol or 1,4-butanediol would provide **267** without the need for ketone methylation.



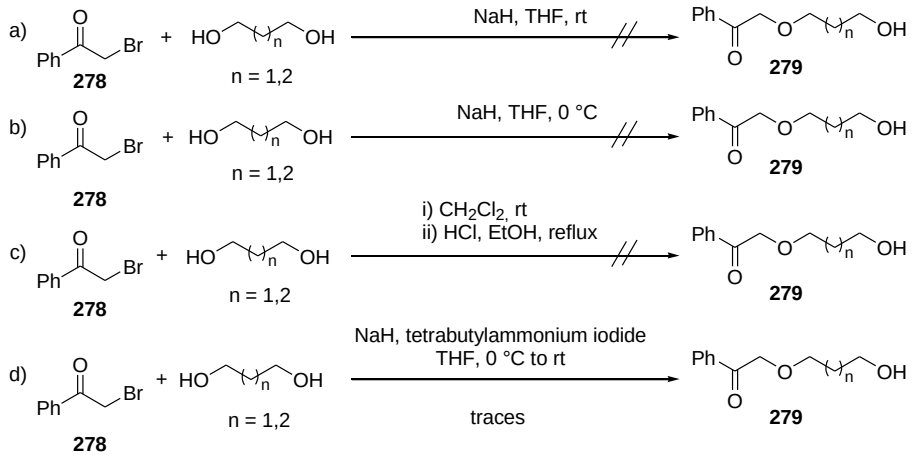
Scheme 94 Routes to synthesise **267**.

Initially, the synthesis of the bromoketone **273** was attempted. Ethyl hydrocinnamate **274** was first reacted with LDA and dibromomethane followed by *n*-BuLi and acetylchloride in an attempt to synthesise bromoketone **273**, but the reaction was not successful (Scheme 95a).[213] Next, the reaction of 4-phenyl-2-butanone **275** with tetrabutylammonium tribromide and methanol was attempted, but yet again, the required bromoketone **273** was not obtained (Scheme 95b).[214] Furthermore, reacting **275** with bromine and methanol also did not result in the formation of **273** (Scheme 95c).[215] However, when 2-methyl-2-propen-1-ol **276** was reacted with *n*-BuLi and TMEDA followed by benzyl bromide, **277** was obtained, albeit in just 19% yield (Scheme 95d).[216] Unfortunately, it was not possible to repeat this reaction, only decomposition of the starting materials was observed when the reaction was attempted subsequently.



Scheme 95 Attempted synthesis of **273** and **277**.

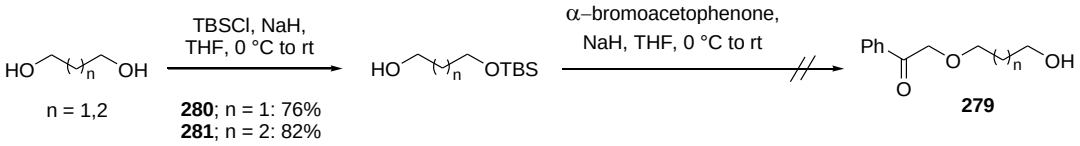
Due to the difficulties with the preparation of **273** and **277**, the focus instead turned towards synthesising aliphatic diazoketones with the phenyl group directly attached to the alkene (*cf*. m = 0, Scheme 94). It was thought that if α-bromoacetophenone **278** was coupled with 1,3-propanediol or 1,4-butanediol, then a Wittig reaction on the coupling products **279** with the ylide derived from $MePPh_3I$ would result in alkenes **267** (*cf*. Scheme 94). First, the diols and α-bromoacetophenone **278** were reacted in the presence of sodium hydride at room temperature (Scheme 96a).[217] Unfortunately, the required product was not obtained. Additionally, lowering the temperature to 0 °C did not result in formation of the desired product and so a different approach was investigated (Scheme 96b).[218] First α-bromoacetophenone **278** was stirred with the diol in room temperature followed by reduction *in vacuo* (Scheme 96c). The residue was subsequently treated with hydrochloric acid according to a procedure published by Stark *et al*.[219] However, the product was not obtained and analysis of the reaction mixture revealed that a complex mixture of compounds had been formed instead. Finally, α-bromoacetophenone **278** and the diols were treated with sodium hydride and tetrabutylammonium iodide in THF at 0 °C to room temperature (Scheme 96d).[220] In these cases, traces of product were obtained as components of very complex mixtures of compounds.



Scheme 96 First attempts of coupling reactions.

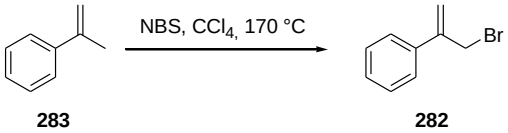
With regard to the results above, it was thought that the problems associated with coupling of the two fragments might be due to the use of unprotected diols. Therefore, coupling of the two fragments with mono-protected diols was attempted. First, 1,3-propanediol and 1,4-butanediol were mono-protected with a *t*-butyldimethylsilyl (TBS) group in 76% and 82% yield respectively (Scheme 97).[221] The protected diols **280**

and **281** were then reacted with α-bromoacetophenone in the presence of sodium hydride. Unfortunately, the required products were not obtained from these reactions.[218]



Scheme 97 Mono-protection of diols.

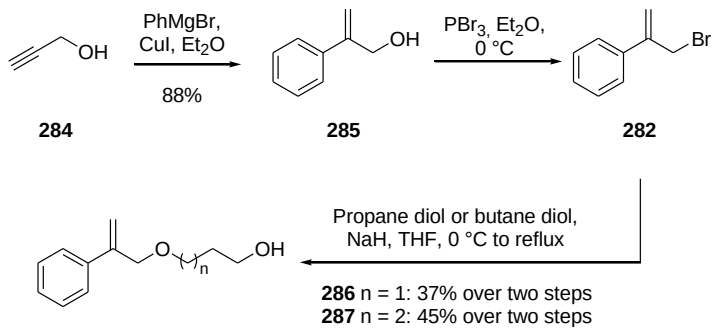
It was then realised that if bromide **282** could be coupled with the appropriate diols, one step (the Wittig reaction), would be saved. Various methods for synthesising bromide **282** were explored. Reaction of α-methyl styrene **283** with NBS in carbon tetrachloride at 170 °C resulted in **282** in good yields according to literature precedent (Scheme 98).[222,223] However, due to high volatility of **282**, an accurate yield could not be calculated.



Scheme 98 Synthesis of **282**.

As well as the conditions described above, a different route for the synthesis of **282** was explored. Propargyl alcohol **284** was reacted with phenylmagnesium bromide and copper(I) iodide, resulting in formation of the allylic alcohol **285** in 88% yield (Scheme 99).[224] Nucleophilic substitution of the alcohol with phosphorus tribromide resulted in formation of bromide **282**.[225] Attempts to generate phosphorus tribromide *in situ* from triphenylphosphine and bromine followed by reaction with **285** resulted in only traces of product.[224] While it was possible to purify **282**, due to its very low boiling point it was difficult to dry this compound without losing significant amounts of the product. As the reaction was fairly clean, the crude product was used in the next step without further purification. Bromide **282** was coupled with either propane diol or butane diol using sodium hydride in refluxing THF.[226] Alcohol **286** was obtained in 37% over two steps and

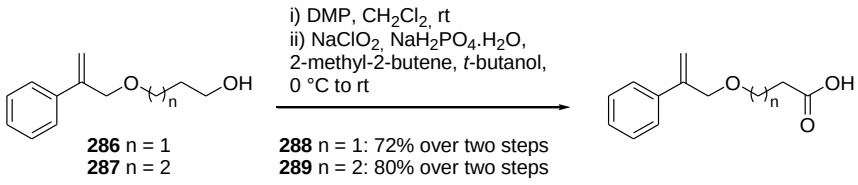
alcohol **287** in 45% over two steps. For both reactions, only traces of the doubly alkylated by-product were obtained.



Scheme 99 Synthesis of precursors **286** and **287**.

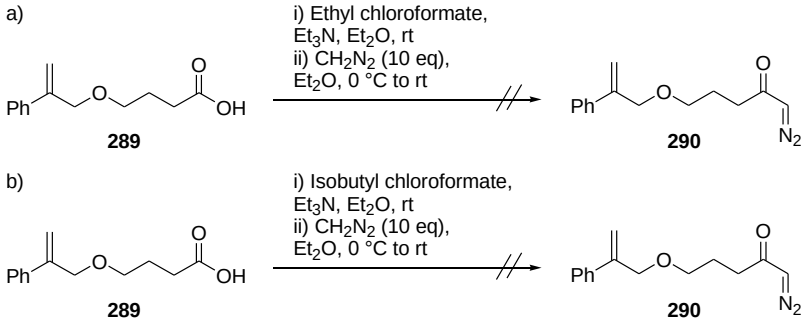
With compounds **286** and **287** in hand, the first diazoketones that were of interest were the terminal diazoketones. These would be obtained through oxidation of the alcohols to the corresponding carboxylic acids followed by acylation of diazomethane.

The carboxylic acids were synthesised from **286** and **287** in two steps (Scheme 100). Dess-Martin oxidation afforded the aldehydes, which were not isolated. The crude aldehydes were subsequently oxidised to give the carboxylic acids through a Pinnick oxidation.[227] Carboxylic acid **288** was obtained in 72% over two steps and carboxylic acid **289** was obtained in 80% over two steps.



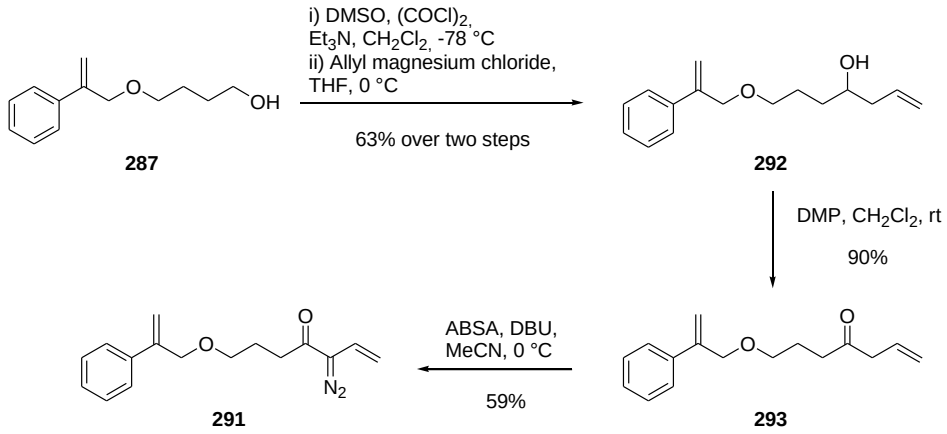
Scheme 100 Synthesis of carboxylic acids **288** and **289**.

From the carboxylic acids, we envisaged forming the corresponding terminal diazoketones by acylation of diazomethane. This reaction was carried out with carboxylic acid **289**. In order for acylation of diazomethane to be successful, the carboxylic acid first needs to be activated. This was attempted for **289** through the formation of the ethyl anhydride (Scheme 101a) and the formation of isobutyl anhydride (Scheme 101b). Unfortunately, neither reaction was successful and both reactions resulted in decomposition of the starting material.



Scheme 101 Acylation of diazomethane with **289**.

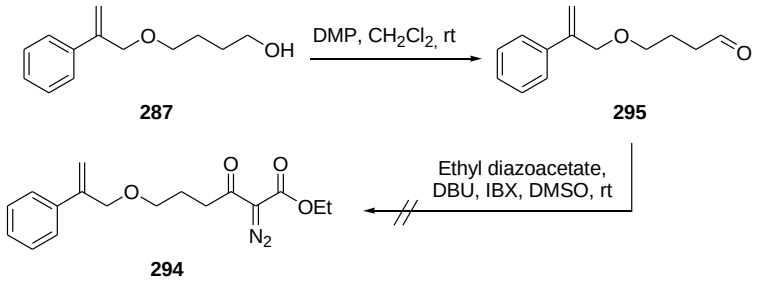
The work towards the synthesis of aliphatic diazoketones continued with the synthesis of the aliphatic vinyl diazoketone **291** (Scheme 102). Here, oxidation of alcohol **287** using Swern conditions resulted in formation of the corresponding aldehyde, which was used in the next step without further purification. Grignard reaction with allylmagnesium chloride resulted in allylic alcohol **292** in 63% yield over two steps. Alternatively, use of Dess-Martin oxidation instead of Swern oxidation resulted in a 61% yield of **292** over the two steps. Oxidation of **292** with Dess-Martin periodinane afforded the ketone **293** in 90% yield. The diazoketone **291** was then obtained through diazotransfer using ABSA and DBU in 59% yield.[14,86]



Scheme 102 Synthesis of vinyl diazoketone **291**.

The next aliphatic diazoketone to be synthesised was the aliphatic α-diazo ß-keto ester **294**. At the outset, it was anticipated that the diazoketone **294** would be synthesised according to the same procedure as the aromatic equivalent (*cf*. Scheme 77). Oxidation of alcohol **287** using Dess-Martin periodinane resulted in aldehyde **295** (Scheme 103). The product obtained was very clean, so the crude aldehyde was used in the next step

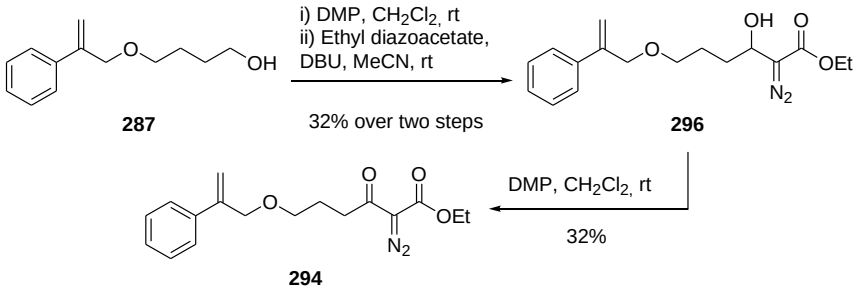
without further purification. However, no reaction took place when an aldol-type reaction with ethyl diazoacetate and subsequent oxidation with IBX was attempted in a one-pot fashion.



287 **295** **294**

Scheme 103 Synthesis of diazoketone **294** – first route.

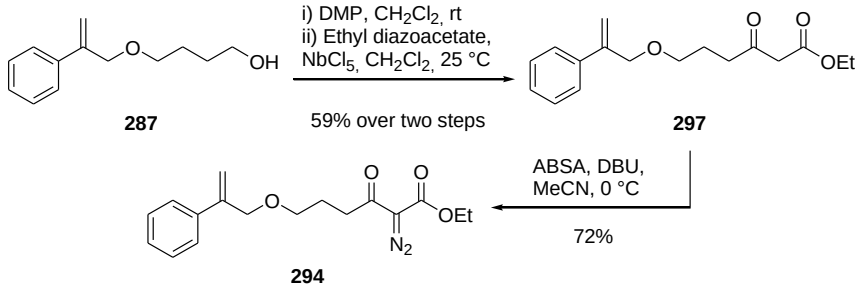
Rather than attempting a one-pot reaction, the same procedure was carried out in a stepwise fashion (Scheme 104).[200] First, **287** was oxidised using Dess-Martin periodinane. The crude aldehyde was reacted with ethyl diazoacetate and DBU, which resulted in formation of the hydroxy diazoketone **296** in 32% yield over two steps. Further oxidation with Dess-Martin periodinane afforded the α-diazo β-ketoester **294** in 32% yield.



287 **296** **294**

Scheme 104 Stepwise aldol-type reaction followed by oxidation.

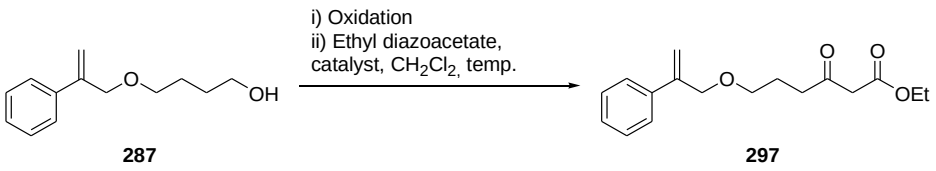
Although **294** had been synthesised, the yields were quite low and so an alternative route was pursued (Scheme 105). Again, the synthesis commenced with a Dess-Martin oxidation of **287** to the corresponding aldehyde. The crude aldehyde was coupled with ethyl diazoacetate catalysed by niobium(V) chloride, resulting in the β-ketoester **297** in 59% yield over two steps.[228] Diazoketone **294** was obtained from **297** by diazotransfer using ABSA and DBU in a 72% yield.



Scheme 105 Synthesis of **294** – route two.

With regard to the above results, the ß-keto ester **297** was synthesised by reaction with ethyl diazoacetate in the presence of $NbCl_5$. However, tin(II) chloride could also be used.[209] At first, small scale reactions were performed with both $SnCl_2$ (Table 1, Entry 1) and $NbCl_5$ (Table 1, Entry 2). While the yields for the reactions were 47% and 46% respectively, the reaction mediated by $NbCl_5$ was complete within 7 hours, while the reaction performed using $SnCl_2$ took almost two days. Therefore, attempts to scale up the reaction were first performed with $NbCl_5$. Having said this, on a scale of 1.0 mmol, while the yield increased to 59%, the reaction time also increased significantly to 65 h (Table 1, Entry 3). On a scale of 4.8 mmol a 45% yield was obtained, but the reaction time of 40 h was still rather long (Table 1, Entry 4). Therefore, on a scale-up to 10 mmol, $SnCl_2$ was tested (Table 1, Entry 5). This did result in a yield of 78%, the best yield obtained, but the reaction time of three days is a drawback.

Table 1 Synthesis of ß-keto ester **297**.



Entry	Oxidation	Catalyst	Temp.	Scale	Duration	Yield (two steps)
1	Dess-Martin	$SnCl_2$	rt	0.15 mmol	46 h	47%
2	Dess-Martin	$NbCl_5$	25 °C	0.14 mmol	7 h	46%
3	Dess-Martin	$NbCl_5$	25 °C	1.0 mmol	65 h	59%
4	Swern	$NbCl_5$	25 °C	4.8 mmol	40 h	45%
5	Swern	$SnCl_2$	rt	10 mmol	3 days	78%

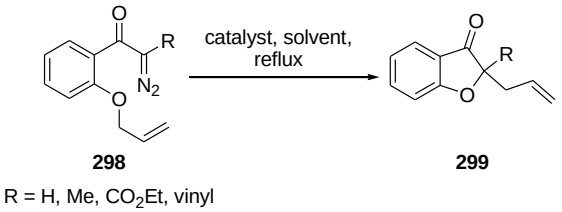
With the successful synthesis of a variety of diazoketones, both aromatic and aliphatic, attention now turned towards the oxonium ylide generation and subsequent rearrangement of these substrates.

7.2 Formation and rearrangement of ylides or ylide-like intermediates generated using achiral catalysts

The decomposition and rearrangement of diazocarbonyl compounds were first performed in racemic mode, using a variety of copper or rhodium catalysts such as $Cu(acac)_2$ or $Rh_2(OAc)_4$. This enabled the testing of reaction conditions, and produced racemic material that would be required for the optimisation of enantiomer separation using chiral HPLC in subsequent studies.

7.2.1 Aromatic diazoketones

Various aromatic diazoketones **298** were treated with copper and rhodium complexes to form various benzofuranones **299**. These reactions proceeded by sequential carbenoid generation and rearrangement of a free oxonium ylide intermediate or the metal-bound equivalent resulting from nucleophilic attack of the allylic ether on the carbenoid (Scheme 106). The initial results are shown in Table 2.



298 **299**

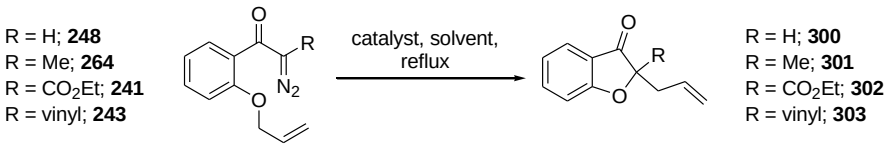
R = H, Me, CO_2Et, vinyl

Scheme 106 The decomposition and rearrangement of aromatic diazoketones.

Non-stabilised diazocarbonyl compounds were found to react faster and at lower reaction temperatures. For example, when terminal diazoketone **248** was reacted with $Cu(acac)_2$ in CH_2Cl_2, the reaction proceeded to full conversion in 45 min and a yield of 57% was obtained (Table 2, Entry 1). Attempting to slightly modify the catalysts, $Cu(hfacac)_2$ was tested. In refluxing CH_2Cl_2 and at the same catalyst concentration, the yield for this reaction was also 57% (Table 2, Entry 2). Methyl substituted diazoketone **264** also reacted with $Cu(acac)_2$ in CH_2Cl_2 at reflux to produce the desired compound in a satisfying 73% yield, although it took 18 h for the reaction to proceed to full conversion (Table 2, Entry 3). Under the same conditions the α-diazo ß-keto ester **241** did not react with $Cu(acac)_2$ in CH_2Cl_2 at reflux (Table 2, Entry 4). However, changing the solvent to 1,2-DCE enabled the reaction to be performed at significantly higher reaction temperature and the product was obtained in 61% yield, albeit after a prolonged period of 20 h (Table 2, Entry 5).

The vinyl substituted diazoketone **243** transpired to be a more capricious substrate. As mentioned previously, while other diazoketones could be stored in the freezer for weeks without decomposition, the aromatic vinyl diazoketone started to polymerise when stored in the freezer over night. The catalytic decomposition and subsequent rearrangement reaction also proved more troublesome than for previous diazoketones. The reactions with the previous substrates were very clean, and only the [2,3]-sigmatropic rearrangement product was obtained in each case. However, reactions of the vinyl diazoketone delivered very complex product mixtures in every case. Initially, $Cu(acac)_2$ was used as catalyst in various solvents at reflux. In these cases, no reaction took place when refluxing CH_2Cl_2 was used (Table 2, Entry 6), only traces of the product were observed when the reaction was performed in refluxing 1,2-DCE (Table 2, Entry 7) and no product was obtained despite all starting material being consumed when the reaction was performed in refluxing toluene or THF (Table 2, Entries 8 and 9). This was surprising because it was considered more likely that traces of product would be observed at either the highest reaction temperature (in refluxing toluene) or at the lowest reaction temperature (in refluxing THF), rather than at the intermediate reaction temperature (in refluxing 1,2-DCE). Next, the catalyst was varied. Using $Cu(hfacac)_2$ as a catalyst resulted in the formation of traces of product, both in toluene at reflux (Table 2, Entry 10) or in 1,2-DCE at reflux (Table 2, Entry 11). Only traces of the product were obtained when the reaction was performed using a copper catalyst and so various rhodium catalysts were tested in hope that more successful results would be obtained. Unfortunately, the use of both $Rh_2(OAc)_4$ and $Rh_2(tfa)_4$ as catalysts in refluxing 1,2-DCE resulted in the formation of only traces of product (Table 2, Entries 12 and 13).

Table 2 Racemic decomposition and rearrangement of aromatic diazoketones.



Entry	Diazoketone	Catalyst	[cat.]	Solvent	Duration	Yield
1	**248**	$Cu(acac)_2$	5 mol%	CH_2Cl_2	45 min	57%
2	**248**	$Cu(hfacac)_2$	5 mol%	CH_2Cl_2	45 min	57%
3	**264**	$Cu(acac)_2$	10 mol%	CH_2Cl_2	18 h	73%
4	**241**	$Cu(acac)_2$	10 mol%	CH_2Cl_2	n/a	no reaction
5	**241**	$Cu(acac)_2$	10 mol%	1,2-DCE	20 h	61%
6	**243**	$Cu(acac)_2$	5 mol%	CH_2Cl_2	n/a	no reaction
7	**243**	$Cu(acac)_2$	5 mol%	1,2-DCE	4 h	traces
8	**243**	$Cu(acac)_2$	5 mol%	Toluene	2 h	0%
9	**243**	$Cu(acac)_2$	5 mol%	THF	18 h	0%
10	**243**	$Cu(hfacac)_2$	5 mol%	Toluene	2 h	traces
11	**243**	$Cu(hfacac)_2$	5 mol%	1,2-DCE	3 h	traces
12	**243**	$Rh_2(OAc)_4$	5 mol%	1,2-DCE	5 h	traces
13	**243**	$Rh_2(tfa)_4$	5 mol%	1,2-DCE	4 h	traces

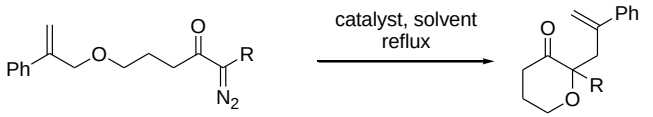
Despite varying success shown in Table 2, we were very pleased to have obtained the required products in good quantities from the reactions of three diazoketone substrates. For the vinyl substituted diazoketone only traces of product were obtained. As a multitude of reactions were being performed at the same time, the work towards finding a general enantioselective method for the catalytic decomposition and rearrangement of diazoketones continued without focus on the vinyl diazoketone.

7.2.2 Aliphatic diazoketones

The aliphatic diazoketone substrates that had been prepared were treated with a variety of copper and rhodium complexes (Table 3). First, the α-diazo ß-keto ester **294** was treated with 5 mol% of $Cu(hfacac)_2$ in refluxing CH_2Cl_2 (Table 3, Entry 1).

Unfortunately, no reaction took place even after several days. By increasing both the catalyst concentration to 10 mol% and the reaction temperature by substituting refluxing CH_2Cl_2 for refluxing 1,2-DCE, a satisfactory yield of 60% was obtained, albeit after a prolonged reaction time (Table 3, Entry 2). At the same reaction temperature and catalyst concentration, the catalyst was replaced by $Cu(acac)_2$ (Table 3, Entry 3). Disappointingly, in this case the required reaction did not take place. Turning to $Rh_2(OAc)_4$ as the catalyst, a pleasing yield of 75% was obtained after 3 days in refluxing 1,2-DCE (Table 3, Entry 4). When the vinyl substituted diazo carbonyl compound **291** was treated with $Cu(hfacac)_2$ in 1,2-DCE at reflux, the product **305** was obtained in 24% yield (Table 3, Entry 5). However, with $Rh_2(OAc)_4$ as catalyst, the only result was decomposition of the starting material (Table 3, Entry 6).

Table 3 Racemic decomposition and rearrangement of aliphatic diazoketones.



294: R = CO_2Et
291: R = vinyl

304: R = CO_2Et
305: R = vinyl

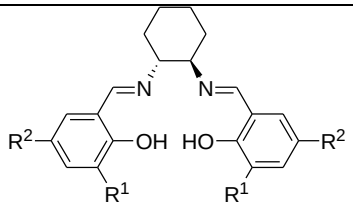
Entry	Diazoketone	Catalyst	[cat.]	Solvent	Duration	Yield
1	**294**	$Cu(hfacac)_2$	5 mol%	CH_2Cl_2	n/a	no reaction
2	**294**	$Cu(hfacac)_2$	10 mol%	1,2-DCE	6 days	60%
3	**294**	$Cu(acac)_2$	10 mol%	1,2-DCE	n/a	no reaction
4	**294**	$Rh_2(OAc)_4$	10 mol%	1,2-DCE	3 days	75%
5	**291**	$Cu(hfacac)_2$	5 mol%	1,2-DCE	4 h	24%
6	**291**	$Rh_2(OAc)_4$	5 mol%	1,2-DCE	n/a	decomp.

7.3 Synthesis of chiral ligands

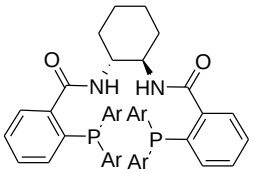
For the asymmetric rearrangement of the oxonium ylides or metal-bound ylide equivalent, chiral copper complexes generated *in situ* from $[Cu(MeCN)_4]PF_6$ and various chiral ligands were screened. Initially, chiral ligands were chosen from ligand classes such as salen,[186,185] Trost,[187] SEGPHOS,[188,189] DUPHOS,[190] bisoxazoline,[191,192,36] MonoPhos,[193] QuinoxP,[194] pyridine bisoxazoline[195] and phosphinooxazoline ligands[196]

(Chart 1). These ligands are representative of different types of chiral ligands that have previously been used in asymmetric copper-catalysed reactions, often with very good results. Many of these ligands are commercially available or easily synthesised.

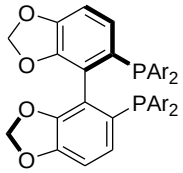
Chart 2 Chiral ligands for initial screening.



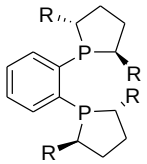
Salen-type



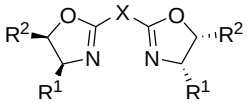
Trost-type



SEGPHOS-type



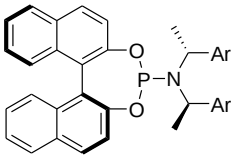
DUPHOS-type



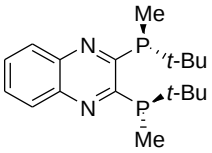
Bisoxazoline-type

(R = CH_2, CMe_2)

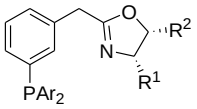
Pyridine bisoxazoline-type
(R = 2,6-pyridyl)



MonoPhos-type



QuinoxP

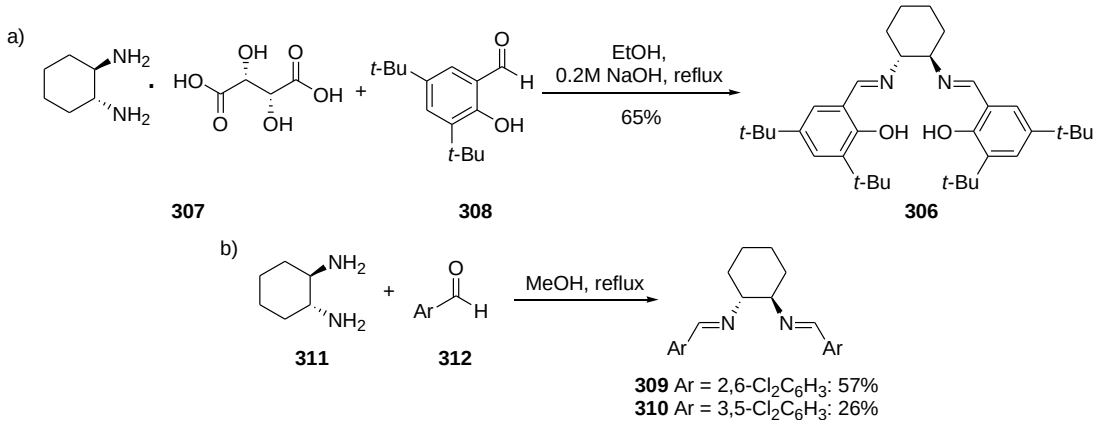


Phosphinooxazoline-type

7.3.1 Synthesis of Salen- and Trost-type ligands

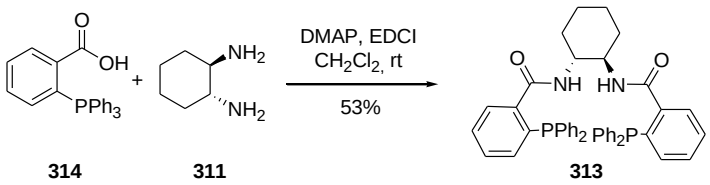
Although complexes of several commercially available chiral ligands were screened as catalysts, it was also necessary to synthesise many of the chiral ligands required for the study.

Jacobsen's ligand **306** was synthesised from (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate **307** and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde **308** in one step with a yield of 65% (Scheme 107a). In addition, various salen-type ligands (**309**,**310**) that were established to give asymmetric induction in the course of previous work within the Clark group, were also synthesised in one step from diaminocyclohexane **311** and a suitable aldehyde **312** (Scheme 107b).



Scheme 107 Synthesis of Salen-type ligands.

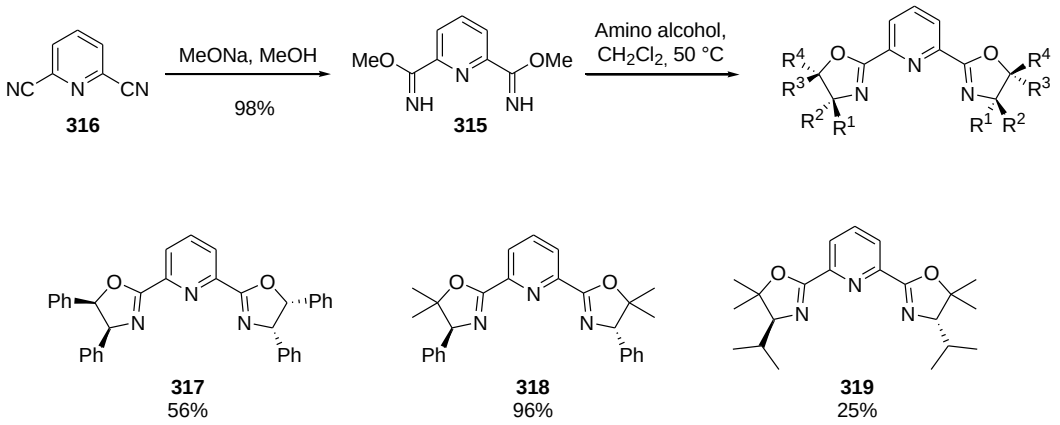
The Trost-type ligand **313** was also synthesised from diaminocyclohexane **311**, through an amide formation with 2-triphenylphosphinebenzoic acid **314** (Scheme 108). The ligand **313** was obtained in 53% yield.



Scheme 108 Synthesis of a Trost-type ligand.

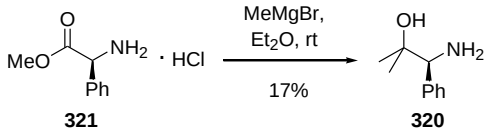
7.3.2 Synthesis of bisoxazoline and pyridine bisoxazoline ligands

Following preparation of the above ligands, pyridine bisoxazoline ligands were synthesised using a procedure developed by Beller *et al*. (Scheme 109).[229] First, dimethyl pyridine-2,6-dicarboximidate **315** was prepared from pyridine-2,6-carbodinitrile **316** in one step and in excellent yield (98%), using a catalytic amount of sodium methoxide in methanol as described by Bradshaw *et al*.[230] Imidate **315** was then reacted with various amino alcohols at 50 °C in a sealed tube, resulting in formation of the pyridine bisoxazoline ligands **317**, **318** and **319**. The isolated yields of the ligands varied from 25% to 96%.



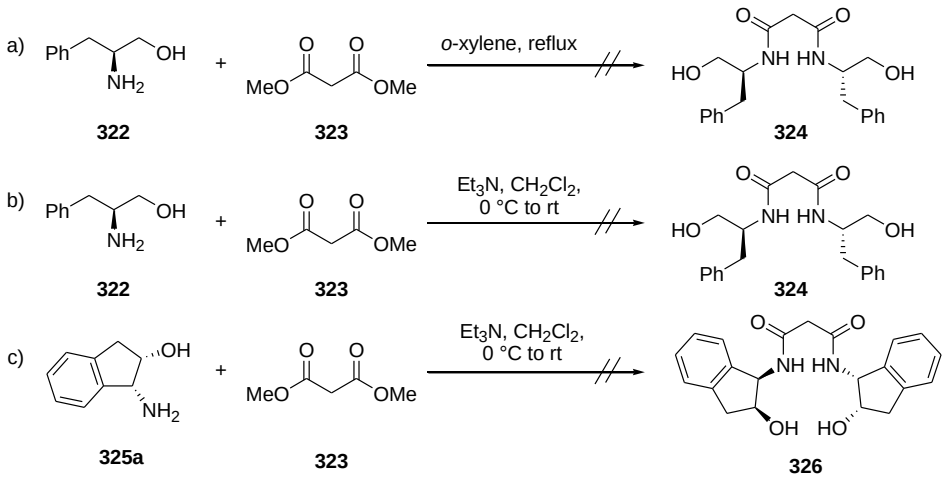
Scheme 109 Synthesis of pyridine bisoxazoline ligands.

The amino alcohol 1-amino-2-methyl-1-phenyl-2-propanol **320** (used to prepare **318**) was not commercially available and so it was synthesised in one step, but in low yield, from phenylglycine methyl ester hydrochloride **321** *via* a Grignard addition reaction of methyl magnesium bromide (Scheme 110).[229] It is possible that protecting the amine of **321**, *e.g.* with a Boc protecting group, prior to the reaction would have resulted in higher yields. However, enough of **320** was obtained to prepare **318** in sufficient amounts and so further optimisation of this reaction was not explored.



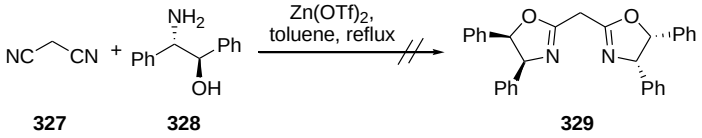
Scheme 110 Synthesis of amino alcohol **320**.

At this stage, the preparation of additional methylene-bridged bisoxazoline ligands was attempted, following a literature protocol.[231,232] Unfortunately, reaction of phenylalanol **322** with dimethyl malonate **323** in *o*-xylene at reflux did not produce diamide **324**, the precursor to the desired ligand (Scheme 111a).[231] The same reaction was attempted with triethyl amine in dichloromethane at 0 °C before warming to room temperature but again, **324** was not obtained (Scheme 111b).[232] Furthermore, exchanging aminoalcohol **322** for 1-amino-2-indanol **325a** did not provide the diamide **326** (Scheme 111c).[233,231]



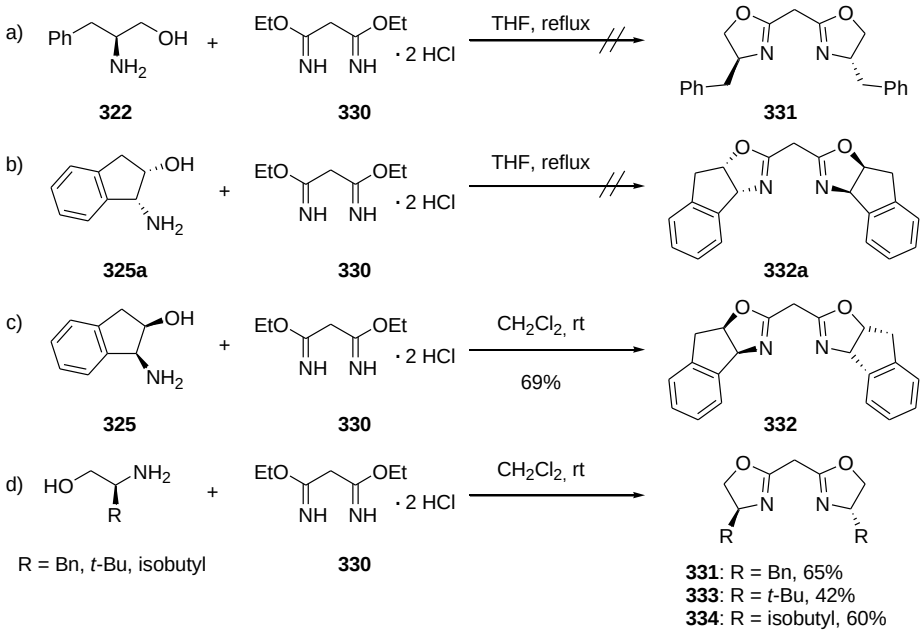
Scheme 111 Attempts to synthesise bisoxazoline ligands in two steps.

Next, malononitrile **327** was reacted with amino alcohol **328** in the presence of zinc(II) triflate, according to a procedure by Villalba *et al*.[234] Unfortunately, the bisoxazoline **329** was not obtained from this reaction (Scheme 112).



Scheme 112 Attempts to synthesise bisoxazoline **329**.

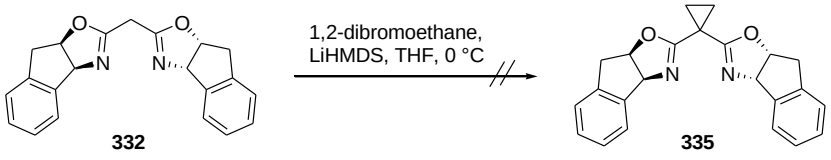
In spite of the results above, the synthesis of methylene-bridged bisoxazoline ligands was attempted in a manner similar to that used to synthesise pyridine bisoxazoline ligands. Reacting amino alcohol **322** with diethylmalonimidate dihydrochloride **330** in THF at reflux did not deliver the required bisoxazoline **331** (Scheme 113a).[235] Again, exchanging the amino alcohol for 1-amino-2-indanol **325a** did not deliver the bisoxazoline **332a** (Scheme 113b). However, upon changing the solvent to dichloromethane and lowering the temperature to room temperature, ligand **332** was obtained in 69% yield (Scheme 113c).[235] At this point, depending on which amino alcohol was employed, three different methylene-bridged bisoxazoline ligands, **331**, **333** and **334**, were prepared in one step with yields of 42-65% (Scheme 113d).



Scheme 113 Synthesis of methylene-bridged bisoxazoline ligands.

Furthermore, an attempt was made to form a cyclopropane at the methylene bridge (Scheme 114).[235] While ligand **332** is in itself quite a structurally rigid molecule, it was anticipated that addition of the rigid cyclopropyl group at the methylene bridge would enhance the rigidity of the ligand's framework. Consequently, a more rigid C_2-symmetric environment would be created around the metal centre providing a higher level of asymmetric induction in the stereochemistry-defining step of the reaction (either reaction of the lone-pair electrons with the metal carbenoid or rearrangement of a metal-bound ylide-like intermediate).

According to a literature procedure published by Zhang *et al.*, ligand **332** could be reacted with 1,2-dibromoethane and LiHMDS in THF at 0 °C. However, in our hands, the cyclopropyl ligand **335** was not obtained and so this project was continued to the next phase without having access to this ligand.



Scheme 114 Attempt to substitute at methylene bridge.

The fact that a library of chiral ligands was available meant that it was possible to focus attention on the asymmetric formation and rearrangement of oxonium ylides generated from the diazoketones synthesised previously.

7.4 Formation and rearrangement of ylides or ylide-like intermediates generated using chiral catalysts

7.4.1 Resolution of enantiomers

Although optical rotation analysis of the products gives some information whether asymmetric induction has been achieved during a reaction, it does not provide very precise data. Enantiomerically pure molecules have widely varying optical rotations, and for some compounds the rotation can be quite small. Also, if the optical rotation of the enantiomerically pure molecule is unknown, a positive or negative value for the optical rotation simply indicates is that there is an excess of one enantiomer over the other in the sample and does not provide any absolute value for the *ee*. A series of samples makes it possible to identify the samples with the highest degree of enantiomeric excess, but again it is not known if the enantiomeric excess is large or small.

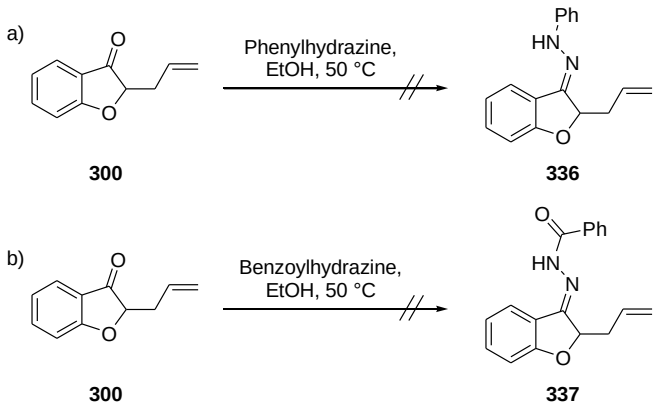
A more precise method to determine the degree of enantiomeric excess is by analysis of the sample using chiral high-performance liquid chromatography (HPLC). Unlike ordinary HPLC it is not just differences in polarity and relative size of the molecules that lead to different interactions with the stationary phase of the column, it is also molecular shape. The stationary phase of a chiral column consists of one enantiomer of a chiral compound, quite often based on cellulose or cyclodextrin. It is differences in the interactions of enantiomers with the stationary phase, often through hydrogen bonding, that leads to the separation of enantiomers.

In order to be able to determine the enantiomeric excesses of the products obtained when a chiral catalyst is used to generate the carbenoid, the separation was first optimised using the racemic material obtained through the decomposition and subsequent rearrangement of diazoketones using achiral catalysts (*cf*. Table 2).

Benzofuranone **302** was easily separated without further modification; but benzofuranone **300** was not.

The enantiomers of benzofuranone **302** were separated by chiral HPLC using a Chiralcel AD column. Using 0.5% *i*-PrOH in hexane as the eluent, with a flow rate of 1.25 mL/min and a temperature of 25 ºC, the retention times of the two enantiomers were 10.2 min and 13.3 min. Benzofuranone **300** however did not separate as easily using this chiral column. Therefore, various derivatisations were explored in order to increase the interaction between **300** and the chiral stationary phase. It was considered that possibly a hydrazone derivative of the benzofuranone would have a greater propensity to hydrogen bond to the stationary phase (Scheme 115). In addition, if this was successful, no additional chiral centres would be formed upon derivatisation and so the sample would not contain a mixture of diastereomers as well as a mixture of enantiomers.

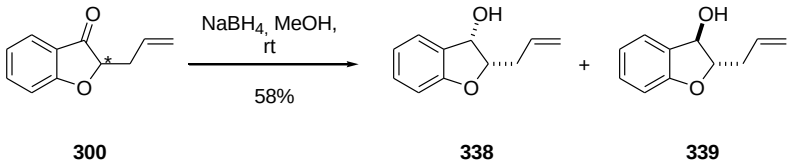
Reacting benzofuranone **300** with phenylhydrazine in ethanol at 50 ºC in a sealed pressure tube led to total decomposition of the starting material rather than formation of the desired hydrazone **336** (Scheme 115a).[236] Exchanging the phenylhydrazine for benzoylhydrazine in an attempt to synthesise **337**, resulted in no reaction (Scheme 115b).



Scheme 115 Attempts to synthesise hydrazones.

At this point, a different approach was taken. Reduction of **300** with $NaBH_4$ resulted in the two diastereomers **338** and **339** (Scheme 116). The hydroxyl group provides greater interaction with the chiral stationary phase than the ketone, and the enantiomers for both diastereomers are separable by chiral HPLC using a Chiralcel OD-H column. Using 0.8% *i*-PrOH in hexane as the eluent, with a flow rate of 1.20 mL/min and a temperature of 25 ºC, the retention times of the two enantiomers of **338** were 22.4 min

and 24.5 min. For the enantiomers of **339**, the retention times were 31.2 min and 37.3 min under the same conditions.



300 **338** **339**

Scheme 116 Reduction of **300**.

Although the two diastereomers were separable using flash column chromatography, it was not a trivial separation and quite often chromatography had to be repeated two or three times. Consequently, HPLC analysis was performed directly on the mixture of diastereomers obtained from the reduction reaction followed by rapid purification by filtering through a short silica plug. NMR analysis of the separated products allowed for the determination of the diastereomers, with the coupling constant of the aligned protons at C2 and C3 being 7.2 Hz for **338** and the coupling constant being 3.3 Hz for the more staggered protons of **339**. In addition, **338** and **339** were obtained in a 2:1 ratio. The major product is expected to be the *syn* diastereomer **338**, formed when the sodium borohydride approaches the ketone **300** from the less hindered face, rather than the *anti* diastereomer **339**, where the sodium borohydride would approach the ketone from the more hindered face. This supported the conclusions from the NMR analysis. Previous HPLC analysis of the separated and isolated diastereomers **338** and **339** allowed retention times of the individual products to be determined and so when the mixture of diastereomers was analysed, it was clear what diastereomer resulted in which peaks of the chromatogram. Although this method of analysis did involve the formation of diastereomers, it proved to be an efficient method for *ee* determination.

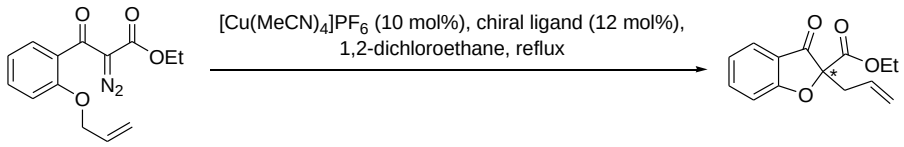
7.4.2 Initial screening of various chiral catalysts

Initial screening was carried out using various chiral catalysts, formed *in situ via* a procedure developed in the Clark group.[185] $[Cu(MeCN)_4]PF_6$ and the chiral ligand were reacted in refluxing CH_2Cl_2 to form the active copper complex, after which the diazoketone was added dropwise. As previously mentioned, a variety of commercially available ligands, as well as ligands synthesised in the lab were tested, as they had

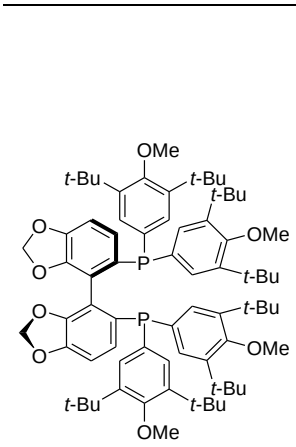
previously given positive results for enantioselective copper-catalysed reactions (*cf*. Chart 1).

Diazoketone **241** was chosen as the substrate for the preliminary screen because the product ß-ketoester benzofuranone **302** was readily resolved by chiral HPLC. The reaction temperature and catalyst concentration had been optimised with achiral catalysts (*cf*. Table 2). The product yields varied considerably, from 9 — 89% (Chart 3). Unfortunately, with regard to the enantioselectivity of the reactions, most of the catalysts simply produced racemic product. In fact, only three ligands gave products with a measurable enantiomeric excess; the Segphos ligand (Chart 3, Entry 4) with 5% *ee*, the pyridine bisoxazoline ligand (Chart 3, Entry 8) with 2% *ee* and the bisoxazoline ligand (Chart 3, Entry 11) with 18% *ee*. It could be argued that 2 and 5% *ee* is within the margin of error for chiral HPLC, but in both cases the product had a clear, albeit very small, optical rotation, which was not the case for any of the products that were assessed to be racemic by chiral HPLC. Interestingly, both of the salen-type ligands that were found to result in asymmetric induction during the reaction with other diazoketone substrates by our research group, here afforded racemic products (Chart 3, Entries 2 and 6).[185]

Chart 3 Initial screening of chiral ligands.

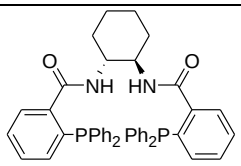


241 **302**



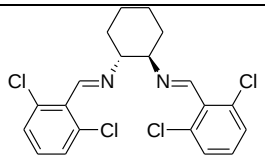
47%
5% *ee*

4



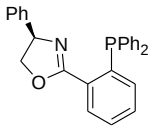
9%
racemic

1



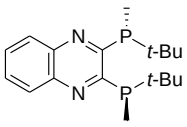
89%
racemic

2



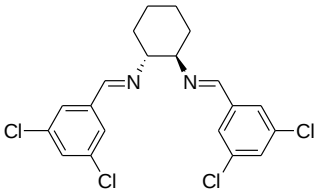
81%
racemic

3



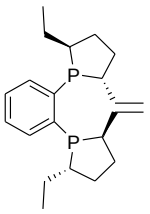
64%
racemic

5



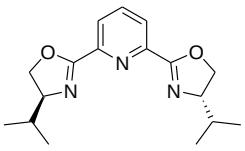
69%
racemic

6



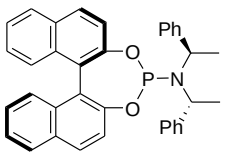
54%
racemic

7



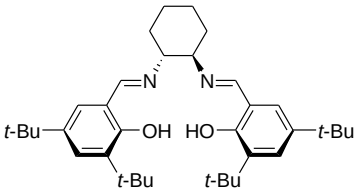
64%
2% *ee*

8



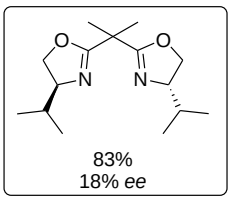
43%
racemic

9



55%
racemic

10



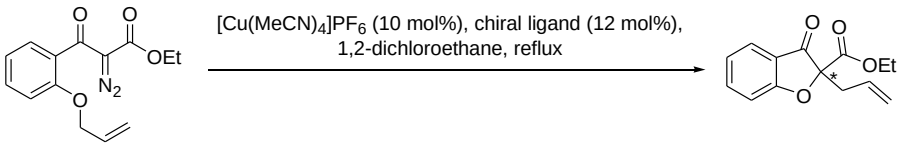
83%
18% *ee*

11

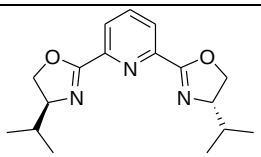
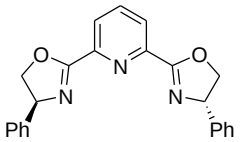
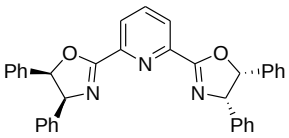
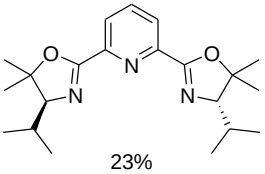
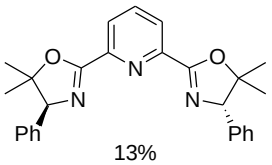
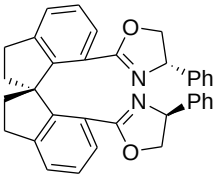
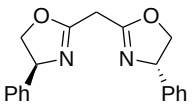
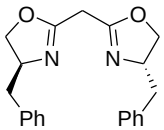
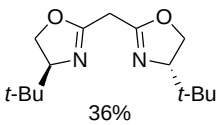
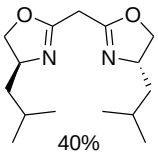
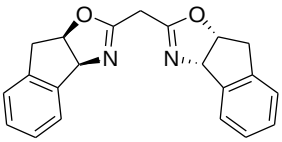
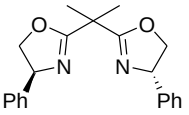
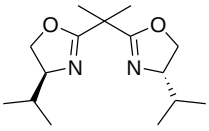
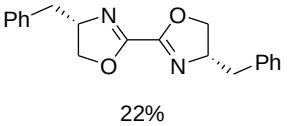
7.4.3 Screening of bisoxazoline ligands

The best result obtained from the initial screening process was that obtained using a copper complex bearing a bisoxazoline ligand and so it was decided to continue screening various ligands of this type (Chart 4). Ligands with various substituents on the oxazoline rings and a variety of bridges were screened.

Chart 4 Screening of various bisoxazoline ligands.



241 **302**

 64% 2% *ee*	 43% racemic	 20% racemic	 23% racemic
1	**2**	**3**	**4**
 13% racemic	 12% racemic	 39% 22% *ee*	 71% 15% *ee*
5	**6**	**7**	**8**
 36% 3% *ee*	 40% 9% *ee*	 64% 22% *ee*	 86% 22% *ee*
9	**10**	**11**	**12**
 83% 18% *ee*	 22% 18% *ee*		
13	**14**		

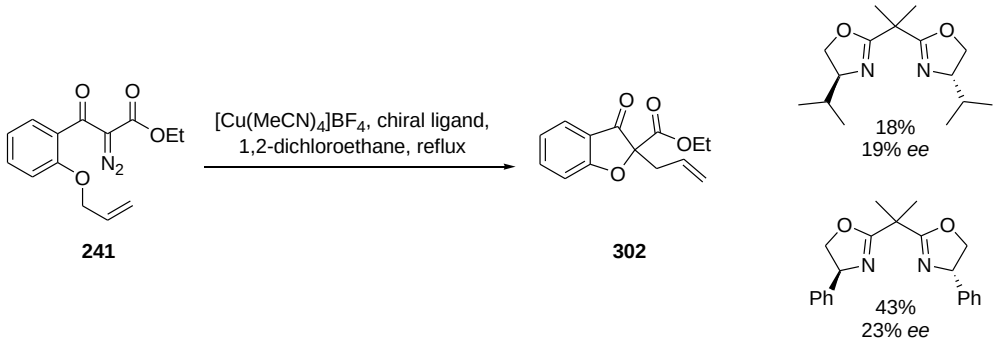
Reactions in which copper complexes bearing pyridine bisoxazoline ligands were used mainly delivered racemic products, as well as low to moderate yields. As previously mentioned, isopropyl substituted pyridine bisoxazoline (Chart 4, Entry 1) resulted in 64% yield and 2% *ee*. More bulky phenyl substituted pyridine bisoxazoline (Chart 4, Entry 2) resulted in a lower yield of 43% and provided a racemic product. Attempts to incorporate substituents — either a large phenyl group or the smaller methyl group — at

the 5-position of the oxazoline also delivered racemic product and low yields of 13-23% (Chart 4, Entries 3-5).

The pyridine bisoxazoline ligands were not providing acceptable results and so different types of bisoxazoline ligands were screened. A chiral spiro-bisoxazoline ligand was tested, in the hope that the more rigid system would result in good enantioselectivity. In addition, this type of ligand has previously proved efficient for asymmetric carbenoid X-H insertion.[237,238,239,191] Unfortunately, not only did this type of ligand result in racemic material, the product yield was very low (Chart 4, Entry 6).

During the initial screen of chiral catalysts, the most encouraging result was obtained using a bisoxazoline ligand with a methylene bridge (Chart 3, Entry 11). Therefore, a screen of methylene bridge bisoxazoline ligands was performed. Groups of various sizes and bulkiness were used as substituents on the oxazoline ring including phenyl- (Chart 4, Entry 7), benzyl- (Chart 4, Entry 8), *tert*-butyl- (Chart 4, Entry 9) and *iso*-butyl-groups (Chart 4, Entry 10). A very bulky and more rigid bisoxazoline ligand was tested and again the product was obtained with an *ee* of 22% (Chart 4, Entry 11). Ligands with methyl-substituted methylene bridges provided excellent yields of 83% and 86% respectively, but the product enantiomeric excesses of 18% and 22% respectively offered no significant improvement over previous results (Chart 4, Entries 12 and 13). Removing the bridge altogether did not improve the enantioselectivity; the low yield was rather disappointing (Chart 4, Entry 14).

In addition to the above results, $[Cu(MeCN)_4]BF_4$ was tested as an alternative copper source (Scheme 117). The same conditions as used previously were then applied. With $[Cu(MeCN)_4]PF_6$ as the copper source and an *iso*-propyl substituted bisoxazoline ligand, the product had been obtained in 83% yield and with 18% *ee* (Chart 3, Entry 11). Although enantioselectivity of 19% *ee* is the same as before within the margin of error, the yield was markedly lower at 18%. With $[Cu(MeCN)_4]PF_6$ and phenyl substituted bisoxazoline the result had been 39% yield and 22% *ee* (Chart 4, Entry 7). In this case, the yield of 43% and the enantioselectivity of 23% *ee* do not offer any significant improvement either (Scheme 117).

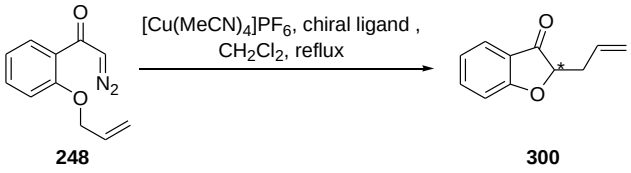


Scheme 117 Reaction of **241** using $[Cu(MeCN)_4]BF_4$ as copper source.

Disappointingly, no enantiomeric excess of greater than 22-23% was obtained when any chiral complexes generated from either $[Cu(MeCN)_4]PF_6$ or $[Cu(MeCN)_4]BF_4$ were used as catalysts. In spite of this, the fact that several different bisoxazoline ligands do deliver products with significant enantiomeric excess suggests that the ligand class has potential for asymmetric generation and [2,3]-rearrangement of oxonium ylides or their metal-bound equivalents.

7.4.4 Asymmetric reactions of **248**

Taking into consideration the initial results, the more successful ligands were tested on the alternative terminal diazoketone substrate **248** (Scheme 118). As mentioned previously, product **300** was reduced by sodium borohydride and HPLC analysis was performed on the resulting diastereomeric mixture of the alcohols **338** and **339** (Scheme 116).

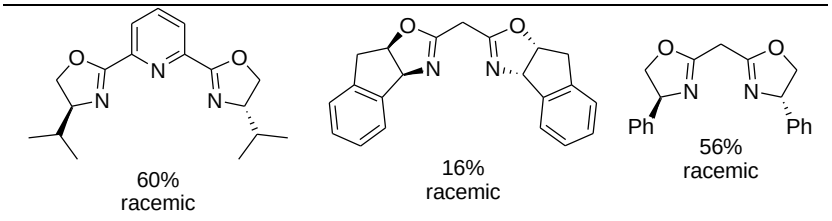


Scheme 118 Rearrangement of **248**.

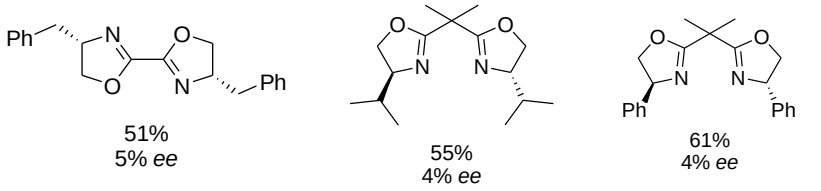
Although pyridine bisoxazoline ligands had previously resulted in significant but low levels of asymmetric induction (*cf*. Chart 3, Entry 8), in this case only racemic product was obtained (Chart 5, Entry 1). Similarly, the methylene-bridged bisoxazoline ligands that previously provided products with enantiomeric excess of 22% (*cf*. Chart 4, Entries

7 and 11) now delivered racemic material (Chart 5, Entries 2 and 3). The complex of the non-bridged bisoxazoline did deliver non-racemic product, although the *ee* was very low (5% *ee*) (Chart 5, Entry 4). Complexes of methyl-substituted methylene-bridged bisoxazoline ligands previously delivered products with enantiomeric excess of 18% and 22% respectively (Chart 4, Entries 12 and 13), both also show markedly lower selectivity and gave **300** with an enantiomeric excess of 5% (Chart 5, Entries 5 and 6). In addition to this, the yields had previously been above 80%, and when **300** was reacted with a copper catalyst we observed a significant decrease in reaction efficiency.

Chart 5 Asymmetric rearrangement of **248**.



1 **2** **3**



4 **5** **6**

7.5 Summary and conclusions

A set of diazoketones has been synthesised in satisfactory yield. Both aromatic and aliphatic diazoketones have been synthesised, with various substituents such as β-keto ester or vinyl. These substrates have been treated with either a copper or rhodium catalyst to provide racemic material arising from generation and rearrangement of an oxonium ylide or metal-bound equivalent.

In addition to this, attempts were made to perform an asymmetric variant of the reaction using various chiral copper complexes as the catalyst. The enantiomeric excess was determined using chiral HPLC analysis, either directly on the rearrangement

product (**302**) or on the diastereomeric mixture of alcohols (**338** and **339**) produced by reduction of the benzofuranone formed (**300**).

Initially, various chiral ligands from different classes were screened; both commercially available ligands and ligands that were synthesised during the course of this project were used. Diazoketone **241** was chosen as a suitable substrate for carrying out preliminary screening. It was found that the catalyst generated from a bisoxazoline ligand delivered low levels of asymmetric induction with the product having 18% enantiomeric excess (Chart 3, Entry 11); the catalyst generated from a pyridine bisoxazoline ligand produced material with very low enantiomeric excess (Chart 3, Entry 8).

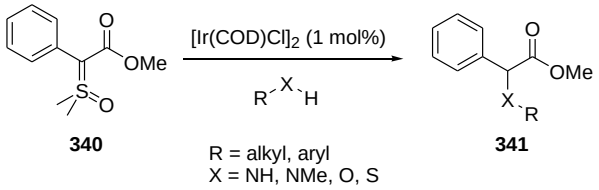
With these promising results in hand, various bisoxazoline ligands were screened. These included ligands with varying bridges. Pyridine-bridged, methylene-bridged or, in one instance, a spiro-bridged ligand were explored. Also ligands with various types of substituents, in both the 4- and the 5-position, were tested. Varying size, bulkiness and rigidity of the substituents were factors that were considered. In several instances, asymmetric induction was obtained and products having 18-23% enantiomeric excess were isolated.

The most promising ligands were tested on the alternative diazoketone susbtrate **248**. Unfortunately, racemic material or that with very low enantioselective excess was obtained, possibly due to problems with racemisation during purification.

Despite the low levels asymmetric induction that were obtained — 18-23% enantiomeric excess for the most efficient catalysts — we were pleased that a new category of chiral ligands with potential for asymmetric [2,3]-rearrangement of oxonium ylides generated from copper carbenoids had been identified.

8 Iridium-Catalysed Rearrangement

In 2009, Mangion *et al*. published a paper regarding X-H insertion of sulfoxonium ylides (Scheme 119).[240] In the example shown below, a ß-carbonyl sulfoxonium ylide compound **340** was reacted with $[Ir(COD)Cl]_2$ to form an iridium carbenoid, which then underwent an X-H insertion reaction with amines, alcohols or thiophenols. In their publication, Mangion *et al*. used the sulfoxonium ylide as a more stable precursor for the formation of iridium carbenoids as compared to diazocarbonyls. We anticipated that if iridium carbenoids could be formed from sulfoxonium ylides, it was likely that they could also be generated from diazoketones under similar conditions and then participate in subsequent oxonium ylide formation.



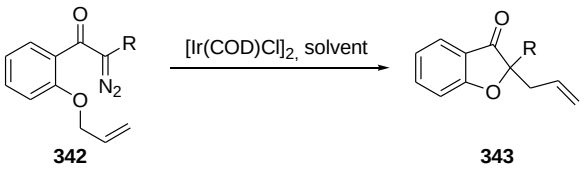
Scheme 119 X-H insertion of sulfoxonium ylides.

One of the advantages of using iridium catalysts for this transformation is that low catalyst loadings are generally required, such as the case shown in Scheme 119, where the catalyst loading is only 1 mol%. As chiral ligands often are expensive, and more unusual structures are difficult to prepare, low catalyst loading is an advantage in any catalytic reaction but in particular for enantioselective catalysis.

In 2007, Katsuki *et al*. reported the use of an iridium(III)-salen complex in asymmetric cyclopropanation, obtaining both high stereo- and enantioselectivity.[241] Here, iridium

carbenoids were formed by reacting diazoketones with the iridium catalyst. The report of asymmetric cyclopropanation was later followed by reports of asymmetric C-H insertion as well as enantioselective Si-H insertion.[242,56] However, to date there does not appear to be any publications concerning the generation and rearrangement of ylides or ylide-like intermediates from iridium carbenoids.

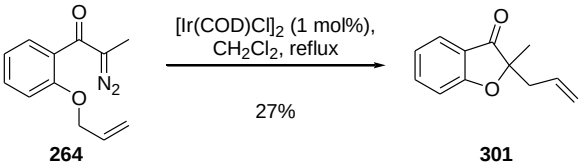
The transformation shown in Scheme 119 bears some similarity to the reactions of interest in this project. Consequently, we attempted to carry out the decomposition and rearrangement of diazoketones using $[Ir(COD)Cl]_2$ as catalyst, as shown in Scheme 120.



342 **343**

Scheme 120 Rearrangement using $[Ir(COD)Cl]_2$.

Our initial attempt to react the methyl-substituted diazoketone **264** with $[Ir(COD)Cl]_2$ in refluxing CH_2Cl_2 did result in the formation of the corresponding benzofuranone **301** in 27% yield (Scheme 121, Table 4, Entry 1). To the best of our knowledge, this was the first example of the generation of an iridium carbenoid from a diazoketone with subsequent generation and rearrangement of an oxonium ylide or ylide-like intermediate.



264 **301**

Scheme 121 The first successful ylide generation and [2,3]-rearrangement using $[Ir(COD)Cl]_2$.

Attempts to optimise this reaction were performed by varying the solvent and reaction temperature (Table 4, Entries 1 – 5). Performing the same reaction in CH_2Cl_2 at room temperature resulted in a very low yield (8%) (Table 4, Entry 2) The best yield (49%) was obtained when the reaction was performed in benzene at room temperature (Table 4,

Entry 3). In this case, raising the reaction temperature to reflux resulted in a reduced yield (Table 4, Entry 4). Performing the reaction in THF at room temperature also resulted in a very low yield (Table 4, Entry 5). A possible explanation for the relatively modest yields is that, unlike the reactions catalysed by copper complexes, the iridium-catalysed reactions are not as selective for ylide generation. In fact, a complex reaction mixture was obtained in many cases. It is also possible that the methyl-substituted diazoketone **264** underwent ß-hydride elimination to provide a reduced derivative that could not undergo the rearrangement reaction. To explore this possibility, the reaction was also tested using the α-diazo ß-keto ester **241**, as ß-hydride elimination would not be possible in this case (Table 4, Entries 6 — 13). With this substrate, however, the yields were also modest. When the reaction was performed in CH_2Cl_2 at room temperature a very low yield (6%) of the expected product was obtained (Table 4, Entry 6). The reaction was then performed in various solvents and the reaction temperature was varied. In benzene at room temperature reaction did not take place, but on increasing the temperature to 40 ºC a yield of 11% was obtained (Table 4, Entry 7). Raising the reaction temperature to 60 ºC increased the yield to 18% (Table 4, Entry 8). When the reaction was performed in toluene at room temperature no reaction took place, but by increasing the reaction temperature to 40 ºC a very low yield (4%) could be obtained (Table 4, Entry 9). A further improvement in the yield to 21% was achieved by increasing the reaction temperature to reflux (Table 4, Entry 10). In 1,2-DCE at 60 ºC a very low yield (7%) was obtained (Table 4, Entry 11). However, when the reaction was performed at reflux temperature, a yield of 39% was obtained, which transpired to be the highest yield achieved for this substrate. (Table 4, Entry 12). Unfortunately, increasing the catalyst loading to 5 mol% resulted in no improvement in the chemical yield (Table 4, Entry 13). However, this result does demonstrate that only a very low catalyst loading is required. The terminal diazoketone **248** was also tested under the same conditions that resulted in the best yields with $Cu(acac)_2$ as the catalyst. However, only a 9% yield was obtained (Table 4, Entry 14). Vinyl diazoketone **243** was also reacted in refluxing 1,2-DCE, but despite full consumption of the starting material, the expected product was not obtained (Table 4, Entry 15). This result is most likely due to the substrate structure rather than difficulties with the catalyst, because only traces of product had been observed when this substrate was subjected to both copper- or rhodium-catalysed reactions.

Table 4 Optimisation of reactions using $[Ir(COD)Cl]_2$ as the catalyst.

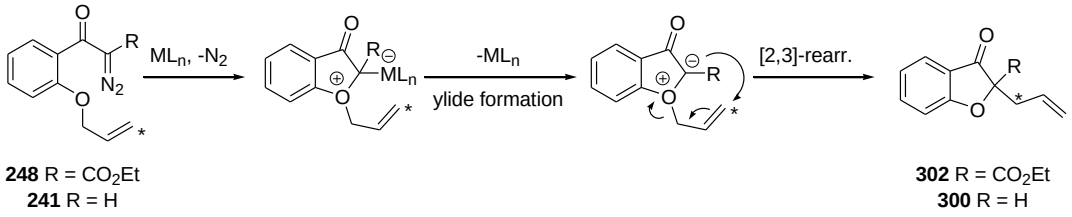
Entry	Diazoketone	R	Solvent	Temperature	[cat.]	Yield
1	**264**	Me	CH_2Cl_2	reflux	1 mol%	27%
2	**264**	Me	CH_2Cl_2	rt	1 mol%	8%
3	**264**	Me	benzene	rt	1 mol%	49%
4	**264**	Me	benzene	reflux	1 mol%	11%
5	**264**	Me	THF	rt	1 mol%	5%
6	**241**	CO_2Et	CH_2Cl_2	rt	1 mol%	6%
7	**241**	CO_2Et	benzene	rt — 40 °C	1 mol%	11%
8	**241**	CO_2Et	benzene	60 °C	1 mol%	18%
9	**241**	CO_2Et	toluene	rt — 40 °C	1 mol%	4%
10	**241**	CO_2Et	toluene	reflux	1 mol%	21%
11	**241**	CO_2Et	1,2-DCE	60 °C	1 mol%	7%
12	**241**	CO_2Et	1,2-DCE	reflux	1 mol%	39%
13	**241**	CO_2Et	1,2-DCE	reflux	5 mol%	36%
14	**248**	H	CH_2Cl_2	reflux	1 mol%	9%
15	**243**	vinyl	1,2-DCE	reflux	1 mol%	0%

Unlike the tandem ylide forming and rearrangement reactions performed with copper catalysts, the iridium-catalysed reaction gave very complex mixtures of products in all cases. Until this point, the project had focussed on the use of copper catalysts due to their selectivity with regard to ylide generation, and it was considered that both the selectivity and the yields were too low to devote more attention to iridium-catalysed reactions. Following further successes regarding the use of copper catalysts for this transformation, it was decided to not explore the optimisation of the iridium-catalysed reactions any further.

In spite of the modest yields for the reaction performed with $[Ir(COD)Cl]_2$, we were pleased to discover that this complex can be utilised for formation of iridium carbenoids from diazoketones, with subsequent generation and rearrangement of oxonium ylides or ylide-like intermediates.

9 Mechanistic Study

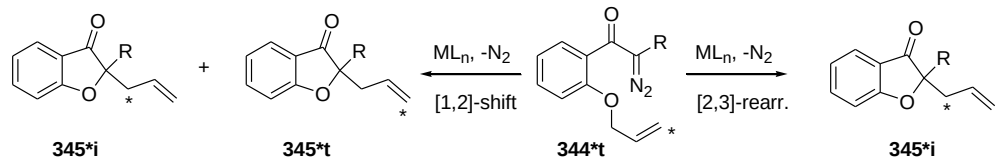
As mentioned previously, the conventional view of the reaction is that it proceeds by formation of an allylic oxonium ylide that undergoes [2,3]-sigmatropic rearrangement.[120,121] The proposed mechanism for the ylide formation and rearrangement sequence is presented in Scheme 122. Here, it is clearly shown that the terminal carbon in the allyl group will shift to an internal position during the rearrangement reaction, as shown in the benzofuranone product. This has been established through the rearrangement of substituted allylic oxonium ylides, where analysis of the structure of the rearrangement product, or products, indicates the mechanism involved. To investigate this process further in a sterically unbiased system, we propose to use an isotopically labelled starting substrate. The outcome of these reactions would provide solid mechanistic information, because in this case no other factors, such as steric or electronic factors, would interfere with the rearrangement reaction as might be the case when there are substituents on the allyl group.



Scheme 122 Mechanism of the [2,3]-sigmatropic rearrangement of oxonium ylides.

Conventional [2,3]-sigmatopic rearrangement of a labelled ylide **344*t**, labeled in the allylic terminal position, would result in a product labelled such as **345*i**, labelled in the allylic internal position. If the reaction did not proceed by a formal [2,3]-rearrangement of an oxonium ylide, we considered it likely that there might be evidence of a product that is labelled in the terminal position of the allyl group, such as

product **345*t**, as shown in Scheme 123. This product would be obtained if the reaction proceeds through a [1,2]-shift of the oxonium ylide. If [1,2]-shift occurs during the reaction, the ratio of [1,2]- and [2,3]-rearrangement products should be independent of the catalyst, as both products are generated from a common single oxonium ylide, the structure of which is independent of the catalyst used to generate the original carbenoid.



345*i **345*t** **344*t** **345*i**

Scheme 123 Possible products from formal rearrangement of allylic oxonium ylides.

If the reaction does not proceed by rearrangement of a free oxonium ylide, but instead involves a metal-bound ylide equivalent, scrambling of the labelled allyl group might also occur. This ratio of labelled products would in this scenario most likely be dependent on the catalyst used to generate the carbenoid.

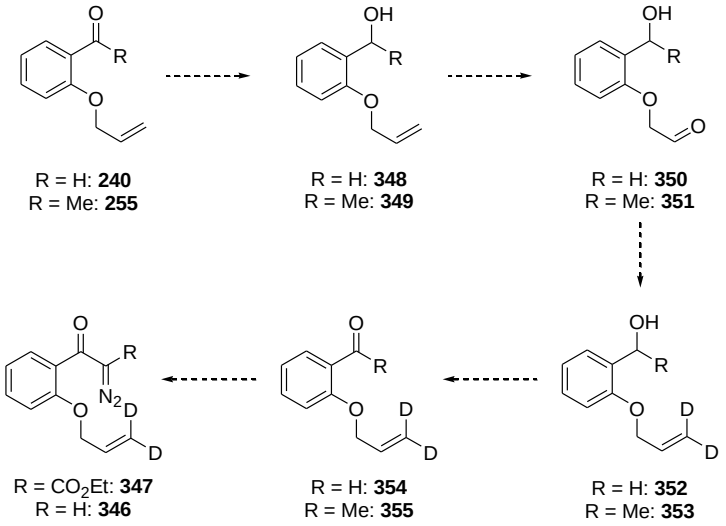
9.1 Synthesis of isotopically labelled substrates

9.1.1 Deuterated substrates

For the purposes of our mechanistic study, deuterated substrates were considered suitable. As only protons appear in ^{1}H-NMR spectra and not deuterium atoms, integration of the ^{1}H-NMR spectrum for the product should clearly show which product, or products, have been obtained, as well as the ratio between the two, if a mixture of [2,3]-rearrangement and [1,2]-shift products is produced.

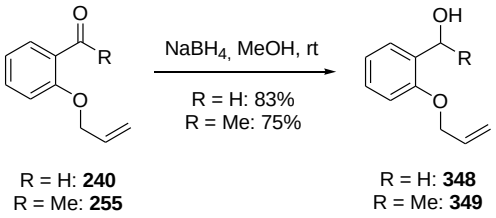
The first route for the synthesis of the deuterated diazoketones **346** and **347** is shown below (Scheme 124). The sequence begins with the reduction of carbonyl compounds **240** and **255** to provide the alcohols **348** and **349**. Subsequent oxidative cleavage of the allyloxy group results in aldehydes **350** and **351**, which, after a Wittig reaction with

CD_2PPh_3, was expected to result in formation of the deuterated alcohols **352** and **353**. Further oxidation would provide the ketones **354** and **355**, from which diazoketones **346** and **347** could be obtained through either diazo transfer or a one-pot aldol-type reaction with ethyl diazoacetate.



Scheme 124 First route for the synthesis of diazoketones **346** and **347**.

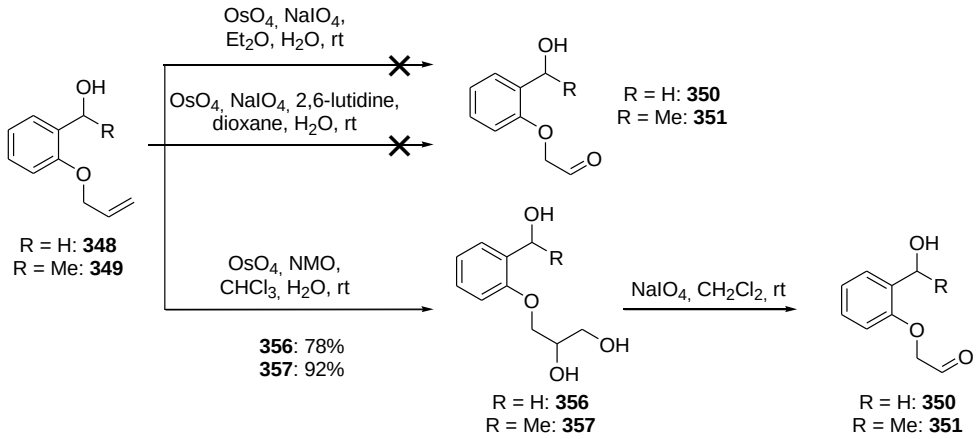
As shown in Scheme 125, reduction of the corresponding carbonyl compounds using $NaBH_4$ resulted in alcohol **348** in 83% yield and alcohol **349** in 75% yield.[243]



Scheme 125 Reduction of carbonyl compounds **240** and **255**.

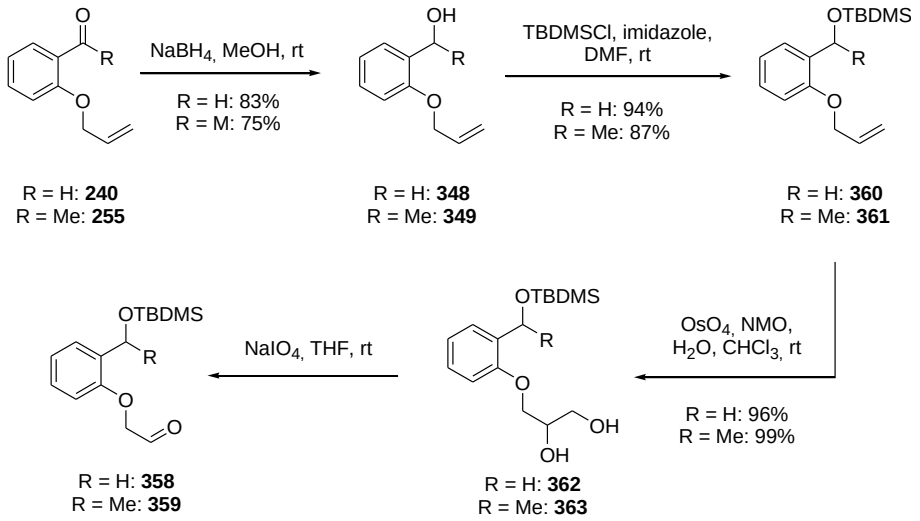
Aldehyde formation by dihydroxylation using osmium tetroxide with subsequent oxidative cleavage of the resulting 1,2-diol using sodium *meta*-periodate was explored initially (Scheme 126). A one-pot procedure using osmium tetroxide and sodium *meta*-periodate with substrate **348** or **349** was carried out, as described by Arndt and Carroll but the required product was not obtained.[244] Therefore, a modified procedure using osmium tetroxide, sodium *meta*-periodate and 2,6-lutidine, as described by Jin *et al.* was investigated but once again the desired product was not obtained.[245] Rather than

attempting to prepare the aldehyde using a one-pot procedure, the next approach was to perform the reaction in two steps, as described by Billault *et al*.[246] Dihydroxylation of **348** and **349** using osmium tetroxide and *N*-methyl morpholine oxide (NMO) resulted in formation of the triols **356** in a satisfying 78% yield and **357** in an excellent 92% yield. Cleavage of the triols with sodium *meta*-periodate resulted in the formation of aldehydes **350** and **351**. Due to their sensitivity, the aldehydes **350** and **351** were not isolated.



Scheme 126 Aldehyde formation.

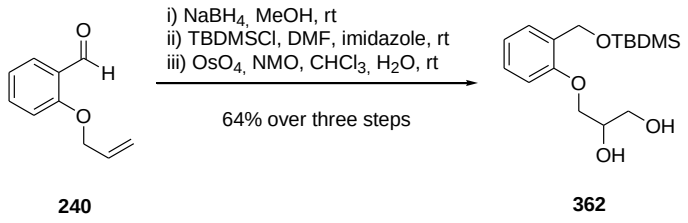
At this point, it was considered that the subsequent Wittig reaction was likely to proceed more smoothly if the free hydroxyl groups in compounds **356** and **357** were protected as a silyl ether. A *t*-butyl-dimethyl silyl (TBDMS) protecting group was chosen, which could be removed easily after the Wittig reaction. Using this alternative strategy, the route for synthesising aldehydes was amended (Scheme 127).



Scheme 127 Amended route for the synthesis of aldehydes **358** and **359**.

As before, alcohols **348** and **349** were obtained by reduction of **240** and **255** with sodium borohydride. The resulting alcohols were subsequently protected using TBDMSCl and imidazole in DMF,[247] which afforded silyl ether **360** in 94% yield and silyl ether **361** in 87% yield. Dihydroxylation of **360** and **361** with osmium tetroxide and NMO in chloroform and water afforded diols **362** and **363** in 94% and 99% yield respectively. Cleavage of the diols using sodium *meta*-periodate in THF resulted in the formation of aldehydes **358** and **359** (Scheme 127). Due to the sensitive nature of the aldehydes, the crude products were used without further purification as shown in Scheme 129.

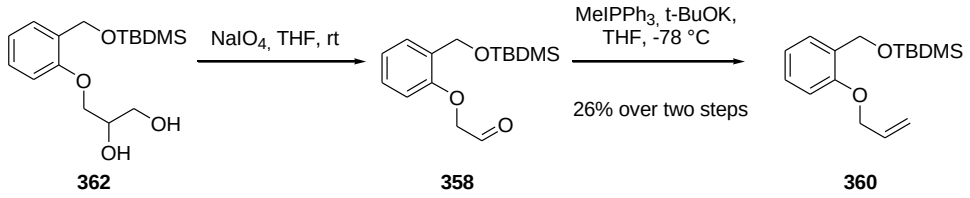
Diol **362** could also be obtained from aldehyde **240** *via* a three-step sequence, without purification of the intermediates; the yield over three steps was 64% (Scheme 128). However, the combined yield of the three steps when the intermediates were isolated was 75%.



Scheme 128 Diol formation in three steps.

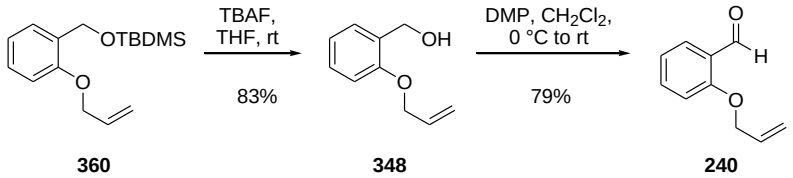
With the desired aldehyde in hand, the Wittig reaction was first attempted using the phosphonium ylide generated from the reaction of $MePPh_3I$ with *t*-BuOK in THF at

−78 °C. The resulting silyl ether **360** was obtained in 26% yield over two steps from diol **362** (Scheme 129). The reaction was also performed at 0 °C, but in this case the product was not obtained even though all of the starting material was consumed.



Scheme 129 Wittig reaction with $MePPh_3I$.

Deprotection of the hydroxyl group with TBAF in THF afforded the alcohol **348** in an 83% yield (Scheme 130).[248] Subsequent oxidation of **348** using Dess-Martin periodinane produced the aldehyde **240** in 79% yield.[249]



Scheme 130 Deprotection and oxidation of **360**.

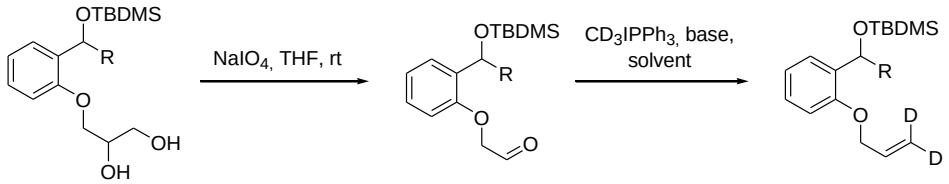
It was anticipated that applying these conditions to diol **363** would not be problematic, as substrate **240** is the most sensitive system. Later, this assumption was proved correct when in the same manner, silyl ether **367** was carried through the two-step procedure, providing ketone **369** (Scheme 131).

These two compounds had been used as starting materials for the synthesis of either a terminal diazoketone, through diazo transfer, or an α-diazo ß-keto ester, through a one-pot aldol-type reaction followed by oxidation (see Chapters 7.1.1.1 and 7.1.1.3). Unfortunately, when this procedure was adapted for the synthesis of deuterated derivatives, problems with proton-transfer during the Wittig reaction occurred resulting in substrates with a significant level of ^{1}H-atom incorporation rather than exclusive ^{2}H-atom incorporation at the terminus of the alkene. In order to obtain reliable data from the decomposition and rearrangement of ^{2}H-labelled diazoketones, it would be necessary to have less than 1% of ^{1}H-atoms in the ^{2}H-labelled position of the diazoketone substrate because this is roughly the limit of the NMR sensitivity. If there is

a significant amount of ^{1}H-substrate present, problems will occur with the ^{1}H-NMR analysis because integration will not be reliable due to overlapping of peaks generated from the ^{1}H-product and from the two ^{2}H-products.

During the Wittig reaction of D_2CPPh_3 with aldehydes **358** and **359**, not only did the yield of the reaction vary considerably, but also a large amount of proton transfer was occurring. At first, the Wittig reaction was attempted using *t*-BuOK as the base. At 0 °C, yields of 0-10% over two steps were obtained, with 85% of ^{1}H-product being obtained (Table 5, Entry 1). Lowering the temperature to −78 °C increased the yield, up to 58% and 57% for both substrates (Table 5, Entries 2 and 3). However, the amount of product having ^{1}H-atoms rather than ^{2}H-atoms at the terminus of the alkene was between 60% and 85%. The base *t*-BuOK is hygroscopic and it was thought that the results could be due to water absorbed by the base, so alternative bases were screened. Using sodium hydride at room temperature led to decomposition of the starting material (Table 5, Entry 4). Lowering the reaction temperature to 0 °C also resulted in decomposition of the starting material (Table 5, Entry 5). Using NaHMDS at 0 °C to generate the ylide resulted in a yield of 30% over two steps, but with 42% of ^{1}H-product (Table 5, Entry 6). Using *n*-BuLi at −78 °C only resulted in the formation of traces of product (Table 5, Entry 7). Increasing the reaction temperature to 0 °C resulted in an improved yield, but with 13% of the ^{1}H-product present (Table 5, Entry 8). At room temperature, yields were less than 37%, and between 22% and 42% of the ^{1}H-product was present in the mixture (Table 5, Entries 9 and 10).

Table 5 Wittig reaction with D_2CPPh_3.



R = H: **362**
R = Me: **363**

R = H: **358**
R = Me: **359**

R = H: **364**
R = Me: **365**

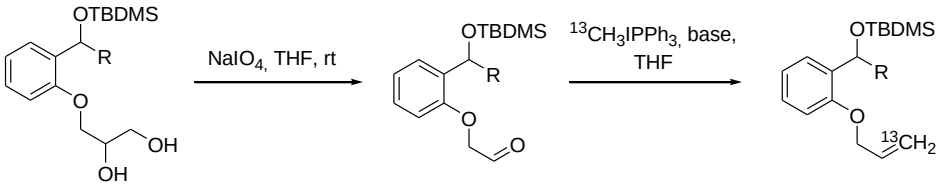
Entry	R	Base	Temperature	Yield	% with ^1H
1	Me	*t*-BuOK	0 °C	0-10% over two steps	85%
2	Me	*t*-BuOK	−78 °C	22-58% over two steps	52-65%
3	H	*t*-BuOK	−78 °C	57% over two steps	75%
4	Me	NaH	rt	decomposition	n/a
5	Me	NaH	0 °C	decomposition	n/a
6	H	NaHMDS	0 °C	30% over two steps	42%
7	Me	*n*-BuLi	−78 °C	traces	n/a
8	Me	*n*-BuLi	0 °C	0-54% over two steps	13%
9	H	*n*-BuLi	rt	17% over two steps	42%
10	Me	*n*-BuLi	rt	0-37% over two steps	22%

Unfortunately, it was not possible to obtain a deuterated substrate with less than 1 % of the ^1H-derivative present. If these substrates had been used, the margin of error during NMR analyses would be too great to provide reliable results and so a different approach was required. As the problem of obtaining high-quality labelled substrate was most likely due to proton transfer during the Wittig reaction, it was believed that labelling the same site in each substrate with a ^{13}C-atom rather than ^2H-atoms would provide the same information about the rearrangement products and proton transfer during the Wittig reaction would not affect the quality of the labelled materials.

9.1.2 ^{13}C-Labelled substrates

Provided the Wittig reaction was performed with $^{13}CH_2PPh_3$ rather than D_2CPPh_3, the route described above would deliver the ^{13}C-labelled diazoketones. Therefore, the synthesis commenced with the formation of aldehydes **358** and **359** followed by a Wittig reaction (Table 6). Using $^{13}CH_3PPh_3I$, the Wittig reaction proved capricious. Both *n*-BuLi and *t*-BuOK were tested as bases at varying temperatures, but chemical yields were less than 37%. While the yields were rather low, the reaction did provide enough pure material to continue the synthesis of ^{13}C-labelled diazoketones **372*t** and **373*t**.

Table 6 Wittig reaction with $^{13}CH_2PPh_3$.



R = H: **362**
R = Me: **363**

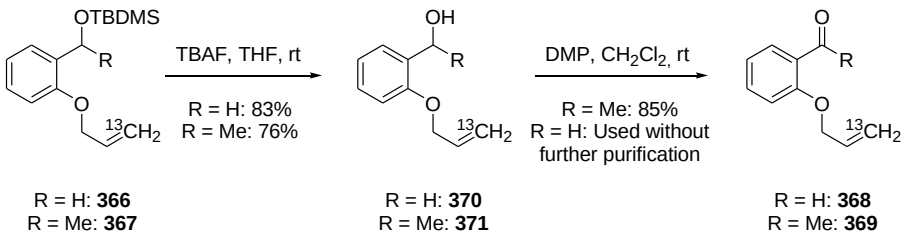
R = H: **358**
R = Me: **359**

R = H: **366**
R = Me: **367**

Entry	R	Base	Temperature	Yield
1	H	*n*-BuLi	rt	37% over two steps
2	Me	*n*-BuLi	rt	13% over two steps
3	Me	*n*-BuLi	rt	21% over two steps
4	Me	*t*-BuOK	−78 °C to rt	28% over two steps
5	H	*t*-BuOK	−78 °C to rt	26% over two steps
6	Me	*t*-BuOK	−78 °C to rt	No product
7	H	*t*-BuOK	−78 °C to rt	26% over two steps

With the isotopic label in place, the syntheses of carbonyl compounds **368** and **369** were completed in two steps (Scheme 131). First, deprotection of silyl ethers **366** and **367** with TBAF resulted in the corresponding alcohols **370** and **371** in yields of 83% and 76% respectively. Subsequent Dess-Martin oxidation of the alcohols provided both desired carbonyl compounds in reasonable yield. Ketone **369** was obtained in 85% yield and aldehyde **368** was obtained through a clean reaction resulting in full conversion. The presence of the aldehyde group was confirmed by ^{1}H-NMR analysis. However, due to

its sensitivity, the aldehyde **368** was used directly in the next step without further purification.



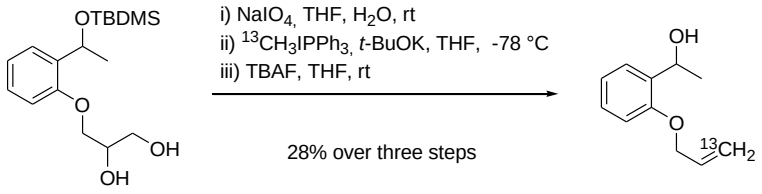
R = H: **366**
R = Me: **367**

R = H: **370**
R = Me: **371**

R = H: **368**
R = Me: **369**

Scheme 131 Synthesis of carbonyls **368** and **369**.

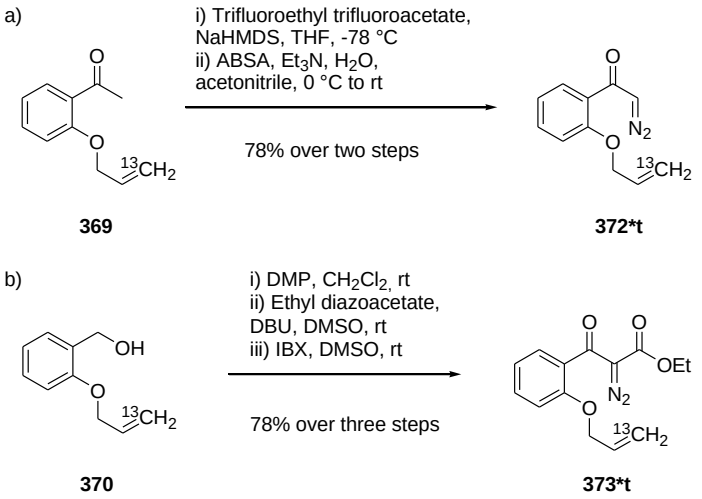
In an attempt to optimise this synthetic sequence, aldehyde formation, Wittig reaction and deprotection was performed without purification at each stage (Scheme 132). It was thought that the low yields obtained from the Wittig reaction were due to purification problems. However, a yield of 28% over three steps was obtained when the purification of intermediates was avoided, demonstrating that losses upon this was not a significant problem.



363 **371**

Scheme 132 Synthesis of **371** in three steps.

The final steps necessary to synthesise diazoketones **372*t** and **373*t** had previously been performed using the non-labelled substrates (Scheme 77, Scheme 83). From ketone **369** the terminal diazoketone **372*t** was synthesised in 78% yield over two steps (Scheme 133a). The ß-keto ester diazoketone **373*t** was synthesised from alcohol **370** in 78% yield over three steps (Scheme 133b).



Scheme 133 Synthesis of diazoketones **372*t** and **373*t**.

9.2 Rearrangement study

During the synthesis of the ^{13}C-labelled diazoketones it became apparent that not only did ^{13}C-NMR analysis provide information about the rearrangement products; in fact, both ^{1}H- and ^{13}C-NMR spectra of the ^{13}C-labelled substrates had distinct differences compared to the NMR spectra of the non-labelled derivatives. In the ^{1}H-NMR spectra, additional splitting was generally obtained if the protons were within coupling range of the ^{13}C-carbon. The ^{1}H-^{13}C ^{1}J-coupling constant were in some instances very large, in the range of 100-150 Hz. In fact, the two protons at the sp^3-hybridised carbon in the allyl group of the benzofuranone rearrangement products produced two different multiplets depending on whether the sp^3-carbon was a ^{12}C-carbon or a ^{13}C-carbon. The multiplets in the part of the ^{1}H-NMR spectra corresponding to the two protons, that are bonded to the sp^3-carbon of the allyl group are shown in Figure 7. First the non-labelled product is shown (Figure 7a), followed by the product with 100% of the ^{13}C-atoms in the internal position of the allyl group (Figure 7b) and finally, a 53:47 mixture of products with ^{13}C-labels in the internal and terminal position of the allyl group is shown (Figure 7c). That the couplings in Figure 7a appear different to those in Figure 7c is due to small splitting resulting from ^{1}H-^{13}C ^{3}J-coupling in the product labelled at the terminal position. In Figure 7c, complete baseline separation of the two multiplets shown in Figure 7a and Figure 7b is obtained, and so it is possible to quantify the ratio of the rearrangement products through integration of both ^{1}H-NMR and ^{13}C-NMR spectra. During this investigation, it became apparent that there was a good correlation between

the integration of the ^{1}H-spectrum and the integration of the ^{13}C-spectrum even though integration of ^{13}C-NMR spectra is generally considered to have a greater margin of error.

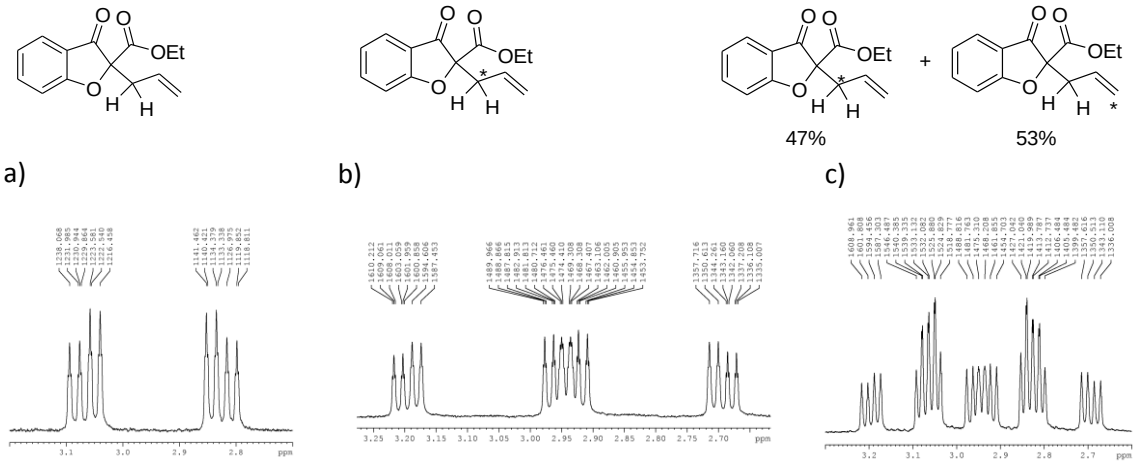
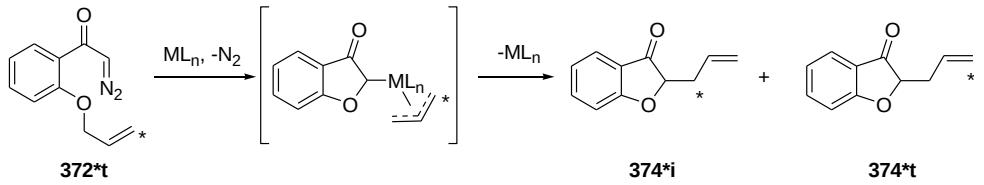


Figure 7 Benzofuranone **302** with (a) 100% ^{12}C-carbons, (b) 100% ^{13}C-carbons in the allylic internal position and (c) a 47:53 mixture of products labelled with ^{13}C in the allylic internal and terminal positions.

Following preparation of the labelled diazoketones, the rearrangement study with ^{13}C-labelled substrates commenced. The rearrangement reactions of the labelled substrates were performed in the same manner as previously: the diazoketone was slowly added to a solution of catalyst at reflux. Rearrangement of terminal diazoketone **372*t** can result in either the rearrangement product **374*i**, labelled in the allylic internal position, or the product **374*t**, labelled in the allylic terminal position. Assuming that products are obtained from the free oxonium ylides, benzofuranone **374*i** can be obtained either through a [2,3]-rearrangement or an apparent [1,2]-shift reaction, benzofuranone **374*t** only through an apparent [1,2]-shift. It is possible that if some **374*i** is obtained through a [1,2]-shift, more or less equal amounts of **374*t** should be obtained due to the delocalised status of the allyl group. However, if the reaction involves the metal-bound ylide equivalent as an intermediate, by-passing the oxonium ylide intermediate altogether, scrambling can also occur. An example of this is shown in Scheme 134.



Scheme 134 Example of scrambling during the reaction involving the metal-bound ylide equivalent.

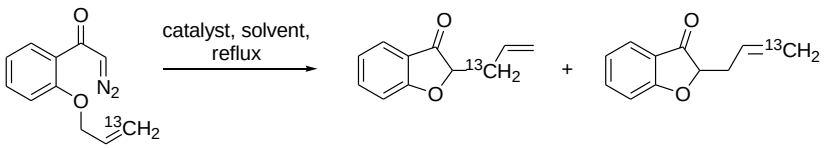
The rearrangement of **372*t** using $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 resulted in a 26% yield of product **374*i**. The product **374*t** was not produced during the reaction (Table 7, Entry 1) according to ^{1}H-NMR analysis, and only trace amounts according to ^{13}C-NMR analysis. It was considered that the catalyst ligands might affect the reaction, so ligands with varying electron density, such as trifluoroacetate and triphenylacetate, were tested and the reactions were performed in refluxing CH_2Cl_2. Employing $Rh_2(tfa)_4$ (Table 7, Entry 2) as a catalyst, a yield of 62% was obtained. Again only trace amounts of **374*t** were obtained, according to both ^{1}H- and ^{13}C-NMR analysis. The use of $Rh_2(tpa)_4$ as the catalyst did result in small amounts of **374*t**, with a ratio of 95:5 of **374*i**:**374*t** with regard to ^{1}H-NMR analysis and 97:3 with regard to ^{13}C-NMR analysis (Table 7, Entry 3).

Copper complexes were investigated as catalysts next. Rearrangement reactions with both $Cu(acac)_2$ and $Cu(hfacac)_2$ resulted in the formation of trace amounts of **374*t** (Table 7, Entries 4 and 5). According to ^{1}H-NMR analysis, the ratios **374*i**:**374*t** are 96:4 and 98:2 respectively, and with regard to ^{13}C-NMR analysis the ratios are 98:2 and 98.5:1.5 respectively. The yields of 14% and 48% respectively are surprisingly low. In order to increase the reaction temperature, the rearrangement reaction was performed with $Cu(hfacac)_2$ in 1,2-DCE at reflux. Again, only a small amount of the product **374*t** was obtained, with the same product ratios as when the reaction was performed in refluxing CH_2Cl_2, but the overall yield of 77% was much improved (Table 7, Entry 6). The fact that the ratios of **374*i** and **374*t** are the same whether the reaction is performed in refluxing CH_2Cl_2 or refluxing 1,2-DCE suggests that the reaction pathway is not temperature dependent, or at least not very strongly temperature dependent. In order to test a different type of copper complex, $[Cu(MeCN)_4]PF_6$ was employed as the catalyst. Unfortunately, the reaction with $[Cu(MeCN)_4]PF_6$ produced only small amounts of benzofuranone products and insufficient quantities were obtained to establish which type of reaction had taken place (Table 7, Entry 7). At this stage, results were consistent with the formal [2,3]-sigmatropic rearrangement of oxonium ylides generated from either rhodium or copper carbenoids. Trace amounts of the terminally labelled

product **374*t** had been observed, but not in significant amounts. It was not possible to make any firm conclusions as to whether the reaction had proceeded through an oxonium ylide, or stereoselectively through a metal-bound ylide intermediate.

The results from the rhodium- and copper-catalysed reactions of the diazoketone **372*t** prompted us to investigate whether the same results would be obtained when complexes of other transition metals are employed as catalysts. In order to test a metal other than either rhodium or copper, ylide formation and rearrangement with $[Ir(COD)Cl]_2$ was performed, again in refluxing CH_2Cl_2. This rearrangement resulted in a drastically different product ratio (Table 7, Entry 8). Here, a 52:48 ratio of **374*i** and **374*t** was obtained according to ^{13}C-NMR analysis, suggesting that the reaction to form the benzofuranone product proceeds almost exclusively through an alternative mechanism. Although all starting material was consumed during the reaction, very low yields of the product were obtained and so NMR analysis was performed using the crude product. Nevertheless, the ^{1}H-NMR analysis also suggested an almost 1:1 ratio of the two products. Clearly it is very important what sort of metal carbenoid is used to generate the oxonium ylide or ylide-like intermediate.

Table 7 Rearrangement of **372*t**.



372*t **374*i** **374*t**

Entry	Catalyst	Solvent	Yield	**374*i**:**374*t** (^{1}H)	**374*i**:**374*t** (^{13}C)
1	$Rh_2(OAc)_4$	CH_2Cl_2	26%	100:0	98:2
2	$Rh_2(tfa)_4$	CH_2Cl_2	62%	99:1	98:2
3	$Rh_2(tpa)_4$	CH_2Cl_2	25%	95:5	97:3
4	$Cu(acac)_2$	CH_2Cl_2	14%	96:4	98:2
5	$Cu(hfacac)_2$	CH_2Cl_2	48%	98:2	98.5:1.5
6	$Cu(hfacac)_2$	1,2-DCE	77%	98:2	98.5:1.5
7	$[Cu(MeCN)_4]PF_6$	CH_2Cl_2	traces	n/a	n/a
8[a]	$[Ir(COD)Cl]_2$	CH_2Cl_2	traces	n/a	52:48

[a]Due to low yield, the analysis was performed on the crude product.

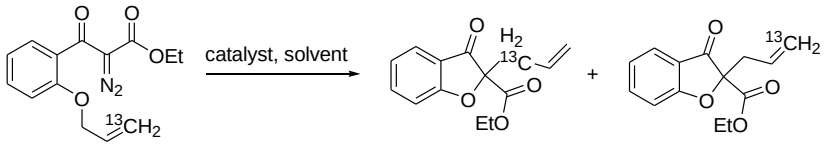
At this stage it seemed possible that the stability of the putative oxonium ylide might affect the ratio of the two products. Therefore, the alternative diazoketone **373*t** was used in order to generate more delocalised oxonium ylide (Table 8). Due to the increased stability of the diazo group (caused by the presence of the pendant ester group), the reaction was performed at higher temperature as carbenoid formation does not take place at reflux in dichloromethane.

The reaction performed using $Rh_2(OAc)_4$ as the catalyst in refluxing 1,2-DCE (Table 8, Entry 1) resulted in a very good 76% yield. The terminally labelled product **375*t** was not observed using ^{1}H-NMR analysis and a 98:2 ratio of **375*i** and **375*t** was obtained according to ^{13}C-NMR analysis. Reactions performed using the two contrasting rhodium catalysts, $Rh_2(tfa)_4$ and $Rh_2(tpa)_4$, in 1,2-DCE resulted in formation of very small amounts of **375*t**, with ratios of 96:4 and 95:5 respectively of **375*i** and **375*t**, with regard to ^{1}H-NMR analysis, and 97:3 and 96:4 respectively as judged by ^{13}C-NMR analysis (Table 8, Entries 2 and 3). Performing the reaction with the catalysts $Cu(acac)_2$, $Cu(hfacac)_2$ and $[Cu(MeCN)_4]PF_6$ in refluxing 1,2-DCE resulted in ratios of 84:16 (43% yield), 85:15 (75% yield) and 88:12 (63% yield) respectively according to ^{1}H-NMR analysis for the products **375*i** and **375*t** (Table 8, Entries 4-6). Analysis by ^{13}C-NMR gave ratios of 85:15, 87:13 and 90:10 respectively. These results strongly suggest that in addition to the products expected from formal [2,3]-rearrangement, a significant amount of product has been generated by either a [1,2]-shift reaction or some other rearrangement process. These results can not be explained by the [1,2]-shift reaction of a free oxonium ylide because the product ratio is dependent on the catalyst employed. If a [1,2]-shift reaction of the oxonium ylide was occurring, the same product ratio would be obtained regardless of the rhodium or copper catalyst employed, suggesting that what occurs is an alternative pathway, involving a metal-bound ylide equivalent as the intermediate rather than the oxonium ylide. In addition, it is also very clear that there is a good correlation between the ratios obtained by ^{1}H- and ^{13}C-NMR analysis, even though only small amounts of **375*t** are obtained.

Considering the importance of the solvent chosen for the reaction, the reaction was also performed with $Cu(acac)_2$ as catalyst in various solvents. Rather surprisingly, no reaction occurred in toluene at 80 °C or in THF at reflux (Table 8, Entries 7 and 9). However, when the reaction was performed with $Cu(acac)_2$ in refluxing toluene, a yield of 25% was obtained (Table 8, Entry 8). The product ratio according to ^{1}H-NMR analysis was 90:10, and the product ratio was 86:14 according to ^{13}C-NMR analysis. As these results do not differ markedly from those obtained in refluxing 1,2-DCE, it seems likely that the nature of solvent is not of significant importance regarding the mechanistic

pathway. However, both reaction temperature and choice of solvent appears to be of importance for initial formation of the metal carbenoid from the diazocarbonyl precursor. Previously, it was found that for an unstable oxonium ylide or ylide-like intermediate generated from terminal diazoketone **372*t**, the choice of catalyst greatly affects the outcome of the reaction. In order to investigate the outcome with a delocalised oxonium ylide, $[Ir(COD)Cl]_2$ was used as catalyst for the reaction of **373*t**. A yield of 37% was obtained, and an isomer ratio of 44:56 of **375*i** and **375*t** was observed according to ^{1}H-NMR analysis, and a ratio of 47:53 according to ^{13}C-NMR analysis (Table 8, Entry 10).

Table 8 Rearrangement of **373*t**.

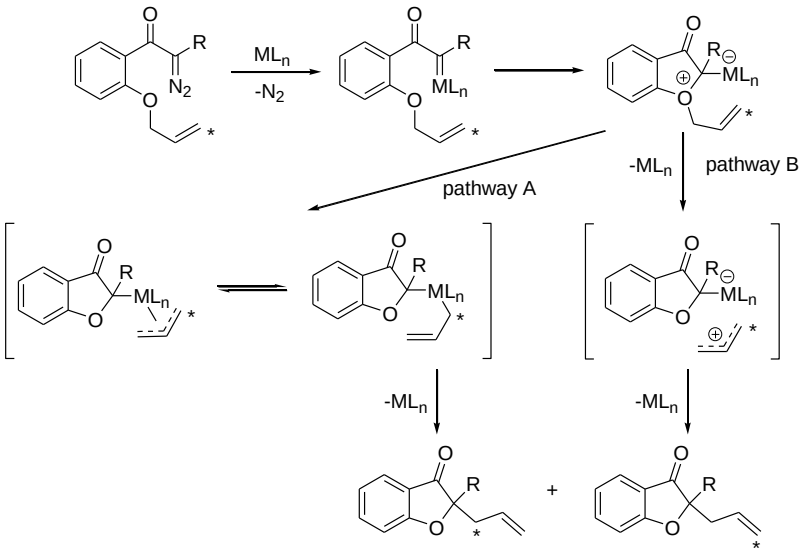


373*t **375*i** **375*t**

Entry	Catalyst	Solvent	Temp.	Yield	**375*i**:**375*t** (^{1}H)	**375*i**:**375*t** (^{13}C)
1	$Rh_2(OAc)_4$	1,2-DCE	reflux	76%	100:0	98:2
2	$Rh_2(tfa)_4$	1,2-DCE	reflux	20%	96:4	97:3
3	$Rh_2(tpa)_4$	1,2-DCE	reflux	34%	95:5	96:4
4	$Cu(acac)_2$	1,2-DCE	reflux	43%	84:16	85:15
5	$Cu(hfacac)_2$	1,2-DCE	reflux	75%	85:15	87:13
6	$[Cu(MeCN)_4]PF_6$	1,2-DCE	reflux	63%	88:12	90:10
7	$Cu(acac)_2$	toluene	80 °C	no rxn	n/a	n/a
8	$Cu(acac)_2$	toluene	reflux	25%	90:10	86:14
9	$Cu(acac)_2$	THF	reflux	no rxn	n/a	n/a
10	$[Ir(COD)Cl]_2$	1,2-DCE	reflux	37%	44:56	47:53

From the results above, it is evident that the reaction is not occurring exclusively through a [2,3]-sigmatropic rearrangement pathway. It is possible that more than one reaction is taking place at the same time, or that the reaction proceeds through a mechanism that does not involve a free ylide at all. Different pathway possibilities for the rearrangement which might lead to the scrambling of the labelled allyl group are shown in Scheme 135. Here, pathway A involves a mechanism that proceeds *via* a metal-

bound ylide equivalent rather than through the free ylide itself, with coordination to the metal centre. Furthermore, it is possible that after the formation of the metal-bound ylide equivalent, the allyl group dissociates, as shown in pathway B. Recombination of the two fragments would most likely result in a mixture of the two products. This is certainly possible for the reaction performed using $[Ir(COD)Cl]_2$ as the catalyst (Table 8, Entry 10). The increased selectivity of products being obtained when the reactions are performed with *e.g.* copper catalysts could also be explained by two different reactions taking place competitively, one involving the standard [2,3]-rearrangement process and the other involving metal-bound ylide equivalent.

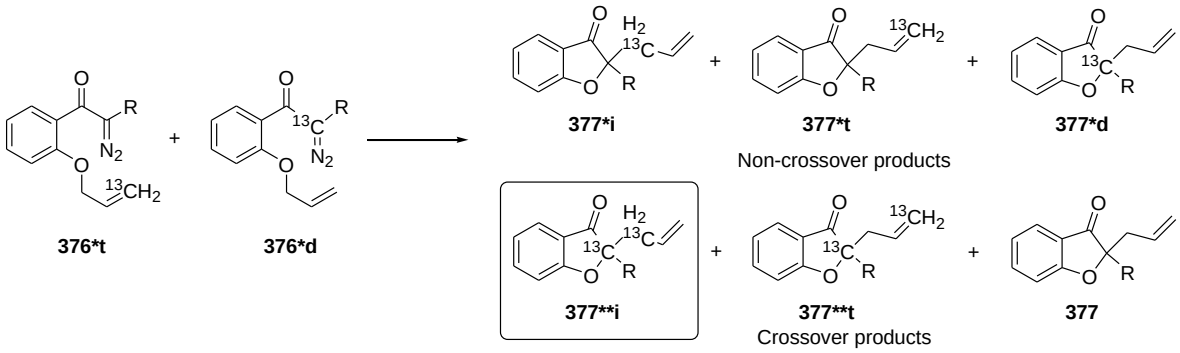


Scheme 135 Possible pathways for the rearrangement with dissociation of the allyl group.

It would appear that there are two factors that influence the mechanism and selectivity of the rearrangement reaction: the choice of transition metal and delocalisation of the ylide or metal-bound ylide. The more delocalised the system, the more likely it appears that the reaction will proceed through a metal-bound ylide intermediate. However, even where a less delocalised oxonium ylide would have been formed, a reaction involving the metal-bound ylide was seemingly the more predominant reaction mechanism when the reaction was performed with $[Ir(COD)Cl]_2$. With regard to the efficiency of the reactions analysed, yields vary quite markedly and in several instances are rather low. This can possibly be explained by the fact that all reactions were performed on small scale. Most crude products were purified by column chromatography between two and four times in order to provide very clean spectra, for NMR analysis.

9.3 Crossover study

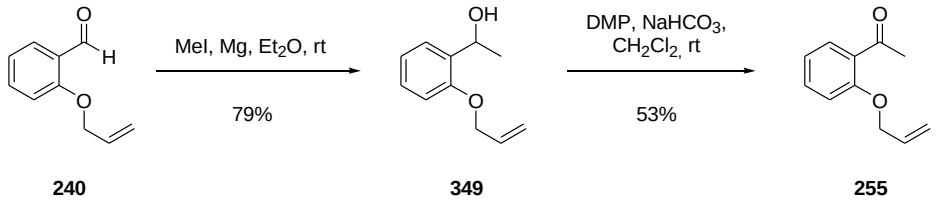
To further investigate the mechanistic pathway for this transformation, consideration was given to whether the allyl group dissociates during the course of the rearrangement reaction, or if scrambling results from internal transfer of the allyl group. If the allyl group does dissociate, it seemed likely that performing this reaction using a 1:1 mixture of isotopically labelled diazoketones such as **376*t**, labelled in the allylic terminal position and **376*d**, labelled at the diazo carbon, would result in the formation of crossover products (Scheme 136). However, intramolecular transfer of the allyl group would only result in the non-crossover products. Of the six possible products that can be formed during this transformation, the presence of the crossover product **377**i** should clearly be visible in the ^{13}C-NMR spectrum due to the coupling of the two ^{13}C-atoms. This should be visible as two doublets in the spectrum. The natural abundancy of ^{13}C-atoms is so low that a ^{13}C-^{13}C coupling is not normally visible in the ^{13}C-spectrum for a non-labelled derivative. Consequently, the crossover product, **377**i**, cannot be obtained through the classic [2,3]-sigmatropic rearrangement of an allylic oxonium ylide with a non-labelled diazoketone or with the labelled diazoketones **376*t** and **376*d**. Consequently, any of product **377**i** that is formed during this reaction must be obtained through a crossover of intermediates generated from diazoketones **376*t** and **376*d**.



Scheme 136 Crossover experiment.

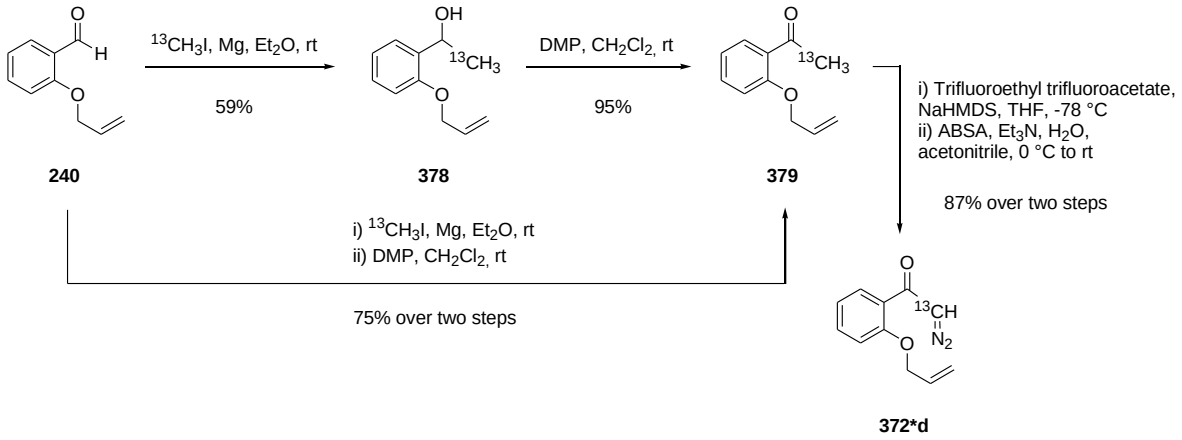
9.3.1 Synthesis of crossover substrate

The synthesis of the labelled diazoketones for the crossover experiment was first attempted with non-labelled substrates to test the synthetic sequence (Scheme 137).[250] The synthesis commenced with reaction of 2-allyloxybenzaldehyde **240** with a Grignard reagent to form alcohol **349** in 79% yield. Dess-Martin oxidation resulted in formation of the ketone **255** in 53% yield. Having established that this route is viable, the synthesis of labelled substrates continued.



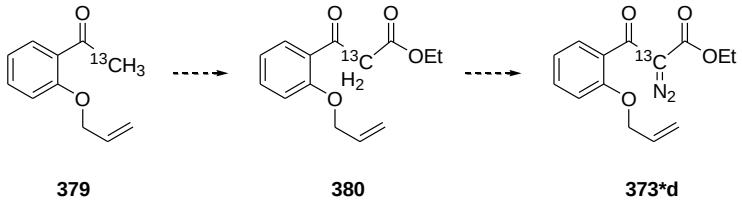
Scheme 137 Synthesis of ketone **255**.

To install the ^{13}C-atom, the same reaction was performed with a Grignard reagent prepared from $^{13}CH_3I$ to provide alcohol **378** in 59% yield (Scheme 138). Oxidation with Dess-Martin periodinane resulted in an improved yield (95%) of the ketone **379**. In an attempt to further increase the yield of this sequence, the two reactions were also performed without purification of the alcohol; a yield of 75% was obtained over two steps. From this point, diazoketone **372*d** was synthesised in two steps, as has previously been described for non-labelled derivatives. Diazoketone **372*d** was obtained in 87% yield over a further two steps.



Scheme 138 Synthesis of diazoketone **372*d**.

For the formation of diazoketone **373*d**, it was expected that a Claisen condensation reaction of the ketone **379** would provide the ß-keto ester **380** (Scheme 139). As the carbon in the α-position is activated, it was believed that a diazotransfer reaction would result in the formation of diazoketone **373*d** in good yield.

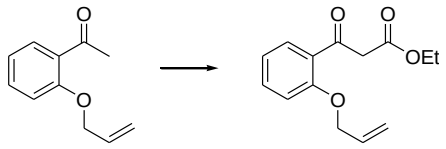


Scheme 139 Planned route for synthesis of diazoketone **373*d**.

The first step was to prepare the ß-keto ester through a Claisen condensation reaction, again testing with non-labelled substrates before using labelled materials. There are several examples of this reaction in the literature in which yields of greater than 90% have been obtained, but in our hands this transformation proved difficult. In fact, when attempting to react **255** with diethyl carbonate in the presence of sodium hydride no reaction took place, whether the reaction was carried out in diethyl ether at reflux (Table 9, Entry 1),[251] in toluene at reflux (Table 9, Entry 2)[252] or in tetrahydrofuran at reflux (Table 9, Entry 3).[253] This was extremely frustrating due to the literature precedent available. Furthermore, exchanging the base for LDA and changing the temperature to −78 °C still did not result in any conversion of the methyl ketone into the desired ß-keto ester product (Table 9, Entry 4).

At this point, the reaction was attempted using ethyl chloroformate instead of diethyl carbonate as the electrophile.[254] Performing Claisen condensation with diethyl carbonate would generate an ethoxy leaving group and the exchange of diethyl carbonate with ethyl chloroformate was done in order to vary the leaving group. However, no reaction took place between **255** and ethyl chloroformate in the presence of sodium hydride at reflux (Table 9, Entry 5). In spite of these results, we were pleased to observe that lowering of the temperature to −78 °C as well as changing the base to NaHMDS resulted in an 8% yield of **381** (Table 9, Entry 6). Increasing the number of equivalents of reagent and base very marginally increased the yield to 12% (Table 9, Entry 7). Increasing the temperature to 0 °C did not increase the yield further (Table 9, Entry 8), but when the reaction was performed at room temperature the required ß-keto ester was obtained in 38% yield (Table 9, Entry 9). Doubling the equivalents of reagent and base resulted in a slight lowering of the yield (Table 9, Entry 10).

Table 9 Claisen condensation to form ß-keto ester **381**.



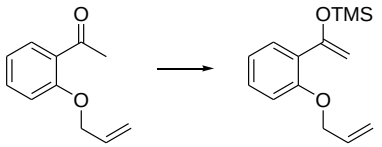
255 **381**

Entry	Conditions	Eq. reagent	Eq. base	Yield
1	Diethyl carbonate, NaH, Et_2O, reflux	2	2.1	No reaction
2	Diethyl carbonate, NaH, toluene, reflux	3	3.1	No reaction
3	Diethyl carbonate, NaH, THF, reflux	10	1.1	No reaction
4	Diethyl carbonate, LDA, THF, −78 °C	2	2	No reaction
5	Ethyl chloroformate, NaH, THF, reflux	10	1.1	No reaction
6	Ethyl chloroformate, NaHMDS, THF, −78 °C	1.5	3	8%
7	Ethyl chloroformate, NaHMDS, THF, −78 °C	4.5	9	12%
8	Ethyl chloroformate, NaHMDS, THF, 0 °C	4.5	9	10%
9	Ethyl chloroformate, NaHMDS, THF, rt	4.5	9	38%
10	Ethyl chloroformate, NaHMDS, THF, rt	9	18	34%

An investigation was also conducted to establish whether it would be possible to perform a Mukaiyama-type reaction using the trimethyl silyl enol ether **382** in order to prepare the ß-keto ester **381**.

The first attempt to prepare **382** from **255** used TMSOTf and Et_3N, and was performed according to a procedure by Itoh *et al*. (Table 10, Entry 1).[255] Unfortunately, the only result was decomposition of the starting material. Using TMSCl and LDA at −78 °C also led to decomposition (Table 10, Entry 2). Pleasingly, the reaction with TMSOTf and LDA at −78 °C with either 1.1 equivalents or 2 equivalents of reagent and base resulted in traces of **382** (Table 10, Entries 3 and 4). Finally, it was found that the reaction of **255** with TMSOTf and the milder base Et_3N (either 1.5 and 3 equivalents respectively or 3 and 6 equivalents respectively) in CH_2Cl_2 at 0 °C resulted in full conversion of **255** to **382** (Table 10, Entries 5 and 6). However, attempts to purify the silyl enol ether **382** resulted in either decomposition or hydrolysis of **382** upon which ketone **255** reformed. Therefore, the crude trimethyl silyl enol ether **382** was used directly in the next step.

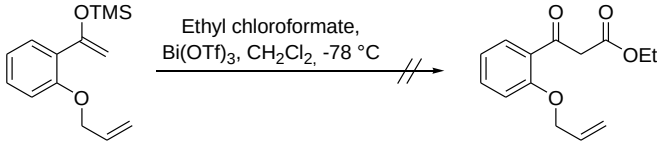
Table 10 Formation of trimethyl silyl enol ether **382**.



255 **382**

Entry	Conditions	Eq. reagent	Eq. base	Temp.	Yield
1	TMSOTf, Et_3N, CH_2Cl_2	1	1	rt	Decomp.
2	TMSCl, LDA, THF	1.1	1	−78 ºC	Decomp.
3	TMSOTf, LDA, THF	1.1	1.1	−78 ºC	Traces
4	TMSOTf, LDA, THF	2	2	−78 ºC	Traces
5	TMSOTf, Et_3N, CH_2Cl_2	1.5	3	0 ºC	Full conversion
6	TMSOTf, Et_3N, CH_2Cl_2	3	6	0 ºC	Full conversion

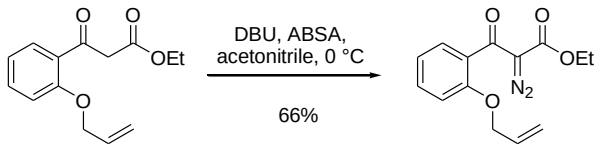
The crude trimethyl silyl enol ether **382** was reacted with ethyl chloroformate and the Lewis acid $Bi(OTf)_3$ (Scheme 140).[256] However, rather than formation of the ß-keto ester **381**, this led to hydrolysis of **382** and reformation of ketone **255**. Rather than continuing this pathway, it was decided that the initially used Claisen condensation reaction would suffice to prepare the necessary ß-keto ester.



382 **381**

Scheme 140 Attempted Mukaiyama-type reaction.

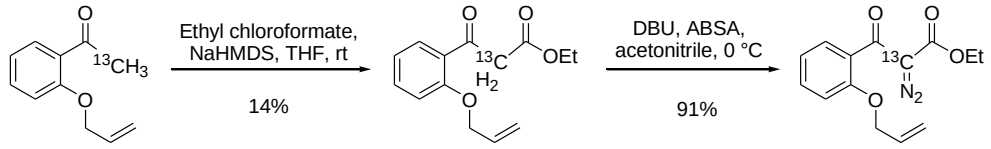
The final step required to synthesise diazoketone **241** was a diazotransfer reaction of **381** with ABSA and DBU in acetonitrile according to a procedure of Davies *et al.* (Scheme 141).[88] This resulted in the formation of **241** in 66% yield.



381 **241**

Scheme 141 Synthesis of diazoketone **241**.

Following the successful implementation of the synthesis using non-labelled substrates, attention turned to the synthesis of the ^{13}C-labelled compound. Unfortunately, performing the Claisen condensation with the ^{13}C-labelled ketone **379** resulted in much lower yields than had been obtained using the non-labelled ketone (Scheme 142). Yields were more commonly around 10%, with 14% as the best yield. Despite this, the diazotransfer reaction resulted in the significantly improved yield of 91%, providing sufficient quantities of material to be able to attempt the crossover experiments.

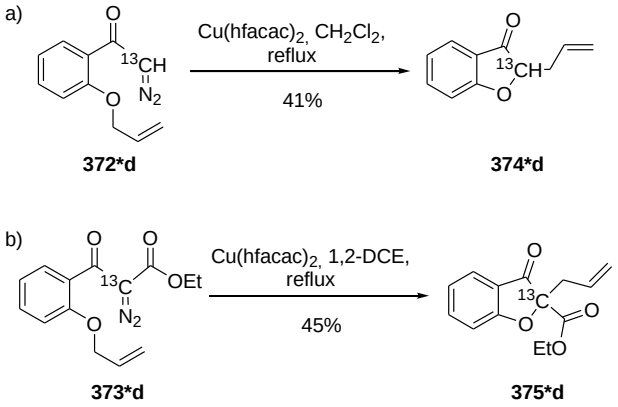


379 **380** **373*d**

Scheme 142 Synthesis of diazoketone **373*d**.

9.3.2 Crossover study

The reactions of diazoketones **372*d** and **373*d** were first performed individually, in order to obtain NMR spectra of the pure benzofuranone compounds **374*d** and **375*d** as reference material before the crossover experiment was attempted. Benzofuranone **374*d** was obtained in 41% yield (Scheme 143a) and benzofuranone **375*d** was obtained in 45% yield (Scheme 143b).



Scheme 143 Rearrangement of **372*d** and **373*d**.

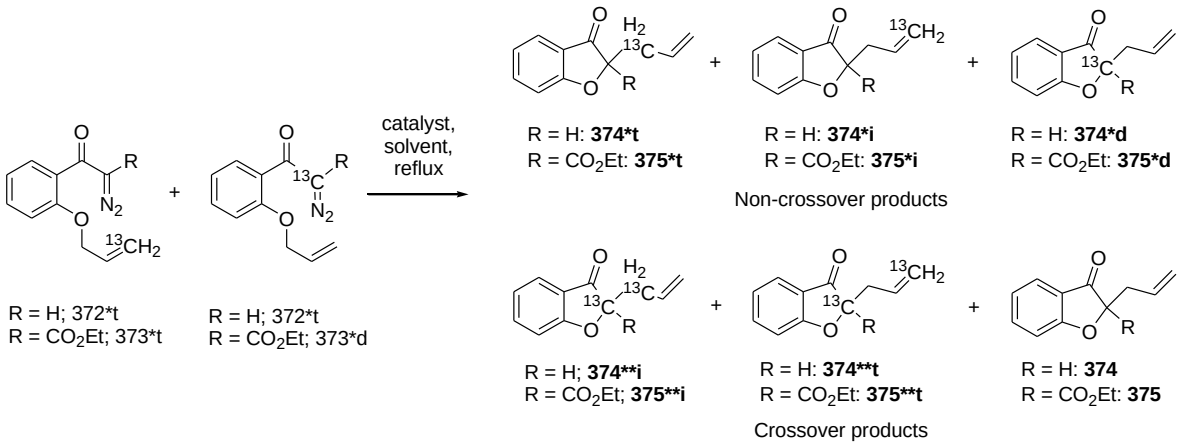
As stated previously, if the allyl group does dissociate during the reaction and crossover then takes place, six products should be obtained and one of those should be clearly visible in the ^{13}C-NMR spectrum due to a ^{13}C-^{13}C coupling (Scheme 136). The presence of this coupling would provide firm evidence that crossover does indeed take place and that at some point during the catalytic decomposition of diazoketones followed by rearrangement of the allylic oxonium ylide or metal-bound equivalent, the allyl group dissociates.

The crossover experiment was first attempted with the terminal diazoketones **372*t** and **372*d** (Table 11, Entry 1). As the only catalyst that provided any clear amount of scrambling for the terminal diazoketone was $[Ir(COD)Cl]_2$, this catalyst was chosen for the rearrangement. However, as previously noted, the yield for this reaction with $[Ir(COD)Cl]_2$ as catalyst is very low, and firm conclusions could not be drawn from the NMR data obtained.

The rearrangement of **373*t** with $[Ir(COD)Cl]_2$ resulted in almost equal amounts of the two labelled products but in significantly higher yield and so this crossover experiment was attempted using a 1:1 mixture of **373*t** and **373*d**. With $[Ir(COD)Cl]_2$ as catalyst and performing this reaction at a concentration of 0.041 M, only traces of the crossover product were obtained (Table 11, Entry 2). However, by increasing the concentration to 0.31 M, we were pleased to find that the ratio of crossover product **375**i** compared with the non-crossover product obtained was about 1:2 (Table 11, Entry 3). The crossover product **375**i** was clearly visible in the ^{13}C-NMR spectrum as a doublet with coupling constant ^{1}J = 38 Hz, common for ^{13}C-^{13}C ^{1}J coupling constants. Indisputably, the iridium-mediated rearrangement proceeds with dissociation of the allyl group at some point during the reaction. When the same crossover reaction was performed using $Cu(hfacac)_2$ as the catalyst at the same concentration, 4% of crossover product was

observed (Table 11, Entry 4), suggesting that the copper-mediated reaction proceeds mainly through intramolecular rearrangement.

Table 11 Crossover experiment.



Entry	R	Catalyst	Solvent	Conc.	Total yield	Amount **374**i**/**375**i**
1	H	$[Ir(COD)Cl]_2$	CH_2Cl_2	0.62 M	traces	n/a
2	CO_2Et	$[Ir(COD)Cl]_2$	1,2-DCE	0.041 M	11%	traces
3	CO_2Et	$[Ir(COD)Cl]_2$	1,2-DCE	0.31 M	25%	35%
4	CO_2Et	$Cu(hfacac)_2$	1,2-DCE	0.31 M	18%	traces

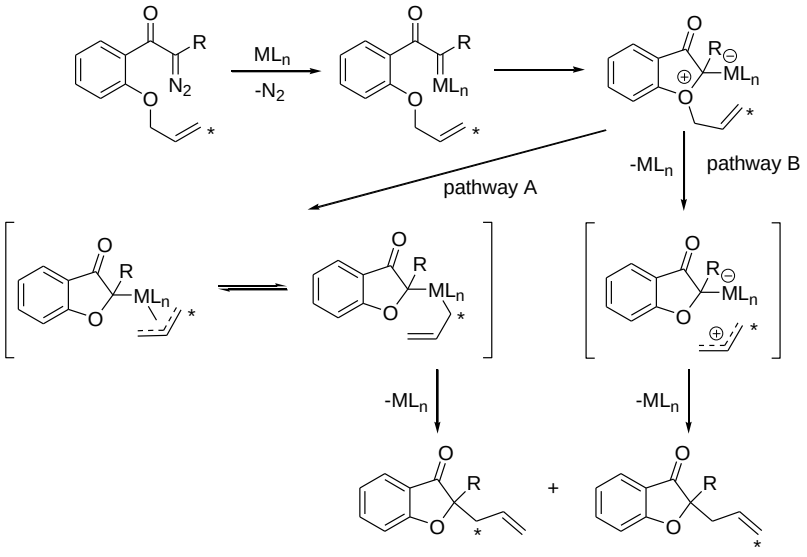
9.4 Summary and conclusions

The rearrangement of ^{13}C-labelled diazoketones clearly shows that the rearrangement of allylic oxonium ylides does not simply proceed through a formal [2,3]-sigmatropic rearrangement in every case. It seems likely that the mechanistic pathway followed depends on the stability of the oxonium ylide as well as the choice of catalyst. In general, increasing the stability of the oxonium ylides appears to increase the chance of the reaction following an alternative pathway. Additionally, the choice of metal appears to be important to the selectivity.

In the case of the labelled terminal diazoketone **372*t**, while small amounts of the scrambled products were observed with both the rhodium- and copper-mediated reaction, it can be argued that these observations are within the margin of error for the

analysis method and so it is not possible to make any firm conclusions. While it is possible that the reaction proceeds through a conventional [2,3]-rearrangement from an oxonium ylide, it is also possible that the reaction involve direct stereoselective rearrangement from the metal-bound ylide equivalent without scrambling. With regard to the iridium-mediated reaction of **372*t**, more or less complete scrambling of the product of the label occurs, suggesting that the iridium-mediated reaction does not proceed through a classical [2,3]-rearrangement of an oxonium ylide.

In the case of the more delocalised labelled α-diazo ß-ketoester **373*t**, it is clear that the copper- and iridium-mediated reaction does not proceed through a [2,3]-rearrangement of a "free" ylide. The fact that the catalyst influences the ratio of the labelled products suggests that the scrambling is not due to a mixture of [2,3]-rearrangement and competing [1,2]-shift of the formed ylide — once formed, the ylide would give an identical ratio of [2,3]-rearrangement product and [1,2]-shift product regardless of which catalyst was used to generate the ylide. Therefore, it seems likely that the reaction proceeds through a reaction pathway involving a metal-bound ylide equivalent as shown in Scheme 144. With regard to the rhodium-mediated reaction, it is possible that the reaction proceeds by formation of an ylide and subsequent [2,3]-sigmatropic rearrangement — rhodium catalysts appears to favour the products expected from the conventional [2,3]-rearrangement pathway. However, small amounts of scrambling suggest that in this case a metal-bound ylide equivalent may be involved. Furthermore, that there have been reports of asymmetric rearrangement of the rhodium-mediated reaction upon employment of chiral catalysts, suggests that the reaction does not proceed through the "free" ylide.[158,159,160]



Scheme 144 Possible pathways for the rearrangement reaction.

The presence of benzofuranone **375**i** during the iridium-mediated crossover experiment of **373*t** and **373*d** clearly suggests that at some point during the reaction, the allyl group dissociates from the metal-bound oxonium ylide which leads to scrambling of the product. Furthermore, the observation of the crossover product **375**i** was found to be dependent on the concentration. At 0.31 M, the ratio of **375**i** and the non-crossover product **375*i** was found to be approximately 1:2. In comparison, performing the crossover product by copper catalysis only resulted in about 4% of the crossover product **375**i**.

Overall, it remains clear that in order for a general chiral catalyst to be designed to induce high enantioselectivity during the rearrangement of allylic oxonium ylides, it must be taken into consideration what type (or types) of mechanism the reaction proceeds through. Indeed, dissociation of the allyl group will undoubtedly make it more difficult to achieve high enantioselectivity for this transformation, whereas for a reaction proceeding through the metal-bound ylide equivalent, it would most likely be easier to induce asymmetry compared to the reaction proceeding through a free oxonium ylide.

10 Future Work

Clearly, the reaction mechanism of the rearrangement of allylic oxonium ylides or ylide-like intermediates is not fully understood and requires further study. In order to validate the conclusion that the stability of the oxonium ylide or ylide-like intermediate to some extent influences the pathway taken during the reaction, various diazoketones should be screened. As varying the metal complex used for carbenoid generation results in significant changes in selectivity, various complexes that are known to form metal carbenoids from diazoketones should be screened. It would be logical to commence this screen with cobalt complexes, which have been successfully employed in both asymmetric cyclopropanation and [2,3]-sigmatropic rearrangements of sulfonium ylides.[257,258] In addition, cobalt is found in the same group of transition metals as rhodium and iridium, the two metals that have been found to give radically different reaction outcomes. Furthermore, the extent to which copper-mediated rearrangement reactions proceed with dissociation of the allyl group during the reaction should be investigated further. Traces of crossover product for the copper-mediated crossover experiment suggests that this might be a factor, which would greatly affect the use of chiral copper catalysts for asymmetric induction. In addition, a closer study of the ligand effect on the reaction selectivity would be of interest.

Regarding the asymmetric rearrangement studies, it would be beneficial to gain a better understanding of the reaction mechanism. Having said that, there are some further aspects of this project that would be of great interest. Leaving aside mechanistic issues, there are two issues that would be interesting to investigate whilst in the process of designing a chiral catalyst suitable for this type of rearrangement. It has been shown that copper catalysts in combination with bisoxazoline ligands do deliver some asymmetric induction, so it seems likely that continuing the screening process with this type of ligand would result in the design of catalysts that would give greater levels of asymmetric induction. For example, ligands with very bulky substituents, groups at the methylene bridge or those with different types of bridges could be tested (Figure 8).

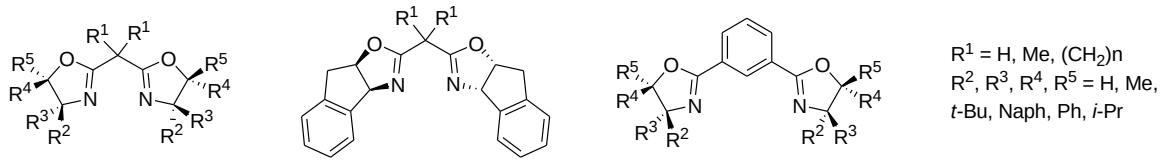


Figure 8 Various ligands to be screened.

In addition to this, based on the mechanistic study, it appears that the allylic group does not dissociate significantly from oxonium ylides or ylide-like intermediates generated from rhodium carbenoids, even for oxonium ylides derived from α-diazo ß-keto esters. This might be an advantage when attempting to perform asymmetric reactions. Despite the fact that copper carbenoids are more selective than rhodium carbenoids towards the generation of ylide-like intermediates instead of competing reactions, it is possible that the answer to the problem of asymmetric rearrangement lies with rhodium catalysts.

Finally, the reaction of iridium carbenoids with allylic ethers is very interesting because the course of the reaction differs markedly from reactions involving copper or rhodium carbenoids. In order to produce asymmetric induction during this reaction, it might be interesting to attempt to use the iridium(III)-salen catalyst employed by Katsuki *et al*. to perform asymmetric X-H insertion. However, it appears that total dissociation of the allyl group can occur during the reaction, which would make it more difficult to design a suitable chiral iridium catalyst for the transformation. For this part of the project, a better understanding of the reaction mechanism is vital before proceeding further.

11 Experimental Section

11.1 General conditions

Air-sensitive reactions were performed using glassware that had been flame-dried prior to use under an argon atmosphere. Dry solvents were acquired from a Pure Solv™ solvent purification system. Liquid reagents were distilled prior to use if necessary. All reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated. Diazo transfer reagents and diazocarbonyl compounds were handled with a Teflon coated spatula or with syringes equipped with a PTFE needle.

The reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F_{254} coated aluminium plates from Merck. The TLC plates were developed under UV-light and/or using basic potassium permanganate solution, ethanoic anisaldehyde solution or phosphomolybdic acid hydrate solution. Column chromatography was performed using silica gel (Fluorochem LC60A, 35-70 µ) as solid support and HPLC-grade solvent as eluent.

NMR spectra were recorded on a Bruker 400 or 500 MHz Spectrospin spectrometer at ambient temperature, ^{1}H-NMR at 400 or 500 MHz and ^{13}C-NMR at 100 or 125 MHz. Chemical shifts are reported in ppm, using the residual $CHCl_3$ peak (δ = 7.26) or TMS as internal standard (δ = 0) for ^{1}H-NMR and for ^{13}C-NMR the shifts are given relative to the central resonance of $CDCl_3$ (δ = 77.16). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of these, which refers to the spin-spin coupling pattern observed. DEPT135 and two-dimensional (COSY, HSQC) NMR spectroscopy were used when appropriate to assist the assignments of signals in the ^{1}H- and ^{13}C-NMR spectra.

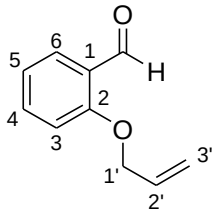
IR spectra were recorded on a Shimadzu FTIR-8400 apparatus without any preparation for both solid and liquid samples. High and low resolution mass spectra (HRMS and LRMS) were obtained from a JEOL JMS700 (MStation) instrument under EI, CI or FAB conditions by the analytical services at the University of Glasgow.

HPLC analysis was performed on a Shimadzu apparatus with Chiralcel AD or OD-H analytical columns at 25 ºC using mixtures of HPLC-grade hexane and isopropanol as eluents.

Elemental analyses were carried out using an Exeter Analytical Elemental Analyser EA 440. Melting points were recorded with an Electrothermal IA 9100 apparatus. Optical rotations were determined on chloroform solutions of samples and irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter at ambient temperature. $[\alpha]_D$-values are given in units 10^{-1} deg cm^2 g^{-1}

11.2 Experimental details

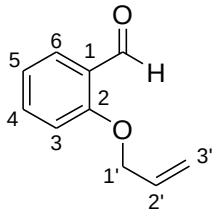
2-Allyloxybenzaldehyde **240**[259]



Allyl bromide (4.80 mL, 56.7 mmol) was added to a mixture of salicylaldehyde (5.40 mL, 51.7 mmol) and K_2CO_3 (7.68 g, 55.6 mmol) in acetone (50 mL) and the mixture was heated at reflux. After 21 h, the reaction was cooled to room temperature before it was filtered and the filtrate was then reduced *in vacuo*. The residue was dissolved in ethyl acetate (50 mL), washed with successively aqueous 1 M NaOH solution (30 mL), water (50 mL) and brine (50 mL), then dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate—triethylamine, 89:10:1) afforded 2-allyloxybenzaldehyde (6.35 g, 39.1 mmol, 76%) as a colourless oil. R_f = 0.38 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3078, 2862, 1682, 1597, 1481 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (1H, s, CHO), 7.85 (1H, dd, *J* = 7.6, 1.8 Hz, CH-C6), 7.54 (1H, ddd, *J* = 8.5, 7.4, 1.8 Hz, CH-C4), 7.04 (1H, app. t, *J* = 7.6 Hz, CH-C5), 6.98 (1H, d, *J* = 8.5 Hz, CH-C3), 6.09 (1H, ddt, *J* = 17.2, 10.5, 5.1, CH-C2'), 5.46 (1H, ddt,

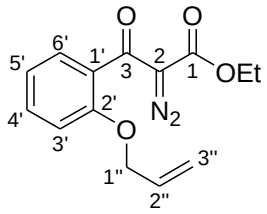
J = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3'), 5.35 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3'), 4.67 (2H, dt, *J* = 5.1, 1.5 Hz, CH_2-C1'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9 (CHO), 161.0 (C-C2), 136.0 (CH-C4), 132.5 (CH-C2'), 128.6 (CH-C6), 125.2 (C-C1), 121.0 (CH-C5), 118.2 (CH_2-C3'), 112.9 (CH-C3), 69.3 (CH_2-C1'); HRMS (CI-isobutane) for $C_{10}H_{11}O_2$ ($[M+H]^+$) calcd 163.0759, found 163.0755; LRMS (CI-isobutane) *m/z* (intensity); 163.2 ($[M+H]^+$) (100), 135.2 (35), 123.1 (28). Anal. calcd. for $C_{10}H_{10}O_2$: C 74.05%; H 6.23%. Found: C 74.01%; H 6.23%.

2-Allyloxybenzaldehyde **240**



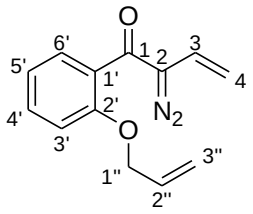
A suspension of Dess-Martin periodinane (125 mg, 0.295 mmol) in anhydrous CH_2Cl_2 (1.2 mL) was added dropwise to a solution of 2'-allyloxyphenyl methanol **348** (43.9 mg, 0.267 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C, after which the reaction mixture was allowed to warm to room temperature. After 80 min, the reaction was diluted with diethyl ether (5 mL). The mixture was transferred into 1 M aqueous NaOH (5 mL). After stirring for 20 min, the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic fractions were washed with 1 M aqueous NaOH (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate—triethyl amine, 89:10:1) afforded 2-allyloxybenzaldehyde (34.2 mg, 0.211 mmol, 79%) as a colourless oil. Spectroscopic data identical with above.

Ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate **241**[260]



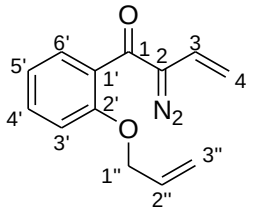
DBU (150 µL, 1.00 mmol) and 2-allyloxybenzaldehyde **240** (1.50 mL, 10.0 mmol) was added to a solution of ethyl diazoacetate (1.25 mL, 11.9 mmol) in anhydrous DMSO (80 mL) at room temperature. A solution of IBX (5.43 g, 19.4 mmol) in anhydrous DMSO (100 mL) was added and the reaction was left stirring in the dark at room temperature. After 3 days, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (100 mL) and the mixture was extracted with dichloromethane (4 × 100 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (3 × 100 mL) followed by water (100 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate—triethylamine, 89:10:1) afforded ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate (1.67 g, 6.10 mmol, 61%) as a yellow oil. R_f = 0.23 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 2984, 2137, 1732, 1626, 1599, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, ddd, *J* = 8.3, 7.5, 1.8 Hz, CH-C4'), 7.34 (1H, dd, *J* = 7.5, 1.8 Hz, CH-C6'), 7.01 (1H, app. td, *J* = 7.5, 0.8 Hz, CH-C5'), 6.89 (1H, d, *J* = 8.3 Hz, CH-C3'), 5.99 (1H, ddt, *J* = 17.3, 10.5, 5.0 Hz, CH-C2''), 5.37 (1H, ddt, *J* = 17.3, 1.6, 1.6 Hz, *trans*-CH_2-C3''), 5.26 (1H, ddt, *J* = 10.5, 1.6, 1.6 Hz, *cis*-CH_2-C3''), 4.54 (2H, dt, *J* = 5.0, 1.6 Hz, CH_2-C1''), 4.18 (2H, q, *J* = 7.1 Hz, CH_2-Et), 1.20 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3 (C-C3), 161.1 (C-C1), 156.1 (C-C2'), 132.8 (CH-C2''), 132.5 (CH-C4'), 128.8 (CH-C6'), 128.4 (C-C1'), 121.0 (CH-C5'), 117.5 (CH_2-C3''), 112.1 (CH-C3'), 69.4 (CH_2-C1''), 61.4 (CH_2-Et), 53.6 (C-C2), 14.3 (CH_3-Et); HRMS (EI) for $C_{14}H_{14}O_4N_2$ (M^+) calcd 274.0954, found 274.0952; LRMS (EI) *m/z* (intensity); 274.0 (M^+) (29), 246.0 (5), 219.0 (19), 173.0 (56), 148.9 (88), 133.0 (100), 105.0 (52).

1-(2-Allyloxyphenyl)-2-diazo-3-buten-1-one **243**



DBU (1.40 mL, 9.36 mmol) was added dropwise to a solution of 1-(2-allyloxyphenyl)-3-buten-1-one **247** (898 mg, 4.44 mmol) and ABSA (1.29 g, 5.37 mmol) in anhydrous acetonitrile (11 mL) at 0 ºC. After 28 h at 0 ºC, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (11 mL). The mixture was extracted with diethyl ether (4 × 10 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2-allyloxyphenyl)-2-diazo-3-buten-1-one (801 mg, 3.51 mmol, 79%) as an orange oil. R_f = 0.30 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3075, 3026, 2987, 2922, 2869, 2080, 1597, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42—7.38 (2H, m, CH-C4', CH-C6'), 7.03 (1H, app. td, *J* = 7.5, 0.8 Hz, CH-C5'), 6.93 (1H, dd, *J* = 8.7, 0.8 Hz, CH-C3'), 6.41 (1H, br s, CH-C3), 6.01 (1H, ddt, *J* = 17.2, 10.5, 5.0 Hz, CH-C2''), 5.39 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.27 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 5.20 (1H, br d, *J* = 10.5 Hz, *cis*-CH_2-C4), 4.91 (1H, d, *J* = 17.4 Hz, *trans*-CH_2-C4), 4.59 (2H, dt, *J* = 5.0, 1.5 Hz, CH_2-C1''); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.5 (C-C1), 155.3 (C-C2'), 132.5 (CH-C2''), 132.2 (CH-C4'), 129.6 (CH-C6'), 128.0 (C-C1'), 121.3 (CH-C5'), 121.1 (CH-C3), 117.6 (CH_2-C3''), 112.6 (CH-C3'), 107.9 (CH_2-C4), 69.3 (CH_2-C1'') (C-C2 not visible); HRMS (CI-isobutane) for $C_{13}H_{13}O_2N_2$ ($[M+H]^+$) calcd 229.0977, found 229.0978; LRMS (CI-isobutane) *m/z* (intensity); 229.3 ($[M+H]^+$) (100), 201.3 (81), 85.2 (38).

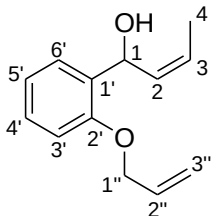
1-(2-Allyloxyphenyl)-2-diazo-3-buten-1-one **243**



ABSA (300 mg, 1.25 mmol) was added to a solution of 1-(2'-allyloxyphenyl)-2-buten-1-one **245** (207 mg, 1.02 mmol) in acetonitrile (10 mL) at 0 ºC. DBU (190 µL, 1.27 mmol)

was added dropwise and the mixture was allowed to warm to room temperature overnight. The reaction was quenched after 42 h by the addition of a mixture of saturated aqueous $NaHCO_3$ and CH_2Cl_2 (1:1, 30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate—trietyl amine, 89:10:1) afforded 1-(2-allyloxyphenyl)-2-diazo-3-buten-1-one (48.5 mg, 0.212 mmol, 21%) as an orange oil. Spectroscopic data identical with above.

1-(2'-Allyloxyphenyl)-2-buten-1-ol **244**

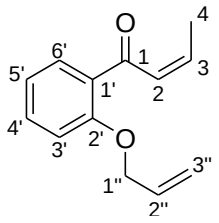


1-Propenylmagnesium bromide (0.5 M in tetrahydrofuran, 6.0 mL, 3.0 mmol) was added dropwise to a solution of 2-allyloxybenzaldehyde **240** (334 mg, 2.07 mmol) in anhydrous tetrahydrofuran (8 mL) at 0 °C. After 1 h, the reaction was quenched by the addition of saturated aq.

NH_4Cl solution (5 mL). The reaction mixture was allowed to warm to room temperature and then extracted with diethyl ether (3 × 10 mL). The combined organic fractions were washed with water (2 × 10 mL) followed by brine (10 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2'-allyloxyphenyl)-2-buten-1-ol (324 mg, 1.59 mmol, 77%) as a pale yellow oil. R_f = 0.25 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3410, 3075, 2916, 1489 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 7.5, 1.8 Hz, CH-C6'), 7.23 (1H, ddd, *J* = 8.2, 7.5, 1.8 Hz, CH-C4'), 6.96 (1H, app. dt, *J* = 7.5, 0.8 Hz, CH-C5'), 6.88 (1H, dd, *J* = 8.2, 0.8 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.2, 10.5, 5.3 Hz, CH-C2''), 5.77 (1H, dd, *J* = 8.7, 5.0 Hz, CH-C1), 5.73 (1H, ddt, *J* = 9.3, 8.7, 1.4 Hz, CH-C2), 5.63 (1H, dq, *J* = 9.3, 6.8 Hz, CH-C3), 5.42 (1H, ddt, *J* = 17.2, 1.4, 1.4 Hz, *trans*-CH_2-C3''), 5.30 (1H, ddt, *J* = 10.5, 1.4, 1.4 Hz, *cis*-CH_2-C3''), 4.60 (2H, dt, *J* = 5.3, 1.4 Hz, CH_2-C1''), 2.75 (1H, d, *J* = 5.0 Hz, OH), 1.75 (3H, dd, *J* = 6.8, 1.4 Hz, CH_3-C4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7 (C-C2'), 133.0 (CH-C2''), 131.9 (CH-C2), 131.8 (C-C1'), 128.4 (CH-C4'), 127.3 (CH-C6'), 126.2 (CH-C3), 121.1 (CH-C5'), 117.9 (CH_2-C3''), 111.8 (CH-C3'), 68.9 (CH_2-

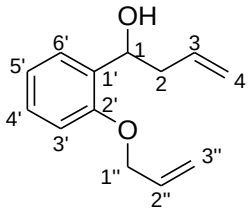
C1''), 66.6 (CH-C1), 13.4 (CH_3-C4); HRMS (EI) for $C_{13}H_{16}O_2$ (M^+) calcd 204.1150, found 204.1152; LRMS (EI) *m/z* (intensity); 204 (M^+) (10), 164 (100).

1-(2'-Allyloxyphenyl)-2-buten-1-one **245**



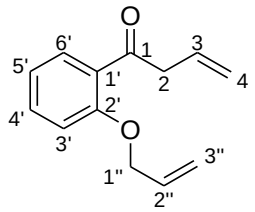
MnO_2 (0.88 g, 10 mmol) was added to a solution of 1-(2'allyloxyphenyl)-2-buten-1-ol **244** (0.11 g, 0.54 mmol) in anhydrous pentane (10 mL). The mixture was heated at reflux for 15 h, before the reaction mixture was cooled to room temperature. The reaction mixture was filtered through celite (diethyl ether) and the filtrate was reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2'-allyloxyphenyl)-2-buten-1-one (42 mg, 0.21 mmol, 39%) as a colourless oil. R_f = 0.55; (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3034, 2922, 1659, 1611, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, dd, *J* = 7.6, 1.8 Hz, CH-C6'), 7.41 (1H, ddd, *J* = 8.4, 7.4, 1.8 Hz, CH-C4'), 7.01 (1H, ddd, *J* = 7.6, 7.4, 0.7 Hz, CH-C5'), 6.93 (1H, dd, *J* = 8.4, 0.7 Hz, CH-C3'), 6.78 (1H, dq, *J* = 11.5, 1.8 Hz, CH-C2), 6.28 (1H, dq, *J* = 11.5, 7.2 Hz, CH-C3), 6.04 (1H, ddt, *J* = 17.3, 10.6, 4.9 Hz, CH-C2''), 5.44 (1H, ddt, *J* = 17.3, 1.6, 1.6 Hz, *trans*-CH_2-C3''), 5.28 (1H, ddt, *J* = 10.6, 1.6 Hz, *cis*-CH_2-C3''), 4.61 (2H, dt, *J* = 4.9, 1.6 Hz, CH_2-C1''), 2.16 (3H, dd, *J* = 7.2, 1.8 Hz, CH_3-C4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8 (C-C1), 157.1 (C-C2'), 142.2 (CH-C3), 132.9 (CH-C4'), 132.5 (CH-C2''), 130.6 (CH-C6'), 130.3 (C-C1'), 129.7 (CH-C2), 121.0 (CH-C5'), 117.5 (CH_2-C3''), 113.0 (CH-C3'), 69.4 (CH_2-C1''), 16.4 (CH_3-C4); HRMS (CI-isobutane) for $C_{13}H_{15}O_2$ ($[M+H]^+$) calcd 203.1072, found 203.1072; LRMS (CI-isobutane) *m/z* (intensity); 203.2 ($[M+H]^+$) (100), 163.2 (45), 147.2 (10).

1-(2'-Allyloxyphenyl)-3-buten-1-ol **246**[261]



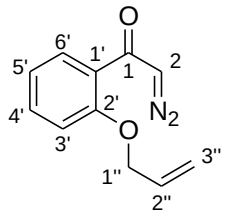
A solution of 2-allyloxybenzaldehyde **240** (4.00 g, 24.7 mmol) in anhydrous tetrahydrofuran (25 mL) was cooled to 0 °C. Allylmagnesium chloride (2.0 M in tetrahydrofuran, 25.0 mL, 50.0 mmol) was added dropwise. After 3 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (25 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 25 mL). The combined organic fractions were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2-allyloxyphenyl)-3-buten-1-ol (4.30 g, 21.1 mmol, 85%) as a colourless oil. R_f = 0.25 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3410, 3075, 2916, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 7.5, 1.7 Hz, CH-C6'), 7.22 (1H, ddd, *J* = 8.2, 7.5, 1.7 Hz, CH-C4'), 6.97 (1H, app. td, *J* = 7.5, 0.9 Hz, CH-C5'), 6.87 (1H, dd, *J* = 8.2, 0.9 Hz, CH-C3'), 6.06 (1H, ddt, *J* = 17.2, 10.4, 5.0 Hz, CH-C2''), 5.86 (1H, ddt, *J* = 17.2, 10.2, 7.2 Hz, CH-C3), 5.42 (1H, dq, *J* = 17.2, 1.5 Hz, *trans*-CH_2-C3''), 5.30 (1H, dq, *J* = 10.4, 1.5 Hz, *cis*-CH_2-C3''), 5.17—5.09 (2H, m, CH_2-C4), 5.01 (1H, dt, *J* = 8.0, 5.4 Hz, CH-C1), 4.59 (2H, dt, *J* = 5.0, 1.5 Hz, CH_2-C1''), 2.66—2.59 (1H, m, CH_2-C2), 2.54 (1H, d, *J* = 5.4 Hz, OH), 2.56—2.48 (1H, m, CH_2-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (C-C2'), 135.2 (CH-C3), 133.0 (CH-C2''), 132.0 (C-C1'), 128.2 (CH-C4'), 126.9 (CH-C6'), 120.9 (CH-C5'), 117.7 (CH_2-C4), 117.5 (CH_2-C3''), 111.6 (CH-C3'), 69.8 (CH-C1), 68.7 (CH_2-C1''), 41.9 (CH_2-C2); HRMS (EI) for $C_{13}H_{16}O_2$ (M^+) calcd 204.1150, found 204.1152; LRMS (EI) *m*/*z* (intensity); 204 (M^+) (10), 164 (100). Anal. calcd. for $C_{13}H_{16}O_2$: C 76.44%; H 7.91%. Found: C 76.28%; H 7.93%.

1-(2'-Allyloxyphenyl)-3-buten-1-one **247**



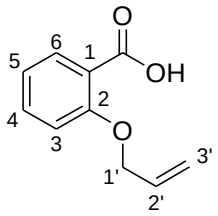
A solution of 1-(2'-allyloxyphenyl)-3-buten-1-ol **246** (323 mg, 1.58 mmol) in anhydrous dichloromethane (9 mL) was added dropwise to a suspension of Dess-Martin periodinane (1.08 g, 2.55 mmol) in anhydrous dichloromethane (9 mL) at room temperature. The flask was rinsed with additional anhydrous dichloromethane (1 mL), which was also transferred to the reaction flask. After 2 h, the reaction mixture was diluted with diethyl ether (10 mL). The reaction mixture was washed with a mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution (1:1, 60 mL) followed by brine (2 × 60 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2-allyloxyphenyl)-3-buten-1-one (286 mg, 1.41 mmol, 89%) as a colourless oil. R_f = 0.53 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3077, 2922, 1672, 1597, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (1H, dd, *J* = 7.7, 1.8 Hz, CH-C6'), 7.43 (1H, ddd, *J* = 8.4, 7.5, 1.8 Hz, CH-C4'), 7.00 (1H, ddd, *J* = 7.7, 7.5, 0.7 Hz, CH-C5'), 6.95 (1H, dd, *J* = 8.4, 0.7 Hz, CH-C3'), 6.14—6.02 (2H, m, CH-C3 and CH-C2''), 5.44 (1H, ddt, *J* = 17.3, 1.5, 1.4 Hz, *trans*-CH_2-C3''), 5.33 (1H, ddt, *J* = 10.5, 1.4, 1.3 Hz, *cis*-CH_2-C3''), 5.16 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C4), 5.14 (1H, ddt, *J* = 17.0, 1.6, 1.6 Hz, *trans*-CH_2-C4), 4.65 (2H, dt, *J* = 5.4, 1.5 Hz, CH_2-C1''), 3.80 (2H, dt, *J* = 6.9, 1.4 Hz, CH_2-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (C-C1), 157.5 (C-C2'), 133.4 (CH-C4'), 132.6 (CH-C2''), 131.7 (CH-C3), 130.6 (CH-C6'), 128.4 (C-C1'), 120.9 (CH-C5'), 118.4 (CH_2-C3''), 118.0 (CH_2-C4), 112.7 (CH-C3'), 69.4 (CH_2-C1''), 48.6 (CH_2-C2); HRMS (CI-isobutane) for $C_{13}H_{15}O_2$ ($[M+H]^+$) calcd 203.1072, found 203.1075; LRMS (CI-isobutane) *m/z* (intensity); 203.3 ($[M+H]^+$) (100), 163.2 (20).

1-(2'-Allyloxyphenyl)-2-diazoethanone **248**[86]



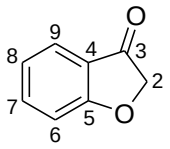
A solution of 1-(2'-allyloxyphenyl)ethanone **255** (355 mg, 2.01 mmol) in anhydrous tetrahydrofuran (4 mL) was added dropwise to a solution of LiHMDS (1.0 M in tetrahydrofuran, 3.20 mL, 3.20 mmol) in anhydrous tetrahydrofuran (6 mL) at −78 °C. After 30 min, trifluoroethyl trifluoroacetate (0.48 mL, 3.6 mmol) was rapidly added in one portion. The reaction mixture was allowed to warm to room temperature in 10 min before the reaction mixture was transferred to a separation funnel containing aqueous HCl solution (0.5 M, 15 mL) and diethyl ether (15 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 12 mL). The combined organic fractions were washed with brine (12 mL) and reduced *in vacuo*. The resulting residue was dissolved in acetonitrile (7.5 mL) and cooled to 0 °C. Water (38 µL, 2.1 mmol) and triethylamine (420 µL, 3.00 mmol) was added. A solution of ABSA (721 mg, 3.00 mmol) in acetonitrile (7.5 mL) was added dropwise to the reaction mixture, after which the reaction was allowed to warm to room temperature. After 3.5 h, the reaction was reduced *in vacuo*. The yellow residue was dissolved in diethyl ether (15 mL), washed with 10% aqueous NaOH solution (3 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2'-allyloxyphenyl-2-diazoethanone (315 mg, 1.64 mmol, 82%) as a bright yellow solid. R_f = 0.23 (petroleum ether—ethyl acetate, 9:1); m.p. = 56—57 °C {Lit.[86] m.p. = 56—57 °C}; ν_{max} (neat) 3090, 2926, 2111, 1591 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, br d, *J* = 6.9 Hz, CH-C6'), 7.43 (1H, ddd, *J* = 8.4, 7.3, 1.9 Hz, CH-C4'), 7.05 (1H, ddd, *J* = 7.8, 7.3, 0.8 Hz, CH-C5'), 6.94 (1H, dd, *J* = 8.4, 0.8 Hz, CH-C3'), 6.40 (1H, br s, CH-C2), 6.10 (1H, ddt, *J* = 17.2, 10.6, 5.4 Hz, CH-C2''), 5.46 (1H, ddt, *J* = 17.2, 1.4, 1.4 Hz, *trans*-CH_2-C3''), 5.36 (1H, ddt, *J* = 10.6, 1.4, 1.4 Hz, *cis*-CH_2-C3''), 4.64 (2H, dt, *J* = 5.4, 1.4 Hz, CH_2-C1''); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1 (C-C1), 157.3 (C-C2'), 133.3 (CH-C4'), 132.5 (CH-C2''), 130.5 (CH-C6'), 126.4 (C-C1'), 121.1 (CH-C5'), 118.7 (CH_2-C3''), 112.8 (CH-C3'), 69.6 (CH_2-C1''), 57.9 (CH-C2); LRMS (CI-isobutane) *m/z* (intensity); 203.3 ($[M+H]^+$) (22), 175.2 (100), 85.2 (28).

2-Allyloxybenzoic acid **249**[262]



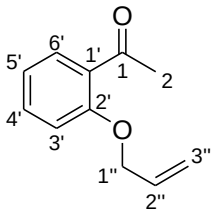
Aqueous hydrogen peroxide (27.5 %, 2.7 mL, 24 mmol) was added dropwise to a mixture of 50% aqueous KOH solution (0.67 mL, 12 mmol) and 2-allyloxybenzaldehyde **240** (0.45 mL, 3.0 mmol) in methanol (5 mL) at 65 °C. After 1h was the reaction mixture cooled to room temperature. The mixture was acidified by the addition of concentrated aqueous HCl solution, causing the yellow mixture to turn colourless, and then extracted with ethyl acetate (3 × 5 mL). To the combined organic fractions was added saturated aqueous $NaHCO_3$ solution (10 mL) and the phases were separated. The organic phase was extracted with saturated aqueous $NaHCO_3$ solution (2 × 5 mL) and the combined aqueous fractions were acidified by the addition of concentrated aqueous HCl solution. The aqueous phase was extracted with ethyl acetate (4 × 10 mL) and the combined organic fractions were washed with water (20 mL) followed by brine (20 mL), dried over Na_2SO_4, filtered and reduced *in vacuo* to afford 2-allyloxybenzoic acid (0.50 g, 2.8 mmol, 93%) as a colourless solid. R_f = 0.45 (petroleum ether—ethyl acetate, 2:3); m.p. = 58—60 °C {Lit.[262] m.p. = 45.2—45.8 °C; Lit.[263] m.p. = 59—61 °C; Lit.[264] m.p. = 64—65 °C}; ν_{max} (neat) 3256-2886, 2608, 1721, 1697, 1605, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.89 (1H, br s, COOH), 8.20 (1H, dd, *J* = 8.1, 1.8 Hz, CH-C6), 7.56 (1H, ddd, *J* = 8.8, 7.3, 1.8 Hz, CH-C4), 7.15 (1H, ddd, *J* = 8.1, 7.3, 0.7 Hz, CH-C5), 7.06 (1H, dd, *J* = 8.8, 0.7 Hz, CH-C3), 6.10 (1H, ddt, *J* = 17.2, 10.6, 5.7 Hz, CH-C2'), 5.50 (1H, ddt, *J* = 17.2, 1.3, 1.3, *trans*-CH_2-C3'), 5.45 (1H, ddt, *J* = 10.6, 1.3, 1.3 Hz, *cis*-CH_2-C3'), 4.81 (2H, dt, *J* = 5.7, 1.3 Hz, CH_2-C1'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (COOH), 157.1 (C-C2), 135.0 (CH-C4), 133.9 (CH-C6), 130.8 (CH-C2'), 122.4 (CH-C5), 120.7 (CH_2-C3'), 117.9 (C-C1), 112.9 (CH-C3), 70.8 (CH_2-C1'); HRMS (EI) for $C_{10}H_{10}O_3$ (M^+) calcd 178.0630, found 178.0632; LRMS (EI) *m/z* (intensity); 178.0 (M^+) (19), 120.0 (100), 92.0 (45), 82.9 (28).

3-Benzofuranone **253**[265]



Isobutyl chloroformate (150 μL, 1.16 mmol) was added dropwise to a solution of 2-allyloxybenzoic acid **249** (164 mg, 0.920 mmol) and triethylamine (175 μL, 1.26 mmol) in anhydrous diethyl ether (11.5 mL). A white precipitate formed and the mixture was then filtered and the solid was washed with diethyl ether. The filtrate was added dropwise to freshly distilled ethereal diazomethane (~9.3 mmol, ~10 eq.). The reaction was left stirring at 0 °C in the dark and was slowly allowed to warm to room temperature. After 43 h, the reaction was quenched by the addition of glacial acetic acid (1.5 mL). The mixture was poured into saturated aqueous NH_4Cl solution (30 mL) and was stirred vigorously for 15 min. The phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were washed with brine (30 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 3-benzofuranone (77.9 mg, 0.581 mmol, 63%) as a yellow solid. R_f = 0.15; (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 2934, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, ddd, *J* = 7.4, 1.4, 0.5 Hz, CH-C9), 7.62 (1H, ddd, *J* = 8.5, 7.4, 1.4 Hz, CH-C7), 7.15 (1H, d, *J* = 8.5 Hz, CH-C6), 7.10 (1H, app. td, *J* = 7.4, 0.8 Hz, CH-C8), 4.63 (2H, s, CH_2-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9 (C-C3), 174.0 (C-C5), 137.9 (CH-C7), 124.1 (CH-C9), 122.0 (CH-C8), 121.2 (C-C4), 113.7 (CH-C6), 74.7 (CH_2-C2); LRMS (EI) *m/z* (intensity); 134.0 (M^+) (78), 105.0 (70), 82.9 (100), 76.0 (49).

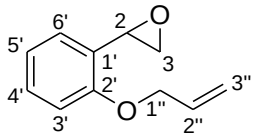
1-(2'-Allyloxyphenyl)-ethanone **255**[266]



Allyl bromide (8.50 mL, 98.2 mmol) was added to a stirred mixture of 2'-hydroxyacetophenone (6.00 mL, 49.8 mmol) and K_2CO_3 (13.9 g, 101 mmol) in acetone (120 mL) and the mixture was heated to reflux. After 17 h, the reaction was cooled to room temperature before it was filtered. The filtrate was reduced *in vacuo* and the

residue was dissolved in ethyl acetate (20 mL). The solution was washed successively with 1 M aqueous NaOH solution (2 × 20 mL), water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2'-allyloxyphenyl)-ethanone (8.48 g, 48.1 mmol, 97%) as a colourless oil. R_f = 0.40 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3074, 2996, 2927, 2872, 1671, 1596, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, dd, *J* = 7.7, 1.8 Hz, CH-C6'), 7.44 (1H, ddd, *J* = 8.3, 7.6, 1.8 Hz, CH-C4'), 7.00 (1H, app. td, *J* = 7.7, 0.6 Hz, CH-C5'), 6.93 (1H, dd, *J* = 8.3, 0.6 Hz, CH-C3'), 6.09 (1H, ddt, *J* = 17.2, 10.5, 5.3 Hz, CH-C2''), 5.44 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.33 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 4.64 (2H, dt, *J* = 5.3, 1.5 Hz, CH_2-C1''), 2.64 (3H, s, CH_3-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0 (C-C1), 157.9 (C-C2'), 133.5 (CH-C4'), 132.6 (CH-C2''), 130.4 (CH-C6'), 128.6 (C-C1'), 120.8 (CH-C5'), 118.2 (CH_2-C3''), 112.7 (CH-C3'), 69.4 (CH_2-C1''), 32.0 (CH_3-C2); HRMS (EI) for $C_{11}H_{12}O_2$ (M^+) calcd 176.0837, found 176.0841; LRMS (EI) *m/z* (intensity); 176.1 (M^+) (20), 161.1 (33), 133.1 (35), 121.1 (100), 105.1 (39).

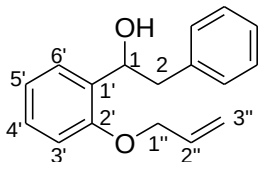
2-(2'-Allyloxyphenyl)-oxirane **257**



Sodium hydride (60% dispersion in mineral oil, 49.4 mg, 1.24 mmol) was washed with anhydrous pentane and dried *in vacuo*. Anhydrous DMSO (2 mL) and trimethylsulfonium iodide (254 mg, 1.24 mmol) was subsequently added at room temperature. After 30 min the reaction mixture was cooled to 0 °C. A solution of 2-allyloxybenzaldehyde **240** (160 µL, 1.06 mmol) in anhydrous DMSO (0.3 mL) was added dropwise to the reaction mixture, which was then allowed to warm to room temperature. After 30 min the reaction was quenched by the addition of water (3 mL) and the reaction mixture was extracted with diethyl ether (3 × 15 mL). The combined organic fractions were washed with water (3 × 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude product was used without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, app. td, *J* = 8.2, 1.1 Hz (CH-C4'), 7.15 (1H, dd, *J* = 7.3, 1.1 Hz, CH-C6'), 6.95 (1H, app. t, *J* = 7.5 Hz, CH-C5'), 6.87 (1H, d, *J* = 8.0 Hz, CH-C3'), 6.08 (1H, ddt, *J* = 17.2, 10.5, 5.1 Hz, CH-C2''), 5.43 (1H, ddt, *J* = 17.2, 1.4, 1.3 Hz, *trans*-CH_2-C3''), 5.30 (1H, ddt, *J* = 10.5, 1.3, 1.1 Hz, *cis*-CH_2-C3''), 4.62—4.58 (2H, m, CH_2-C1''), 4.26 (1H, br t, *J* = 3.3 Hz, CH-C2), 3.15 (1H, dd, *J* = 5.6, 3.3 Hz, CH_2-C3),

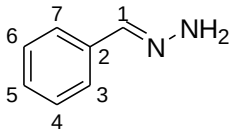
2.71 (1H, dd, *J* = 5.6, 3.3 Hz, CH_2-C3); HRMS (EI) for $C_{11}H_{12}O_2$ (M^+) calcd 176.0837, found 176.0839; LRMS (EI) *m/z* (intensity); 176 (M^+) (70), 163 (100), 135 (100), 121 (100), 107 (100).

1-(2'-Allyloxyphenyl)-2-phenyl ethanol **258**[86]



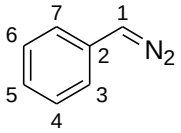
A solution of benzyl bromide (0.32 mL, 2.7 mmol) in anhydrous diethyl ether (20 mL) was slowly added to magnesium turnings (0.13 g, 5.4 mmol) at room temperature, causing the mixture to reflux. A solution of 2-allyloxybenzaldehyde **240** (0.33 g, 2.0 mmol) in anhydrous diethyl ether (5 mL) was slowly added to the Grignard reagent at 0 ºC. After 3 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). The reaction mixture was warmed to room temperature and extracted with diethyl ether (3 × 10 mL). The combined organic fractions were washed with water (2 × 10 mL) followed by brine (10 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 1-(2'-allyloxyphenyl)-2-phenylethanol (0.16 g, 0.63 mmol, 31%) as a colourless oil. R_f = 0.25 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3420, 2038, 2920, 1601, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35—7.20 (7H, m, 7 × CH-Ar), 6.96 (1H, app. t, *J* = 7.5 Hz, CH-Ar), 6.88 (1H, d, *J* = 8.2 Hz, CH-Ar), 6.08 (1H, ddt, *J* = 17.0, 10.5, 5.1 Hz, CH-C2''), 5.45 (1H, dd, *J* = 17.0, 1.0 Hz, *trans*-CH_2-C3''), 5.32 (1H, dd, *J* = 10.5, 1.0 Hz, *cis*-CH_2-C3''), 5.18 (1H, ddd, *J* = 8.6, 5.4, 4.2 Hz, CH-C1), 4.58 (2H, d, *J* = 5.1 Hz, CH_2-C1''), 3.17 (1H, dd, *J* = 13.5, 4.2 Hz, CH_2-C2), 2.94 (1H, dd, *J* = 13.5, 8.6 Hz, CH_2-C2), 2.44 (1H, d, *J* = 5.4 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4 (C-C2'), 139.0 (C-Ph), 133.2 (CH-C2''), 132.3 (C-1'), 129.6 (2 × CH-Ph), 128.5 (2 × CH-Ph), 128.4 (CH-Ar), 126.9, CH-Ar), 126.5 (CH-Ar), 121.1 (CH-C5'), 117.8 (CH_2-C3''), 111.7 (CH-C3'), 71.7 (CH_2-C1''), 68.9 (CH-C1), 44.4 (CH_2-C2); HRMS (EI) for $C_{17}H_{18}O_2$ (M^+) calcd 254.1307, found 254.1303; LRMS (EI) *m/z* (intensity); 254 (M^+) (10), 191 (20), 164 (100), 135 (100), 121 (100), 107 (100).

Benzaldehyde hydrazone **261**[267,268]



Benzaldehyde (0.96 mL, 9.4 mmol) and hydrazine monohydrate (2.0 mL, 41 mmol) were heated at 100 °C in a sealed tube. After 6 h, the reaction mixture was cooled to room temperature. The mixture was extracted with dichloromethane (3 × 2 mL). The combined organic extracts were washed with water and reduced *in vacuo*. Benzaldehyde hydrazone (1.0 g, 8.4 mmol, 89%) was afforded as a yellow oil. R_f = 0.30 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3379, 3194, 3024, 2901, 1597, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, s, CH-C1), 7.56—7.53 (2H, m, 2 × CH-Ph), 7.37—7.28 (3H, m, 3 × CH-Ph), 5.52 (2H, br s, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (CH-C1), 135.1 (C-C2), 128.7 (CH-C5), 128.6 (CH-C4, CH-C6), 126.2 (CH-C3, CH-C7).

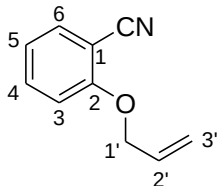
Phenyl diazomethane **262**[17]



Oxalyl chloride (0.18 mL, 2.1 mmol) was added dropwise to a stirred mixture of anhydrous DMSO (0.16 mL, 2.2 mmol) in anhydrous tetrahydrofuran (14 mL) at −55 °C. The reaction temperature was maintained at −60—(−55) °C while gas evaluation was observed (ca. 15 min). The reaction mixture was cooled to −78 °C and a solution of triethylamine (0.59 mL, 4.2 mmol) and benzaldehyde hydrazone **261** (241 mg, 2.00 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise over 5 min. Upon addition of the hydrazone solution, the reaction mixture started turning intensely peach-coloured. The reaction mixture was left stirring in the dark at −78 °C, during which time a white precipitate was formed. After 2 h, the reaction mixture was vacuum filtered under an argon atmosphere into a round bottom flask cooled at −78 °C. The reaction flask and the precipitate were rinsed with additional anhydrous tetrahydrofuran (5 mL). The crude peach-coloured product was used without further purification. R_f = 0.67 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 2060, 1458, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, app. t, *J* = 6.1 Hz, CH-C4, CH-C6), 7.03

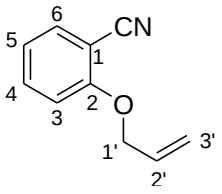
(1H, app. t, *J* = 6.1 Hz, CH-C5), 6.92 (2H, d, *J* = 6.1 Hz, CH-C3, CH-C7), 4.95 (1H, s, CH-C1).

2-Allyloxybenzonitrile **263**[269]



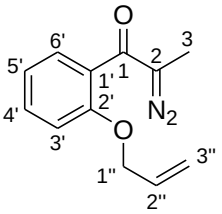
A mixture of 2-allyloxybenzaldehyde **240** (1.50 mL, 9.98 mmol), nitroethane (1.50 mL, 20.9 mmol) and sodium acetate (1.64 g, 20.0 mmol) in glacial acetic acid (3.5 mL) was heated at reflux. After 8 h, the reaction was cooled to room temperature before diethyl ether (15 mL) was added and the mixture was transferred onto ice (35 g). The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (2 × 20 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 2-allyloxybenzonitrile (677 mg, 4.25 mmol, 43%) as a pale yellow oil. R_f = 0.35 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3083, 2928, 2227, 1598, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, dd, *J* = 7.6, 1.8 Hz, CH-C6), 7.51 (1H, ddd, *J* = 8.6, 7.6, 1.8 Hz, CH-C4), 7.01 (1H, app. td, *J* = 7.6, 0.8 Hz, CH-C5), 6.96 (1H, br d, *J* = 8.6 Hz, CH-C3), 6.05 (1H, ddt, *J* = 17.3, 10.5, 5.0 Hz, CH-C2'), 5.49 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, *trans*-CH_2-C3'), 5.34 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3'), 4.67 (2H, dt, *J* = 5.0, 1.5 Hz, CH_2-C1'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (C-C2), 134.2 (CH-C4), 133.8 (CH-C6), 131.9 (CH-C2'), 120.9 (CH-C5), 118.3 (CH_2-C3'), 116.4 (C-CN), 112.6 (CH-C3), 102.3 (C-C1), 69.5 (CH_2-C1'); HRMS (EI) for $C_{10}H_9NO$ (M^+) calcd 159.0684, found 159.0689; LRMS (EI) *m/z* (intensity); 159.1 (M^+) (100), 119.1 (48), 91.1 (52), 83.0 (38).

2-Allyloxybenzonitrile **263**[269]



Iodine (838 mg, 3.30 mmol) was added to a stirred mixture of 2-allyloxybenzaldehyde **240** (487 mg, 3.00 mmol) in an aqueous solution of NH_4OH (25%, 33.5 mL) and tetrahydrofuran (3 mL) at room temperature. After 1.5 h, the reaction was quenched by the addition of aqueous $Na_2S_2O_3$ solution (5%, 15 mL). The mixture was extracted with diethyl ether (2 × 45 mL) and the combined organic fractions were washed with water (45 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 2-allyloxybenzonitrile (450 mg, 2.83 mmol, 94%) as a colourless oil. Spectroscopic data identical with above.

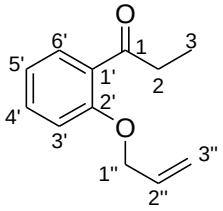
1-(2'-Allyloxyphenyl)-2-diazopropan-1-one **264**[86]



A solution of 1-(2'-allyloxyphenyl)-1-propanone **266** (3.06 g, 16.1 mmol) in anhydrous tetrahydrofuran (32 mL) was added dropwise to a solution of NaHMDS (2 M in tetrahydrofuran, 13.0 mL, 26.0 mmol) in tetrahydrofuran (35 mL) at −78 °C. After 50 min, trifluoroethyl trifluoroacetate (3.90 mL, 29.1 mmol) was added rapidly in one portion and the reaction was allowed to warm to room temperature. After 1 h, the reaction mixture was transferred to a separating funnel containing aqueous HCl solution (0.5 M, 120 mL) and diethyl ether (120 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 100 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The resulting residue was dissolved in acetonitrile (60 mL) and cooled at 0 °C before water (300 µL, 16.7 mmol) and triethylamine (3.40 mL, 24.4 mmol) was added. A solution of ABSA (5.77 g, 24.0 mmol) in acetonitrile (60 mL) was added dropwise. The reaction was left stirring in the dark and was slowly allowed to warm to room temperature. After 18 h the reaction mixture was reduced under vacuum and the crude

product was dissolved in diethyl ether (120 mL). The ethereal solution was washed with 10 % aqueous NaOH solution (3 × 80 mL) followed by brine (60 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (10—20% petroleum ether in ethyl acetate) afforded 2-(2'-allyloxyphenyl)-2-diazopropan-1-one (2.19 g, 10.1 mmol, 63%) as a yellow oil. R_f = 0.18 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3076, 2926, 2173, 2073, 1687, 1597, 1485, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 7.7 Hz, CH-C6'), 7.39—7.35 (1H, m, CH-C4'), 7.01 (1H, app. td, *J* = 7.7, 0.5 Hz, CH-C5'), 6.91 (1H, d, *J* = 8.3 Hz, CH-C3'), 6.04 (1H, ddt, *J* = 17.2, 10.4, 5.0 Hz, CH-C2''), 5.41 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.29 (1H, ddt, *J* = 10.4, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 4.59 (2H, dt, *J* = 5.0, 1.5 Hz, CH_2-C1''), 2.12 (3H, s, CH_3-C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4 (C-C1), 155.1 (C-C2'), 132.8 (CH-C2''), 131.7 (CH-C4'), 129.5 (CH-C6'), 128.1 (C-C1'), 121.2 (CH-C5'), 117.4 (CH_2-C3''), 112.4 (CH-C3'), 69.3 (CH_2-C1''), 65.3 (C-C2), 8.7 (CH_3-C3); HRMS (CI-isobutane) for $C_{12}H_{12}O_2N_2$ ($[M+H]^+$) calcd 217.0977, found 217.0979; LRMS (CI-isobutane) *m/z* (intensity); 217.2 ($[M+H]^+$) (12), 189.2 (100), 163.2 (16), 149.1 (9).

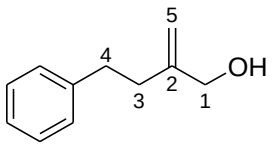
1-(2'-Allyloxyphenyl)-1-propanone **266**[86]



Allyl bromide (1.75 mL, 20.2 mmol) was added to a mixture of 1-(2'-hydroxyphenyl)-1-propanone (1.57 mL, 11.4 mmol) and K_2CO_3 (2.78 g, 20.1 mmol) in acetone (30 mL). The mixture was heated at reflux with vigorous stirring. After 18 h, the reaction was cooled to room temperature and then filtered. The filtrate was concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (10 mL) and washed with successively aqueous NaOH solution (1 M, 2 × 10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. 1-(2'-Allyloxyphenyl)-1-propanone (2.08 g, 10.9 mmol, 96%) was afforded as a colourless oil. R_f = 0.45 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3075, 2978, 1674, 1597, 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, dd, *J* = 7.5, 1.8 Hz, CH-C6'), 7.42 (1H, ddd, *J* = 8.4, 7.5, 1.8 Hz, CH-C4'), 7.00 (1H, app. td, *J* = 7.5, 0.7 Hz, CH-C5'), 6.94 (1H, dd, *J* = 8.4, 0.7 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.3, 10.6, 5.3 Hz, CH-C2''), 5.43 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.32 (1H, ddt, *J* = 10.6, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 4.63 (2H, dt, *J* = 5.3, 1.5 Hz, CH_2-C1''), 3.02 (2H, q, *J* = 7.3 Hz, CH_2-C2), 1.17 (3H, t, *J* = 7.3 Hz, CH_3-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6 (C-C1), 157.4 (C-C2'), 133.0 (CH-C4'), 132.7

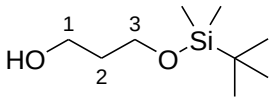
(CH-C2''), 130.3 (CH-C6'), 128.8 (C-C1'), 120.8 (CH-C5'), 118.1 (CH_2-C3''), 112.7 (CH-C3'), 69.4 (CH_2-C1''), 37.1 (CH_2-C2), 8.5 (CH_3-C3); HRMS (EI) for $C_{12}H_{14}O_2$ (M^+) calcd 190.0994, found 190.0992; LRMS (EI) *m*/*z* (intensity); 190.1 (M^+) (16), 161.1 (100), 121.1 (59), 105.1 (56), 83.0 (68).

2-Methylene-4-phenyl-1-butanol **277**[270]



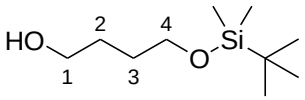
n-Butyl lithium (4.90 mL of a 2.5 M solution in hexanes, 12.3 mmol) was added dropwise to a solution of TMEDA (1.85 mL, 12.3 mmol) in anhydrous pentane (2.1 mL) within a temperature range of −20 to −15 °C. After 30 min the reaction was cooled to −78 °C and 2-methyl-2-propen-1-ol (0.50 mL, 5.9 mmol) was added dropwise. The reaction was left stirring for 21 h while slowly warming to room temperature. The reaction was cooled to −78 °C before a solution of benzyl bromide (0.59 mL, 5.0 mmol) in anhydrous tetrahydrofuran (2.1 mL) was added slowly. The reaction was allowed to warm to room temperature. After 20 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was extracted with diethyl ether (4 × 10 mL), and the extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 1:1) afforded 2-methylene-4-phenyl-1-butanol (0.16 g, 0.97 mmol, 19%) as a light yellow oil. R_f = 0.60 (petroleum ether—ethyl acetate, 1:1); ν_{max} (neat) 3325, 3126, 2924, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30—7.27 (2H, m, 2 × CH-Ph), 7.21—7.17 (3H, m, 3 × CH-Ph), 5.07 (1H, s, CH_2-C5), 4.93 (1H, s, CH_2-C5), 4.09 (2H, d, *J* = 6.0 Hz, CH_2-C1), 2.79 (2H, t, *J* = 8.0 Hz, CH_2-C4), 2.39 (2H, t, *J* = 8.0 Hz, CH_2-C3), 1.37 (1H, t, *J* = 6.0 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6 (C-C2), 141.9 (C-Ph), 128.5 (2 × CH-Ph), 128.5 (2 × CH-Ph), 126.1 (CH-Ph), 110.0 (CH_2-C5), 66.2 (CH_2-C1), 34.8 (CH_2-C3), 34.4 (CH_2-C4); HRMS (CI-isobutane) for $C_{11}H_{13}$ ([M-OH]$^+$) calcd 145.1017, found 145.1018; LRMS (CI-isobutane) *m*/*z* (intensity); 163.2 ([M+H]$^+$) (4), 145.2 ([M-OH]$^+$) (100), 107.1 (8), 91.1 (19).

3-(*tert*-Butyldimethylsilanyloxy)-1-propanol **280**[271]



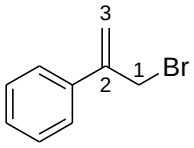
Sodium hydride (60% dispersion in mineral oil, 0.42 g, 10 mmol) was added portionwise to a solution of 1,3-propanediol (0.72 mL, 10 mmol) in anhydrous tetrahydrofuran (11 mL) with stirring at 0 ºC. After 45 min, a solution of TBDMSCl (1.5 g, 10 mmol) in anhydrous tetrahydrofuran (4.2 mL) was added. The reaction mixture was stirred at room temperature for 20 h and at 30 ºC for 23 h. The reaction was quenched by the addition of water (10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (4 × 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (40 mL) and brine (50 mL), then dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 7:3) afforded 3-(*tert*-butyldimethylsilanyloxy)-1-propanol (1.5 g, 7.6 mmol, 76%) as a pale yellow oil. R_f = 0.55 (petroleum ether—ethyl acetate, 7:3); ν_{max} (neat) 3347, 2953, 2930, 2886, 2857, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (2H, t, *J* = 5.5 Hz, CH_2-C3), 3.81 (2H, q, *J* = 5.5 Hz, CH_2-C1), 2.59 (1H, t, *J* = 5.5 Hz, OH), 1.78 (2H, quintet, *J* = 5.5 Hz, CH_2-C2), 0.90 (9H, s, 3 × CH_3-*t*-Bu), 0.08 (6H, s, 2 × Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.2 (CH_2-C3), 62.7 (CH_2-C1), 34.2 (CH_2-C2), 26.0 (3 × CH_3-*t*-Bu), 18.3 (C-*t*-Bu), –5.4 (2 × Me); HRMS (CI-isobutane) for $C_9H_{23}O_2Si$ ($[M+H]^+$) calcd 191.1467, found 191.1463; LRMS (CI-isobutane) *m*/*z* (intensity); 191.4 ($[M+H]^+$) (100), 133.3 (5), 113.3 (6), 97.3 (7).

4-(*tert*-Butyldimethylsilanyloxy)-1-butanol **281**[272]



Sodium hydride (60% dispersion in mineral oil, 0.47 g, 12 mmol) was added portionwise to a solution of 1,4-butanediol (0.89 mL, 10 mL) in anhydrous tetrahydrofuran (11 mL) with stirring at 0 ºC. The mixture was stirred at room temperature for 45 min, after which a solution of TBDMSCl (1.5 g, 9.8 mmol) in anhydrous tetrahydrofuran (4.2 mL) was added. The reaction mixture was stirred at room temperature for 20 h before the reaction was quenched by the addition of water (10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (4 × 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (40 mL) and brine (50 mL), then dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 7:3) afforded 4-(*tert*-butyldimethylsilanyloxy)-1-butanol (1.7 g, 8.1 mmol, 82%) as a pale yellow oil. R_f = 0.50 (petroleum ether—ethyl acetate, 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (2H, t, *J* = 5.7 Hz, CH_2-C4), 3.65 (2H, q, *J* = 5.7 Hz, CH_2-C1), 2.51 (1H, t, *J* = 5.7 Hz, OH), 1.68—1.62 (4H, m, CH_2-C2, CH_2-C3), 0.91 (9H, s, 3 × CH_3-*t*-Bu), 0.07 (6H, s, 2 × Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.5 (CH_2-C4), 62.9 (CH_2-C1), 30.4 (CH_2-C3), 30.0 (CH_2-C2), 26.0 (3 × CH_3-*t*-Bu), 18.4 (C-*t*-Bu), —5.3 (2 × Me); HRMS (CI-isobutane) for $C_{10}H_{25}O_2Si$ ($[M+H]^+$) calcd 205.1624, found 205.1621; LRMS (CI-isobutane) *m/z* (intensity); 205.4 ($[M+H]^+$) (100), 147.3 (9).

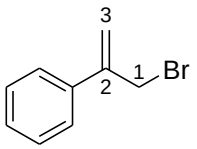
1-(Bromomethyl vinyl)-benzene **282**[273]



A mixture of NBS (4.45 g, 25.0 mmol), α-methylstyrene (5.25 mL, 40.4 mmol) and carbon tetrachloride (2.5 mL) was heated at 170 ºC until all solid material had dissolved and the exothermic reaction had subsided. The reaction mixture was slowly cooled to room temperature. After 3 h, the mixture was filtered and the filtrate was reduced *in vacuo*. Flash column chromatography (petroleum ether) afforded 1-(bromomethyl vinyl)-benzene as an orange oil. Due to the high volatililty of the product, an accurate yield could not be calculated. R_f = 0.33 (petroleum ether); ν_{max} (neat) 3058, 1949, 1885,

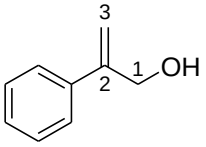
1824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51—7.48 (2H, m, 2 × CH-Ph), 7.41—7.31 (3H, m, 3 × CH-Ph), 5.56 (1H, s, CH_2-C3), 5.50 (1H, s, CH_2-C3), 4.39 (2H, s, CH_2-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (C-C2), 137.6 (C-Ph), 128.5 (2 × CH-Ph), 128.3 (CH-Ph), 126.1 (2 × CH-Ph), 117.2 (CH_2-C3), 34.2 (CH_2-C1); LRMS (EI) *m/z* (intensity); 198.0 ($[M+H]^+$) (20), 117.1 (69), 91.0 (100).

1-(Bromomethyl)vinylbenzene **282**[273]



Phosphorous tribromide (1.15 mL, 12.2 mmol) was added to a solution of 2-phenyl-2-propen-1-ol **285** (1.32 g, 9.87 mmol) in anhydrous diethyl ether (25 mL) at 0 °C. After 16 h, the reaction was diluted with petroleum ether (60 mL) and diethyl ether (60 mL). The mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 80 mL) followed by brine (80 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether) afforded 1-(bromomethyl)vinylbenzene as an orange oil. Due to the high volatililty of the product, an accurate yield could not be calculated. Spectroscopic data identical with above.

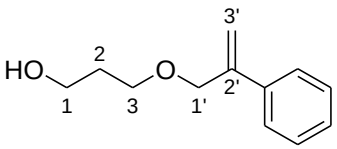
2-Phenyl-2-propen-1-ol **285**[274]



Phenylmagnesium bromide (2.8 M in diethyl ether, 9.0 mL, 25 mmol) was added to a stirred mixture of CuI (290 mg, 1.52 mmol) in anhydrous diethyl ether (60 mL). After 1 h, a solution of propargyl alcohol (0.59 mL, 10 mmol) in anhydrous diethyl ether (10 mL) was slowly added and the reaction mixture was heated to reflux. After 18 h the reaction was cooled to room temperature and quenched by the addition of saturated aqueous NH_4Cl solution (20 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic fractions were washed with brine (50 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 4:1) afforded 2-phenyl-2-propen-1-ol

(1.19 g, 8.89 mmol, 88%) as a colourless oil. R_f = 0.22 (petroleum ether—ethyl acetate, 4:1); ν_{max} (neat) 3317, 3057, 2867, 1954, 1889, 1812, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47—7.45 (2H, m, 2 × CH-Ph), 7.38—7.29 (3H, m, 3 × CH-Ph), 5.48 (1H, s, CH_2-C3), 5.38 (1H, s, CH_2-C3), 4.56 (2H, d, *J* = 6.1 Hz, CH_2-C1), 1.58 (1H, t, *J* = 6.1 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3 (C-C2), 138.5 (C-Ph), 128.5 (2 × CH-Ph), 128.0 (CH-Ph), 126.1 (2 × CH-Ph), 112.6 (CH_2-C3), 65.1 (CH_2-C1); HRMS (EI) for $C_9H_{10}O$ (M^+) calcd 134.0732, found 134.0729; LRMS (EI) *m/z* (intensity); 134.1 (M^+) (100), 103.1 (86), 92.1 (59), 77.1 (60).

3-(2'-Phenylallyloxy)-1-propanol **286**

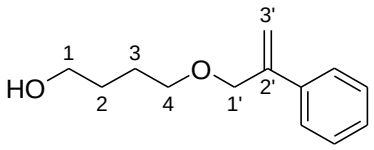


Phosphorous tribromide (520 μL, 5.53 mmol) was added dropwise to a solution of 2-phenyl-2-propen-1-ol **285** (671 mg, 5.00 mmol) in anhydrous diethyl ether (25 mL) at 0 °C. The solution was allowed to warm slowly to room temperature. After 19 h, the reaction was diluted with diethyl ether (30 mL) and petroleum ether (30 mL). The mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 40 mL) followed by brine (40 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The crude product was used without further purification.

A solution of 1,3-propanediol (1.80 mL, 24.9 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 256 mg, 6.40 mmol) in anhydrous tetrahydrofuran (14 mL) at 0 °C. A solution of the crude (1-bromomethylvinyl)benzene **282** in anhydrous tetrahydrofuran (2 mL) was added dropwise after 1.5 h, and the reaction was then heated to reflux. After 2 h, the reaction was cooled to room temperature and quenched by the addition of water (25 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 40 mL). The combined organic fractions were washed with water (40 mL) then brine (40 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 1:9) afforded 3-(2'-phenylallyloxy)-1-propanol (429 mg, 2.23 mmol, 45% over two steps) as a colourless oil. R_f = 0.33 (petroleum ether—ethyl acetate, 1:1); ν_{max} (neat) 3379, 3055, 2940, 2862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47—7.43 (2H, m, 2 × CH-Ph), 7.37—7.27 (3H, m, 3 × CH-Ph), 5.51 (1H, s, CH_2-C3'), 5.31 (1H, d, *J* = 1.2 Hz, CH_2-C3'), 4.39 (2H, s, CH_2-C1'), 3.69 (2H, q,

J = 5.7 Hz, CH_2-C1), 3.65 (2H, t, J = 5.7 Hz, CH_2-C3), 1.97 (1H, td, J = 5.7, 2.0 Hz, OH), 1.82 (2H, quintet, J = 5.7 Hz, CH_2-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2 (C-C2'), 138.6 (C-Ph), 128.4 (2 × CH-Ph), 127.9 (CH-Ph), 126.1 (2 × CH-Ph), 114.5 (CH_2-C3'), 73.1 (CH_2-C1'), 69.1 (CH_2-C3), 61.9 (CH_2-C1), 61.9 (CH_2-C2); HRMS (CI-isobutane) for $C_{12}H_{17}O_2$ ($[M+H]^+$) calcd 193.1229, found 193.1230; LRMS (CI-isobutane) *m/z* (intensity); 193.3 ($[M+H]^+$) (100), 119.3 (21). Anal. calcd. for $C_{12}H_{16}O_2$: C 74.97%; H 8.38%. Found: C 74.82%; H 8.41%.

4-(2'-Phenylallyloxy)-1-butanol **287**

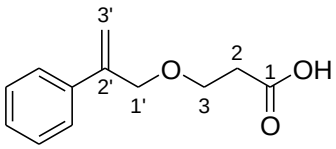


Phosphorous tribromide (110 μL, 1.17 mmol) was added dropwise to a solution of 2-phenyl-2-propen-1-ol **285** (138 mg, 1.03 mmol) in anhydrous diethyl ether (5 mL) at 0 °C. The solution was allowed to warm slowly to room temperature. After 24 h, the reaction was diluted with diethyl ether (6 mL) and petroleum ether (6 mL). The mixture was washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL) followed by brine (10 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The crude product was used without further purification.

A solution of 1,4-butanediol in anhydrous tetrahydrofuran (4 mL) was added dropwise to a mixture of sodium hydride (60% dispersion in mineral oil, 48.6 mg, 1.22 mmol) in anhydrous tetrahydrofuran (14 mL) at 0 °C. A solution of the crude (1-bromomethylvinyl)benzene **282** in anhydrous tetrahydrofuran was added dropwise after 1 h, after which the reaction was heated to reflux. After 3 h, the reaction was cooled to room temperature and quenched by the addition of water (25 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 40 mL). The combined organic fractions were washed with water (40 mL) followed by brine (40 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 1:9) afforded 4-(2'-phenylallyloxy)-1-butanol (79.0 mg, 0.383 mmol, 37% over two steps) as a colourless oil. R_f = 0.35 (petroleum ether—ethyl acetate, 1:1); ν_{max} (neat) 3368, 3057, 2938, 2862 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47—7.44 (2H, m, 2 × CH-Ph), 7.36—7.26 (3H, m, 3 × CH-Ph), 5.52 (1H, m, CH_2-C3'), 5.33 (1H, app. q, J = 1.2 Hz, CH_2-C3'), 4.38 (2H, m, CH_2-C1'), 3.60 (2H, q, J = 5.8 Hz, CH_2-C1), 3.53 (2H, t, J = 5.8 Hz, CH_2-C4), 1.91 (1H, t, J = 5.8 Hz, OH),

1.72—1.58 (4H, m, CH_2-C2, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (C-C2'), 138.8 (C-Ph), 128.3 (2 × CH-Ph), 127.8 (CH-Ph), 126.1 (2 × CH-Ph), 114.3 (CH_2-C3'), 72.9 (CH_2-C1'), 70.1 (CH_2-C4), 62.7 (CH_2-C1), 30.1 (CH_2-C2), 26.5 (CH_2-C3); HRMS (CI-isobutane) for $C_{13}H_{19}O_2$ ($[M+H]^+$) calcd 207.1385, found 207.1384; LRMS (CI-isobutane) *m/z* (intensity); 207.3 ($[M+H]^+$) (100), 193.3 (30).

3-(2'-Phenylallyloxy)-propionic acid **288**

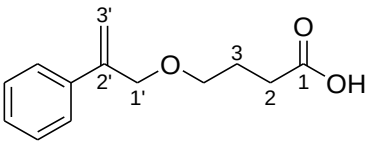


A solution of 3-(2'-phenylallyloxy)-1-propanol **286** (69.6 mg, 0.362 mmol) in anhydrous dichloromethane (3.5 mL) was added to a suspension of Dess-Martin periodinane (230 mg, 0.543 mmol) in anhydrous dichloromethane (3.5 mL) at room temperature. After 3 h, the reaction was diluted with diethyl ether, washed with a mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution (1:1, 20 mL) followed by brine (20 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude aldehyde product was used without further purification.

An aqueous solution of $NaClO_2$ (80%, 296 mg, 3.27 mmol) was added to a solution of $NaH_2PO_4 \cdot H_2O$ (139 mg, 1.01 mmol) in water (5 mL). This solution was subsequently added to a solution of 2-methyl-2-butene (1.00 mL, 9.44 mmol) and crude aldehyde in *tert*-butanol (5 mL), precooled to 0 ºC. The mixture was stirred at room temperature for 2 h, before being reduced *in vacuo*. The residue was extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with brine (15 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The residue was partitioned between diethyl ether (5 mL) and 1 M aqueous NaOH solution (5 mL). The aqueous phase was washed with diethyl ether (3 × 5 mL) and acidified with aqueous HCl solution (1 M) before being extracted with diethyl ether (3 × 5 mL). The combined organic fractions were washed with water (10 mL) followed by brine (10 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. 3-(2'-Phenylallyloxy)-propionic acid (53.7 mg, 0.260 mmol, 72% over two steps) was obtained as a colourless solid. R_f = 0.15 (petroleum ether—ethyl acetate, 1:4); ν_{max} (neat) 3038—2544, 1695, 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (1H, br s, CO_2H), 7.47—7.44 (2H, m, 2 × CH-Ph), 7.35—7.27 (3H, m, 3 × CH-Ph), 5.54 (1H, s, CH_2-C3'), 5.34 (1H, d, *J* = 1.0 Hz, CH_2-C3'), 4.42 (2H, s, CH_2-C1'), 3.77 (2H, t, *J* = 6.2 Hz, CH_2-C3), 2.64 (2H, t, *J* = 6.2 Hz, CH_2-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0

(CO_2H), 143.8 (C-C2'), 138.5 (C-Ph), 128.4 (2 × CH-Ph), 127.8 (CH-Ph), 126.1 (2 × CH-Ph), 114.7 (CH_2-C3'), 73.2 (CH_2-C1'), 65.0 (CH_2-C3), 34.8 (CH_2-C2); HRMS (CI-isobutane) for $C_{12}H_{15}O_3$ ($[M+H]^+$) calcd 207.1021, found 207.1020; LRMS (CI-isobutane) *m/z* (intensity); 207.3 ($[M+H]^+$) (100), 193.3 (15), 133.2 (17).

4-(2'-Phenylallyloxy)-butyric acid **289**

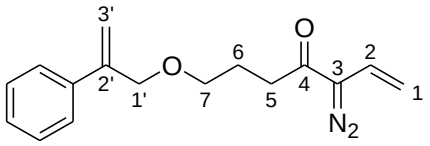


A solution of 4-(2'-phenylallyloxy)-1-butanol **287** (210 mg, 1.02 mmol) in anhydrous dichloromethane (6 mL) was added to a stirred suspension of Dess-Martin periodinane (560 mg, 1.32 mmol) in anhydrous dichloromethane (6 mL) at room temperature. After 2 h, the reaction mixture was diluted with diethyl ether (10 mL), washed with a mixture of saturated aqueous $NaHCO_3$ solution (20 mL) and 10% aqueous $Na_2S_2O_3$ solution (20 mL) followed by brine (45 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude aldehyde product was used without further purification.

An 80% aqueous solution of $NaClO_2$ (574 mg, 6.35 mmol) was added to a solution of $NaH_2PO_4 \cdot H_2O$ (287 mg, 2.08 mmol) in water (10 mL). This solution was subsequently added to a solution of 2-methyl-2-butene (2.00 mL, 18.9 mmol) and the crude aldehyde in *tert*-butanol (10 mL), precooled to 0 ºC. The mixture was stirred at room temperature for 1 h before being reduced *in vacuo*. The residue was extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with brine (30 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The residue was partitioned between diethyl ether (20 mL) and 1 M aqueous NaOH solution (20 mL). The aqueous phase was washed with diethyl ether (4 × 15 mL) and acidified with aqueous HCl solution (1 M) before being extracted with diethyl ether (4 × 15 mL). The combined organic fractions were washed with water (30 mL) followed by brine (30 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. 3-(2'-Phenylallyloxy)-butyric acid (181 mg, 0.819 mmol, 80% over two steps) was obtained as a colourless solid. R_f = 0.48 (petroleum ether—ethyl acetate, 1:1); ν_{max} (neat) 3040-2545, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (1H, br s, CO_2H), 7.46-7.43 (2H, m, 2 × CH-Ph), 7.36–7.27 (3H, m, 3 × CH-Ph), 5.52 (1H, dt, *J* = 1.1, 0.6 Hz, CH_2-C3'), 5.32 (1H, dt, *J* = 1.1, 0.9 Hz, CH_2-C3'), 4.37 (2H, dd, *J* = 0.9, 0.6 Hz, CH_2-C1'), 3.53 (2H, t, *J* = 6.1 Hz, CH_2-C4), 2.42 (2H, t, *J* = 7.2 Hz, CH_2-C2), 1.91 (2H, tt, *J* = 7.2, 6.1 Hz, CH_2-C3); HRMS (CI-isobutane) for $C_{13}H_{17}O_3$ ($[M+H]^+$)

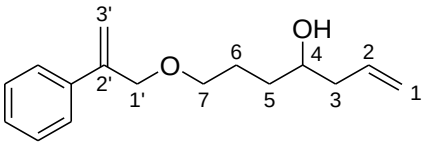
calcd 221.1178, found 221.1175; LRMS (CI-isobutane) *m/z* (intensity); 221.3 ($[M+H]^+$) (13), 133.2 (21), 87.2 (100).

3-Diazo-7-(2'-phenylallyloxy)-1-hepten-4-one **291**



DBU (0.63 mL, 4.2 mmol) was added dropwise to a solution of 7-(2-phenylallyloxy)-1-hepten-4-one **293** (861 mg, 3.49 mmol) and ABSA (1.01 g, 4.22 mmol) in anhydrous acetonitrile (40 mL) at 0 °C. After 2 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (4 × 10 mL). The combined organic fractions were washed with brine (30 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 1:9) afforded 3-diazo-7-(2'-phenylallyloxy)-1-hepten-4-one (556 mg, 2.05 mmol, 59%) as an orange oil. R_f = 0.43 (petroleum ether—diethyl ether, 3:2); ν_{max} (neat) 3055, 2859, 2072, 1647, 1609 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46—7.43 (2H, m, 2 × CH-Ph), 7.36—7.28 (3H, m, 3 × CH-Ph), 6.24 (1H, br s, CH-C2), 5.51 (1H, m, CH_2-C3'), 5.30 (1H, dt, *J* = 1.3, 1.0 Hz, CH_2-C3'), 5.17 (1H, br d, *J* = 10.8 Hz, *cis*-CH_2-C1), 4.84 (1H, d, *J* = 17.4 Hz, *trans*-CH_2-C1), 4.36 (2H, d, *J* = 1.0 Hz, CH_2-C1'), 3.50 (2H, t, *J* = 5.9 Hz, CH_2-C7), 2.51 (2H, t, *J* = 7.2 Hz, CH_2-C5), 1.93 (2H, tt, *J* = 7.2, 5.9 Hz, CH_2-C6); DEPTQ NMR (125 MHz, $CDCl_3$) δ 144.4 (C-C2'), 138.7 (C-Ph), 128.3 (2 × CH-Ph), 127.8 (CH-Ph), 126.1 (2 × CH-Ph), 120.1 (CH-C2), 114.4 (CH_2-C3'), 108.2 (CH_2-C1), 72.7 (CH_2-C1'), 68.6 (CH_2-C7), 34.9 (CH_2-C5), 24.3 (CH_2-C6) (C-C4 and C-C3 not visible); HRMS (CI-isobutane) for $C_{16}H_{19}O_2N_2$ ($[M+H]^+$) calcd 271.1447, found 271.1446; LRMS (CI-isobutane) *m/z* (intensity); 271.3 ($[M+H]^+$) (61), 245.3 (53), 193.3 (70), 137.2 (94), 111.2 (100).

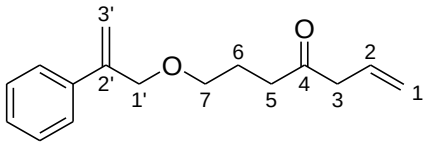
7-(2'-Phenylallyloxy)-1-hepten-4-ol **292**



A solution of DMSO (1.70 mL, 24.0 mmol) in anhydrous dichloromethane (40 mL) was added dropwise to a solution of oxalyl chloride (1.03 mL, 12.0 mmol) in anhydrous dichloromethane (40 mL) at −78 °C. After 40 min, a solution of 4-(2'-phenylallyloxy)-1-butanol **287** (1.55 g, 7.52 mmol) in anhydrous dichloromethane (40 mL) was slowly added at −78 °C. After 1.5 h, triethylamine (5.40 mL, 39.0 mmol) was added and after an additional 5 minutes the reaction mixture was allowed to warm slowly back to room temperature over 0.5 h. The mixture was washed with saturated aqueous NH_4Cl solution (40 mL) followed by brine (40 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*.

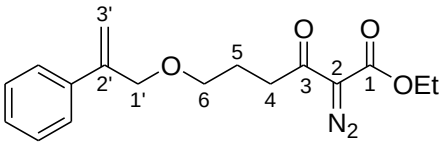
Allylmagnesium chloride (2.0 M in tetrahydrofuran, 7.50 mL, 15.0 mmol) was slowly added to a solution of the crude aldehyde in anhydrous tetrahydrofuran (8 mL) at 0 °C. After 2.5 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (8 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic fractions were washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 3:2) afforded 7-(2'-phenylallyloxy)-1-hepten-4-ol (1.16 g, 4.73 mmol, 63% over two steps) as a colourless oil. R_f = 0.23 (petroleum ether—diethyl ether, 3:2); ν_{max} (neat) 3402, 3078, 2924, 2862, 1636, 1497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47—7.44 (2H, m, 2 × CH-Ph), 7.36—7.27 (3H, m, 3 × CH-Ph), 5.85—5.75 (1H, m, CH-C2), 5.52 (1H, d, *J* = 1.0 Hz, CH_2-C3'), 5.33 (1H, d, *J* = 1.0 Hz, CH_2-C3'), 5.13—5.11 (1H, m, *trans*-CH_2-C1), 5.10—5.08 (1H, m, *cis*-CH_2-C1), 4.38 (2H, d, *J* = 0.4 Hz, CH_2-C1'), 3.61 (1H, app. octet, *J* = 4.0 Hz, CH-C4), 3.52 (2H, t, *J* = 6.0 Hz, CH_2-C7), 2.27—2.09 (2H, m, CH_2-C3), 2.16 (1H, d, *J* = 4.0 Hz, OH), 1.78—1.65 (2H, m, CH_2-C6), 1.63—1.53 (1H, m, CH_2-C5), 1.49—1.39 (1H, m, CH_2-C5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3 (C-C2'), 138.8 (C-Ph), 135.0 (CH-C2), 128.3 (2 × CH-Ph), 127.8 (CH-Ph), 126.1 (2 × CH-Ph), 117.8 (CH_2-C1), 114.3 (CH_2-C3'), 72.8 (CH_2-C1'), 70.4 (CH-C4), 70.2 (CH_2-C7), 42.0 (CH_2-C3), 33.9 (CH_2-C5), 26.1 (CH_2-C6); HRMS (CI-isobutane) for $C_{16}H_{23}O_2$ ($[M+H]^+$) calcd 247.1698, found 247.1699; LRMS (CI-isobutane) *m/z* (intensity); 247.3 ($[M+H]^+$) (100), 229.3 (22), 193.3 (34).

7-(2-Phenylallyloxy)-1-hepten-4-one **293**



Dess-Martin periodinane (2.98 g, 7.03 mmol) was added to a solution of 7-(2'-phenylallyloxy)-1-hepten-4-ol **292** (1.13 g, 4.60 mmol) in anhydrous dichloromethane (60 mL) at room temperature. After 5.5 h, the reaction was diluted with diethyl ether (60 mL), washed with a mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution (1:1, 300 mL) followed by brine (150 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 3:2) afforded 7-(2-phenylallyloxy)-1-hepten-4-one (1.01 g, 4.15 mmol, 90%) as a colourless oil. R_f = 0.58 (petroleum ether—diethyl ether, 3:2); ν_{max} (neat) 3082, 2859, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47—7.43 (2H, m, 2 × CH-Ph), 7.40—7.27 (3H, m, 3 × CH-Ph), 5.88 (1H, ddt, *J* = 17.1, 10.2, 7.0 Hz, CH-C2), 5.51 (1H, app. t, *J* = 0.5 Hz, CH_2-C3'), 5.30 (1H, app. q, *J* = 1.3 Hz, CH_2-C3'), 5.16 (1H, ddt, *J* = 10.2, 1.4, 1.4 Hz, *cis*-CH_2-C1), 5.10 (1H, ddt, *J* = 17.1, 1.4, 1.4 Hz, *trans*-CH_2-C1), 4.34 (2H, d, *J* = 0.7 Hz, CH_2-C1'), 3.47 (2H, t, *J* = 6.1 Hz, CH_2-C7), 3.09 (2H, dt, *J* = 7.0, 1.4 Hz, CH_2-C3), 2.46 (2H, t, *J* = 7.1 Hz, CH_2-C5), 1.85 (2H, tt, *J* = 7.1, 6.1 Hz, CH_2-C6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4 (C-C4), 144.4 (C-C2'), 138.8 (C-Ph), 130.7 (CH-C2), 128.3 (2 × CH-Ph), 127.8 (CH-Ph), 126.1 (2 × CH-Ph), 118.7 (CH_2-C1), 114.3 (CH_2-C3'), 72.7 (CH_2-C1'), 68.9 (CH_2-C7), 47.7 (CH_2-C3), 38.8 (CH_2-C5), 23.6 (CH_2-C6). Anal. calcd. for $C_{16}H_{20}O_2$: C 78.65%; H 8.25%. Found: C 78.43%; H 8.22%.

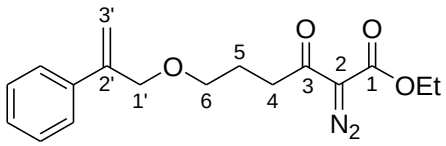
Ethyl 2-diazo-3-oxo-6-(2'-phenylallyloxy) hexanate **294**



Dess-Martin periodinane (144 mg, 0.339 mmol) was added to a solution of ethyl 2-diazo-3-hydroxy-6-(2'-phenylallyloxy) hexanate **296** (80.3 mg, 0.252 mmol) in anhydrous dichloromethane (7 mL) at room temperature. After 3 h, the reaction was diluted with diethyl ether (7 mL), washed with a mixture of saturated aqueous $NaHCO_3$ solution (15 mL) and 10% aqueous $Na_2S_2O_3$ solution (15 mL) followed by brine (30 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum

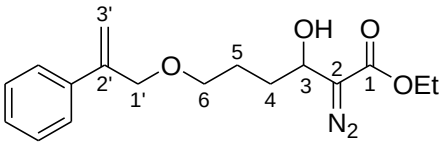
ether—diethyl ether, 4:1) afforded ethyl 2-diazo-3-oxo-6-(2'-phenylallyloxy) hexanate (25.8 mg, 81.6 μmol, 32%) as a yellow oil. R_f = 0.25 (petroleum ether—diethyl ether, 4:1); ν_{max} (neat) 3084, 2849, 2131, 1715, 1655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47—7.43 (2H, m, 2 × CH-Ph), 7.35—7.24 (3H, 3 × CH-Ph), 5.51 (1H, d, *J* = 0.6 Hz, CH_2-C3'), 5.32 (1H, app. q, *J* = 1.2 Hz, CH_2-C3''), 4.35 (2H, s, CH_2-C1'), 4.28 (2H, q, *J* = 7.1 Hz, CH_2-Et), 3.53 (2H, t, *J* = 6.3 Hz, CH_2-C6), 2.90 (2H, t, *J* = 7.2 Hz, CH_2-C4), 1.94 (2H, quintet, *J* = 6.7 Hz, CH_2-C5), 1.32 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4 (C-C3), 161.4 (C-C1), 144.4 (C-C2'), 138.8 (C-Ph), 128.3 (2 × CH-Ph), 127.7 (CH-Ph), 126.1 (2 × CH-Ph), 114.1 (CH_2-C3'), 72.7 (CH_2-C1'), 69.1 (CH_2-C6), 61.3 (CH_2-Et), 36.9 (CH_2-C4), 24.2 (CH_2-C5), 14.4 (CH_3-Et) (C-C2 not visible); HRMS (CI-isobutane) for $C_{17}H_{21}O_4N_2$ ($[M+H]^+$) calcd 317.1501, found 317.1542; LRMS (CI-isobutane) *m/z* (intensity); 317.4 ($[M+H]^+$) (22), 289.3 (61), 271.3 (29), 155.2 (100).

Ethyl 2-diazo-3-oxo-6-(2'-phenylallyloxy) hexanate **294**



DBU (1.25 mL, 8.34 mmol) was added to a solution of ethyl 3-oxo-6-(2'-phenylallyloxy) hexanate **297** (2.22 g, 7.64 mmol) and ABSA (2.21 g, 9.18 mmol) in anhydrous acetonitrile (20 mL) at 0 ºC. The reaction was slowly allowed to warm to room temperature. After 23 h the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (20 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic fractions were washed with brine (50 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded ethyl 2-diazo-3-oxo-6-(2'-phenylallyloxy) hexanate (1.73 g, 5.48 mmol, 72%) as a yellow oil. Spectroscopic data identical with above.

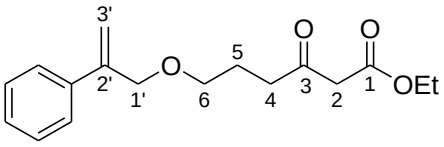
Ethyl 2-diazo-3-hydroxy-6-(2'-phenylallyloxy) hexanate **296**



A solution of 4-(2'-phenylallyloxy)-1-butanol **287** (32.3 mg, 0.157 mmol) in anhydrous dichloromethane (1.5 mL) was added to a stirred suspension of Dess-Martin periodinane (73.8 mg, 0.174 mmol) in anhydrous dichloromethane (1.5 mL) at room temperature. After 1.5 h, the reaction mixture was diluted with diethyl ether (5 mL), washed with a mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution (1:1, 6 mL) followed by brine (8 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude aldehyde product was used without further purification.

To a solution of ethyl diazoacetate (20 µL, 0.19 mmol) in anhydrous acetonitrile (0.4 mL) at room temperature was added successively a solution of DBU (10 µL, 0.067 mmol) in anhydrous acetonitrile (0.2 mL) and a solution of the crude aldehyde in anhydrous acetonitrile (1.4 mL). After 3 days, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (3 mL) and extracted with dichloromethane (3 × 4 mL). The combined organic fractions were washed with brine (5 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 3:2) afforded ethyl 2-diazo-3-hydroxy-6-(2'-phenylallyloxy) hexanate (16.1 mg, 50.6 µmol, 32% over two steps) as a yellow oil. R_f = 0.13 (petroleum ether—diethyl ether, 7:3); ν_{max} (neat) 3421, 2976, 2857, 2089, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47—7.44 (2H, m, 2 × CH-Ph), 7.36—7.29 (3H, m, 3 × CH-Ph), 5.52 (1H, m, CH_2-C3'), 5.32 (1H, app. q, *J* = 1.3 Hz, CH_2-C3'), 4.63 (1H, ddd, *J* = 6.5, 6.5, 4.2 Hz, CH-C3), 4.38 (2H, d, *J* = 0.7 Hz, CH_2-C1'), 4.23 (2H, q, *J* = 7.1 Hz, CH_2-Et), 3.55—3.50 (2H, m, CH_2-C6), 2.90 (1H, br s, OH), 1.82—1.66 (4H, m, CH_2-C4, CH_2-C5), 1.28 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C-C1), 144.2 (C-C2'), 138.7 (C-Ph), 128.4 (2 × CH-Ph), 127.8 (CH-Ph), 126.1 (2 × CH-Ph), 114.4 (CH_2-C3'), 72.9 (CH_2-C1'), 69.5 (CH_2-C6), 66.2 (CH-C3), 60.9 (CH_2-Et), 31.6 (CH_2-C5), 25.9 (CH_2-C4), 14.5 (CH_3-Et) (C-C2 not visible).

Ethyl 3-oxo-6-(2'-phenylallyloxy)-hexanate **297**



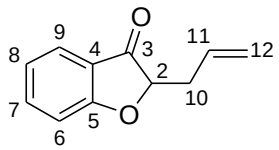
A solution of 4-(2'-phenylallyloxy)-1-butanol **287** (207 mg, 1.00 mmol) in anhydrous dichloromethane (6 mL) was added to a stirred mixture of Dess-Martin periodinane (551 mg, 1.30 mmol) in anhydrous dichloromethane (6 mL) at room temperature. After 3 h, the reaction mixture was diluted with diethyl ether (10 mL) and washed with a mixture of saturated aqueous $NaHCO_3$ solution (20 mL) and 10% aqueous $Na_2S_2O_3$ solution (20 mL) followed by brine (45 mL), dried over Na_2SO4, filtered and reduced *in vacuo*. Ethyl diazoacetate (0.13 mL, 1.2 mmol) was added dropwise to a mixture of the crude aldehyde and $NbCl_5$ (15.3 mg, 56.6 μmol) in anhydrous dichloromethane (10 mL) at 25 ºC. After 65 h the reaction was diluted with dichloromethane (10 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded ethyl 3-oxo-6-(2'-phenylallyloxy)-hexanate (171 mg, 0.590 mmol, 59% over two steps) as a colourless oil. R_f = 0.20 (petroleum ether—diethyl ether, 4:1); ν_{max} (neat) 3057, 2933, 2862, 1740, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47—7.38 (2H, m, 2 × CH-Ph), 7.37—7.28 (3H, m, 3 × CH-Ph), 5.51 (1H, dt, *J* = 1.3, 0.6 Hz, CH_2-C3'), 5.30 (1H, app. q, *J* = 1.3 Hz, CH_2-C3'), 4.34 (2H, dd, *J* = 1.3, 0.6 Hz, CH_2-C1'), 4.18 (2H, q, *J* = 7.2 Hz, CH_2-Et), 3.48 (2H, t, *J* = 6.0 Hz, CH_2-C6), 3.35 (2H, s, CH_2-C2), 2.55 (2H, t, *J* = 7.1 Hz, CH_2-C4), 1.87 (2H, tt, *J* = 7.1, 6.0 Hz, CH_2-C5), 1.27 (3H, t, *J* = 7.2 Hz, CH_3-Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.6 (C-C3), 167.2 (C-C1), 144.3 (C-C2'), 138.7 (C-Ph), 128.6 (2 × CH-Ph), 127.8 (CH-Ph), 126.1 (2 × CH-Ph), 114.3 (CH_2-C3'), 72.7 (CH_2-C1'), 68.6 (CH_2-C6), 61.3 (CH_2-Et), 49.3 (CH_2-C2), 39.6 (CH_2-C4), 23.6 (CH_2-C5), 14.1 (CH_3-Et); HRMS (CI-isobutane) for $C_{17}H_{23}O_4$ ($[M+H]^+$) calcd 291.1596, found 291.1597; LRMS (CI-isobutane) *m/z* (intensity); 291.4 ($[M+H]^+$) (11), 243.3 (18), 193.3 (62), 157.2 (10). Anal. calcd. for $C_{17}H_{22}O_4$: C 70.32%; H 7.64%. Found: C 69.98%; H 7.64%.

Standard procedure for cyclisation reaction

A solution of diazoketone in appropriate solvent (1 mL per 0.1 mmol of diazoketone) was added dropwise to a solution of catalyst (1—10 mol%) in an equivalent volume of

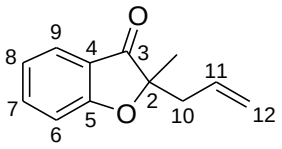
the same solvent at reflux. For asymmetric cyclisation reactions, chiral ligand (1.2—12 mol%) was also present in the catalyst solution. The reaction was monitored by TLC until completion, when it was cooled to room temperature and quenched by the addition of aqueous 0.5 M K_2CO_3 solution. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic fractions were washed with water followed by brine, dried over $MgSO_4$, filtered and reduced *in vacuo*. The residue was purified by flash column chromatography to give the product.

2-Allyl-3-benzofuranone **300**



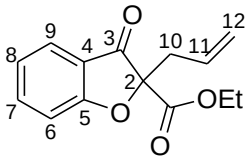
Following the general procedure, 1-(2'-allyloxyphenyl)-2-diazoethanone **248** (66.6 mg, 0.347 mmol) in anhydrous dichloromethane was added to a solution of $Cu(acac)_2$ (5 mol%) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-allyl-3-benzofuranone (34.7 mg, 0.199 mmol, 57%) as a colourless oil. R_f = 0.45 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3079, 2921, 1712, 1612, 1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, ddd, *J* = 7.8, 1.5, 0.7 Hz, CH-C9), 7.62 (1H, ddd, *J* = 8.5, 7.1, 1.5 Hz, CH-C7), 7.14 (1H, app. dt, *J* = 8.5, 0.7 Hz, CH-C6), 7.09 (1H, ddd, *J* = 7.8, 7.1, 0.7 Hz, CH-C8), 5.83 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH-C11), 5.24 (1H, ddt, *J* = 17.1, 1.3, 1.3 Hz, *trans*-CH_2-C12), 5.14 (1H, ddt, *J* = 10.2, 1.3, 1.3 Hz, *cis*-CH_2-C12), 4.63 (1H, dd, *J* = 7.4, 4.2 Hz, CH-C2), 2.81 (1H, dddt, *J* = 14.9, 6.9, 4.2, 1.3 Hz, CH_2-C10), 2.53 (1H, dddt, *J* = 14.9, 7.4, 6.9, 1.3 Hz, CH_2-C10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4 (C-C3), 172.7 (C-C5), 138.1 (CH-C7), 131.7 (CH-C11), 124.3 (CH-C9), 121.9 (CH-C8), 121.0 (C-C4), 119.0 (CH_2-C12), 113.6 (CH-C6), 84.6 (CH-C2), 35.5 (CH_2-C10); HRMS (EI) for $C_{11}H_{10}O_2$ (M^+) calcd 174.0681, found 174.0684; LRMS (EI) *m/z* (intensity); 174.13 (M^+) (80), 134.11 (100), 120.07 (50).

2-Allyl-2-methyl-3-benzofuranone **301**[86]



Following the general procedure, 1-(2'-allyloxyphenyl-2-diazopropan-1-one **264** (258 mg, 1.20 mmol) in anhydrous dichloromethane (5 mL) was added dropwise to a solution of $Cu(acac)_2$ (10 mol%) in anhydrous dichloromethane (20 mL) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 9:1) afforded 2-allyl-2-methyl-3-benzofuranone (165 mg, 0.877 mmol, 73%) as a colourless oil. R_f = 0.43 (petroleum ether—ethyl acetate, 96:4); ν_{max} (neat) 3078, 2980, 1714, 1611, 1464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, ddd, *J* = 7.7, 1.5, 0.7 Hz, CH-C9), 7.61 (1H, ddd, *J* = 8.5, 7.2, 1.5 Hz, CH-C7), 7.10—7.04 (2H, m, CH-C6, CH-C8), 5.69 (1H, ddt, *J* = 17.2, 10.1, 7.2 Hz, CH-C11), 5.14 (1H, ddt, *J* = 17.2, 1.4, 1.1 Hz, *trans*-CH_2-C12), 5.06 (1H, ddt, *J* = 10.1, 1.9, 1.1 Hz, *cis*-CH_2-C12), 2.55 (2H, dt, *J* = 7.2, 1.1 Hz, CH_2-C10), 1.44 (3H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0 (C-C3), 171.7 (C-C5), 138.2 (CH-C7), 131.0 (CH-C11), 124.7 (CH-C9), 121.8 (CH-C8), 120.5 (C-C4), 119.8 (CH_2-C12), 113.6 (CH-C6), 89.6 (C-C2), 41.2 (CH_2-C10), 21.4 (CH_3-Me); HRMS (EI) for $C_{12}H_{12}O_2$ (M^+) calcd 188.0837, found 188.0838; LRMS (EI) *m/z* (intensity); 188.0 (M^+) (100), 148.0 (100), 121.0 (100), 91.0 (100), 84.9 (100).

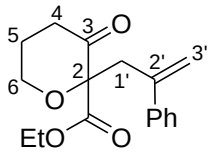
2-Allyl-2-carboethoxy-3-oxo-2,3-dihydrobenzofuran **302**[260]



Following the general procedure, ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate **241** (29.2 mg, 0.106 mmol) in anhydrous 1,2-dichloroethane (9 mL) was added dropwise to a solution of $Cu(acac)_2$ (10 mol%) in anhydrous 1,2-dichloroethane (3 mL) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-allyl-2-carboethoxy-3-oxo-2,3-dihydrobenzofuran (16.6 mg, 0.0674 mmol, 61%) as a colourless oil. R_f = 0.35 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3078, 2924, 1751, 1721, 1613, 1466 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69—7.64 (2H, m, CH-C7, CH-C9), 7.25—7.22 (1H, m, C6), 7.13 (1H, app. td, *J* = 7.2, 0.6 Hz, CH-C8), 5.68 (1H, ddt, *J* = 17.1, 10.1, 7.1 Hz, CH-C11), 5.23 (1H, ddt, *J* = 17.1, 1.4, 1.2 Hz, *trans*-CH_2-C12),

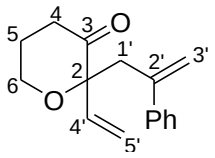
5.11 (1H, ddt, *J* = 10.1, 1.7, 1.2 Hz, *cis*-CH_2-C12), 4.28—4.20 (2H, m, CH_2-Et), 3.07 (1H, ddt, *J* = 14.4, 7.1, 1.2 Hz, CH_2-C10), 2.83 (1H, ddt, *J* = 14.4, 7.1, 1.2 Hz, CH_2-C10), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7 (C-C3), 172.4 (C-CO_2Et), 165.6 (C-C5), 138.7 (CH-C7), 129.7 (CH-C11), 125.0 (CH-C9), 122.7 (CH-C8), 120.8 (CH_2-C12), 119.7 (C-C4), 113.7 (CH-C6), 90.9 (C-C2), 62.8 (CH_2-Et), 38.4 (CH_2-C10), 14.1 (CH_3-Et); HRMS (EI) for $C_{14}H_{14}O_4$ (M^+) calcd 246.0892, found 246.0893; LRMS (EI) *m*/*z* (intensity); 246 (M^+) (44), 173 (78), 121 (36), 85 (100).

3-Oxo-2-(2'-phenylallyl)-tetrahydropyran-2-carboxylic acid ethyl ester **304**



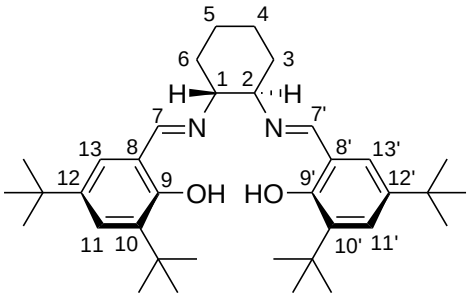
Following the general procedure, ethyl 2-diazo-3-oxo-6-(2'-phenylallyloxy) hexanate **294** (66.4 mg, 0.210 mmol) in anhydrous 1,2-dichloroethane was added dropwise to a solution of $Rh_2(OAc)_4$ (10 mol%) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-(2'-phenylallyl)-2-vinyl dihydro-3-pyranone (45.3 mg, 0.157 mmol, 75%) as a colourless oil. R_f = 0.15; (petroleum ether—diethyl ether, 4:1); ν_{max} (neat) 3369, 2977, 1728, 1629 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39—7.36 (2H, m, 2 × CH-Ph), 7.31—7.20 (3H, m, 3 × CH-Ph), 5.36 (1H, d, *J* = 1.5 Hz, CH_2-C3'), 5.24 (1H, dt, *J* = 1.5, 0.9 Hz, CH_2-C3'), 4.05 (1H, ddd, *J* = 12.0, 11.0, 3.3 Hz, CH_2-C6), 3.93 (1H, dddd, *J* = 12.0, 4.9, 3.2, 1.7 Hz, CH_2-C6), 3.86 (1H, dq, *J* = 10.8, 7.1 Hz, CH_2-Et), 3.75 (1H, dq, *J* = 10.8, 7.1 Hz, CH_2-Et), 3.43 (1H, dd, *J* = 14.8, 0.9 Hz, CH_2-C1'), 2.97 (1H, dd, *J* = 14.8, 0.9 Hz, CH_2-C1'), 2.51 (1H, dddd, *J* = 15.6, 5.5, 4.2, 1.7 Hz, CH_2-C4), 2.41 (1H, ddd, *J* = 15.6, 11.4, 6.4 Hz, CH_2-C4), 2.13—2.04 (1H, m, CH_2-C5), 2.03 (1H, m, CH_2-C5), 1.10 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.2 (C-C3), 168.3 (C-CO_2Et), 142.7 (C-C2'), 141.6 (C-Ph), 128.0 (2 × CH-Ph), 127.3 (CH-Ph), 126.8 (2 × CH-Ph), 118.1 (CH_2-C3'), 86.7 (C-C2), 63.6 (CH_2-C6), 61.7 (CH_2-Et), 39.6 (CH_2-C1'), 37.5 (CH_2-C4), 26.3 (CH_2-C5), 13.9 (CH_3-Et); HRMS (EI) for $C_{17}H_{20}O_4$ (M^+) calcd 288.1362, found 288.1359; LRMS (EI) *m*/*z* (intensity); 288.1 (M^+) (60), 257.0 (23), 215.1 (64), 145.0 (43), 117.1 (100).

2-(2'-Phenylallyl)-2-vinyl dihydro-3-pyranone **305**



Following the general procedure, 3-diazo-7-(2'-phenylallyloxy)-1-hepten-4-one **291** (25.4 mg, 0.0940 mmol) in anhydrous 1,2-dichloroethane was added dropwise to a solution of $Cu(hfacac)_2$ (5 mol%) in anhydrous 1,2-dichloroethane at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-(2'-phenylallyl)-2-vinyl dihydro-3-pyranone (5.4 mg, 0.022 mmol, 24%) as a colourless oil. R_f = 0.35 (petroleum ether—diethyl ether, 4:1); ν_{max} (neat) 3393, 2962, 2360, 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38—7.35 (2H, m, 2 × CH-Ph), 7.30 (3H, m, 3 × CH-Ph), 5.77 (1H, dd, *J* = 17.6, 10.8 Hz, CH-C4'), 5.32 (1H, d, *J* = 1.7 Hz, CH_2-C3'), 5.20 (1H, dd, *J* = 17.6, 0.8 Hz, *trans*-CH_2-C5'), 5.18 (1H, dd, *J* = 10.8, 0.8 Hz, *cis*-CH_2-C5'), 5.17 (1H, m, CH_2-C3'), 3.81—3.72 (2H, m, CH_2-C6), 3.12 (1H, dd, *J* = 14.6, 0.9 Hz, CH_2-C1'), 2.85 (1H, dd, *J* = 14.6, 0.7 Hz, CH_2-C1'), 2.43—2.27 (2H, m, CH_2-C4), 2.01—1.91 (1H, m, CH_2-C5), 1.90—1.81 (1H, m, CH_2-C5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9 (C-C3), 144.2 (C-C2'), 142.5 (C-Ph), 138.1 (CH-C4'), 127.9 (2 × CH-Ph), 127.1 (CH-Ph), 126.9 (2 × CH-Ph), 117.4 (CH_2-C3'), 116.2 (CH_2-C5'), 87.4 (C-C2), 61.4 (CH_2-C6), 43.2 (CH_2-C1'), 36.3 (CH_2-C4), 24.4 (CH_2-C5); HRMS (EI) for $C_{16}H_{18}O_2$ (M^+) calcd 242.1307, found 242.1310; LRMS (EI) *m/z* (intensity); 242.1 (M^+) (6), 83.9 (100), 49.0 (88).

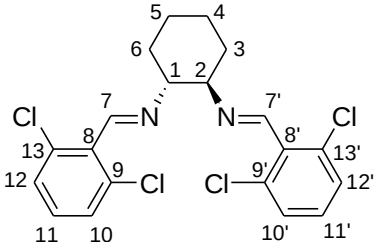
(*R*,*R*)-(—)-*N*,*N*'-Bis(3,5-di-*tert*-butylsalicylidene)1,2-cyclohexanediimine **306**[275]



A solution of (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate (265 mg, 1.00 mmol) in a mixture of 0.2 M aqueous NaOH and abs. ethanol (1:2, 35 mL) was added dropwise to 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (468 mg, 2.00 mmol), causing a yellow

precipitate. The mixture was heated at reflux for 1.5 h before it was cooled to room temperature. The reaction mixture was filtered and the precipitate was washed with abs. ethanol. The filtrate was extracted with dichloromethane (50 mL + 3 × 15 mL). The yellow precipitate was washed with dichlorometane until the solid was colourless. The combined organic fractions were washed with brine (40 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 19:1) afforded (*R*,*R*)-(—)-*N*,*N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (344 mg, 0.630 mmol, 63%) as a yellow solid. R_f = 0.63 (petroleum ether—ethyl acetate, 19:1); m.p. = 205—207 °C {Lit.[275] m.p. = 200—203 °C; Lit.[276] m.p. = 202—203 °C}; $[\alpha]_D^{25}$ —260.0 (*c* = 1.00, $CHCl_3$) {Lit.[275] $[\alpha]_D^{20}$ —315 (*c* = 1.00, $CHCl_3$); Lit.[276] $[\alpha]_D^{20}$ —309 (*c* = 1.00, CH_2Cl_2); Lit.[277] $[\alpha]_D^{20}$ —308.7 (*c* = 1.00, CH_2Cl_2); Lit.[278] $[\alpha]_D^{22}$ —312 (*c* = 1.00, CH_2Cl_2)}; ν_{max} (neat) 2951, 2864, 2596, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.71 (2H, s, 2 × OH), 8.30 (2H, s, CH-C7, CH-C7'), 7.30 (2H, d, *J* = 1.9 Hz, 2 × CH-Ar), 6.98 (2H, d, *J* = 1.9 Hz, 2 × CH-Ar), 3.35—3.24 (2H, m, CH-C1, CH-C2), 1.98—1.90 (2H, m, 2 × cyclic H), 1.90—1.82 (2H, m, 2 × cyclic H), 1.80—1.64 (2H, m, 2 × cyclic H), 1.50—1.44 (2H, m, 2 × cyclic H), 1.41 (18H, s, 6 × CH_3-*t*-Bu), 1.23 (18H, s, 6 × CH_3-*t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (CH-C7, CH-C7'), 158.1 (C-C9, C-C9'), 140.0 (C-C12, C-C12'), 136.4 (C-C10, C-C10'), 126.8 (2 × CH-Ar), 126.1 (2 × CH-Ar), 117.9 (2 × Ar-C-C1), 72.5 (CH-C1, CH-C2), 35.0 (2 × C-*t*-Bu), 34.1 (2 × C-*t*-Bu), 33.4 (2 × CH_2-cyclohexane), 31.5 (6 × CH_3-*t*-Bu), 29.5 (6 × CH_3-*t*-Bu), 24.5 (2 × CH_2-cyclohexane); HRMS (CI-isobutane) for $C_{36}H_{55}O_2N_2$ ($[M+H]^+$) calcd 547.4264, found 547.4274; LRMS (CI-isobutane) *m*/*z* (intensity); 547.7 ($[M+H]^+$) (100), 235.4 (10), 113.2 (8).

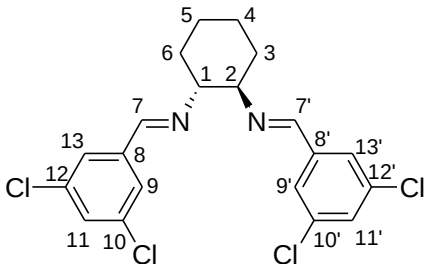
(+)-*N*,*N'*-Bis(2',6'-dichlorobenzylidene)-*trans*-1,2-diamino-cyclohexane **309**[279]



A solution of (1*R*,2*R*)-(—)-1,2-diaminocyclohexane (117 mg, 1.03 mmol) and 2,6-dichlorobenzaldehyde (351 mg, 2.01 mmol) in anhydrous methanol (10 mL) was heated at reflux. After 5.5 h, the reaction was cooled to room temperature, causing

precipitation. The mixture was filtered, and the precipitate washed with cold methanol then dried *in vacuo* to afford (+)-*N*,*N'*-bis(2',6'-dichlorobenzylidene)-*trans*-1,2-diaminocyclohexane (246 mg, 0.574 mmol, 57%) as a colourless solid. R_f = 0.30 (petroleum ether—ethyl acetate, 9:1); m.p. = 150—152 °C; $[\alpha]_D^{25}$ +43.7 (*c* = 1.00, $CHCl_3$) {Lit.[279] $[\alpha]_D^{20}$ +18.3 (*c* = 1.60, $CHCl_3$)}; ν_{max} (neat) 2931, 2855, 1645, 1582, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (2H, s, CH-C7, CH-C7'), 7.28 (4H, d, *J* = 8.4 Hz, CH-C10, CH-C10', CH-C12, CH-C12'), 7.17 (2H, t, *J* = 8.4 Hz, CH-C11, CH-C11'), 3.62—3.59 (2H, m, CH-C1, CH-C2), 1.90 (6H, s, 3 × CH_2), 1.52 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6 (CH-C7, CH-C7'), 134.8 (C-C9, C-C9', C-C13, C-C13'), 132.9 (C-C8, C-C8'), 130.0 (CH-C11, CH-C11'), 128.6 (CH-C10, CH-C10', CH-C12, CH-C12'), 74.9 (CH-C1, CH-C2), 32.9 (2 × CH_2), 24.2 (2 × CH_2); HRMS (CI-isobutane) for $C_{20}H_{19}N_2Cl_4$ ($[M+H]^+$) calcd 427.0302, found 427.0307; LRMS (CI-isobutane) *m*/*z* (intensity); 429.1 ($[M+H]^+$) (100), 393.1 (11), 255.2 (7).

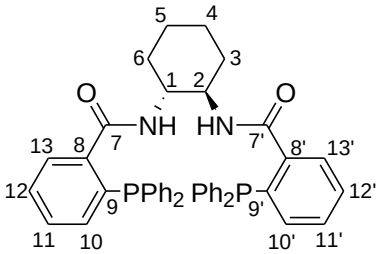
(+)-*N*,*N'*-Bis(3',5'-dichlorobenzylidene)-*trans*-1,2-diamino-cyclohexane **310**[280]



A solution of (1*R*,2*R*)-(—)-1,2-diaminocyclohexane (118 mg, 1.03 mmol) and 3,5-dichlorobenzaldehyde (356 mg, 2.04 mmol) in anhydrous methanol (10 mL) was heated at reflux. After 5 h, the reaction was cooled to 0 °C. A yellow oil, insoluble in methanol, was produced. The methanol was decanted off and the oil was washed with cold methanol. When the oil was dried under high vacuum, crystallization of the product occurred. (—)-*N*,*N'*-Bis(3',5'-dichlorobenzylidene)-*trans*-1,2-diaminocyclo-hexane (112 mg, 0.262 mmol, 26%) was afforded as a yellow solid. R_f = 0.45 (petroleum ether—ethyl acetate, 9:1); m.p. = 110—112 °C {Lit.[280] m.p. = 112—114 °C}; $[\alpha]_D^{26}$ +183.0 (*c* = 1.03, $CHCl_3$) {Lit.[280] $[\alpha]_D^{20}$ +252.3 (*c* = 0.40, MeOH)}; ν_{max} (neat) 3078, 2932, 2854, 1644, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, s, CH-C7, CH-C7'), 7.47 (4H, d, *J* = 1.6 Hz, CH-C9, CH-C9', CH-C13, CH-C13'), 7.33 (2H, s, CH-C11, CH-C11'), 3.42—3.36 (2H, m, CH-C1, CH-C2), 1.89—1.72 (6H, m, 3 × CH_2), 1.54—1.43 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (CH-C7, CH-C7'), 139.0 (C-C8, C-C8'), 135.3 (C-C10, C-C10',

C-C12, C-C12'), 130.2 (CH-C11, CH-C11'), 126.2 (CH-C9, CH-C9', CH-C13, CH-C13'), 73.7 (CH-C1, CH-C2), 32.7 (CH_2-C3, CH_2-C6), 24.2 (CH_2-C4, CH_2-C5); HRMS (CI-isobutane) for $C_{20}H_{19}N_2Cl_4$ ($[M+H]^+$) calcd 427.0302, found 427.0298; LRMS (CI-isobutane) *m*/*z* (intensity); 429.0 ($[M+H]^+$) (90), 271.1 (10), 185.1 (100).

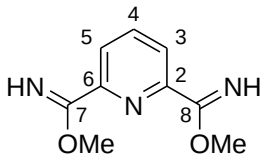
(+)-(1*R*,2*R*)-1,2-Bis[(*o*-diphenylphosphanyl)benzoylamino]-cyclohexane **313**[281,282]



(1*R*,2*R*)-(−)-1,2-Diaminocyclohexane (118 mg, 1.03 mmol) was added to a solution of 2-(diphenylphosphino)benzoic acid (680 mg, 2.22 mmol), DMAP (12.6 mg, 0.103 mmol) and EDCI (465 mg, 2.43 mmol) in anhydrous dichloromethane (7 mL) at room temperature. Diethyl ether (15 mL) was added after 20 h. The resulting mixture was washed with successively aqueous 1M HCl solution (3 × 15 mL), water (15 mL) and brine (15 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Recrystallisation (acetonitrile) afforded (+)-(1*R*,2*R*)-1,2-bis[(*o*-diphenylphosphanyl)benzoylamino]-cyclohexane (377 mg, 0.546 mmol, 53%) as a light yellow solid. R_f = 0.20 (petroleum ether—ethyl acetate, 9:1); m.p. = 144—145 ºC {Lit.[282] m.p. = 136—139 ºC}; $[\alpha]_D^{28}$ +48.6 (*c* = 1.02, $CHCl_3$) {Lit.[282] $[\alpha]_D^{24}$ +55.6 (*c* = 2.30, CH_2Cl_2); Lit.[281] $[\alpha]_D$ +55.1 (*c* = 2.85, CH_2Cl_2); Lit.[283] $[\alpha]_D^{21}$ +61 (*c* = 2.30, $CHCl_3$); Lit.[284] $[\alpha]_D^{25}$ +59 (*c* = 1.00, $CHCl_3$)}; ν_{max} (neat) 3289, 3051, 2924, 1782, 1717, 1634, 1537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58—7.55 (2H, m, CH-C13, CH-C13'), 7.31—7.18 (24H, m, 20 × CH-Ph, CH-C11, CH-C11', CH-C12, CH-C12'), 6.92—6.89 (2H, m, CH-C10, CH-C10'), 6.33 (2H, d, *J* = 7.4 Hz, 2 × NH), 3.81—3.72 (2H, m, CH-C1, CH-C2), 1.85 (2H, d, *J* = 13.4 Hz, *ax*-CH_2-C4, *ax*-CH_2-C5), 1.64 (2H, d, *J* = 9.3 Hz, *eq*-CH_2-C4, *eq*-CH_2-C5), 1.20 (2H, dddd, *J* = 10.1, 10.1, 10.1, 10.1 Hz, *eq*-CH_2-C3, *eq*-CH_2-C6), 0.98 (2H, m, *ax*-CH_2-C3, *ax*-CH_2-C6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (C-C7, C-C7'), 140.8 (d, *J* = 24.5, C-C9, C-C9'), 137.7 (q, *J* = 5.9 Hz, 4 × C-Ph), 136.6 (d, *J* = 21.5 Hz, C-C14, C-C14'), 134.3 (2 × CH), 133.9 (d, *J* = 20.2 Hz, 8 × CH), 130.2 (2 × CH), 128.8 (2 × CH), 128.6 (d, *J* = 5.6 Hz, 4 × CH), 128.5 (d, *J* = 2.9 Hz, 4 × CH), 128.4 (d, *J* = 7.4 Hz, 4 × CH), 127.5 (2 × CH), 53.9 (CH-C1, CH-C2), 32.0 (CH_2-C3, CH_2C6), 24.6 (CH_2-C4, CH_2-C5); HRMS (FAB) for $C_{44}H_{41}O_2N_2P_2$ ($[M+H]^+$) calcd

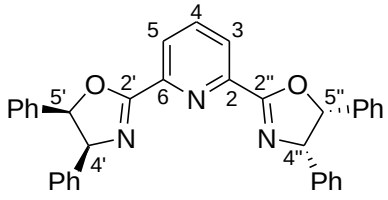
691.2643, found 691.2639; LRMS (FAB) *m/z* (intensity); 691.2 ([M+H]$^+$) (93), 387.2 (22), 304.1 (100), 289.1 (29), 228.3 (26).

Dimethyl pyridine-2,6-dicarboximidate **315**[285]



Sodium methoxide (25.2 mg, 0.466 mmol) was added to a mixture of pyridine-2,6-carbodinitrile (504 mg, 3.90 mmol) in anhydrous methanol (8 mL) at room temperature. After 3 h, the reaction was quenched by the addition of glacial acetic acid (29 µL, 0.51 mmol). The solvent was removed *in vacuo*. Dimethyl pyridine-2,6-dicarboximidate (741 mg, 3.83 mmol, 98%) was obtained as a colourless solid. R_f = 0.15 (petroleum ether—ethyl acetate, 9:1); m.p. = 100—102 ºC {Lit.[286] m.p. = 100—103 ºC}; ν_{max} (neat) 2945, 1689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (2H, br s, 2 × NH), 7.94—7.93 (3H, m, CH-C3, CH-C4, CH-C5), 4.04 (6H, s, 2 × CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (C-C7, C-C8), 147.0 (C-C2, C-C6), 139.0 (CH-C4), 122.6 (CH-C3, CH-C5), 54.1 (2 × CH_3-Me); HRMS (CI-isobutane) for $C_9H_{12}O_2N_3$ ([M+H]$^+$) calcd 194.0930, found 194.0927; LRMS (CI-isobutane) *m/z* (intensity); 194.3 ([M+H]$^+$) (100), 162.3 (15).

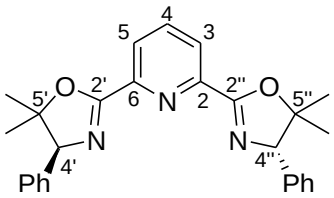
(—)-2,6-Bis-(4',5'-diphenyl-4',5'-dihydro-2'-oxazolyl)-pyridine **317**



A solution of dimethyl pyridine-2,6-dicarboximidate **315** (71.2 mg, 0.369 mmol) and (1*R*,2*S*)-(—)-2-amino-1,2-diphenylethanol (158 mg, 0.739 mmol) in anhydrous dichloromethane (1.5 mL) was heated at 50 ºC in a sealed tube under argon atmosphere. After 4 days, the reaction was cooled to room temperature. The reaction mixture was washed with water (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Recrystallisation (ethyl acetate) afforded (—)-2,6-bis-(4',5'-diphenyl-

4',5'-dihydro-2'-oxazolyl)-pyridine (112 mg, 0.214 mmol, 58%) as a colourless solid. R_f = 0.20 (dichloromethane—methanol, 98:2); m.p. = 238—240 °C; $[\alpha]_D^{26}$ —308 (*c* = 0.98, $CHCl_3$); ν_{max} (neat) 3431, 3025, 1629, 1572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (2H, d, *J* = 7.8 Hz, CH-C3, CH-C5), 8.04 (1H, t, *J* = 7.8 Hz, CH-C4), 7.08—6.96 (20H, m, 20 × CH-Ph), 6.14 (2H, d, *J* = 10.3 Hz, CH-C5', CH-C5''), 5.83 (2H, *J* = 10.3 Hz, CH-C4', CH-C4''); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (C-C2', C-C2''), 147.2 (C-C2, C-C6), 137.6 (2 × C-Ph), 137.2 (2 × C-Ph), 136.0 (CH-C4), 127.9 (4 × CH-Ar), 127.7 (4 × CH-Ar), 127.6 (4 × CH-Ar), 127.5 (2 × CH-Ar), 127.1 (2 × CH-Ar), 126.6 (4 × CH-Ar), 126.5 (2 × CH-Ar), 86.3 (CH-C5', CH-C5''), 74.5 (CH-C4', CH-C4''); HRMS (EI) for $C_{35}H_{27}O_2N_3$ (M^+) calcd 521.2103, found 521.2101; LRMS (EI) *m/z* (intensity); 521.5 (M^+) (30), 284.2 (18), 248.1 (24), 180.1 (100).

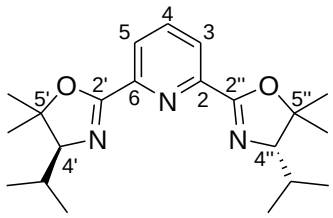
(+)-2,6-Bis-(4'-phenyl-5',5'-dimethyl-4',5'-dihydro-2'-oxazolyl)-pyridine **318**



A solution of dimethyl pyridine-2,6-dicarboximidate **315** (49.0 mg, 0.254 mmol) and (+)-(S)-1-amino-2-methyl-1-phenyl-2-propanol **320** (83.4 mg, 0.505 mmol) in anhydrous dichloromethane (1.0 mL) was heated at 50 °C in a sealed tube under argon atmosphere. After 3 days the reaction was cooled to room temperature. The mixture was washed with water (5 mL) and brine (5 mL), then dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (dichloromethane—methanol, 98:2) afforded (+)-2,6-bis-(4'-phenyl-5',5'-dimethyl-4',5'-dihydro-2'-oxazolyl)-pyridine (102 mg, 0.239 mmol, 96%) as a colourless solid. R_f = 0.14 (dichloromethane—methanol, 98:2); m.p. = 58—60 °C; $[\alpha]_D^{26}$ +49.4 (*c* = 0.88, $CHCl_3$); ν_{max} (neat) 3028, 2977, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (2H, d, *J* = 7.8 Hz, CH-C3, CH-C5), 7.92 (1H, t, *J* = 7.8 Hz, CH-C4), 7.36—7.26 (10H, m, 10 × CH-Ph), 5.13 (2H, s, CH-C4', CH-C4''), 1.72 (6 H, s, 2 × CH_3-Me), 1.00 (6H, s, 2 × CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (C-C2', C-C2''), 147.6 (C-C2, C-C6), 138.4 (2 × C-Ph), 137.3 (CH-C4), 128.3 (4 × CH-Ph), 127.6 (2 × CH-Ph), 127.3 (4 × CH-Ph), 126.1 (CH-C3, CH-C5), 88.8 (C-C5', C-C5''), 78.7 (CH-C4', CH-C4''), 29.3 (2 × CH_3-Me), 24.0 (2 × CH_3-Me); HRMS (FAB) for $C_{27}H_{28}O_2N_3$

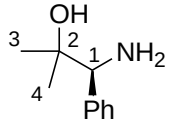
([M+H]$^+$) calcd 426.2182, found 426.2178; LRMS (FAB) *m*/*z* (intensity); 426.2 ([M+H]$^+$) (100), 131.1 (30).

(—)-2,6-Bis[5',5'-dimethyl-4'-(*S*)-isopropyloxazolin-2'-yl] pyridine **319**



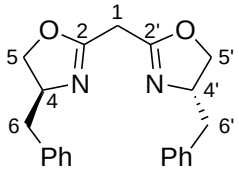
Dimethyl pyridine-2,6-dicarboximidate **315** (132 mg, 0.684 mmol), (*S*)-3-amino-2,4-dimethyl-2-pentanol hydrochloride (230 mg, 1.37 mmol) and anhydrous dichloromethane (2.8 mL) were heated at 50 ºC in a sealed tube. After 3 days, the reaction was cooled to room temperature. The reaction mixture was washed with water (5 mL) followed by brine (5 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (dichloromethane—methanol, 98:2) afforded (—)-2,6-bis-(4'-isopropyl-5',5'-dimethyl-4',5'-dihydro-2-oxazolyl)-pyridine (59.1 mg, 0.166 mmol, 25%) as a colourless solid. R_f = 0.10 (dichloromethane—methanol, 98:2); m.p. = 105—107 ºC; $[\alpha]_D^{26}$ —67.5 (*c* = 0.94, $CHCl_3$); ν_{max} (neat) 3072, 2970, 1627, 1457, 1372, 1074, 831, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H, d, *J* = 7.8 Hz, CH-C3, CH-C5), 7.82 (1H, t, *J* = 7.8 Hz, CH-C4), 3.49 (2H, d, *J* = 9.2 Hz, 2 × CH-C4'), 1.92 (2H, dqq, *J* = 9.2, 6.5, 6.5 Hz, 2 × CH-*i*-Pr), 1.60 (6H, s, 2 × CH_3-Me), 1.40 (6H, s, 2 × CH_3-Me), 1.22 (6H, d, *J* = 6.5 Hz, 2 × CH_3-*i*-Pr), 1.02 (6H, d, *J* = 6.5 Hz, 2 × CH_3-*i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, (2 × C-C2'), 147.6 (C-C2, C-C6), 137.1 (CH-C4), 125.3 (CH-C3, CH-C5), 88.1 (2 × C-C5'), 81.0 (2 × CH-C4'), 29.2 (2 × Me), 29.0 (2 × CH-*i*-Pr), 21.4 (2 × Me), 21.3 (2 × CH_3-*i*-Pr), 21.0 (2 × CH_3-*i*-Pr); HRMS (EI) for $C_{21}H_{31}O_2N_3$ (M^+) calcd 357.2416, found 357.2419; LRMS (EI) *m*/*z* (intensity); 357.3 (M^+) (11), 314.3 (100), 284.3 (13), 244.2 (10), 202.2 (25).

(+)-(*S*)-1-Amino-2-methyl-1-phenyl-2-propanol **320**[229]



Methylmagnesium bromide (3.0 M in diethyl ether, 16.5 mL, 49.5 mmol) was added dropwise to a mixture of phenylglycine methyl ester hydrochloride (1.01 g, 4.99 mmol) in anhydrous diethyl ether (20 mL) at 0 °C, after which the reaction was allowed to warm to room temperature. After 21 h, the reaction was quenched by the slow addition of acetone (15 mL) at 0 °C. Aqueous ammonia solution (25%, 14 mL) and saturated aqueous NH_4Cl solution (28 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 25 mL) and the combined organic fractions were washed with water (20 mL) before being extracted with aqueous HCl solution (0.5 M, 3 × 30 mL). NaOH (6 g) was added to the combined aqueous extracts, which were then extracted with diethyl ether (4 × 30 mL). The ethereal extracts were dried with K_2CO_3, filtered and reduced *in vacuo*. Flash column chromatography (ethyl acetate—methanol—triethylamine, 95:5:1) afforded (+)-(S)-1-amino-2-methyl-1-phenyl-2-propanol (143 mg, 0.864 mmol, 17%) as a colourless solid. R_f = 0.30; (ethyl acetate—methanol, 1:1); m.p. = 47—49 °C {Lit.[229] m.p. = 47—50 °C}; $[\alpha]_D^{26}$ +19.0 (*c* = 1.00, $CHCl_3$) {Lit.[229] $[\alpha]_D^{25}$ +25 (*c* = 1.21, $CHCl_3$)}; ν_{max} (neat) 3358—2888, 1601, 1451 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35—7.25 (5H, m, 5 × CH-Ph), 3.81 (1H, s, CH-C1), 2.05 (3H, br s, NH_2, OH), 1.22 (3H, s, CH_3-C3 or CH_3-C4), 1.04 (3H, s, CH_3-C3 or CH_3-C4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5 (C-Ph), 128.1 (2 × CH-Ph), 127.8 (2 × CH-Ph), 127.3 (CH-Ph), 72.2 (C-C2), 64.5 (CH-C1), 27.6 (CH_3-C3 or CH_3-C4), 24.8 (CH_3-C3 or CH_3-C4); HRMS (CI-isobutane) for $C_{10}H_{16}ON$ ($[M+H]^+$) calcd 166.1232, found 166.1228; LRMS (CI-isobutane) *m/z* (intensity); 166.3 ($[M+H]^+$) (100), 148.3 (34), 106.2 (33).

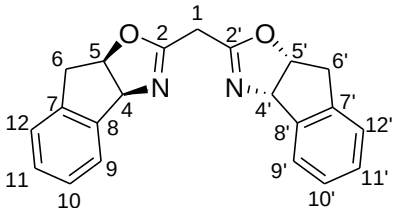
(—)-Bis[2-((4*S*)-benzyl)-1,3-oxazolinyl)]methane **331**[37]



L-Phenylalaninol (610 mg, 4.03 mmol) and diethylmalonimidate dihydrochloride (463 mg, 2.00 mmol) in anhydrous dichloromethane (10 mL) was stirred at room temperature for 29 h before the reaction was quenched by the addition of saturated

aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic fractions were washed with water (25 mL) followed by brine (25 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (dichloromethane—methanol, 19:1) afforded (—)-bis[2-((4*S*)-benzyl)-1,3-oxazolinyl)] methane (436 mg, 1.31 mmol, 65%) as a yellow oil. R_f = 0.45 (dichloromethane—methanol, 9:1); $[\alpha]_D^{22}$ —38.6 (*c* = 1.01, $CHCl_3$) {Lit.[37] $[\alpha]_D^{23}$ —62.7 (*c* = 1.26, EtOH)}; ν_{max} (neat) 3027, 2900, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32—7.27 (4H, m, 4 × CH-Ph), 7.24—7.19 (6H, m, 6 × CH-Ph), 4.48—4.39 (2H, m, CH-C4, CH-C4'), 4.24 (2H, dd, *J* = 9.9, 8.5 Hz, CH_2-C5, CH_2-C5'), 4.02 (2H, dd, *J* = 8.5, 7.2 Hz, CH_2-C5, CH_2-C5'), 3.32 (2H, s, CH_2-C1), 3.12 (2H, dd, *J* = 13.8, 5.4 Hz, CH_2-C6, CH_2-C6'), 2.68 (2H, dd, *J* = 13.8, 8.5 Hz, CH_2-C6, CH_2-C6'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (C-C2, C-C2'), 137.7 (2 × C-Ph), 129.2 (CH-Ph), 128.5 (2 × CH-Ph), 126.5 (2 × CH-Ph), 72.3 (CH_2-C5, CH_2-C5'), 67.4 (CH-C4, CH-C4'), 41.5 (CH_2-C6, CH_2-C6'), 28.4 (CH_2-C1); HRMS (EI) for $C_{21}H_{22}O_2N_2$ (M^+) calcd 334.1681, found 334.1685; LRMS (EI) *m/z* (intensity); 334.2 (M^+) (62), 243.1 (100), 109.0 (88), 91.0 (100).

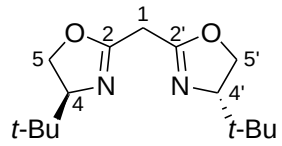
(—)-2,2'-Methylenebis[(3a*R*,8a*S*)-3a,8a-dihydro-8H-indene[1,2-d]oxazole] **332**[287]



(1*S*,2*R*)-(—)-*cis*-1-Amino-2-indanol (605 mg, 4.05 mmol) and diethylmalonimidate dihydrochloride (465 mg, 2.01 mmol) in anhydrous dichloromethane (10 mL) was stirred at room temperature for 17 h before the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic fractions were washed with water (25 mL) followed by brine (25 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (dichloromethane—methanol, 19:1) afforded (—)-2,2'-methylene-bis[(3a*R*,8a*S*)-3a,8a-dihydro-8H-indene[1,2-d]oxazole] (457 mg, 1.38 mmol, 69%) as a white solid. R_f = 0.60 (dichloromethane—methanol, 9:1); m.p. = 216—218 °C {Lit.[288] m.p. = 207—209 °C}; $[\alpha]_D^{22}$ —342.5 (*c* = 1.01, $CHCl_3$) {Lit.[288] $[\alpha]_D^{22}$ —352.7 (*c* = 3.00, $CHCl_3$); Lit.[287] $[\alpha]_D^{23}$ —377 (*c* = 1.00, $CHCl_3$); Lit.[235] $[\alpha]_D^{25}$ —271.9 (*c* = 3.11, $CHCl_3$)}; ν_{max} (neat) 3026, 2986, 2940,

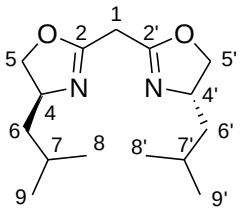
1658, 1459 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.44 (2H, m, 2 × CH-Ar), 7.29—7.22 (6H, m, 6 × CH-Ar), 5.57 (2H, d, *J* = 8.0 Hz, CH-C4, CH-C4'), 5.35 (2H, ddd, *J* = 8.0, 7.1, 1.4 Hz, CH-C5, CH-C5'), 3.39 (2H, dd, *J* = 18.0, 7.1 Hz, CH_2-C6, CH_2-C6'), 3.27 (2H, s, CH_2-C1), 3.17 (2H, dd, *J* = 18.0, 1.4 Hz, CH_2-C6, CH_2-C6'); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (C-C2, C-C2'), 141.6 (C-C8, C-C8'), 139.7 (C-C7, C-C7'), 128.5 (2 × CH-Ar), 127.5 (2 × CH-Ar), 125.4 (2 × CH-Ar), 125.2 (2 × CH-Ar), 83.6 (CH-C5, CH-C5'), 76.6 (CH-C4, CH-C4'), 39.7 (CH_2-C6, CH_2-C6'), 28.7 (CH_2-C1); HRMS (EI) for $C_{21}H_{18}O_2N_2$ (M^+) calcd 330.1368, found 330.1371; LRMS (EI) *m/z* (intensity); 330.1 (M^+) (76), 173.1 (100), 130.1 (66), 115.0 (60), 104.1 (55).

(—)-Bis[2-((4*S*)-*tert*-butyl)-1,3-oxazolinyl)]methane **333**[289]



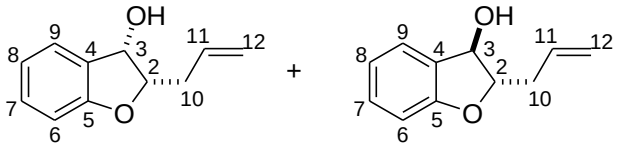
(*S*)-*tert*-Leucinol (960 mg, 8.19 mmol) and diethylmalonimidate dihydrochloride (948 mg, 4.10 mmol) was stirred at room temperature in anhydrous dichloromethane (15 mL). After 22 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic fractions were washed with water (50 mL) followed by brine (50 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (dichloromethane—methanol, 9:1) afforded (—)-bis[2-((4*S*)-*tert*-butyl)-1,3-oxazolinyl)]methane (458 mg, 1.72 mmol, 42%) as a colourless solid. R_f = 0.48 (dichloromethane—methanol, 9:1); m.p. = 39—40 °C {Lit.[289] m.p. = 51—52 °C; Lit.[37] m.p. = 52 °C; Lit.[38] m.p. = 48—49 °C}; $[\alpha]_D^{29}$ —66.6 (*c* = 1.00, $CHCl_3$) {Lit.[37] $[\alpha]_D^{23}$ —149.3 (*c* = 1.13, EtOH); Lit.[38] $[\alpha]_D$ —120 (*c* = 0.51, $CHCl_3$)}; ν_{max} (neat) 3341, 3187, 2955, 1667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.20 (2H, dd, *J* = 10.1, 8.3 Hz, CH_2-C5, CH_2-C5'), 4.09 (2H, app. t, *J* = 8.3 Hz, CH_2-C5, CH_2-C5'), 3.90—3.86 (2H, m, CH-C4, CH-C4'), 3.35 (2H, s, CH_2-C1), 0.89 (18 H, s, 6 × CH_3-*t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5 (C-C2, C-C2'), 75.8 (CH-C4, CH-C4'), 69.1 (CH_2-C5, CH_2-C5'), 33.7 (2 × C-*t*-Bu), 28.3 (CH_2-C1), 25.7 (6 × CH_3-*t*-Bu) ; HRMS (CI-isobutane) for $C_{15}H_{27}O_2N_2$ ($[M+H]^+$) calcd 267.2073, found 267.2071; LRMS (CI-isobutane) *m/z* (intensity); 267.5 ($[M+H]^+$) (100), 185.3 (44).

(−)-Bis[2-((4*S*)-isobutyl)-1,3-oxazolinyl)]methane **334**



(*S*)-(+)-Leucinol (0.53 mL, 4.2 mmol) was added to a mixture of diethylmalonimidate dihydrochloride (465 mg, 2.01 mmol) in anhydrous dichloromethane (10 mL) at room temperature. After 13 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic fractions were washed with water (25 mL) followed by brine (25 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (dichloromethane—methanol, 19:1) afforded (−)-bis[2-((4*S*)-isobutyl)-1,3-oxazolinyl)]methane (319 mg, 1.20 mmol, 60%) as a yellow oil. R_f = 0.60 (dichloromethane—methanol, 9:1); $[\alpha]_D^{22}$ −97.4 (*c* = 0.96, $CHCl_3$); ν_{max} (neat) 2955, 2870, 1665, 1589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (2H, dd, *J* = 9.4, 8.1 Hz, CH_2-C5, CH_2-C5'), 4.21—4.07 (2H, m, CH-C4, CH-C4'), 3.86 (2H, t, *J* = 8.1 Hz, CH_2-C5, CH_2-C5'), 3.32 (2H, t, *J* = 1.0 Hz, CH_2-C1), 1.80—1.70 (2H, m, CH-C7, CH-C7'), 1.61 (2H, ddd, *J* = 13.5, 6.8, 6.5 Hz, CH_2-C6, CH_2-C6'), 1.33—1.26 (2H, m, CH_2-C6, CH_2-C6'), 0.93 (12H, t, *J* = 6.8, CH_3-C8, CH_3-C9, CH_3-C8', CH_3-C9') ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (C-C2, C-C2'), 73.5 (CH_2-C5, CH_2-C5'), 64.8 (CH-C4, CH-C4'), 45.3 (CH_2-C6, CH_2-C6'), 28.5 (CH_2-C1), 25.4 (CH-C7, CH-C7'), 22.7 (CH_3-C8, CH_3-C8'), 22.7 (CH_3-C9, CH_3-C9'); HRMS (CI-isobutane) for $C_{15}H_{27}O_2N_2$ ($[M+H]^+$) calcd 267.2073, found 267.2075; LRMS (CI-isobutane) *m/z* (intensity); 267.4 ($[M+H]^+$) (100), 185.3 (71), 132.2 (25).

2-Allyl-2,3-dihydro-3-benzofuranol **338** & **339**



338 339

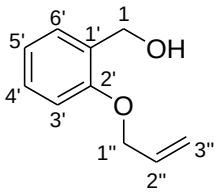
A solution of 2-allyl-3-benzofuranone **300** (24.1 mg, 0.138 mmol) in anhydrous ethanol (2 mL) was added slowly to a stirred suspension of $NaBH_4$ (21.3 mg, 0.563 mmol) in anhydrous ethanol (1 mL) at 0 °C. The reaction was slowly allowed to warm to room

temperature. After 4 h, the reaction was quenched by the addition of glacial acetic acid (0.5 mL). The mixture was partitioned between 1 M aqueous HCl solution (2 mL) and diethyl ether (2 mL) and the aqueous phase was extracted with diethyl ether (3 × 3 mL). The combined organic extracts were washed with successively saturated aqueous $NaHCO_3$ solution (2 × 5 mL), water (5 mL) and brine (5 mL). The combined ethereal extracts were then dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-allyl-2,3-dihydro-3-benzofuranol **338** and **339** (14.1 mg, 80.0 μmol, 58%) as a colourless oil. The product was afforded as a 2:1 mixture of the *syn* and *anti* diastereomers, which upon further flash column chromatography could be separated.

338: R_f = 0.28 (petroleum ether—diethyl ether, 4:1); ν_{max} (neat) 3362, 2916, 2849 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, ddd, *J* = 7.4, 1.3, 0.7 Hz, CH-C9), 7.25 (1H, app. td, *J* = 8.1, 1.3 Hz, CH-C7), 6.94 (1H, app. td, *J* = 7.4, 0.9 Hz, CH-C8), 6.88 (1H, d, *J* = 8.1 Hz, CH-C6), 6.02 (1H, ddt, *J* = 17.1, 10.2, 6.8 Hz, CH-C11), 5.29 (1H, ddt, *J* = 17.1, 1.6, 1.4 Hz, *trans*-CH_2-C12), 5.20 (1H, ddt, *J* = 10.2, 1.4, 1.3 Hz, *cis*-CH_2-C12), 5.12 (1H, dd, *J* = 7.2, 6.2 Hz, CH-C3), 4.49 (1H, ddd, *J* = 13.0, 7.2, 5.8 Hz, CH-C2), 2.78—2.65 (2H, m, CH_2-C10), 1.55 (1H, d, *J* = 6.2 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (C-C5), 134.2 (CH-C11), 130.9 (CH-C7), 128.9 (C-C4), 125.8 (CH-C9), 121.1 (CH-C8), 117.8 (CH_2-C12), 110.6 (CH-C6), 86.2 (CH-C2), 72.5 (CH-C3), 32.8 (CH_2-C10); HRMS (EI) for $C_{11}H_{12}O_2$ (M^+) calcd 176.0837, found 176.0835; LRMS (EI) *m/z* (intensity); 176.1 (M^+) (45), 158.1 (38), 131.1 (33), 121.0 (31), 82.9 (78).

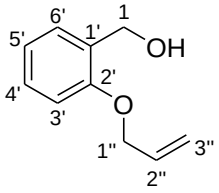
339: R_f = 0.25; (petroleum ether—diethyl ether, 4:1); ν_{max} (neat) 3338, 2916, 2849 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40—7.37 (1H, m, CH-C9), 7.25 (1H, ddd, *J* = 8.3, 7.9, 1.4 Hz, CH-C7), 6.94 (1H, app. td, *J* = 7.5, 0.9 Hz, CH-C8), 6.86 (1H, d, *J* = 8.3 Hz, CH-C6), 5.86 (1H, ddt, *J* = 17.2, 10.3, 7.0 Hz, CH-C11), 5.20 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C12), 5.16 (1H, ddt, *J* = 10.3, 2.0, 1.2 Hz, *cis*-CH_2-C12), 5.06 (1H, dd, *J* = 7.9, 3.3 Hz, CH-C3), 4.59 (1H, td, *J* = 6.7, 3.3 Hz, CH-C2), 2.55—2.38 (2H, m, CH_2-C10), 1.87 (1H, d, *J* = 7.9 Hz, OH) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (C-C5), 132.8 (CH-C11), 130.8 (CH-C7), 127.8 (C-C4), 125.6 (CH-C9), 120.9 (CH-C8), 118.5 (CH_2-C12), 110.6 (CH-C6), 90.0 (CH-C2), 76.6 (CH-C3), 37.7 (CH_2-C10); HRMS (EI) for $C_{11}H_{12}O_2$ (M^+) calcd 176.0837, found 176.0838; LRMS (EI) *m/z* (intensity); 176.1 (M^+) (50), 158.1 (23), 134.0 (100), 121.0 (36), 107.0 (38).

2'-Allyloxyphenyl methanol **348**[290]



$NaBH_4$ (140 mg, 3.71 mmol) was added to a solution of 2-allyloxybenzaldehyde **240** (301 mg, 1.85 mmol) in anhydrous methanol at room temperature. After 23 h, the reaction was quenched by the addition of glacial acetic acid (0.5 mL). The mixture was reduced *in vacuo* and the residue was partitioned between aqueous HCl solution (1 M, 10 mL) and diethyl ether (10 mL). The aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic fractions were washed with successively saturated aqueous $NaHCO_3$ solution (2 × 10 mL), water (10 mL) and brine (10 mL), then dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded 2'-allyloxyphenyl methanol (226 mg, 1.38 mmol, 75%) as a colourless oil. R_f = 0.13 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3377, 3076, 2869, 1603, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30—7.24 (2H, m, CH-C6' and CH-C4'), 6.95 (1H, td, *J* = 7.4, 0.9 Hz, CH-C5'), 6.88 (1H, d, *J* = 8.2 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.3, 10.5, 5.2 Hz, CH-C2''), 5.42 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.30 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 4.72 (2H, d, *J* = 6.4 Hz, CH_2-C1), 4.60 (2H, dt, *J* = 5.2, 1.5 Hz, CH_2-C1''), 2.34 (1H, t, *J* = 6.4 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (C-C2'), 133.0 (CH-C2''), 129.4 (C-C1'), 128.9 (CH-C4' or CH-C6'), 128.9 (CH-C4' or CH-C6'), 120.9 (CH-C5'), 117.7 (CH_2-C3''), 111.5 (CH-C3'), 68.7 (CH_2-C1''), 62.3 (CH_2-C1); HRMS (EI) for $C_{10}H_{12}O_2$ (M^+) calcd 164.0837, found 164.0834; LRMS (EI) *m/z* (intensity); 164.2 (M^+) (66), 121.1 (33), 106.1 (100), 78.1 (100).

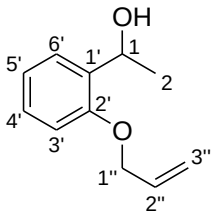
2'-Allyloxyphenyl methanol **348**



TBAF (1.0 M in THF, 0.40 mL, 0.40 mmol) was added to a solution of (2-allyloxybenzyloxy)-*tert*-butyldimethylsilane **366** (102 mg, 0.366 mmol) in anhydrous

tetrahydrofuran (1 mL) at room temperature. After 22 h, the reaction was quenched by the addition of water (2 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic fractions were washed with brine (10 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 7:3) afforded 2'-allyloxyphenyl methanol (49.6 mg, 0.302 mmol, 83%) as a colourless oil. Spectroscopic data identical with above.

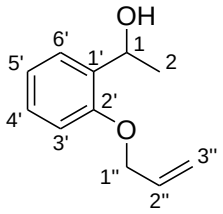
1-(2'-Allyloxyphenyl)-ethanol **349**[291]



A solution of 1-(2'-allyloxyphenyl)-ethanone **255** (213 mg, 1.21 mmol) in anhydrous methanol (3 mL) was added to a stirred mixture of $NaBH_4$ (54.6 mg, 1.44 mmol) in anhydrous methanol (8 mL) at room temperature. After 18 h, the reaction was quenched by the addition of glacial acetic acid (0.5 mL) and the mixture was reduced *in vacuo*. The residue was partitioned between diethyl ether (10 mL) and 1 M aqueous HCl solution (10 mL) and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic fractions were washed with successively saturated aqueous $NaHCO_3$ solution (2 × 10 mL), water (10 mL) and brine (10 mL), then dried over $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 1:9) afforded 1-(2'-allyloxyphenyl)-ethanol (180 mg, 1.01 mmol, 83%) as a colourless oil. R_f = 0.18 (petroleum ether—ethyl acetate, 1:9); ν_{max} (neat) 3378, 3078, 2973, 1601, 1489 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 7.5, 1.7 Hz, CH-C6'), 7.22 (1H, app. td, *J* = 8.0, 1.7 Hz, CH-C4'), 6.97 (1H, app. td, *J* = 7.5, 0.7 Hz, CH-C5'), 6.87 (1H, dd, *J* = 8.0, 0.7 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.2, 10.5, 5.1 Hz, CH-C2''), 5.43 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.30 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 5.14 (1H, dq, *J* = 6.1, 6.1 Hz, CH-C1), 4.60 (2H, dt, *J* = 5.1, 1.5 Hz, CH_2-C1''), 2.61 (1H, d, *J* = 6.1 Hz, OH), 1.53 (3H, d, *J* = 6.1 Hz, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C-C2'), 133.7 (C-C1'), 133.0 (CH-C2''), 128.2 (CH-C4'), 126.2 (CH-C6'), 121.0 (CH-C5'), 117.6 (CH_2-C3''), 111.6 (CH-C3'), 68.7 (CH_2-C1''), 66.7 (CH-C1), 22.9 (CH_3-C2); HRMS (EI) for $C_{11}H_{14}O_2$ (M^+) calcd 178.0994, found 178.0995;

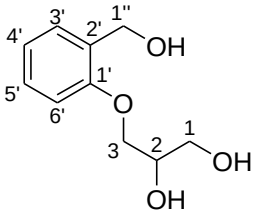
LRMS (EI) *m/z* (intensity); 178.1 (M^+) (92), 163.1 (79), 135.1 (79), 121.1 (100), 120.1 (100), 91.1 (90).

1-(2'-Allyloxyphenyl)-ethanol **349**



A solution of MeI (0.17 mL, 2.8 mmol) in anhydrous diethyl ether (2 mL) was added dropwise to a stirred suspension of magnesium turnings (65 mg, 2.7 mmol) in anhydrous diethyl ether (1 mL) at room temperature, causing the suspension to heat to reflux. After 40 min, a solution of 2-allyloxybenzaldehyde **240** (0.38 mL, 2.5 mmol) in anhydrous diethyl ether (2 mL) was added dropwise. After 18 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (3 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic fractions were washed with brine (10 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 1:4) afforded 1-(2'-allyloxyphenyl)-ethanol (353 mg, 1.98 mmol, 79%) as a colourless oil. Spectroscopic data identical with above.

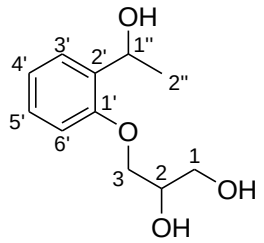
3-(2'-Hydroxymethylphenoxy)-1,2-propanediol **356**



NMO (72.5 mg, 0.619 mmol) was added to a mixture of 2'-allyloxyphenyl methanol **348** (77.9 mg, 0.474 mmol) in chloroform (3.4 mL) and water (0.09 mL). Aqueous OsO_4 solution (4%, 90 µL, 14 µmol) was slowly added to the mixture at room temperature. After 4 h, the reaction was quenched by addition of saturated aqueous sodium thiosulfate solution (2 mL). The mixture was reduced *in vacuo* and the residue was diluted with toluene and reduced *in vacuo* four times. Flash column chromatography

(dichloromethane—methanol, 9:1) afforded 3-(2'-hydroxy-methylphenoxy)-1,2-propanediol (73.1 mg, 0.369 mmol, 78%) as a colourless oil. R_f = 0.30 (dichloromethane—methanol, 9:1); ν_{max} (neat) 3325, 2932, 1603, 1493, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, ddd, *J* = 8.1, 7.5, 1.7 Hz, CH-C4'), 7.24 (1H, dd, *J* = 7.5, 1.7 Hz, CH-C6'), 6.95 (1H, app. td, *J* = 7.5, 0.9 Hz, CH-C5'), 6.88 (1H, dd, *J* = 8.1, 0.9 Hz, CH-C3'), 4.70 (1H, d, *J* = 12.3 Hz, CH_2-C1''), 4.63 (1H, d, *J* = 12.3 Hz, CH_2-C1''), 4.16 (1H, app. dt, *J* = 6.3, 6.3 Hz, CH-C2), 4.08—4.04 (2H, m, *J* = CH_2-C3), 3.84—3.71 (3H, m, OH-C2, CH_2-C1), 3.03 (1H, br s, OH-C1''), 2.79 (1H, br t, *J* = 4.6 Hz, OH-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (C-C2'), 129.7 (CH-C6'), 129.5 (CH-C4'), 129.2 (C-C1'), 121.3 (CH-C5'), 112.4 (CH-C3'), 70.4 (CH_2-C3), 70.3 (CH-C2), 63.6 (CH_2-C1), 62.2 (CH_2-C1''), ; HRMS (EI) for $C_{10}H_{14}O_4$ (M^+) calcd 198.0892, found 198.0894; LRMS (EI) *m/z* (intensity); 198.1 (M^+) (46), 149.1 (24), 120.1 (56), 106.1 (100), 78.1 (100).

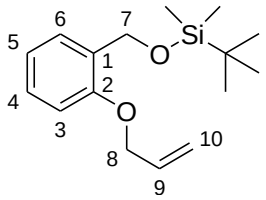
3-[2'-(1''-Hydroxyethyl)-phenoxy]-1,2-propanediol **357**



NMO (43.0 mg, 0.367 mmol) was added to a stirred mixture of 1-(2'-allyloxyphenyl) ethanol **349** (50.7 mg, 0.284 mmol) in chloroform (2 mL) and water (0.05 mL). Aqueous OsO_4 solution (4%, 54 μL, 8.4 μmol) was slowly added to the mixture at room temperature. After 6.5 h, the reaction was quenched by the addition of saturated aqueous sodium thiosulfate solution (1 mL). The mixture was reduced *in vacuo* and the residue was diluted with toluene and reduced *in vacuo* four times. Flash column chromatography (dichloromethane—methanol, 9:1) afforded 3-[2'-(1''-hydroxyethyl)-phenoxy]-1,2-propanediol (55.4 mg, 0.261 mmol, 92%) as a colourless oil. The product was obtained as a mixture of diastereomers. R_f = 0.33 (dichloromethane—methanol, 9:1); ν_{max} (neat) 3333, 3042, 2929, 1491, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, dd, 7.8, 1.7 Hz, CH-C6'), 7.28—7.23 (1H, m, CH-C4'), 6.98 (1H, ddd, *J* = 7.8, 2.3, 1.3 Hz, CH-C5'), 6.88 (1H, app. dt, *J* = 8.1, 1.3 Hz, CH-C3'), 5.10 (1H, br dq, *J* = 12.7, 6.5 Hz, CH-C1''), 4.17—4.05 (3H, m, CH_2-C3, CH-C2), 3.84—3.73 (2H, m, CH_2-C1), 3.39 (1H, br s, OH-C2), 2.92 (1H, br d, *J* = 12.7 Hz, OH-C1''), 2.55 (1H, br dt, *J* = 15.4, 4.5 Hz, OH-C1), 1.56 (3H, dd, *J* = 6.5, 1.8 Hz, CH_3-C2''); ^{13}C NMR (100 MHz, $CDCl_3$) δ

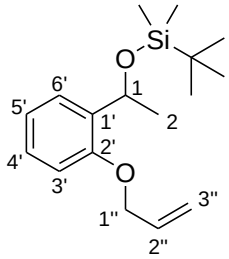
156.3 (d, *J* = 7.1 Hz, C-C2'), 133.2 (C-C1'), 128.8 (CH-C4'), 126.6 (d, *J* = 32.1 Hz, CH-C6'), 121.4 (d, *J* = 3.4 Hz, CH-C5'), 112.4 (d, *J* = 12.5 Hz, CH-C3'), 70.2 (d, *J* = 13.9 Hz, CH-C2), 70.2 (d, *J* = 7.2 Hz, CH_2-C3), 66.9 (d, *J* = 73.8 Hz, CH-C1''), 63.7 (d, *J* = 7.5 Hz, CH_2-C1), 22.4 (d, *J* = 8.8 Hz, CH_3-C2''); HRMS (CI-isobutane) for $C_{11}H_{15}O_3$ ($[M\text{-}OH]^+$) calcd 195.1021, found 195.1022; LRMS (CI-isobutane) *m*/*z* (intensity); 195.3 ($[M\text{-}OH]^+$) (100).

(2-Allyloxybenzyloxy)-*tert*-butyldimethylsilane **360**



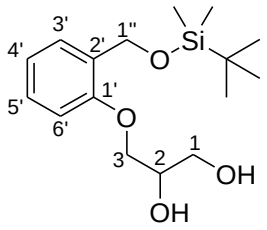
TBDMSCl (3.84 g, 25.5 mmol) and imidazole (2.34 g, 34.4 mmol) was added to a solution of 2-allyloxyphenyl methanol **348** (2.78 g, 16.9 mmol) in anhydrous *N*,*N*-dimethylformamide (15 mL) at room temperature. After 22 h the reaction was quenched by the addition of a mixture of saturated aqueous $NaHCO_3$ solution, water and diethyl ether (1:1:2, 72 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (40 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 9:1) afforded (2-allyloxybenzyloxy)-*tert*-butyldimethylsilane (4.42 g, 15.9 mmol, 94%) as a light yellow oil. R_f = 0.79 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 2928, 2856, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, br d, *J* = 7.5 Hz, CH-C6), 7.19 (1H, br t, *J* = 7.6 Hz, CH-C4), 6.98 (1H, t, *J* = 7.4 Hz, CH-C5), 6.81 (1H, br d, *J* = 8.2 Hz, CH-C3), 6.05 (1H, ddt, *J* = 17.3, 10.4, 5.1 Hz, CH-C9), 5.39 (1H, ddt, *J* = 17.3, 1.4, 1.4 Hz, *trans*-CH_2-C10), 5.27 (1H, ddt, *J* = 10.4, 1.4, 1.4 Hz, *cis*-CH_2-C10), 4.80 (2H, s, CH_2-C7), 4.55 (2H, dt, *J* = 5.1, 1.4 Hz, CH_2-C8), 0.96 (9H, s, 3 × CH_3-*t*-Bu-TBDMS), 0.11 (6H, s, 2 × CH_3-Me-TBDMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (C-C2), 133.5 (CH-C9), 130.1 (C-C1), 127.4 (CH-C4), 126.8 (CH-C6), 120.6 (CH-C5), 117.0 (CH_2-C10), 110.8 (CH-C3), 68.6 (CH_2-C8), 60.1 (CH_2-C7), 26.0 (3 × CH_3-*t*-Bu-TBDMS), 18.5 (C-*t*-Bu-TBDMS), —5.3 (2 × CH_3-Me-TBDMS).

1-(2'-Allyloxyphenyl)-1-*tert*-butyldimethylsilyloxy ethane **361**



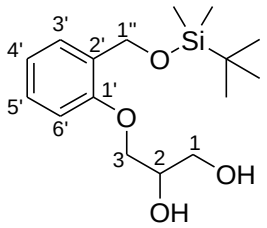
TBDMSCl (8.92 g, 59.2 mmol) and imidazole (5.34 g, 78.5 mmol) was added to a solution of 1-(2'-allyloxyphenyl)-ethanol **349** (6.99 g, 39.2 mmol) in anhydrous dimethylformamide (40 mL) at room temperature. After 18 h, the reaction was quenched by the addition of a mixture of saturated aqueous $NaHCO_3$, water and diethyl ether (1:1:2, 150 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic fractions were washed with brine (80 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—ethyl acetate, 19:1) afforded 1-(2'-allyloxyphenyl)-1-*tert*-butyldimethylsilyloxy ethane (11.5 g, 39.2 mmol, quant. yield) as a colourless oil. R_f = 0.80 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3061, 2928, 2857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* = 7.5, 1.6 Hz, CH-C6'), 7.17 (1H, app. td, *J* = 8.1, 1.6 Hz, CH-C4'), 6.96 (1H, app. td, *J* = 7.5, 0.8 Hz, CH-C5'), 6.80 (1H, dd, *J* = 8.1, 0.8 Hz, CH-C3'), 6.05 (1H, ddt, *J* = 17.3, 10.5, 4.9 Hz, CH-C2''), 5.40 (1H, ddt, *J* = 17.3, 1.6, 1.6 Hz, *trans*-CH_2-C3''), 5.27 (1H, ddt, *J* = 10.5, 1.6, 1.6 Hz, *cis*-CH_2-C3''), 5.26 (1H, q, *J* = 6.0 Hz, CH-C1), 4.56 (2H, dq, *J* = 4.9, 1.6 Hz, CH_2-C1''), 1.37 (3H, d, *J* = 6.0 Hz, CH_3-C2), 0.90 (9H, s, 3 × CH_3-*t*-Bu-TBDMS), 0.04 (3H, s, CH_3-Me-TBDMS), —0.02 (3H, s, CH_3-Me-TBDMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (C-C2'), 135.7 (C-C1'), 133.6 (CH-C2''), 127.3 (CH-C4'), 126.2 (CH-C6'), 120.7 (CH-C5'), 116.8 (CH_2-C3''), 111.1 (CH-C3'), 68.5 (CH_2-C1''), 65.1 (CH-C1), 25.9 (3 × CH_3-*t*-Bu-TBDMS), 25.6 (CH_3-C2), 18.3 (C-*t*-Bu-TBDMS), —4.9 (CH_3-Me-TBDMS), —4.9 (CH_3-Me-TBDMS); HRMS (CI-isobutane) for $C_{17}H_{29}O_2Si$ ($[M+H]^+$) calcd 293.1937, found 293.1930; LRMS (CI-isobutane) *m/z* (intensity); 293.5 ($[M+H]^+$) (5), 235.4 (11), 191.3 (8), 161.3 (100).

3-[2'-*tert*-Butyldimethylsilanyloxymethyl-phenoxy]-1,2-propanediol **362**



Aqueous OsO_4 solution (4%, 0.69 mL, 0.11 mmol) was added to a mixture of (2-allyloxybenzyloxy)-*tert*-butyldimethylsilane **360** (1.00 g, 3.60 mmol) and NMO (549 mg, 4.69 mmol) in chloroform (24 mL) and water (1 mL) at room temperature. After 22 h the reaction was quenched by the addition of saturated aqueous sodium thiosulfate solution (10 mL). The solvent was removed *in vacuo*, and the residue was diluted with toluene and reduced *in vacuo* four times. Flash column chromatography (dichloromethane—methanol, 9:1) afforded 3-[2'-*tert*-butyl-dimethylsilanyloxymethyl-phenoxy]-1,2-propanediol (1.06 g, 3.39 mmol, 94%) as a light brown oil. R_f = 0.56 (dichloromethane—methanol, 9:1); ν_{max} (neat) 3374, 2929, 2858, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, dd, *J* = 7.4, 1.7 Hz, CH-C3'), 7.25 (1H, app. td, *J* = 7.7, 1.7 Hz, CH-C5'), 6.98 (1H, app. td, *J* = 7.4, 0.7 Hz, CH-C4'), 6.87 (1H, dd, *J* = 8.1, 0.7 Hz, CH-C6'), 4.78 (1H, d, *J* = 13.0 Hz, CH_2-C1''), 4.71 (1H, d, *J* = 13.0 Hz, CH_2-C1''), 4.16 (1H, dt, *J* = 6.4, 5.2 Hz, CH-C2), 4.11—4.04 (2H, m, CH_2-C3), 3.86—3.73 (2H, m, CH_2-C1), 3.14 (1H, d, *J* = 5.2 Hz, OH-C2), 2.33 (1H, dd, *J* = 7.0, 5.6 Hz, OH-C1), 0.93 (9H, s, 3 × CH_3-*t*-Bu), 0.10 (3H, s, CH_3-Me), 0.09 (3H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (C-C1'), 129.6 (C-C2'), 128.6 (CH-C5'), 128.5 (CH-C3'), 121.2 (CH-C4'), 111.8 (CH-C6'), 70.4 (CH_2-C3), 70.0 (CH-C2), 63.6 (CH_2-C1), 61.5 (CH_2-C1''), 26.0 (3 × CH_3-*t*-Bu), 18.5 (C-*t*-Bu), —5.1 (CH_3-Me), —5.1 (CH_3-Me); HRMS (CI-isobutane) for $C_{16}H_{29}O_4Si$ ($[M+H]^+$) calcd 313.1835, found 313.1833; LRMS (CI-isobutane) *m/z* (intensity); 313.5 ($[M+H]^+$) (19), 237.4 (35), 181.3 (100).

3-[2'-*tert*-Butyldimethylsilanyloxymethyl-phenoxy]-1,2-propanediol **362**

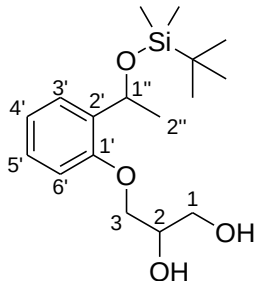


$NaBH_4$ (1.10 g, 29.0 mmol) was added to a solution of 2-allyloxybenzaldehyde **240** (2.27 g, 14.0 mmol) in anhydrous methanol (50 mL) at room temperature. After 16 h, the reaction was quenched by the addition of glacial acetic acid (6 mL). The mixture was reduced *in vacuo*, and the residue was partitioned between 1 M aqueous HCl solution (30 mL) and diethyl ether (30 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with successively saturated aqueous $NaHCO_3$ solution (2 × 30 mL), water (40 mL) and brine (40 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. The crude alcohol product was used without further purification.

TBDMSCl (3.18 g, 21.1 mmol) and imidazole (1.94 g, 28.5 mmol) was added to a solution of the crude alcohol in anhydrous *N*,*N*-dimethylformamide (20 mL) at room temperature. After 22 h, the reaction was quenched by the addition of a mixture of saturated aqueous $NaHCO_3$ solution, water and diethyl ether (1:1:2, 60 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The crude silyl ether was used without further purification.

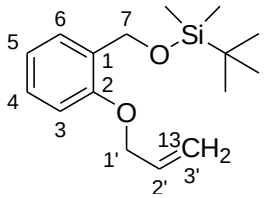
Aqueous OsO_4 solution (4%, 2.7 mL, 0.43 mmol) was added to a mixture of the crude silyl ether and NMO (2.15 g, 18.4 mmol) in chloroform (50 mL) and water (5 mL) at room temperature. After 24 h, the reaction was quenched by the addition of saturated aqueous sodium thiosulfate solution (40 mL). The solvent was removed *in vacuo*, and the residue was diluted with toluene and reduced *in vacuo* four times. Flash column chromatography (dichloromethane—methanol, 19:1) afforded 3-[2'-*tert*-butyl-dimethylsilanyloxymethyl-phenoxy]-1,2-propanediol (2.80 g, 8.95 mmol, 64% over three steps) as a light brown oil. Spectroscopic data identical with above.

3-{2'-[1''-(*tert*-Butyldimethylsilanyloxy)-ethyl]-phenoxy}-propane-1,2-diol **363**



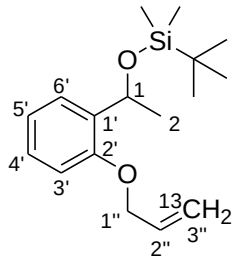
Aqueous OsO_4 solution (4%, 0.69 mL, 0.11 mmol) was added to a stirred mixture of 1-(2'-allyloxyphenyl)-1-*tert*-butyldimethylsilyloxy ethane **361** (1.06 g, 3.62 mmol) and NMO (549 mg, 4.69 mmol) in chloroform (25 mL) and water (1 mL) at room temperature. After 17 h, the reaction was quenched by the addition of saturated aqueous sodium thiosulfate solution (10 mL). The solvent was removed *in vacuo*, and the residue was diluted with toluene and reduced *in vacuo* four times. Flash column chromatography (dichloromethane—methanol, 9:1) afforded 3-{2'-[1''-(*tert*-butyldimethylsilanyloxy)-ethyl]-phenoxy}-propane-1,2-diol (1.17 g, 3.59 mmol, 99%) as a light brown oil. The product was obtained as a mixture of diastereomers. R_f = 0.53 (dichloromethane—methanol, 9:1); ν_{max} (neat) 3364, 3071, 2932, 2855, 1451 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (1H, app. ddd, *J* = 25.0, 7.5, 1.5 Hz, CH-C3'), 7.23—7.17 (1H, m, CH-C5'), 6.97 (1H, dt, *J* = 7.5, 7.3 Hz, CH-C4'), 6.84 (1H, app. dd, *J* = 8.2, 2.3, CH-C6'), 5.10 (1H, app. dq, *J* = 21.4, 6.4 Hz, CH-C1''), 4.15—4.02 (3H, m, CH_2-C3, CH-C2), 3.88—3.83 (1H, m, CH_2-C1), 3.82—3.75 (1H, m, CH_2-C1), 2.74 (1H, app. dd, *J* = 74.4, 4.9 Hz, OH-C2), 2.36—2.06 (1H, m, OH-C1), 1.42 (3H, dd, *J* = 14.7, 6.4 Hz, CH_3-C2''), 0.89 (9H, d, *J* = 4.6 Hz, 3 × CH_3-*t*-Bu-TBDMS), 0.05 (3H, s, CH_3-Me-TBDMS), —0.02 (3H, d, *J* = 2.5 Hz, CH_3-Me-TBDMS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8 and 154.4 (C-C2'), 135.1 and 134.6 (C-C1'), 127.9 and 127.8 (CH-C4'), 127.2 and 126.8 (CH-C6'), 121.3 and 121.2 (CH-C5'), 111.5 and 111.4 (CH-C3'), 70.3 and 70.1 (CH-C2), 70.0 and 69.4 (CH_2-C3), 67.6 and 66.5 (CH-C1''), 63.9 and 63.6 (CH_2-C1), 25.9 (3 × CH_3-*t*-Bu-TBDMS), 25.4 and 25.1 (CH_3-C2''), 18.4 and 18.3 (C-*t*-Bu-TBDMS), —4.9 (CH_3-Me-TBDMS), —4.9 (CH_3-Me-TBDMS); HRMS (CI-isobutane) for $C_{17}H_{31}O_4Si$ ($[M+H]^+$) calcd 327.1992, found 327.1994; LRMS (CI-isobutane) *m/z* (intensity); 327.4 ($[M+H]^+$) (3), 251.3 (45), 195.2 (100), 161.2 (22), 133.2 (50).

3'-[^{13}C]-(2-Allyloxybenzyloxy)-*tert*-butyldimethylsilane **366**



Sodium *meta*-periodate (3.80 g, 17.8 mmol) was added to a solution of 3-[2'-*tert*-butyldimethylsilanyloxymethyl-phenoxy]-1,2-propanediol **362** (919 mg, 2.94 mmol) in anhydrous tetrahydrofuran (20 mL) at room temperature. After 35 minutes the reaction mixture was filtered through celite (diethyl ether). The filtrate was washed with brine (10 mL), dried over Na_2SO_4, filtered and reduced *in vacuo*. The crude silyl ether product was used without further purification. Potassium *tert*-butoxide (477 mg, 4.25 mmol) was added to a mixture of $^{13}CH_3PPh_3I$ (1.77 g, 4.37 mmol) in anhydrous tetrahydrofuran (35 mL) at −78 °C, causing the formation of a yellow solution. After 40 minutes a solution of the crude aldehyde in anhydrous tetrahydrofuran (10 mL) was added slowly. The reaction was allowed to warm to room temperature slowly. After 17 h the reaction was reduced *in vacuo* and the resulting residue was partitioned between dichloromethane (10 mL) and water (10 mL). The aqueous phase was extracted with dichloromethane (4 × 10 mL). The combined organic fractions were then washed with brine (30 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 19:1) afforded 3'-[^{13}C]-(2-allyloxybenzyloxy)-*tert*-butyldimethylsilane (214 mg, 0.767 mmol, 26% over two steps) as a light yellow oil. R_f = 0.79 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 2928, 2856, 1490 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (1H, dddd, *J* = 7.5, 1.8, 1.0, 1.0 Hz, CH-C6), 7.21—7.17 (1H, m, CH-C4), 6.98 (1H, app. td, *J* = 7.5, 0.7 Hz, CH-C5), 6.81 (1H, dd, *J* = 8.1, 0.7 Hz, CH-C3), 6.05 (1H, ddt, *J* = 17.4, 10.4, 5.3 Hz, CH-C2'), 5.39 (1H, dddt, *J* = 155.7, 17.4, 1.7, 1.7 Hz, *trans*-CH_2-C3'), 5.26 (1H, dddt, *J* = 159.3, 10.4, 1.7, 1.7 Hz, *cis*-CH_2-C3'), 4.80 (2H, s, CH_2-C7), 4.55 (2H, ddt, *J* = 5.3, 5.3, 1.7 Hz, CH_2-C1'), 0.96 (9H, s, 3 × CH_3-*t*-Bu), 0.11 (6H, s, 2 × CH_3-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0 (C-C2), 133.5 (d, *J* = 72.3 Hz, CH-C2'), 130.2 (C-C1), 127.4 (CH-C4), 126.8 (CH-C6), 120.6 (CH-C5), 117.0 ($^{13}CH_2$-C3'), 110.8 (CH-C3), 68.6 (CH_2-C1'), 60.1 (CH_2-C7), 26.0 (3 × CH_3-*t*-Bu), 18.5 (C-*t*-Bu), −5.3 (2 × CH_3-Me); LRMS (CI-isobutane) *m*/*z* (intensity); 279.3 (M^+) (14), 148.2 (100).

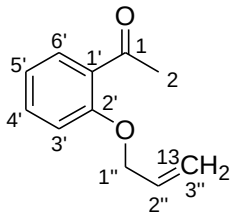
3''-[^{13}C]-[1-(2'-Allyloxyphenyl)-ethoxy]-*tert*-butyldimethyl silane **367**



Sodium *meta*-periodate (7.89 g, 36.9 mmol) was added to a solution of 3-{2'-[1''-(*tert*-butyldimethylsilanyloxy)-ethyl]-phenoxy}-1,2-propanediol **363** (1.99 g, 6.10 mmol) in anhydrous tetrahydrofuran (40 mL). After 35 min, the reaction mixture was filtered through celite (diethyl ether). The filtrate was washed with brine (20 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude aldehyde product was used without further purification.

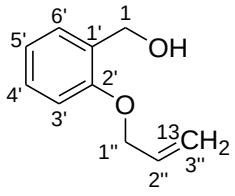
Potassium *tert*-butoxide (1.04 g, 9.25 mmol) was added to a mixture of $^{13}CH_3PPh_3I$ (3.73 g, 9.20 mmol) in anhydrous tetrahydrofuran (60 mL) at −78 °C, causing the formation of a yellow solution. After 40 minutes a solution of crude aldehyde in anhydrous tetrahydrofuran (20 mL) was slowly added. The reaction was slowly allowed to warm to room temperature. After 17 h, the reaction was reduced *in vacuo*. The residue was partitioned between dichloromethane (30 mL) and water (30 mL) and the aqueous phase was then extracted with dichloromethane (4 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 19:1) afforded 3''-[^{13}C]-[1-(2'-allyloxyphenyl)-ethoxy]-*tert*-butyldimethyl silane (502 mg, 1.17 mmol, 28% over two steps) as a light yellow oil. R_f = 0.80; (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3061, 2928, 2857 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* = 7.6, 1.7 Hz, CH-C6'), 7.16 (1H, ddd, *J* = 8.1, 7.7, 1.7 Hz, CH-C4'), 6.96 (1H, ddd, *J* = 7.7, 7.6, 0.8 Hz, CH-C5'), 6.80 (1H, dd, *J* = 8.1, 0.8 Hz, CH-C3'), 6.05 (1H, ddt, *J* = 17.3, 10.5, 5.1 Hz, CH-C2''), 5.40 (1H, dddt, *J* = 155.7, 17.3, 1.6, 1.6 Hz, *trans*-CH_2-C3''), 5.26 (1H, dddt, *J* = 159.3, 10.5, 1.6, 1.6 Hz, *cis*-CH_2-C3''), 5.26 (1H, q, *J* = 6.2 Hz, CH-C1), 4.55 (2H, dddt, *J* = 5.1, 5.1, 1.6, 1.6 Hz, CH_2-C1''), 1.37 (3H, d, *J* = 6.2 Hz, CH_3-C2), 0.90 (9H, s, 3 × CH_3-*t*-Bu), 0.04 (3H, s, CH_3-Me), −0.02 (3H, s, CH_3-Me).

3''-[^{13}C]-1-(2'-Allyloxyphenyl) ethanone **369**



Dess-Martin periodinane (774 mg, 1.82 mmol) was added to a solution of 3''-[^{13}C]-1-(2'-allyloxyphenyl)-ethanol **371** (216 mg, 1.21 mmol) in anhydrous dichloromethane (10 mL) at room temperature. After 2 h, the reaction mixture was diluted with diethyl ether (15 mL), washed with a mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution (1:1, 20 mL) followed by brine (20 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 3''-[^{13}C]-1-(2'-allyloxyphenyl) ethanone (150 mg, 0.919 mmol, 76%) as a colourless oil. R_f = 0.40 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3074, 2996, 2927, 2872, 1671, 1596, 1450 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (1H, dd, *J* = 7.6, 1.8 Hz, CH-C6'), 7.44 (1H, ddd, *J* = 8.4, 7.4, 1.8 Hz, CH-C4'), 7.00 (1H, ddd, *J* = 7.6, 7.4, 0.8 Hz, CH-C5'), 6.95 (1H, d, *J* = 8.4 Hz, CH-C3'), 6.09 (1H, ddt, *J* = 17.2, 10.5, 5.4 Hz, CH-C2''), 5.44 (1H, dddt, *J* = 155.6, 17.2, 1.4, 1.4 Hz, *trans*-CH_2-C3''), 5.32 (1H, dddt, *J* = 159.9, 10.5, 1.4, 1.4 Hz, *cis*-CH_2-C3''), 4.65 (2H, ddt, *J* = 5.4, 5.4, 1.4 Hz, CH_2-C1''), 2.64 (3H, s, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0 (C-C1), 157.9 (C-C2'), 133.5 (CH-C4'), 132.6 (d, *J* = 72.6 Hz, CH-C2''), 130.4 (CH-C6'), 128.6 (C-C1'), 120.8 (CH-C5'), 118.2 ($^{13}CH_2$-C3''), 112.8 (CH-C3'), 69.4 (CH_2-C1''), 32.0 (CH_3-C2); HRMS (EI) for $C_{10}{}^{13}CH_{12}O_2$ (M^+) calcd 177.0871, found 177.0875; LRMS (EI) *m/z* (intensity); 177.1 (M^+) (14), 134.1 (24), 121.1 (86), 86.0 (100), 84.0 (100).

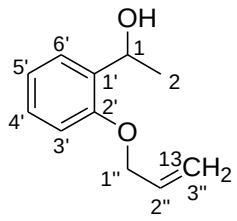
3''-[^{13}C]-(2'-Allyloxyphenyl)-methanol **370**



TBAF (1.0 M in tetrahydrofuran, 0.85 mL, 0.85 mmol) was added to a solution of 3'-[^{13}C]-(2-allyloxybenzyloxy)-*tert*-butyldimethylsilane **366** (214 mg, 0.767 mmol) in anhydrous tetrahydrofuran (5 mL) at room temperature. After 16 h, the reaction was quenched by the addition of water (4 mL). The phases were separated and the aqueous

phase was extracted with diethyl ether (3 × 5 mL). The combined organic fractions were washed with brine (10 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 7:3) afforded 3''-[^{13}C]-(2'-allyloxyphenyl)-methanol (105 mg, 0.633 mmol, 83%) as a colourless oil. R_f = 0.13 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3377, 3076, 2869, 1603, 1490 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30—7.23 (2H, m, CH-C4' and CH-C6'), 6.95 (1H, app. td, *J* = 7.4, 0.9 Hz, CH-C5'), 6.88 (1H, d, *J* = 8.2 Hz, CH-C3'), 6.07 (1H, ddt *J* = 17.3, 10.4, 5.2 Hz, CH-C2''), 5.42 (1H, dddt, *J* = 155.6, 17.3, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.30 (1H, dddt, *J* = 159.7, 10.4, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 4.72 (2H, t, *J* = 3.0 Hz, CH_2-C1), 4.60 (2H, ddt, *J* = 5.2, 5.2, 1.5 Hz, CH_2-C1''), 2.31 (1H, t, *J* = 6.5 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5 (C-C2'), 133.0 (d, *J* = 72.8 Hz, CH-C2''), 129.4 (C-C1'), 128.9 (CH-C4' or CH-C6'), 128.8 (CH-C4' or CH-C6'), 120.9 (CH-C5'), 117.7 ($^{13}CH_2$-C3''), 111.5 (CH-C3'), 68.7 (CH_2-C1''), 62.3 (CH_2-C1); HRMS (EI) for $C_9{}^{13}CH_{12}O_2$ ([M+H]$^+$) calcd 165.0871, found 165.0874; LRMS (CI-isobutane) *m/z* (intensity); 165.1 ([M+H]$^+$) (33), 135.0 (23), 106.0 (48), 83.9 (100), 78.0 (55).

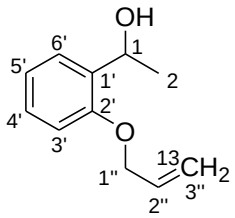
3''-[^{13}C]-1-(2'-Allyloxyphenyl)-ethanol **371**



TBAF (1.0 M in THF, 1.90 mL, 1.90 mmol) was added to a solution of 3''-[^{13}C]-[1-(2'-allyloxyphenyl)-ethoxy]-*tert*-butyldimethyl silane **367** (502 mg, 1.71 mmol) in anhydrous tetrahydrofuran (10 mL) at room temperature. After 17 h, the reaction was quenched by the addition of water (20 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 7:3) afforded 3''-[^{13}C]-1-(2'-allyloxyphenyl)-ethanol (218 mg, 1.22 mmol, 71%) as a colourless oil. R_f = 0.18 (petroleum ether—ethyl acetate, 1:9); ν_{max} (neat) 3378, 3078, 2973, 1601, 1489 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (1H, dd, 7.5, 1.7 Hz, CH-C6'), 7.22 (1H, ddd, *J* = 8.1, 7.7, 1.7 Hz, CH-C4'), 6.97 (1H, ddd, *J* = 7.7, 7.5, 0.8 Hz, CH-C5'), 6.87 (1H, dd, *J* = 8.1, 0.8 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.2, 10.5, 5.2 Hz, CH-C2''), 5.43 (1H, dddt, *J* = 155.6, 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.30 (1H, dddt, *J* = 159.6, 10.5, 1.5,

1.5 Hz, *cis*-CH_2-C3''), 5.15 (1H, q, *J* = 6.1 Hz, CH-C1), 4.60 (2H, ddt, *J* = 5.2, 5.2, 1.5 Hz, CH_2-C1''), 2.61 (1H, d, *J* = 6.1 Hz, OH), 1.53 (3H, d, *J* = 6.1 Hz, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C-C2'), 133.7 (C-C1'), 133.0 (d, *J* = 70.1 Hz, CH-C2''), 128.2 (CH-C4'), 126.2 (CH-C6'), 121.0 (CH-C5'), 117.6 ($^{13}CH_2$-C3''), 111.7 (CH-C3'), 68.8 (CH_2-C1''), 66.7 (CH-C1), 22.9 (CH_3-C2); HRMS (CI-isobutane) for $C_{10}{}^{13}CH_{13}O$ ($[M\text{-}OH]^+$) calcd 162.1000, found 162.0997; LRMS (CI-isobutane) *m/z* (intensity); 162.3 ($[M\text{-}OH]^+$) (84), 75.2 (100).

3''-[^{13}C]-1-(2'-Allyloxyphenyl)-ethanol **371**



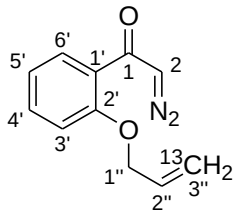
Sodium *meta*-periodate (7.93 g, 37.1 mmol) was added to a solution of 3-{2'-[1''-(*tert*-butyldimethylsilanyloxy)-ethyl]-phenoxy}-1,2-propanediol **363** (2.05 g, 6.28 mmol) in anhydrous tetrahydrofuran (40 mL). After 35 min, the reaction mixture was filtered through celite (diethyl ether). The filtrate was washed with brine (20 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude aldehyde product was used without further purification.

Potassium *tert*-butoxide (1.06 g, 9.43 mmol) was added to a mixture of $^{13}CH_3PPh_3I$ (3.69 g, 9.12 mmol) in anhydrous tetrahydrofuran (60 mL) at −78 °C, causing the formation of a yellow solution. After 45 min, a solution of the crude aldehyde in anhydrous tetrahydrofuran (30 mL) was slowly added. The reaction was allowed to warm slowly to room temperature. After 15 h, the reaction was reduced *in vacuo*. The residue was partitioned between dichloromethane (30 mL) and water (30 mL). The aqueous phase was extracted with dichloromethane (4 × 30 mL). The combined organic fractions were washed with brine (100 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. The crude silyl ether product was used without further purification.

TBAF (7.0 mL of a 1.0 M solution in THF, 7.0 mmol) was added to a solution of the crude silyl ether in anhydrous tetrahydrofuran (40 mL) at room temperature. After 22 h, the reaction was quenched by the addition of water (100 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 60 mL). The combined organic fractions were washed with brine (150 mL), dried with $MgSO_4$, filtered and

reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 7:3) afforded 3''-[^{13}C]-1-(2'-allyloxyphenyl)-ethanol (320 mg, 1.78 mmol, 28% over three steps) as a colourless oil. Spectroscopic data identical with above.

3''-[^{13}C]-1-(2'-Allyloxyphenyl)-2-diazoethanone **372*t**

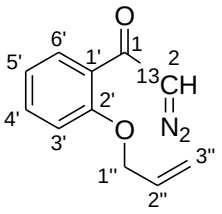


A solution of 3''-[^{13}C]-1-(2'-allyloxyphenyl) ethanone **369** (246 mg, 1.39 mmol) in anhydrous tetrahydrofuran (6 mL) was added dropwise to a solution of NaHMDS (2.0 M in tetrahydrofuran, 1.15 mL, 2.30 mmol) in anhydrous tetrahydrofuran (10 mL) at —78 °C. After 1 h, trifluoroethyl trifluoroacetate (340 µL, 2.54 mmol) was added rapidly in one portion, after which the reaction mixture was allowed to warm to room temperature. After 10 min, the reaction mixture was transferred into a separation funnel containing aqueous HCl solution (0.5 M, 10 mL) and diethyl ether (10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and reduced *in vacuo*.

The residue was dissolved in acetonitrile (20 mL) and cooled to 0 °C. Water (9 µL, 0.5 mmol) and triethylamine (290 µL, 2.09 mmol) were added. A solution of ABSA (503 mg, 2.09 mmol) in acetonitrile (10 mL) was added dropwise to the reaction mixture, after which the reaction was allowed to warm to room temperature. After 3.5 h, the reaction mixture was reduced *in vacuo*. The yellow residue was dissolved in diethyl ether (15 mL), washed with 10% aqueous NaOH solution (3 × 20 mL) followed by brine (20 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 3''-[^{13}C]-1-(2'-allyloxyphenyl-2-diazoethanone (220 mg, 1.08 mmol, 78%) as a yellow solid. R_f = 0.23 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3090, 2926, 2111, 1591 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (1H, m, CH-C6'), 7.42 (1H, ddd, *J* = 8.4, 7.5, 1.9 Hz, CH-C4'), 7.04 (1H, ddd, *J* = 7.8, 7.5, 0.7 Hz, CH-C5'), 6.94 (1H, dd, *J* = 8.4, 0.7 Hz, CH-C3'), 6.38 (1H, br s, CH-C2), 6.10 (1H, ddt, *J* = 17.3, 10.6, 5.4 Hz, CH-C2''), 5.46 (1H, dddt, *J* = 155.5, 17.3, 1.4, 1.4 Hz, *trans*-CH_2-C3''), 5.35 (1H, dddt, *J* = 159.9, 10.6, 1.4, 1.4 Hz, *cis*-CH_2-C3''), 4.64 (2H, ddt, *J* = 5.4, 5.4, 1.4 Hz, CH_2-C1''); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1 (C-C1), 157.3 (C-C2'), 133.4 (CH-C4'), 132.4 (d, *J* = 67.5 Hz, CH-C2''),

130.5 (CH-C6'), 126.4 (C-C1'), 121.1 (CH-C5'), 118.7 ($^{13}CH_2$-C3''), 112.8 (CH-C3'), 69.6 (CH_2-C1''), 58.0 (CH-C2); LRMS (CI-isobutane) *m/z* (intensity); 204.2 ($[M+H]^+$) (80), 176.2 (100).

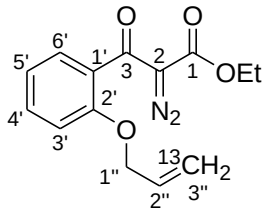
2-[^{13}C]-1-(2'-Allyloxyphenyl)-2-diazoethanone **372*d**



A solution of 2-[^{13}C]-1-(2'-allyloxyphenyl) ethanone **379** (502 mg, 2.83 mmol) in anhydrous tetrahydrofuran (15 mL) was added dropwise to a solution of NaHMDS (2.0 M in tetrahydrofuran, 2.30 mL, 4.60 mmol) in anhydrous tetrahydrofuran (20 mL) at −78 °C. After 1 h, trifluoroethyl trifluoroacetate (680 µL, 5.08 mmol) was added rapidly in one portion, after which the reaction mixture was allowed to warm to room temperature. After 10 min, the reaction mixture was transferred into a separation funnel containing aqueous HCl solution (0.5 M, 20 mL) and diethyl ether (20 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic fractions were washed with brine (30 mL) and reduced *in vacuo*. The resulting residue was dissolved in acetonitrile (40 mL) and cooled to 0 °C. Water (18 µL, 1.0 mmol) and triethylamine (590 µL, 4.23 mmol) were added. A solution of ABSA (1.02 g, 4.25 mmol) in acetonitrile (20 mL) was then added dropwise to the reaction mixture, after which the reaction was allowed to warm to room temperature. After 22 h, the reaction mixture was reduced *in vacuo*. The yellow residue was dissolved in diethyl ether (50 mL), washed with 10% aqueous NaOH solution (3 × 70 mL) followed by brine (70 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-[^{13}C]-1-(2'-allyloxyphenyl-2-diazoethanone (474 mg, 2.45 mmol, 87%) as a yellow solid. R_f = 0.23 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3090, 2926, 2111, 1591 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (1H, br d, *J* = 5.7 Hz, CH-C6'), 7.42 (1H, ddd, *J* = 8.4, 7.3, 1.9 Hz, CH_2-C4'), 7.04 (1H, m, CH-C5'), 6.94 (1H, dd, *J* = 8.4, 0.5 Hz, CH-C3'), 6.39 (1H, br d, *J* = 203.4 Hz, CH-C2), 6.10 (1H, ddt, *J* = 17.2, 10.6, 5.3 Hz, CH-C2''), 5.46 (1H, ddt, *J* = 17.2, 1.3, 1.3 Hz, *trans*-CH_2-C3''), 5.35 (1H, ddt, *J* = 10.6, 1.3, 1.3 Hz, *cis*-CH_2-C3''), 4.63 (2H, dt, *J* = 5.3, 1.3 Hz, CH_2-C1''); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1 (d, *J* = 64.1 Hz, C-C1), 157.3 (C-C2'), 133.3 (CH-C4'), 132.4 (CH-C2''), 130.5 (CH-C6'),

127.6 (C-C1'), 121.1 (CH-C5'), 118.7 (CH_2-C3''), 112.8 (CH-C3'), 69.6 (CH_2-C1''), 57.9 (^{13}CH-C2); HRMS (CI-isobutane) for $C_{10}{}^{13}CH_{11}O_2N_2$ ([M+H]$^+$) calcd 208.0854, found 204.0853; LRMS (CI-isobutane) *m/z* (intensity); 204.2 ([M+H]$^+$) (82), 176.2 (100).

3''-[^{13}C]-Ethyl 3-(2'-Allyloxyphenyl)-2-diazo-3-oxo-propionate **373*t**

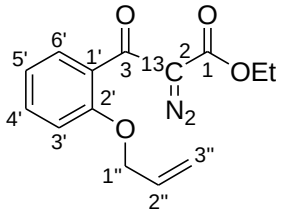


Dess-Martin periodinane (409 mg, 0.965 mmol) was added to a solution of 3''-[^{13}C]-(2'-allyloxyphenyl)-methanol **370** (107 mg, 0.645 mmol) in anhydrous dichloromethane (5 mL) at room temperature. After 2 h, the reaction was diluted with diethyl ether (5 mL). The reaction mixture was washed with a mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution (1:1, 8 mL) followed by brine (6 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude aldehyde product was used without further purification.

Ethyl diazoacetate (0.15 mL, 1.4 mmol) was added to a solution of the crude aldehyde and DBU (30 µL, 0.19 mmol) in anhydrous DMSO (2 mL) at room temperature. A solution of IBX (724 mg, 2.59 mmol) in anhydrous DMSO (12 mL) was added and the reaction was left stirring at room temperature in the dark. After 65 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (7 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (4 × 7 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ solution (3 × 7 mL) followed by water (7 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 3''-[^{13}C]-ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate (138 mg, 0.504 mmol, 78% over three steps) as a yellow oil. R_f = 0.23 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 2984, 2137, 1732, 1626, 1599, 1489 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (1H, ddd, *J* = 8.4, 7.5, 1.8 Hz, CH-C4'), 7.35 (1H, dd, *J* = 7.5, 1.8 Hz, CH-C6'), 7.01 (1H, app. td, *J* = 7.5, 0.9 Hz, CH-C5'), 6.89 (1H, d, *J* = 8.4 Hz, CH-C3'), 5.98 (1H, ddt, *J* = 17.3, 10.5, 5.1 Hz, CH-C2''), 5.37 (1H, dddt, *J* = 155.7, 17.3, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.26 (1H, dddt, *J* = 161.0, 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 5.54 (2H, ddt, *J* = 5.1, 5.1, 1.5 Hz, CH_2-C1''),

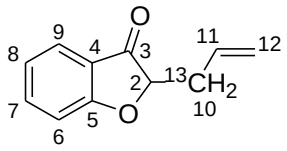
4.18 (2H, q, *J* = 7.1 Hz, CH_2-Et), 1.20 (3H, t, *J* = 7.1 Hz, CH_3-Et) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2 (C-C3), 161.0 (C-C1), 156.0 (C-C2'), 132.7 (d, *J* = 68.9 Hz, CH-C2''), 132.3 (CH-C4'), 128.7 (CH-C6'), 128.4 (C-C1'), 120.9 (CH-C5'), 117.4 ($^{13}CH_2$-C3''), 112.0 (CH-C3'), 69.3 (CH_2-C1''), 61.3 (CH_2-Et), 14.2 (CH_3-Et); HRMS (EI) for $C_{13}{}^{13}CH_{14}O_4N_2$ (M^+) calcd 275.0988, found 275.0988; LRMS (EI) *m/z* (intensity); 275.1 (M^+) (5), 174.0 (16), 149.0 (17), 133.0 (27), 83.9 (100).

2-[^{13}C]-Ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate **373*d**



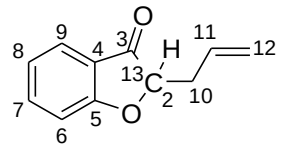
DBU (0.13 mL, 0. mmol) was added to a solution of 2-[^{13}C]-ethyl 3-(2'-allyloxyphenyl)-3-oxo-propionate **380** (73.4 mg, 0.296 mmol) and ABSA (144 mg, 0.597 mmol) in anhydrous acetonitrile (4 mL) at 0 °C. The reaction was slowly allowed to warm to room temperature. After 14 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (4 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 6 mL). The combined organic fractions were washed with brine (10 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded ethyl 2-[^{13}C]-3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate (67.6 mg, 0.246 mmol, 83%) as a yellow oil. R_f = 0.23 (petroleum ether—ethyl acetate, 9:1); v_{max} (neat) 2984, 2137, 1732, 1626, 1599 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43—7.39 (1H, m, CH-C4'), 7.34 (1H, dd, *J* = 7.5, 1.7 Hz, CH-C6'), 7.01 (1H, app. t, *J* = 7.5 Hz, CH-C5'), 6.89 (1H, d, *J* = 8.4 Hz, CH-C3'), 5.98 (1H, ddt, *J* = 17.2, 10.4, 5.0 Hz, CH-C2''), 5.37 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.26 (1H, ddt, *J* = 10.4, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 4.54 (2H, dt, *J* = 5.0, 1.5 Hz, CH_2-C1''), 4.18 (2H, q, *J* = 7.1 Hz, CH_2-Et), 1.20 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2 (d, *J* = 66.7 Hz, C-C3), 160.9 (d, *J* = 97.5 Hz, C-C1), 156.0 (C-C2'), 132.7 (CH-C2''), 132.3 (CH-C4'), 128.7 (CH-C6'), 128.3 (d, *J* = 20.5 Hz, C-C1'), 120.9 (CH-C5'), 117.4 (CH_2-C3''), 112.0 (CH-C3'), 69.3 (CH_2-C1''), 61.3 (CH_2-Et), 21.0 (^{13}C-C2), 14.2 (CH_3-Et); LRMS (CI-isobutane) *m/z* (intensity); 248.2 (M–N_2]$^+$) (10), 162.2 (11), 113.2 (27), 85.2 (72).

10-[^{13}C]-2-Allyl-3-benzofuranone **374*i**



Following the general procedure, 3''-[^{13}C]-1-(2'-allyloxyphenyl)-2-diazoethanone **372*t** (15.3 mg, 0.0796 mmol) in anhydrous dichloromethane (2 mL) was added to a solution of Cu(hfacac)$_2$ (10 mol%) in dichloromethane (3 mL) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 10-[^{13}C]-2-allyl-3-benzofuranone (10.2 mg, 0.0582 mmol, 73%) as a colourless oil. R_f = 0.45 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3079, 2921, 1712, 1612 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (1H, ddd, *J* = 7.8, 1.4, 0.7 Hz, CH-C9), 7.62 (1H, ddd, *J* = 8.5, 7.2, 1.4 Hz, CH-C7), 7.13 (1H, ddd, *J* = 8.5, 0.7, 0.7 Hz, CH-C6), 7.08 (1H, ddd, *J* = 7.8, 7.2, 0.7 Hz, CH-C8), 5.82 (1H, dddt, *J* = 17.1, 10.7, 6.8, 4.5 Hz, CH-C11), 5.23 (1H, dddt, *J* = 17.1, 7.3, 1.5, 1.5 Hz, *trans*-CH_2-C12), 5.13 (1H, dddt, *J* = 12.9, 10.7, 1.5, 1.2 Hz, *cis*-CH_2-C12), 4.62 (1H, dt, *J* = 7.9, 4.1 Hz, CH-C2), 2.96—2.36 (2H, m, CH_2-C10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3 (C-C3), 172.7 (C-C5), 138.1 (CH-C7), 131.7 (d, *J* = 40.8 Hz, CH-C11), 124.3 (CH-C9), 121.9 (CH-C8), 121.0 (C-C4), 118.9 (CH_2-C12), 113.5 (CH-C6), 84.6 (d, *J* = 35.7 Hz, CH-C2), 35.5 (CH_2-C10); HRMS (CI-isobutane) for $C_{10}{}^{13}CH_{11}O_2$ ([M+H]$^+$) calcd 176.0793, found 176.0796; LRMS (CI-isobutane) *m*/*z* (intensity); 176.2 ([M+H]$^+$) (100), 113.2 (17), 97.2 (22).

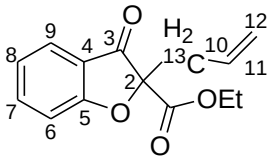
2-[^{13}C]-2-Allyl-3-benzofuranone **374*d**



Following the general procedure, 2-[^{13}C]-1-(2'-allyloxyphenyl-2-diazoethanone **372*d** (54.3 mg, 0.267 mmol) in anhydrous dichloromethane was added to a solution of Cu(hfacac)$_2$ (13.0 mg, 0.0272 mmol) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-[^{13}C]-2-allyl-3-benzofuranone (19.1 mg, 0.109 mmol, 41%) as a colourless oil. R_f = 0.45 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3079, 2921, 1712, 1612 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (1H, dd, *J* = 7.7, 0.5 Hz, CH-C9), 7.62 (1H, ddd, *J* = 8.5, 7.3, 1.4 Hz, CH-C7), 7.13 (1H, d, *J* = 8.5 Hz, CH-C6), 7.08 (1H, app. t, *J* = 7.4 Hz, CH-C8), 5.83 (1H, dddd, *J* = 17.0, 12.8,

6.9, 2.5 Hz, CH-C11), 5.23 (1H, ddt, *J* = 17.0, 2.6, 1.3 Hz, *trans*-CH_2-C12), 5.15—5.13 (1H, m, *cis*-CH_2-C12), 4.62 (1H, ddd, *J* = 151.8, 7.7, 4.2 Hz, CH-C2), 2.84—2.77 (1H, m, CH_2-C10), 2.57—2.49 (1H, m, CH_2-C10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3 (d, *J* = 41.8 Hz, C-C3), 173.1 (d, *J* = 85.7 Hz, C-C5), 138.1 (CH-C7), 131.7 (d, *J* = 3.0 Hz, CH-C11), 124.3 (d, *J* = 2.5 Hz, CH-C9), 121.9 (CH-C8), 121.0 (d, *J* = 16.9 Hz, C-C4), 118.9 (d, *J* = 3.5 Hz, CH_2-C12), 113.5 (d, *J* = 2.0 Hz, CH-C6), 84.6 (CH-C2), 35.5 (d, *J* = 36.7 Hz, CH_2-C10); HRMS (CI-isobutane) for $C_{10}{}^{13}CH_{11}O_2$ ($[M+H]^+$) calcd 176.0793, found 176.0797; LRMS (CI-isobutane) *m*/*z* (intensity); 176.2 ($[M+H]^+$) (100), 71.1 (91).

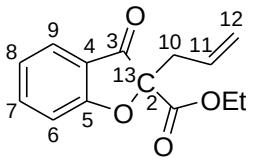
10-[^{13}C]-2-Allyl-2-carboxylic acid ethyl ester-3-benzofuranone **375*i**



Following the general procedure, 3''-[^{13}C]-ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate **373*t** (31.7 mg, 0.116 mmol) in anhydrous 1,2-dichloroethane (2 mL) was added to a solution of $Rh_2(OAc)_4$ (10 mol%) in anhydrous 1,2-dichloroethane (5 mL) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 10-[^{13}C]-2-allyl-2-carboxylic acid ethyl ester-3-benzofuranone (21.9 mg, 0.0886 mmol, 76%) as a colourless oil. R_f = 0.35 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3078, 2924, 1751, 1721, 1613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (1H, ddd, *J* = 7.2, 3.2, 1.4 Hz, CH-C7), 7.65 (1H, dd, *J* = 7.2, 1.4 Hz, CH-C9), 7.23 (1H, d, *J* = 8.6 Hz, CH-C6), 7.13 (1H, app. td, *J* = 7.2, 0.7 Hz, CH-C8), 5.68 (1H, ddddd, *J* = 17.1, 10.2, 7.2, 7.2, 4.3 Hz, CH-C11), 5.23 (1H, dddt, *J* = 17.1, 7.2, 1.5, 1.4 Hz, *trans*-CH_2-C12), 5.11 (1H, dddd, *J* = 10.2, 1.5, 0.8, 0.8 Hz, *cis*-CH_2-C12), 4.24 (2H, m, CH_2-Et), 2.94 (2H, ddddt, *J* = 132.7, 96.7, 14.5, 7.2, 1.1 Hz, CH_2-C10), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6 (C-C3), 172.3 (C-CO_2Et), 165.6 (C-C5), 138.6 (CH-C7), 129.6 (d, *J* = 42.0 Hz, CH-C11), 124.9 (CH-C9), 122.6 (CH-C8), 120.7 (CH_2-C12), 119.6 (C-C4), 113.6 (CH-C6), 90.8 (d, *J* = 36.8 Hz, C-C2), 62.7 (CH_2-Et), 38.3 ($^{13}CH_2$-C10), 14.1 (CH_3-Et); HRMS (EI) for $C_{13}{}^{13}CH_{14}O_4$ (M^+) calcd 247.0926, found 247.0929; LRMS (EI) *m*/*z* (intensity); 247.0 (M^+) (18), 174.0 (35), 85.9 (100).

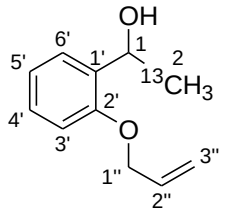
2-[^{13}C]-2-Allyl-2-carboethoxy-3-oxo-2,3-dihydrobenzofuran

375*d



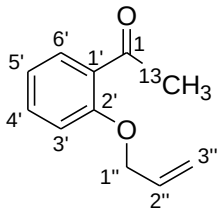
Following the general procedure, 2-[^{13}C]-ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate **373*d** (13.9 mg, 0.0507 mmol) in anhydrous 1,2-dichloroethane (3 mL) was added to a solution of Cu(hfacac)$_2$ (2.6 mg, 5.4 μmol) at reflux. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-[^{13}C]-2-allyl-2-carboxylic acid ethyl ester-3-benzofuranone (5.7 mg, 23.1 μmol, 46%) as a colourless oil. R_f = 0.35 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3078, 2924, 1751, 1721, 1613 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68—7.64 (2H, m, CH-C7 and CH-C9), 7.23 (1H, d, *J* = 8.7 Hz, CH-C6), 7.13 (1H, app. t, *J* = 7.5 Hz, CH-C8), 5.68 (1H, dddd, *J* = 17.1, 11.9, 7.1, 1.8 Hz, CH-C11), 5.23 (1H, ddt, *J* = 17.1, 2.6, 1.3 Hz, *trans*-CH_2-C12), 5.12—5.08 (1H, m, *cis*-CH_2-C12), 4.29—4.19 (2H, m, CH_2-Et), 3.09—3.04 (1H, m, CH_2-C10), 2.85—2.80 (1H, m, CH_2-C10), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6 (d, *J* = 43.1 Hz, C-C3), 172.3 (C-CO_2Et), 165.5 (d, *J* = 64.7 Hz, C-C5), 138.6 (CH-C7), 129.6 (d, *J* = 3.7 Hz, CH-C11), 124.9 (d, *J* = 2.2 Hz, CH-C9), 122.6 (CH-C8), 120.7 (d, *J* = 2.9 Hz, CH_2-C12), 119.6 (d, *J* = 16.6 Hz, C-C4), 113.5 (d, *J* = 2.3 Hz, CH-C6), 90.8 (C-C2), 62.7 (CH_2-Et), 38.3 (d, *J* = 36.8 Hz, CH_2-C10), 14.0 (CH_3-Et); HRMS (EI) for $C_{13}{}^{13}CH_{14}O_4$ (M^+) calcd 247.0926, found 247.0928; LRMS (EI) *m*/*z* (intensity); 247.0 (M^+) (7), 174.1 (19), 83.9 (100).

2-[^{13}C]-1-(2'-Allyloxyphenyl)-ethanol **378**



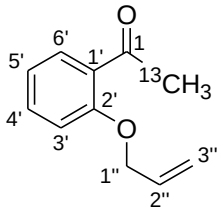
A solution of $^{13}CH_3I$ (0.35 mL, 5.6 mmol) in anhydrous diethyl ether (4 mL) was added dropwise to a stirred suspension of magnesium turnings (125 mg, 5.13 mmol) in anhydrous diethyl ether (2 mL) at room temperature, causing the suspension to heat to reflux. After 45 min, a solution of 2-allyloxybenzaldehyde **240** (833 mg, 5.13 mmol) in anhydrous diethyl ether (4 mL) was added dropwise. After 4.5 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (6 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 1:4) afforded 2-[^{13}C]-1-(2'-allyloxyphenyl)-ethanol (545 mg, 3.04 mmol, 59%) as a colourless oil. R_f = 0.18 (petroleum ether—ethyl acetate, 1:9); ν_{max} (neat) 3378, 3078, 2973, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (1H, dd, *J* = 7.5, 1.7 Hz, CH-C6'), 7.22 (1H, ddd, *J* = 8.1, 7.5, 1.7 Hz, CH-C4'), 6.97 (1H, ddd, *J* = 7.5, 7.5, 0.8 Hz, CH-C5'), 6.87 (1H, dd, *J* = 8.1, 0.8 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.2, 10.5, 5.1 Hz, CH-C2''), 5.43 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.30 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 5.14 (1H, ddq, *J* = 6.5, 5.8, 2.9 Hz, CH-C1), 4.60 (2H, dt, *J* = 5.1, 1.5 Hz, CH_2-C1''), 2.61 (1H, app. t, *J* = 5.8 Hz, OH), 1.53 (3H, dd, *J* = 126.7, 6.5 Hz, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5 (C-C2'), 133.7 (C-C1'), 133.0 (CH_2-C2''), 128.2 (CH-C4'), 126.2 (CH-C6'), 121.0 (CH-C5'), 117.6 (CH_2-C3''), 111.6 (CH-C3'), 68.7 (CH_2-C1''), 66.6 (d, *J* = 38.7 Hz, CH-C1), 22.9 ($^{13}CH_3$-C2); HRMS (EI) for $C_{10}{}^{13}CH_{14}O_2$ (M^+) calcd 179.1028, found 179.1031; LRMS (EI) *m/z* (intensity); 179.1 (M^+) (33), 163.1 (29), 135.1 (32), 121.1 (68), 84.0 (100).

2-[^{13}C]-1-(2'-Allyloxyphenyl) ethanone **379**



Dess-Martin periodinane (1.67 g, 3.93 mmol) was added to a solution of 2-[^{13}C]-1-(2'-allyloxyphenyl)-ethanol **378** (540 mg, 3.01 mmol) in anhydrous dichloromethane (20 mL) at room temperature. After 4 h, the reaction mixture was diluted with diethyl ether (20 mL), washed with a mixture of saturated aqueous $NaHCO_3$ solution and 10% aqueous $Na_2S_2O_3$ solution (1:1, 40 mL) followed by brine (40 mL), dried with Na_2SO_4, filtered and reduced under vacuum. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-[^{13}C]-1-(2'-allyloxyphenyl) ethanone (508 mg, 2.87 mmol, 95%) as a colourless oil. R_f = 0.38 (petroleum ether—diethyl ether, 4:1); ν_{max} (neat) 3074, 2996, 2927, 2872, 1671, 1596 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (1H, dd, *J* = 7.7, 1.9 Hz, CH-C6'), 7.44 (1H, ddd, *J* = 8.4, 7.4, 1.9 Hz, CH-C4'), 7.00 (1H, ddd, *J* = 7.7, 7.4, 0.8 Hz, CH-C5'), 6.95 (1H, d, *J* = 8.4 Hz, CH-C3'), 6.09 (1H, ddt, *J* = 17.3, 10.6, 5.3 Hz, CH-C2''), 5.44 (1H, ddt, *J* = 17.3, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.33 (1H, ddt, *J* = 10.6, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 4.65 (2H, dt, *J* = 5.3, 1.5 Hz, CH_2-C1''), 2.64 (3H, d, *J* = 128.2 Hz, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.0 (d, *J* = 43.0 Hz, C-C1), 157.9 (C-C2'), 133.5 (CH-C4'), 132.6 (CH-C2''), 130.4 (CH-C6'), 128.6 (d, *J* = 13.8 Hz, C-C1'), 120.8 (CH-C5'), 118.2 (CH_2-C3''), 112.8 (CH-C3'), 69.4 (CH_2-C1''), 32.0 ($^{13}CH_3$-C2); HRMS (EI) for $C_{10}{}^{13}CH_{12}O_2$ (M^+) calcd 177.0871, found 177.0867; LRMS (EI) *m*/*z* (intensity); 177.1 (M^+) (11), 133.1 (34), 121.0 (72), 84.0 (100).

2-[^{13}C]-1-(2'-Allyloxyphenyl) ethanone **379**

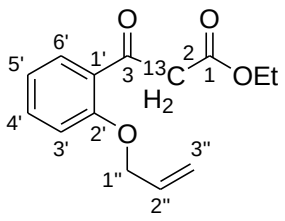


A solution of $^{13}CH_3I$ (0.35 mL, 5.6 mmol) in anhydrous diethyl ether (4 mL) was added dropwise to a stirred suspension of magnesium turnings (127 mg, 5.22 mmol) in anhydrous diethyl ether (2 mL) at room temperature, causing the suspension to warm to

reflux. After 50 min, a solution of 2-allyloxybenzaldehyde **240** (837 mg, 5.16 mmol) in anhydrous diethyl ether (4 mL) was added dropwise. After 18 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. The crude alcohol product was used in the next step without further purification.

Dess-Martin periodinane (2.81 g, 6.63 mmol) was added to a solution of the crude alcohol in anhydrous dichloromethane (20 mL) at room temperature. After 2 h, the reaction mixture was diluted with diethyl ether (20 mL) and transferred to a mixture of saturated aqueous $NaHCO_3$ solution (20 mL) and 10% aqueous $Na_2S_2O_3$ solution (20 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic fractions were washed with brine (40 mL), dried with Na_2SO_4, filtered and reduced under vacuum. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded 2-[^{13}C]-1-(2'-allyloxyphenyl) ethanone (673 mg, 3.79 mmol, 75% over two steps) as a colourless oil. Spectroscopic data identical with above.

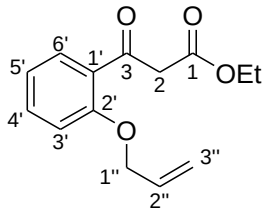
2-[^{13}C]-Ethyl 3-(2'-allyloxyphenyl)-3-oxo-propionate **380**



A solution of 2-[^{13}C]-1-(2'-allyloxyphenyl) ethanone **379** (236 mg, 1.33 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise to a solution of NaHMDS (2.0 mL of a 2 M solution in tetrahydrofuran, 4.0 mmol) in anhydrous tetrahydrofuran (1 mL) at room temperature. After 1 h, a solution of ethylchloroformate (0.25 mL, 2.6 mmol) in anhydrous tetrahydrofuran (2 mL) was added dropwise. After 20 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (4 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 6 mL). The combined organic fractions were washed with water (10 mL) followed by brine (10 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 9:1) afforded 2-[^{13}C]-ethyl 3-(2'-allyloxyphenyl)-3-oxo-propionate (45.5 mg, 0.183 mmol, 14%) was afforded as a pale yellow oil. R_f = 0.35

(petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3077, 2984, 1736, 1672, 1597 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (1H, dd, *J* = 7.8, 1.8 Hz, CH-C6'), 7.47 (1H, ddd, *J* = 8.5, 7.3, 1.8 Hz, CH-C4'), 7.05—7.01 (1H, m, CH-C5'), 6.94 (1H, d, *J* = 8.0 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.3, 10.6, 5.5 Hz, CH-C2''), 5.41 (1H, ddt, *J* = 17.3, 1.4, 1.4 Hz, *trans*-CH_2-C3''), 5.33 (1H, ddt, *J* = 10.6, 1.4, 1.4 Hz, *cis*-CH_2-C3''), 4.65 (2H, dt, *J* = 5.5, 1.4 Hz, CH_2-C1''), 4.17 (2H, q, *J* = 7.1 Hz, CH_2-Et), 4.01 (2H, d, *J* = 125.6 Hz, CH_2-C2), 1.23 (3H, t, *J* = 7.1 Hz, CH_3-Et); HRMS (CI-isobutane) for $C_{13}{}^{13}CH_{17}O_4$ ($[M+H]^+$) calcd 250.1161, found 250.1165; LRMS (CI-isobutane) *m/z* (intensity); 250 ($[M+H]^+$) (100), 210 (28), 162 (56).

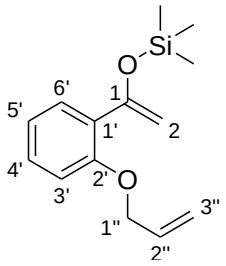
Ethyl 3-(2'-allyloxyphenyl)-3-oxo-propionate **381**



A solution of 1-(2'-allyloxyphenyl)-ethanone **255** (100 mg, 0.568 mmol) in anhydrous tetrahydrofuran (1 mL) was added dropwise to a solution of NaHMDS (2 M in tetrahydrofuran, 2.60 mL, 5.20 mmol) in anhydrous tetrahydrofuran (1 mL) at room temperature. After 1 h, a solution of ethylchloroformate (0.24 mL, 2.6 mmol) in anhydrous tetrahydrofuran (1 mL) was added dropwise. The reaction was quenched after 18 h by the addition of saturated aqueous NH_4Cl solution (2 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 3 mL). The combined organic fractions were washed with water (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 17:3) afforded ethyl 3-(2'-allyloxyphenyl)-3-oxo-propionate (53.3 mg, 0.215 mmol, 38%) as a pale yellow oil. R_f = 0.35 (petroleum ether—ethyl acetate, 9:1); ν_{max} (neat) 3077, 2984, 1736, 1672, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, dd, *J* = 7.8, 1.8 Hz, CH-C6'), 7.47 (1H, ddd, *J* = 8.4, 7.3, 1.8 Hz, CH-C4'), 7.04—7.01 (1H, m, CH-C5'), 6.94 (1H, d, *J* = 8.4 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.2, 10.6, 5.5 Hz, CH-C2''), 5.41 (1H, ddt, *J* = 17.2, 1.4, 1.4 Hz, *trans*-CH_2-C3''), 5.33 (1H, ddt, *J* = 10.6, 1.4, 1.4 Hz, *cis*-CH_2-C3''), 4.65 (2H, dt, *J* = 5.5, 1.4 Hz, CH_2-C1''), 4.17 (2H, q, *J* = 7.1 Hz, CH_2-Et), 4.01 (2H, s, CH_2-C2), 1.23 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4 (C-C3), 168.2 (C-C1), 158.1 (C-C2'), 134.4 (CH-C4'), 132.4 (CH-C2''), 131.2 (CH-C6'), 126.8 (C-C1'), 121.0 (CH-C5'), 118.8 (CH_2-C3''), 112.7

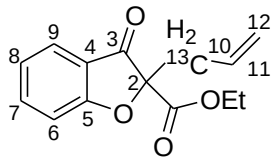
(CH-C3'), 69.5 (CH_2-C1''), 61.0 (CH_2-Et), 50.6 (CH_2-C2), 14.09 (CH_3-Et); HRMS (CI-isobutane) for $C_{14}H_{17}O_4$ ($[M+H]^+$) calcd 249.1127, found 249.1137; LRMS (CI-isobutane) *m/z* (intensity); 249 ($[M+H]^+$) (100), 209 (57), 163 (35).

[1-(2'-Allyloxyphenyl)-vinyloxy] trimethylsilane **382**



A solution of 1-(2'-allyloxyphenyl)-ethanone **255** (154 mg, 0.874 mmol) in anhydrous dichloromethane (2 mL) and TMSOTf (0.22 mL, 1.3 mmol) was added to a solution of triethylamine (0.36 mL, 2.6 mmol) in anhydrous dichloromethane (2 mL) at 0 °C. After 2 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic fractions were washed with water (5 mL) followed by brine (5 mL), dried with Na_2SO_4, filtered and reduced *in vacuo*. The crude product was used without further purification. R_f = 0.78 (petroleum ether—diethyl ether, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, dd, *J* = 7.7, 1.8 Hz, CH-6'), 7.22 (1H, ddd, *J* = 8.2, 7.4, 1.8 Hz, CH-C4'), 6.93 (1H, app. td, *J* = 7.5, 1.1 Hz, CH-C5'), 6.88 (1H, dd, *J* = 8.2, 0.8 Hz, CH-C3'), 6.07 (1H, ddt, *J* = 17.2, 10.5, 5.1 Hz, CH-C2''), 5.43 (1H, ddt, *J* = 17.2, 1.5, 1.5 Hz, *trans*-CH_2-C3''), 5.27 (1H, ddt, *J* = 10.5, 1.5, 1.5 Hz, *cis*-CH_2-C3''), 5.07 (1H, d, *J* = 0.6 Hz, CH_2-C2), 4.65 (1H, d, *J* = 0.6 Hz, CH_2-C2), 4.59 (2H, dt, *J* = 5.1, 1.5 Hz, CH_2-C1''), 0.22 (9H, 3 × CH_3-Me); HRMS (CI-isobutane) for $C_{14}H_{21}O_2Si$ ($[M+H]^+$) calcd 249.1311, found 29.1313; LRMS (CI-isobutane) *m/z* (intensity); 249.3 ($[M+H]^+$) (3), 177.2 (100).

Crossover Experiment



A solution of 3''-[^{13}C]-ethyl 3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate (21.1 mg, 76.9 µmol) in anhydrous 1,2-DCE (0.2 mL) was added to a solution of ethyl 2-[^{13}C]-3-(2'-allyloxyphenyl)-2-diazo-3-oxo-propionate (21.0 mg, 76.6 µol) in anhydrous 1,2-DCE (0.1 mL). This solution was subsequently added to a solution of $[Ir(COD)Cl]_2$ (5.3 mg, 7.89 µmol) in anhydrous 1,2-DCE (0.2 mL) at reflux. After 50 h, the reaction was cooled to room temperature and quenched by the addition of 0.5 M aqueous K_2CO_3 solution (1 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 2 mL). The combined organic fractions were washed with water (5 mL) followed by brine (5 mL), dried with $MgSO_4$, filtered and reduced *in vacuo*. Flash column chromatography (petroleum ether—diethyl ether, 4:1) afforded a mixture of rearrangement products (9.6 mg, 38.8 µmol, 25%) as a colourless oil.

References

(1) Fischer, E. O.; Maasbol, A. *Angew. Chem. Int. Ed.* **1964**, *3*, 580.
(2) Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796.
(3) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230.
(4) von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1888.
(5) von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 855.
(6) Arndt, F.; Eistert, B.; Partale, W. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1364.
(7) Arndt, F.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 1122.
(8) Bradley, W.; Robinson, R. *J. Chem. Soc.* **1928**, 1310.
(9) Dimroth, O. *Justus Liebigs Ann. Chem.* **1910**, *373*, 336.
(10) Regitz, M. *Angew. Chem. Int. Ed.* **1967**, *6*, 733.
(11) Regitz, M. *Synth.-Int. J. Methods* **1972**, 351.
(12) Regitz, M.; Menz, F.; Ruter, J. *Tetrahedron Lett.* **1967**, 739.
(13) Regitz, M. R., J.; Liedhegener, A. *Org. Synth.* **1971**, *51*, 86.
(14) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
(15) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663.
(16) Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1962**, *27*, 1490.
(17) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 878.
(18) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.
(19) Ouihia, A.; Rene, L.; Guilhem, J.; Pascard, C.; Badet, B. *J. Org. Chem.* **1993**, *58*, 1641.
(20) Marino, J. P.; Osterhout, M. H.; Price, A. T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849.
(21) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.
(22) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385.
(23) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203.
(24) Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed.* **1994**, *33*, 1797.
(25) Maxwell, J. L.; Brown, K. C.; Bartley, D. W.; Kodadek, T. *Science* **1992**, *256*, 1544.
(26) Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376.
(27) Silberrad, O.; Roy, C. S. *J. Chem. Soc.* **1906**, *89*, 179.
(28) Dave, V.; Warnhoff, E. W. *Org. React.* **1970**, *18*, 217.
(29) Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R. *Tetrahedron Lett.* **1966**, 59.
(30) Wittig, G.; Schwarzenback, K. *Justus Liebigs Ann. Chem.* **1961**, *650*, 1.
(31) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.
(32) Doyle, M. P.; Peterson, C. S.; Parker, D. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 1334.
(33) Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1141.
(34) Moser, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 1135.
(35) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.
(36) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.
(37) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232.
(38) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.

(39) Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073.
(40) Brunner, H.; Singh, U. P.; Boeck, T.; Altmann, S.; Scheck, T.; Wrackmeyer, B. *J. Organomet. Chem.* **1993**, *443*, C16.
(41) Paulisse, R; Reimling, H; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1973**, 2233.
(42) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968.
(43) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709.
(44) Callot, H. J.; Albrechtgary, A. M.; Aljoubbeh, M.; Metz, B.; Metz, F. *Inorg. Chem* **1989**, *28*, 3633.
(45) Nakamura, A.; Konishi, A.; Tatsuno, Y.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3443.
(46) Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137.
(47) Dzhemilev, U. M.; Dokichev, V. A.; Maidanova, I. O.; Nefedov, O. M.; Tomilov, Y. V. *Russ. Chem. B+* **1993**, *42*, 697.
(48) Maas, G.; Werle, T.; Alt, M.; Mayer, D. *Tetrahedron* **1993**, *49*, 881.
(49) Demonceau, A.; Saive, E.; Defroidmont, Y.; Noels, A. F.; Hubert, A. J.; Chizhevsky, I. T.; Lobanova, I. A.; Bregadze, V. I. *Tetrahedron Lett.* **1992**, *33*, 2009.
(50) Smith, D. A.; Reynolds, D. N.; Woo, L. K. *J. Am. Chem. Soc.* **1993**, *115*, 2511.
(51) Wolf, J. R.; Hamaker, C. G.; Djukic, J. P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.
(52) Hanks, T. W.; Jennings, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 5023.
(53) Maas, G. *Top Curr. Chem.* **1987**, *137*, 75.
(54) Doyle, M. P.; Griffin, J. H.; Daconceicao, J. *J. Chem. Soc. Chem. Comm.* **1985**, 328.
(55) Tamblyn, W. H.; Hoffmann, S. R.; Doyle, M. P. *J. Organomet. Chem.* **1981**, *216*, C64.
(56) Yasutomi, Y.; Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 4510.
(57) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.
(58) Zhang, Z. H.; Wang, J. B. *Tetrahedron* **2008**, *64*, 6577.
(59) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.
(60) Meerwein, S.; Rathjen, H. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1610.
(61) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S. E., Ed.; Pergamon Press: New York, 1995; Vol. 12.
(62) Taber, D. F. In *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3.
(63) Doyle, M. P. In *Homogeneous Transition Metal Catalysts in Organic Synthesis*; Moser, W. R., Slocum, D. W., Eds.; American Chemical Society: Washington D. C., 1992.
(64) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
(65) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
(66) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
(67) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons: New York, 1998.
(68) Bergman, R. G. *Nature* **2007**, *446*, 391.
(69) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.
(70) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
(71) Adams, J.; Poupart, M. A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749.
(72) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.
(73) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765.
(74) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, 3798.
(75) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837.
(76) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539.
(77) Lee, E.; Choi, I. S.; Song, S. Y. *J. Chem. Soc. Chem. Comm.* **1995**, 321.
(78) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295.

(79) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.
(80) John, J. P.; Novikov, A. V. *Org. Lett.* **2007**, *9*, 61.
(81) Shi, W. F.; Zhang, B.; Zhang, J.; Liu, B. G.; Zhang, S. W.; Wang, J. B. *Org. Lett.* **2005**, *7*, 3103.
(82) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896.
(83) Caballero, A.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 1446.
(84) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173.
(85) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc. Chem. Comm.* **1990**, 361.
(86) Ye, T.; García, C. F.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1373.
(87) Doyle, M. P.; Vanoeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W. *J. Am. Chem. Soc.* **1991**, *113*, 8982.
(88) Denton, J. R.; Davies, H. M. *Org. Lett.* **2009**, *11*, 787.
(89) Marchand, A. P.; Brockway, N. M. *Chem. Rev.* **1974**, *74*, 431.
(90) Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: New York, 1978.
(91) Stork, G.; Ficini, J. *J. Am. Chem. Soc.* **1961**, *83*, 4678.
(92) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44.
(93) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.
(94) Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.
(95) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S. E., Ed.; Pergamon Press: New York, 1995; Vol. 12.
(96) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655.
(97) Noyori, R.; Takaya, H.; Nakanisi, Y.; Nozaki, H. *Can. J. Chem.* **1969**, *47*, 1242.
(98) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1986**, *25*, 1005.
(99) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553.
(100) Pique, C.; Fahndrich, B.; Pfaltz, A. *Synlett* **1995**, 491.
(101) Leutenegger, U.; Umbricht, G.; Fahrni, C.; Vonmatt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.
(102) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
(103) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613.
(104) Doyle, M. P.; Pieters, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Muller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423.
(105) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q. L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.
(106) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860.
(107) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007.
(108) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129.
(109) Schroeter, G. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2336.
(110) Wolff, L. *Justus Liebigs Ann. Chem.* **1912**, *394*, 23.
(111) Ihara, M.; Suzuki, T.; Katogi, M.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc. Chem. Comm.* **1991**, 646.
(112) Büchner, E.; Curtius, T. *Chem. Ber.* **1885**, *18*, 2371.
(113) O'Neill, S.; O'Keeffe, S.; Harrington, F.; Maguire, A. R. *Synlett* **2009**, 2312.
(114) Clark, J. S. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry: A Practical Approach*; Clark, J. S., Ed.; Oxford University Press: Oxford, 2002.
(115) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S. E., Ed.; Pergamon Press: New York, 1995; Vol. 12.

(116) Ando, W.; Yamato, H.; Kohoda, H.; Migita, T.; Kondo, S.; Ichibori, K.; Imai, I.; Nakaido, S.; Nakayama, K. *J. Am. Chem. Soc.* **1972**, *94*, 3870.
(117) Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* **1966**, *22*, 3393.
(118) Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1965**, 2563.
(119) Kirmse, W.; Kapps, M. *Chem. Ber.* **1968**, *101*, 994.
(120) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060.
(121) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.
(122) McKervey, M. A.; Ye, T. *J. Chem. Soc. Chem. Comm.* **1992**, 823.
(123) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892.
(124) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
(125) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 2511.
(126) Iwamura, H.; Imahashi, Y.; Kushida, K. *Tetrahedron Lett.* **1975**, 1401.
(127) Maeda, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1491.
(128) Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479.
(129) Marmsater, F. P.; Vanecko, J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657.
(130) Ito, K.; Yoshitake, M.; Katsuki, T. *Tetrahedron* **1996**, *52*, 3905.
(131) (a) Ito, K.; Katsuki, T. *Chem. Lett.* **1994**, 1857 (b) Ito, K.; Yoshitake, M.; Katsuki, T. *Heterocycles* **1996**, *42*, 305.
(132) Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Tedrow, J. S. *Tetrahedron Lett.* **1997**, *38*, 4367.
(133) Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578.
(134) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561.
(135) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 6323.
(136) Desai, V. N.; Saha, N. N.; Dhavale, D. D. *J. Chem. Soc. Perkin Trans. 1* **2000**, 147.
(137) Franzen, V.; Fikentscher, L. *Liebigs Ann. Chem.* **1958**, *617*, 1.
(138) Olah, G. A.; Doggweiler, H.; Felberg, J. D. *J. Org. Chem.* **1984**, *49*, 2116.
(139) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.
(140) Doyle, M. P.; Bagheri, V.; Harn, N. K. *Tetrahedron Lett.* **1988**, *29*, 5119.
(141) Doyle, M. P.; Peterson, C. S. *Tetrahedron Lett.* **1997**, *38*, 5265.
(142) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 437.
(143) Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9867.
(144) Clark, J. S.; Baxter, C. A.; Dossetter, A. G.; Poigny, S.; Castro, J. L.; Whittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040.
(145) Clark, J. S.; Vignard, D.; Parkin, A. *Org. Lett.* **2011**, *13*, 3980.
(146) Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144.
(147) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027.
(148) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4347.
(149) Mack, D. J.; Batory, L. A.; Njardarson, J. T. *Org. Lett.* **2012**, *14*, 378.
(150) Kitagaki, S.; Yanamoto, Y.; Tsutsui, H.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2001**, *42*, 6361.
(151) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; Vanleusen, D. *J. Org. Chem.* **1984**, *49*, 1917.
(152) West, F. G.; Eberlein, T. H.; Tester, R. W. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2857.
(153) Brogan, J. B.; Zercher, C. K.; Bauer, C. B.; Rogers, R. D. *J. Org. Chem.* **1997**, *62*, 3902.
(154) Brogan, J. B.; Zercher, C. K. *Tetrahedron Lett.* **1998**, *39*, 1691.
(155) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193.
(156) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983.
(157) Pierson, N.; Fernandez-García, C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705.
(158) Shimada, N.; Nakamura, S.; Anada, M.; Shiro, M.; Hashimoto, S. *Chem. Lett.* **2009**, *38*, 488.
(159) Calter, M. A.; Sugathapala, P. M. *Tetrahedron Lett.* **1998**, *39*, 8813.
(160) Li, Z. J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 396.
(161) Kurth, M. J.; Tahir, S. H.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 2286.
(162) Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445.

(163) Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435.
(164) Reiter, M.; Turner, H.; Mills-Webb, R.; Gouverneur, V. *J. Org. Chem.* **2005**, *70*, 8478.
(165) Bunnelle, E. M.; Smith, C. R.; Lee, S. K.; Singaram, S. W.; Rhodes, A. J.; Sarpong, R. *Tetrahedron* **2008**, *64*, 7008.
(166) Sampson, P.; Roussis, V.; Drtina, G. J.; Koerwitz, F. L.; Wiemer, D. F. *J. Org. Chem.* **1986**, *51*, 2525.
(167) Sayama, S. *Heterocycles* **2005**, *65*, 1347.
(168) Winkler, J. D.; Oh, K.; Asselin, S. M. *Org. Lett.* **2005**, *7*, 387.
(169) Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.
(170) Smith, A. B.; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219.
(171) Jerris, P. J.; Smith, A. B. *J. Org. Chem.* **1981**, *46*, 577.
(172) Chimichi, S.; Boccalini, M.; Cosimelli, B.; Dall'Acqua, F.; Viola, G. *Tetrahedron* **2003**, *59*, 5215.
(173) Langer, P.; Krummel, T. *Chem. Commun.* **2000**, 967.
(174) Langer, P.; Krummel, T. *Chem. Eur. J.* **2001**, *7*, 1720.
(175) Marson, C. M.; Edaan, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. *Chem. Commun.* **2007**, 2494.
(176) Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381.
(177) Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron* **2006**, *62*, 73.
(178) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773.
(179) Clark, J. S.; Labre, F.; Thomas, L. H. *Org. Biomol. Chem.* **2011**, *9*, 4823.
(180) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385.
(181) Clark, J. S.; Guerot, C.; Wilson, C.; Blake, A. J. *Chem. Commun.* **2007**, 4134.
(182) Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. J. *Eur. J. Org. Chem.* **2006**, 323.
(183) Clark, J. S.; Dossetter, A. G.; Whittingham, W. G. *Tetrahedron Lett.* **1996**, *37*, 5605.
(184) Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Li, W. S.; Whittingham, W. G. *Chem. Commun.* **1999**, 749.
(185) Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97.
(186) Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. *Tetrahedron* **2004**, *60*, 1849.
(187) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779.
(188) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.
(189) Lipshutz, B. H.; Lower, A.; Kucejko, R. J.; Noson, K. *Org. Lett.* **2006**, *8*, 2969.
(190) Boezio, A. A.; Pytkowicz, J.; Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260.
(191) Liu, B.; Zhu, S. F.; Zhang, W.; Chen, C.; Zhou, Q. L. *J. Am. Chem. Soc.* **2007**, *129*, 5834.
(192) Doyle, M. P.; Hu, W. H. *J. Org. Chem.* **2000**, *65*, 8839.
(193) deVries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 2374.
(194) Kim, H.; Yun, J. *Adv. Synth. Catal.* **2010**, *352*, 1881.
(195) Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3777.
(196) Sagasser, I.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 261.
(197) King, M. L.; Chiang, C. C.; Ling, H. C.; Fujita, E.; Ochiai, M.; McPhail, A. T. *J. Chem. Soc. Chem. Comm.* **1982**, 1150.
(198) Kinnel, R.; Duggan, A. J.; Eisner, T.; Meinwald, J. *Tetrahedron Lett.* **1977**, 3913.
(199) Brimble, M. A.; Flowers, C. L.; Trzoss, M.; Tsang, K. Y. *Tetrahedron* **2006**, *62*, 5883.
(200) Erhunmwunse, M. O.; Steel, P. G. *J. Org. Chem.* **2008**, *73*, 8675.
(201) Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599.
(202) Jang, S.; Jung, J. C.; Oh, S. *Bioorg. Med. Chem.* **2007**, *15*, 4098.
(203) Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192.
(204) Cong, Z. Q.; Wang, C. I.; Chen, T.; Yin, B. Z. *Synth. Comm.* **2006**, *36*, 679.

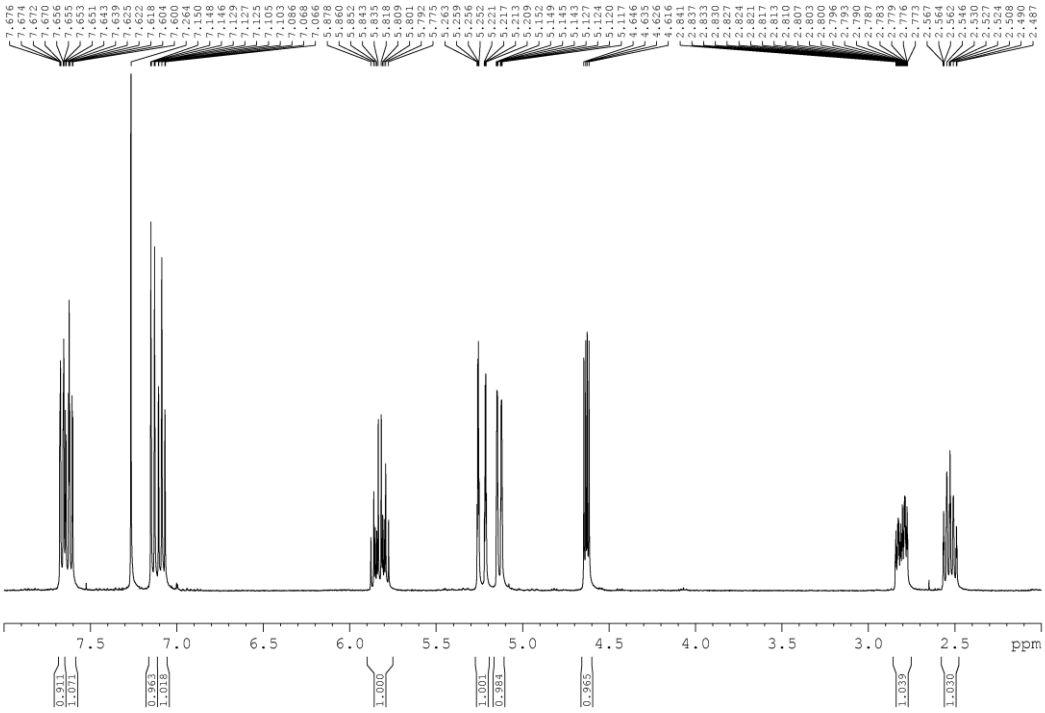
(205) Tsuchiya, Y.; Kumamoto, T.; Ishikawa, T. *J. Org. Chem.* **2004**, *69*, 8504.
(206) Nishiyama, H.; Yokoyama, H.; Narimatsu, S.; Itoh, K. *Tetrahedron Lett.* **1982**, *23*, 1267.
(207) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202.
(208) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789.
(209) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.
(210) Karmarkar, S. N.; Kelkar, S. L.; Wadia, M. S. *Synthesis* **1985**, 510.
(211) Talukdar, S.; Hsu, J. L.; Chou, T. C.; Fang, J. M. *Tetrahedron Lett.* **2001**, *42*, 1103.
(212) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901.
(213) Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140.
(214) Connolly, S.; Bennion, C.; Botterell, S.; Croshaw, P. J.; Hallam, C.; Hardy, K.; Hartopp, P.; Jackson, C. G.; King, S. J.; Lawrence, L.; Mete, A.; Murray, D.; Robinson, D. H.; Smith, G. M.; Stein, L.; Walters, I.; Wells, E.; Withnall, W. J. *J. Med. Chem.* **2002**, *45*, 1348.
(215) Roman, G.; Riley, J. G.; Vlahakis, J. Z.; Kinobe, R. T.; Brien, J. F.; Nakatsu, K.; Szarek, W. A. *Bioorgan. Med. Chem.* **2007**, *15*, 3225.
(216) Lipshutz, B. H.; Sharma, S.; Dimock, S. H.; Behling, J. R. *Synthesis* **1992**, 191.
(217) McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.
(218) Webb, S. J.; Greenaway, K.; Bayati, M.; Trembleau, L. *Org. Biomol. Chem.* **2006**, *4*, 2399.
(219) Meier, G.; Krause, M.; Huls, A.; Ligneau, X.; Pertz, H. H.; Arrang, J. M.; Ganellin, C. R.; Schwartz, J. C.; Schunack, W.; Stark, H. *J. Med. Chem.* **2004**, *47*, 2678.
(220) Chollet, G.; Guillerez, M. G.; Schulz, E. *Chem. Eur. J.* **2007**, *13*, 992.
(221) Wang, J. S.; Hsung, R. P.; Ghosh, S. K. *Org. Lett.* **2004**, *6*, 1939.
(222) Wen, Y. H.; Zhao, B. G.; Shi, Y. *Org. Lett.* **2009**, *11*, 2365.
(223) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.* **2008**, *10*, 285.
(224) Duan, Z. C.; Hu, X. P.; Zhang, C.; Wang, D. Y.; Yu, S. B.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 9191.
(225) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190.
(226) Kadota, I.; Kawada, M.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 7439.
(227) Belanger, G.; Dore, M.; Menard, F.; Darsigny, V. *J. Org. Chem.* **2006**, *71*, 7481.
(228) Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Reddy, P. N. *Tetrahedron* **2005**, *61*, 875.
(229) Tse, M. K.; Bhor, S.; Klawonn, M.; Anilkumar, G.; Jiao, H. J.; Dobler, C.; Spannenberg, A.; Magerlein, W.; Hugl, H.; Beller, M. *Chem. Eur. J.* **2006**, *12*, 1855.
(230) Jones, B. A.; Bradshaw, J. S.; Brown, P. R.; Christensen, J. J.; Izatt, R. M. *J. Org. Chem.* **1983**, *48*, 2635.
(231) Kurosu, M.; Porter, J. R.; Foley, M. A. *Tetrahedron Lett.* **2004**, *45*, 145.
(232) Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884.
(233) Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.
(234) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martinez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. *Synlett* **2005**, 2321.
(235) Barnes, D. M.; Ji, J. G.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097.
(236) Rabasso, N.; Fadel, A. *Synthesis* **2008**, 2353.
(237) Zhu, S. F.; Chen, C.; Cai, Y.; Zhou, Q. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 932.
(238) Zhang, Y. Z.; Zhu, S. F.; Cai, Y.; Mao, H. X.; Zhou, Q. L. *Chem. Commun.* **2009**, 5362.
(239) Zhang, Y. Z.; Zhu, S. F.; Wang, L. X.; Zhou, Q. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 8496.
(240) Mangion, I. K.; Nwamba, I. K.; Shevlin, M.; Huffman, M. A. *Org. Lett.* **2009**, *11*, 3566.
(241) Kanchiku, S.; Suematsu, H.; Matsumoto, K.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 3889.
(242) Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 14218.
(243) Wilson, R. A.; Chan, L.; Wood, R.; Brown, R. C. D. *Org. Biomol. Chem.* **2005**, *3*, 3228.
(244) Arndt, H. C.; Carroll, S. A. *Synthesis* **1979**, 202.
(245) Yu, W. S.; Mei, Y.; Kang, Y.; Hua, Z. M.; Jin, Z. D. *Org. Lett.* **2004**, *6*, 3217.

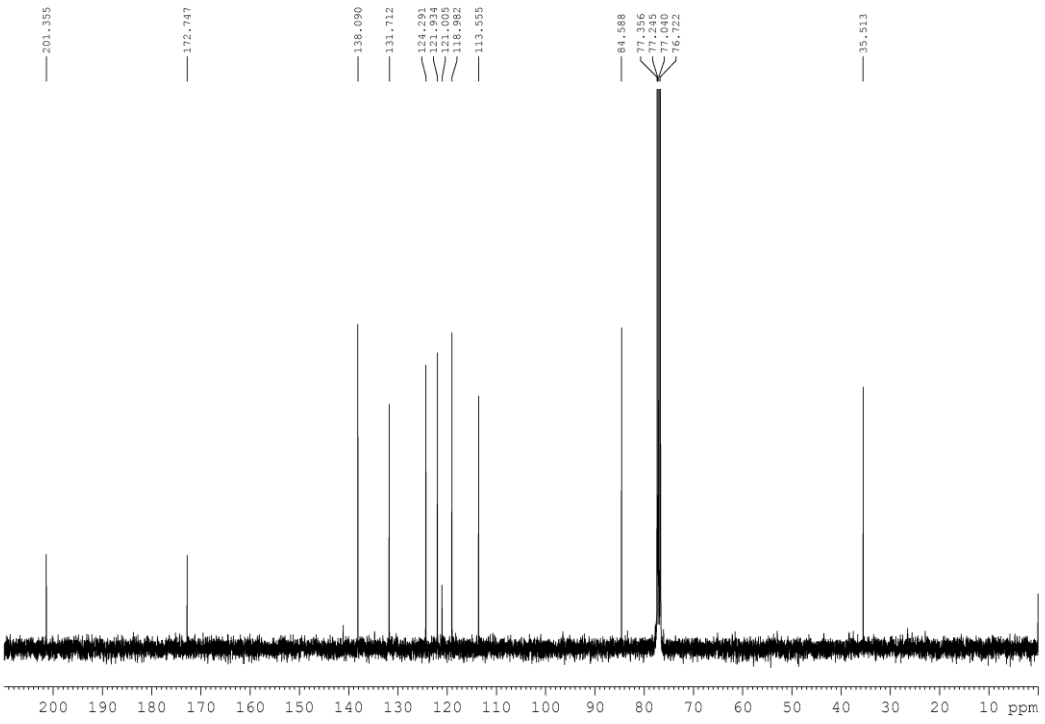
(246) Baillif, V.; Robins, R. J.; Billault, I.; Lesot, P. *J. Am. Chem. Soc.* **2006**, *128*, 11180.
(247) Zhang, S. H.; Xu, L.; Trudell, M. L. *Synthesis* **2005**, 1757.
(248) Boyer, F. D.; Le Goff, X.; Hanna, I. *J. Org. Chem.* **2008**, *73*, 5163.
(249) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(250) Kuninobu, Y.; Ueda, H.; Kawata, A.; Takai, K. *J. Org. Chem.* **2007**, *72*, 6749.
(251) Crombie, L.; Jones, R. C. F.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 317.
(252) Chen, K.; Kuo, S. C.; Hsieh, M. C.; Mauger, A.; Lin, C. M.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **1997**, *40*, 2266.
(253) Zhu, Y. Q.; Zou, X. M.; Hu, F. Z.; Yao, C. S.; Liu, B.; Yang, H. Z. *J. Agr. Food Chem.* **2005**, *53*, 9566.
(254) Chen, Y. T.; Bannister, T. D.; Weiser, A.; Griffin, E.; Lin, L.; Ruiz, C.; Cameron, M. D.; Schurer, S.; Duckett, D.; Schroter, T.; LoGrasso, P.; Feng, Y. B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6406.
(255) Itoh, T.; Miyazaki, M.; Nagata, K.; Ohsawa, A. *Tetrahedron* **2000**, *56*, 4383.
(256) Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* **1998**, 1249.
(257) Fukuda, T.; Katsuki, T. *Synlett* **1995**, 825.
(258) Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1997**, *38*, 3435.
(259) McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972.
(260) Murphy, G. K.; West, F. G. *Org. Lett.* **2006**, *8*, 4359.
(261) Shi-Hui, H.; Hirakawa, T.; Fukuba, T.; Hayase, S.; Kawatsura, M.; Itoh, T. *Tetrahedron Asym.* **2007**, *18*, 2484.
(262) Tsuchida, H.; Tamura, M.; Hasegawa, E. *J. Org. Chem.* **2009**, *74*, 2467.
(263) Barczak, N. T.; Jarvo, E. R. *Chem. Eur. J.* **2011**, *17*, 12912.
(264) Padwa, A.; Carlsen, P. H. J.; Ku, A. *J. Am. Chem. Soc.* **1978**, *100*, 3494.
(265) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.
(266) Bennett, C. J.; Caldwell, S. T.; McPhail, D. B.; Morrice, P. C.; Duthie, G. G.; Hartley, R. C. *Bioorgan. Med. Chem.* **2004**, *12*, 2079.
(267) Ellis, D.; Arias-Wood, A. *Synth. Commun.* **2011**, *41*, 1703.
(268) Gordon, M. S.; Sojka, S. A.; Krause, J. G. *J. Org. Chem.* **1984**, *49*, 97.
(269) Sayyed, I. A.; Thakur, V. V.; Nikalje, M. D.; Dewkar, G. K.; Kotkar, S. P.; Sudalai, A. *Tetrahedron* **2005**, *61*, 2831.
(270) Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, *6*, 3047.
(271) Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 6707.
(272) Heumann, L. V.; Keck, G. E. *Org. Lett.* **2007**, *9*, 4275.
(273) Su, Y.; Rabalakos, C.; Mitchell, W. D.; Wulff, W. D. *Org. Lett.* **2005**, *7*, 367.
(274) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.
(275) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y. P.; Nie, X. Y.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.
(276) Yao, X. Q.; Qiu, M.; Lu, W. R.; Chen, H. L.; Zheng, Z. *Tetrahedron Asym.* **2001**, *12*, 197.
(277) Zhou, Z. H.; Li, Z. M.; Wang, Q. Y.; Liu, B.; Li, K. Y.; Zhao, G. F.; Zhou, Q. L.; Tang, C. C. *J. Organomet. Chem.* **2006**, *691*, 5790.
(278) Hansen, T. V.; Skattebol, L. *Tetrahedron Lett.* **2005**, *46*, 3829.
(279) Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010**, *12*, 2112.
(280) Du, H. F.; Zhang, X.; Wang, Z.; Ding, K. L. *Tetrahedron* **2005**, *61*, 9465.
(281) Trost, B. M.; Vanvranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.
(282) Fuchs, S.; Berl, V.; Lepoittevin, J. P. *Eur. J. Org. Chem.* **2007**, 1145.
(283) Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Eur. J.* **1998**, *4*, 2539.
(284) Oppolzer, W.; Kuo, D. L.; Hutzinger, M. W.; Leger, R.; Durand, J. O.; Leslie, C. *Tetrahedron Lett.* **1997**, *38*, 6213.
(285) Tsubogo, T.; Kano, Y.; Ikemoto, K.; Yamashita, Y.; Kobayashi, S. *Tetrahedron Asym.* **2010**, *21*, 1221.
(286) Watanabe, K. I.; Kidokoro, K. *Chem. Lett.* **1975**, 67.

(287) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 813.
(288) Ghosh, A. K.; Packiarajan, M.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815.
(289) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875.
(290) Nayak, S. K.; Bhatt, S.; Roy, K. *Synth. Commun.* **2010**, *40*, 2969.
(291) Padwa, A.; Wong, G. S. K. *J. Org. Chem.* **1986**, *51*, 3125.

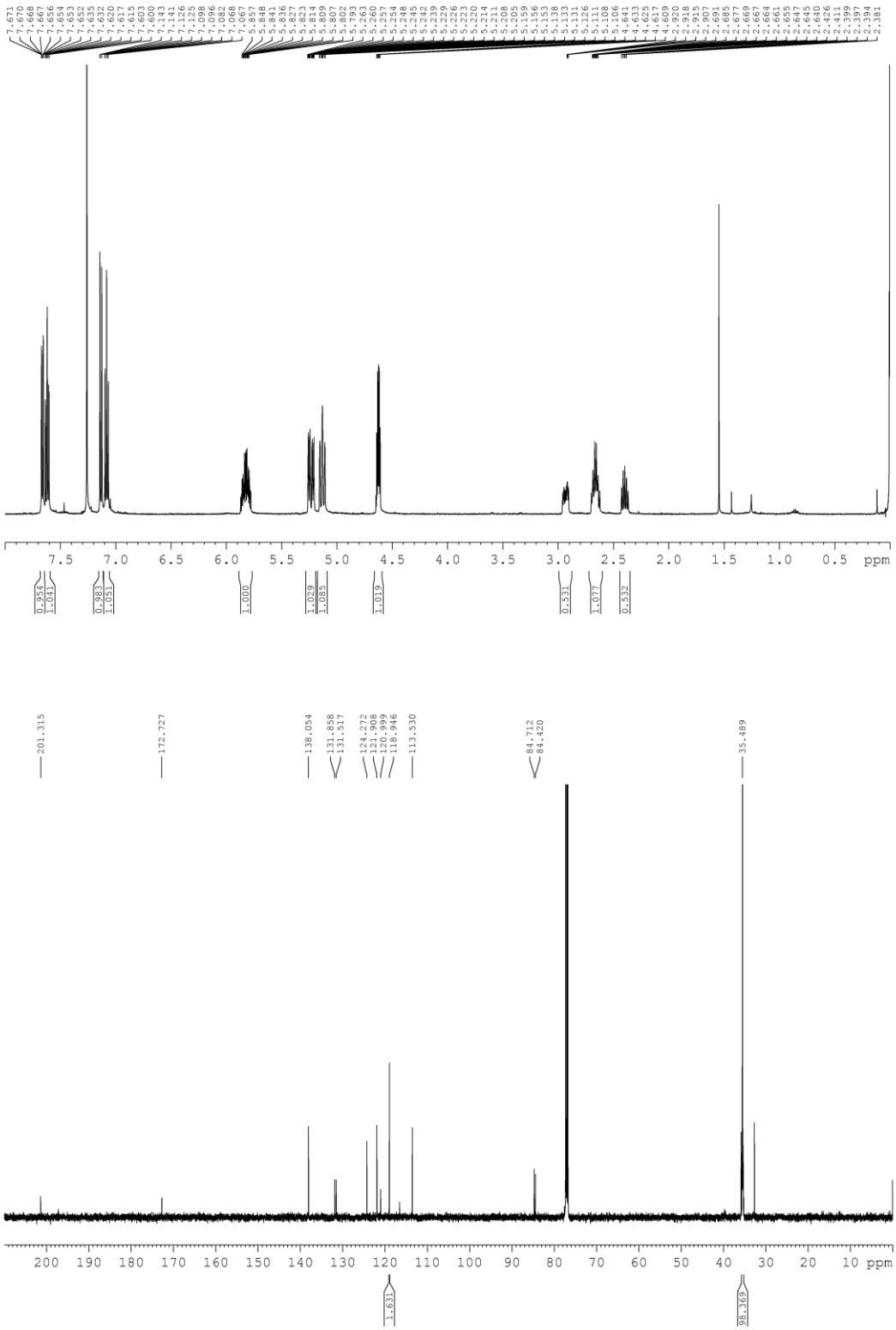
Appendix

1 ^{1}H- and ^{13}C-NMR Spectra of **300** (unlabelled) from the $Cu(acac)_2$-mediated reaction of the α-diazoketone **248** (unlabelled)

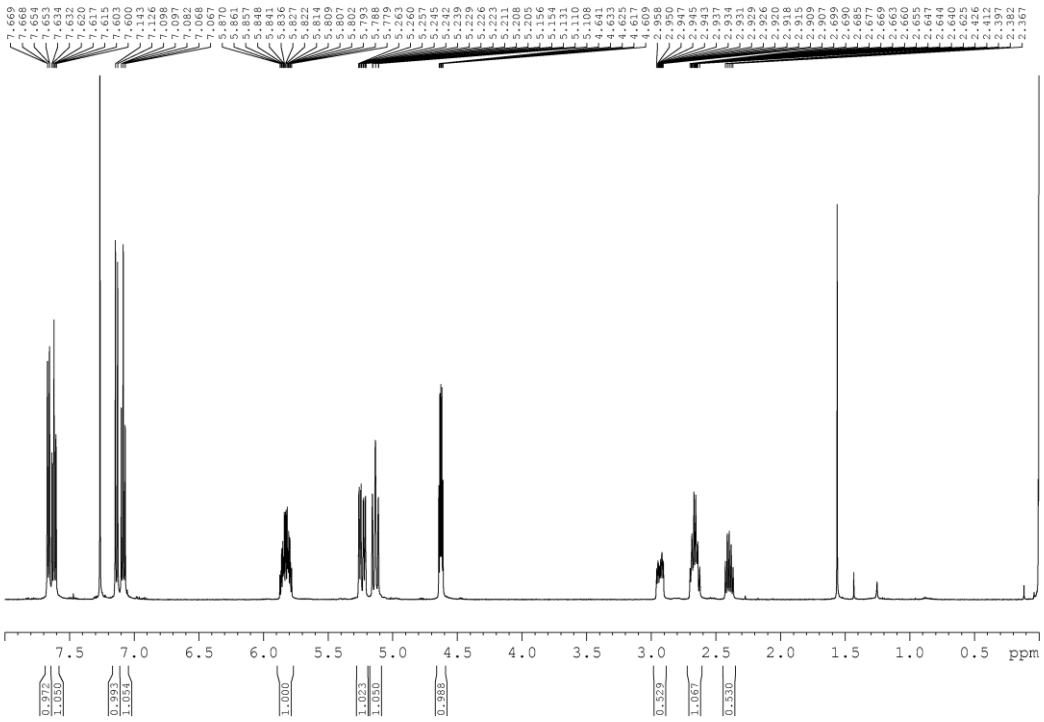


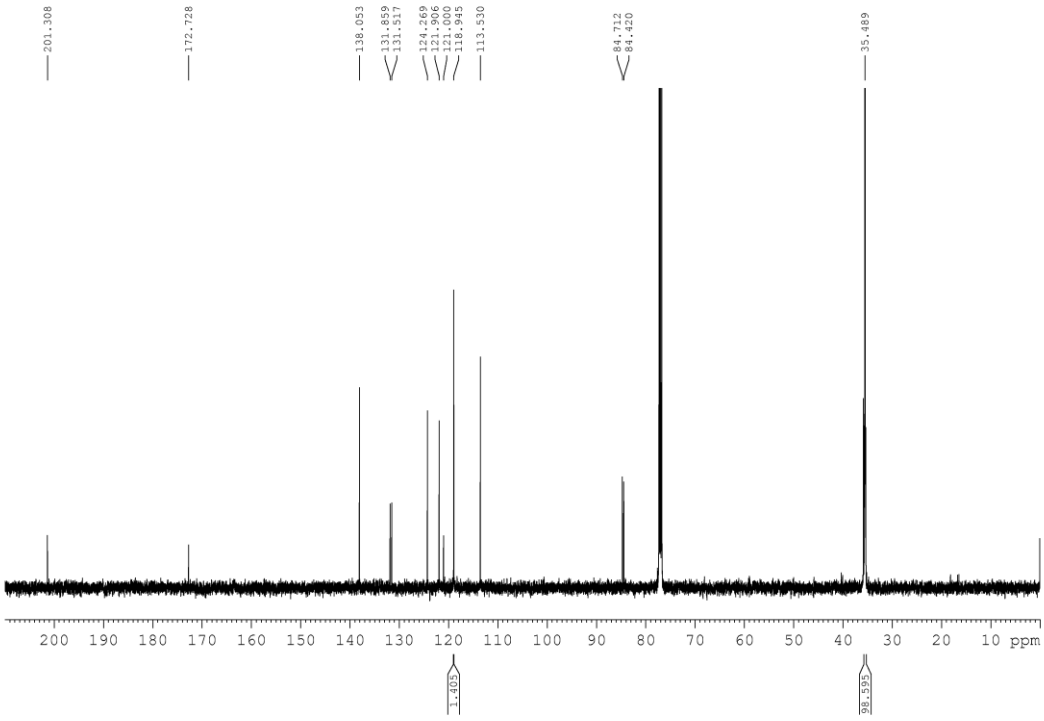


2 ^{1}H- and ^{13}C-NMR Spectra of **374*i** and **374*t** from the $Rh_2(tfa)_4$-mediated reaction of the α-diazoketone **372*t**

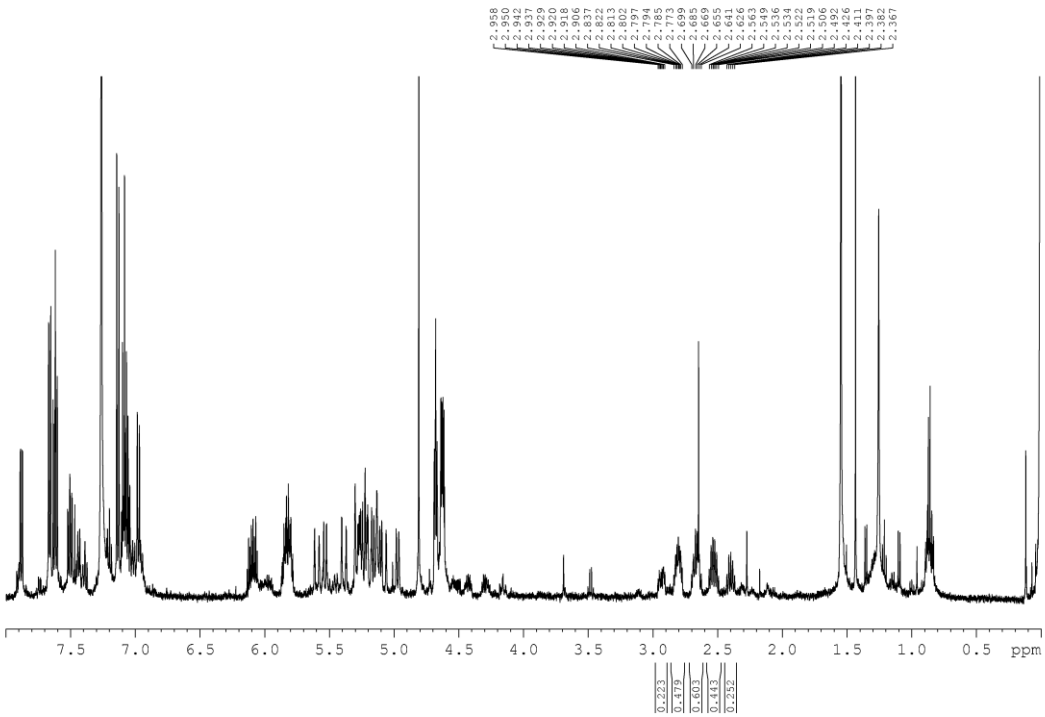


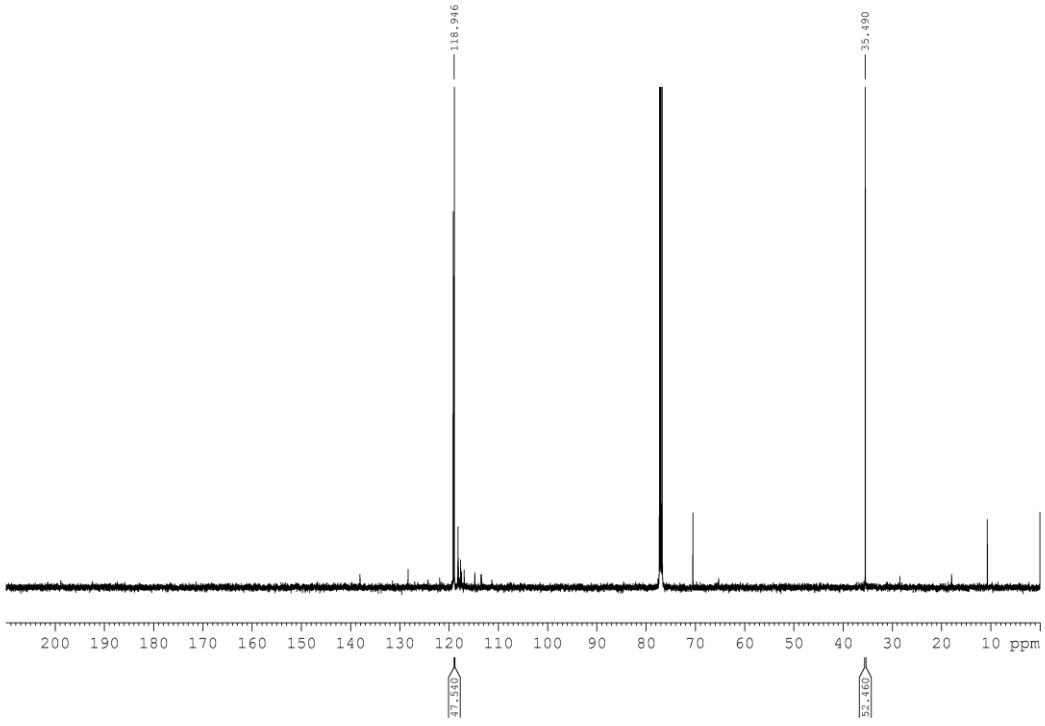
3 ^{1}H- and ^{13}C-NMR Spectra of **374*i** and **374*t** from the Cu(hfacac)$_2$-mediated reaction of the α-diazoketone **372*t**



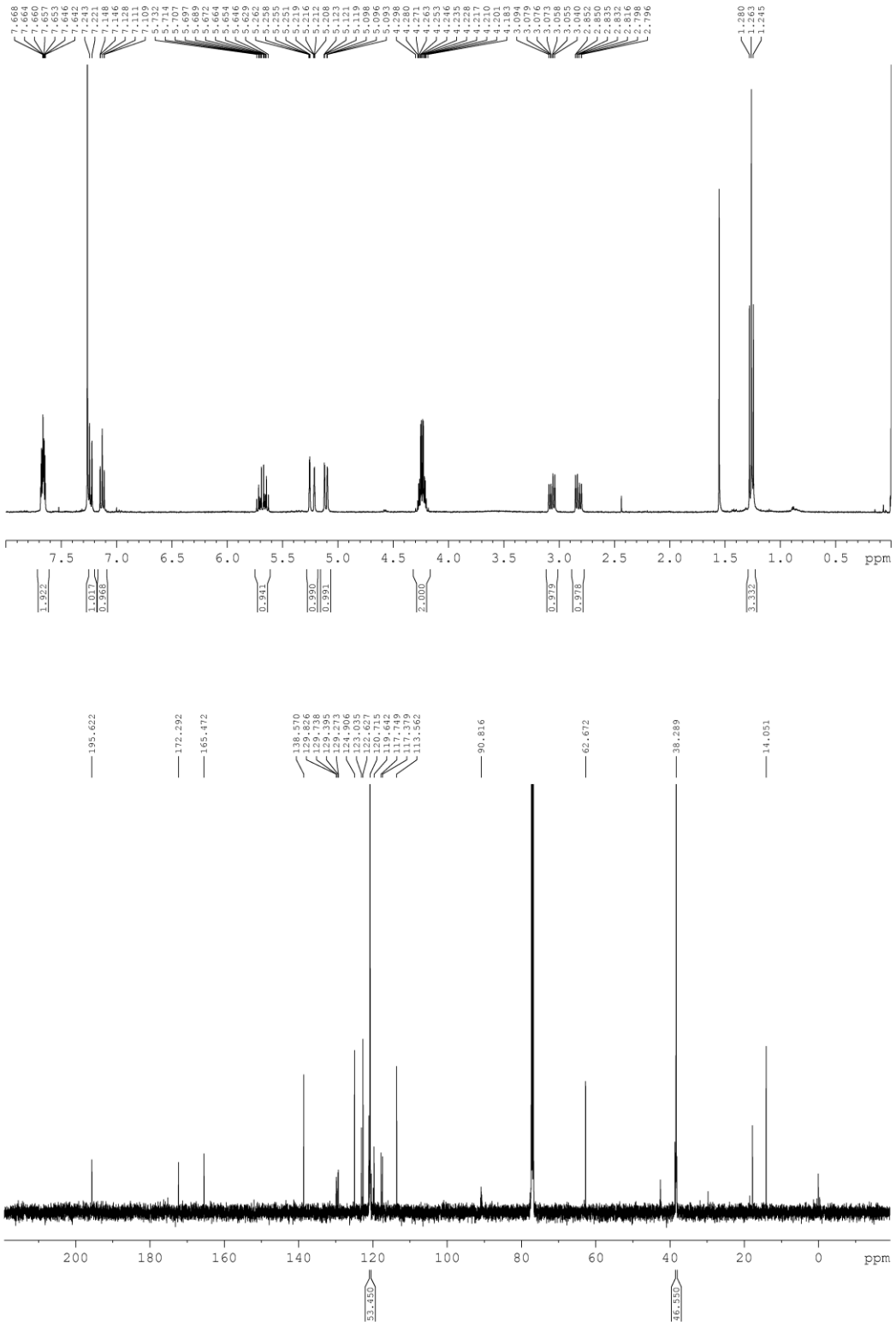


4 ^{1}H- and ^{13}C-NMR Spectra of **374*i** and **374*t** from the $[Ir(COD)Cl]_2$-mediated reaction of the α-diazoketone **372*t**

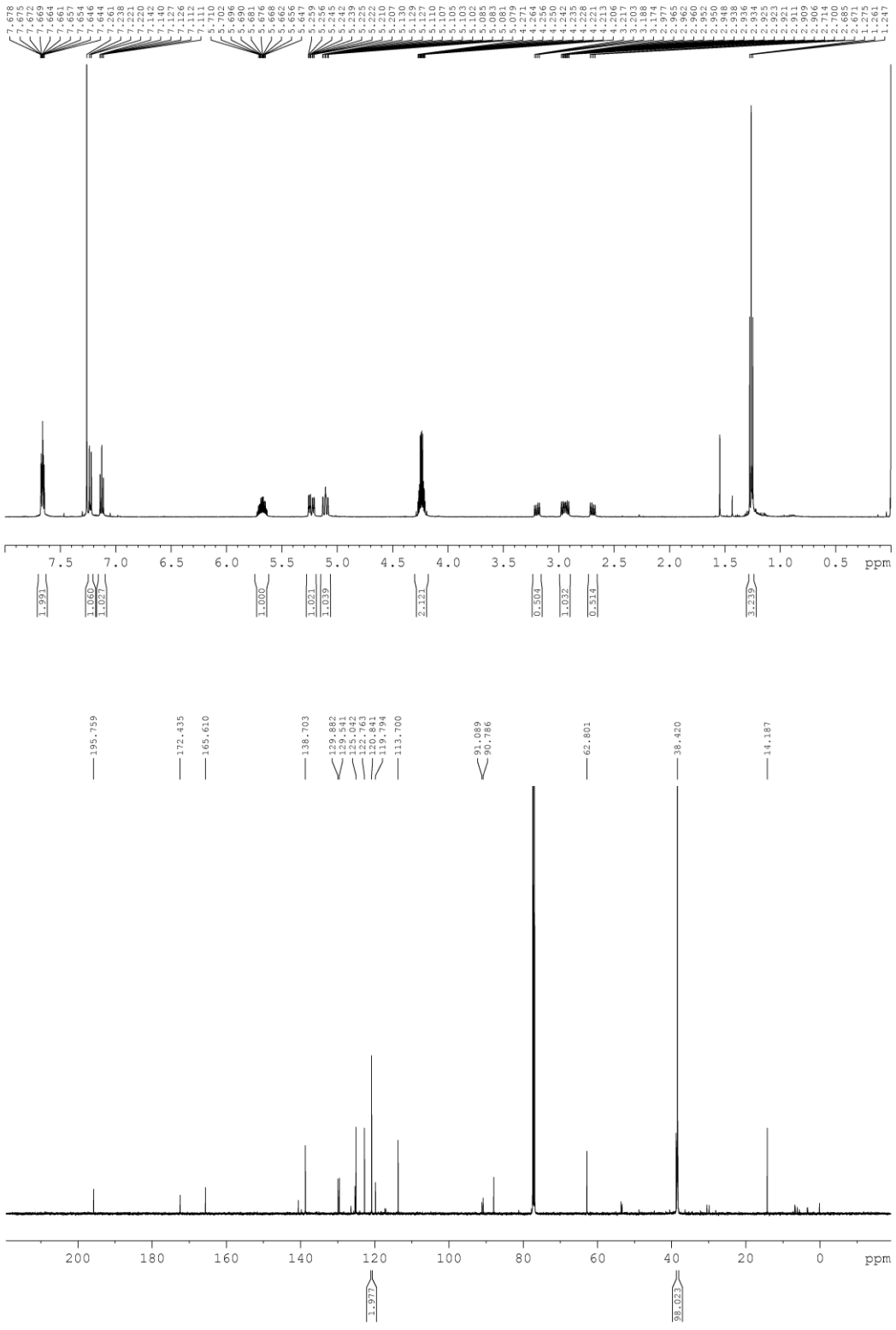




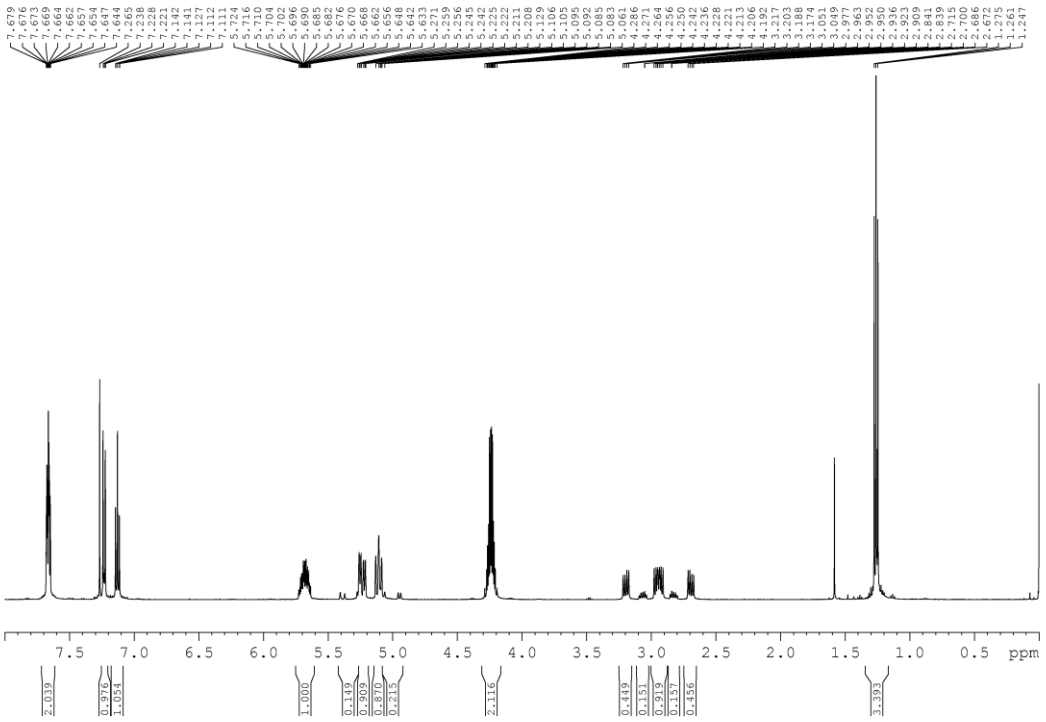
5 ^{1}H- and ^{13}C-NMR Spectra of **302** (unlabelled) from the Cu(acac)$_2$-mediated reaction of the α-diazoketone **241** (unlabelled)

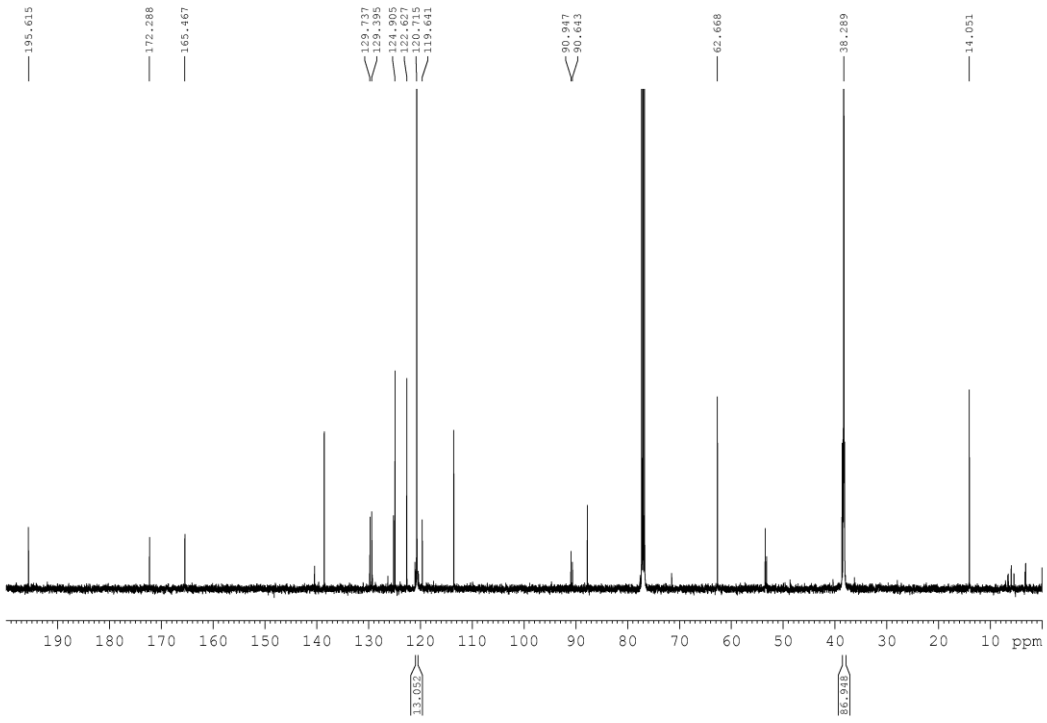


6 ^{1}H- and ^{13}C-NMR Spectra of **375*i** and **375*t** from the $Rh_2(OAc)_4$-mediated reaction of the α-diazoketone **373*t**

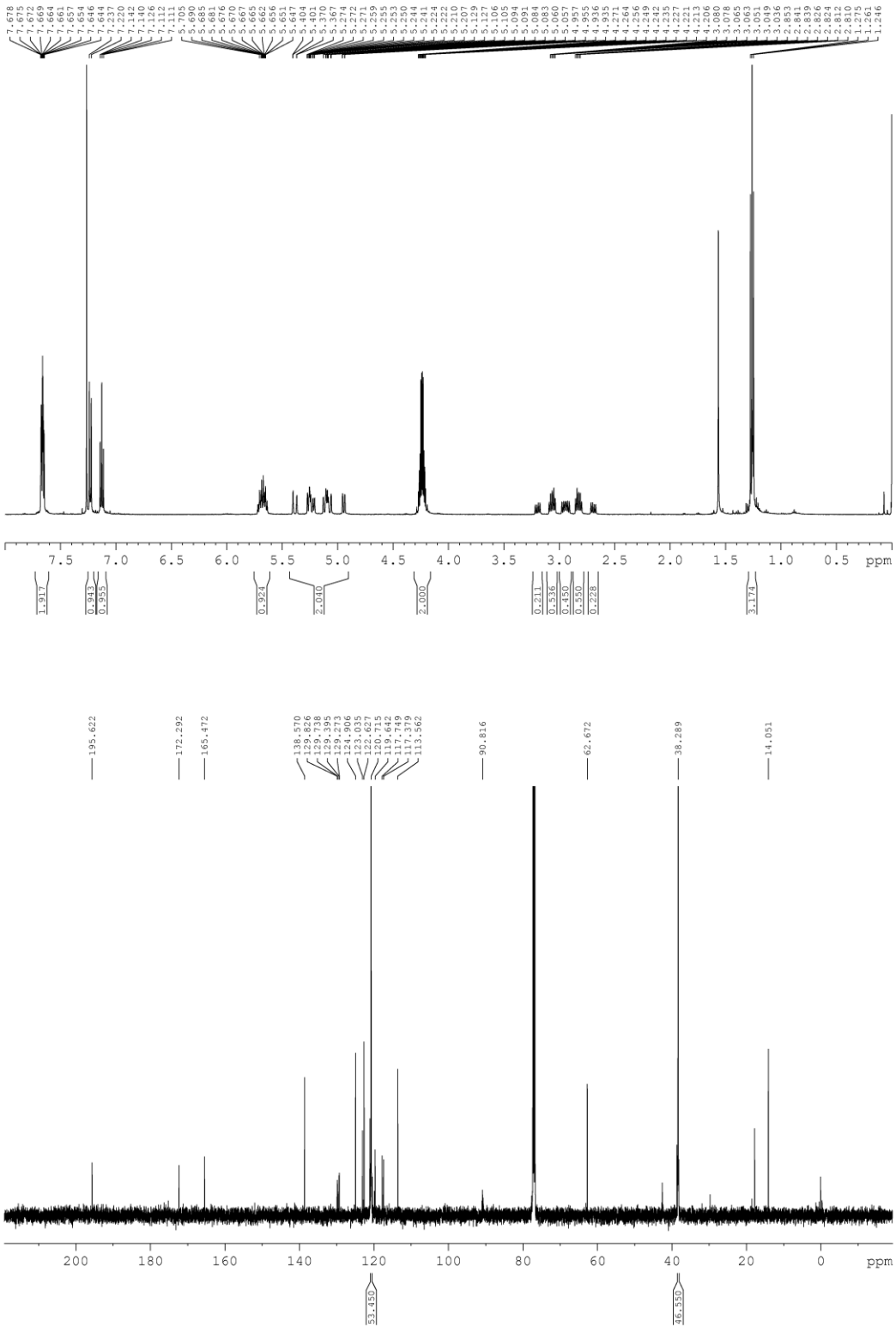


7 ^{1}H- and ^{13}C-NMR Spectra of **375*i** and **375*t** from the Cu(hfacac)$_2$-mediated reaction of the α-diazoketone **373*t**





8 ^{1}H- and ^{13}C-NMR Spectra of **375*i** and **375*t** from the [Ir(COD)Cl]$_2$-mediated reaction of the α-diazoketone **373*t**



9 ^{13}C-NMR Spectrum of products from the $[Ir(COD)Cl]_2$-mediated crossover experiment involving the α-diazoketones **373*t** and **373*d**