SINGLE ELECTRON TRANSFER REACTIONS OF 2,2,2-TRICHLORO-1-ARYL-ETHANONES AND DEVELOPMENT OF TRACELESSLY REMOVABLE BIOCONJUGATION REAGENTS

by

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A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

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Certificate

This is to certify that the entitled thesis “Single Electron Transfer Reactions of 2,2,2-Trichloro-1-aryl-ethanones and Development of Tracelessly Removable Bioconjugation Reagents” has been prepared under my supervision at the School of Chemistry / Newcastle University for the degree of PhD in the field of Organic Chemistry.

Signature
Supervisor: Michael J Hall
Date: January 2015

Signature
Student: Ali H E Alyunis
Date: January 2015

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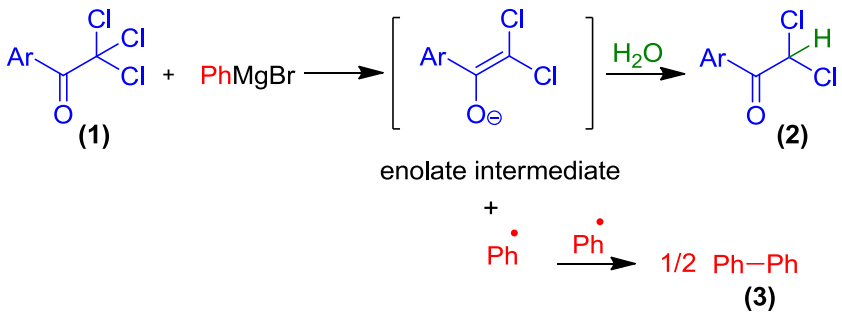
Abstract

This thesis covers two projects, the first project involves the study of single electron transfer mechanisms of the reaction between Grignard reagents and trichloroacetyl substituted aromatic compounds. The second project involves the synthesis of bioconjugation reagents capable of "traceless" removal under biocompatible, mild basic conditions.

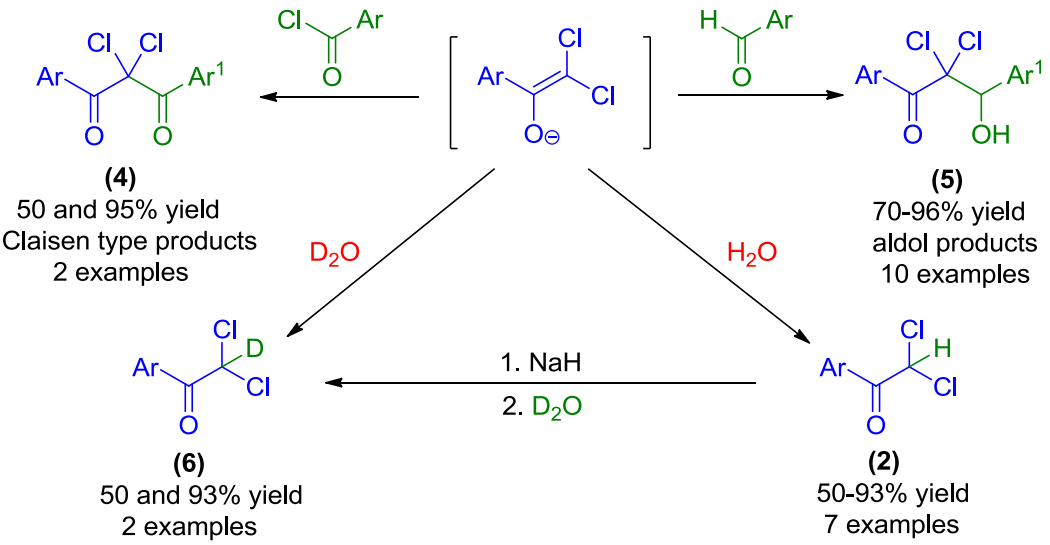
Project 1:

We have investigated the reaction of Grignard reagents with trichloroacetyl substituted aromatics. We found that high yielding reductions to the corresponding 2,2-dichloro-1-arylethanones **(2)** occurred. A single electron transfer mechanism for the reaction is proposed based on trapping experiments and EPR studies.

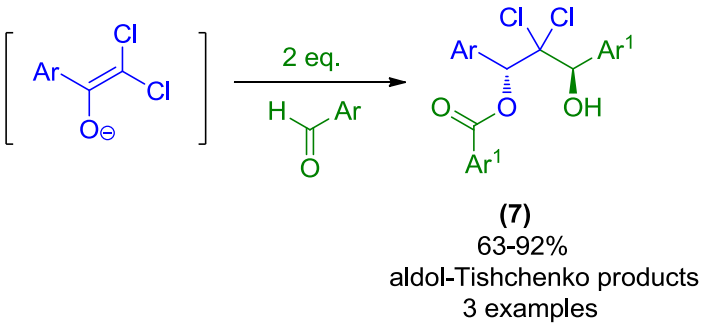


The major by-product observed and identified as 1,1'- biphenyl **(3)**, the formation of significant quantities of which is most likely to arise from the dimerization of phenyl radicals generated during the reaction.

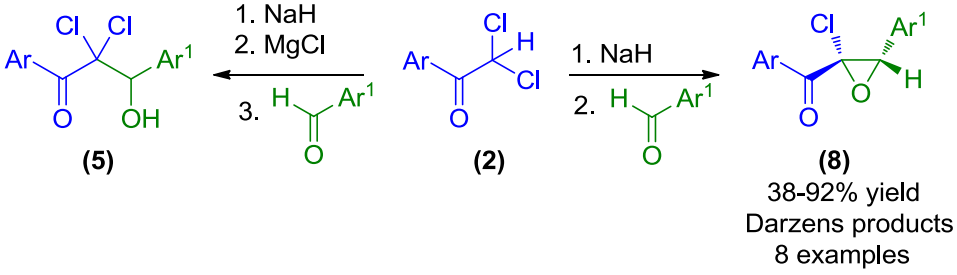
Reaction of the intermediate magnesium enolates with a range of electrophiles is described, providing a convenient route to substituted α,α-dichloro-β-hydroxyketones (**4**,**5** and **6**) and related molecules.



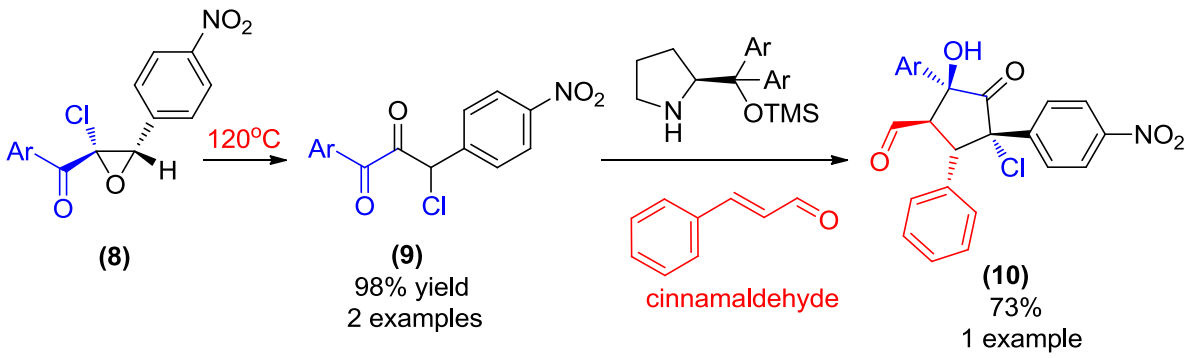
A number of different products could also be generated from the intermediate enolates with 2 equivalents of aldehyde **(7)** (aldol-Tishchenko products).



We also compared the reactivity of similar enolates with different counter ions. Whilst the reaction of magnesium enolates gave aldol products **(5)**, sodium enolates gave Darzens products **(8)**.



Finally, Darzens products were shown to undergo thermal rearrangement to give β-chlorodiketones **(9)**. The β-chlorodiketones prepared were then subjected to organo-catalyzed reactions with cinnamaldehyde to prepare cyclopentanone derivatives **(10)** with four contiguous strereogenic centers with excellent diastereo and enantioselectivity.

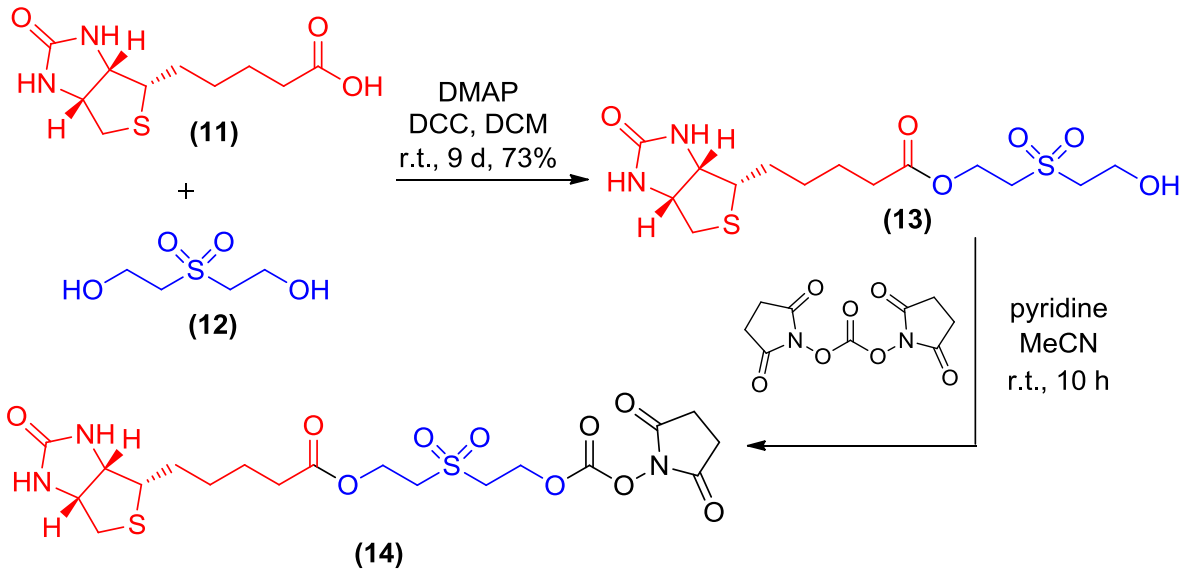


Project 2:

We designed and synthesized molecules that can be used as tracelessly removable bioconjugation reagents.

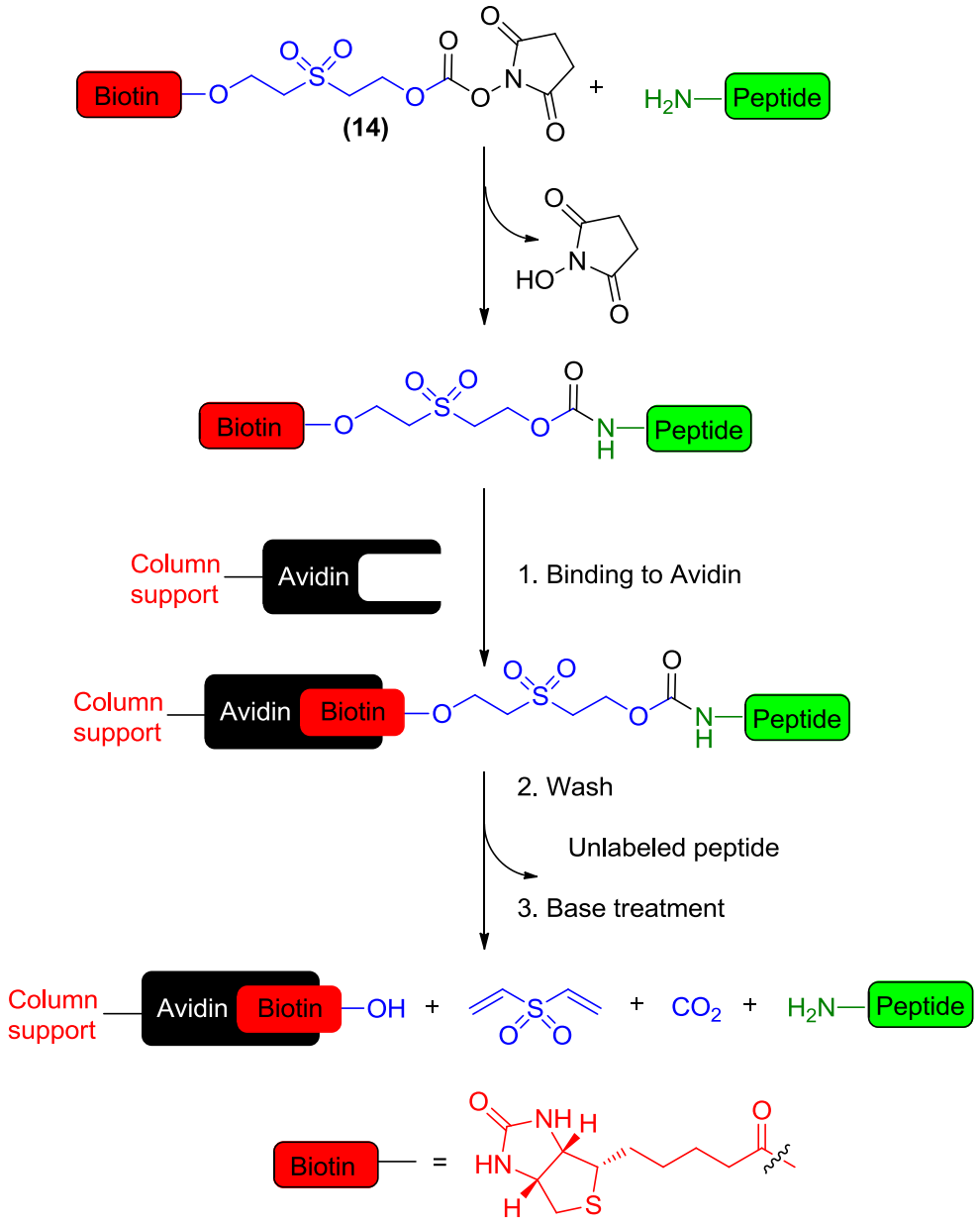
Our design was based on the use of a sulfonyl group to promote traceless removal of our bioconjugation tag via an $E1_{CB}$ reaction.

Based on the success of preliminary experiments we designed a first generation tagging reagent **(14)**, which would incorporate three key functionalities, a bio-conjugating NHS ester, a biotin and a 2-(alkylsulfonyl)ethanol core to allow base catalysed removal.



Scheme 2: Synthesis of bioconjugation reagent (**14**).

Bioconjugation of **14** to P.520 peptide and HA antigen peptides was successful. Simple treatment with mild base then released the unmodified peptide. Reagent **14** has subsequently been used to reversibly bioconjugate protein (BSA) and cell membrane proteins.



Bioconjugation of **14** to BSA can then be used for the purification of BSA by avidin affinity chromatography. Mild base can be used to release "native" BSA from avidin, providing the mildest known conditions for avidin release.

Publications from this work

Chapter 2

Reduction of 2,2,2-trichloro-1-arylethanones by RMgX: mechanistic investigation and the synthesis of substituted α, α-dichloroketones; ***Ali H. Essa***, Reinner I. Lerrick, Floriana Tuna, Ross W. Harrington, William Clegg and Michael J. Hall, *Chem. Commun*., **2013**, *49*, 2756-2758 (Appendix)

List of Abbreviations

Ac_2O	Acetic acid anhydride
$AlCl_3$	Aluminium(III)chloride
AOA	2-amino-octynoic acid
BOC	Di-*t*-butyl dicarbonate
BSA	Bovine serum albumin
CuAAC	copper-catalyzed azide alkyne cycloaddition
Cbz	carboxybenzyl
mCPBA	3-chlorobenzoperoxoic acid
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DHPMs	3,4-dihydropyrimidinones
DMAP	4-Dimethylaminopyridine
DMA	Dimethylacetamide
DTT	1,4-dimercaptobutane-2,3-diol
E^+	Electrophile(s)
EPR	Electron Paramagnetic Resonance
Et_2O	Ether
EtOH	Ethanol
$E1_CB$	Elimination Unimolecular conjugate Base
eq.	Equivalent
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometer
HPLC	High-performance liquid chromatography
IR	Infra-red
J	Coupling constant
m.p.	Melting point
NCL	native chemical ligation
NMR	Nuclear Magnetic Resonance
ppm	Part per million
PBS	phosphate buffered saline
R_f	Retention factor

r.t.	Room temperature
TCAC	Trichloro acetylchloride
TFA	Trifluoroacetic acid
THF	Tetrahidrofuran
TLC	Thin Layer Chromatography
TCEP	tris(2-carboxyethyl)phosphine
UV	Ultra-violet

Table of Contents

Chapter 7: Experimental

1.1: Single Electron transfer (SET)

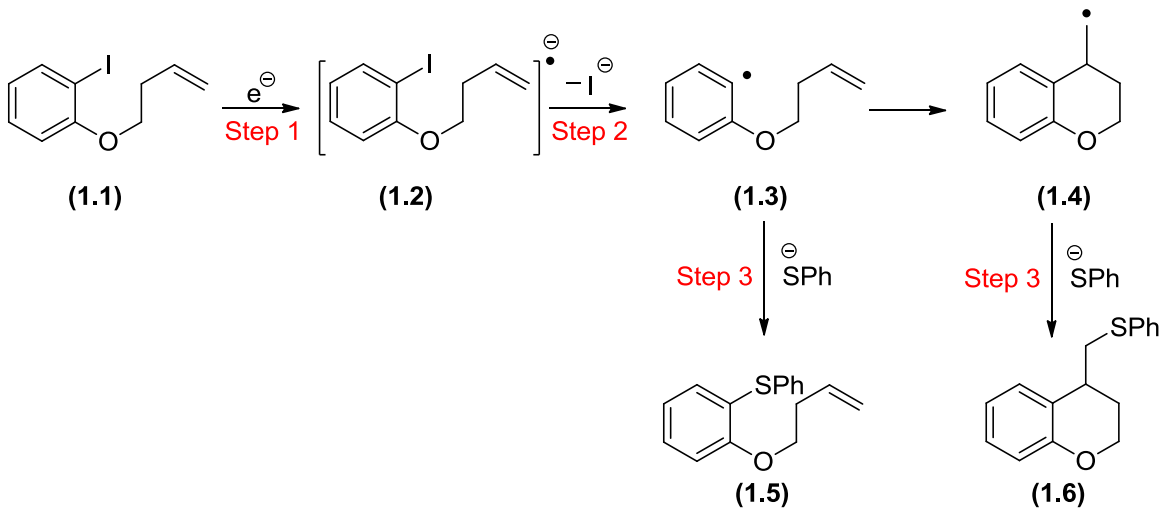
The transfer of one electron from an electron rich donor to an electron deficient acceptor is called a Single Electron Transfer (SET) reaction. There are several common SET reaction mechanisms, which will be discussed here.

1.1.1: Radical-nucleophilic aromatic substitution ($S_{RN}1$) mechanisms

Nucleophilic aromatic substitutions that occur by single electron transfer (ET), with radical anions as intermediates, are called $S_{RN}1$.[1]

Kornblum [2] and Russell [3] proposed a $S_{RN}1$ mechanism in 1966 for aliphatic systems with electron withdrawing groups (EWG) whilst Bunnett [4] proposed a similar mechanism in 1970 for aromatic systems.

There are three steps in the radical chain process in a Radical Nucleophilic Aromatic Substitution ($S_{RN}1$) reaction (Scheme 1-1).[1]

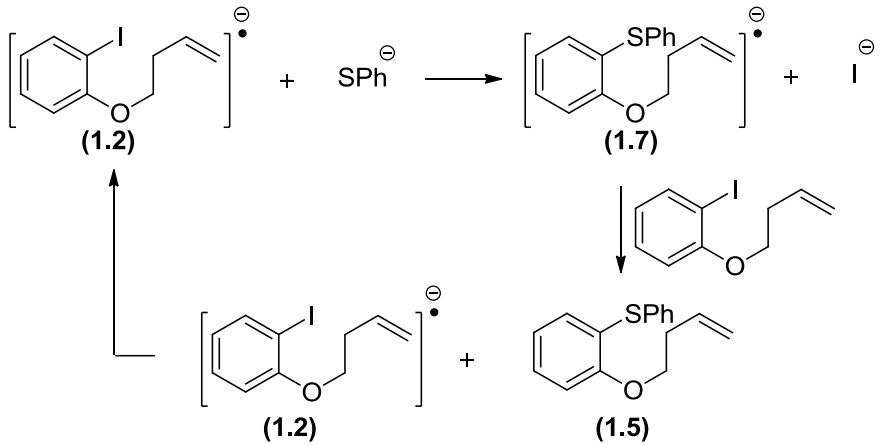


Scheme (1-1): Proposed mechanism of the $S_{RN}1$ reaction of **1.5** and **1.6**

Photostimulation or electrocatalysis used to start the reaction by promoting single electronic transfer to ArX (**1.1**) to give radical anion $ArX^{\bullet\ominus}$ (**1.2**)(step 1). This radical anion can become a radical ($Ar^{\bullet}$) (**1.3**) or (**1.4**) and an anion ($X^{\ominus}$) (step2). The $Ar^{\bullet}$ (**1.3**) and (**1.4**) then react with a nucleophile to give a substitution aromatic compound (**1.5**) and (**1.6**) respectively.

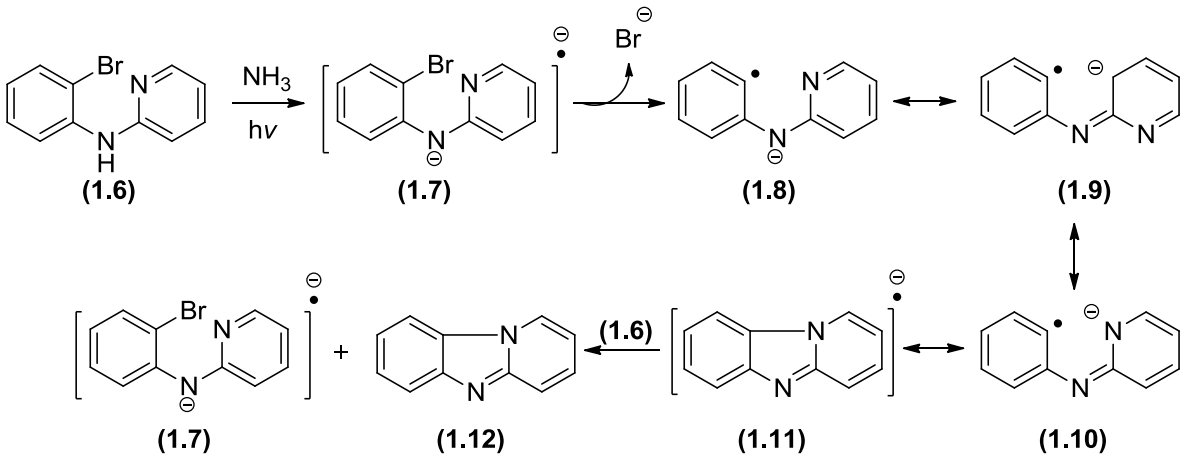
Denney and Denney [5] proposed that the radical anion ($ArX^{\bullet\ominus}$) does not fragment in the $S_{RN}2$ reaction, instead it is reacted with the nucleophile to give the radical anion of the

substitution product and anion of the leaving group, then followed by the electron transfer (ET) to the substrate (scheme 1-2).



Scheme (1-2): Proposed mechanism of the $S_{RN}2$ reaction of **1.5**

The formation of radical anion in both mechanisms requires the same initiation step. The electron can be generated from alkali metals in liquid ammonia, electrons from a cathode, or from sodium amalgam. Also, both mechanisms give the same substitution product. For example, photo-stimulated $S_{RN}1$ reaction of 2-(2-bromophenylamino)pyridines (**1.6**) in liquid ammonia in the presence of 2 equivalents of potassium *tert*-butoxide was anticipated to form pyrido[1,2-α]benimidazoles via C-N bond construction and not α-carbolines by C-C formation (Scheme 1-3).[6]

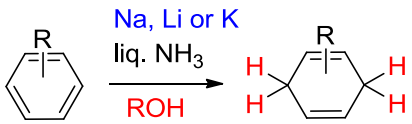


Scheme (1-3): Photo-stimulated $S_{RN}1$ reaction of 2-(2-bromophenylamino)pyridines **(1.6)**

1.2: Birch reduction

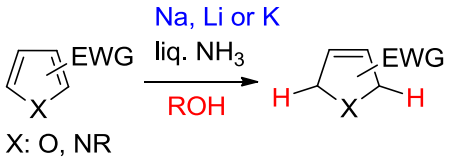
The Birch reduction was reported by Arthur Birch in 1944.[7] It is one example of a SET reaction which is particularly useful in synthetic organic chemistry, and has been

widely used for the partial hydrogenation of aromatic and heteroaromatic compounds.[8] The Birch reduction starts by generating single electron metallic sodium, lithium or potassium dissolved in liquid ammonia in the presence of an alcohol. Under these conditions, conjugated alkenes, α,β-unsaturated carbonyl compounds, styrenes and heterocycles, (eg. pyridines, pyrroles and furans) are reduced.[8-11]



Scheme (1-4): Birch reduction

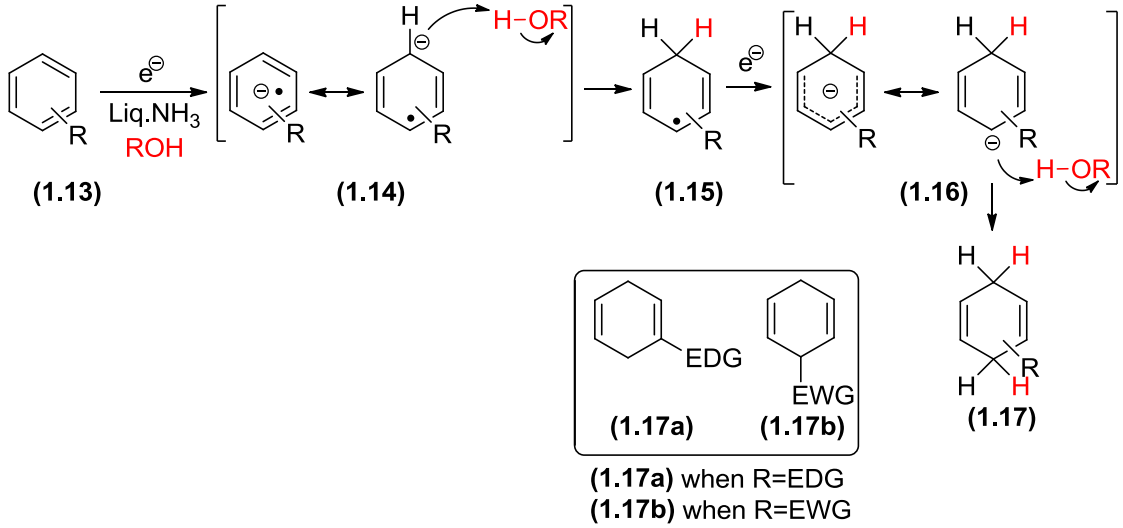
Higher reaction rates for the Birch reduction of aromatic compounds are seen with electron withdrawing substituents. In contrast, lower reduction rates are observed with electron-donating substituents. Electron-rich heterocycles such as furans and thiophenes are not reduced unless electron withdrawing substituents are present (Scheme 1-5).



Scheme (1-5): Birch reduction of heterocycles compounds

1.2.1: Mechanism of Birch reduction

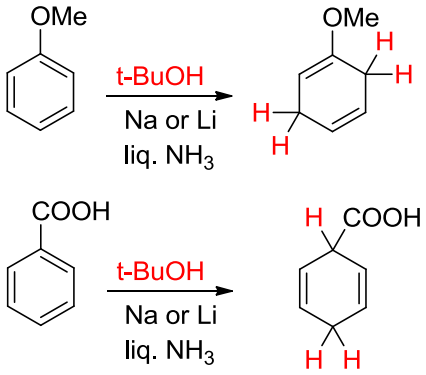
The mechanism of Birch reduction is shown in Scheme (1-6). The first step involves formation of a free electron in solution from the metal. The single electron adds to the aromatic ring (**1.13**) to give radical anion (**1.14**) which is then be protonated by the alcohol to produce a cyclohexadienyl radical (**1.15**). A second electron is then transferred to the cyclohexadienyl radical to give a cyclohexadienyl carbanion (**1.16**). Finally, cyclohexadienyl carbanion (**1.16**) accepts a proton from the alcohol forming the unconjugated cyclohexadienyl product (**1.17**). [11]



Scheme (1-6): The mechanism of Birch reduction

1.2.2: Synthetic applications of Birch reduction

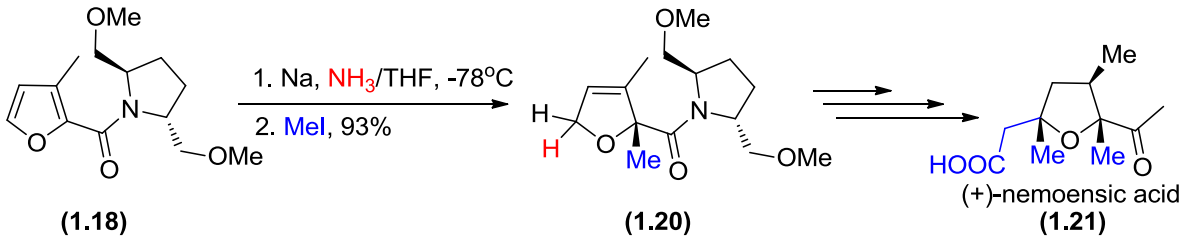
Simplest examples of the Birch reduction are the reductions of anisole and benzoic acid (Scheme 1-7).[12]



Scheme (1-7): Birch reduction of anisole and benzoic acid

The regioselectivity of the reaction is determined in the first step by the stability of the radical anion. So the reduction of anisole (Scheme 1-7) which contains an electron donor (OMe) will protonate *ortho* to the substituent, while with electron withdrawing groups such as benzoic acid (Scheme 1-7), the protonation will be *ipso* to the substituent.

Donohoe *et al.* performed a stereoselective Birch reduction during the total synthesis of (+)- nemoensic acid (**1.21**) (Scheme 1-8).[13, 14]

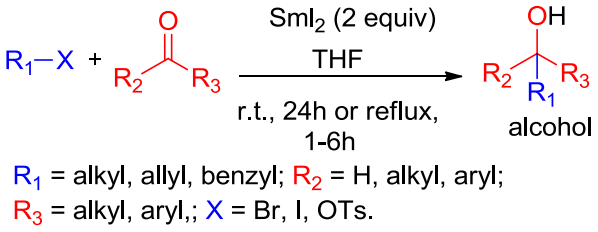


Scheme (1-8): Stereoselective Birch reduction during the total synthesis of (+)- nemoensic acid **(1.21)**

1.3: Kagan-Molander samarium diiodide-mediated coupling

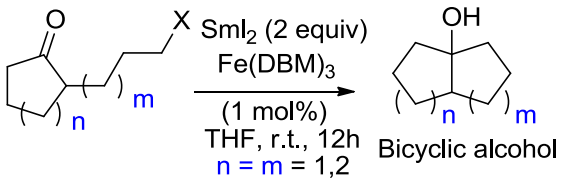
The reducing properties of lanthanide (II) iodides were studied by Kagan during the late 1970s.[11, 15,16] He found that the alcohols can be prepared by the reaction between alkyl bromides or tosylates with aldehydes or ketones in the presence of two equivalents of samarium diiodide. Molander reported in 1984 the first intramolecular version of this transformation.[17] He also discovered that in the presence of samarium diiodide and catalytic amount of an iron (III) salt, ω-iodoesters undergo intramolecular acyl substitution. These reactions are referred to as Kegan-Molander samarium diiodide-mediated couplings.[18, 19]

a) Intermolecular reaction (Kagan 1985)

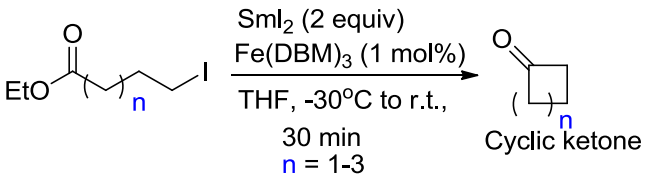


R_1 = alkyl, allyl, benzyl; R_2 = H, alkyl, aryl;
R_3 = alkyl, aryl,; X = Br, I, OTs.

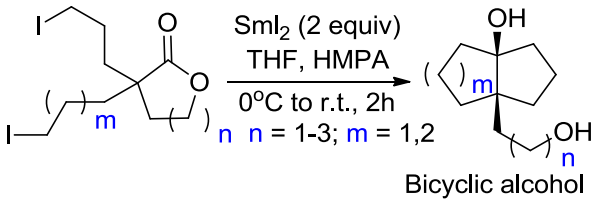
b) Intramolecular reaction (Molander1984)



c) Nucleophilic acyl substitution (Molander 1993)



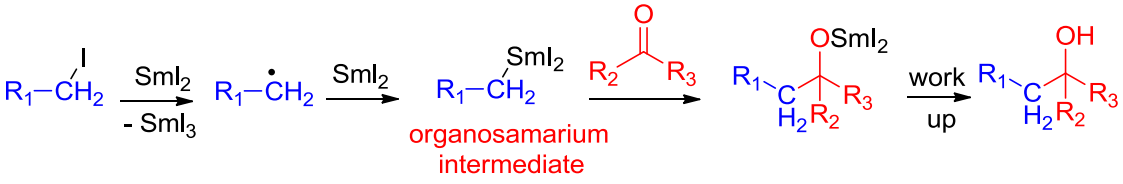
d) Tandem reaction (Molander1995)



Scheme (1-9): Examples of Kegan-Molander samarium diiodide-mediated couplings

1.3.1: Mechanism of samarium diiodide-mediated coupling

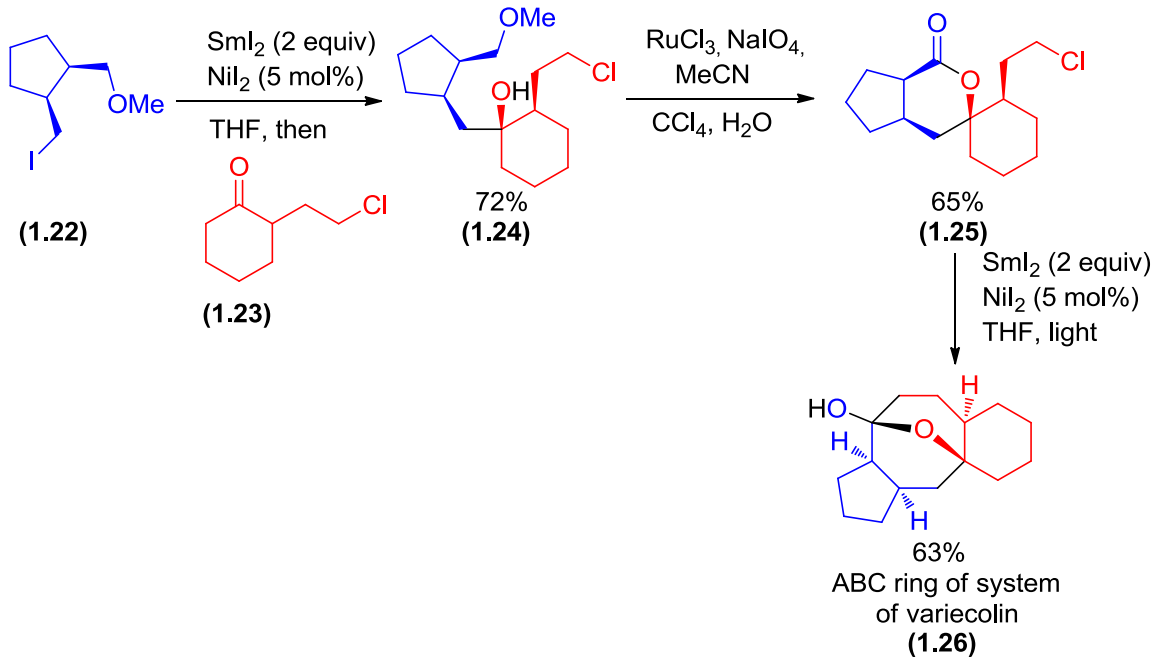
The reaction is postulated to through an organosamarium intermediate formed by SET reduction of the alkyl halide (Scheme 1-10).



Scheme (1-10): Mechanism of samarium diiodide-mediated coupling

1.3.2: Synthetic Applications of samarium diiodide-mediated coupling

Two samarium diiodide mediated processes have been used in the synthesis of variecolin (**1.26**). The total synthesis of ABC ring system of variecolin was accomplished by Molander and co-workers in 2001.[20] (1*S*,2*R*)-1-(iodomethyl)-2-(methoxymethyl)cyclopentane (**1.22**) was reacted with 2-(2-chloroethyl)cyclohexanone (**1.23**) in the presence of two equivalents of samarium diiodide and catalytic nickel (II) iodide to give (1*S*,2*R*)-2-(2-chloroethyl)-1-(((1*R*,2*R*)-2-(methoxymethyl)cyclopentyl)methyl)cyclohexanol (**1.24**). Subsequent oxidation produced chlorolactone ((1*S*,2*R*,4a'*R*,7a'*R*)-2-(2-chloroethyl)hexahydro-1'*H*-spiro[cyclohexane-1,3'-cyclopenta[c]pyran]-1'-one (**1.25**)). The carbon skeleton of variecolin (**1.26**) was formed via an intramolecular nucleophilic addition to the ester under samarium diiodide control. In this step, irradiation with visible light is required to encourage reaction of the less reactive alkyl chlorides (Scheme 1-11).

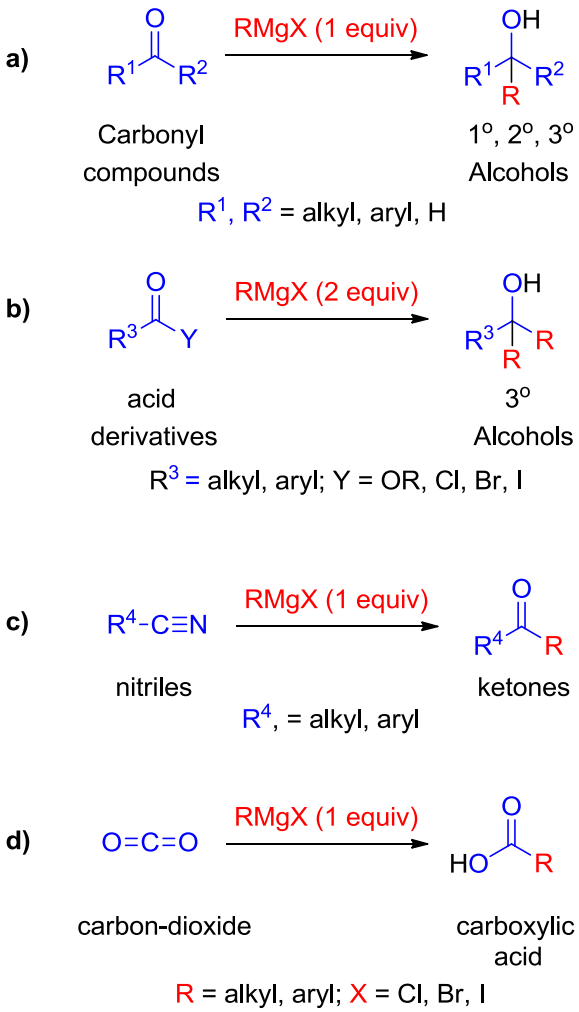


Scheme (1-11): The total synthesis of ABC ring system of variecolin

1.4: Grignard reactions

The reaction between an alkyl halide (RX) and magnesium metal (Mg) in diethyl ether typically gives an organomagnesium compound (RMgX), which can then react with

carbonyl containing compounds (ketones and aldehydes) to give secondary or tertiary alcohols respectively (Scheme 1-12). [21, 22]



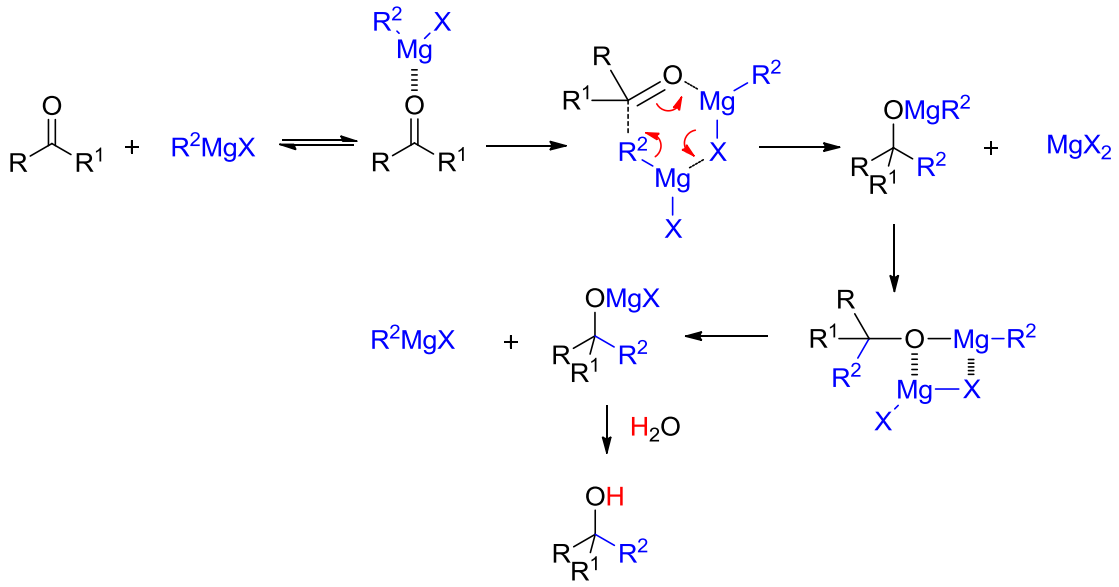
Scheme (1-12): Reaction of Grignard reagent with; **a)** carbonyl compounds; **b)** acid derivatives; **c)** nitriles; **d)** carbon dioxide

1.4.1: Mechanism for Grignard addition to a carbonyl

The reaction of a Grignard reagent with a carbonyl containing compound to form a C-C bond occurs according two limiting mechanisms, ionic (polar) or Single Electron Transfer (SET)) mechanisms depending on the solvent, halogen, alkyl group, temperature and concentration.

1.4.1.1: Ionic (polar) mechanism

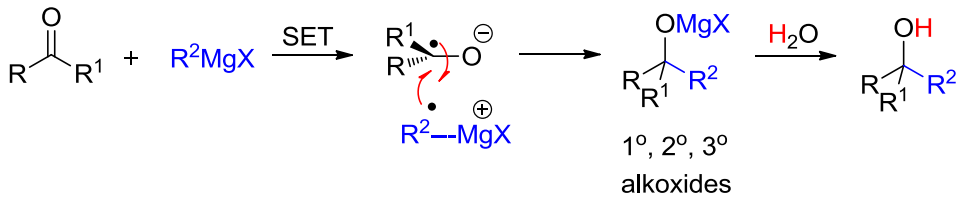
In the ionic mechanism, the Grignard reagent acts as nucleophilic source of R, and attacks the carbonyl carbon. The ionic Grignard reaction proceeds through a six-membered transition state (Scheme 1-13).[23-25]



Scheme (1-13): The ionic mechanism of Grignard reagent

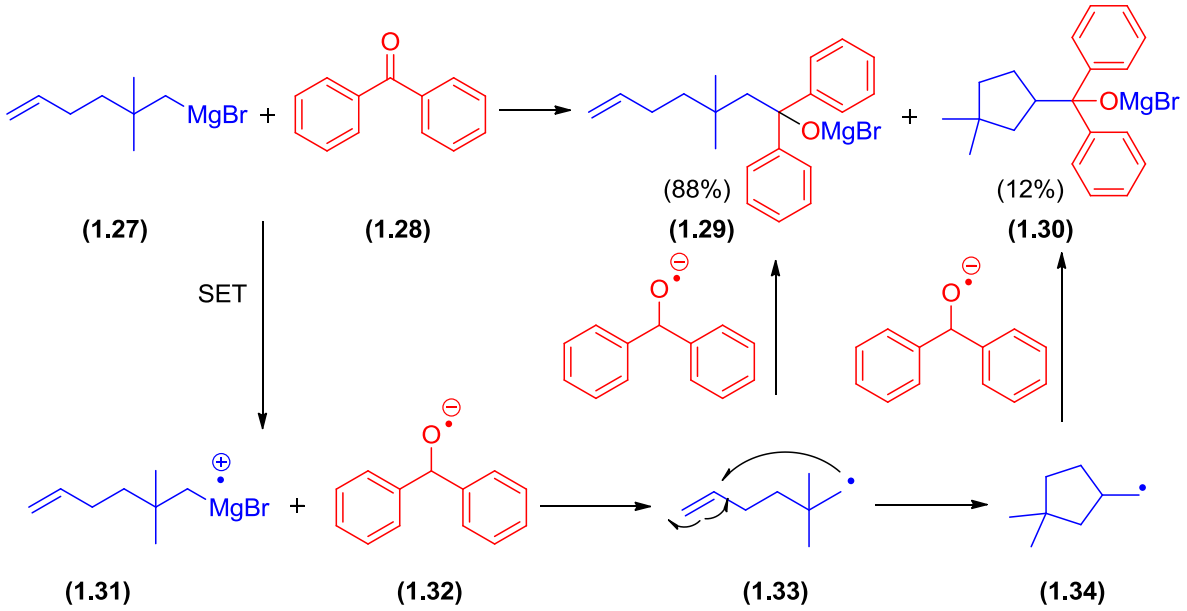
1.4.1.2: Single electron Transfer (SET) mechanism

The reaction of Grignard reagents with a carbonyl compound via Single Electron Transfer (SET) occurs with sterically demanding substrates and bulky Grignard reagents with weak C-Mg bonds. A radical pathway mechanism proposed an electron-transfer (ET) from RMgBr to the substrate (Scheme 1-14).[25]



Scheme (1-14): A radical pathway mechanism of Grignard reagent

To demonstrate the presence of radical intermediate in Grignard reaction, radical traps were used. The appearance of cyclized products would show radicals (Scheme 1-15).[26]



Scheme (1-15): Cyclized products through a radical pathway mechanism of Grignard reagent

1.5. Wurtz Coupling

The coupling of two alkyl halides in the presence of a metal (Na, Mg, Zn, Cu, etc.) produces symmetrical alkanes. This reaction is known as Wurtz coupling.

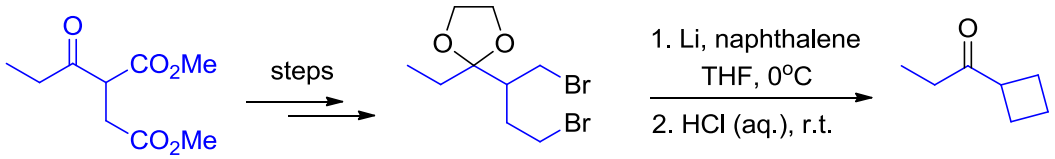
Undesired Wurtz coupling can also during the formation of Grignard reagent (Scheme 1-16).

$$2RX + Mg \longrightarrow R\text{-}R + MgX_2$$

$$RMgX + RX \longrightarrow R\text{-}R + MgX_2$$

Scheme (1-16): Wurtz coupling

For example, Wurtz reaction has been used as efficient method to synthesis of cyclobutyl ketones starting from acyl succinates. The reaction was catalyzed by naphthalene (Scheme 1-17).[27]



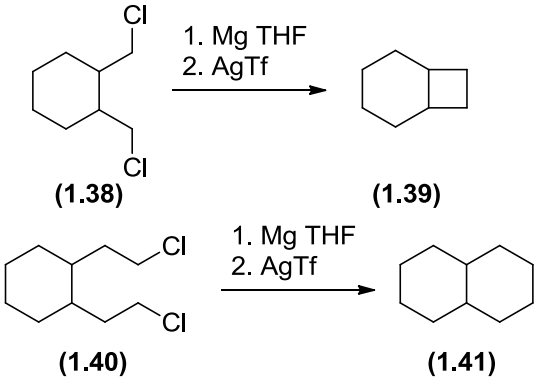
dimethyl propionyl succinate **(1.35)** | 1,4-dibromide **(1.36)** | propionyl cyclobutane **(1.37)**

Scheme (1-17): Synthesis of propionyl cyclobutane **(1.37)**

1.6: Alkyl, aryl Cross-coupling of Grignard reagents

1.6.1: Sp^3 – Sp^3 Cross-coupling of Grignard reagents

G. M. Whitesides and F. D. Gutowski provided a useful method for making four, five, and six-membered rings by the intramolecular Wurtz coupling of Grignard reagents in the presence of silver(I) triflate (Scheme 1-18).[28]

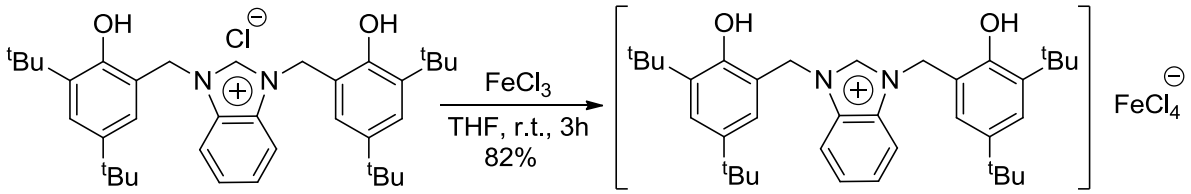


Scheme (1-18): intramolecular Wurtz coupling of Grignard reagent in the presence of silver (I) salts

It is proposed that the reaction involves a transmetalation to give an organo-silver intermediate which couple to the Grignard.

1.6.2: Sp^2 – Sp^3 Cross-coupling of Grignard reagents

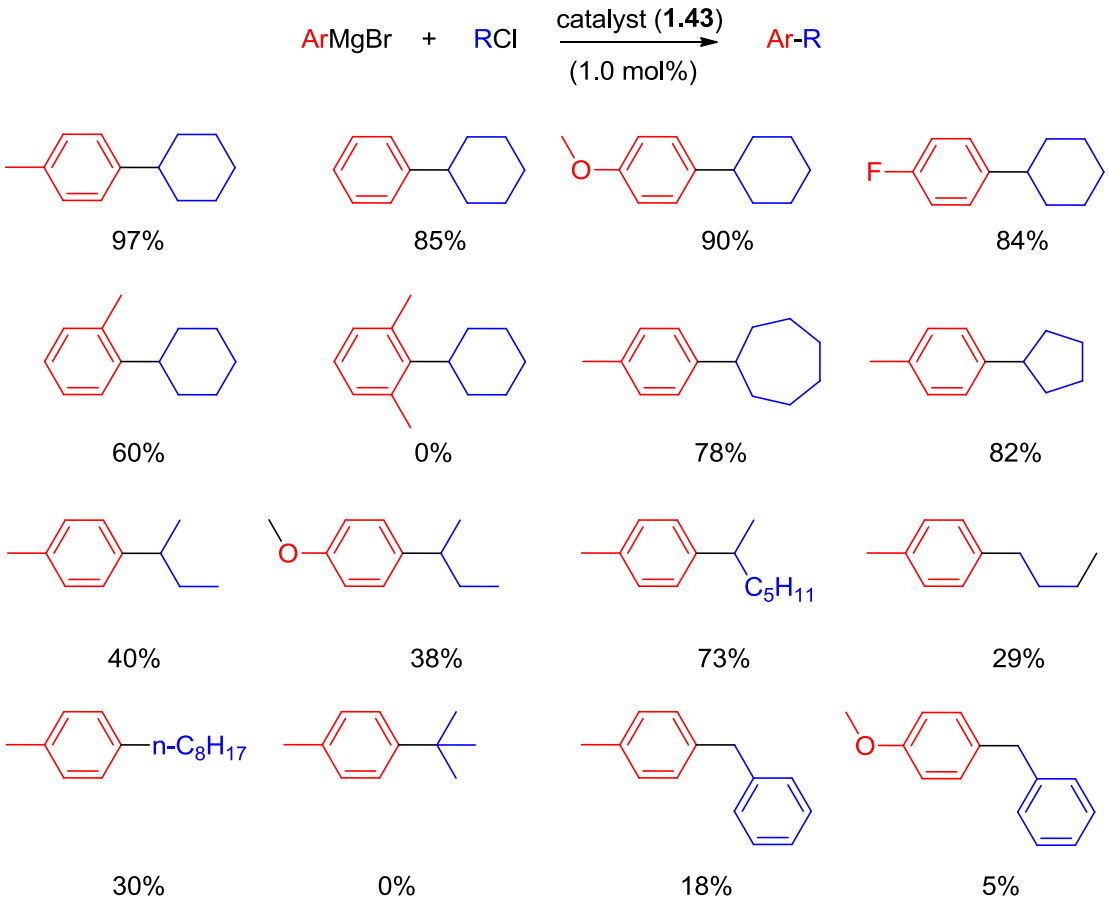
Chong-Liang Xia *et al* has designed an iron catalyst capable of coupling Grignard reagents to alkyl chlorides (Scheme 1-19).[29]



(1.42) **(1.43)**

Scheme (1-19): Synthesis of catalyst **1.43**

The cross-coupling reactions of aryl magnesium bromides with primary and secondary alkyl halides were studied by using **1.43** as a catalyst (Scheme 1-20), the results of which are shown below.

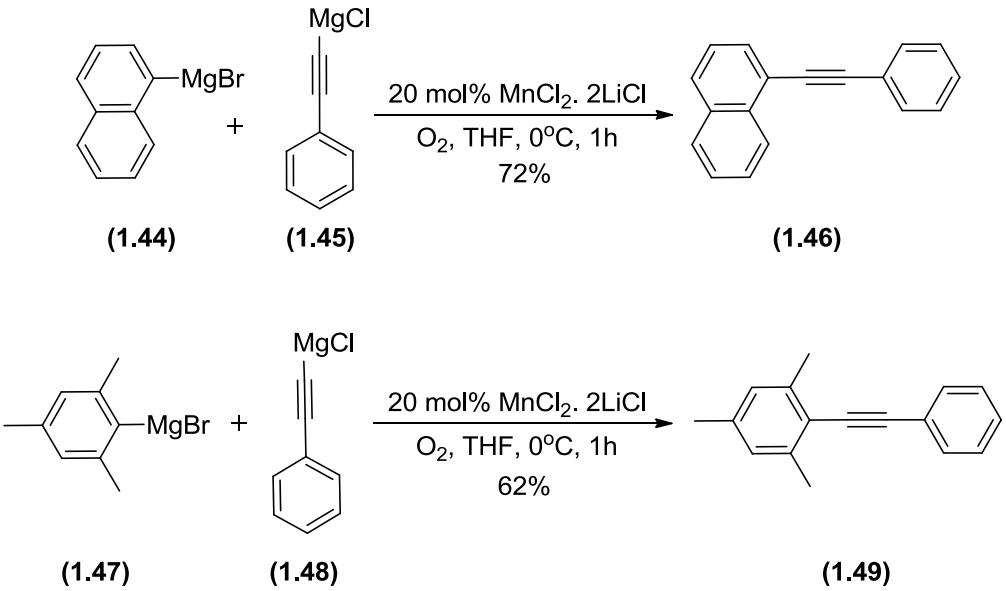


Scheme (1-20): Cross-coupling reactions of aryl magnesium bromides with primary and secondary alkyl halides

Good results (84-99 % yields) were obtained with secondary cyclic alkyl chlorides, however poor yields were observed with sterically hindered systems.

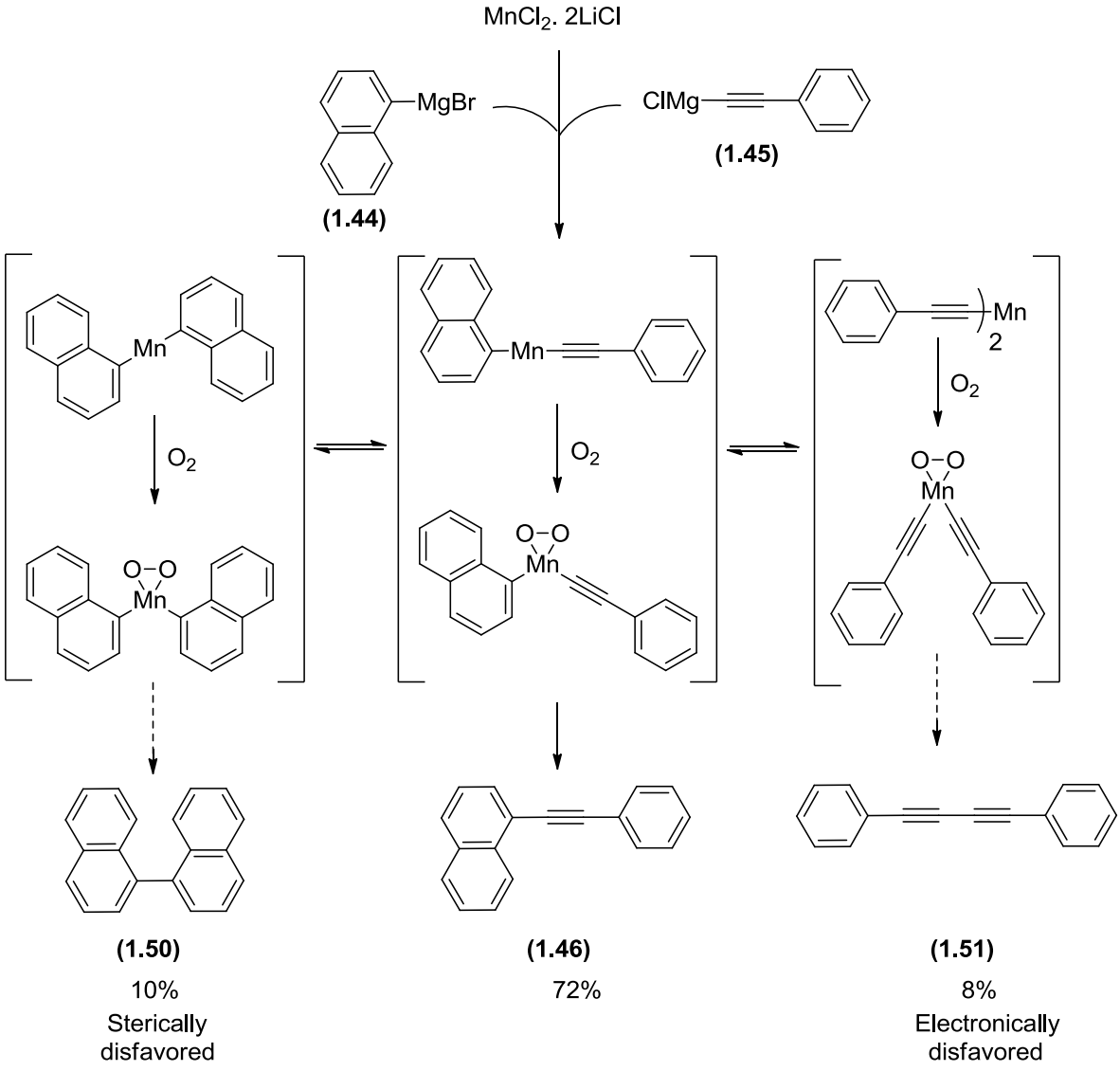
1.6.3: Sp^2 – Sp Grignard- Grignard coupling reactions

In 2009, Cahiez *et al* studied the heterocoupling of Grignards by combining an electron-rich but sterically hindered aryl Grignard. The coupling of one equivalent of mesityl- or 1-naphthylmagnesium bromide (**1.44**) with one equivalent of phenylethynylmagnesium chloride (**1.45**) in the presence of manganese chloride are shown below (Scheme 1-21).[30]



Scheme (1-21): Sp^2 – Sp Grignard- Grignard coupling reactions

It is proposed that an equilibrating mixture of three organomanganese (II) species (**1.46**), (**1.50**), and (**1.51**) is generated from the reaction of naphthalen-1-ylmagnesium bromide (**1.44**) and (phenylethynyl) magnesium chloride (**1.45**) with manganese chloride. The organomanganese (II) species is oxidized by O_2 to a manganese (IV) species followed by cross-coupling (Scheme 1-22).

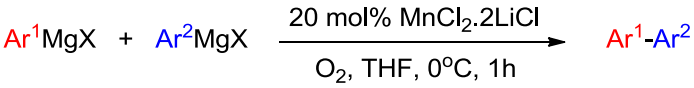


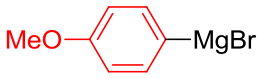
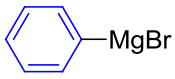
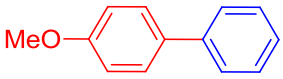
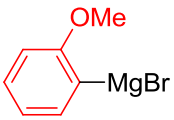
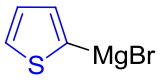
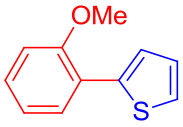
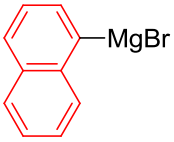
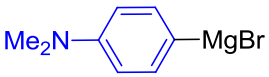
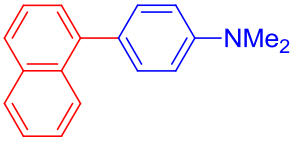
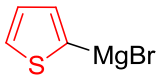
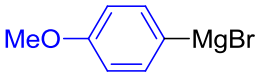
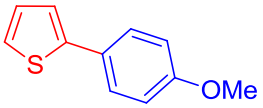
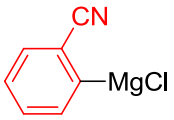
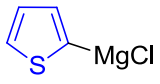
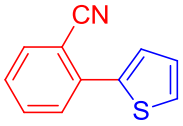
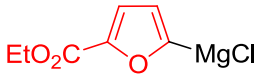
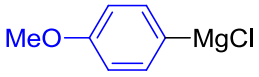
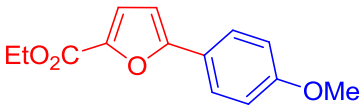
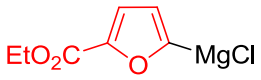
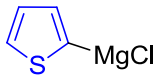
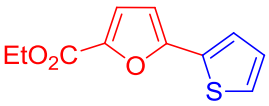
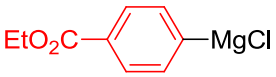
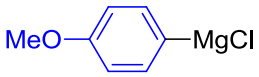
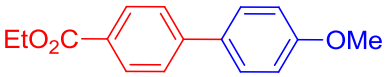
Scheme (1-22): Tentative mechanism for Mn-catalyzed oxidative heterocoupling

1.6.4: $Sp^2 – Sp^2$ Cross-coupling of Grignard reagents

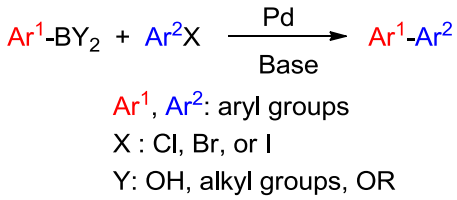
Manganese-catalyzed oxidative cross-coupling of aryl Grignard reagents has been studied by Cahiez *et al*.[30] The selectivity is very dependent on the nature of the Ar^1 and Ar^2 groups (Table 1-1).

Table 1-1: $Sp^2 - Sp^2$ Cross-coupling of Grignard reagents



Ar^1MgX	Ar^2MgX	Coupling products	Yield Ar^1-Ar^2	Yield of Ar^1-Ar^1
			80%	12%
			76%	13%
			68%	6%
			65%	20%
			81%	8%
			59%	10%
			69%	7%
			63%	15%

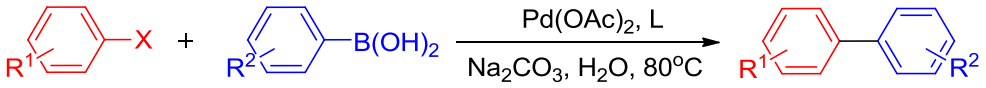
One of the most reputable methodologies in the synthesis of symmetric and unsymmetrical biaryls in organic synthesis is Suzuki-Miyaura coupling reaction. According to Suzuki reaction, the formation of a carbon-carbon single bond can be generated by coupling of arylboron species (Ar-BY2) with a arylhalide (Ar-X) in the presence of palladium catalyst and a base (Scheme 1-23).



Scheme (1-23): Suzuki-Miyaura coupling reaction

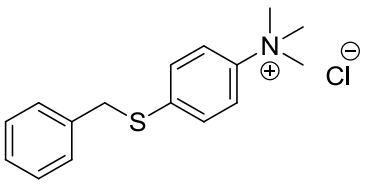
Recently, Liu and co-authors have been developed a water-soluble palladium catalyst ($Pd(OAc)_2$ and 4-(benzythio)-*N,N,N*-trimethylbenzenammonium chloride (L)) for the Suzuki Miyaura coupling reaction of aryl boronic acid with aryl halide in the presence of Na_2CO_3 in water.[31] The yield was obtained in good to excellent yields (Table 1-2).

Table 1-2: Suzuki coupling reaction of aryl halide with arylboronic acids



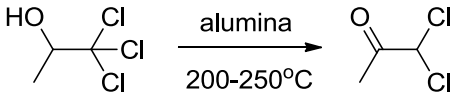
Entry	R^1	R^2	X	Product yield%
1	H	p-OMe	Br	74%
2	*p*-OMe	p-OMe	Br	88%
3	*p*-Me	p-OMe	Br	86%
4	*p*-NO_2	p-OMe	Br	50%
5	*p*-CN	p-OMe	Br	52%
6	*p*-COMe	p-OMe	Br	69%
7	*o*-Me	p-OMe	Br	33%
8	*p*-OMe	p-OMe	Br	40%
9	*p*-OMe	H	Br	81%
10	*p*-OMe	p-Me	Br	84%
11	*p*-OMe	P-F	Br	80%
12	H	p-OMe	I	90%
13	H	F	I	86%
14	*p*-OMe	p-OMe	I	95%
15	*p*-Cl	p-OMe	I	89%
16	*p*-COMe	p-OMe	I	94%
17	*p*-CN	p-OMe	I	71%

L:



1.7: Synthesis of dichloroacetyl group

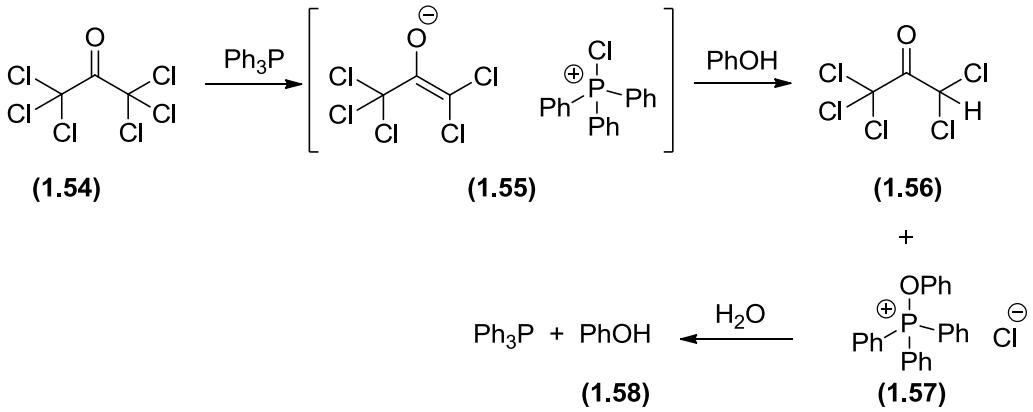
α,α-dichloroketones are significant intermediates for the preparation of heterocycles[32], unsaturated acids[33] and cyclopropanation reactions.[34] Pierce and co-workers have been studied the reduction of 1,1,1-trichloropropan-2-ol.[35] They found that the reaction of 1,1,1-trichloropropan-2-ol (**1.52**) with alumina or zinc chloride in hydrochloric acid solution at elevated temperature gave 1,1-dichloropropan-2-one (**1.53**) resulting from dehydrochlorination (Scheme 1-24).



(1.52) **(1.53)**

Scheme (1-24): Reduction of 1,1,1-trichloropropan-2-ol (**1.52**) with alumina

Rajendran *et al* reported a convenient laboratory preparation of pentachloroacetone (PCA)(**1.56**) from hexachloroacetone (HCA)(**1.54**). The dechlorination occurs with triphenylphosphine in the presence of methanol or phenol (Scheme 1-25).[36]



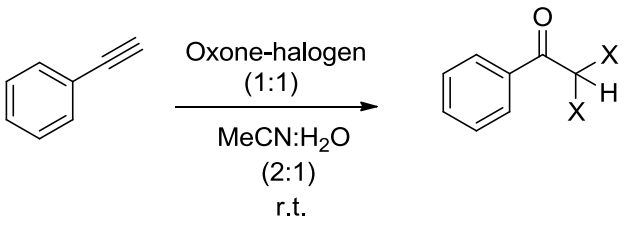
(1.54) **(1.55)** **(1.56)** **(1.57)** **(1.58)**

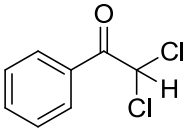
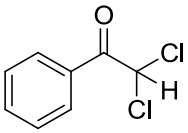
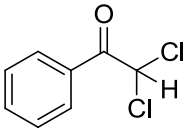
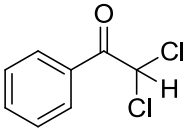
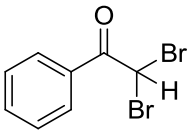
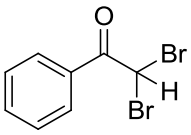
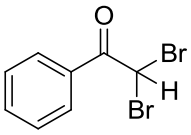
Scheme (1-25): Preparation of pentachloroacetone (PCA)(**1.56**)

In another study, Madabhushi *et al* prepared α,α-dihaloketones by oxyhalogenation of alkynes using oxone.[37]

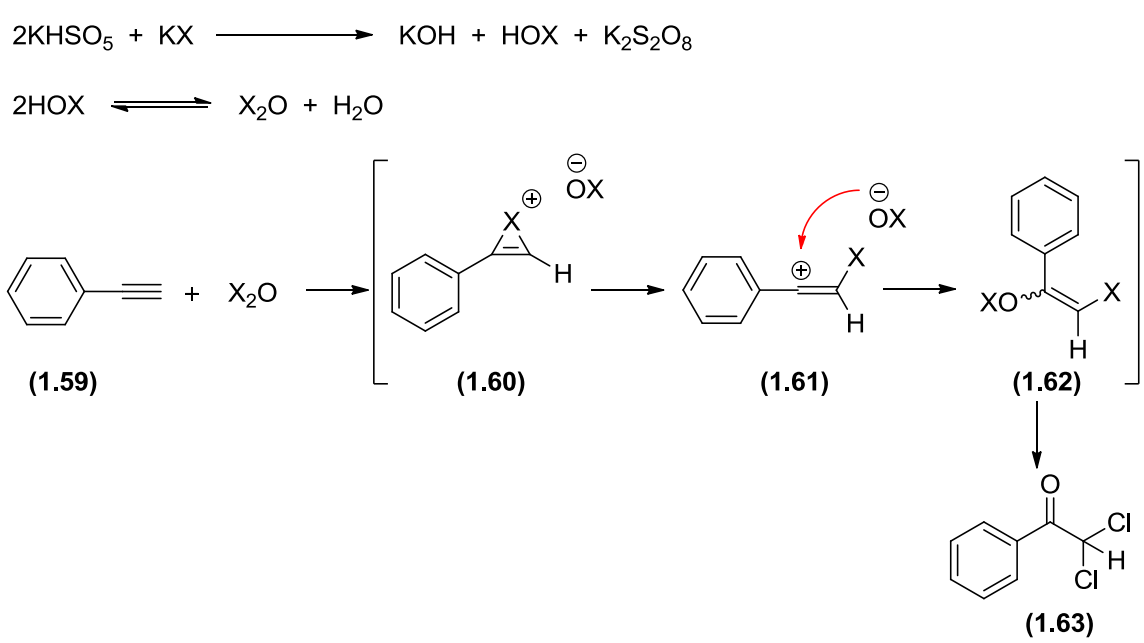
When they used KCl the product yield (2,2-dichloro-1-phenylethanone) (entry 4, Table 1-3) was 98%. Whilst KBr gave 99% of 2,2-dibromo-1-phenylethanone (entry 7, Table 1-3). That is mean the potassium halides gave the best results.

Table 1-3: Conversion of phenyacetylene into a α,α-dihaloacetophenone using oxone as oxidant



Entry	Halogen source	Product	Reaction time	Yield%
1	50% aq. HCl		60	66
2	NH_4Cl		60	75
3	NaCl		60	80
4	KCl		10	98
5	48% aq. HBr		60	50
6	NH_4Br		60	60
7	KBr		15	99

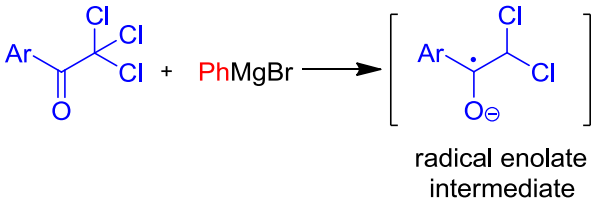
The proposed mechanism for the formation of α-α-dihaloketones is shown below (Scheme 1-26). The first step of this mechanism involves the formation of hypohalous acid (HOX) from the reaction of KX with water. Hypohalous acid gives dihalo monoxide (X_2O) which reacts with alkyne to give a cyclic alkyne-halonium ion complex which converts to more stable vinyl carbocation. Nucleophilic addition reaction of $XO^{\ominus}$ toward vinyl carbocation produces the final product (**1.63**) (Scheme 1-26).



Scheme (1-26): Mechanism of formation of α-α-dihaloketones

1.8. Project plan

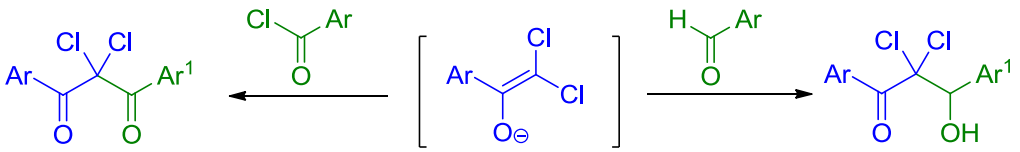
The overarching goal of the project is to study the single electron transfer reactions of Grignard reagents. We chose the reaction of Grignard reagents with trichloroacetyl substituted aromatics to generate radical enolate intermediate.



Scheme (1-27): Generation of radical enolate intermediate

A single electron transfer mechanism for the reaction will be studied based on trapping experiments and EPR studies.

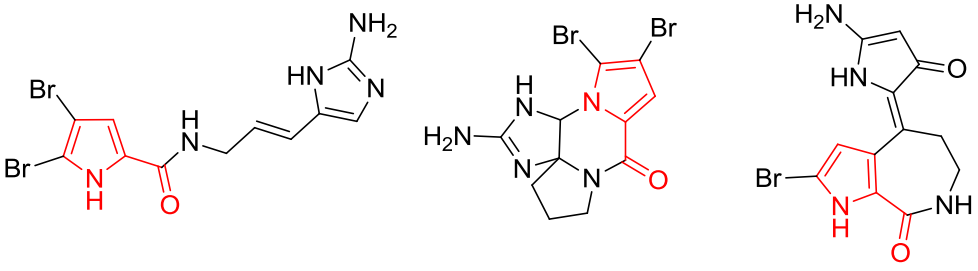
The radical intermediate magnesium enolates will then traped with a range of electrophiles to synthesis of α,α-dichloro-β-hydroxyketones and related molecules.



Scheme (1-28): Synthesis of α,α-dichloro-β-hydroxyketones

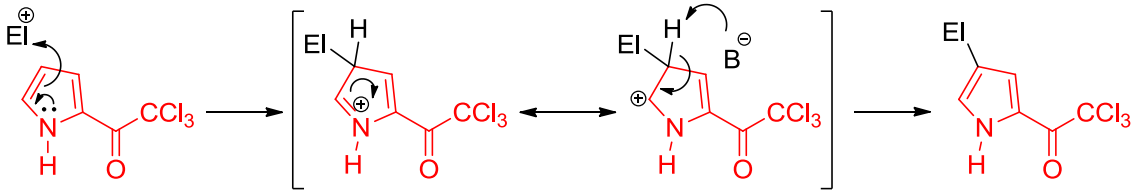
2.1: Introduction

The synthesis of many natural product[38] and medicinal chemistry targets[39] involves the use of trichloroacetyl-substituted aromatic rings. For example, 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanones have been used in the synthesis of oroidin (**2.1**) and related oroidin alkaloids such as the naturally occouing kinase inhibitors hymenialdisine (**2.2**) and debromohymenialdisine (**2.3**).



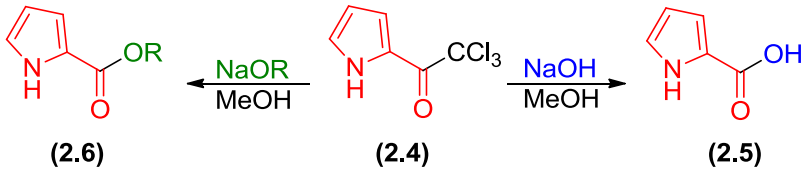
(2.1) **(2.2)** **(2.3)**

The electron withdrawing trichloroacetyl functional group finds particular utility in the chemistry of pyrrole by facilitating highly C-3 regioselective electrophilic aromatic substitution reactions (Scheme 2-1).



Scheme (2-1): Resonance Contributors of trichloroacetyl pyrrole

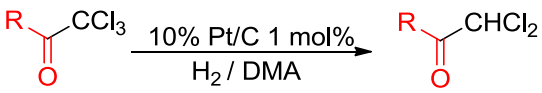
Other functional groups such as carboxylic acid (**2.5**) or ester (**2.6**) can easy synthesized from trichloroacetyl groups through reaction with hydroxide or alkoxides (Scheme 2-2).[40]



(2.6) **(2.4)** **(2.5)**

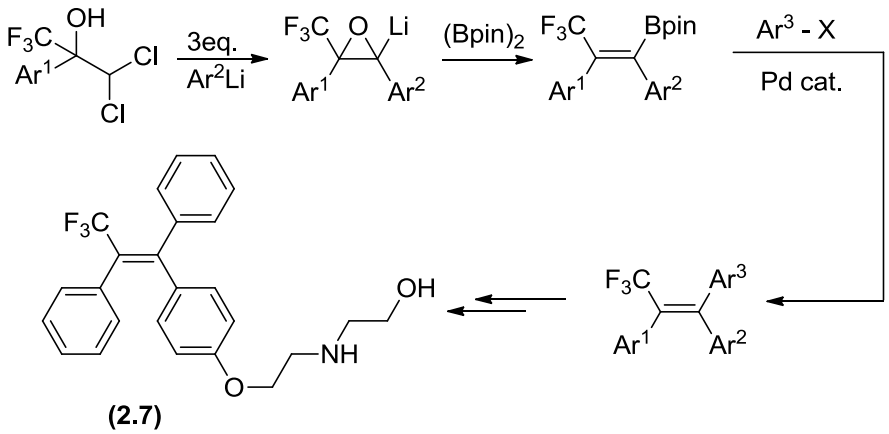
Scheme (2-2): Reactions of trichloroacetyl pyrrole

Recently, platinum on carbon-catalyzed hydrogenation was used to reduce trichloroacetyl groups to the corresponding dichloroacetyls (Scheme 2-3).[41]



Scheme (2-3): Reduction of trichloroacetyl group

Shimizu *et al.* has then employed this versatile functional group in a stereoselective synthesis of the anti-cancer drug panomifene (**2.7**) (Scheme 2-4).[42,43]



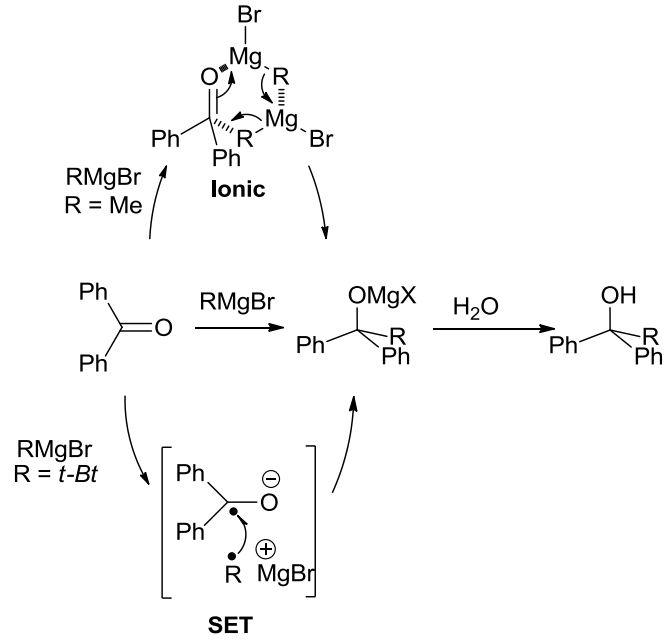
(2.7)

Scheme (2-4): synthesis of the anti-cancer drug panomifene (**2.7**)

2.2: Reduction of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone by RMgX

2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone is a sterically hindered and electron deficient aromatic ketone. In the presence of a suitable single electron donor such as an electron rich organometallic species (RMgX), we thought that this ketone might form reactive ketyl radical anions.[44]

There are two limiting mechanistic extremes for the reaction of Grignard reagents with carbonyl compounds, a Lewis acid activated polar mechanism, or a Single Electron Transfer (SET) to give a ketyl radical anion followed by radical recombination (Scheme 2-5).[45, 46] Which reaction mechanism occurs depends on the solvent, halogen, R groups, carbonyl structure temperature and concentration.



Scheme (2-5): Ionic and SET mechanism of Grignard reagent

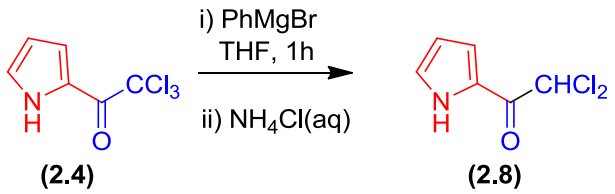
The reactions of Grignard reagents that involving SET reactions have limited direct synthetic application despite a number of mechanistic studies. A range of novel chemistry would become available, using commercially available Grignard reagents, if an alternative reaction pathway to radical recombination was available to the intermediate ketyl radical anions.

2,2,2-Trichloro-1-(1*H*-pyrrol-2-yl)ethanone (**2.4**) may be expected to follow a SET mechanistic pathway in reactions with RMgX because SET mechanisms are often observed with sterically hindered aromatic carbonyls.[47,48] Thus novel and interesting reaction chemistry might be anticipated when a suitable Grignard reagent was reacted with a 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone .

2.3: 2,2-Dichloro-1-(1*H*-pyrrol-2-yl)ethanone

2.3.1: Reactions of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl) ethanone with RMgX

In order to examine the reaction of Grignard reagents with trichloroactyl substituted aromatics, 1 eq. of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl) ethanone (**2.4**) was reacted with 1.1 eq of PhMgBr in THF at 0°C at r.t. After 1h the reaction quenched with aqueous NH_4Cl to give 2,2-dichloro-1-(1*H*-pyrrol-2-yl) ethanone (**2.8**) in 50% or 55% yield respectively resulting from a formal C-Cl to C-H reduction (Scheme 2-6), (Table 2.1 entry 1-2).



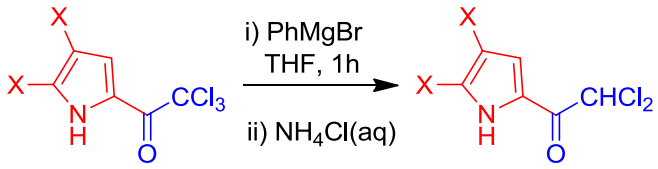
(2.4) (2.8)

Scheme (2-6): Reduction of trichloroacetyl pyrrole by PhMgBr

The formation of **2.8** was confirmed from the appearance of a singlet in the ^{1}H NMR spectrum at 6.41 ppm corresponding to the $CHCl_2$ group.

We postulated that the reaction may not be going to completion due to PhMgBr acting as a base and deprotonating the pyrrole N-H. Therefore, we investigated the use of 2.2 equivalents of PhMgBr, 1 equivalent to complete the deprotonation and the other to reduce the trichloroacetyl group. Three di-halogenated pyrrole derivatives (**2.9**, **2.11**, and **2.13**) were reacted with 2.2 eq. of PhMgBr, resulting in a significant improvement in yields (Table 2-1 entry 3-6).

Table 2-1: Reaction of PhMgBr with substituted 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanones.

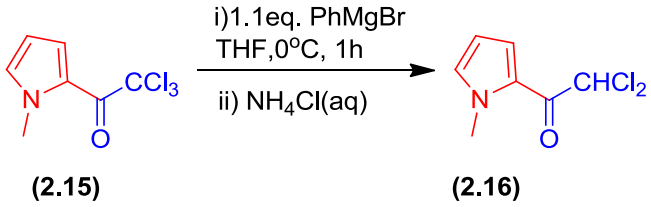


(A) (B)

Entry	X	Comp. No. (A)	PhMgBr	Temp.	Comp. No. (B)	Yield [a]
1	H	2.4	1.1 eq.	0 °C	2.8	50%
2	H	2.4	1.1 eq.	r.t.	2.8	55%
3	H	2.4	2.2 eq.	r.t.	2.8	90%
4	Cl	2.9	2.2 eq.	r.t.	2.10	87%
5	Br	2.11	2.2 eq.	r.t.	2.12	95%
6	I	2.13	2.2 eq.	r.t.	2.14	93%

The reactions were performed by reverse addition of 1 mmol of ketone in 1 mL of THF to a 2M solution of PhMgBr in THF. [a]Isolated Yield.

To confirm that deprotonation of the pyrrole N-H was occurring, an *N*-methyl pyrrole was examined. The reaction of *N*-methyl trichloroacetyl pyrrole (**2.15**) with 1.1 equivalent of PhMgBr gave a 94% yield of the reduced product (**2.16**) (scheme 2-7). Crystals of **2.16** were grown by slow evaporation from $CHCl_3$ and the structure was confirmed by single crystal X-ray analysis (Figure 2-1).



(2.15) **(2.16)**

Scheme (2-7): Reduction of *N*-methyl trichloroacetyl pyrrole (**2.15**) by PhMgBr

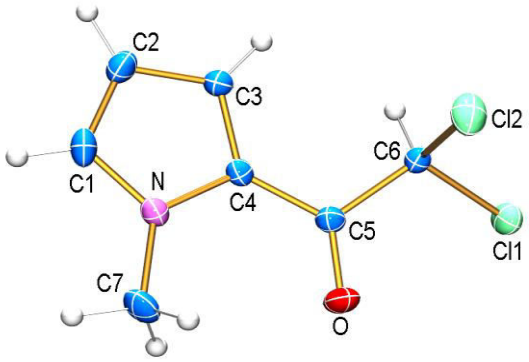


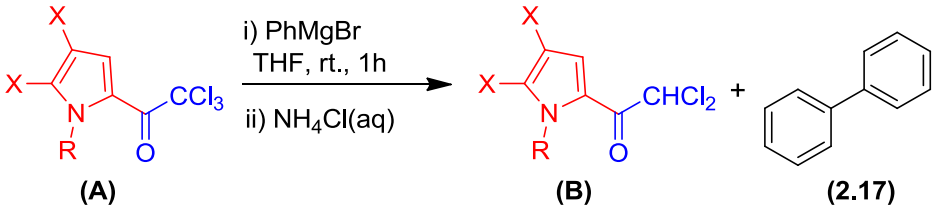
Figure (2-1): X-ray crystal structure of **2.16**

The reduced product (**2.16**) prompted us to further investigate of the formation of these C-Cl reduced products and study the mechanism of the reaction.

2.3.2: Formation of Biaryl By-products

The reaction between trichloroacetyl pyrrole derivatives and PhMgBr gives, along with reduced products, biphenyl which is observed by GCMS and ^{1}H NMR spectroscopy of the crude reaction mixtures. The biphenyl was isolated from the previous set of reaction and the yields are given below (Table 2-2).

Table 2-2: biphenyl yields



(A) **(B)** **(2.17)**

Entry	R	X	Comp. No. (A)	Comp. No. (B)	Yield of **2.17**
1	H	H	2.4	2.8	36%
2	H	Cl	2.9	2.10	26%
3	H	Br	2.11	2.12	39%
4	H	I	2.13	2.14	31%
5	Me	H	2.15	2.16	52%

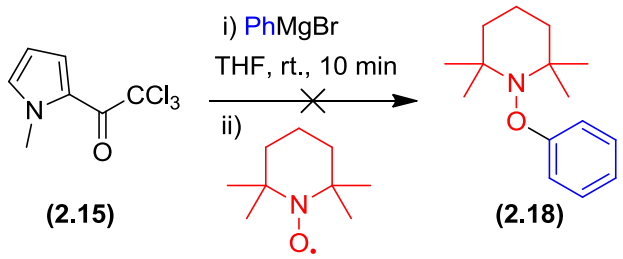
In the case of entry 5, 40 mg of Ph-Ph was isolated corresponding to a 52% yield of the total added PhMgBr. This suggests that the biphenyl may be formed from the dimerization of two phenyl radicals generated during the reaction.

2.4: Radical trapping experiments

2.4.1: Trapping with TEMPO

The reaction between 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**) and Grignard reagent offers a phenyl free radical which couples together to form biphenyl. We postulate that adding a radical trap such as (2,2,6,6-Tetramethylpiperidin-1-yl)oxy (TEMPO) to the reaction may give us a phenyl-TEMPO coupling.

The solution of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**) and TEMPO was dissolved in THF before adding to PhMgBr. The reaction was left to stirrer for 10 min before adding ammonium chloride (Scheme 2-8).



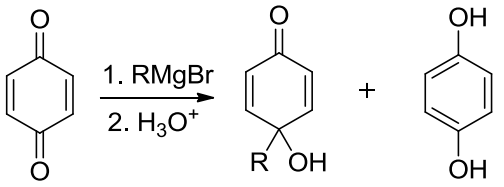
Scheme (2-8): Trapping of 2,2-dichloro-1-(1-methyl-1H-pyrrol-2-yl)ethenolate with TEMPO

Unfortunately, we did not observe any phenyl-TEMPO (2,2,6,6-tetramethyl-1-phenoxypiperidine)(**2.18**) coupling in the product, maybe because TEMPO possesses steric protection provided by the four methyl groups adjacent to the nitroxyl group, makeing the coupling harder than phenyl-phenyl radical coupling.

2.4.2: Trapping with benzoquinone

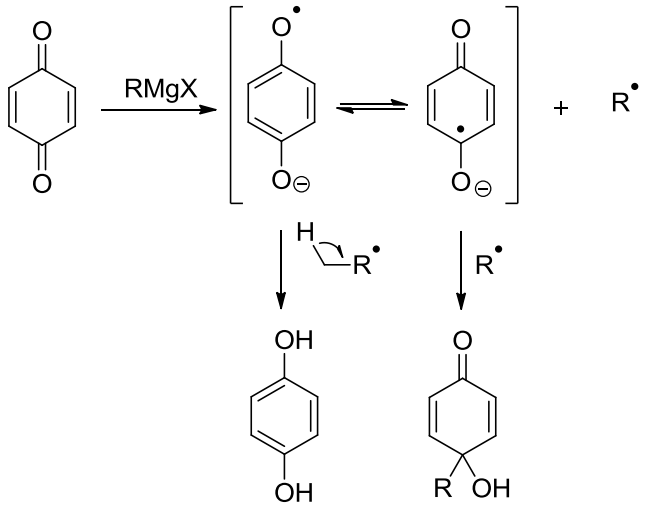
The reaction between benzoquinone (**2.19**) and various Grignard reagents has been studied by McKinley *et al* (Table 2-3).[49]

Table 2-3: reaction of benzoquinone with RMgBr



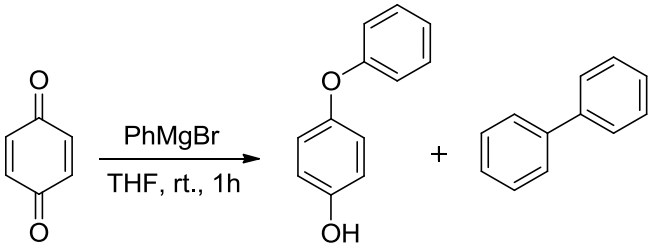
R	Yield% of **2.20**	Yield % of **2.21**
methyl	95%	5%
ethyl	78%	22%
propyl	63%	37%
n-butyl	60%	40%
isopropyl	10%	90%
s-butyl	5%	95%
t-butyl	1%	99%

The single electron reduction of benzoquinone with a Grignard reagent gives the corresponding quinine radical anion and alkyl radical (Scheme 2-9). The steric hindrance and stability of the free radicals formed plays a fundamental role in this reaction.



Scheme (2-9): Reaction of benzoquinone with a Grignard reagent

We found that adding benzoquinone to PhMgBr gave only 4-phenoxyphenol (**2.22**) as a single isomer and the steric effect prevented formation of other isomer (Scheme 2-10). That confirms the formation of phenyl radical which reacted with quinine radical anion to give the corresponding product.

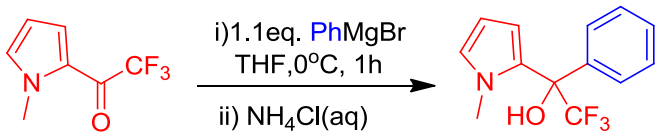


Scheme (2-10): Reaction of benzoquinone with a PhMgBr

2.5: Reaction 2,2,2-trihalo ketone with PhMgBr

2.5.1: Reaction 2,2,2-trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone with PhMgBr

Next we wished to investigate if the other types of α,α,α-trihalo ketones react in the same way as the reaction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**) with Grignard reagents. We chose 2,2,2-trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.23**) as our test molecule (Scheme 2-11).



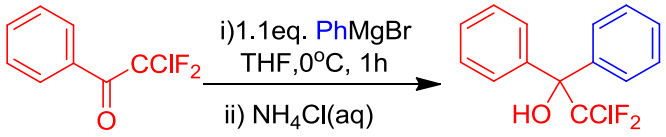
(2.23) **(2.24)**

Scheme (2-11): Reaction 2,2,2-trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone with PhMgBr

When 2,2,2-trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.23**) was added to PhMgBr, we isolated a 96% yield of the addition product 2,2,2-trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)-1-phenylethanol (**2.24**). This suggests the intermediate radical anion formed does not lose fluorine to form the enolate and instead reacts with the Ph radical to form an addition product.

2.5.2: Reaction 2-chloro-2,2-difluoro-1-phenylethanone with PhMgBr

Therefore we decided to replace one of the fluorines with a chloride. However, the reaction of 2-chloro-2,2-difluoro-1-phenylethanone (**2.25**) with PhMgBr still gave 2-chloro-2,2-difluoro-1,1-diphenylethanol (**2.26**) in 66% yield as a normal addition product (Scheme 2-12).



(2.25) **(2.26)**

Scheme (2-12): Reaction 2-chloro-2,2-difluoro-1-phenylethanone with PhMgBr

2.5.3: Conclusions

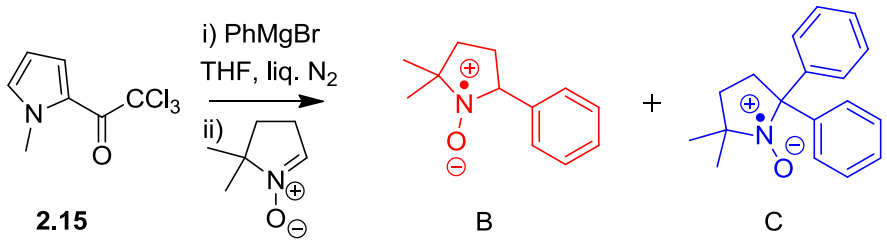
The last two experiments, suggest that both 2,2,2-trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.23**) and 2-chloro-2,2-difluoro-1-phenylethanone (**2.25**) react with the PhMgBr to form a radical anion intermediate, but these do not convert to the enolates as in the case of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**). Instead the radical anions from **2.23** and **2.25** react with a phenyl radical to give addition products.

This may be due to the increased C-F bond strength preventing the loss of halide required to make the enolate.

2.6: Electron paramagnetic resonance (EPR) experiment

In order to investigate the presence of phenyl radicals in the reaction we carried out an electron paramagnetic resonance (EPR) experiment. A solution of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl) ethanone (**2.15**) was placed in an EPR tube and frozen in liquid N_2, then a solution of PhMgBr was added and also frozen in liquid N_2. A spin trap, 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), was added and the sample warmed to 270 K in the EPR tube within the spectrometer.

The EPR spectra showed the appearance of two radical products. The major radical species gave 6 lines in the EPR spectrum corresponding to the addition of a Ph radical to DMPO (2,2-dimethyl-5-phenylpyrrolidin-1-olate radical) (Figure 2-2 B) with ^{1}H and ^{14}N hyperfine coupling constants: α (^{1}H) = 20.3 G and α (^{14}N) = 13.87 G. The minor radical species gave 3 lines in the EPR spectrum with ^{14}N hyperfine coupling constants: α (^{14}N) = 13.87 G), corresponding to a di-Ph-DMPO adduct (2,2-dimethyl-5,5-diphenylpyrrolidin-1-olate radical) (Figure 2-2 C). No radical species (Ph-DMPO or di Ph-DMPO) were observed in the absence of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl) ethanone (**2.15**).



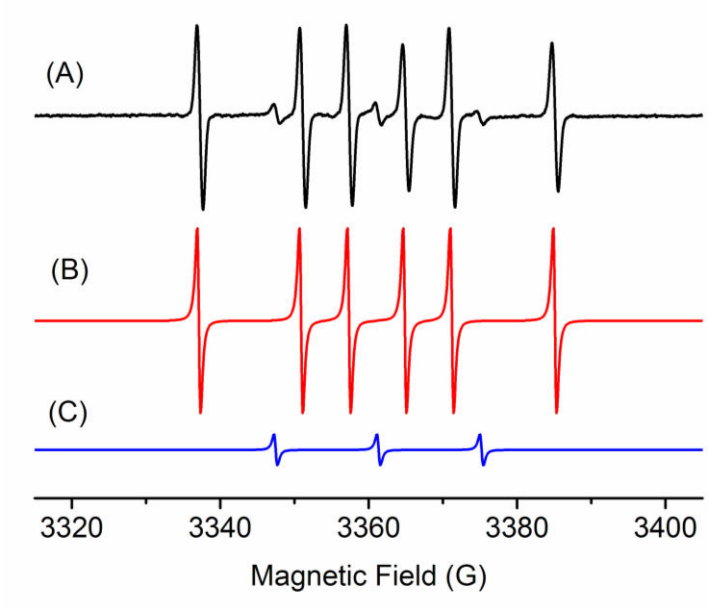
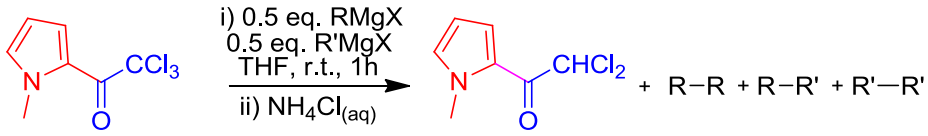


Figure (2-2): (A) X-band EPR spectrum at 270 K of a THF solution resulting from the reaction of PhMgBr with 2,2,2-trichloro-1-(1-methyl-1H-pyrrol-2-yl) ethanone (**2.15**), in the presence of DMPO; (B) simulated spectrum of the Ph–DMPO adduct with the parameters: g = 2.0096; a(^{1}H) = 20.3 G and a(^{14} N) = 13.87 G; (C) simulated spectrum of the di-Ph–DMPO adduct, with g = 2.0095 and a(^{14}N) = 13.87 G. (100 kHz modulation frequency, 1G modulation amplitude, 0.27 mW incident microwave power).

2.7: Investigation of the regiochemistry of biphenyl formation

In order to understand more about the formation of biphenyl like products, we examined the reaction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**) with number of RMgX species, where R was a *para*-substituted phenyl group (Table 2-4).

Table 2-4: Reaction of RMgX/R'MgX with 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl) ethanone (**2.15**)



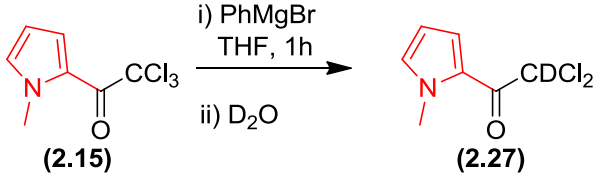
Entry	RMgX	R'MgX	R-R	R-R'	R'-R'
1	4-Me(C_6H_4)MgI	4-Me(C_6H_4)MgI	66%	-	-
2	4-Me(C_6H_4)MgI	PhMgI	14%[b]	24%[b]	23%
3	4-MeO(C_6H_4)MgI	4-Me(C_6H_4)MgI	43%	0%	16%
4	4-MeO(C_6H_4)MgBr	PhMgBr	0%	43%	20%

[a] Isolated yields. [b] Products not separable, yield determined by GC-MS.

A single biphenyl product, 4,4'-dimethyl-1,1'-biphenyl, was observed from the reaction of 4-Me(C_6H_4)MgI with 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl) ethanone (**2.15**). While a mixture of 4,4'-biaryl product was found when a one to one mixture of *para*-substituted phenyl Grignard regents were used (Table 2-3, entries 2-4). The formation of only 4,4'-regioisomers, suggests that the Ar-Ar bond is formed at the same position as the starting material C-Mg bonds. This observation supports our EPR experiment which suggests that the 4,4'-diaryl compounds are formed by coupling of Grignard derived phenyl radicals.

2.8: Source of "H" in C-Cl to C-H redaction.

We suggest that the reaction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl) ethanone (**2.15**) by PhMgBr goes via an enolate intermediate. The quenching of the enolate by aqueous NH_4Cl gives the observed reduction product. In order to investigate the source of the H atom in the product, we employed D_2O as quenching agent (Scheme 2-13).



Scheme (2-13): Trapping of 2,2-dichloro-1-(1-methyl-1H-pyrrol-2- yl)ethenolate with D_2O

The quenching of the reaction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl) ethanone (**2.15**) and PhMgBr with D_2O gave a 89% yield of the corresponding 2,2-dichloro-2-deuterium-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.27**) with high percentage D incorporation. This suggests that the reaction must go via an intermediate enolate.

The ^{1}H NMR shows that the peak of $CHCl_2$ group at 6.54 ppm decreases when D_2O is used, suggesting significant incorporation of D into the product. In the ^{13}C NMR the peak corresponding to the $CDCl_2$ is split by the deuterium atom to give a 1:1:1 triplet (Figure 2-3).

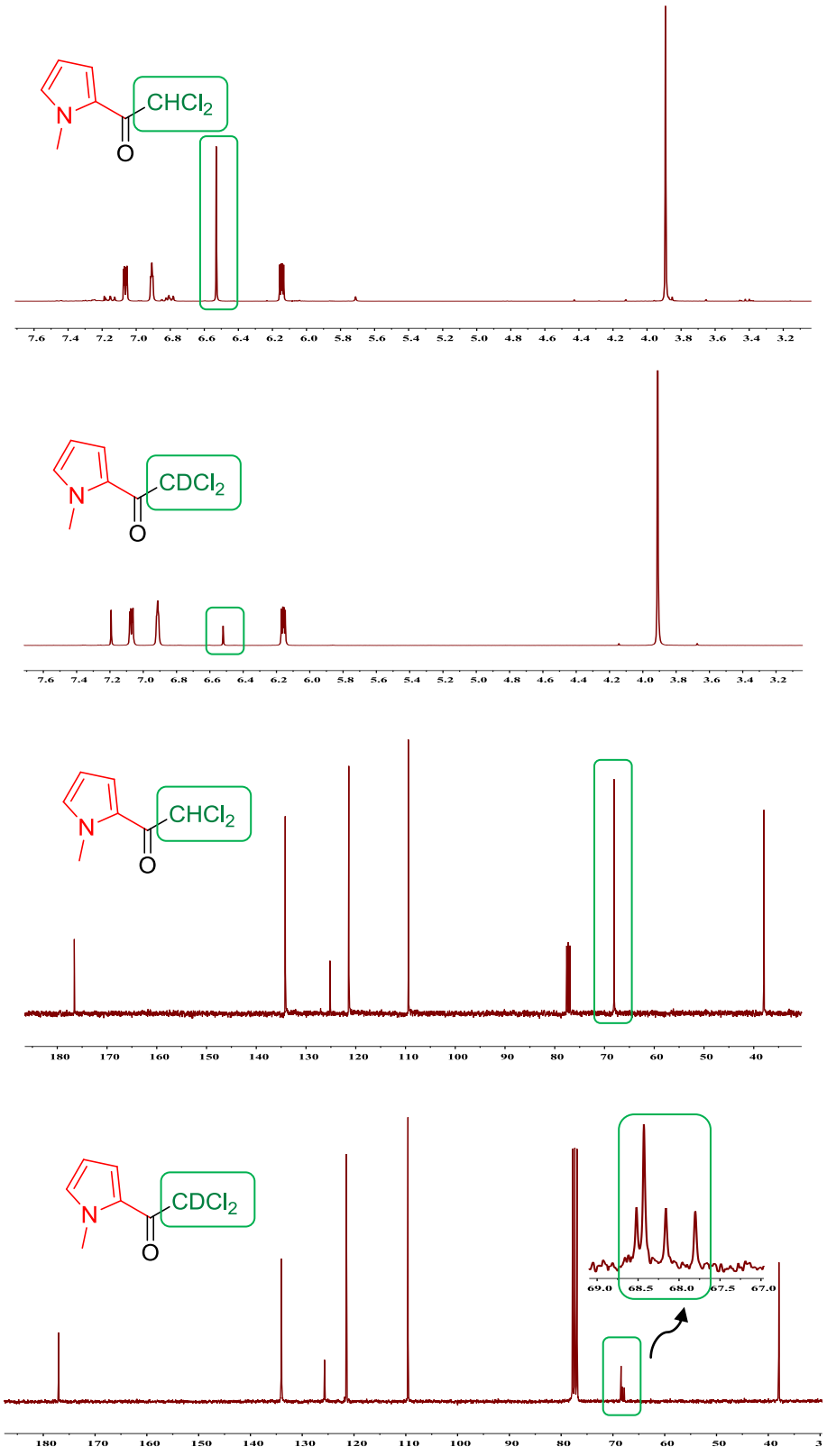
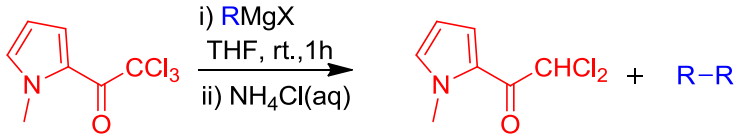


Figure (2-3): ^{1}H and ^{13}C NMR of 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.16**) and the corresponding 2,2-dichloro-2-deuterium-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.27**)

2.9: Influence of the R and X substituent of Grignard reagent

We also investigated what the effect of the variation of both the R and halogen substituents of the Grignard reagent would have on the reaction with trichloroacetyl containing aromatics (Table 2-5).

Table 2-5: Influence of R and X of Grignard reagent.



(2.15) **(2.16)** **(2.17)**

Entry	R	X	Yield of **2.16** [a]	Yield of **2.17** [b]
1	Et	Br	50%	nd[c]
2	iPr	Cl	42%	nd[c]
3	Ph	Cl	61%	45%
4	Ph	Br	94%	52%
5	Ph	I	94%	62%

[a] Isolated yields, [b] yield based on total RMgX added, [c] nd: not determined.

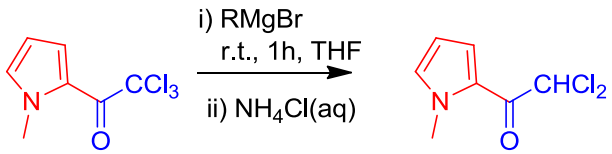
Higher yields of the reduced products (**2.16**) resulted from the use of aryl Grignard rather than aliphatic Grignard reagents.[50] This suggests that both the R and X group are important in modifying the reactivity of the RMgX in the reduction of the trichloroacetyl aromatics. Significantly higher yields were also obtained when X was iodide, compared to bromide or chloride.

However, due to commercial availability we employed PhMgBr in subsequent reactions.

2.10: Solvent Effects

We next studied the solvent effect on the PhMgBr mediated reduction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**). THF, Et_2O and hexane were used in this study (Table 2-6).

Table 2-6: Influence of solvents on the reaction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone and PhMgBr.



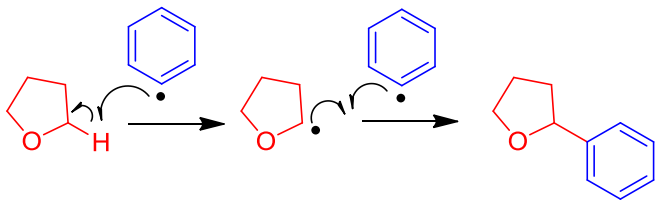
(2.15) **(2.16)**

Entry	Solvent	Total volume/mL[a]	Isolated Yield (**2.16**)	% Conversion [b]
1	THF	1.55	94	>95
2	THF	3.10	nd[c]	>95
3	THF	5.55	nd[c]	>95
4	THF	20.55	nd[c]	67%
5	Et_2O	1.55	95	>95
6	Hexane	1.55	94	>95

[a]All reactions contain ~0.55 mL of THF from the solution of PhMgBr used. [b]Conversion estimated by ^{1}H NMR of crude reaction mixture. [c] nd: not determined.

The initial screening of solvents indicated that the solvent had little effect on the reaction. The concentration of solvent had also a little effect on the reaction, only with extreme dilution was any influence noticeable due slowing of the reaction.

In THF an additional trace by-product, 2-phenyl THF (**2.28**) was observed by ^{1}H NMR and GCMS. We suggest that 2-phenyl THF (**2.28**) is formed through abstraction of $H^{\bullet}$ from the α-position of THF by phenyl radical followed by coupling of the THF radical with a second phenyl radical (Scheme 2-14).

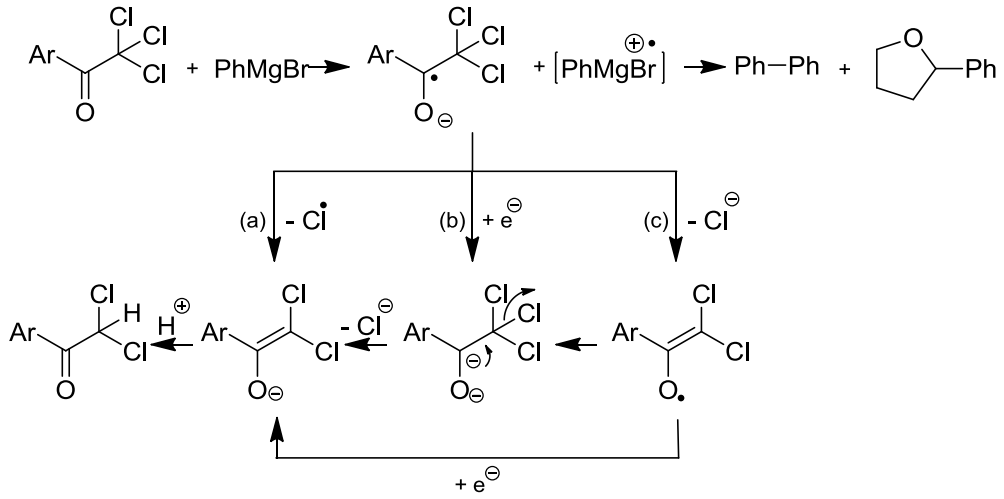


(2.28)

Scheme (2-14): Coupling of the THF radical with a phenyl radical

2.11: Proposed mechanism

Scheme 2-15 shows our proposed mechanism for the Grignard mediated reduction of trichloroacetyl-substituted aromatics. The first step in this mechanism involves transfer of single electron from the Grignard reagent to the ketone to form a ketyl radical and a phenyl radical. This intermediate ketyl radical anion can then form the corresponding magnesium enolate through either (a) loss of a Cl radical or (b) addition of a second electron followed by loss a Cl anion or (c) loss of a Cl anion followed by addition of second electron.



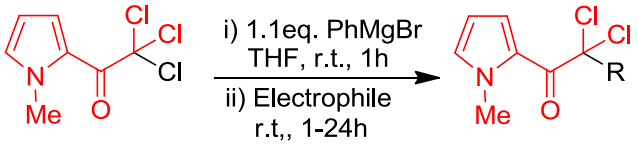
Scheme (2-15): Proposed Reaction Pathways

The biphenyl and 2-phenyl-THF products arise from the further reactions of phenyl radical. We have not observed any evidence for the Cl radical, thus pathway (b) or (c) are preferred. However the source of the second electron is yet to be determined, potentially through reduction of the halide anion or the Mg-X bond. The coupling products of phenyl radical and atomic halogen (C_6H_5Cl, C_6H_5Br) could not be detected by GCMS of the crude reaction mixture.

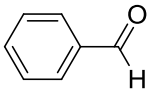
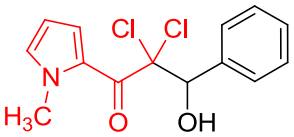
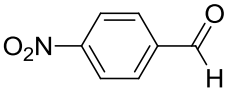
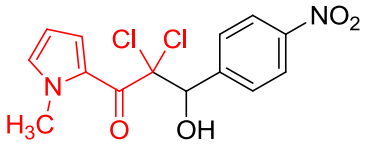
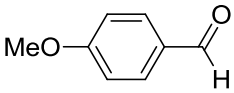
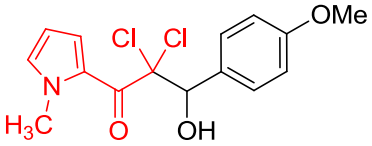
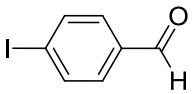
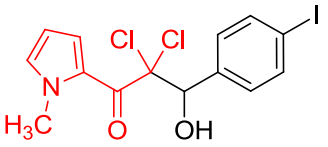
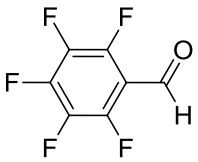
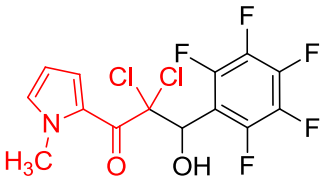
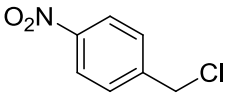
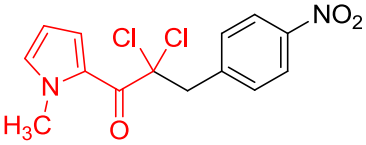
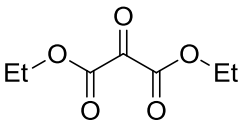
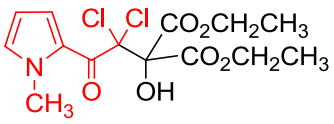
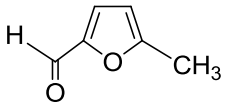
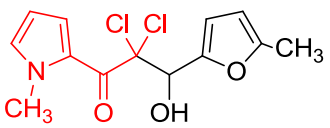
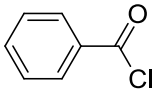
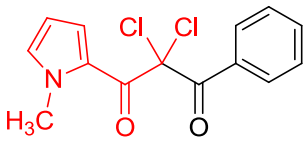
2.12: Enolate Trapping

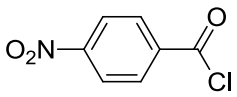
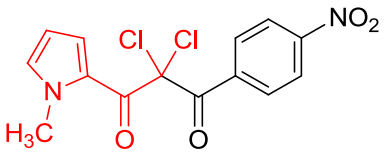
Since the Grignard mediated reduction of a trichloroacetyl aromatic proceeds through an enolate intermediate, we investigated the trapping of enolate derived from *N*-methyl trichloroacetyl pyrrole with a range of alternative electrophiles as a convenient "one-pot" reductive-functionalisation of the 2,2,2-trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (**2.15**) to give α,α-dichloro-ketones (Table 2-7).

Table 2-7: Reaction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**) with PhMgBr followed by electrophiles



(2.15) **(2.29)-(2.38)**

Entry	Electrophiles	R	Product	Comp. no.	Yield [a]
1		PhCH(OH)		**2.29**	81% [b]
2		4-NO_2(C_6H_4)CHO		**2.30**	96% [b]
3		4-MeO(C_6H_4)CHO		**2.31**	85% [b]
4		4-I(C_6H_4)CHO		**2.32**	94%
5		C_6H_5CH(OH)		**2.33**	70%
6		4-NO_2(C_6H_4)CH_2		**2.34**	37% [b]
7		$(EtO_2C)_2C(OH)$		**2.35**	75%
8		5-Me(C_4H_2O)CHO		**2.36**	70%
9		(C_6H_4)C(O)		**2.37**	50%

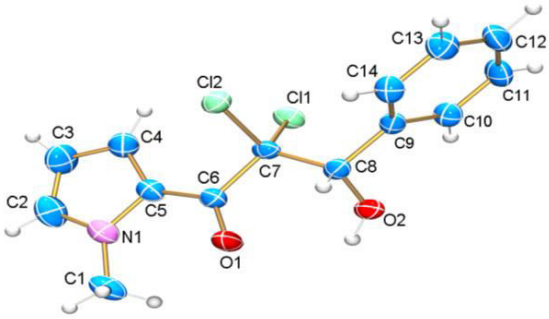
10		4-$NO_2(C_6H_4)C(O)$		**2.38**	95% [b]

[a] Isolated yields, [b] the chemical structures confirmed by single-crystal X-ray analysis.

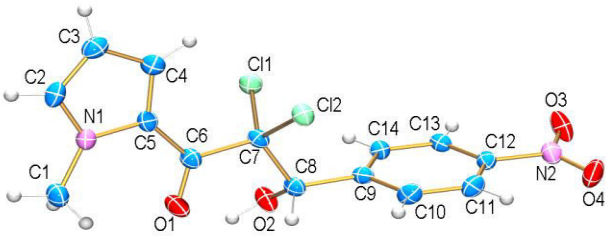
We initially generated *N*-methyl trichloroacetyl pyrrole radical anion by adding *N*-methyl trichloroacetyl pyrrole (1 equiv) to PhMgBr (1.1 equiv) dropwise then let the mixture stir for 1h at room temperature. The resulting enolate was added to the substituted aryl aldehydes at the same temperature to give aldol type products with very good isolated yield (70-96%). Irrespective of the nature of the substituent on the benzaldehyde (electron withdrawing or donating), the reaction afforded 2,2-dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)propan-1-one (**2.30**) and 2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one (**2.31**) with 96% and 85% yield respectively (Table 2-6, entries 2 and 3). 4-Iodo and pentafluoro benzaldehyde afforded aldol products with 74% and 94% yield (Table 2-6, entries 4 - 5). Good yields were also obtained on reaction with diethyl 2-oxomalonate (75%), and 5-methylfuran-2-carbaldehyde (70%) (Table 2-6, entries 7 - 8).

Both benzoyl chloride and 4-nitrobenzoyl chloride gave Claisen type products 2,2-dichloro-1- (1-methyl-1*H*-pyrrol-2-yl)- 3-phenylpropane-1,3-dione (**2.37**) and 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)propane-1,3-dione (**2.38**) in 50% and 95% yields respectively (Table 2-6, entries 9-10).

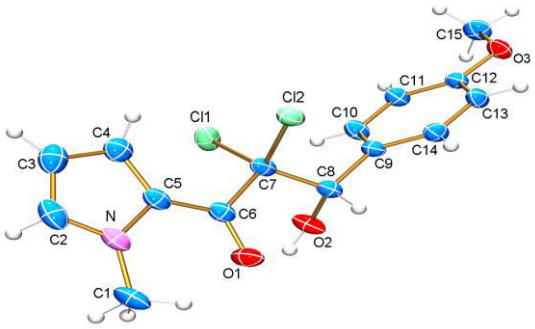
The structures of compounds **2.29**, **2.30**, **2.31**, **2.34** and **2.38** were confirmed by single crystal X-ray analysis (Figure 2-3).



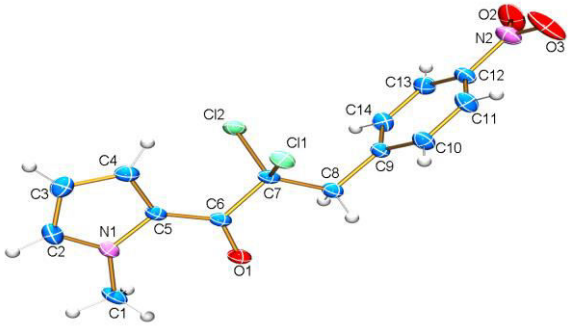
2.29



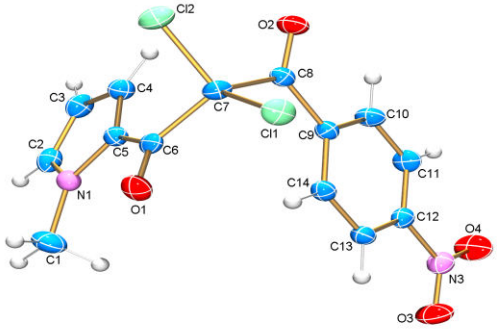
2.30



2.31



2.34



2.38

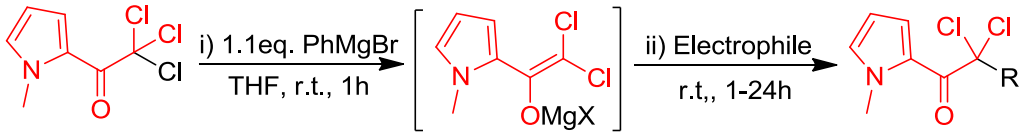
Figure 2-4: X-ray crystal structures of compounds **2.29, 2.30, 2.31, 2.34**, and **2.38**.

2.13: Conclusions

Through the use of Grignard reagents to reduce 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**) to enolates, we developed an efficient and new procedure to form aldol and Claisen type products.

We have shown through EPR experiments that ArMgX reacts with trichloroacetyl substituted aromatics by a single electron transfer mechanism to give the corresponding dichloroacetyl substituted aromatics. Reaction of the intermediate enolates with a range

of electrophiles provides a convenient route to substituted α,α-dichloro-β-hydroxyketones and related molecules, through aldol type reactions.

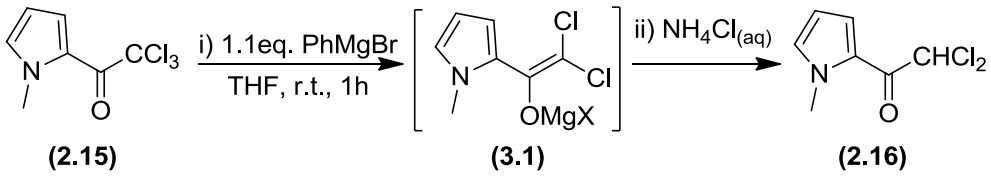


Scheme (2-16): Reaction of the intermediate enolates with a range of electrophiles

3.1: Introduction

α,α-Dichlorocarbonyls are useful as intermediates in the synthesis of chlorinated organic molecules such as chloroalkenes,[51] chlorooxiranes,[52] α-haloacylsilanes,[53] and heteroaromatics.[54] α,α-Dichlorocarbonyls can be synthesized via chlorination,[55] electrochemical or metal mediated reduction,[56] aldol reaction [57] or the cycloaddition of dichloroketenes.[58]

In Chapter 2, we have reported that the addition of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl) ethanone (**2.15**) to PhMgBr, followed by quenching with aqueous NH_4Cl, produced the reduction product 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.16**) (Scheme 3-1).[59]



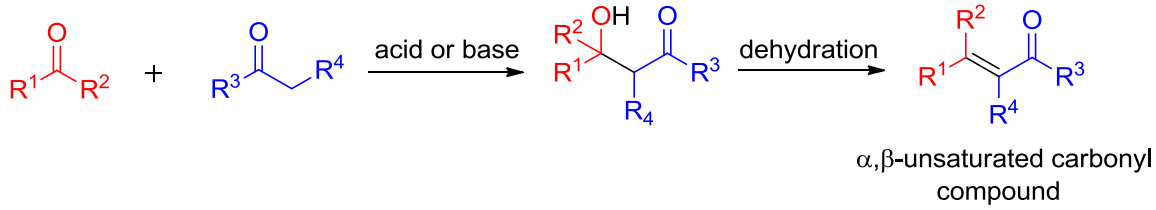
(2.15) **(3.1)** **(2.16)**

Scheme (3-1): RMgX mediated reduction of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone

It was proposed that this reaction involves a single electron transfer from the Grignard reagent to the ketone, conversion to enolate and reaction with water. We thought that we could adapt this reaction to give a synthetically useful reduction/aldol route to substituted α,α-dichlorocarbonyls. Therefore, we describe in this Chapter the synthesis of a novel series of α,α-dichlorocarbonyls starting from 2,2,2-trichloro-1-(*p*-tolyl) ethanones (**3.3**).

3.2: Aldol reaction

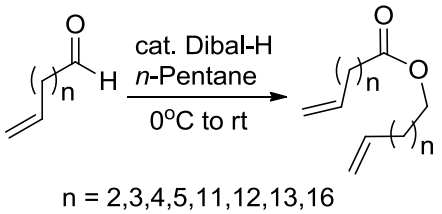
The reaction between a carbonyl compound with an α-hydrogen with an aldehyde or ketone to give a β-hydroxycarbonyl compound is called an *aldol reaction*. β-hydroxycarbonyl compounds can then undergo dehydration under certain conditions to give the corresponding α,β-unsaturated carbonyl compounds (Scheme 3-2).



Scheme (3-2): Aldol reaction

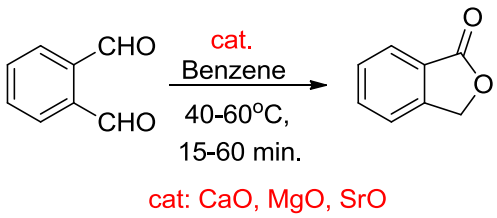
3.3: Tishchenko Reaction

The Tishchenko Reaction is a disproportionation reaction which involves a hydride shift from one aldehyde to another carbonyl forming an ester, often catalyzed by a magnesium, aluminum alkoxides, and Diisobutylaluminum hydride (Dibal-H)(Scheme 3-3).[60]



Scheme (3-3): Tishchenko Reaction

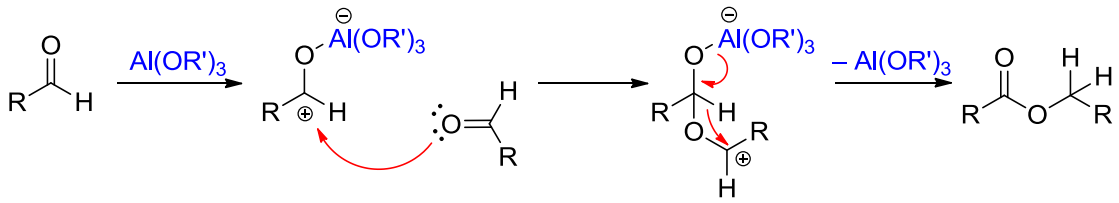
The reaction can occur between the same aldehyde and two different aldehydes (crossed Tishchenko reaction) esters, or in an intramolecular fashion to give lactones (Scheme 3-4).[61]



Scheme (3-4): Heterogeneous catalytic intramolecular Tishchenko reaction of *o*-phthalaldehyde to phthalide with alkaline earth oxides.

3.3.1: Mechanism of Tishchenko reaction

The proposed mechanism of the Tishchenko reaction involves coordination of the aldehyde with aluminum alkoxide followed by attack of a second molecule of aldehyde. Rearrangement occurs by 1,3- hydride shift to form the product (Scheme 3-5).

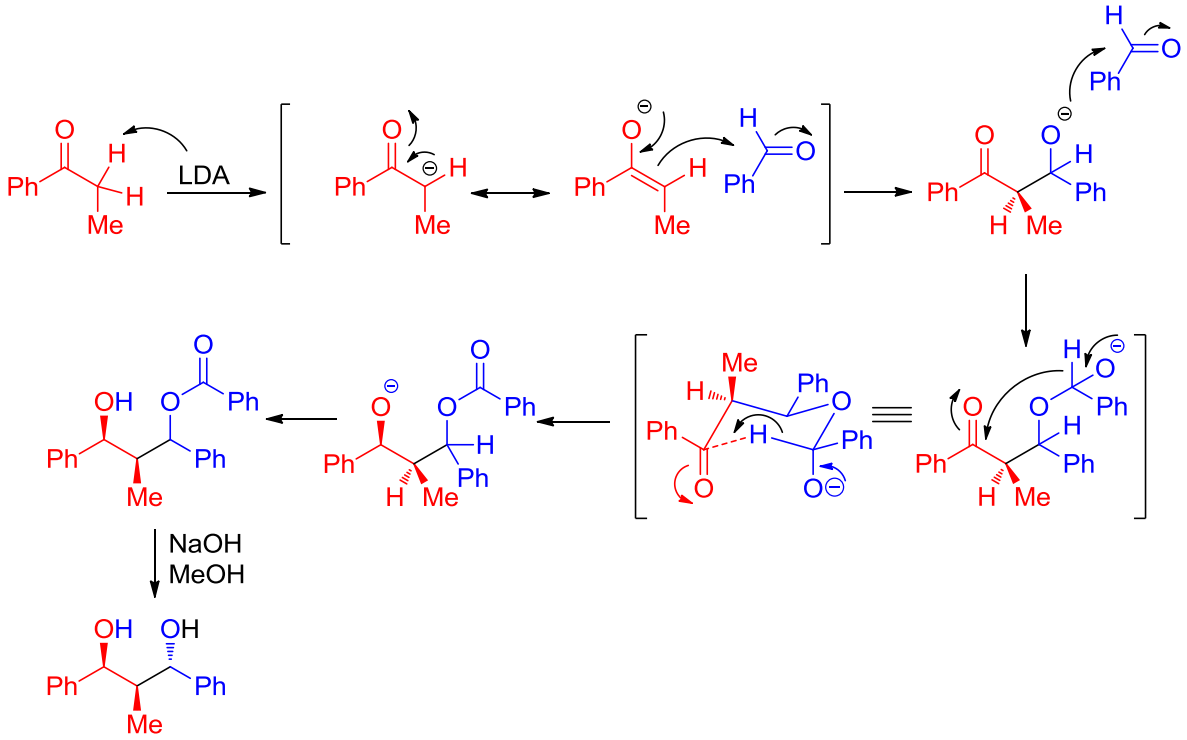


Scheme (3-5): Mechanism of Tishchenko reaction

3.4: Aldol-Tishchenko reaction

The aldol-Tishchenko reaction involves both aldol and Tishchenko steps. Tishchenko and aldol-Tishchenko reactions are competitive with each other. However the reactions can be controlled by choice of the right catalyst. A basic metal hydroxide catalyst is usually required in the aldol-Tishchenko reaction which can activate both aldol reaction and Tishchenko esterification. Metal alkoxides of mono-functional alcohols, polynuclear carbonyl ferrates, and simple metal hydroxides are other catalysts which can be used. In the presence of Lewis acidic catalysts such as aluminum alcoholates, the Tishchenko esterification is usually activated.[62]

The first step in an aldol-Tishchenko reaction involves ionization of a ketone to form an enolate which reacts with the aldehyde to give an alkoxide which is then attacked by a second molecule of aldehyde. After 1,5-hydride shift the catalyst is liberated and monoester is formed. The hydrolysis of the product gives diol as a pure diastereoisomer. (Scheme 3-6).[63, 64]



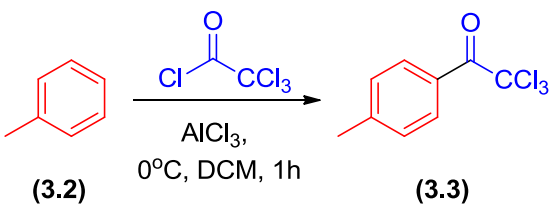
Scheme (3-6): Mechanism of aldol-Tishchenko reaction

3.5: Results and Discussion

3.5.1: Syntheses of 2,2,2-trichloro-1-(*p*-tolyl) ethanone

In order to examine the chemistry of 2,2-dichloro-1-arylethen-1-olate, we required a synthetic route to precursor 2,2,2-trichloro-1-aryl-ethanones.

Friedel-Crafts acylation of toluene was used in the synthesis of trichloro-1-(*p*-tolyl) ethanone. Toluene and 2,2,2-trichloroacetylchloride were reacted under $AlCl_3$ catalysis in DCM. The crude product was then purified by reduced pressure distillation to give 2,2,2-trichloro-1-(*p*-tolyl)ethanone (**3.3**) as a yellow oil in 65% yield (Scheme 3-7).



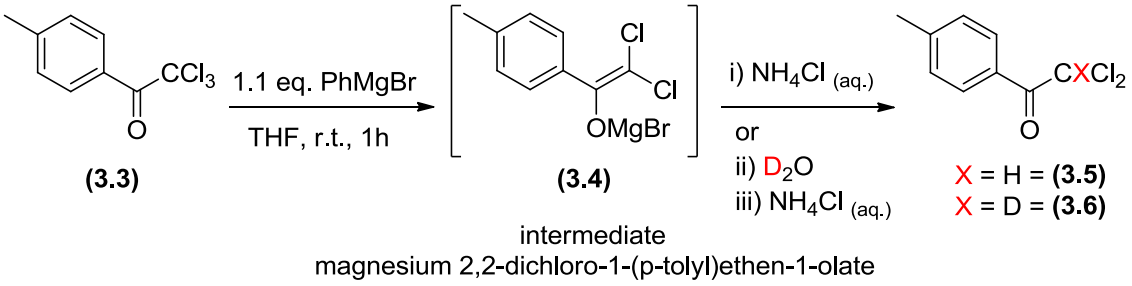
Scheme (3.7): Synthesis of 2,2,2-trichloro-1-(*p*-tolyl)ethanone (**3.3**)

The washing of the crude of **3.3** several time with $K_2CO_{3(aq)}$, brine solution, then with petroleum ether will give 94% yield and no further purification required.

3.5.2: Reduction of 2,2,2-trichloro-1-(*p*-tolyl)ethanone and trapping

First we examined the reduction of 2,2,2-trichloro-1-(*p*-tolyl)ethanone (**3.3**) with PhMgBr to see if the results would be consistent with previous experiments (Chapter 2).

The enolate generated from the reaction between 2,2,2-trichloro-1-(*p*-tolyl)ethanone (**3.3**) and PhMgBr was quenched first with H_2O to give 2,2-dichloro-1-(*p*-tolyl)ethanone (**3.5**) in 68% yield and in a second experiment with D_2O to give 2,2-dichloro-2-deuterium-1-(*p*-tolyl)ethanone (**3.6**) in 50% yield (>95%D incorporation).



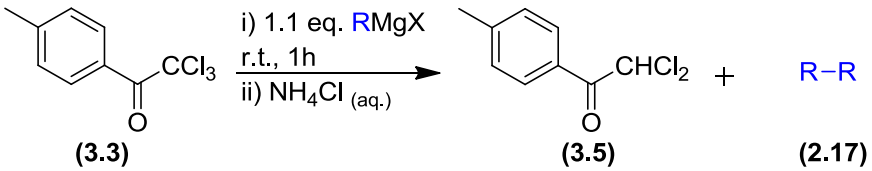
Scheme (3-8): Reduction of 2,2,2-trichloro-1-(*p*-tolyl)ethanone by PhMgBr then quenched with **i)** H_2O, **ii)** D_2O

The ^{1}H NMR spectrum of 2,2-dichloro-1-(*p*-tolyl)ethanone (**3.5**) showed single peak at 6.61 ppm corresponding to $CHCl_2$ group. Whilst for 2,2-dichloro-2-deuterium-1-(*p*-tolyl)ethanone (**3.6**), the ^{1}H NMR spectra showed a reduction (loss) of the same peak. ^{13}C NMR spectrum for 2,2-dichloro-2-deuterium-1-(*p*-tolyl)ethanone (**3.6**) showed a triplet peak at 67.6 ppm with J = 28Hz. The 100%D incorporation was calculated from the ^{1}H NMR spectrum.These trapping experiments therefore confirmed the formation of intermediate magnesium 2,2-dichloro-1-(*p*-tolyl)ethen-1-olate (**3.4**) (Scheme 3-8).

3.5.3: Influence of Grignard reagents

We have also investigated the reaction of various Grignard reagents with 2,2,2-trichloro-1-(*p*-tolyl) ethanone as a comparison with the pyrrole case and to explore the effect of alkyl, aryl, and halogen substitutes of the Grignard reagent on the reaction. The results are summarized in Table (**3-1**)

Table 3-1: Influence of R and X of Grignard reagent on the reaction of 2,2,2-trichloro-1-(*p*-tolyl)ethanone (**3.3**)



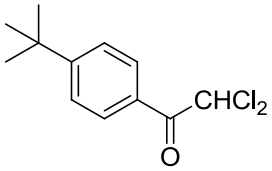
(3.3) **(3.5)** **(2.17)**

Entry	R	X	Yield of (**3.5**)[a]	Yield of (**2.17**)[b]
1	Et	Br	33%	nd[c]
2	iPr	Cl	33%	nd[c]
3	Ph	Cl	47%	35%
4	Ph	Br	68%	38%
5	Ph	I	96%	71%

[a] Isolated yields, [b] yield based on total RMgX added, [c] not determined.

As shown in Table (3-1), variation of R and halogen of the Grignard reagents was assessed in the reaction. All Grignard reagents give moderate to good yields of the reduced product (**3.5**) with aliphatic Grignards giving the lowest yields (33%) whilst aromatic Grignard reagents gave very good yields particularly with PhMgI. More importantly, the reaction provides a useful route to produce dichloro acetyl functionalised benzene which can be used in synthesis of many organic molecules.

Although, PhMgI gave the best yields for the synthesis of 2,2-dichloro-1-(*p*-tolyl)ethanone (**3.5**) (96%) and 1-(4-(*tert*-butyl)phenyl)-2,2-dichloroethanone (**3.7**) (97%). However we used commercial available PhMgBr in further experimental.

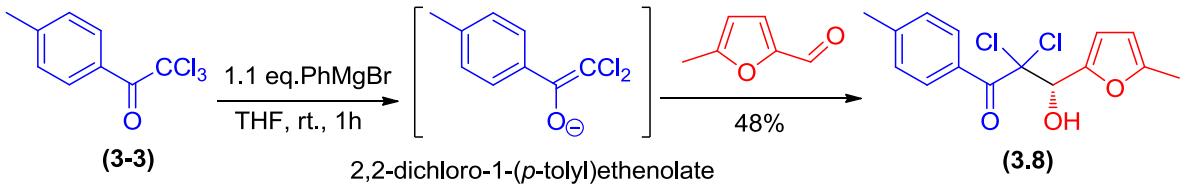


(3.7)

3.6: Trapping of 2,2-dichloro-1-(*p*-tolyl)ethenolate with electrophiles

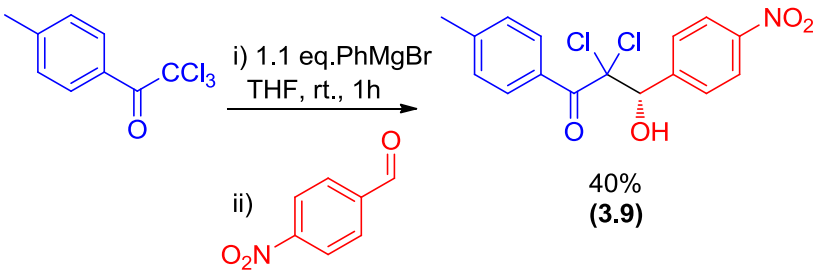
Based on previous results (trapping of enolate derived from *N*-methyl trichloroacetyl pyrrole, Chapter 2), we then looked at the trapping of reduction generated enolates with aldehydes.

The trapping of enolate generated from the reaction between 2,2,2-trichloro-1-(*p*-tolyl)ethanone and PhMgBr, with 5-methylfuran-2-carbaldehyde gave an aldol type product with moderated yield of 2,2-dichloro-3-hydroxy-3-(5-methylfuran-2-yl)-1-(*p*-tolyl)propan-1-one (**3.8**) in 48% yield and 39% yield of Ph-Ph (Scheme 3-9).



Scheme (3-9): Trapping of 2,2-dichloro-1-(p-tolyl)ethenolate with 5-methylfuran-2-carbaldehyde

The trapping of 2,2-dichloro-1-(*p*-tolyl)ethenolate with 1 equivalent of 4-nitrobenzaldehyde at room temperature gave the expected aldol type product of (±)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(*p*-tolyl)propan-1-one (**3.9**) in 40% yield.



Scheme (3-10): Trapping of 2,2-dichloro-1-(p-tolyl)ethenolate with 4-nitrobenzaldehyde

Next we wished to confirm the structure of the product (**3.9**). Therefore single crystals of (±)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(*p*-tolyl)propan-1-one (**3.9**) were grown from the solution in $CHCl_3$ and the structure was determined by X-ray crystallography (Figure 3-1).

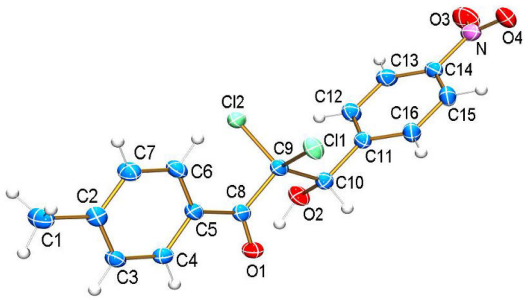


Figure (3-1): X-ray crystal structures of **3.9**

The ^{1}H NMR crude of trapping of 2,2-dichloro-1-(*p*-tolyl)ethenolate with 1 equivalent of 4-nitrobenzaldehyde, showed another product. The crude was purified by column chromatography (SiO_2) and single crystals were grown from the solution in $CHCl_3$ and the by-product diagnosed as (±)-(1*R*,3*R*)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(*p*-tolyl)propyl 4-nitrobenzoate (**3.9**) in 23% yield as a single regio- and diastereoisomer (Figure 3-2).

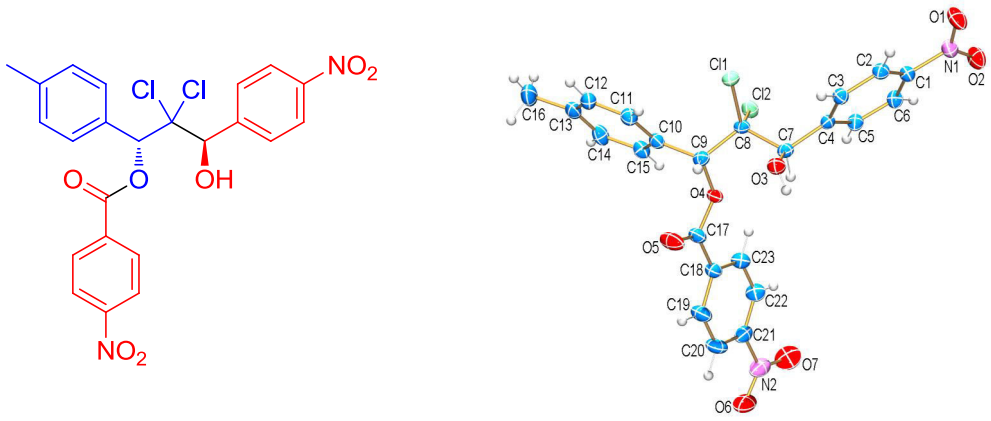


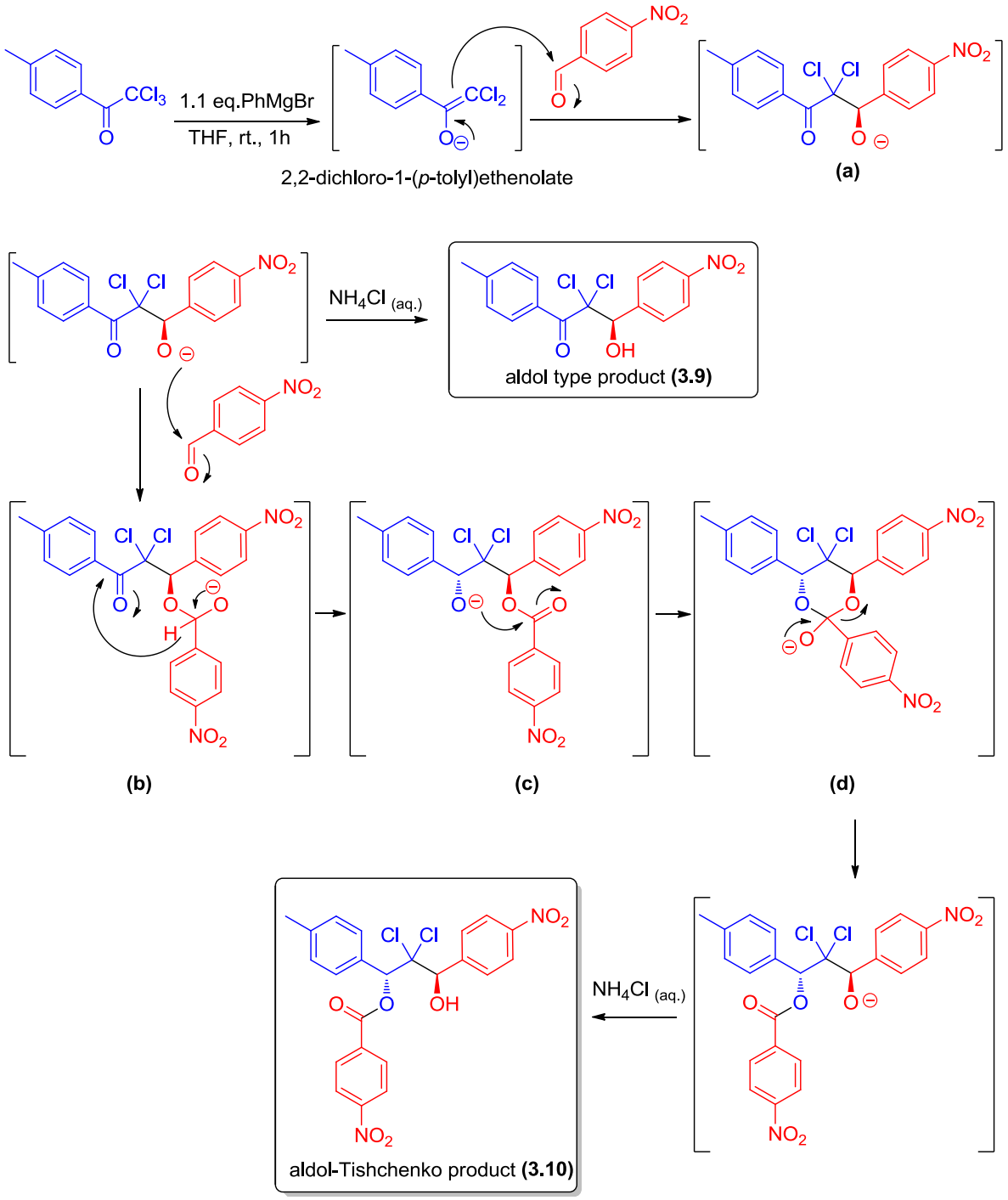
Figure (3-2): Single-crystal X-ray structure of (±)-(1*R*,3*R*)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(*p*-tolyl)propyl 4-nitrobenzoate (**3.10**)

^{1}H, ^{13}C NMR, and IR spectroscopies and HRMS have been used to characterize the product (**3.10**). Usually, the reactions that produce β-hydroxycarbonyl compounds from the reaction of aldehydes or ketones with another carbonyl compounds which have α-hydrogen is known as the aldol reaction. If the aldol product involves α-hydride shift from aldehyde to carbon of another carbonyl molecule to form an ester, the reaction is called the aldol-Tishchenko reaction. In the other hand, the aldol-Tishchenko reaction is one modification of Tishchenko reaction that started according to aldol reaction followed by Tishchenko reaction to give monoesters of 1,3-diols.

The X-ray crystallography showed that an anti-1,3-diol moiety and as such is likely to be formed via an aldol/Tishchenko reaction involving the enolate formed from the reaction of 2,2-dichloro-1-(*p*-tolyl)ethenolate with 2 equivalent of 4-nitrobenzaldehyde followed by a migration of the ester to the newly formed alcohol.

3.6.1: Suggested mechanism

According to the chemical structure of (±)-(1*R*,3*R*)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(*p*-tolyl)propyl 4-nitrobenzoate (**3.10**), we suggested that the product was formed according to an aldol/Tishchenko reaction. The suggested mechanism is shown in Scheme (**3-11**).



Scheme (3-11): Suggested mechanism of aldol/Tishchenko reaction

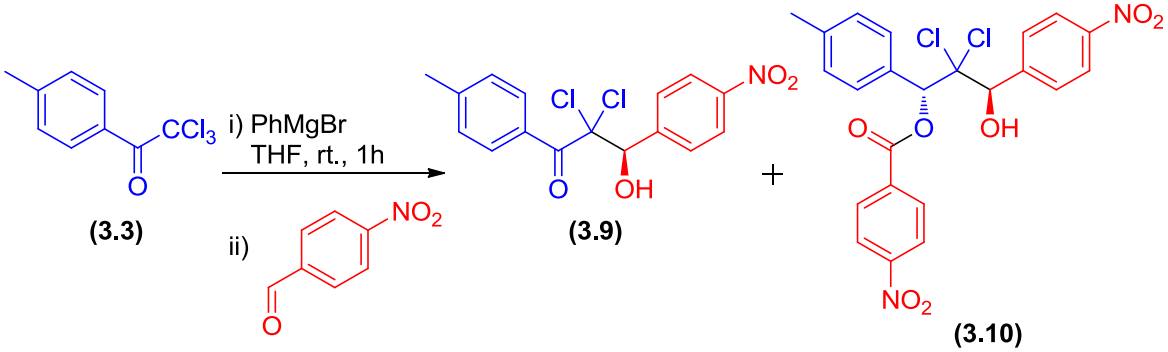
We suggest that the 2,2-dichloro-1-(*p*-tolyl)ethenolate reacted with the 1st equivalent of aldehyde derivatives to give (*R*)-2,2-dichloro-1-(4-nitrophenyl)-3-oxo-3-(p-tolyl)propan-1-olate (Scheme 3-11a) which then either takes a proton from H_2O to give (±)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(*p*-tolyl)propan-1-one (**3.9**) as aldol type product, or attacks the 2nd equivalent of aldehyde to give (2,2-dichloro-1-(4-nitrophenyl)-3-oxo-3-(*p*-tolyl)propoxy)(4-nitrophenyl)methanolate (Scheme 3-11b). The next step involves hydride transfer to the carbonyl group to form (±)-(1*R*,3*R*)-2,2-dichloro-3-((4-nitrobenzoyl)oxy)-3-(4-nitrophenyl)-1-(p-tolyl)propan-1-olate (Scheme 3-11c) followed by a migration of the ester to the newly formed alcohol to give (±)-(1*R*,3*R*)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(*p*-tolyl)propyl 4-nitrobenzoate (**3.10**) as aldol/Tishchenko product (Scheme 3-11)

Interested by this class of reactions, we decided to examine the applications of this aldol/Tishchenko products.

3.7: Experimental design and optimization

In order to find the optimum reaction condition for the formation of 2,2-dichloro-1,3-diarylpropane-1,3-diols as an alternative product from arising from the Grignard mediated reduction of 2,2,2-trichloro-1-aryl-ethanones, we therefore examined the reaction under different conditions. The formation of the 2,2-dichloro-1-(*p*-tolyl)ethenolate was performed under the same conditions as before, whilst the number of equivalents of 4-nitrobenzaldehyde and the reaction temperature for the quenching step were varied. Table (3-2) summarized the results.

Table (3-2): Optimization of reaction conditions



Entry	Reaction conditions	[a]Yield of **3.9**	[a]Yield of **3.10**
1	1 eq. *p*-$NO_2(C_6H_4)$CHO rt., 1h	40%	23%
2	1 eq. *p*-$NO_2(C_6H_4)$CHO, -78°C, 1h	62%	0%
3	2 eq. *p*-$NO_2(C_6H_4)$CHO, -78°C, 1h	0%	95%

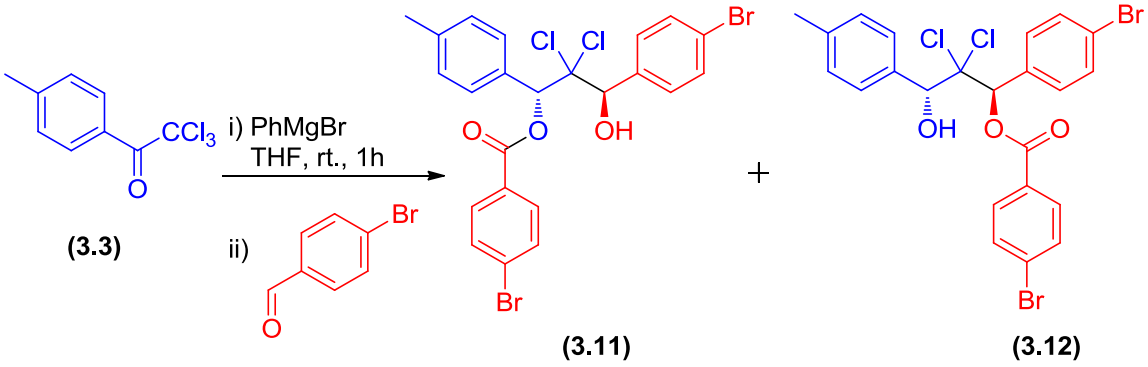
[a:] Isolated yield

The number of equivalents of electrophiles and the temperature of the quenching step proved to be important parameters for this reaction. The yield of compound (**3.9**) formed from an aldol like reaction was notably increased to 62% when the quenching step was carried out at -78°C, with 1 equiv of *p*-$NO_2(C_6H_4)$CHO, and no other products were observed (Table 3-2, entry 2). However an excellent yield (95%) of compound (**3.10**) was observed when the quenching step was carried out at -78°C, with 2 equiv of *p*-$NO_2(C_6H_4)$CHO (Table 3-2, entry 3).

3.8: Trapping with 4-bromobenzaldehyde

Using our optimized conditions (Table 3-2), and in order to establish the scope of aldol-Tishchenko process, we next extended the reaction to examine alternative electrophiles. 4-Bromobenzaldehyde was used to quench 2,2-dichloro-1-(*p*-tolyl)ethenolate formed as previously, the results are summarized in Table (3-3).

Table (3-3): Trapping of 2,2-dichloro-1-(*p*-tolyl)ethenolate with 4-bromobenzaldehyde

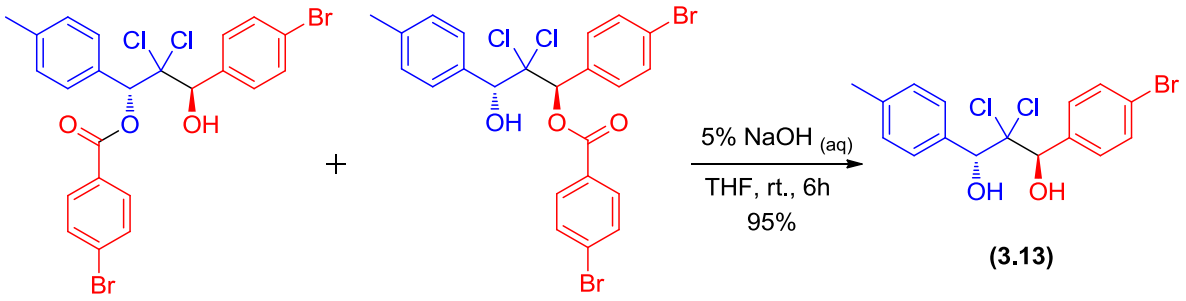


(3.3) (3.11) (3.12)

Entry	Reaction conditions	Yield of (**3.11**) + (**3.12**)
1	2 eq. *p*-Br(C_6H_4)CHO ,rt., 1h	92%
2	2 eq. *p*-Br(C_6H_4)CHO, 0°C, 1h	88%

The effects of temperature and number of equivalents of electrophile on the enolate trapping step was also tested using 4-bromobenzaldehyde. In this case our optimized reaction conditions showed a 1:1 mixture of regioisomers of (±)-(1*R*,3*R*)-3-(4-bromophenyl)-2,2-dichloro-3-hydroxy-1-(*p*-tolyl)propyl 4-bromobenzoate (**3.11**) and (±)-(1*R*,3*R*)-1-(4-bromophenyl)-2,2-dichloro-3-hydroxy-3-(*p*-tolyl)propyl 4-bromobenzoate (**3.12**) were obtained even with variation of reaction temperature (Table 3-3).

Since these compounds were inseparable by chromatography and to support the results, basic hydrolysis of the esters (**3.11**) and (**3.12**) were performed. This gave (±)-(1*R*,3*R*)-1-(4-bromophenyl)-2,2-dichloro-3-(*p*-tolyl)propane-1,3-diol (**3.13**) in 95% yield as single diestereomer supporting the hypothesis that compounds (**3.11**) and (**3.12**) were regioisomers (Scheme 3-12).

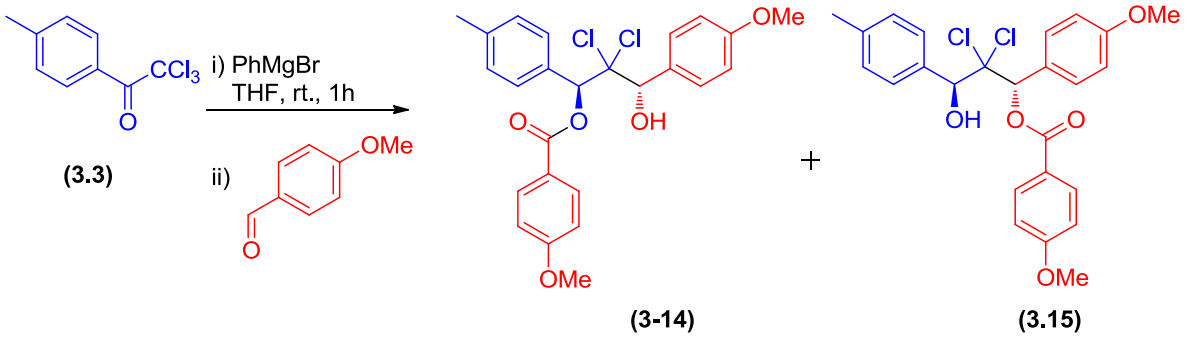


(3.11) (3.12) (3.13)

Scheme (3-12): basic hydrolysis of **3.11** + **3.12**

3.9: Trapping with 4-methoxybenzaldehyde

Trapping of 2,2-dichloro-1-(*p*-tolyl)ethenolate prepared a previously with 1 equivalent of 4-methoxybenzaldehyde at 0°C gave (±)-(1*S*,3*S*)-2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(*p*-tolyl)propyl 4-bromobenzoate (**3.14**) and (±)-(1*S*,3*S*)-2,2-dichloro-3-hydroxy-1-(4-methoxyphenyl)-3-(*p*-tolyl)propyl 4-bromobenzoate (**3.15**) as aldol/Tishchenko products as a mixture of regioisomers in 47% (1:1) (Scheme 3-13).



Scheme (3-13): Trapping of 2,2-dichloro-1-(*p*-tolyl)ethenolate with 4-methoxybenzaldehyde

We also found (±)-2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(*p*-tolyl)propan-1-one (**3.16**) as aldol product in 7% yield. Recrystallization from $CHCl_3$ led to crystals of (**3.16**), whose X-ray structure is shown in Figure (3-4).

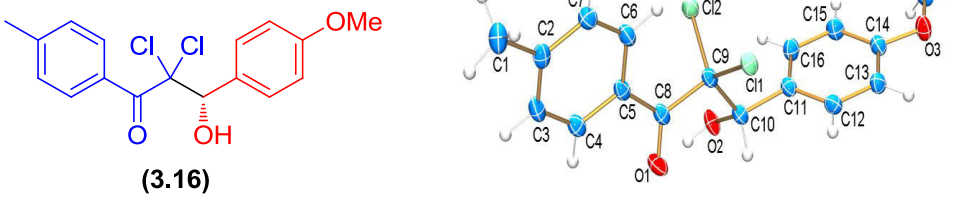
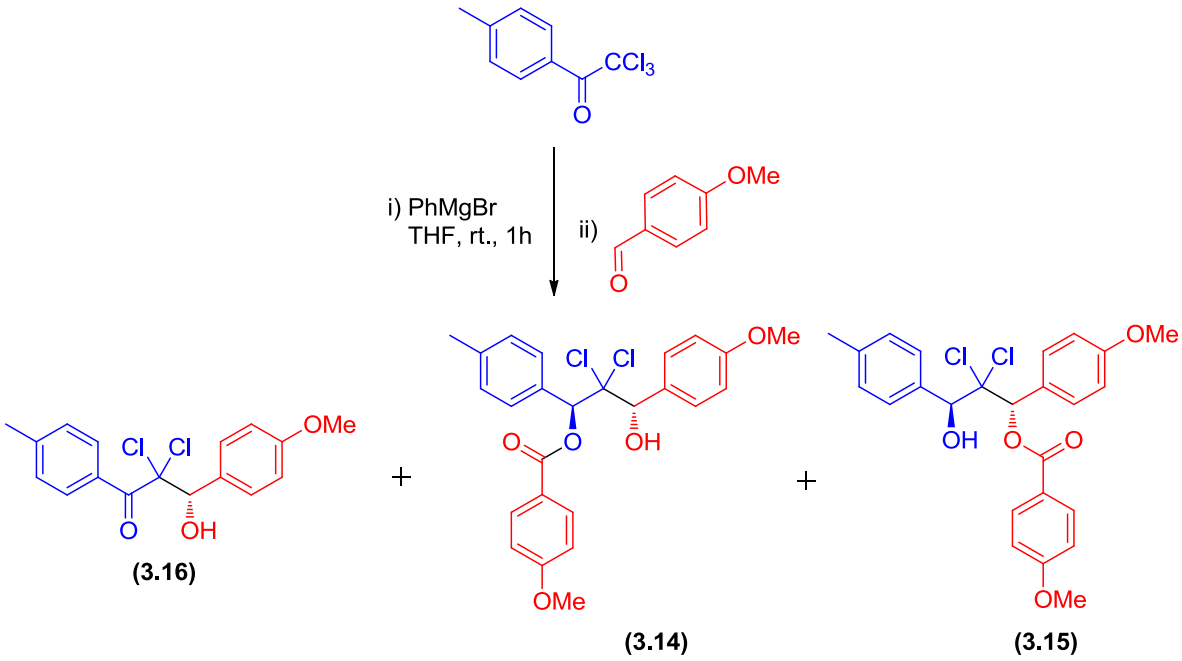


Figure (3-4): Single-crystal X-ray structure of (±)-2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(*p*-tolyl)propan-1-one (**3.16**)

The 2,2-dichloro-1-(*p*-tolyl)ethenolate which was formed as before quenched by different equivalents of 4-methoxybenzaldehyde and the reaction temperature for the quenching step were varied. Table (3-4) summarized the results.

Table (3-4): Quenche of 2,2-dichloro-1-(*p*-tolyl)ethenolate by different equivalents of 4-methoxybenzaldehyde

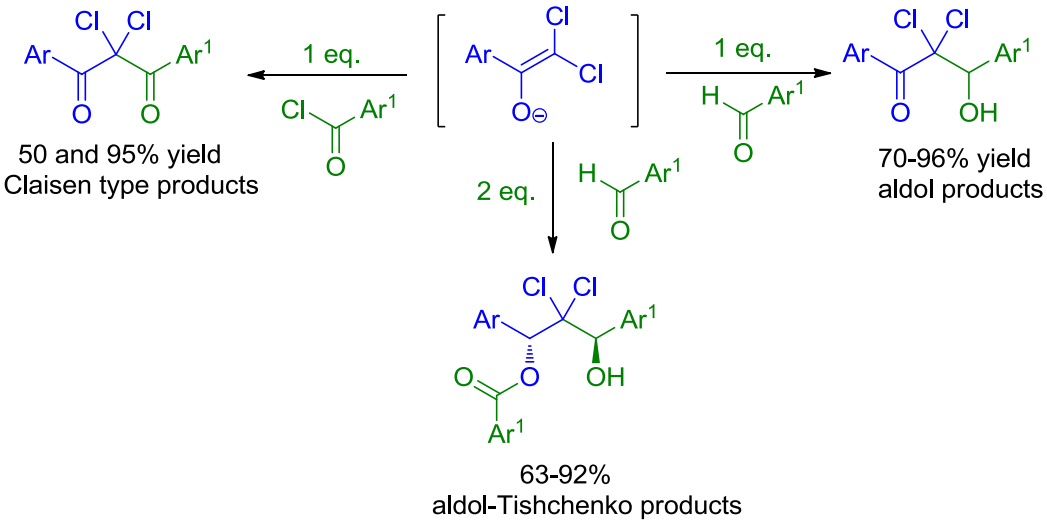


Entry	Reaction conditions	Yield of (**3.16**)	Yield of **(3.14)** + (**3.15**)
1	1 eq. *p*-OMe(C_6H_4)CHO, 0°C, 1h	7%	47%
2	1 eq. *p*-OMe(C_6H_4)CHO, rt., 1h	0%	63%
3	2 eq. *p*-OMe(C_6H_4)CHO ,rt., 1h	0%	72%

Under a range of conditions, the best yield was observed with 2 equivalents of 4-methoxybenzaldehyde. However good overall yield of an unseparated mixture of (±)-(1*S*,3*S*)-2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(*p*-tolyl)propyl 4-bromobenzoate (**3.14**) and (±)-(1*S*,3*S*)-2,2-dichloro-3-hydroxy-1-(4-methoxyphenyl)-3-(*p*-tolyl)propyl 4-bromobenzoate (**3.15**) were obtained, in a 1:1 ratio of two regioisomeric esters.

3.10: Conclusions

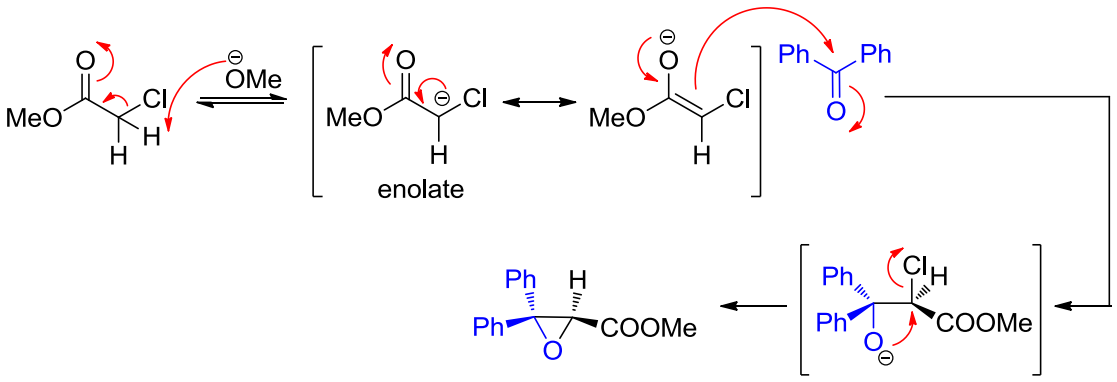
The trapping of the enolate generated from the reaction of 2,2,2-trichloro-1-(*p* tolyl)ethanone and PhMgBr, with different electrophiles can generate aldol, Claisen and aldol/Tishchenko products. The temperature and the number of equivalents of electrophile used play a fundamental role in controlling the product distribution.



Scheme (**3-14**): Generation of aldol, Claisen and aldol/Tishchenko products by trapping of enolate with a different electrophiles

4.1: Introduction

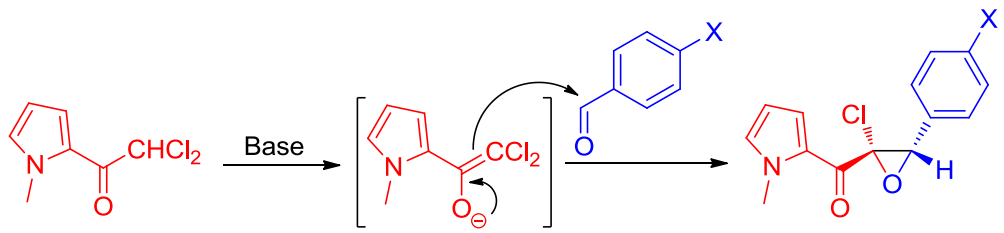
The Darzens reaction involves the reaction of aldehyde or ketone with a α-haloester in the presence of a strong base to give an α,β- epoxyester (glycidic ester).[65-67]



Scheme (4-1): Mechanism of Darzens reaction

The Darzens reaction has been used in the synthesis of many biologically active natural products, including vitamin A,[67] the active component of the antibiotics Virginiamycin M [68] and Roflamycoin,[69] amastatin,[70] and thiam,[71] and as intermediates in the synthesis of thiazoles,[72] oxaziles,[73] and imidazopyridines.[74, 75]

In this Chapter, we will investigate the synthesis of α-chloro-α,β-epoxy ketones, starting from 2,2-dichloro-1-aryl ethanones (synthesized previously) and a range of aromatic aldehydes (Scheme 4-2).



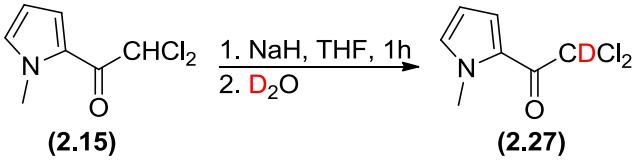
Scheme (4-2): Synthesis of α-chloro-α,β-epoxy ketones

4.2: Results and Discussion

4.2.1: Enolate formation from 2,2-dichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethanone.

In Chapter 2 we have reported the formation of 2,2-dichloro-1-arylethen-1-olates from the reaction of 2,2,2-trichloro-1-arylethen-1-olates with Grignard reagents at rt. In

order to examine the condition effects on the reactivity of 2,2-dichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethenolates, we decided to deprotonate 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.15**) by using NaH. The generated enolate was trapped with D_2O to give (78 % yield) of corresponding deuterated products (2,2-dichloro-2-deuterium-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.27**) (Scheme 4-3).

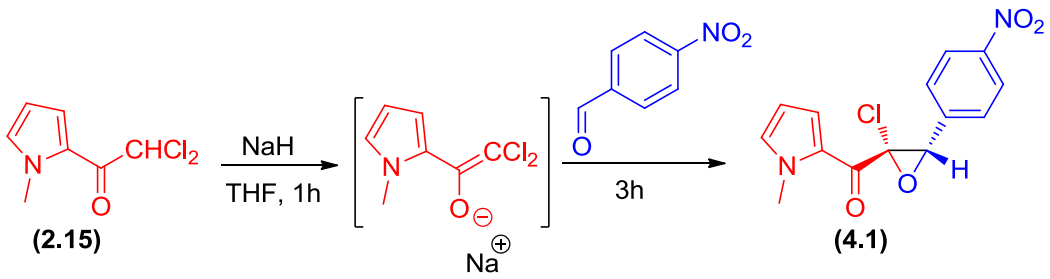


Scheme (4-3): Trapping of 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethenolate with D_2O

4.2.2: Enolate formation by deprotonation of 2,2-dichloro-1-arylethen-1-olates and reactivity

4.2.2.1: Trapping with *p*-nitrobenzaldehyde

In Chapter 2, we have seen that the trapping of 2,2-dichloro-1-arylethen-1-olates generated from the reaction of 2,2,2-trichloro-1-aryl ethan-1-one with PhMgBr with aldehydes and ketones gave aldol products. We then examined the formation of 2,2-dichloro-1-arylethen-1-olates by deprotonation of 2,2-dichloro-1-aryl ethan-1-one with NaH. The trapping of sodium enolate of 2,2-dichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethan-1-one (**2.15**) and NaH with *p*-nitrobenzaldehyde gave not the expected aldol product but a Darzens product (**4.1**) (Scheme 4-4).



Scheme (4-4): Trapping of 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethenolate with *p*-nitrobenzaldehyde

The chemical structure of Darzens product (**4.1**) was confirmed by X-ray crystallography (Figure 4-1). The X-ray showed that the reaction in scheme (4-4) showed a modest selectivity to give only *cis* proudect of **4.1**.

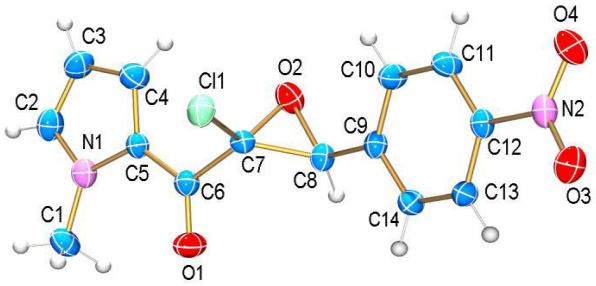
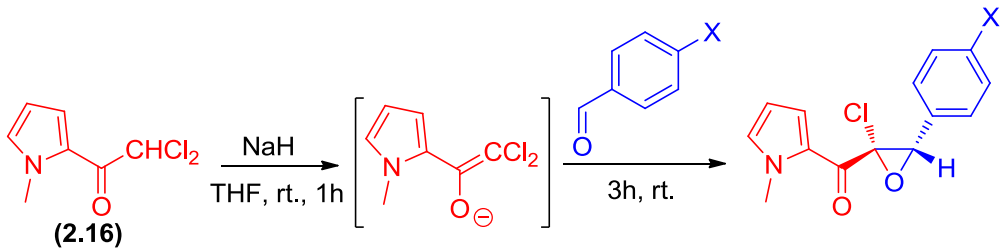


Figure 4-1: X-ray crystallography of **4.1**

In order to check if this reaction was general, the sodium enolate of 2,2-dichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethan-1-one (**2.15**) was quenched with different substituted benzaldehydes. In each case the formation of to α,β-epoxy-α-chloro-ketone was observed Table (4-1).

Table (4-1): Trapping of 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethenolate with different substituted benzaldehydes

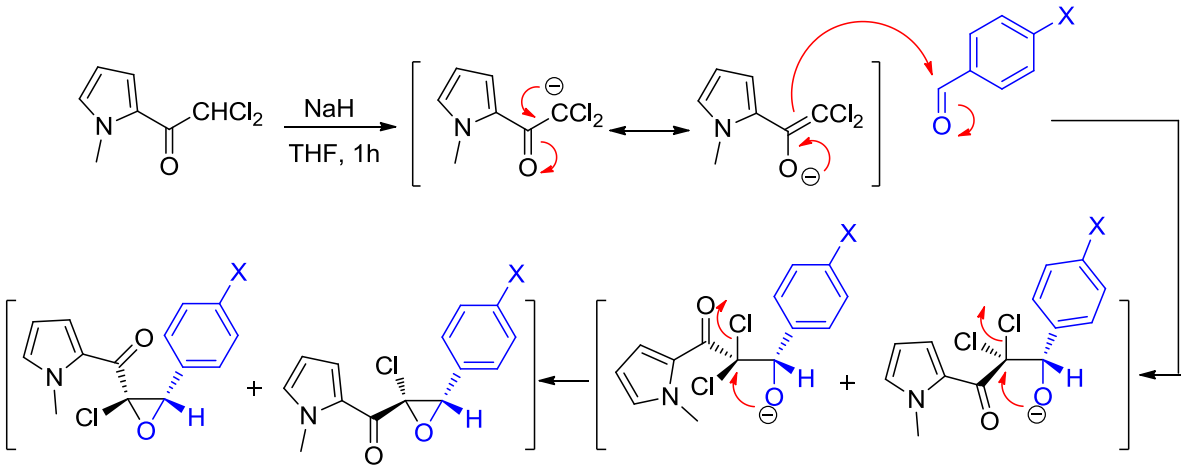


Comp. No.	**4.2**	**4.3**	**4.4**	**4.5**
X	H	OMe	Br	I
Yield %	47%	38%	71%	85%

As we can see in Table (4-1), yield varied from 38% when X = OMe to 85% when X = I. No other products were observed in the reactions that listed in Table 4-1.

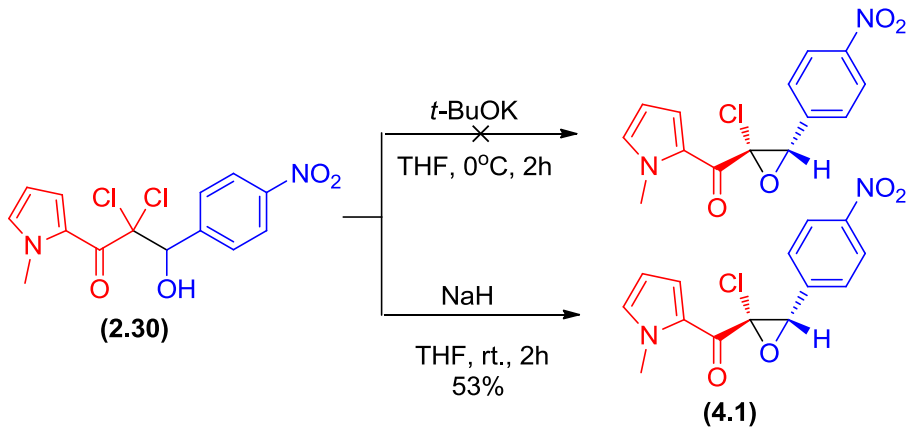
4.2.2.2: Mechanism

The suggested mechanism is shown in Scheme (4-5).



Scheme (4-5): Suggested mechanism for the formation of α-chloro-α,β-epoxy ketones

The mechanism suggests formation of an enolate which attacks substituted aldehyde to give alkoxide ion. The alkoxide attack the carbon holding Cl to produce the product. According to the mechanism, we suggested that the alkoxide can be generated by treated of β-hydroxy-α,α-dichloro ketone (which has already prepared in Chapter 2) with base. No Darzens product (**4.1**) observed when 2,2-dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)propan-1-one (**2.30**) treated with *t*-BuOK (which is usually used with Darzens reaction). However Darzens product (**4.1**) was observed when we used NaH as a base instead of *t*-BuOK (Scheme 4-6).

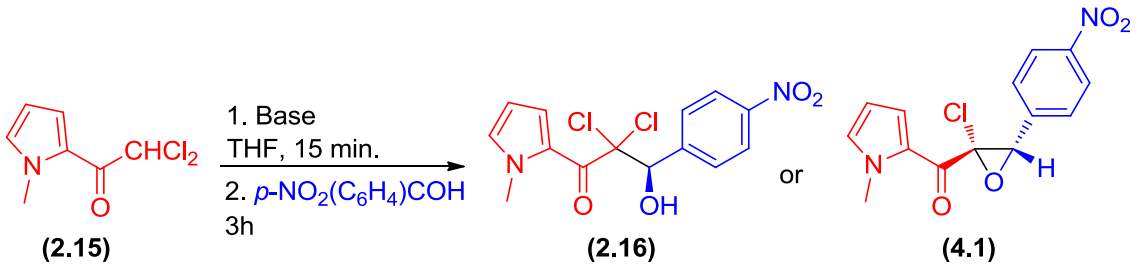


Scheme (4-9): Synthesis of α-chloro-α,β-epoxy ketones from **2.30**

4.2.2.3: Counter ion influence

Since the reactivity of the sodium enolate was markedly different from the previously prepared magnesium enolate, we investigated the deprotonation of 2,2-dichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethan-1-one (**2.15**) with NaH/$MgCl_2$, NaHMDS, and LiHMDS to give the corresponding sodium, magnesium, and lithium enolates. Reaction of these enolates with *p*-nitrobenzaldehyde gave either aldol or Darzens condensation. Aldol products arose only from the magnesium enolate, whilst sodium enolates gave mainly Darzens products and lithium and potassium enolates gave only recovered starting materials (Table 4-2).

Table 4-2: Influence of the counter ion on the formation of aldol, Darzens products



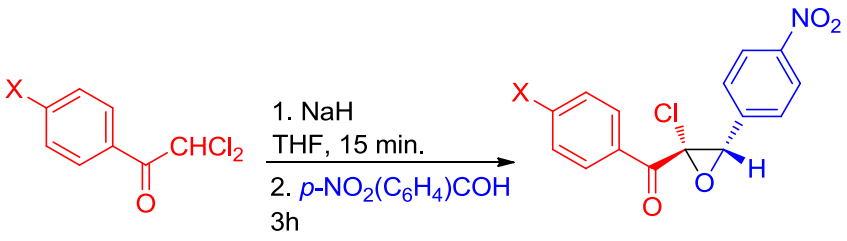
(2.15) (2.16) (4.1)

Entry	1.1 eq. of Base	Yield % (**2.16**)	Yield % (**4.1**)
1	NaH	0%	53%
2	NaH/$MgCl_2$	47%	0%
3	NaHMDS	0%	20%
4	LiHMDS	0%	0%

4.2.3: Sodium enolate formation from 2,2-dichloro-1-arylethan-1-one.

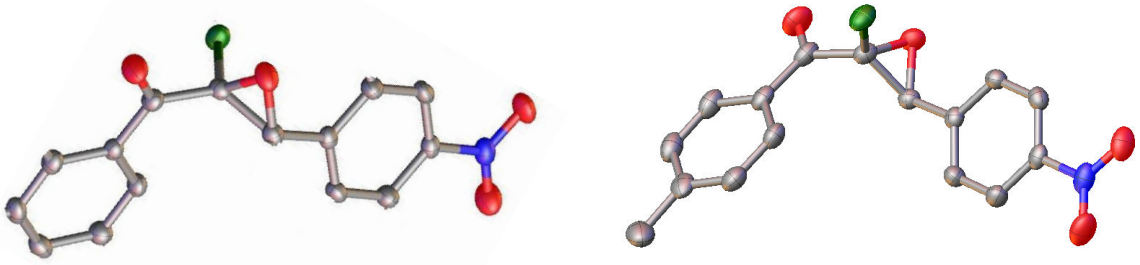
Sodium enolate formation from 2,2-dichloro-1-phenyl ethanone, 2,2-dichloro-1-(*p*-tolyl)ethan-1-one, and 1-(4-(*tert*-butyl)phenyl)-2,2-dichloroethanone with NaH followed by subsequent reaction with *p*-nitrobenzaldehyde gave only *cis*-(2-chloro-3-(4-nitrophenyl)oxiran-2-yl)(aryl)methane-1-one through intramolecular S_N2 attack in 34-92% yields (Table 4-3).

Table 4-3: Reaction of sodium enolate with *p*-nitrobenzaldehyde



Comp. No.	**4.6**	**4.7**	**4.8**
X	H	Me	*t*-Butyl
Yield %	34%	92%	74%

The structure of compounds **4.6** and **4.7** were confirmed by X-ray crystallography analysis (Figure 4-2). The X-ray also confirmed the *cis* isomeric proudects of **4.6** and **4.7**



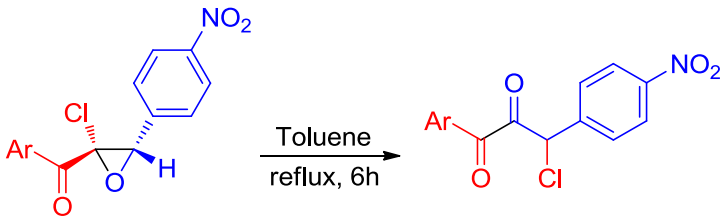
4.6 **4.7**

Figure 4-2: X-ray crystallography of **4.6** and **4.7**

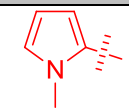
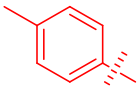
4.2.4: Formation of 3-halo-1,2-diones

In order to examine the synthetic utility of Darzens products, we decided to examine the conversion of Darzens products into 3-halo-1,2-diones. Therefore we heated compounds **4.1**, and **4.7** in toluene. After 6h at reflux α-chloro-β,γ-diones **4.9**, and **4.10** were isolated (Table 4-4).[75]

Table (4-4): Formation of 3-halo-1,2-diones

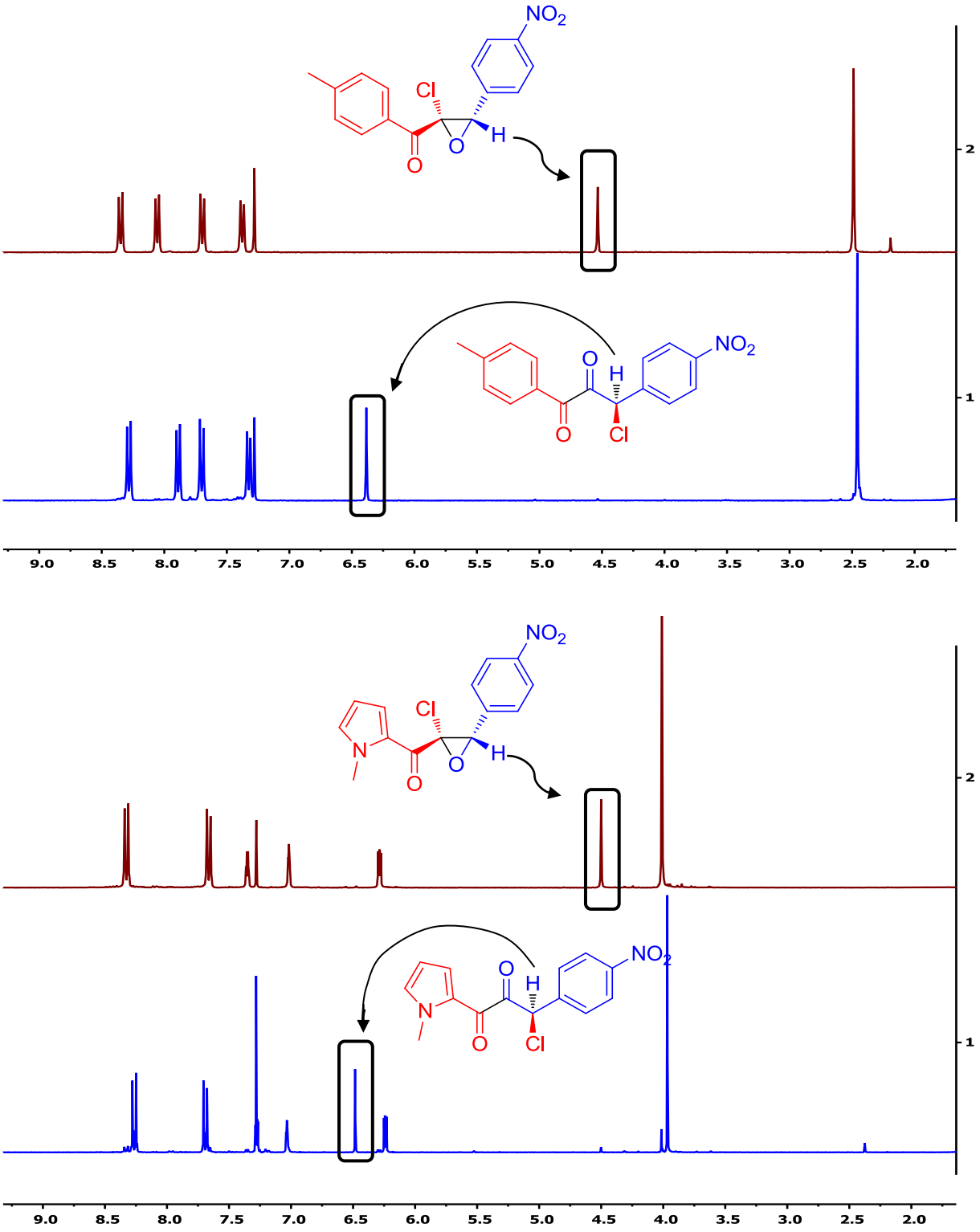


(4.1), (4.6) **(4.9), (4.10)**

entry	Ar	product	Yield (%)
1		**4.9**	98%
2		**4.10**	98%

Comparison of the ^{1}H NMR spectra of epoxides **4.1** and **4.6** and the α-chloro-β,γ-diones **4.9** and **4.10** shows a change in the ^{1}H shift of the benzylic C-H from 3.93 and 4.53 ppm in the epoxides to 6.48 and 6.38 ppm in the α-chloro-β,γ-diones respectively (Scheme 4-7).

This change in chemical shift of the benzylic C-H is due to an increase in the number of electron withdrawing groups adjacent to the C-H, carbonyl and chloro. The IR of **4.9** and **4.10** showed two C=O stretch at 1729, 1624 cm^{-1} and 1720, 1663 cm^{-1} respectively.



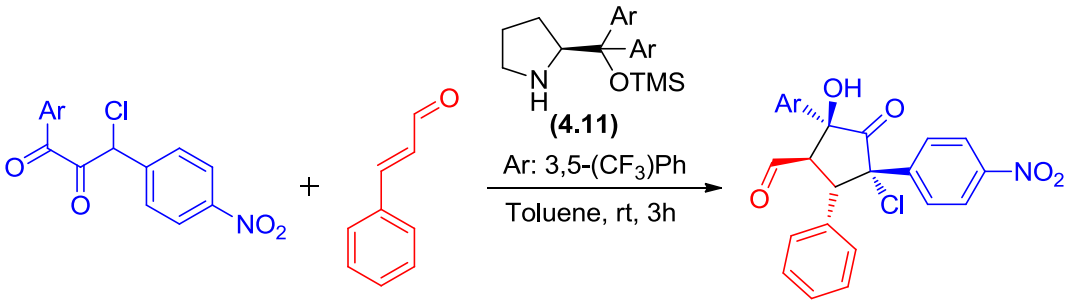
Scheme (4-7): ^{1}H NMR spectra of epoxides (**4.1** and **4.6**) and the α-chloro-β,γ-diones (**4.9**, and **4.10**)

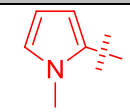
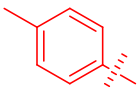
4.3: Organo- catalysted Domino Michael / aldol reactions of 3-halo-1,2-diones

1,2-Diones have been used in a numbers of asymmetric organocatalytic transformations,[76] the number of reactive centers makers 1,2-dicarbonyl compounds an attractive scaffold for furthers functionalization. In the case of α-chloro-β,γ-diones there are three potentially reactive sites, a electrophilic C-Cl and two electrophilic carbonyls.

Lefranc *et al* have been synthesized cylopentanone derivatives by using Michael/aldol reaction of 3-halogeno-1,2-diones to α,β-unsaturated aldehyde with four contiguous strereogenic centers in excellent diastereoselectivities, good yields, and enantioselectivities (up to 94% ee). Therefore, we decided to examine the **4.9** and **4.10** with cinnamaldehyde in the presence of organocatalyst (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**4.11**).[76]

Table (4-5): Organocatalytic Michael/Aldol reactions of **4.10** and Cinnamaldehyde



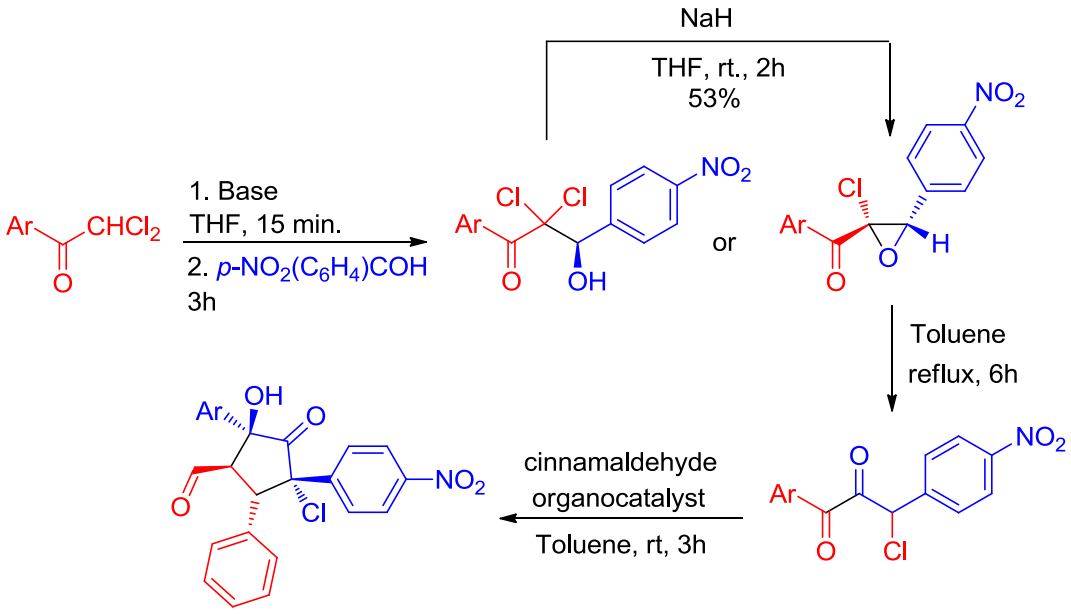
entry	Ar	product	Yield (%)
1		**4.12**	0%
2		**4.13**	73%

Although **4.9** failed to give any isolated product, **4.10** was transformed into **4.13** in high yield.

4.4: Conclusions

We have shown that 2,2-dichloro-1-arylethenolate can undergo a range of reactions depending on their counter ions to give (*R*)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-arylpropan-1-one. In particular Darzens products can be formed allowing

access to reactive synthesis intermediates such as α-chloro-β,γ-diones which have been used to synthesis cylopentanone derivatives with four contiguous strereogenic centers in excellent diastereoselectivities, good yields, and enantioselectivities.



Scheme (4-8): Synthesis of cyclopentanone derivatives using Michael/aldol reaction

5.1: Introduction

This part of the project will look at the design of new reagents for the traceless bioconjugation of proteins. This will involve the use of bioorthogonal reactions to attach functional molecules to a protein to aid in their purification and analysis.

The chemical reactions that can take place in the presence of complex biomolecules or living systems with no interactions with the native biochemical processes are known as bioorthogonal reaction. Bertozzi defined the concept of a bioorthogonal reaction to fulfill the following requirements:[77]

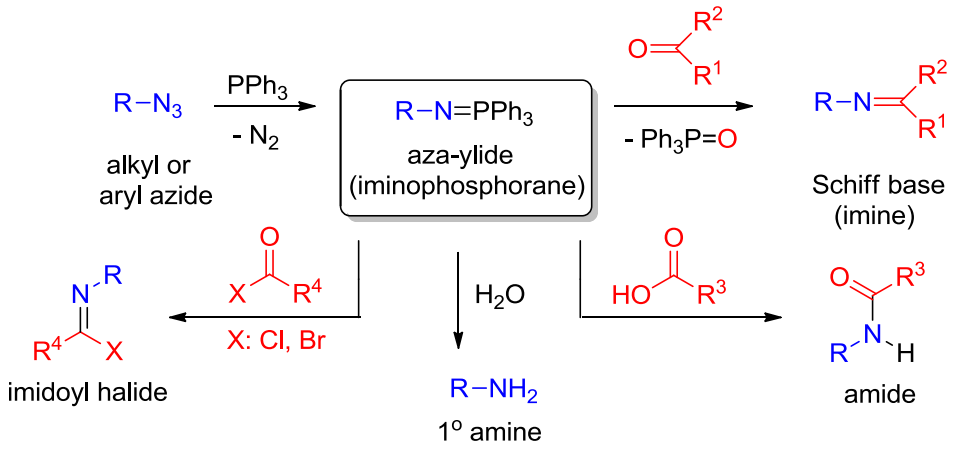
1. A bioorthogonal reaction must have no side reactions with biological functional groups, (eg. the reaction must be highly selective).
2. The reaction and the resulting linkage should not effect on the native chemical functionality of the biomolecule / organism under study.
3. The resulting bond must be stable biological reactions.
4. The reaction conditions should be non-toxic and must occur under biological conditions (pH = 6-8, aqueous environments and at moderate temperatures).

Bioorthogonal reactions must therefore occur in the presence of alkenes, amides, disulfides, esters, phosphodiesters, and other functional groups that can be found in biological macromolecules.

Some examples of bioorthogonal reactions are discussed below:

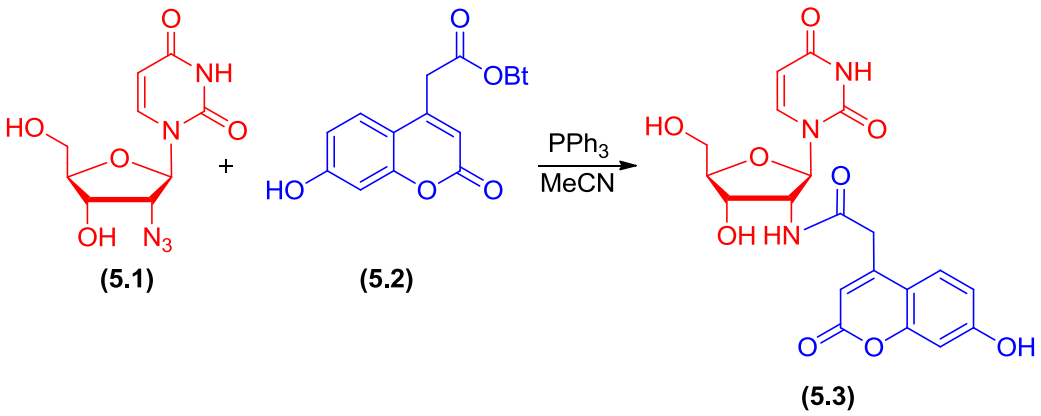
5.2: Staudinger reaction

Staudinger ligation or Staudinger reaction was the first bioorthogonal reaction ever performed in a living system.[78, 79] The reaction of azides with triarylphosphines to afford aza-ylide (iminophosphorane) was reported in 1919 by Staudinger and Meyer.[80, 81] The aza-ylide formed can react with **a)** carbonyl compounds to give Schiff bases (imine). **b)** water to form 1° amines. **c)** carboxylic acids to give *N*-substituted amides, or **d)** acyl halides to generate imydoyl halides (Scheme 5-1).



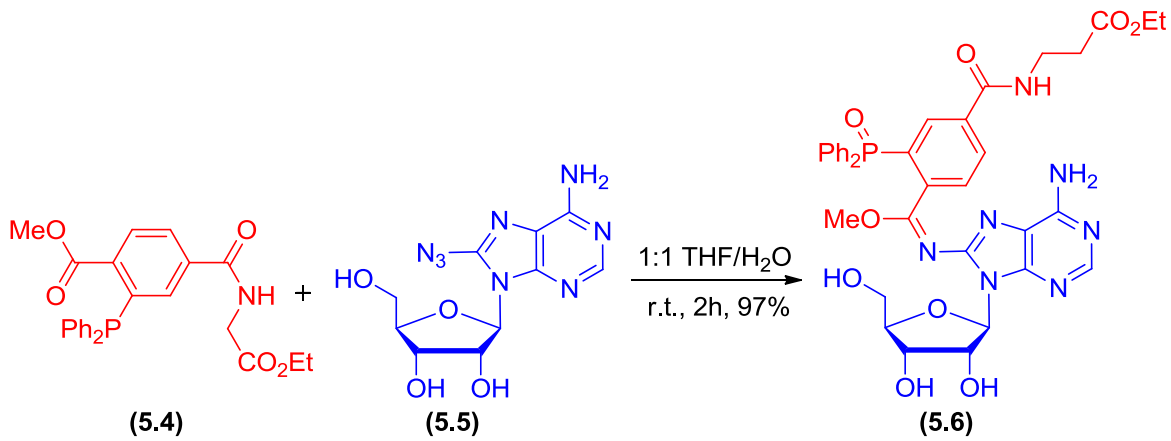
Scheme (5-1): Staudinger reaction between triarylphosphines and azides

The Staudinger reaction has been used in a wide range of applications in the field of chemical biology. For example, Staudinger ligation has been used as a general tool for nucleoside modification which is important for the study of key processes of cell metabolism. Kosiova *et al*. used coumarin to label nucleosides via a Staudinger ligation (Scheme 5-2). This gave fluorescent labelled nucleoside such as **5.3** which have potential application in the generation of labelled oligonucleosides. This reaction may afford some application to the construction of labeled oligomers enzyme assays.[78]



Scheme (5-2): Labelling of Nucleosides by coumarin via a Staudinger ligation

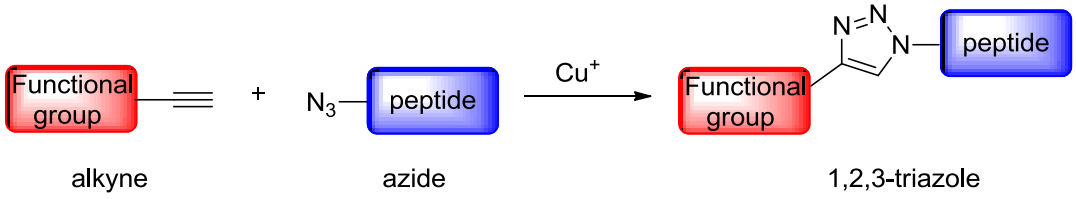
In other work Rajski showed that Staudinger ligation products can also be formed by an *O*-alkyl imidate linkages when *o*-carboalkoxy triarylphosphines react with aryl azides (Scheme 5-3).[83] This provides an alternative linkage to amide bond forming Staudinger ligations.



Scheme (5-3): Formation of *O*-alkyl imidate linkages

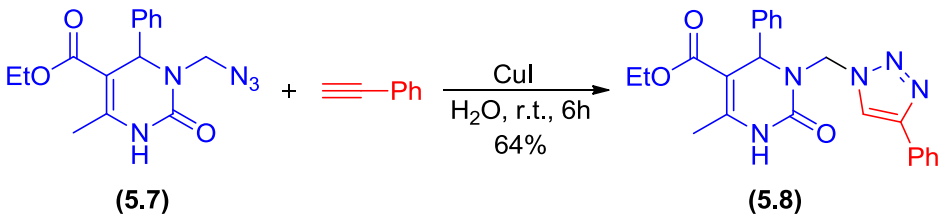
5.3: Cycloaddition reactions

The Azide-Alkyne Huisgen Cycloaddition (Scheme 5-4) is a reaction which can be catalyzed by copper (I) salts. The "copper-catalyzed azide alkyne cycloaddition" (CuAAC), is known as the "click" reaction and been used extensively in bioconjugation chemistry (Scheme 5-4).[84]



Scheme (5-4): Copper-catalyzed azide–alkyne cycloaddition (click chemistry)

For example, 1,3-dipolar cycloaddition between ethyl 3-(azidomethyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5.7**) and with phenylacetylene gave desired product of ethyl 6-methyl-2-oxo-4-phenyl-3-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5.8**) using water as the reaction medium in the presence of 10 mol % of CuI (Scheme 5.5).[84]



Scheme (5.5): 1,3-Dipolar cycloaddition between (**5.7**) and phenylacetylene

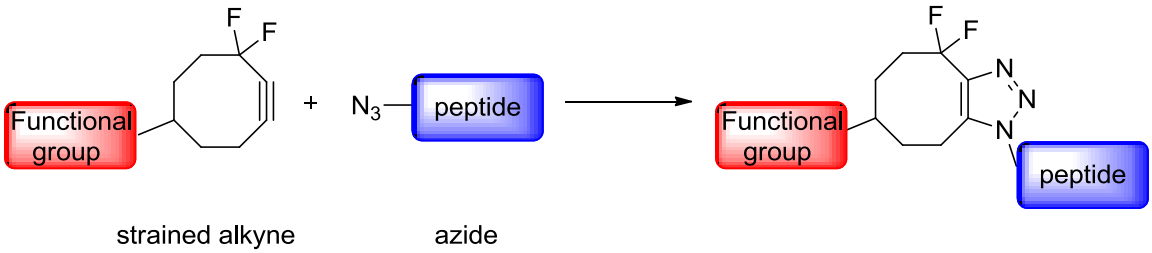
This reaction has attracted considerable interest due to 3,4-dihydropyrimidinones (DHPMs) which has interesting pharmacological properties. The DHPMs has been used as calcium channel modulator, antihypertensive and hepatitis B virus replication suppressor.[85] This reaction also give efficient approach for the one-pot regioselective synthesis including both 1,2,3-triazole rings in their structures and 3,4-dihydropyrimidinones / amides.

The CuAAC reaction is useful as it proceeds in aqueous solution. However the requirement for copper catalysis can limit the reaction.

5.3.1: Copper-Free Click Reaction

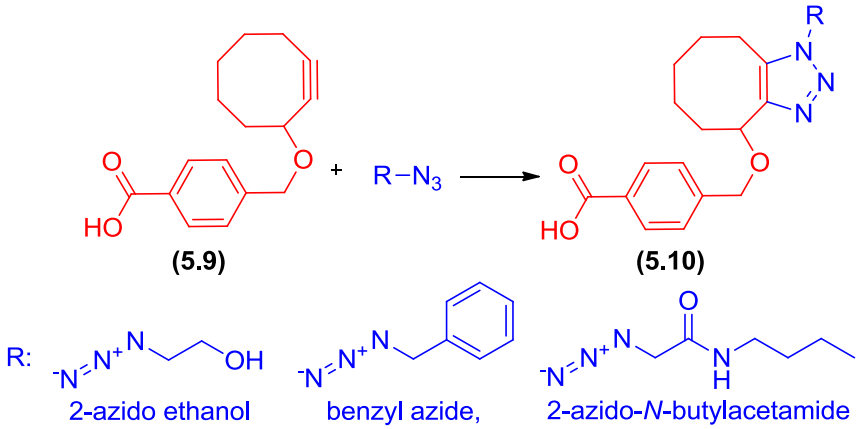
The CuAAC reaction is a fast and effective reaction for bioconjugation. But it is not appropriate for use in very complex systems such as live cells due to the toxicity of Cu (I).[86]

Metal-free azide-alkyne cycloaddition reactions have been developed to avoid this problem.[87] Based on the earlier work of Wittig and Krebs, Bertozzi and co-workers have reported the use of ring strained cyclooctynes to allow copper free click reactions (Scheme 5-6).[88-95]



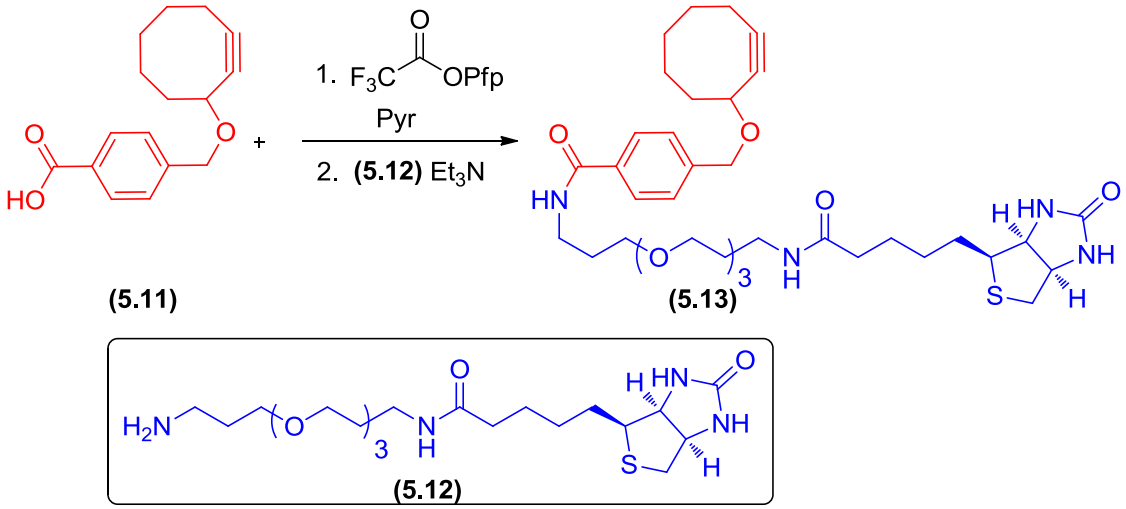
Scheme (5-6): Metal-free azide-alkyne cycloaddition reactions

Agard *et al.* performed model reactions with 4-((cyclooct-2-yn-1-yloxy)methyl)benzoic acid (**5.9**) and 2-azidoethanol, benzyl azide or *N*-butyl-α-azidoacetamide. They found triazoles products in all cases (Scheme 5.7).[96]



Scheme (5-7): Copper-Free Click Reactions

Agard *et al* next applied the reaction for covalent labeling of biomolecules. They synthesized biotinylated cyclooctyne (*N*-(3-(2-(2-(3-aminopropoxy)ethoxy)ethoxy)propyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanamide)(**5.13**) (Scheme 5-8).



Scheme (5.8): Syntheses of biotinylated cyclooctyne (**5.13**)

The biotinylated cyclooctyne (**5.13**) was then applied in the isolation and purification of azide-modified proteins. For example, azide-modified glycoprotein GlyCAM-Ig samples were reacted with biotinylated cyclooctyne (**5.13**).The product was then purified from the unmodified proteins by using an avidin column strategy.[96]

5.4: Functionalization of nature amino acids

The Staudinger ligation and copper-free click reaction are both powerful tools for bioconjugation. However both rely on the introduction of "artificial" azide or alkyne functional groups to a biomolecules. To functionalize a native protein, natural amino acids must be used.

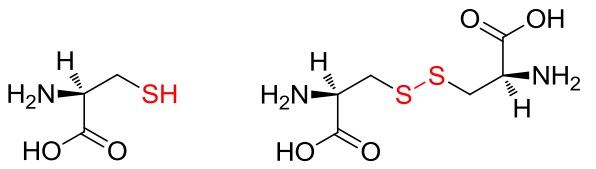
Despite the presence of more than 20 different amino acids and composition of most protein structures, there is only a small number of amino acid functional groups which can be used as a target for practical bioconjugation methods of native proteins.[97, 98]

Table 5-1: Popular crosslinker reactive groups for protein conjugation

Reactivity Class	Chemical Group
Carboxyl-to-amine reactive groups	Carbodiimide (e.g., EDC)
Amine-reactive groups	NHS ester Imidoester Pentafluorophenyl ester Hydroxymethyl phosphine
Sulfhydryl-reactive groups	Maleimide Haloacetyl (Bromo- or Iodo-) Pyridyldisulfide Thiosulfonate Vinylsulfone
Aldehyde-reactive groups i.e., oxidized sugars (carbonyls)	Hydrazide Alkoxyamine
Photoreactive groups i.e., nonselective, random insertion	Diazirine Aryl Azide
Hydroxyl (nonaqueous)-reactive groups	Isocyanate

5.4.1: Thiols (–SH)

The reactive group (–SH) exists in the side chain of the amino acid cysteine (Cys, C). The thiol is disposed to oxidization to form the disulfide (-S-S-) bonds between cysteines. To make disulfide available for bioconjugation, the disulfide must often be reduced to the thiol (Scheme 5-9).



(5.14)
cysteine

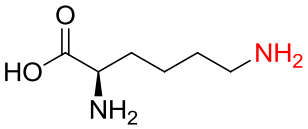
(5.15)
disulfide bridged cysteines

Scheme (5-9): Cysteine and two cysteines bound together by a disulfide bond.

Thiols are soft nucleophiles so can be used in selective bioconjugation reactions. For example, the cysteine can be deprotonated under basic condition to react with soft electrophiles, such as maleimides and iodoacetamides to form carbon-sulfur bond.

5.4.2: Primary amines ($-NH_2$):

The *N*-terminus of a polypeptide chain (called the α-amine) and the side-chains of lysine (Lys, K) amino acids (called the ε-amine) all have primary amine (Scheme 5-10). At physiologic pH; these primary amines are positively charged, therefore they occur mainly on the surface of a native protein. The nucleophilicity of a primary amine makes it a good target for bioconjugation.



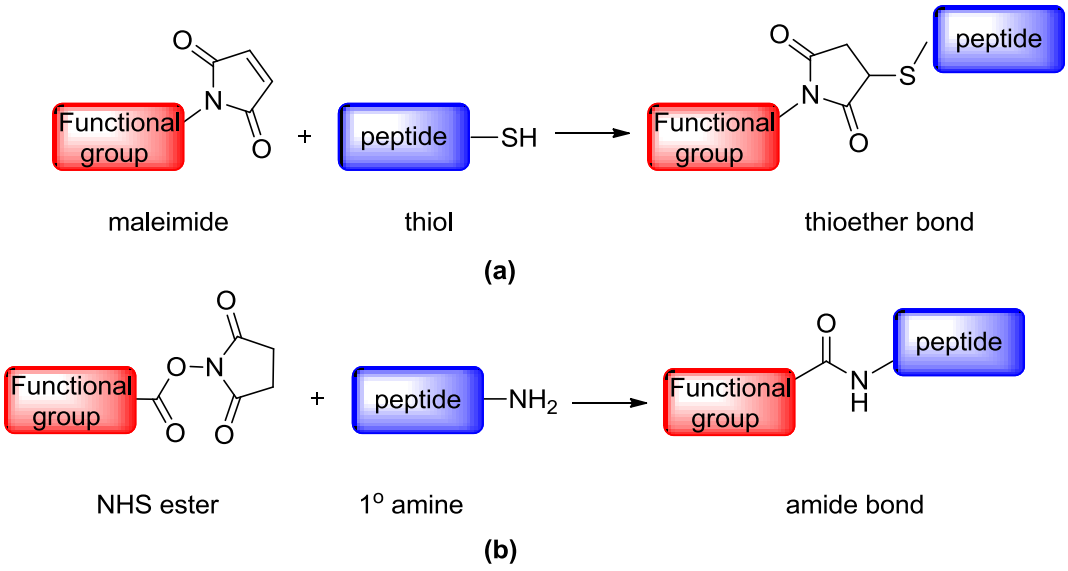
(5.16)

Scheme (5-10): Chemical structure of Lysine

5.5: Bioconjugation reactions of amino acids

5.5.1: Crosslinker Reactive Groups

A number of reactions have been developed to selectively react with common biologically available functional groups. In particular functionalization of proteins by modification of amino acid side chains containing amines or thiols has become common (Scheme 5-11).[99]



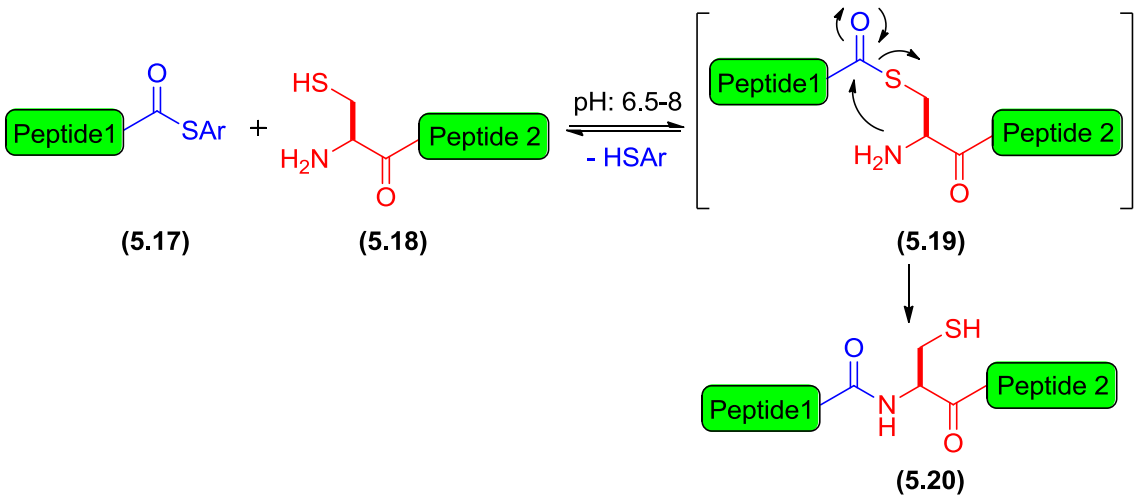
Scheme (5-11): Common bioconjugation reactions of thiol and amine

Maleimides have been used in the selective modification of thiols (cysteine) by Michael addition whilst NHS esters (*N*-hydroxysuccinimide esters) have been used to selectively functionalize primary amines (*N*-terminus, lysines, etc).

5.6: Native Chemical Ligation (NCL)

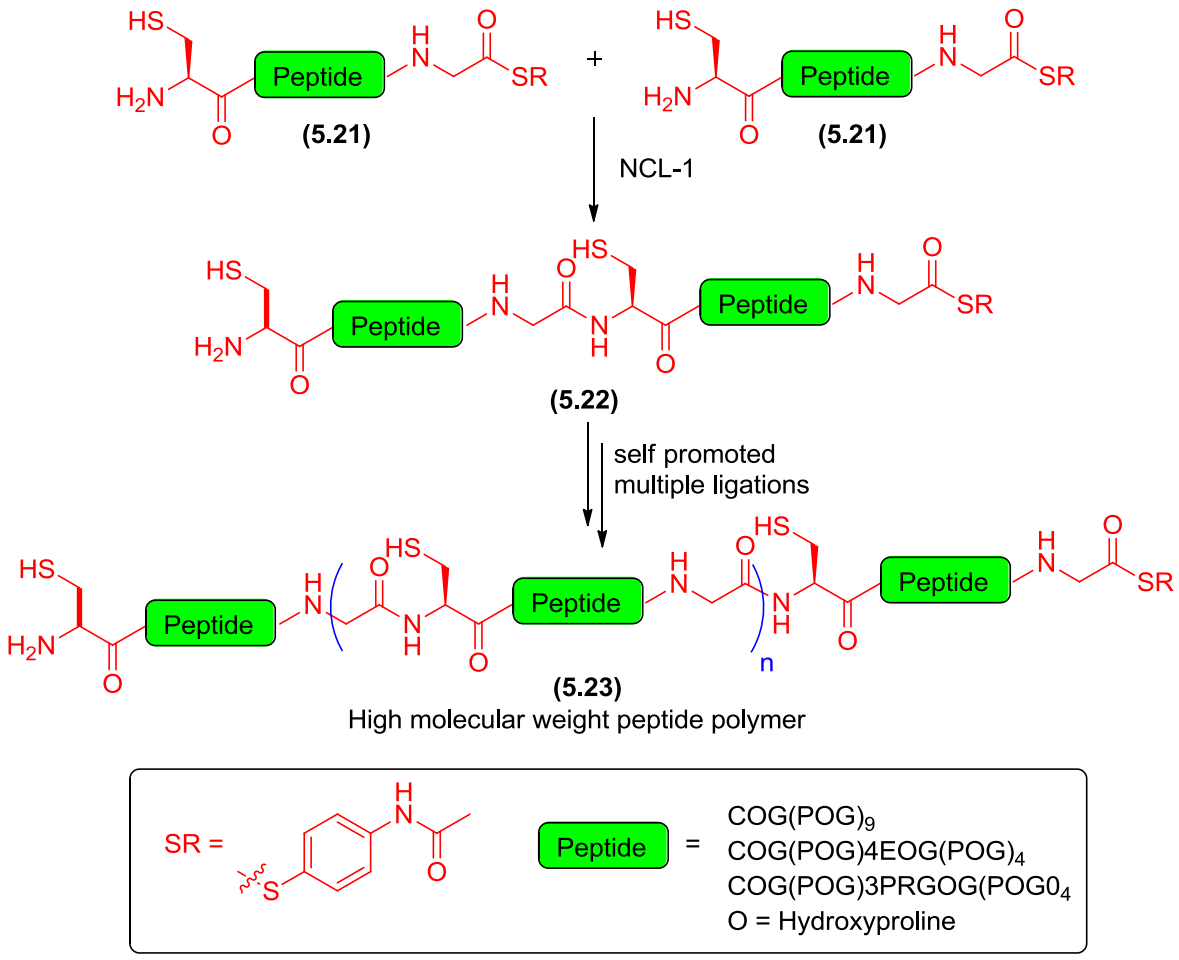
In addition to the functionisation of amino acid side chains, native chemical ligation (NCL) has become a widely used technique for the merger of two peptide fragments: one of them a peptide *C*-terminal thioester and the other an *N*-terminal cysteine residue.[100, 101]

The NCL proceeds through an initial trans-thioesterification between the thioester as the electrophile and the terminal cysteine as the nucleophile to form intermediate (**5.19**). Then an intramolecular acyl transfer occurs before giving the final amide bond (Scheme 5-12).[102, 103]



Scheme (5-12): Native Chemical Ligation (NCL) involves initial formation of thio ester intermediate

NCL has been used in peptide synthesis, for example in the production of high molecular weight collagen by Paramonov *et al* (Scheme 5-13).[104-107]



Scheme (5-13): Production of high molecular weight collagen

5.7: Cleavable bioconjugates

Often after bioconjugation and utilization of the bioconjugate of a protein, it is useful to remove the bioconjugated group prior to further experiments (eg. Mass spectrometry analysis). Therefore a useful feature of a bioconjugation reagent is the ability to remove the added group at a later stage. A number for strategies of releasing biotin bioconjugates have been used in combination with applications in affinity purification and MS analysis.

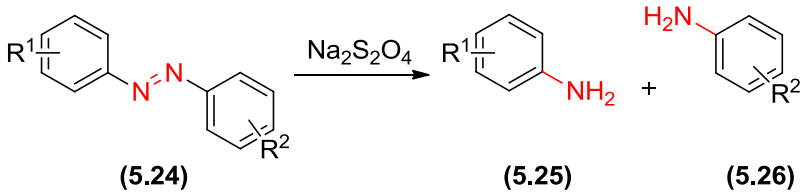
Example cleavable linkers include: diazobenzenes cleaved by sodium dithionite,[99] linkages cleavable via photolysis,[108] vicinal diols cleaved by sodium periodate,[109] acid cleavable hydrazones,[110] disulfide bonds cleaved by 1,4-dimercaptobutane-2,3-diol (DTT),[111] silyl ethers cleaved by fluoride,[112] acid cleavable dimethylmaleic anhydrides,[113] hydrazine cleaved levulinoyl esters [114] and enzymatically cleavable amide linkages.[115] However all of these methods leave residual atoms of the linker attached to the protein. This can make the process of subsequent characterization or utilization of a proteins more complicated.

We will discuss the chemical characteristics and the respective cleavage conditions for common cleavable bioconjugates below:

5.7.1: Diazobenzene linker

The diazene or diimide (HN=NH) is a simplest form of azo compounds. Both hydrogens can be replaced by either aryl or alkyl group to give diazene derivatives (R-N=N-R'). The more stable derivatives of azo compounds contain two aryl groups (PhN=NPh, azobenzene or diphenyldiazene).

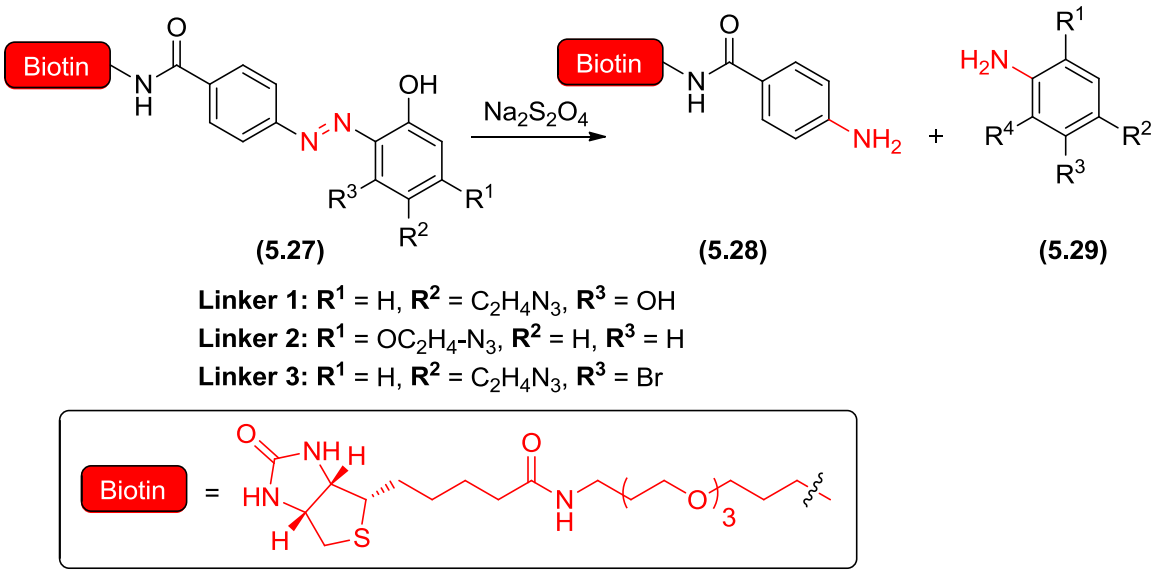
The azobenzene has been used in bioorthogonal chemistry due to the stability of this group and is efficiently cleaved by sodium dithionite ($Na_2S_2O_4$) (Scheme 5-14).[116-119]



(5.24) **(5.25)** **(5.26)**

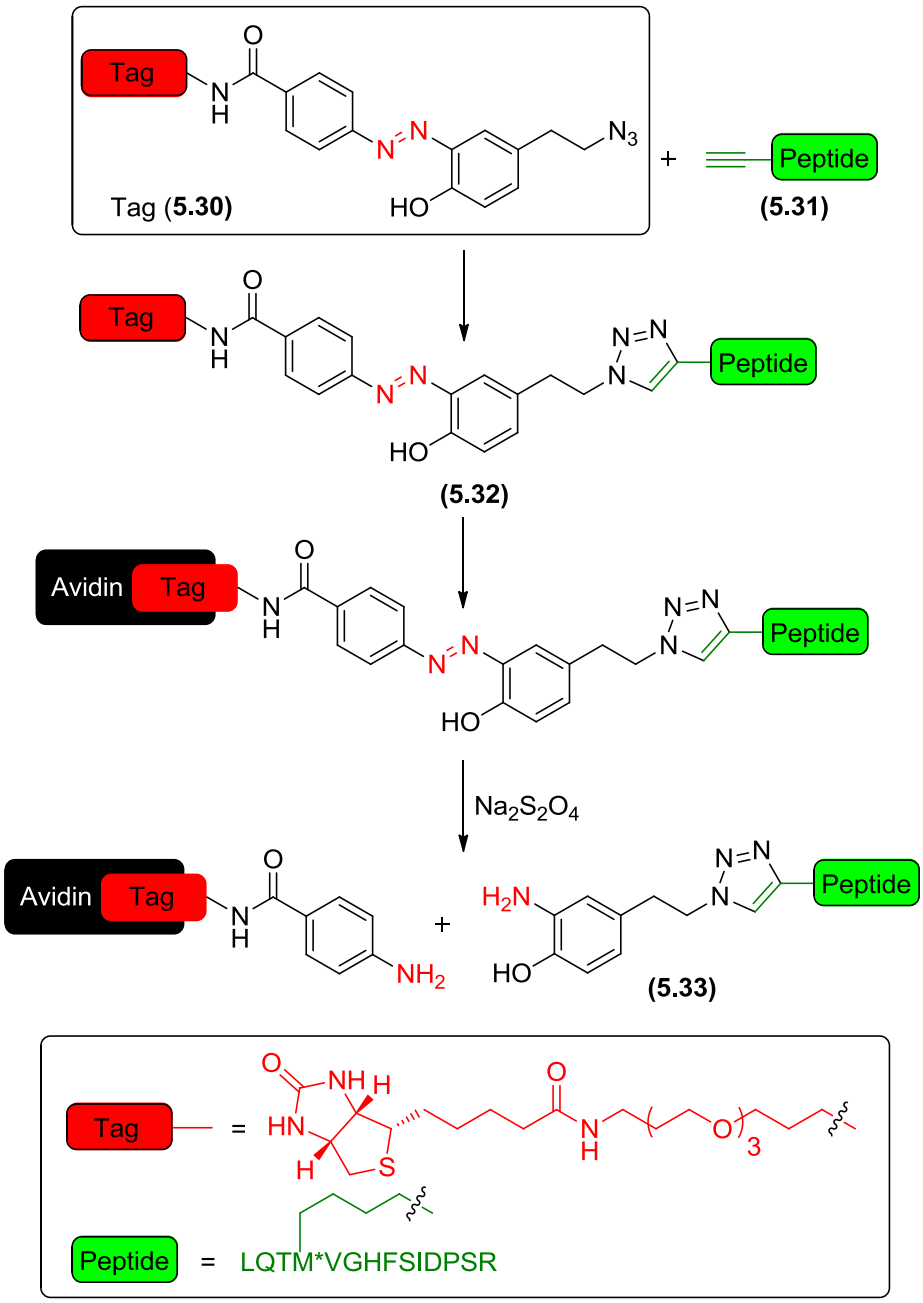
Scheme (5-14): Cleavage of azobenzene by sodium dithionite

Hang and coworkers studied the $Na_2S_2O_4$ cleavage efficiencies of diazobenzene affinity tags to determine discrepancies in their reactivity. They determined that the *ortho*-hydroxyl group of the azobenzene moiety was a key factor for $Na_2S_2O_4$ cleavage, and it is essential for efficient azobenzene cleavage (Scheme 5-15).[99]



Scheme (5-15): Cleavage of azobenzene by sodium dithionite

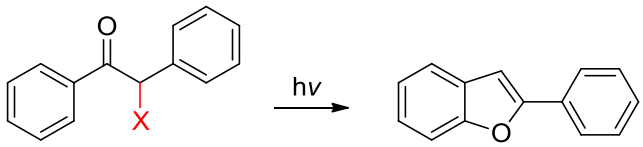
Using this approach, Hang and coworkers developed a biotin tag molecule containing a cleavable azobenzene group to purify proteins by using catch and release biotin-avidin affinity strategy. They examined elution of 2-amino-octynoic acid (AOA)-labeled proteins, which were clicked to biotin tag **(5.30)**. The resulting peptide mixtures were then purified with streptavidin. After treatment with $Na_2S_2O_4$, the peptide was released allowing analysis by LC-MS/MS (Scheme 5-16).[99]



Scheme (5-16): Cleavage of the diazobenzene linker to efficiently release purified proteins

5.7.2: Photolyticslly cleavable

An interesting behavior of benzoin esters and other desyl systems upon irradiation has been reported by Sheehan *et al.*[120] They found that the irradiation of benzoin chloride, tosylate and acetate (**5.34**) give 2-phenylbenzofurane (**5.35**) (Scheme 5-17).



(5.34)

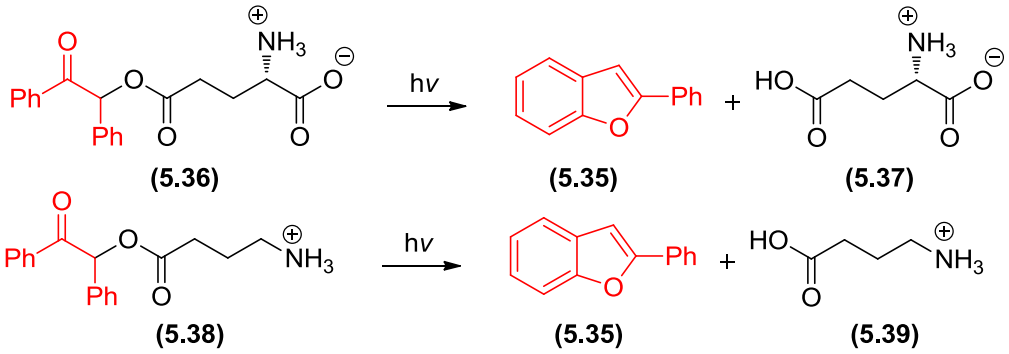
X = OTos, Cl, OAc

(5.35)

Scheme (5.17): Synthesis of 2-phenylbenzofurane (**5.35**)

Over the last years substituted and unsubstituted benzoin and its derivatives became commonly used photoremovable protecting groups.

Gee *et al*. has shown that the glutamic and γ-aminobutyric acid can be photo released from a benzoin protecting group (Scheme 5-18).[121-123]

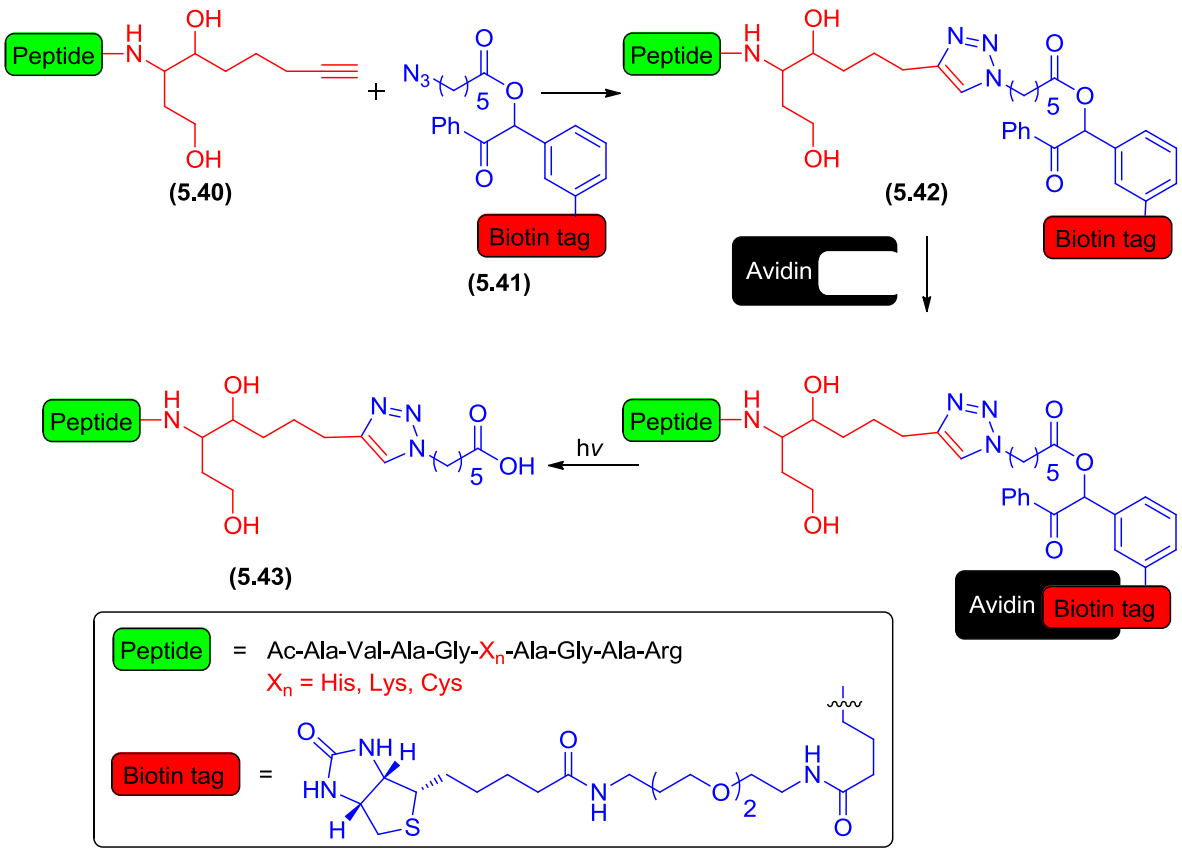


(5.36) (5.35) (5.37)

(5.38) (5.35) (5.39)

Scheme (5-18): Synthesis of 2-phenylbenzofurane (**5.35**)

Kim and coworkers [108] have been developed a photocleavable benzoin reagent that has both azido and biotin groups (**5.41**) for the isolation of proteins or peptides by a streptavidin catch and photorelease strategy (Scheme 5-19).

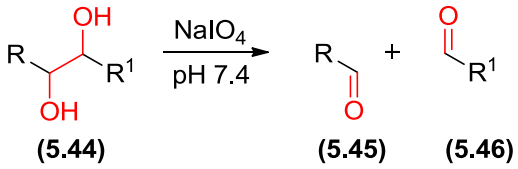


Scheme (5-19): Photolysis of the biotinylation peptides on the streptavidin with a low UV light

Peptides or proteins modified by alkynyl-4-hydroxy-2-nonenal (*a*HNE)(**5.40**) reacted with photocleavable reagent (**5.41**) by click cycloaddition. The modified peptides or proteins were then purified on streptavidin beads. Photolysis of the biotinylation peptides or proteins on the streptavidin with a low UV light releases proteins or peptides allowing purification for analysis (Scheme 5-19).[108]

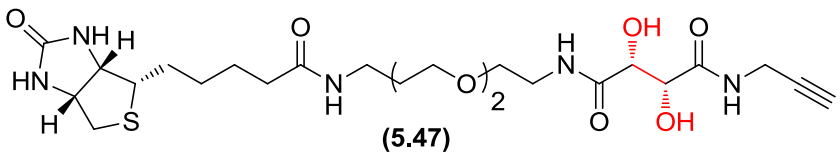
5.7.3: Cleavage of glycols

The carbon-carbon bond between the glycol protein is stable under a wide variety of conditions and can be cleavage efficiently when treated with sodium periodate ($NaIO_4$) at physiological pH. The $NaIO_4$ oxidized the vicinal diols to an aldehyde and cleaving the associated crosslinked molecules (Scheme 5-20).



Scheme (5-20): Cleavage of glycols by sodium periodate ($NaIO_4$)

A new chemical proteomics application of a vicinal diol cleavable linker has been used by Yang and co-workers.[109] The alternative linkers including a sterically hindered disulfide, diazobenzenes, hydrazones, silanes and light sensitive linkers can also be used, but the synthesis of some of these linkers is lengthy or difficult to scale up, which limits their general application in chemical proteomics. By insertion vicinal diol cleavable linker in an active probe and a biotin alkyne tag, the product (**5.47**) is amenable for bioorthogonal ligation.[109]



The biotin-modified terminal alkyne **5.47**, containing a cleavable diol linker, has been used to identified proteins and peptides using biotin/avidin strategy as before. For example, cathepsins (Z, B, C, H, S, J and L1) have been identified in rat liver lysate. It was shown that azide modified cathepsins can undergo click chemistry with alkyne biotin tag (**5.47**) then be purified on an avidin column. The pure cathepsins were released from the avidin column by $NaIO_4$.

5.7.4: Reduction of disulfide bond

A disulfide bond (SS-bond or disulfide bridge) is often the "weak link" in many molecules, it is usually resulting by the coupling of two thiol groups. The overall connectivity is therefore R–S–S–R.

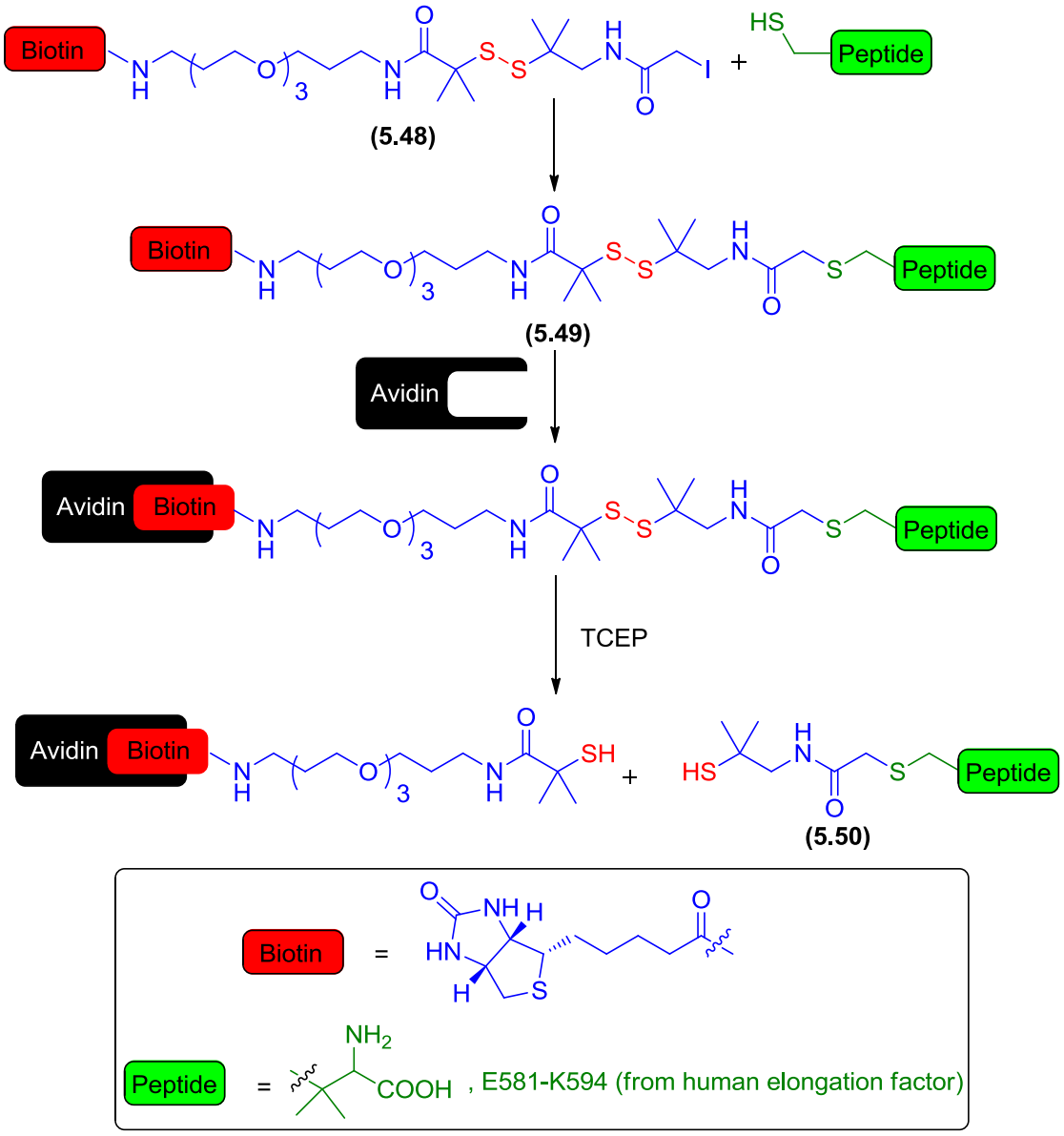
One of the most important things in the chemistry of disulfide bond is their cleavage by reduction. Many of reductants can be used, in biochemistry, dithiothreitol (DTT), mercaptoethanol (b-ME) and *tris*(2-carboxyethyl)phosphine (TCEP) have been used.

The TCEP is more useful reductant because it is selective and works under both alkaline and acidic conditions.[111]

A new reductively cleavable linker with chemical properties that make it ideal for use with isotope labeling protein quantification techniques has been described by Gartner and co-worker. They synthesized a biotin containing molecule that also contained disulfide linker (**2.49**) for use as labeling agent to isolate and purify cysteine containing peptides.

During alkylation of sample cysteines, the hindered disulfide moiety in **5.49** is completely stable to most reductants, but is readily cleaved with phosphine reductants.

Bioconjugates which include a disulfide bond can therefore be cleaved under reducing conditions to give two terminal thiols such as **5.50** (Scheme 5-21).[111]



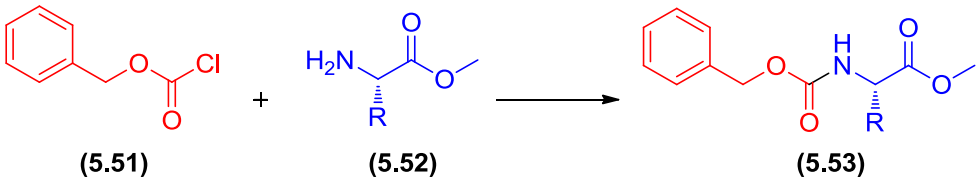
Scheme (5-21): Thiol reducing agent for cleaving protein disulfide bonds

After labeling protein cysteine residues with biotin tag (**5.49**), samples are fractionated and trypsinized. Avidin used to capture of biotinylated peptides, removed of impurities and followed by elution of target directly from the avidin by reduction with TCEP or DDT.

5.7.5: Acid cleavable dimethylmaleic anhydrides

The acid cleavable linker is one of the novel strategies that is used in the protein identification and quantification.[113]

In organic synthesis, carboxybenzyl (Cbz) is commonly used as an amine protecting group by reacting the amine functionality (**5.52**) with benzyl chloroformate (**5.51**) in the presence of a weak base (Scheme 5-22).[113]

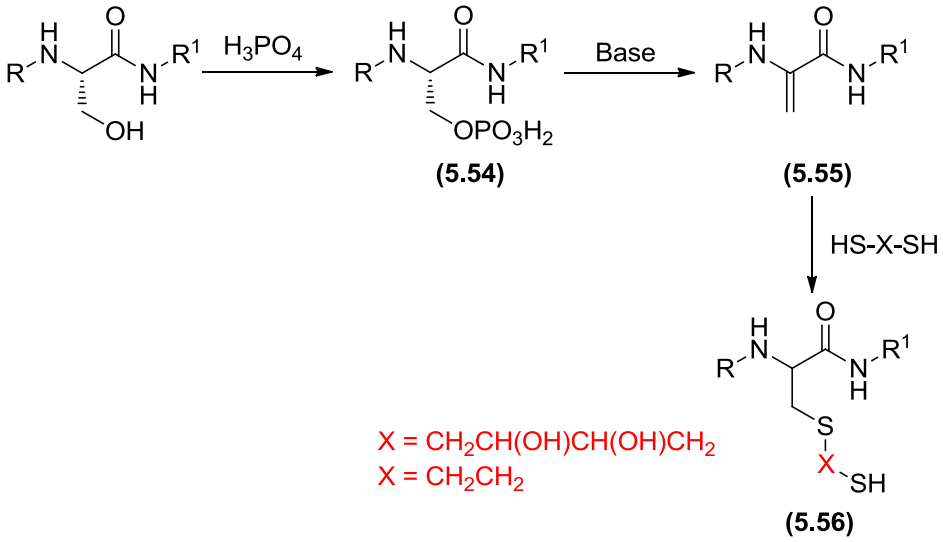


(5.51) **(5.52)** **(5.53)**

Scheme (5-22)

The Cbz protected amines can be cleaved by using catalytic hydrogenation or acidolysis (protic acid or Lewis acid and allows selective deprotection) to give terminal carbamic acid that then easy decarboxylates to yield the free amine.

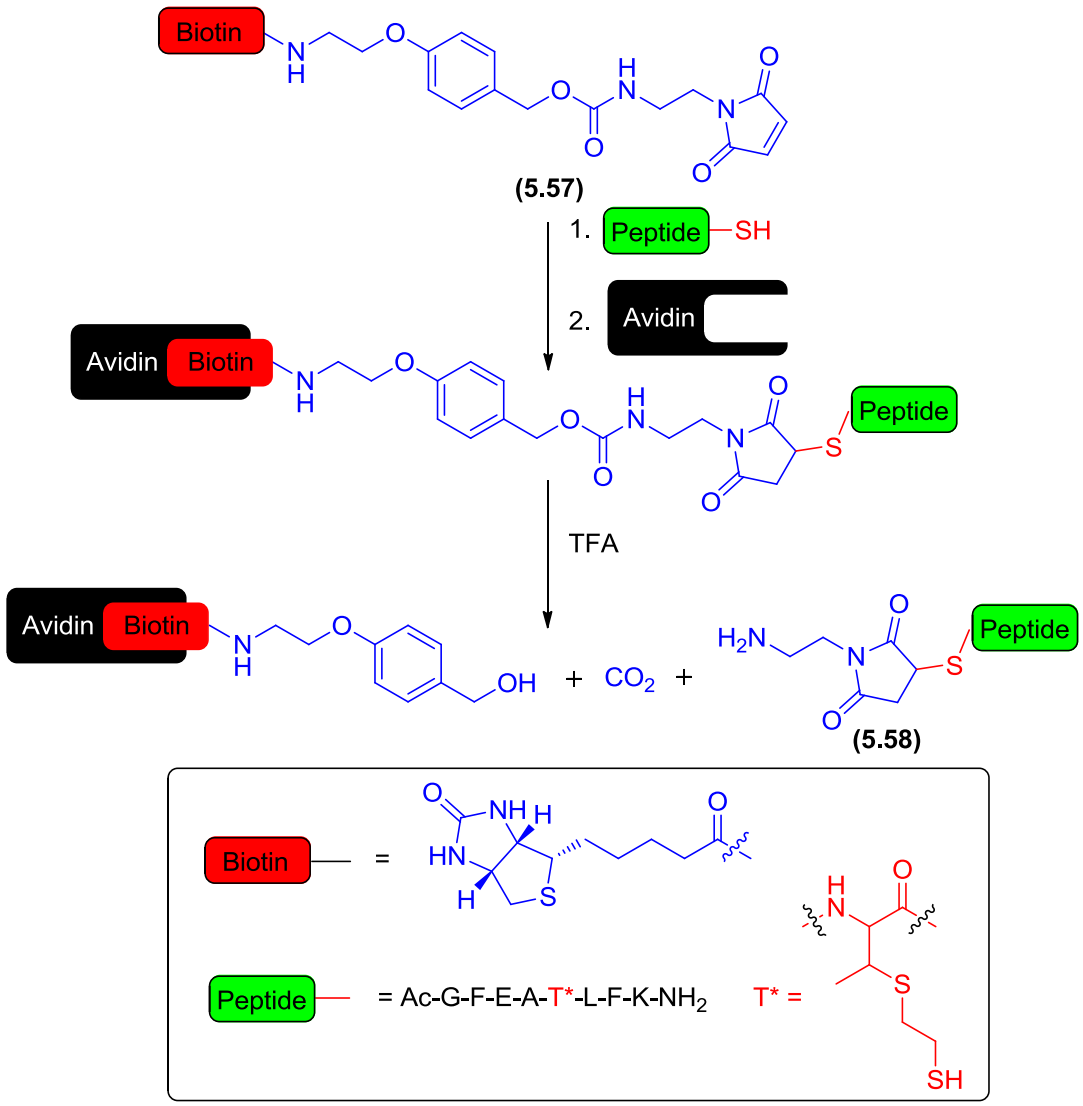
Veken *et al* developed [124] a new chemical probe containing an acid cleavable (Cbz) linker (**5.57**) to isolate, purify and sequence proteins. This strategy involves phosphorylating serine or threonine residues in the peptides or proteins then labeling with a dithiol followed by reaction with cleavable (Cbz) linker (**5.57**) (Scheme 5-24).



(5.54) **(5.55)** **(5.56)**

Scheme (5.23): Base induced β–elimination followed by Michael addition of an SH-containing probe

The peptide was dissolved in MeOH and reacted with biotin tag (**5.54**). The mixture was incubated with avidin and the beads were then washed with buffer and treated with trifluoroacetic acid (TFA). After removal of TFA, the mixture was analyzed by MALDI-TOF mass spectrometry (Scheme 5-24).

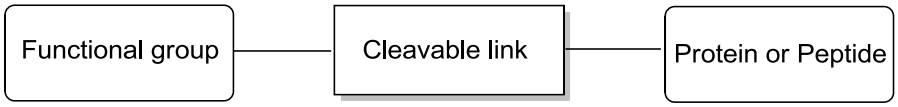


Scheme (5.24): Releasing peptide using an acid cleavable carboxybenzyl (Cbz) linker

5.8: Project plan

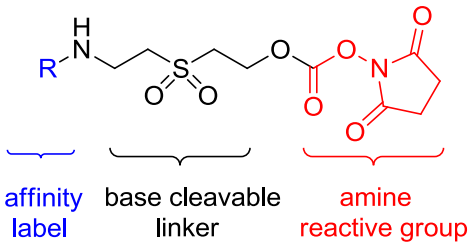
One of the major disadvantages of common removable bioconjugation molecules is that on cleavage they leave a modified peptide/protein.

The aim of this project is therefore to design and demonstrate molecules that can be bioconjugated to an active protein/polypeptide and subsequently undergo traceless removal under mild conditions to regenerate native peptide/proteins.



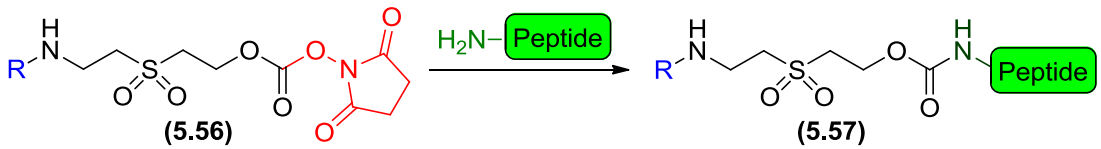
Scheme (5-25)

First of all, we will prepare a test molecule containing an NHS carbonate which can react with a primary amine (*N*-terminus or lysine) and which contains a sulfone which can be used to trigger a subsequent base catalyzed $E1_cB$ cleavage reaction. The proposed structure of our test compound is shown below (Scheme 5-26).



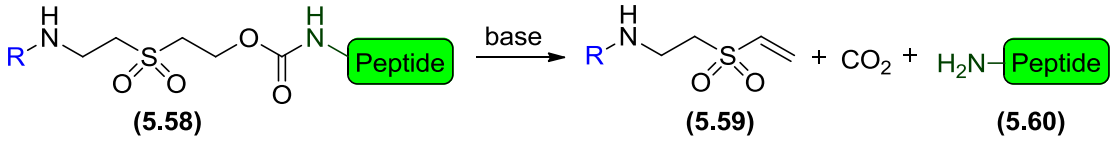
Scheme (5-26)

We plan to couple of our test molecule with a peptide/protein (Scheme 5-27).



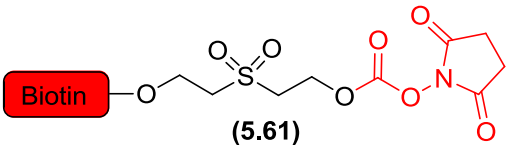
Scheme (5-27)

After successful coupling, we will test the base catalyzed $E1_{CB}$ reaction to show traceless removal of our bioconjugation tag (Scheme 5-28).



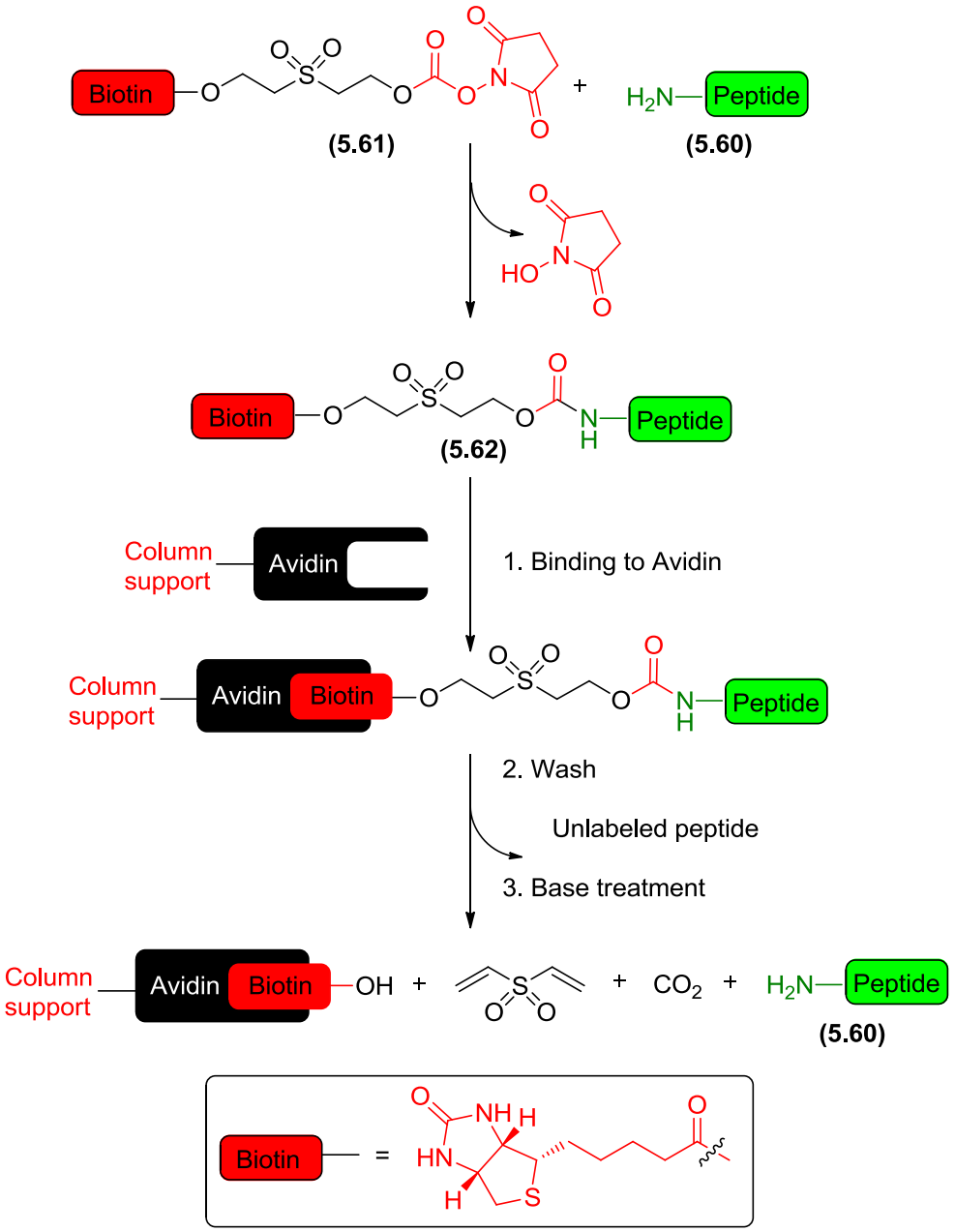
Scheme (5-28)

We then aim to design a similar NHS-carbonate, sulfonyl contain molecules with addition functionality e.g. a biotin. The inclusion of biotin group will allow the use of affinity chromatography to isolate any bioconjugated protein/peptides and cleavage as previously (Scheme 5-29).



Scheme (5-29)

Unmodified "natural" peptide/protein can then be recovered after washing by base cleavage from an avidin column (Scheme 5.30).

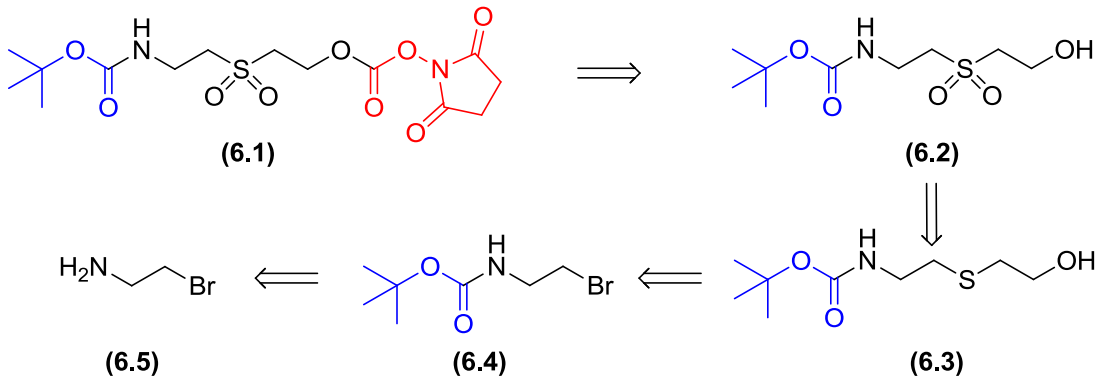


Scheme (5-30)

6.1: Introduction

In our design strategy, we endeavored to prepare a test molecule that has cleavable linker for bioconjugation. The test molecule should also demonstrate traceless removal under mild conditions to regenerate native peptide/proteins.

Our suggested test molecule was *tert*-butyl(2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl)carbamate (**6.1**). Test molecule **6.1** contains a NHS carbonate which can react with the *N*-terminus of a peptide or protein and a sulfone which can be used to trigger a subsequent base catalyzed $E1_{CB}$ cleavage reaction. Our planned retrosynthesis of our traceless cleavable linker **6.1** is shown in Scheme (6-1).

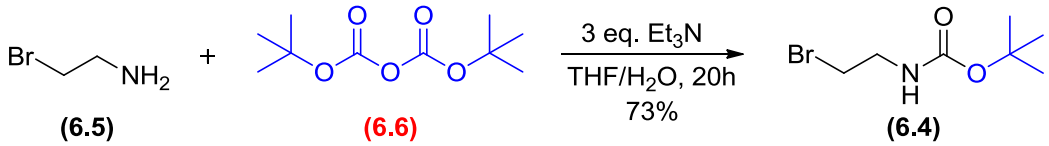


Scheme (6-1): Retrosynthesis of traceless cleavable linker **6.1**

The first step in our retro-synthesis is the formation of **6.1** through the reaction of hydroxyl functional group in **6.2** with bis(2,5-dioxopyrrolidin-1-yl) carbonate. **6.2** could then be formed by the oxidation of thio ether **(6.3)**. **6.3** would be formed by nucleophilic attack by 2-mercaptoethanol into *tert*-butyl (2- bromoethyl) carbamate **(6.4)**. Finally, **6.4** can be formed through a Boc protection of 2-bromoethylamine **(6.5)**.

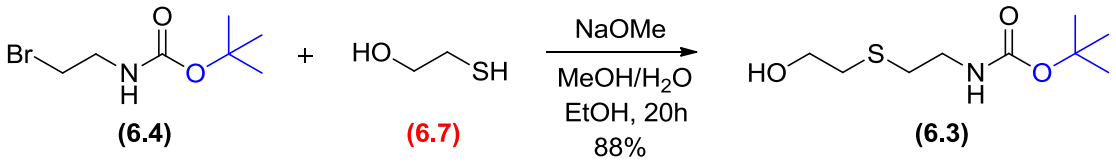
6.1.1: Synthesis of test cleavable linker (6.1)

In order to synthesize our model compound **6.1**, first we needed to form **6.4**. According to the literature,[125] we prepared **6.4** by reaction of 2-bromoethanamine with di-*tert*-butyl dicarbonate (**6.6**) in 74% yield. No purification was needed at this step and the product **6.4** was used directly in the next step (Scheme 6-2).



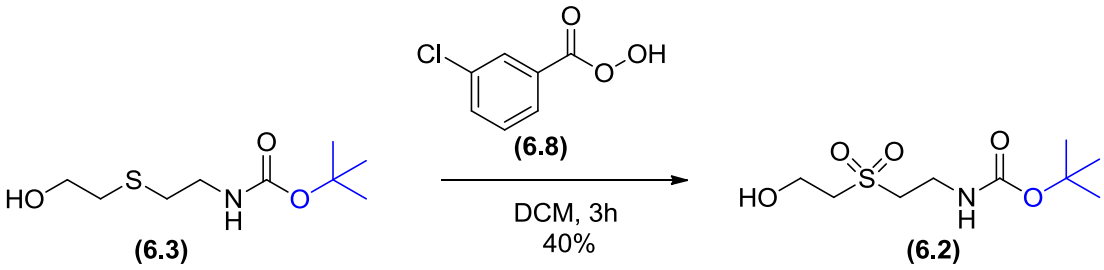
Scheme (6-2): Synthesis of **6.4**

The next step involved preparation of thio ether linker **(6.3)** through an S_N2 reaction. The base catalysed reaction of **6.4** with 2-mercaptoethanol (**6.7**) gave after purification by silica gel column chromatography an 88% yield of *tert*-Butyl (2-((2-hydroxyethyl)thio)ethyl)carbamate **(6.3)** (Scheme 6-3).



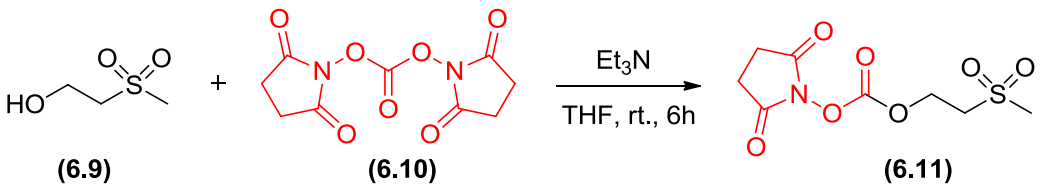
Scheme (6-3): Synthesis of **6.3**

To continue our plan, the *tert*-butyl (2-((2-hydroxyethyl)sulfonyl)ethyl)carbamate (**6.2**) was produced by oxidation of *tert*-butyl (2-((2-hydroxyethyl)thio)ethyl)carbamate **(6.3)** with 3-chlorobenzoperoxoic acid (mCPBA) (**6.8**). After 3h at room temperature in DCM the crude ^{1}H NMR spectrum showed that the yield was more than 95%. After column chromatography the isolated yield was 40% potentially due to loss on column.



Scheme (6-4): Synthesis of **6.2**

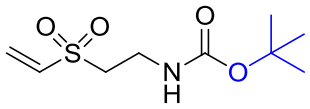
Lefrancois *et al.* has showed that the reaction of 2-(methylsulfonyl)ethanol (**6.9**) with *bis*(2,5-dioxopyrrolidin-1-yl) carbonate (**6.10**) in triethylamine (Et_3N) can give 2,5-dioxopyrrolidin-1-yl (2-(methylsulfonyl)ethyl) carbonate in good yield (**6.11**) (Scheme 6-5).
126



(6.9) (6.10) (6.11)

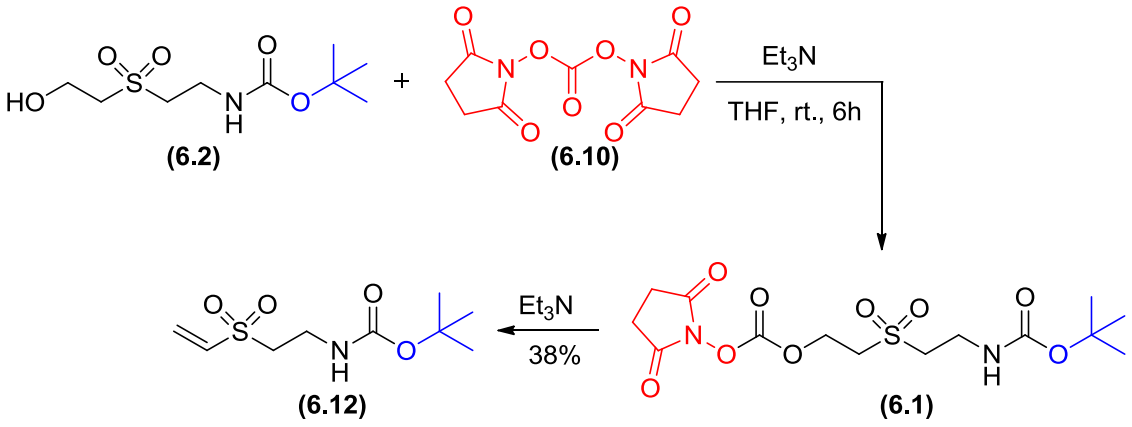
Scheme (6-5)

Therefore, we decided to follow the same procedure trying to prepare **6.1**. Based on this we reacted *bis*(2,5-dioxopyrrolidin-1-yl) carbonate (**6.10**) and *tert*-butyl (2-((2-hydroxyethyl)sulfonyl)ethyl)carbamate **(6.2)** using Et_3N as the base. However instead of observing our expected product (**6.1**), the crude ^1H NMR spectrum showed the formation of an unexpected product in high yield. After silica gel column chromatography we isolated *tert*-butyl (2-(vinylsulfonyl)ethyl)carbamate **(6.12)** in 38% yield**.**



(6.12)

We postulate that the **6.12** may be formed via the successful formation of **6.1**. However **6.1** then reacts with the Et_3N in the reaction by a $E1_CB$ mechanism to give **6.12** (Scheme 6-6).

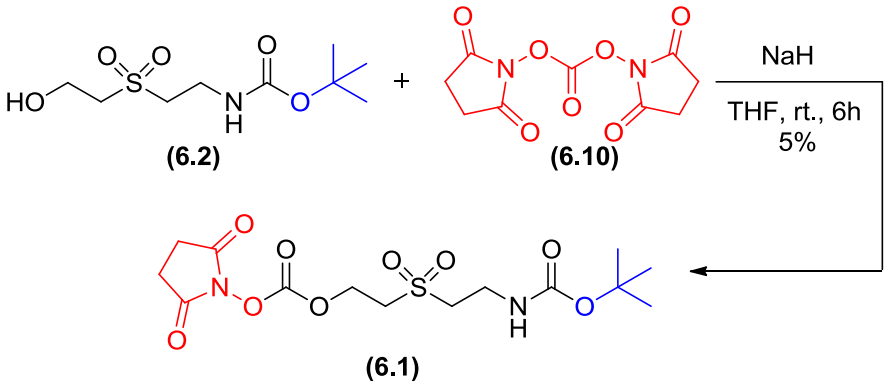


(6.2) (6.10) (6.12) (6.1)

Scheme (6-6): Formation of **6.12**

To avoid the use of Et_3N, we therefore decided to repeat the reaction in scheme **6-6** using an irreversible base such as NaH.

Therefore we used NaH as a base in the reaction of *bis*(2,5-dioxopyrrolidin-1-yl) carbonate (**6.10**) with *tert*-butyl (2-((2-hydroxyethyl)sulfonyl)ethyl)carbamate **(6.2)** (Scheme 6-7).



Scheme (6-7): Synthesis of **6.1**

Crude ^{1}H NMR spectroscopic analysis of the reaction showed that the desired product **6.1** was formed in more than 96% yield. However the product **6.1** decomposed when passed through silica gel and only a 5% yield was isolated. We decided the low yield was still sufficient for bioconjugation testing.

6.2: Bioconjugation and traceless cleavage of *tert*-butyl (2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl) sulfonyl) ethyl)carbamate (6.1) with test peptide (P.520)

After successful preparation and identification of our test molecules (**6.1**), we then moved to use **6.1** in the *N*-terminal labelling of test peptide P.520 peptide. We also want to study the stability of **6.1**/peptide bioconjugates and finally we want to know if **6.1**/peptide undergoes traceless cleavage in base solution.

The peptide used was (P.520). The amino acid sequence for this peptide is: HNDDVRNHAM. P.520 is a 10-er peptide with molecular mass (*m/z*) = 1208.5 $[M+H]^{+}$ / 604.8 $[M+2H]^{++}$. The peptide P.520 does not contain the amino acids lysine or cysteine as they could react with **6.1**. Therefore the P.520 peptide should only react from the terminal amino group.

Both test molecule (**6.1**) and peptide (P.520) have been purified by J. Gray prior to study by HPLC, giving peaks at 21.3 and 12.4 min respectively (Figure 6-1).

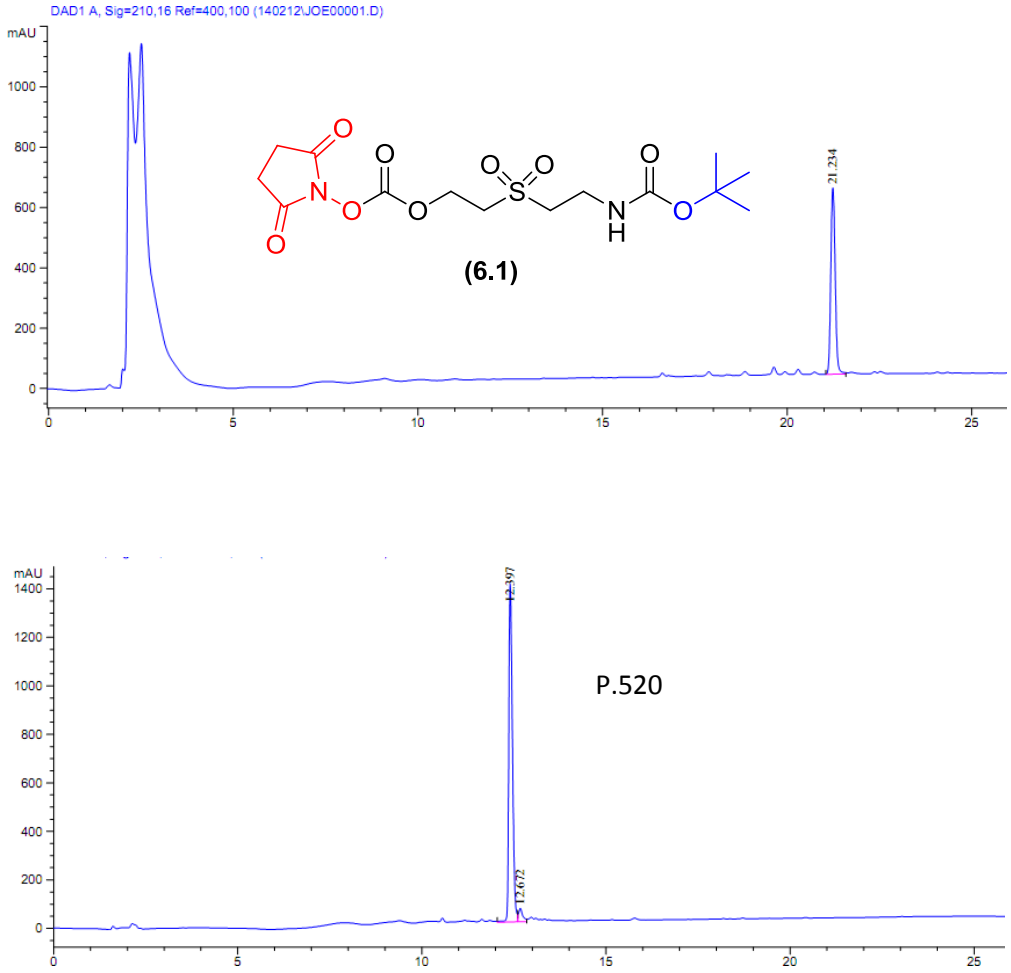


Figure (6-1): HPLC for **6.1** and **P.520**

Mass spectrometry confirmed the identity of both **6.1** and the test peptide (P.520) with masses of $[M+Na]^{+}$: 417.0930 and $[M+2H]^{++}$: 604.7644 respectively.

The peptide (P520) was then reacted with our test molecule (**6.1**) in 50% CAN/50mM TRIS buffer overnight at pH 7.4. HPLC analysis of the reaction showed two peaks, one at 12 and one at 16 minutes.

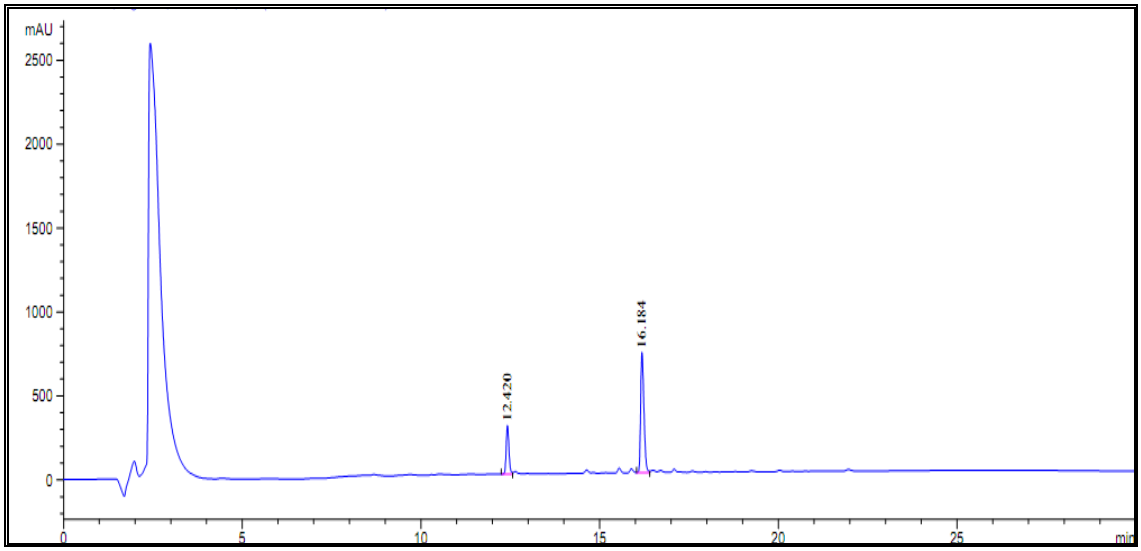


Figure (6-2): HPLC of P.520/**6.1** bioconjugate crude

Both HPLC peaks were collected and analyzed by MS. MS analysis showed that the first peak (12 min) is the unmodified peptide (P.520) whilst the second peak (16 min) is the P.520/**6.1** bioconjugate.

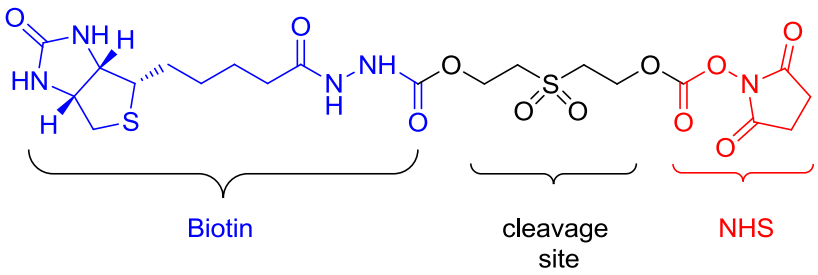
The P.520/**6.1** bioconjugate was treated with aqueous ammonia (15% / 10 min). HPLC gave a single peak at 12 min. that co-elutes with unmodified P520. Analysis by MS confirmed that the peak matched unmodified P520.

6.3: Synthesis of Biotin containing cleavable linkers

6.3.1: Introduction

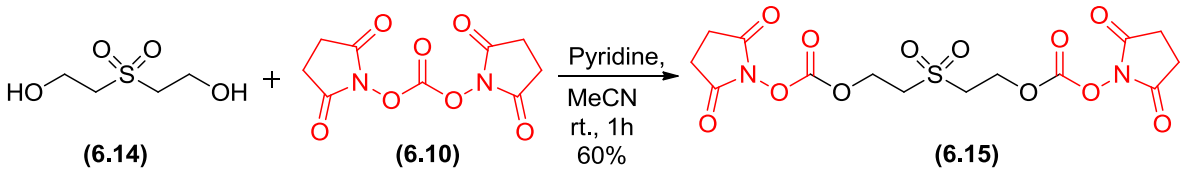
The next step involves the synthesis of biotin containing cleavable linkers for bioconjugate reactions depend on the same chemistry that we did with the test molecule (**6.1**). The biotin containing cleavable linkers that we want to prepare will contain biotin for avidin purification, a base cleavable linker (sulfonyldiethanol) and an amine reactive group (*N*-hydroxysuccinimide (NHS)).

Therefore, we designed 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoyl)hydrazinecarboxylate (**6.13**) that could be used for modifying and isolation of the peptides or proteins molecules



(6.13)

To prepare **6.13**, we first synthesized bis(2,5-dioxopyrrolidin-1-yl) (sulfonylbis(ethane-2,1-diyl)) dicarbonate **(6.15)** by reaction of 2,2'-sulfonyldiethanol (**6.14**) with bis(2,5-dioxopyrrolidin-1-yl) carbonate (**6.10**) (Scheme 6-8).



(6.14) **(6.10)** **(6.15)**

Scheme (6-8): Synthesis of **6.15**

Quenching the reaction with H_2O gave >60% yield of **6.15** (^{1}H NMR yield). However purification of **6.15** by silica gel column chromatography caused decomposition. Also **6.15** decomposed when left under vacuum for 24h.

It is suggested that the difficulty in purifying **6.15** is due to the hydrolysis or elimination by the pyridine. Therefore we decided to use a weak acid in the work up. We found that quenching the reaction between 2,2'-sulfonyldiethanol (**6.14**) and bis(2,5-dioxopyrrolidin-1-yl) carbonate (**6.10**) with ammonium chloride (NH_4Cl) gave a stable, white powder in very good yield.

The ^{1}H NMR spectrum of bis(2,5-dioxopyrrolidin-1-yl) (sulfonylbis(ethane-2,1-diyl)) dicarbonate **(6.15)** showed triplet peak at 4.6 and 3.7 ppm for aliphatic CH_2, and single peak at 2.7 ppm for succinimide protons. We can see also some impurities in the spectrum at 7.6 and 7.4 ppm for pyridine protons and at 2.6 ppm for bis(2,5-dioxopyrrolidin-1-yl) carbonate (**6.10**) (Figure 6-3a). Whilst the ^{1}H NMR spectrum of the white powder gave exactly the same peaks of **6.15** with no impurities. However the ^{1}H NMR spectrum of this powder showing the triplet peaks of NH_4^+ and weak doublet at 7.35 ppm (coupling of the

^{1}H of natural abundance NH_4Cl to ^{14}N as a spin 1 triplet and coupling to ^{15}N as a weak doublet) (Figure 6-3b).

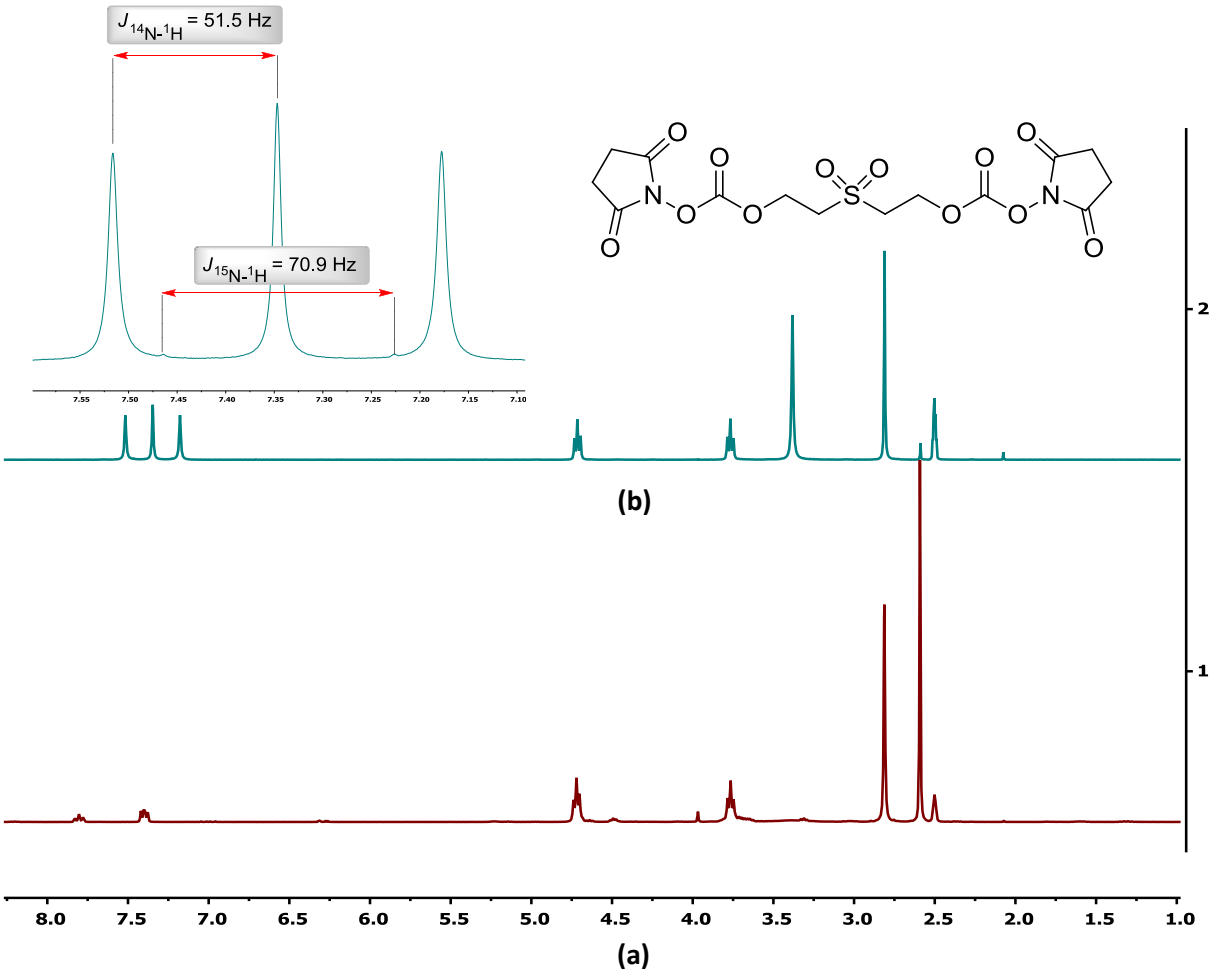
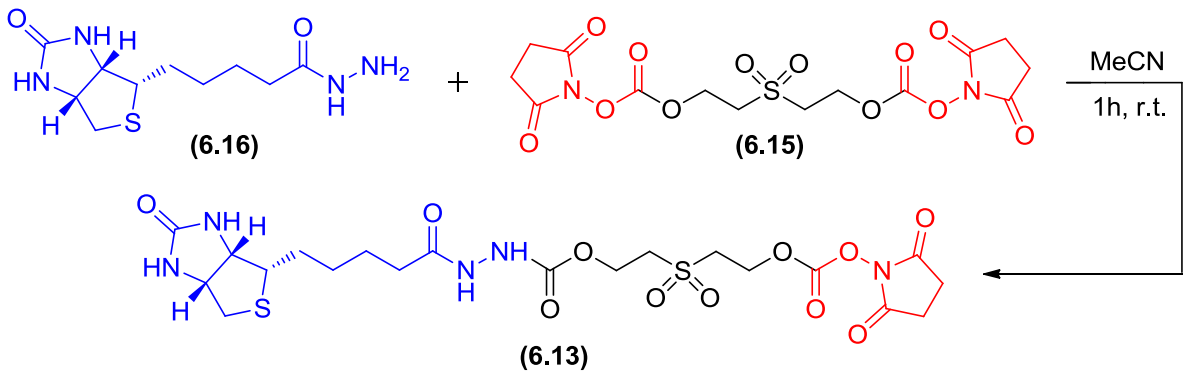


Figure (6-3): The ^{1}H NMR spectrums of **6.15** a: **6.15** crude b: **6.15** with NH_4Cl

The next and final step involved preparation of 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoyl)hydrazine carboxylate (**6.13**) by the reaction of 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanehydrazide (**6.16**) with (**6.15**) as shown in Scheme (6-9).



Scheme (6-9): Synthesis of **6.13**

No product of **6.13** was observed for this reaction when we used bis(2,5-dioxopyrrolidin-1-yl) (sulfonylbis(ethane-2,1-diyl)) dicarbonate **(6.15)** purified by NH_4Cl precipitation. The NH_4Cl may cause decreasing in nucleophilicity of **6.16**. Nevertheless **6.13** was obtained when we used the crude of **6.15** which is not purified by NH_4Cl precipitation.

Unfortunately, we could not purify **6.13** by silica gel column chromatography, however the mass of **6.13** was confirmed by mass spectrometry (HRMS (ES^+)) $[M+Na]^+$ calcd for $C_{20}H_{29}N_5O_{11}S_2$: 602.1203; observed: 602.1232.) (Figure 6-4).

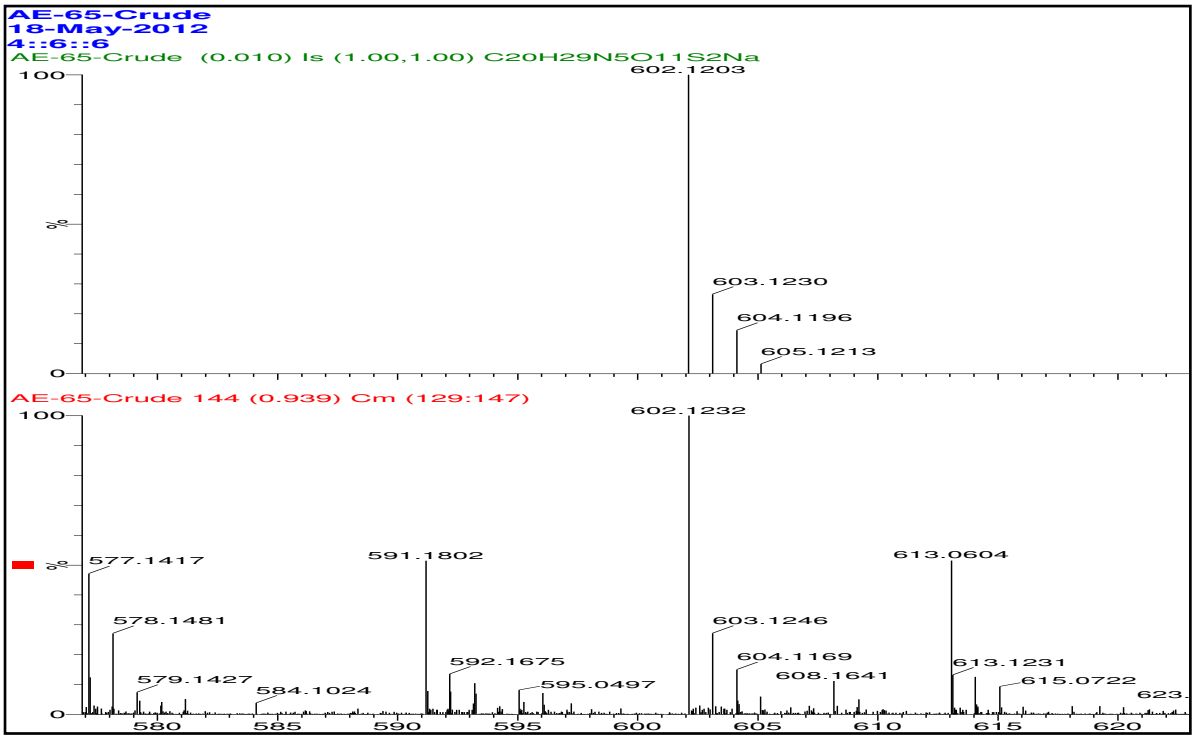
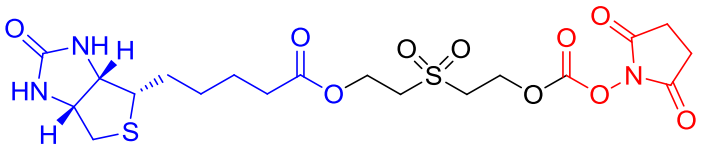


Figure (6-4): MS of **6.13**

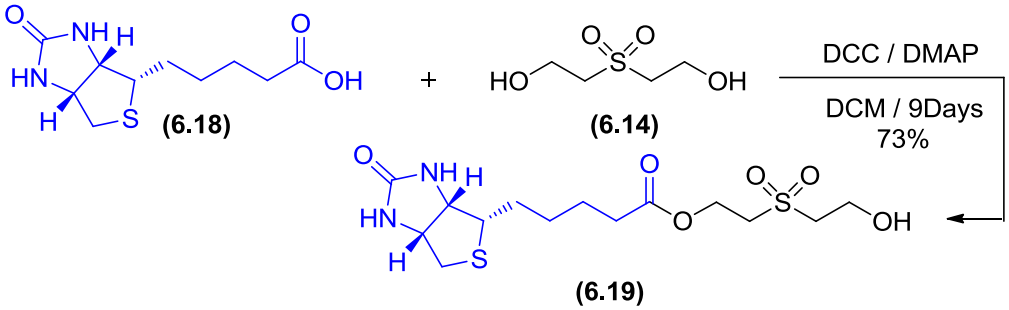
6.13 was not enough stable for HPLC purification even when we used reverse phase chromatography.

Because the problems with purification of **6.15** and **6.13**, we changed our plan to prepare 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate **(6.17)**.



(6.17)

Steglich esterification was used for the formation of the (2-((2-hydroxyethyl)sulfonyl)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (**6.19**). Very good yields were obtained (73%) when biotin (**6.18**) and 2,2'-sulfonyldiethanol (**6.14**) were reacted in the presence of dicyclohexylcarbodiimide (DCC) as a coupling reagent and 4-dimethylaminopyridine (DMAP) as a catalyst (Scheme 6-10).



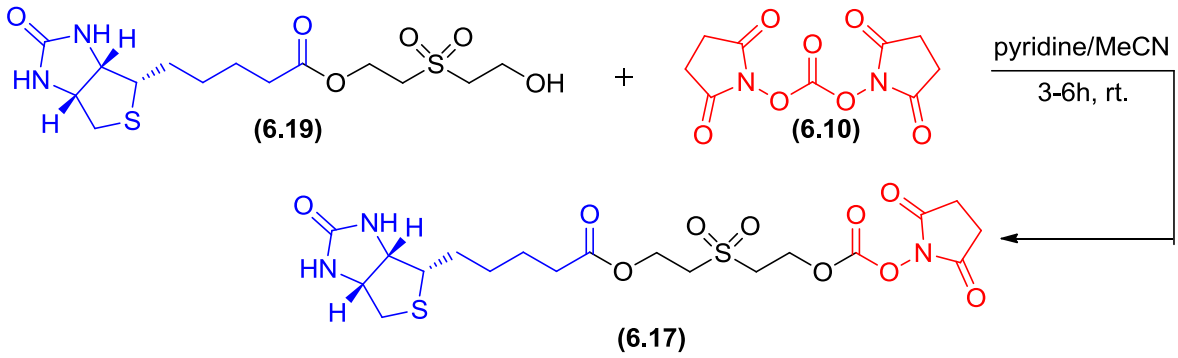
(6.18) **(6.14)** **(6.19)**

Scheme (6-10): Synthesis of **6.19**

The next step involved the synthesis of 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (**6.17**) by reaction of **6.19** with **6.10**.

In order to find the optimum reaction conditions for the synthesis of **6.17**, we have used different bases such as NaH, LDA, Et_3N, iPr_2EtN and pyridine as well as different

solvents such as THF, DMSO, MeCN. The best result was found with pyridine/MeCN (Scheme 6.11)



Scheme (6-11): Synthesis of **6.17**

We could not able to purify **6.17** by silica gel column chromatography; therefore we used preparative high performance liquid chromatography (HPLC).

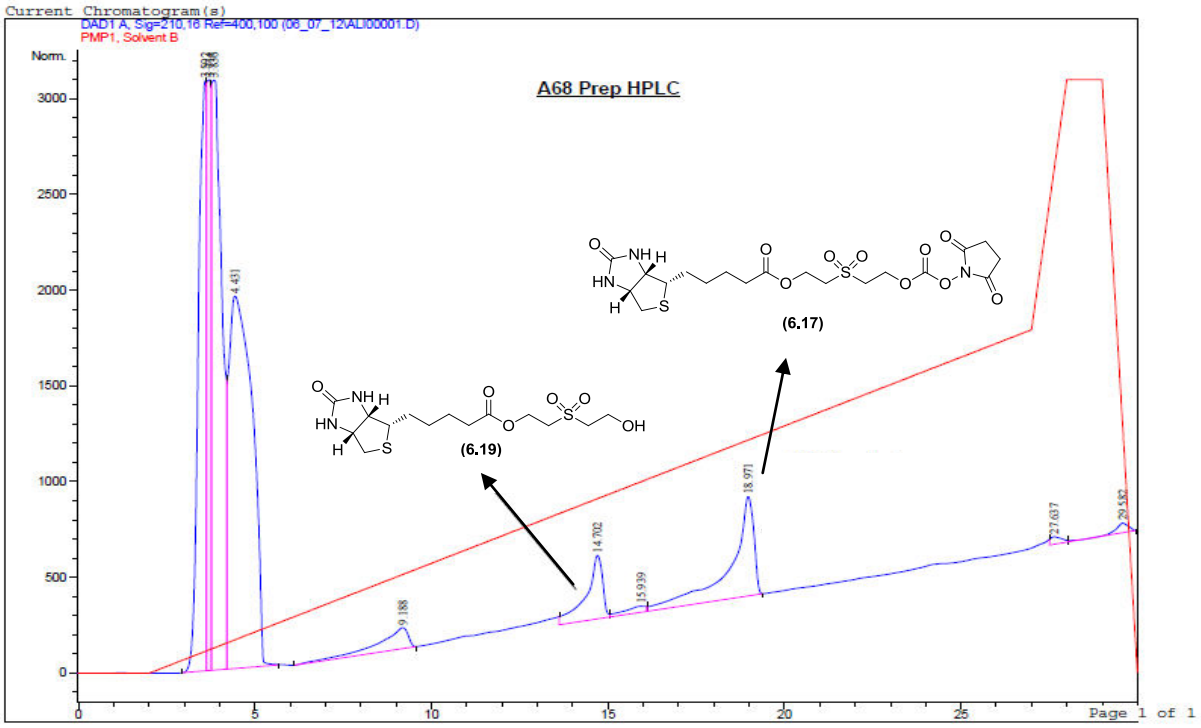
6.3.2: HPLC identification of 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl) oxy)ethyl) sulfonyl) ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (6.17)

Preparative high performance liquid chromatography (HPLC) was therefore used to purify 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl) sulfonyl) ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (**6.17**). [Ace 10 C18-300 column (150 X 2 mm ID) 0.2 mL/min H_2O/0.05% TFA/MeCN]. Analytical HPLC was then performed (MG 5 C-18, 150 X 2 mm ID column, operating at 0.2 mL/min for analytical purpose. The buffer solutions were water / 0.05% TFA (buffer A) and 84% acetonitrile in water / 0.05% TFA (buffer B). Both ran identical gradients: 5 to 60% B in 30 min, followed by 100% B for 1 min, then 15 min re-equilibration at 5% B. The HPLC traces are shown in Figure (6-5).

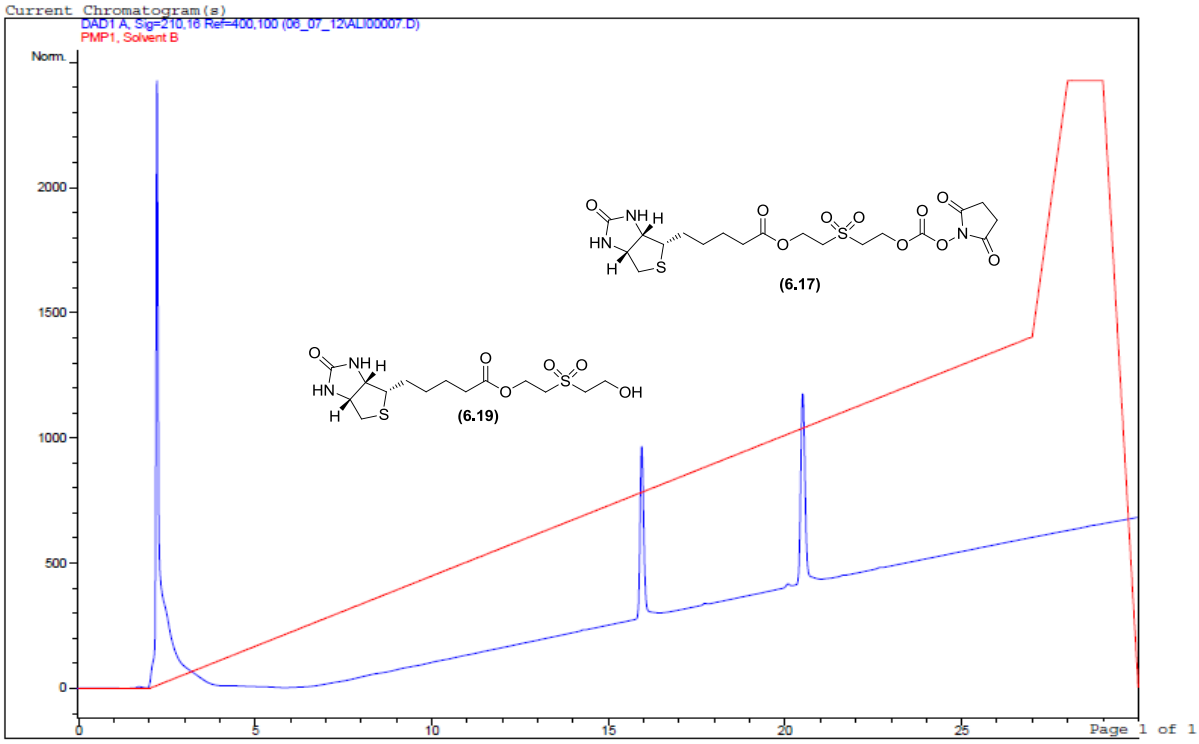
Analysis of the crude reaction mixture of **6.17** showed two peaks with retention time at 14.7 and 19.0 min. The MS analysis showed that the retention time of 14.7 min was for the starting material (2-((2-hydroxyethyl)sulfonyl)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (**6.19**)) and the second retention

time (19.0 min.) was for the product (2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl) sulfonyl)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate **(6.17)**.(Figure 6-5a).

From the preparative HPLC the peak corresponding to **6.17** was collected and dried. The sample was then analyzed by analytical HPLC. A new peak was observed corresponding to **6.19** (Figure 6-5b). This suggests that **6.17** has partially hydrolyzed during HPLC to give a mixture of **6.19** and **6.17**.



(a)



(b)

Figure (6-5): a: Preparative HPLC analysis of **6.17** (crude) **b:** HPLC of **6.17** that collected from **a** (analytical column)

In summary, biotin containing cleavable linker (**6.17**) can be prepared by the reaction of **6.19** and **6.10** in pyridine/MeCN. The **6.17** can be purified using HPLC with partially hydrolysis to give **6.19** as impurity. The **6.17** can be used to test label peptides even if it is not pure for two reasons: first the contamination molecule (**6.19**) would not interfere with labeling and the second is we used excess of **6.17**.

6.3.3: Mass identification of 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl) oxy)ethyl) sulfonyl) ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (6.17)

Next we wished to confirm the structure of **6.17** due to small quantities/purity by mass spectrometry (MS).

The 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (**6.17**) was therefore characterized by HRMS. The molecular ion of **6.17** [M+H$^+$] was shown to be 522.1208 (calcd. 522.1211) to confirm the formula (Figure 6-6).

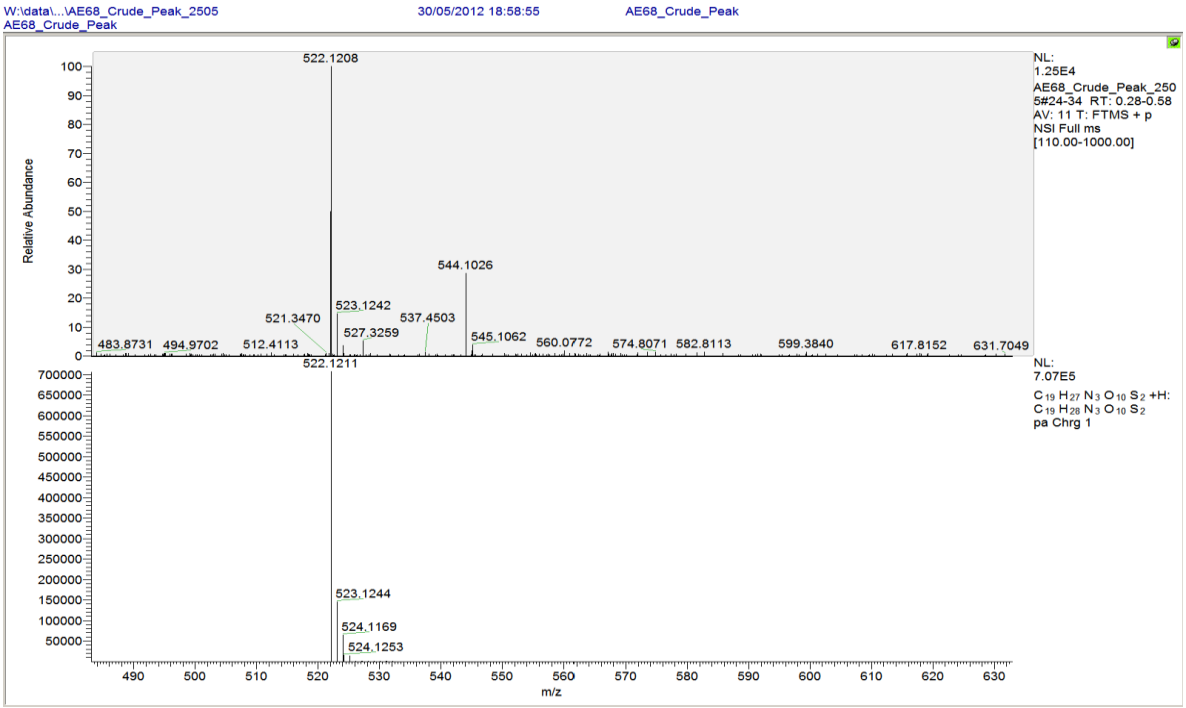


Figure (6-6): HRMS of **6.17**

The structure of **6.17** was then elucidated by fragmentation of the molecular ion (Figure 6-7). The fragmentation pathways are summarized in Scheme (6-12).

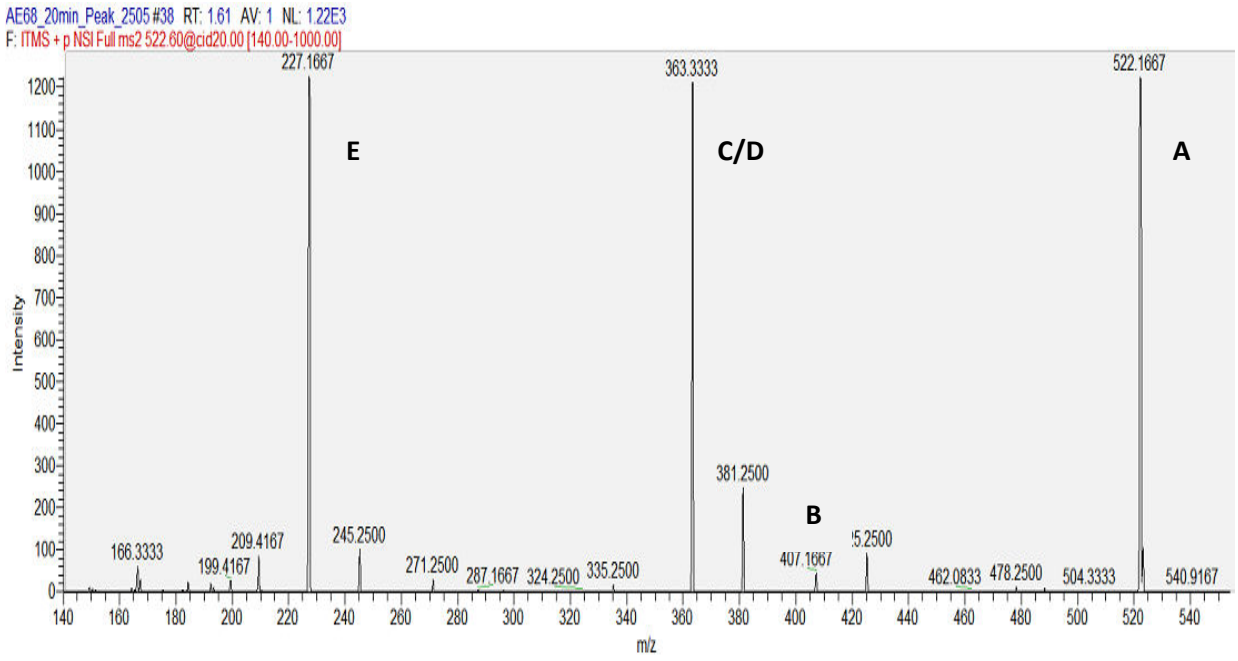
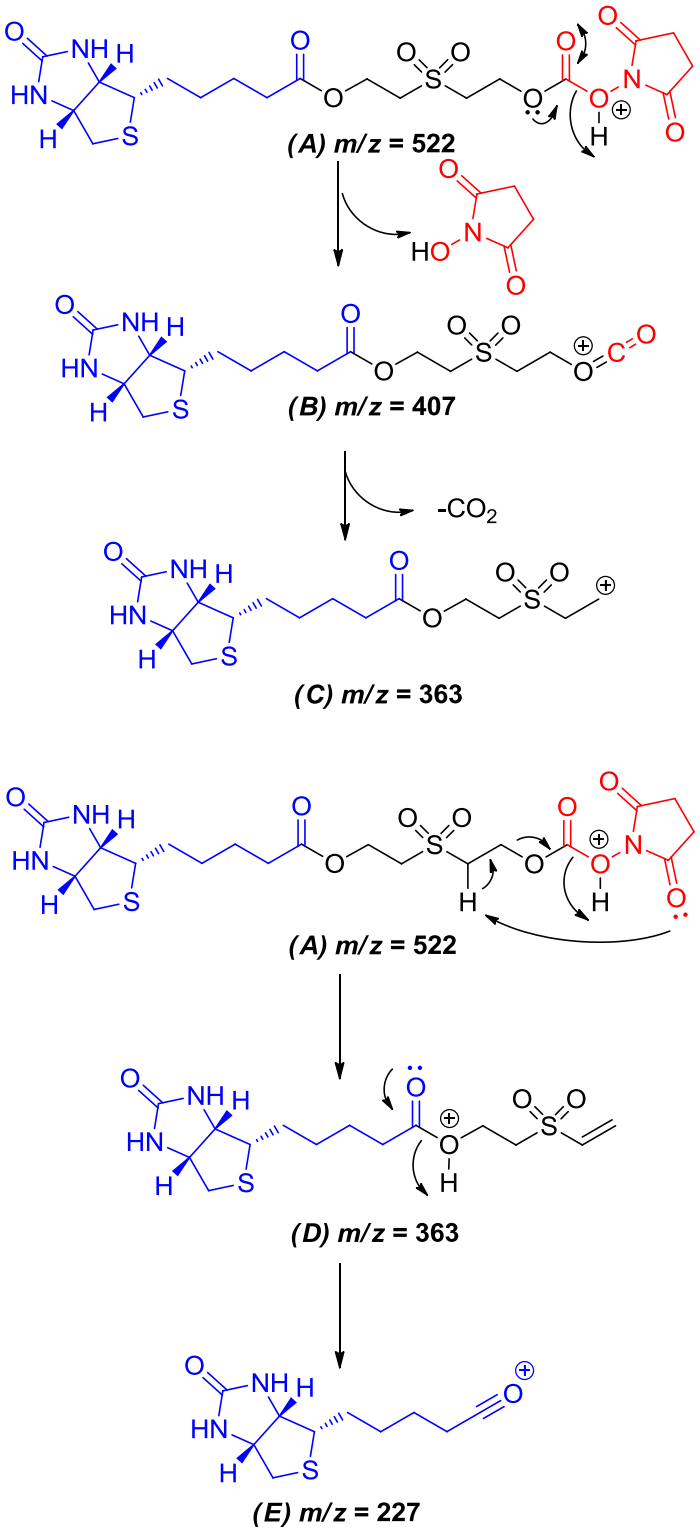


Figure (6-7): Mass fragmentation of **6.17** (*m/z* 522)

The first fragmentation of molecular ion **(A)** *m/z* 522 in Figure (6-7) involving loss of 1-hydroxypyrrolidine-2,5-dione leads to molecular ion **(B)** *m/z* 407 (Scheme 6-12). Molecular ion **(B)** losses CO_2 to give molecular ion **(C)** m/z 363. Losing CO_2 and pyrrolidine-2,5-dione from molecular ion **(A)** leads to molecular ion **(D)** *m/z* 363. Molecular ion **(D)** losses 2-(vinylsulfonyl)ethanol to give molecular ion **(E)** *m/z* 227.



Scheme (6-12): Proposed mass fragmentation of **6.17** (*m/z* 522)

6.4: Bioconjugation and traceless cleavage of 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl) oxy)ethyl) sulfonyl) ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (6.17) with test peptide (P.520), HA antigen peptide and Bovine serum albumin (BSA)

Note: The labeling of peptides and protein, HPLC analysis, MS and PAGE analysis has been performed by J. Gray.

After successful preparation and identification of biotin containing cleavable linkers (**6.17**), we next moved to use **6.17** in labelling of test peptide P.520 peptide, HA antigen peptide and Bovine serum albumin (BSA). We also want to study the stability of **6.17**/peptide bioconjugates applications to streptavidin affinity chromatography and traceless cleavage in base solution.

Commercial and single reaction sites of two test peptides were reacted with biotin containing cleavable linker (**6.17**), P.520 and HA antigen peptide: YPYDVPDYA in phosphate buffer at pH 7.4. A single molecule of **6.17** was incorporated with *N*-terminal amine into both peptides as shown by HPLC and mass spectrometry analysis.

The modified peptides (**6.17**/P.520 and **6.17**/HA antigen peptide) were purified by HPLC then both treated with aqueous ammonia solution.

Electrospray MS/MS analysis of the modified peptide (**6.17**/P.520) showed reaction of **6.17** with *N*-terminal amine. The treatment of modified peptide (**6.17**/P.520) can traceless cleavage by treating with ammonium bicarbonate at pH 8 buffer for 24h. However the cleavage time can be decreased to around 5h if we increase pH to 9.

HA peptide was also labelled with **6.17** and showed selectively to *N*-terminal amine. The modified peptide (**6.17**/HA peptide) bioconjugate could be efficiently bound incubating with neutravidin beads in phosphate buffered saline (PBS) for 1h at RT. The treatment of the neutravidin bound biotinylated peptide with pH8 ammonium bicarbonate buffer for 24h efficiently released the HA peptide in an unmodified form as confirmed by MS.

Bovine serum albumin (BSA) was also labeled by treatment with a 20-fold molar excess of **6.17** in PBS for 1h. MALDI mass spectrometry analysis showed that on average eight **6.17** molecules had reacted with each BSA molecule. The tagged BSA (**6.17**/BSA) was

then captured onto neutravidin beads. Under basic conditions we anticipate that the **6.17**/BSA bioconjugate could be cleaved to release unmodified BSA from the neutravidin beads.

Therefore to study the conditions required for release of BSA from the neutravidin beads through the basic cleavage of the **6.17**/BSA bioconjugate, the **6.17**/BSA-neutravidin beads were split into several batches. Each batch of **6.17**/BSA-neutravidin beads were treated with different bases. The eluants of these experiments were then subjected to PAGE analysis as shown in Figure (6-7), to determine under which conditions BSA was released from the **6.17**/BSA-neutravidin beads.

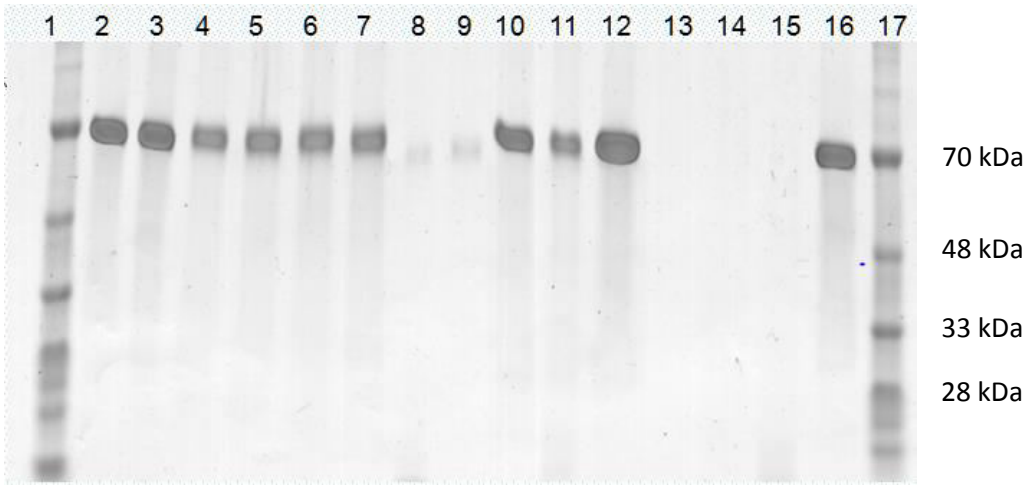


Figure (6-7). PAGE analyses of eluates from **6.17**/BSA-neutravidin beads. Lanes 1 & 17 = MW marker. Lanes 2, 10 & 16 = **6.17**/BSA standard. Lane 3 = BSA. The **6.17**/BSA-neutravidin beads treated as follows: 0.1% NH_4OH (aq) for 1h (lane 4), overnight incubation with 100mM ammonium bicarbonate at pH 8.0 (lane 5), 8.5 (lane 6) and 9.0 (lane 7) and with PBS at pH 7.4 (lane 8). Lane 9 = Eluted beads from lane 7 boiled in sample buffer. Lane 11 = Lane 8 eluted beads boiled in sample buffer. Lane 12 = Supernatant following BSA overnight incubtion with neutravidin beads. Lane 13-14= Overnight treatment of BSA-incubated neutravidin with PBS, pH 7.4 and ammonium bicarbonate pH 9.0 respectively. Lane 15 = BSA-incubated neutravidn beads boiled in sample buffer. Unless stated, all elutions were performed by incubating the beads at 4^{o}C.

The results showed that the aqueous solution of 10% ammonium hydroxide released unmodified BSA from the neutravidin beads within 1 hour through cleavage of the linker molecule (line 4, Figure 6-7). Also the BSA can be released from neutravidin beads when **6.17**/BSA-neutravidin beads are treated with ammonium bicarbonate at pH 8.0, 8.5 and 9.0 (line 5-7 respectively, Figure 6-7). However at pH 7.4 no BSA was released from neutravidin beads (line 8, Figure 6-7).

The neutravidin beads from lane 7 (which washed with ammonium bicarbonate at pH 9.0) were boiled in buffer solution to denature the neutravin and release any remaining bound protein. The PAGE analysis showed that no BSA remained bound to the neutravidin beads. In contrast, the BSA was released after boiling the **6.17**/BSA-neutravidin beads that were taken from lane 8 (which had been washed with PBS at pH 7.4) (lane 11, Figure 6-7).

To show that the BSA binding to neutravidin was due to **6.17**, unmodified BSA was incubated with neutravidin beads. The supernatant is shown in lane 12, showing that neutravidin cannot catch unmodified BSA (lane 12, Figure 6-7).

To confirm that the results were not due to interactions of the neutravidin with the buffer solutions, the BSA-incubated neutravidin from lane 12 was eluated with PBS (lane 13) ammonium bicarbonate pH 9.0 (lane 14) and were denatured by boiling (lane 15). In all cases no BSA was released, suggesting that no BSA capture had occurred.

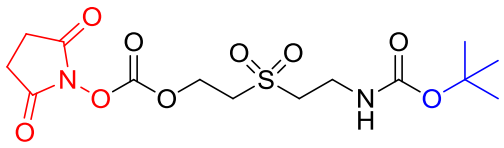
In conclusion, **6.17** can be used as a labeling agent to isolate and study the peptides and proteins by using catch and traceless release biotin-avidin affinity strategy, under mild basic conditions. Depending on the structure of peptides or proteins more than one molecule of **6.17** can react with the peptide or protein. The **6.17**/peptide or protein bioconjugates showed stability against neutral and acidic media. Finally, the treatment of **6.17**/peptides or proteins with ammonium bicarbonate gave the original unmodified peptides or proteins by traceless cleavage of **6.17**.

6.5: Conclusion

Successful demonstration of a reversible tag chemistry under mild basic conditions

Extended to a biotin containing system and applications to protein purification/cell labelling etc

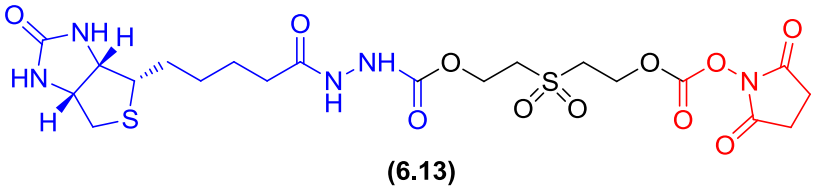
We have successfully synthesized a test molecule (*tert*-butyl (2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl)carbamate) (**6.1**) for capable of successful bioconjugation to peptides. Test molecule **6.1** contains succinimidyl esters which can react with the *N*-terminal amino acids and also contains a sulfonyl group which offers an acidic proton for later elimination reactions.



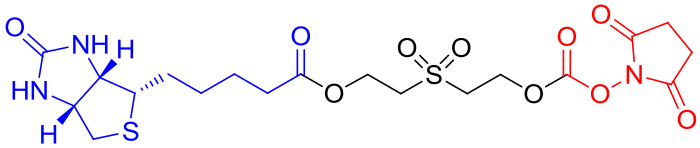
(6.1)

We also used **6.1** to label peptide (P.520) to give a P.520/**6.1** bioconjugate. The P.520/**6.1** bioconjugate can be purified by HPLC and it showed stability toward the acidic conditions. Finally, the P.520/**6.1** bioconjugate showed traceless cleavage under mild basic conditions to regenerate the native peptide (P.520) with no trace of test molecule **6.1**.

Two tracelessly cleavable biotin containing bioconjugation reagents were synthesized (2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoyl)hydrazinecarboxylate (**6.13**) and 2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (**6.17**)).



(6.13)



(6.17)

6.17 has been successfully purified by HPLC. The labeling of P.520, HA peptide and BSA by **6.17** was found to be the most selective to *N*-terminus of peptides and proteins to give peptides or proteins/**6.1** bioconjugate. By using catch and release biotin-avidin affinity strategy the **6.17/**peptides or proteins bioconjugate showed efficient traceless cleavage under base conditions to regenerate the original peptides or proteins with no trace of **6.17**.

Experimental

7.1: General procedure

All reagents and chemicals were purchased from commercial suppliers (Sigma Aldrich, TCI and Alfa Aesar) and used as received. The reaction solvents were distilled under an atmosphere of nitrogen immediately prior to use. Dichloromethane and toluene were distilled from calcium hydride. THF and diethyl ether were distilled from sodium wire in the presence of benzophenone. Thin layer chromatography (TLC) was visualized with ultraviolet light (UV) (λ = 235 nm). Flash column chromatography was used for purification (Merck Kieselgel 60 silica gel).

7.2: NMR spectroscopy, elemental analyses, EPR and mass spectrometry analyses

^{1}H and ^{13}C NMR spectra were recorded directly with a Jeol ECS-400 MHz spectrometer operating at 399.78 and 100.53MHz respectively, or Bruker Avance 300 MHz spectrometer operating at 300.13 and 75.47 MHz respectively. ^{19}F NMR was recorded at 376.17 MHz on Jeol ECS-400 spectrometer. Chemical shift are quoted in part per million (ppm) relative to tetramethylsilane (TMS).

Element analyses were obtained by the Elemental Analysis Service of London Metropolitan University.

EPR spectra were collected with a Bruker MicroEMX EPR spectrometer working at X-band (9.4 GHz) microwave frequency.

Mass spectrometry analyses were done using Micromass LCT Premier Mass Spectrometer in Electron Spray (ES) mode or by National Mass Spectrometry Service (University of Swansea).

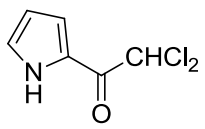
7.3: Crystal structure Detremination

X-ray diffraction data was obtained on an Oxford Diffraction Gemini. Infra-red (IR) spectra were obtained as neat samples using a Varian 800 FT-IR Scimitar Series spectrometer scanning from 4000-600 cm^{-1}.

Optical polarity measurement (α_D^{20}) of the chiral sample was done using POLAAR 2001 at 589 nm of sodium lamp source and 0.5 dcm cell length.

7.4: Compound Experimental

2,2-Dichloro-1-(1*H*-pyrrol-2-yl)ethanone (2.8)



2.8
$C_6H_5Cl_2NO$
MW: 178.02 g. mol^{-1}

Under an atmosphere of nitrogen, PhMgBr (2M, 1.1 mL, 2.2 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloroacetyl pyrrole (**2.4**) (0.212 g, 1.0 mmol) was dissolved in dry THF (1 mL), added dropwise over 10 minutes to the PhMgBr solution and then allowed to stir for an hour at room temperature. The mixture was quenched by the addition of saturated $NH_4Cl_{(aq)}$ (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over magnesium sulphate $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude product as yellow oil. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3), to give 2,2-dichloro-1-(1*H*-pyrrol-2-yl)ethanone (**2.8**) as white solid (0.160 g, 90% yield). R_f = 0.34 (petrol / diethyl ether, 7:3);

Mp: 87-89 ˚C (lit: 89-90˚C).[127]

^{1}H NMR: (300 MHz, $CDCl_3$): δ 9.41 (s, 1H), 7.14-7.09 (m, 2H), 6.41 (s, 1H), 6.32 (app. dt, *J* = 4.0, 2.5 Hz, 1H);

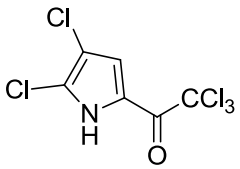
^{13}C NMR: (101 MHz, $CDCl_3$): δ 177.0(C), 127.8 (C-H), 126.1 (C), 119.1 (C-H), 111.9 (C-H), 67.3 (C-H);

IR(neat): υ_{max}/cm^{-1} 3287, 3138, 1667

Anal. Calcd for $C_6H_5Cl_2NO$: C, 40.48; H, 2.83; N, 7.87;. Found: C, 40.57; H, 2.81; N, 7.84

HRMS (APCI) calcd for $C_6H_5Cl_2NO$ $[M+H]^+$: 177.9821; observed: 177.9821.

2,2,2-Trichloro-1-(4,5-dichloro-1H-pyrrol-2-yl)ethanone (2.9)



2.9
$C_6H_2Cl_5NO$
MW: 281.35 g. mol^{-1}

To a solution of 2-(trichloroacetyl) pyrrole (0.85 g, 4 mmol) in chloroform (10 mL) at room temperature was added sulfuryl chloride (1.08 g, 8 mmol). The mixture was stirred for 17 hours in the dark. The reaction was quenched by the addition of 2M sodium bicarbonate solution (15 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic layers were collected, dried over magnesium sulphate ($MgSO_4$), filtered and concentrated under reduced pressure to give

the crude product as a yellow solid. The crude material was purified by column chromatography (SiO_2) (petrol / ethyl acetate, 9:1) to give 2,2,2-trichloro-1-(4,5-dichloro-1*H*-pyrrol-2-yl)ethanone (**2.9**) as a white crystalline solid (0.964 g, 86% yield). R_f = 0.45 (petrol / ethyl acetate, 9:1);

Mp: 128-130˚C (lit: 129-131˚C).[127]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.58 (s, 1H), 7.32 (d, *J* = 3.0 Hz, 1H).

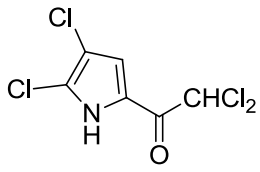
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 173.3 (C), 124.6 (C), 122.6 (C), 119.9 (C-H), 116.0 (C), 94.8 (C)

IR(neat) υ_{max}/cm^{-1} 3267, 3140, 1652

Anal. Calcd for $C_6H_2Cl_5NO$: C, 25.61; H, 0.72; N, 4.98. Found: C, 25.72; H, 0.73; N, 4.93;

HRMS(APCI) calcd for $C_6H_2Cl_5NO$ $[M+H]^+$: 281.8622; observed: 281.8627.

2,2-Dichloro-1-(4,5-dichloro-1*H*-pyrrol-2-yl)ethanone (2.10)



2.10

$C_6H_3Cl_4NO$

MW: 246.91 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 1.1 mL, 2.2 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(4,5-dichloro-*1H*-pyrrol-2-yl)ethanone (**2.9**) (0.282 g, 1.0 mmol) was dissolved in dry THF (1 mL) and added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for an hour at room temperature. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over magnesium sulphate $MgSO_4$, filtered and the solvent removed under reduced pressure to give yellow orange crystals. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3) to give 2,2-dichloro-1-(4,5-dichloro-1*H*-pyrrol-2-yl)ethanone (**2.10**) as a pink crystalline solid (0.172 g, 70% yield). R_f = 0.5 (petrol / diethyl ether, 7:3).

Mp: 104-106˚C (lit. 104-107˚C).[127]

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 10.07 (s, 1H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.28 (s, 1H);

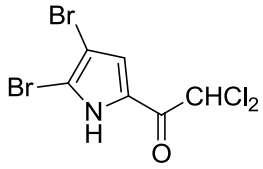
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.4 (C), 124.2 (C), 123.0 (C), 118.7(C-H), 113.2(C), 66.8(C-H);

IR(neat): υ_{max}/cm^{-1} 3247, 3123, 1650;

Anal. Calcd for $C_6H_3Cl_4NO$: C, 29.19; H, 1.22; N, 5.67. Found: C, 29.31; H, 1.23; N, 5.58;

HRMS (APCI) calcd for $C_6H_3Cl_4NO$ $[M+H]^+$: 247.9012; observed: 247.9014.

2,2-Dichloro-1-(4,5-dibromo-1*H*-pyrrol-2-yl)ethanone (2.12)



2.12

$C_6H_3Br_2Cl_2NO$

MW: 335.81 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(4,5-dibromo-*1H*-pyrrol-2-yl)ethanone (**2.11**) (0.185 g, 0.5 mmol) was dissolved in dry THF (1 mL), added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for an hour at room temperature. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over magnesium sulphate $MgSO_4$, filtered and the solvent removed under reduced pressure to give yellow-orange crystals. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1) to give 2,2-dichloro-1-(4,5-dibromo-1*H*-pyrrol-2-yl)ethanone (**2.12**) as a pink crystalline solid (0.175 g, 95% yield). R_f = 0.25 (petrol / diethyl ether, 9:1).

Mp: 127-128˚C (lit. 127-129 ˚C). [127]

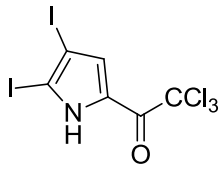
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.86 (s, 1H), 7.22 (d, *J* = 2.9 Hz, 1H), 6.35 (s, 1H);

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.0(C), 126.6(C), 121.2(C-H), 113.4(C), 102.3(C), 66.8(C-H).

IR(neat): υ_{max}/cm^{-1} 3252, 2989, 1646.

HRMS (APCI) calcd for $C_6H_3Br_2Cl_2NO$ $[M+H]^+$: 335.8009; observed: 335.8014.

2,2,2-Trichloro-1-(4,5-diiodo-1*H*-pyrrol-2-yl)ethanone (2.13)



2.13

$C_6H_2Cl_3I_2NO$

MWt: 464.25 g. mol^{-1}

To a mixture of 2-(trichloroacetyl) pyrrole (0.85 g, 4 mmol) and silver trifluoroacetate (1.77 g, 8 mmol) in chloroform (10 mL) at 0˚C (ice bath) under nitrogen atmosphere, was added iodine (2.03 g, 8 mmol) in chloroform (10 mL) dropwise over 10 minutes. The reaction was warmed to room temperature and stirred for 7 h, in the dark, before the addition of aqueous sodium sulphite (15 mL) and brine (15 mL). The reaction mixture was extracted with ethyl acetate (3 × 15 mL), and the combined organic extracts were dried over magnesium sulphate ($MgSO_4$). The crude was purified by silica gel column chromatography (petrol / ethyl acetate, 9:1) to give 2,2,2-

trichloro-1-(4,5-diiodo-1*H*-pyrrol-2-yl)ethanone (**2.13**) a yellow crystalline solid (1.48 g, 80% yield). Rf = 0.32 (petrol / ethyl acetate, 9:1);.

Mp 176-178 ˚C (lit. 176-177˚C).[127]

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.60 (s, 1H), 7.37 (d, *J* = 2.8 Hz);

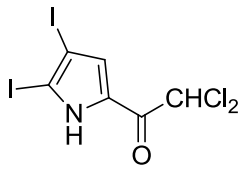
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.4 (C), 129.1 (C), 128.0 (C-H), 93.7 (C), 90.2 (C), 79.0 (C);

IR(neat) υ_{max}/cm^{-1} 3286, 3129, 1649.

Anal. Calcd for $C_6H_2Cl_3I_2NO$: C, 15.52; H, 0.43; N, 3.02. Found: C, 15.63; H, 0.49; N, 3.00

HRMS (APCI) calcd for $C_6H_2Cl_3I_2NO$ $[M+H]^+$: 463.7364; observed: 463.7368.

2,2-Dichloro-1-(4,5-diiodo-1*H*-pyrrol-2-yl)ethanone (2.14)



2.14

$C_6H_3Cl_2I_2NO$

MW: 429.81 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.275 mL, 0.55 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(4,5-diiodo-*1H*-pyrrol-2-yl)ethanone (**2.13**) (0.116 g, 0.25 mmol) was dissolved in dry THF (1 mL) and added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for an hour at room temperature. The reaction was quenched by adding saturated $NH_4Cl_{(aq)}$ (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over magnesium sulphate $MgSO_4$, filtered and the solvent removed under reduced pressure to give yellow-orange crystals. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1) to give 2,2-dichloro-1-(4,5-diiodo-1*H*-pyrrol-2-yl)ethanone (**2.14**) as a yellow crystalline solid (0.108 g, 93% yield). R_f = 0.19 (petrol / diethyl ether, 9:1).

Mp: 138-140 ˚C

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 9.61 (s, 1H), 7.23 (d, *J* = 2.7 Hz, 1H), 6.33 (s, 1H).

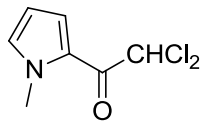
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 175.3 (C), 131.8 (C), 126.1 (C-H), 90.3 (C), 78.7 (C), 66.6 (C-H).

IR(neat): υ_{max}/cm^{-1} 3260, 2942, 1629

HRMS (APCI) calcd for $C_6H_3Cl_2I_2NO$ $[M+H]^+$: 429.7754, observed: 429.7745

Anal. Calcd for $C_6H_3Cl_2I_2NO$: C, 16.77; H 0.70; N, 3.26. Found: C, 16.84; H, 0.60; N, 3.19.

2,2-Dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (2.16)



2.16

$C_7H_7Cl_2NO$

MW: 192.04 g. mol^{-1}

Under an atmosphere of nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethanone (**2.15**) (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL), added to the dropwise over 10 minutes to the PhMgBr solution and allowed to stir for an hour at room temperature. The mixture was quenched by the addition of saturated $NH_4Cl_{(aq)}$ (20 mL) and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over magnesium sulphate $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude as yellow oil. The crude product was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1) to give 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.16**) as a white crystalline solid (0.181 g, 94% yield).

Mp: 67-68˚C (lit. 65-66 ˚C).[128] R_f = 0.37 (petrol / diethyl ether, 9:1);

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.05 (dd, *J* = 4.4, 1.6 Hz, 1H), 6.90 (br s, 1H), 6.54 (s, 1H), 6.12 (dd, *J* = 4.4, 2.5 Hz, 1H), 3.87 (s, 3H);

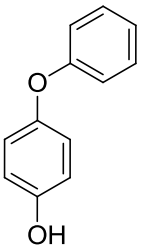
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 176.6 (C), 134.2(C-H), 125.2(C), 121.4(C-H), 109.4(C-H), 68.1(C-H), 38.0(C-H);

IR(neat): υ_{max}/cm^{-1} 3117, 3022, 1656;

HRMS (NSI) calcd for $C_7H_7Cl_2NO$ $[M+H]^+$: 191.9977, observed: 191.9978;

Anal: Calcd for $C_7H_7Cl_2NO$: C, 43.78; H 3.67; N, 7.29, Found; C, 43.82; H, 3.75; N, 7.23.

4-phenoxyphenol (2.22)



2.22

$C_{12}H_{10}O_2$

MW: 186.21g mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. The benzoquinone (0.108 g, 1.0 mmol) was dissolved in dry THF (1 mL) and the solution was added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude was purified by column chromatography

(SiO_2) (petrol / diethyl ether, 8:2). The product (**2.22**) was obtained as yellow crystalline solid (0.07 g, 38% yield).

MP: 80-82˚C (lit. 83-85˚C). [129]

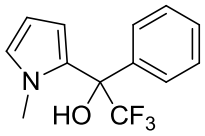
^{1}H NMR (300 MHz, CDCl3) δ 7.34 – 6.69 (m, 9H), 4.60 (s, 1H).

^{13}C NMR (100 MHz, CDCl3) δ 158.50 (C), 151.76 (C), 150.33 (C), 129.69 (C-H), 122.55 (C-H), 121.08 (C-H), 117.68 (C-H), 116.38 (C-H).

IR: υmax/cm-1 3206 (O-H), 3070 (C-H).

HRMS (EI) calcd for $C_{12}H_{10}O_2$ $[M+H]^+$: 187.0751; observed: 187.0754.

2,2,2-trifluoro-1-(1-methyl-1H-pyrrol-2-yl)-1-phenylethanol (2.24)



2.24

$C_{13}H_{12}F_3NO$

MW: 255.24 g mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trifluoro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.177 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further two hour. The mixture was added to diethyl ketomalonate (0.174 g, 1.0 mmol / 1 mL dry THF) and left to stir for 2h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give brown solid crude. The crude was purified by column chromatography (SiO_2) (petrol/diethyl ether, 9:1). The product (**2.24**) was obtained as white solid crystals, (0.245 g, 96% yield), R_f = 0.44 (petrol/diethyl ether 9:1).

MP: 57-58˚C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 5H), 6.65 – 6.55 (m, 1H), 6.53 – 6.45 (m, 1H), 6.08 (dd, *J* = 2.8Hz, 1H), 3.13 (s, 3H), 2.82 (s, 1H).

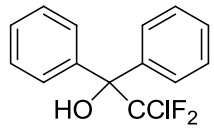
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.35 (C), 128.73 (C-H), 128.11(C-H), 127.77 (C), 127.55 (C-H), 126.04 (C), 125.36 (C-H), 123.20 (C), 110.41 (C-H), 106.37 (C-H), 35.15 (CH_3).

IR: υ_{max}/cm^{-1} 3450 (O-H).

Anal. Calcd for $C_{13}H_{12}F_3NO$: C, 61.17; H 4.74; N, 5.49. Found: C, 61.27; H, 4.78; N, 5.39.

HRMS calcd for $C_{13}H_{12}F_3NO$ $[M+H]^+$:256.0940; observed: 256.0940.

3-(2-chloro-2,2-difluoro-1-hydroxy-1-phenylethyl)benzene-1-ylium (2.26)



2.26
$C_{14}H_{11}ClF_2O$
MW: 268.69 $gmol^{-1}$

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask The 2-chloro-2,2-difluoro-1-phenylethanone (0.190 g, 1.0 mmol) was dissolved in dry THF (1 mL) and added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried by magnesium sulphate $MgSO_4$, filtered and the solvent removed under reduced pressure to give yellow oil crude. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1). The product (**2.26**) was obtained as white crystalline solid (0.178 g, 66% yield), mp = 74-76 ˚C (lit. 73-77.5 ˚C).[130] R_f = 0.53 (petrol / diethyl ether, 9:1)

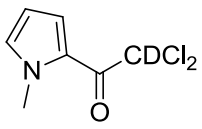
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.58 (m, 4H), 7.47 – 7.36 (m, 6H), 3.25 – 3.09 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.60 (C), 131.44 (C), 128.48 (C-H), 128.08 (C-H), 127.56 (C-H), 82.50 (C).

IR: υ_{max}/cm^{-1} 3542 (OH).

HRMS (APCl) calcd for $C_{14}H_{11}ClF_2O$ $[M\text{-}OH]^+$: 251.0434 ; observed: 251.0433.

2,2-dichloro-2-deuterium -1-(1-methyl-1H-pyrrol-2-yl)ethanone (2.27)



2.27
$C_7H_6DCl_2NO$
MW: 193.05g. mol^{-1}

PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask under an atmosphere of nitrogen. The 2,2,2-trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (**2.15**) (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL), added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for an hour. The mixture was quenched by adding D_2O (0.18 mL, 10 mmol) and then saturated $NH_4Cl_{(aq)}$ (20 mL). The product was extracted using ethyl acetate (3 x 15 mL), the combined organic extracts were dried over magnesium sulphate $MgSO_4$, filtered and the solvent removed under reduced pressure to give yellow oil. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3) to give 2-deutero-2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**2.27**) as a white crystalline solid (0.166 g, 86% yield, 89% deuterium incorporation by ^{1}H NMR).

Procedure 2

Under nitrogen, NaH, 60% dispersion in mineral oil (52mg, 2.2 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (0.192 g, 1.0 mmol) was dissolved in dry THF (1 mL) and added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was quenched by adding D2O (0.5 mL) and then adding to NH_4Cl (20 mL).The product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over magnesium sulphate MgSO4, filtered and the solvent removed under reduced pressure to give yellow oil crude. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1). The product (**2.27**) was obtained as white crystalline solid (0.152 g, 78% yield), mp: 68-70˚C R_f = 0.31 (petrol / diethyl ether, 9:1).

Mp: 68-70˚C

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.07 (dd, *J* = 4.3, 1.6 Hz, 1H), 6.92 – 6.91 (m, 1H), 6.16 (dd, *J* = 4.3, 2.4 Hz, 1H), 3.91 (s, 3H)

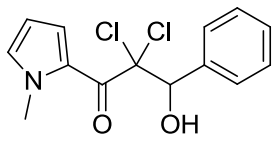
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.0 (C), 134.0 (C-H), 125.7 (C), 121.5 (C-H), 109.6 (C-H), 68.2 ($J_{C\text{-}D}$ = 27.0 Hz), 38.0(C-H);

IR(neat): υ_{max}/cm^{-1} 3117, 1650

Anal. Calcd for $C_7H_6DCl_2NO$: C, 43.55; H 4.18; N, 7.26. Found: C, 43.46; H, 4.09; N, 7.19

HRMS (APCI): calcd. for $C_7H_6DCl_2NO$ $[M+H]^+$: 193.0040; observed: 193.0038.

2,2-Dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-phenylpropan-1-one(2.29)



2.29

$C_{14}H_{13}Cl_2NO_2$

MW: 298.16 g. mol^{-1}

PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask under nitrogen. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution, dropwise over 10 minutes and allowed to stir for a further one hour. The reaction mixture was added to benzaldehyde (0.10 mL, 1.0 mmol) in THF (1 mL) and left to stir for 1h. The reaction was quenched by addition to saturated $NH_4Cl_{(aq)}$ (20 mL), and the product was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give dark oil. The crude was purified by column chromatography (SiO_2) (petrol / diethyl

ether, 8:2) to give 2,2-dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-phenylpropan-1-one (**2.29**) as white powder (0.24 g, 81% yield). R_f = 0.38 (petrol / diethyl ether, 7:3).

Mp: 91-93 ˚C

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.67 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.65-7.63 (m, 2H), 7.44-7.37 (m, 2H), 6.96 (app t, *J* = 2.0 Hz, 1H), 6.25 (dd, *J* = 4.4, 2.4 Hz, 1H), 5.57 (d, *J* = 3.8 Hz, 1H), 4.16 (d, *J* = 3.8 Hz, 1H), 3.98 (s, 3H)

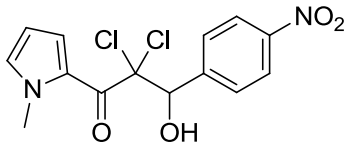
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 182.0 (C=O), 136.0 (C), 133.5 (C-H), 129.9 (C-H), 128.8 (C-H), 127.5 (C-H), 125.1 (C), 124.7 (C-H), 108.9 (C-H), 87.0 (C), 78.3 (C-H), 38.7 (CH_3).

IR(neat): υ_{max}/cm^{-1} 3525, 1627

Anal. Calcd for $C_{14}H_{13}Cl_2NO_2$: C, 56.39; H 4.39; N, 4.70. Found: C, 56.42; H, 4.40; N, 4.80

HRMS (NSI): calcd. for $C_{14}H_{13}Cl_2NO_2$ $[M+Na]^+$: 320.0216; observed: 320.0216.

2,2-Dichloro-3-hydroxy-1-(1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl)propan-1-one (2.30)



2.30

$C_{14}H_{12}Cl_2N_2O_4$

MW: 343.16 g. mol^{-1}

Procedure 1

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for a further one hour. The reaction mixture was added to aolution of *p*-nitrobenzalaldehyde (0.15 g, 1.0 mmol) in THF (1 mL) and left to stir for 1h. The reaction mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by silica gel column chromatography (petrol / diethyl ether, 5:5) to give 2,2-dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)propan-1-one (**2.30**) as brown solid (0.33 g, 96% yield).

Procedure 2

Under nitrogen, NaH, 60% dispersion in mineral oil (11 mg, 0.28 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (48 mg, 0.25 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5

minutes and allowed to stir for a further one hour. $MgCl_2$ (50 mg, 0.52 mmol) was added to the reaction mixture and allowed to stir again for a further one hour. The mixture was added to *p*-nitrobenzalaldehyde (38 mg, 0.25 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 5:5). The product (**2.30**) was obtained as white solid (40 mg, 47% yield). R_f = 0.4 (petrol / diethyl ether 5:5).

Mp: 170-173 ˚C

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.18 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.55 (dd, *J* = 4.4, 1.6 Hz, 1H), 6.90 (t, *J* = 2.0 Hz, 1H), 6.16 (dd, *J* = 4.5, 2.4 Hz, 1H), 5.55 (d, *J* = 3.4 Hz, 1H), 4.21 (d, *J* = 3.5 Hz, 1H), 3.91 (s, 3H)

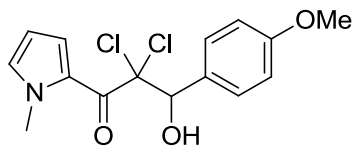
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 181.5 (C), 148.1(C), 142.8(C), 133.9(C-H), 130.9(C-H), 125.0(C-H), 124.6(C), 122.4(C-H), 109.1(C-H), 85.4(C), 38.7(CH_3);

IR(neat): υ_{max}/cm^{-1} 3499, 3132, 1644

HRMS (APCI) calcd for $C_{14}H_{12}Cl_2N_2O_4$ $[M+H]^+$: 341.0090; observed: 341.0090

Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_4$: C, 49.00; H 3.52; N, 8.16. Found: C, 49.09; H, 3.43; N, 8.10.

2,2-Dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one(2.31)



2.31

$C_{15}H_{15}Cl_2NO_3$

MW: 328.19 g. mol^{-1}

PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask under nitrogen. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution, dropwise over 10 minutes and allowed to stir for a further two hour. The reaction mixture was added to a solution of *p*-methoxy benzaldehyde (0.136 g, 1.0 mmol) in 1 mL of THF and left to stir for 3h. The reaction mixture was quenched by the addition of saturated $NH_4Cl_{(aq)}$ (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give dark oil. The

crude was purified by silica gel column chromatography (petrol/diethyl ether, 8:2) to give 2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one (**2.31**) as a pink solid, (0.280 g, 85% yield). R_f = 0.17 (petrol / diethyl ether, 8:2).

Mp: 125-127 ˚C

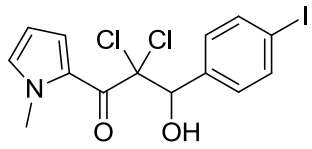
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.66 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.55 (d, *J* = 8.7, 2H), 6.97-6.90 (m, 3H), 6.24 (dd, *J* = 4.4, 2.4 Hz, 1H), 5.52 (d, *J* = 3.6 Hz, 1H), 4.16 (d, *J* = 3.6 Hz, 1H), 3.96 (s, 3H), 3.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 182.0 (C=O), 160.0 (C), 133.4 (C-H), 131.0(C-H), 128.2 (C), 125.2 (C), 124.7 (C-H), 112.9 (C-H), 108.9 (C-H), 87.6 (C), 77.9 (C-H), 55.3 (CH_3), 38.7 (CH_3).

IR(neat): υ_{max}/cm^{-1} 3505, 1618

HRMS (NSI): calcd for $C_{15}H_{15}Cl_2NO_3$ $[M+Na]^+$: 350.0321; observed: 350.0323.

2,2-Dichloro-3-hydroxy-3-(4-iodophenyl)-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one (2.32)



2.32

$C_{14}H_{12}Cl_2INO_2$

MW: 424.06 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution, dropwise over 10 minutes and the reaction was allowed to stir for a further one hour. The mixture was added to a solution of *p*-iodobenzaldehyde (0.232 g, 1.0 mmol) in THF (1 mL) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give yellow oil which was purified by silica gel column chromatography (petrol / diethyl ether, 7:3) to give 2,2-Dichloro-3-hydroxy-3-(4-iodophenyl)-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one (**2.32**) as a white solid (0.399 g, 94% yield). R_f = 0.31 (petrol 7/ diethyl ether 3).

Mp: 117-118˚C.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.61 (d, *J* = 8.3 Hz, 2H), 7.52 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.82 (app t, *J* = 2.0 Hz, 1H), 6.11 (dd, *J* = 4.4, 2.4 Hz, 1H), 5.37 (d, *J* = 3.7 Hz, 1H), 4.10 (d, *J* = 3.7 Hz, 1H), 3.83 (s, 3H)

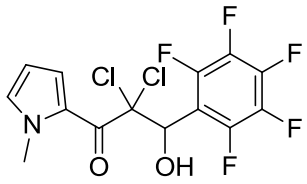
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 181.81 (C=O), 136.6 (C-H), 135.8(C), 133.7 (C-H), 131.9 (C-H), 124.9 (C-H), 124.9 (C-H), 109.1 (C-H), 95.1 (C), 86.4 (C), 77.8 (C-H), 38.8 (CH_3).

IR(neat): υ_{max}/cm^{-1} 3475, 3104, 1629

Anal. Calcd for $C_{14}H_{12}Cl_2INO_2$: C, 39.65; H 2.85; N, 3.30. Found: C, 39.73; H, 2.80; N, 3.27;

HRMS (NSI): calcd for $C_{14}H_{12}Cl_2INO_2$ $[M+H]^+$: 423.9363; observed: 423.9360.

2,2-Dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(perfluorophenyl)propan-1-one (2.33)



2.33

$C_{14}H_8Cl_2F_5NO_2$

MW: 388.12 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to pentafluoro benzaldehyde (0.196 g, 1.0 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give yellow oil. The crude was purified by silica gel column chromatography (petrol / diethyl ether, 7:3) to give 2,2-dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(perfluorophenyl)propan-1-one (**2.33**) as a white solid (0.270 g, 70% yield). R_f = 0.30 (petrol 7/ diethyl ether 3).

Mp: 98-99˚C

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.56 (dd, *J* = 4.4, 1.6 Hz, 1H), 6.89 (app t, *J* = 2.0 Hz, 1H), 6.16 (dd, *J* = 4.4, 2.4 Hz, 1H), 5.99 (d, *J* = 6.2 Hz, 1H), 4.04 (d, *J* = 6.2 Hz, 1H), 3.89 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 180.3 (C=O), 133.9 (C-H), 124.6 (C-H), 124.4 (C-H), 109.1 (C-H), 85.8(C), 73.4(C-H), 38.7(CH_3).

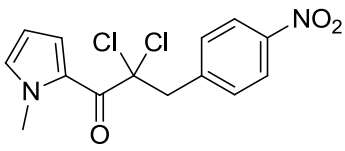
^{19}F NMR (376 MHz, $CDCl_3$): δ_F -134.5 (d, *J* = 20.8 Hz), -151.3 (t, *J* = 21.0 Hz), -161.7 (app t, *J* = 21.0 Hz)

IR(neat): υ_{max}/cm^{-1} 3371, 2963, 1656

Anal. Calcd for $C_{14}H_8Cl_2F_5NO_2$: C, 43.32; H 2.08; N, 3.61. Found: C, 43.38; H, 1.99; N, 3.56;

HRMS (NIS): calcd for $C_{14}H_8Cl_2F_5NO_2$ $[M+Na]^+$:409.9744; observed: 409.9747.

2,2-Dichloro-1-(1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl)propan-1-one (2.34)



2.34

$C_{14}H_{12}Cl_2N_2O_3$

MW: 327.16 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for a further two hours. The reaction mixture was added to a solution of 4-nitrobenzyl chloride (0.171 g, 1.0 mmol) and NaI (0.015 g) in THF (1 mL) and left to stir for 24h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give brown solid. The crude was purified by silica gel column chromatography (petrol / diethyl ether, 4:1) to give 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)propan-1-one (**2.34**) as a white solid (0.120 g, 37%), R_f = 0.46 (petrol / diethyl ether, 4:1)

Mp: 140-142 ˚C.

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.22 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.61-7.60 (m, 1H), 6.95 (s, 1H), 6.23 (dd, *J* = 4.4, 2.4 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 2H)

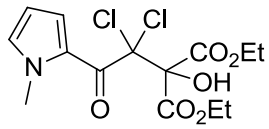
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 179.4 (C), 147.6 (C), 141.8 (C), 133.1 (C-H), 133.0 (C-H), 124.5 (C), 123.6 (C-H), 123.0 (C-H), 108.7 (C-H), 85.5 (C), 48.8 (CH_2), 38.60 (CH_3).

IR(neat): υ_{max}/cm^{-1} 1640

HRMS(APCI): calcd for $C_{14}H_{12}Cl_2N_2O_3$ $[M+H]^+$: 327.0298; observed: 327.0295

Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.40; H 3.70; N, 8.56. Found: C, 51.49; H, 3.72; N, 8.58.

Diethyl 2-(1,1-dichloro-2-(1-methyl-1H-pyrrol-2-yl)-2-oxoethyl)-2-hydroxymalonate (2.35)



2.35

$C_{14}H_{17}Cl_2NO_6$

MW: 366.19 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for a further two hours. The mixture was added to diethyl ketomalonate (0.174 g, 1.0 mmol) in THF (1 mL) and left to stir for two hours. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a brown solid. The crude was purified by silica gel column chromatography (petrol / diethyl ether, 9:1 then with 6.4) to give diethyl 2-(1,1-dichloro-2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl)-2-hydroxymalonate (**2.35**) was obtained as a yellow oil, (0.310 g, 79% yield). R_f = 0.28 (petrol / diethyl ether 6.4).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.66 (dd, *J* = 4.4, 1.6 Hz, 1H), 6.92 (app t, *J* = 2.0 Hz, 1H), 6.21 (dd, *J* = 4.4, 2.4 Hz, 1H), 4.66 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 4H), 3.88 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 6H)

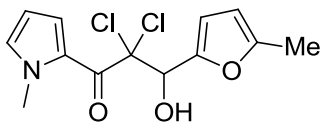
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 178.8 (C=O), 166.8 (C=O), 133.3 (C-H), 124.2 (C), 123.9 (C-H), 108.8 (C-H), 85.0 (C), 82.7 (C-H), 63.2 (CH_3), 38.5 (CH_2), 14.0 (CH_3).

IR(neat): υ_{max}/cm^{-1} 3454, 1738, 1646

HRMS (NSI): calcd for $C_{14}H_{17}Cl_2NO_6$ [M+H] : 366.0506; observed: 366.0512

Anal. Calcd for $C_{14}H_{17}Cl_2NO_6$: C, 45.92; H 4.68; N, 3.82. Found: C, 46.02; H, 4.59; N, 3.75.

2,2-Dichloro-3-hydroxy-1-(1-methyl-1H-pyrrol-2-yl)-3-(5-methylfuran-2-yl)propan-1-one (2.36)



2.36

$C_{13}H_{13}Cl_2NO_3$

MW: 302.15 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution, dropwise over 10 minutes and allowed to stir for a further one

hour. The mixture was added to 5-methylfuran-2-carbaldehyde (0.11 g, 1.0 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by silica gel column chromatography (petrol / diethyl ether, 6:4) to give 2,2-dichloro-3-hydroxy-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(5-methylfuran-2-yl)propan-1-one (**2.36**) as a dark brown solid, (0.210 g, 70% yield). R_f = 0.19 (petrol / diethyl ether, 8:2).

Mp: 82-84 ˚C

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 7.65 (dd, *J* = 4.4, 1.6 Hz, 1H), 6.94 (app t, *J* = 2.0 Hz, 1H), 6.48 (d, *J* = 3.1 Hz, 1H), 6.24 (dd, *J* = 4.4, 2.4 Hz, 1H), 6.02 (dt, *J* = 3.1, 1.0 Hz, 1H), 5.54 (d, *J* = 5.8 Hz, 1H), 3.96 (s, 3H), 3.90 (d, *J* = 5.8 Hz, 1H), 2.34 (s, 3H)

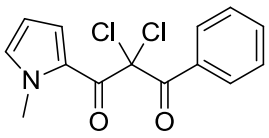
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 181.1 (C=O), 152.4 (C), 148.3 (C), 133.4 (C-H), 124.9 (C), 124.3 (C-H), 111.3 (C-H), 108.9 (C-H), 106.6 (C-H), 86.4 (C), 74.0 (C-H), 38.7 (CH_3), 13.8 (CH_3).

IR(neat): υ_{max}/cm^{-1} 3107, 2921, 1624

HRMS (NSI) calcd for $C_{14}H_{11}O_4N_2Cl_2$ $[M+Na]^+$: 324.0165, observed: 324.0168

Anal. Calcd for $C_{13}H_{13}Cl_2NO_3$: C, 51.68; H 4.34; N, 4.64. Found: C, 51.59; H, 4.46; N, 4.78.

2,2-Dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)-3-phenylpropane-1,3-dione (2.37)



2.37
$C_{14}H_{11}Cl_2NO_2$
MW: 296.15 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 2.2 mL, 4.4 mmol) was added to a 50 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.904 g, 4 mmol) was dissolved in dry THF (4 mL) and then added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for a further two hour. The mixture was added to benzoyl chloride (0.464 mL, 4.0 mmol) in THF (4 mL) and left to stir for 1h. The mixture was quenched by adding to saturated $NH_4Cl_{(aq)}$ (50 mL), and the product was extracted using ethyl acetate (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give brown solid crude. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 5:1) to give 2,2-Dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)-3-phenylpropane-1,3-dione (**2.37**) as white-yellow solid (0.590 g, 50% yield). R_f = 0.26 (petrol / diethyl ether, 5:1).

Mp. 67-68 ˚C

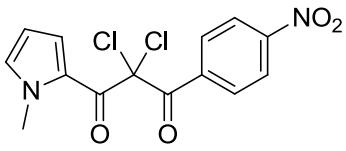
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.03 (dd, *J* = 4.5, 1.6 Hz, 1H), 6.86 (app t, *J* = 2.0 Hz, 1H), 6.09 (dd, *J* = 4.5, 2.4 Hz, 1H), 3.94 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 185.1 (C=O), 175.6 (C=O), 134.0 (C-H), 133.6 (C-H), 132.0 (C), 130.4 (C-H), 128.7 (C-H), 125.1 (C), 123.0 (C-H), 109.6 (C-H), 88.9 (C), 36.4 (CH_3).

IR(neat): υ_{max}/cm^{-1} 2951, 1699, 1659

HRMS (APCI): calcd for $C_{14}H_{11}Cl_2NO_2$ $[M+H]^+$: 296.0240; observed: 296.0244.

2,2-Dichloro-1-(1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl)propane-1,3-dione (2.38)



2.38

$C_{14}H_{10}Cl_2N_2O_4$

MW: 341.15 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(1-methyl-*1H*-pyrrol-2-yl) ethanone (0.226 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution dropwise over 10 minutes and allowed to stir for a further two hours. The reaction mixture was added to 4-nitrobenzoyl chloride (0.186 g, 1.0 mmol) in THF (1 mL) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give brown solid. The crude was purified by silica gel column chromatography (petrol / diethyl ether, 9:1) to give 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(4-nitrophenyl)propane-1,3-dione (**2.38**) as a yellow solid, (0.325 g, 95% yield). R_f = 0.14(petrol / diethyl ether, 9:1).

Mp: 160-162 ˚C;

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.24 (m, 2H), 8.14 (m, 2H), 7.12 (dd, *J* = 4.3, 1.6 Hz, 1H), 6.93 (t, *J* = 2.0 Hz, 1H), 6.14 (dd, *J* = 4.4, 2.4 Hz, 1H), 3.94 (s, 3H)

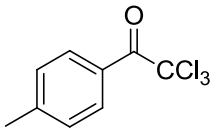
^{13}C NMR (101 MHz, $CDCl_3$): δ_C 184.0 (C=O), 175.4 (C=O), 150.4 (C), 137.0 (C), 134.2 (C-H), 131.4 (C-H), 124.8 (C), 123.7 (C-H), 123.5 (C-H), 109.9 (C-H), 87.7 (C), 38.5 (CH_3).

IR(neat): υ_{max}/cm^{-1} 3121, 1660

HRMS (APCI) calcd for $C_{14}H_{11}O_4N_2Cl_2$ $[M+H]^+$: 341.0090; observed: 341.0090

Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_4$: C, 49.29; H 2.95; N, 8.21. Found: C, 49.35; H, 2.92; N, 8.15.

2,2,2-Trichloro-1-(*p*-tolyl)ethanone (3.3)



3.3
$C_9H_7Cl_3O$
MW: 237.51 g. mol^{-1}

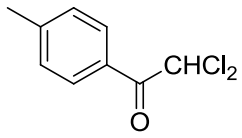
Procedure 1: To a round bottom flask was added sequentially $AlCl_3$ (8.82 g, 66 mmol) and DCM (30 mL). The reaction mixture was cooled to 0 ^oC, toluene (6.4 mL, 60 mmol) and then 2,2,2-trichloroacetylchloride (7.4 mL, 66 mmol) were added. The solution was stirred for 1 hour under nitrogen atmosphere. The reaction was quenched with 30 mL of saturated $Na_2CO_{3(aq)}$, washed with 30 mL of brine then dried over $MgSO_4$. The solvent was removed under reduce pressure to give an oil. The crude product was purified by reduced pressure distillation (0.02 torr, b.p. = 115-116 ^oC) to give 2,2,2-trichloro-1-(*p*-tolyl)ethanone (**3.3**) as a yellow oil (9.23 g, 65%). R_f : 0.46 (UV active, petrol 40/60 : ether = 90: 1).

Procedure 2

To a 100 mL round bottom flask under nitrogen was added sequentially $AlCl_3$ (7.34 g, 55 mmol) and toluene (5.33 mL, 50 mmol). The reaction mixture was cooled to 0 ^oC, 2,2,2-trichloroacetylchloride (6.14 mL, 55 mmol) was added and the reaction stirred for 1 hour. The reaction was quenched with 30 mL of saturated $K_2CO_{3(aq)}$, washed with 30 mL of brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give an oil. Petrol (40/60, 20 mL) was added to give a biphasic solution, the mixture was stirred, allowed to separate and the petrol removed by decantation. This procedure was repeated twice more, the residual solvent was removed under reduced pressure to give 2,2,2-trichloro-1-(*p*-tolyl)ethanone **(1b)** as a colourless oil (11.12 g, 94%). R_f : 0.22 (UV active, petrol 40/60).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.19 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 2.47 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 180.6 (CO), 145.6 (C), 131.8 (C-H), 129.3 (C-H), 126.2 (C), 95.9 (C), 21.5 (CH_3).
IR (neat): ν_{max}/cm^{-1} 1705;
HRMS (APCI): calcd for $C_9H_8OCl_3$ $[M+H]^+$: 236.9641, found 236.9637.

2,2-Dichloro-1-(*p*-tolyl)ethanone (3.5)



3.5
$C_9H_8Cl_2O$
MW: 203.07 g. mol^{-1}

Procedure 1: Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether 9.5:0.5). The product (**3.5**) was obtained as white crystal solid (0.138 g, 68% yield).

Procedure 2: Under nitrogen, PhMgI (0.38M, 2.9 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgI solution dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was quenched by adding to saturated $NH_4Cl_{(aq)}$ (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether 9.9:0.1) to give 2,2-Dichloro-1-(*p*-tolyl)ethanone (**3.5**) as a white crystaline solid (0.195 g, 96% yield). R_f = 0.38 (petrol / diethyl ether, 9.5:0.5).

Mp: 58-59˚C;

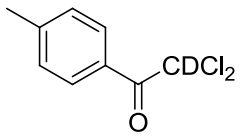
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.61 (s, 1H), 2.35 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 185.7 (C), 146.0 (C), 129.9(C-H), 129.7 (C-H), 128.8 (C), 67.9 (C-H), 21.9 (CH_3)

IR(neat): υ_{max}/cm^{-1} 3017, 1689

HRMS (APCI) calcd for $C_9H_8Cl_2O$ $[M+H]^+$: 203.0025; observed: 203.0027.

2,2-dichloro-2-deuterium-1-(p-tolyl)ethanone (3.6)



3.6

$C_9H_7DCl_2O$

MW: 204.07 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 2,2,2-Trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr solution, dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was quenched by adding D_2O (1 mL), and after 10 min. NH_4Cl (20 mL) was added. The product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by silica gel column chromatography (petrol / diethyl ether 9.5:0.5) to give 2,2-dichloro-2-deuterium-1-(*p*-tolyl)ethanone (**3.6**)

as an oil (0.102 g, 50% yield, >95% deuterium incorporation by ^{1}H NMR).

R_f = 0.30 (petrol / diethyl ether, 49/1).

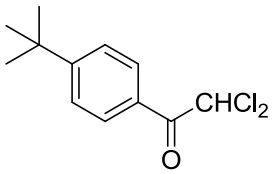
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.19 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 2.46(s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 185.7 (C), 146.0 (C), 129.9 (C-H), 129.7 (C-H), 128.8 (C), 67.6 ($J_{C\text{-}D}$ = 27.1 Hz), 21.9 (CH_3);

IR(neat): υ_{max}/cm^{-1} 2924, 1690.

MS (ES$^+$): calcd. for $C_9H_7DCl_2O$ $[M+Na]^+$: 225; observed: 225

1-(4(t-Butyl)phenyl)-2,2-dichloroethanone (3.7)



3.7

$C_{12}H_{14}Cl_2O$

MW: 245.14 g. mol^{-1}

Under nitrogen, PhMgI (0.38M, 2.9 mL, 1.1 mmol) was added to a 25 mL round bottomed flask. 1-(4-(*tert*-Butyl)phenyl)-2,2,2-trichloroethanone (0.279 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgI solution dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was quenched by adding to saturated $NH_4Cl_{(aq)}$ (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether 9.9:0.1) to give 1-

(4(*t*-butyl)phenyl)-2,2-dichloroethanone (**3.7**) as a white crystalline solid (0.239 g, 98% yield). R_f : 0.43 (UV active, petrol 40/60 : ether = 50: 1).

Mp: 63-64˚C**.**

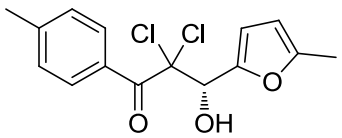
^{1}H NMR (300 MHz, $CDCl_3$): δ_H 8.05 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 6.70 (s, 1H), 1.37 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ_C 185.5 (C), 158.6(C), 129.7(C-H), 128.8 (C), 125.8 (C-H), 67.8 (C-H), 35.3 (C), 30.9 (CH_3).

IR(neat): ν_{max}/cm^{-1} 2964.6, 2869.9, 1703.6, 852.9, 701.3

MS (ES): calcd. for $C_{12}H_{14}OCl_2$ $[M+Na]^+$ 267, found 267.

(±)-2, 2-dichloro-3-hydroxy-3-(5-methylfuran-2-yl)-1-(p-tolyl) propan-1-one (3.8)



3.8

$C_{15}H_{14}Cl_2O_3$

MW: 313.18 g. mol^{-1}

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to 5-methylfuran-2-carbaldehyde (0.110 g, 0.099 mL, 1.0 mmol) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product (**3.8**) was obtained as green oil (0.149 g, 48 % yield). R_f = 0.66 (petrol / diethyl ether 7:3).

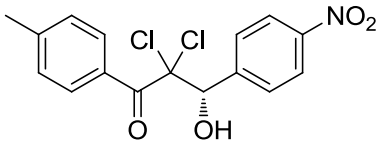
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.15 (m, 2H), 7.33 – 7.23 (m, 2H), 6.49 (d, *J* = 3.2 Hz, 1H), 6.09 – 5.97 (m, 1H), 5.60 (s, 1H), 3.78 (s, 1H), 2.45 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6 (C=O), 152. 5 (C), 148.1 (C), 145.3 (C), 131.3 (C-H), 129.1(C), 129.0 (C-H), 111.4 (C-H), 106.7 (C-H), 86.1 (C), 73.7 (C-H), 21.9 (CH_3), 13.7 CH_3).

IR: υ_{max}/cm^{-1} 3427 (OH), 2923 (C-H), 1683 (C=O).

MS (ES) calcd for $C_{15}H_{14}Cl_2O_3$: 313; observed: 313.

(±)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(p-tolyl)propan-1-one (3.9)



3.9

$C_{16}H_{13}Cl_2NO_4$

MW: 354.18 g. mol^{-1}

Procedure 1: Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzaldehyde (0.151 g, 1.0 mmol) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product (**3.9**) was obtained as white powder (0.143g, 40% yields). $R_{f=}$ 0.51 (petrol / diethyl ether 7:3).

Procedure 2:

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes at rt., and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzaldehyde (0.151 g, 1.0 mmol) at -78°C and left to stir for 1h at rt.. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product (**3.9**) was obtained as white powder (0.219g, 62% yield), $R_{f=}$ 0.51 (petrol / diethyl ether 7:3).

MP: 236-238˚C.

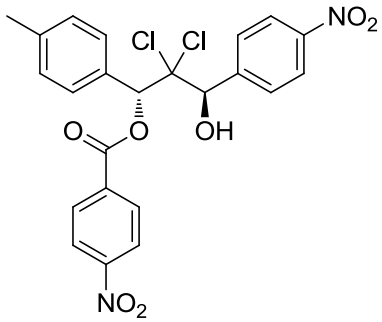
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 – 8.21 (m, 4H), 7.88 – 7.78 (m, 2H), 7.32 (dd, *J* = 8.7, 0.8 Hz, 2H), 5.68 (d, *J* = 3.7 Hz, 1H), 4.02 (d, *J* = 3.8 Hz, 1H), 2.47 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0 (C=O), 148.3 (C), 146.0 (C), 142.6 (C), 131.7 (C-H), 131.0 (C-H), 129.2 (C-H), 128.5 (C), 122.6 (C-H), 85.4 (C), 77.1 (C-H), 21.9 (CH_3).

IR: υ_{max}/cm^{-1} 3537 (OH), 2921 (C-H), 1664 (C=O).

HRMS (NSI) calcd for $C_{16}H_{13}Cl_2NO_4$ $[M+Na]^+$: 378.0084; observed: 378.0086.

(±)-(1R,3R)-2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(p-tolyl)propyl 4-nitrobenzoate (3.10)



3.10
$C_{24}H_{21}Cl_2NO_5$
MW: 474.33 g. mol^{-1}

Procedure 1: Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzaldehyde (0.151 g, 1.0 mmol) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product (**3.10**) was obtained as white powder (0116g, 23% yield).

Procedure 2:

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzaldehyde (0.302 g, 2 mmol) at -78°C and left to stir for 1h at r.t.. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product (**3.10**) was obtained as white powder (0.430g, 85% yield). $R_{f=}$ 0.16 (petrol / diethyl ether 8:2).

MP: 148-150˚C.

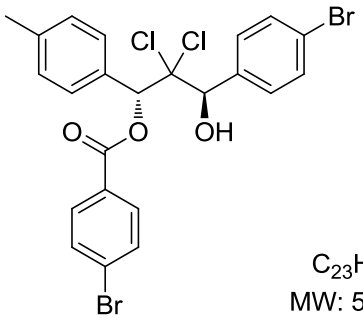
^{1}H NMR (300 MHz, DMSO) δ 8.46 – 8.38 (m, 2H), 8.37 – 8.30 (m, 2H), 8.29 – 8.19 (m, 2H), 7.96 – 7.87 (m, 2H), 7.54 – 7.42 (m, 2H), 7.25 – 7.13 (m, 3H), 6.55 (s, 1H), 5.49 (d, *J* = 5.6 Hz, 1H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 162.8 (C=O), 151.1 (C), 147.9 (C-H), 146.7 (C), 139.1 (C), 134.8 (C), 131.9 (C), 131.6 (C-H), 131.5 (C),129.8 (C-H), 128.9 (C-H), 124.6 (C-H), 122.8 (C-H), 94.6 (C-H), 78.1 (C-H), 75.8 (C), 21.3 (CH_3) .

IR: υ_{max}/cm^{-1} 3497 (OH), 2960, 2872 (C-H), 1727 (C=O).

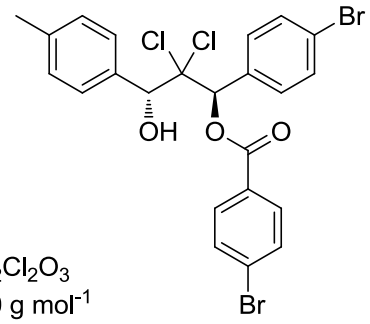
HRMS (NSI) calcd for $C_{23}H_{18}Cl_2N_2O_7$ $[M+NH_4]^+$: 522.0825; observed: 522.0829.

(±)-(1R,3R)-1,4-bis(4-bromophenyl)-3,3-dichloro-4-hydroxy-2-(p-tolyl)butan-1-one (3.11) and (±)-(1R,3R)-1-(4-bromophenyl)-2,2-dichloro-3-oxo-3-(p-tolyl)propyl 4-bromobenzoate (3.12)



3.11

$C_{23}H_{18}Br_2Cl_2O_3$
MW: 573.10 g mol^{-1}



3.12

Procedure 1: Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour at room temperature. The mixture was added to 4-bromo benzaldehyde (0.270 g, 2 mmol) at 0°C and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using DCM (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 8:2). The product (**3.11** and **3.12**) was obtained as white yellow solid (0.490 g, 88 % yield). R_f = 0.30 (petrol / diethyl ether 8:2).

Procedure 2

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour at room temperature. The mixture was added to 4-bromo benzaldehyde (0.270 g, 2 mmol) at room temperature and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using DCM (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 8:2). The product (**3.11** and **3.12**) was obtained as white yellow solid (0.525 g, 92 % yield). $R_{f=}$ 0.30 (petrol / diethyl ether 8:2).

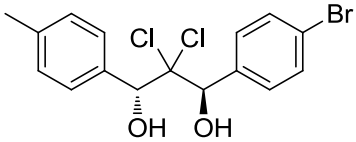
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.97 (m, 4H), 7.68 (d, *J* = 7.8 Hz, 4H), 7.60-7.50 (m, 12H) 7.28 – 7.18 (m, 4H), 6.64 (s, 2H), 5.15 (d, *J* = 5.3 Hz, 1H), 5.10 (d, *J* = 5.4 Hz, 1H), 3.65 (d, *J* = 5.4 Hz, 1H), 3.19 (d, *J* = 5.5 Hz, 1H), 2.39 (s, 3H), 2.36 (s, 3H),

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0 (C), 164.3 (C), 139.5 (C), 139.1 (C), 135.9 (C), 133.8 (C), 133.6(C), 132.2 (C-H), 131.6 (C-H), 131.5 (C-H), 131.4 (C-H), 131.2 (C-H), 131.1 (C-H), 130.8 (C-H), 129.7 (C-H), 129.5 (C), 129.4 (C), 129.1 (C-H), 128.7 (C-H),128.6 (C-H),127.9 (C-H), 123.7 (C), 123.2 (C), 93.9 (C-H), 77.8 (C), 77.7 (C), 21.4 (CH_3), 21.3 (CH_3).

IR: υ_{max}/cm^{-1} 3528 (OH), 1705 (C=O).

HRMS (NSI) calcd for $C_{23}H_{18}Br_2Cl_2O_3$ $[M+NH_4]^+$: 589.9317; observed: 589.9313.

(±)-(1R,3R)-1-(4-bromophenyl)-2,2-dichloro-3-(p-tolyl)propane-1,3-diol (3.13)



3.13

$C_{16}H_{13}BrCl_2O_2$

MW: 390.10 g. mol^{-1}

NaOH (5%, w/v) was added to a 25 mL round bottom flask. The product (**3.11** and **3.12**) (60 mg, 0.1mmol) was stirred at room temperature with NaOH (5%, w/v) in 25 mL round bottom flask for 6h. HCl (10%) was added until the solution became acidic. The product was extracted with DCM (3 x 15 mL). The organic layer washed with saturated solution of NaHCO3 (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column

chromatography (SiO_2) (petrol / diethyl ether, 9:1). The product (**3.13**) was obtained as white solid (37 mg, 95 % yield). $R_{f=}$ 0.1(petrol / diethyl ether 8:2).

MP: 131-133˚C.

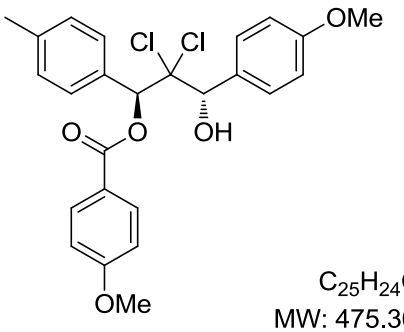
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 6H), 7.22 (d, *J* = 7.8 Hz, 2H), 5.30 (s, 1H), 5.27 (s, 1H), 3.86 (s,1H), 3.52 (s,1H), 2.40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (C), 136.2 (C), 133.7 (C), 131.0 (C-H), 130.9 (C-H) 129.0 (C-H), 128.7(C-H), 123.1 (C), 94.6 (C), 79.7 (C-H), 78.3 (C-H), 21.4 (CH_3).

IR: υ_{max}/cm^{-1} 3410 (OH), 2922, (C-H).

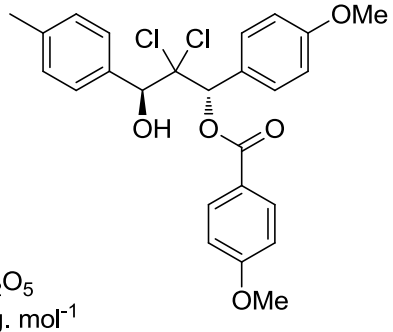
HRMS (NSI) calcd for $C_{16}H_{15}BrCl_2O_2$ $[2M+Na]^+$: 802.9113; observed: 802.9113.

(±)-(1S,3S)-2,2-dichloro-3-hydroxy-1-(4-methoxyphenyl)-3-(p-tolyl)propyl 4-methoxybenzoate (3.14) and (±)-(1S,3S)-3,3-dichloro-4-hydroxy-1,4-bis(4-methoxyphenyl)-2-(p-tolyl)butan-1-one (3.15)



3.14

$C_{25}H_{24}Cl_2O_5$
MW: 475.36 g. mol^{-1}



3.15

Procedure 1. Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to 4-methoxybenzaldehyde (0.272 g, 0.242 mL, 1.0 mmol) at 0°C and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product was obtained as yellow solid (0.111 g, 47 % yield).

Procedure 2

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry

THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to 4-methoxybenzaldehyde (0.272 g, 0.242 mL, 1.0 mmol) and left to stir for 1h at room temperature. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product (**3.14** and **3.15**) was obtained as yellow solid (0.150 g, 63 % yield).

Procedure 3

Under nitrogen, PhMgBr (2M, 0.55 mL, 1.1 mmol) was added to a 25 mL round bottom flask. The 2, 2, 2-trichloro-1-(*p*-tolyl) ethanone (0.237 g, 1.0 mmol) was dissolved in dry THF (1 mL) and then added to the PhMgBr dropwise over 10 minutes and allowed to stir for a further one hour. The mixture was added to 4-methoxybenzaldehyde (0.544 g, 0.484 mL, 2.0 mmol) and left to stir for 1h at room temperature. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 7:3). The product (**3.14** and **3.15**) was obtained as yellow solid (0.172 g, 72 % yield). R_f = 0.20 (petrol / diethyl ether 8:2).

MP: 119-121˚C

^{1}H NMR (300 MHz, DMSO) δ 8.08 – 7.99 (m, 2H), 7.54 – 7.40 (m, 4H), 7.22 – 7.08 (m, 4H), 6.98 – 6.86 (m, 2H), 6.65 – 6.58 (m, 1H), 6.50 (s, 1H), 5.19 (d, *J* = 5.2 Hz, 1H), 3.86 (s, 3H), 3.75 (d, *J* = 1.7 Hz, 3H), 2.30 (s, 3H).

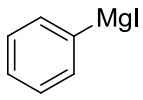
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5(C), 164.2 (C), 160.2 (C), 159.9 (C), 139.1 (C), 138.6(C), 134.1 (C), 132.3 (C-H), 131.8 (C), 131.2 (C-H), 130.6 (C-H), 129.8 (C-H), 129.3 (C-H), 129.2 (C), 128.6 (C-H), 128.4 (C-H), 126.9 (C), 121.4 (C), 114.1 (C-H), 113.2 (C-H), 113.0 (C-H), 94.9 (C), 55.7 (OCH_3), 55.3 (OCH_3), 21.4 (CH_3).

IR: υ_{max}/cm^{-1}: 3446.65 (OH), 2962.65, 2839.86 (CH_3), 1720.87 (C=O).

HRMS (NSI) calcd for $C_{25}H_{24}Cl_2O_5$ $[M+NH_4]^+$: 492.1339; observed: 492.1337.

Synthesis of Grignard Reagents

phenylmagnesium iodide



C_6H_5IMg
MW: 228.31 $gmol^{-1}$

A 250 mL Schlenk flask was placed under N_2 and Magnesium (0.67 g, 27.5 mmol) was added. Iodobenzene solution (5.1 g, 25 mmol /25 mL dry THF) was added to the Schlenk flask and allowed to stir at room temperature for 24h before filtered. The concentration of Grignard reagent was determined by acid-base titrations and used directly in the next reaction.

Titration Procedure

To 100mL conical flask, 5mL of Grignard reagent was added. 15mL of water was added to the Grignard reagent dropwise. The solution was acidifying by HCl (0.1M, 40mL). Few drops of phenolphthalein were added as indicator. The solution was titrating with NaOH (0.1M).

The vol. of NaOH = 21mL

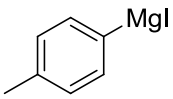
The vol. of HCl that reacted with Mg(I)OH is 40-21 = 19

M_1V_1 (PhMgI) = M_2V_2 (HCl)

M_1*5 = 0.1 * 19

M_1 = 0.38M

p-methylphenylmagnesium iodide



C_7H_7IMg
MW: 242.34 $gmol^{-1}$

A 250 mL Schlenk flask was placed under N_2 and Magnesium (0.67 g, 27.5 mmol) was added. *p*-Iodotoluene solution (5.45 g, 25 mmol /25 mL dry THF) was added to the Schlenk flask and allowed to stir at room temperature for 24h before filtered. The concentration of Grignard reagent was determined by acid-base titrations and used directly in the next reaction.

Titration Procedure

To 100mL conical flask, 2mL of Grignard reagent was added. 10mL of water was added to the Grignard reagent dropwise. The solution was acidifying by HCl (0.1M, 10mL). Few

drops of phenolphthalein were added as indicator. The solution was titrating with NaOH (0.1M).

The vol. of NaOH = 4mL

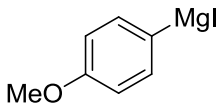
The vol. of HCl that reacted with Mg(I)OH is 10-4 = 6

M_1V_1 (p-TolMgI) = M_2V_2 (HCl)

M_1*2 = 0.1 * 6

M_1 = 0.30M

p-methoxyphenylmagnesium iodide



C_7H_7IMgO

MW: 258.34 $gmol^{-1}$

A 250 mL Schlenk flask was placed under N_2 and Magnesium (0.67 g, 27.5 mmol) was added. Iodo-4-methoxybenzene solution (5.85 g, 25 mmol /25 mL dry THF) was added to the Schlenk flask and allowed to stir at room temperature for 24h before filtered. The concentration of Grignard reagent was determined by acid-base titrations and used directly in the next reaction.

Titration Procedure

To 100mL conical flask, 0.5mL of Grignard reagent was added. 10mL of water was added to the Grignard reagent dropwise. The solution was acidifying by HCl (0.1M, 5mL). Few drops of phenolphthalein were added as indicator. The solution was titrating with NaOH (0.1M).

The vol. of NaOH = 3.2mL

The vol. of HCl that reacted with Mg(I)OH is 5-3.2 = 1.8

M_1V_1 (p-MeO(C_6H_6)MgI) = M_2V_2 (HCl)

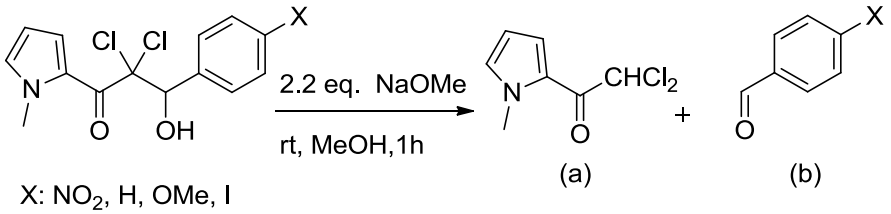
M_1*0.5 = 0.1 * 1.8

M_1 = 0.36M

Retro-aldol Degradations

a: Degradation of 2,2-dichloro-3-hydroxy-3-(4-substituted)-1-(1-methyl-1H-pyrrol-2-yl)propan-1-one

General procedure



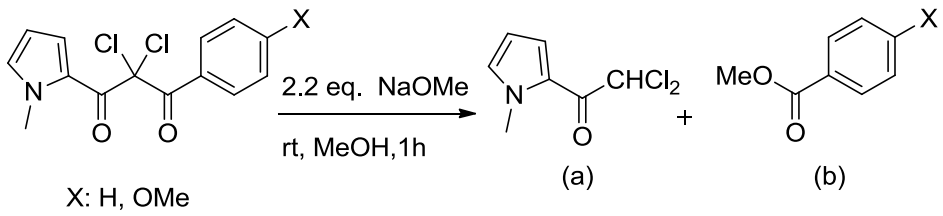
Under nitrogen, 2,2-dichloro-3-hydroxy-3-(4-substituted)-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one (1 mmol) was dissolved in MeOH (1mL) and added to NaOMe (2N, 1.1 mL, 2.2 eq.) at 0°C in 25 mL round bottomed flask. The mixture allowed stirring for a further one hour at room temperature. The solvents were evaporated under reduced pressure before adding 30 mL of water. The product was extracted using ethyl acetate (3 x 15 mL) and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure.

X	NO_2 [c]	H [c]	I [c]	OMe [d]
Yield %	> 97%	100%	> 98%	a: 87%, b: 88%

c: NMR Yield, d: Isolated yield (the crude product was purified by column chromatography (SiO_2) (petrol / diethyl ether, 8:2). The product (a) was obtained as white solid (150 mg, 78% yield). R_f = 0.52 (petrol / diethyl ether 7:3), (b) white oil (120 mg, 88% yield). R_f = 0.40 (petrol / diethyl ether 7:3).

b: Degradation of 2,2-dichloro-1-(1-methyl-1H-pyrrol-2-yl)-3-(4-substituted) propane -1,3-dione.

General procedure

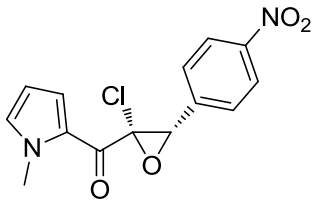


Under nitrogen, 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)-3-(4-substituted) propane -1,3-dione (1 mmol) was dissolved in MeOH (1mL) and added to NaOMe (2N, 1.1 mL, 2.2 eq.) at 0°C in 25 mL round bottomed flask. The mixture allowed stirring for a further one hour at room temperature. The solvents were evaporated under reduced pressure before adding 30 mL of water. The product was extracted using ethyl acetate (3 x 15 mL) and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure.

X	H [a]	OMe [a]
Yield %	100%	100%

a: NMR Yield,

2-chloro-3-(4-nitrophenyl)oxiran-2-yl)(1-methyl-1H-pyrrol-2-yl)methanone (4.1)



4.1

$C_{14}H_{11}ClN_2O_4$

MW: 306.70 g mol^{-1}

Procedure 1: Under nitrogen, sodium bis(trimethylsilyl) amide (2M in THF, 0.275 mL, 0.55 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-*1H*-pyrrol-2-yl)ethanone (96 mg, 0.50 mmol) was dissolved in dry THF (1 mL) and then added to the sodium bis(trimethylsilyl) amide dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzalaldehyde (76 mg, 0.50 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 5:5). The product (**4.1**) was obtained as white solid (30 mg, 20% yield).

Procedure 2

Under nitrogen, NaH, 60% dispersion in mineral oil (22 mg, 0.55 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (96 mg, 0.50 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzalaldehyde (76 mg, 0.50 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 5:5). The product (**4.1**) was obtained as white solid (81 mg, 53% yield). mp = 123-124˚C, R_f = 0.40 (petrol / diethyl ether 5:5). R_f = 0.40 (petrol / diethyl ether 5:5).

MP: 123-124˚C,

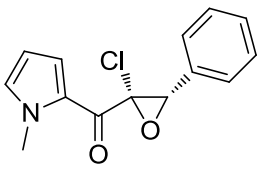
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 – 8.31 (m, 2H), 7.68 – 7.65 (m, 2H), 7.35 (dd, *J* = 4.3, 1.7 Hz, 1H), 7.02 (t, *J* = 2.0 Hz, 1H), 6.29 (dd, *J* = 4.3, 2.4 Hz, 1H), 4.50 (s, 1H), 4.01(s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0 (C=O), 148.5 (C), 138.8 (C), 133.8 (C-H), 128.4 (C-H), 125.8 (C), 123.6 (C-H), 123.0 (C-H), 118.5 (C-H), 109.8 (C-H), 80.8 (C), 61.7 (C-H), 37.8 (CH_3).

IR: υ_{max}/cm^{-1} 1647.7 (C=O).

HRMS (APCI) calcd for $C_{14}H_{11}ClN_2O_4$ $[M+H]^+$: 307.0480, observed: 307.0482.

***(2-chloro-3-phenyloxiran-2-yl)(1-methyl-1H-pyrrol-2-yl)methanone* (4.2)**



4.2
$C_{14}H_{12}ClNO_2$
MW: 261.70 $gmol^{-1}$

Under nitrogen, NaH, 60% dispersion in mineral oil (44 mg, 1.1 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-1H-pyrrol-2-yl)ethanone (192 mg, 1mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to benzalaldehyde (106 mg, 1 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 1:1). The product (**4.2**) was obtained as yellow solid (120 mg, 47% yield). R_f = 0.18 (petrol / diethyl ether 9:1).

MP: 95-96˚C,

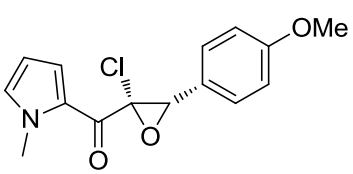
1H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H), 7.42 – 7.35 (m, 3H), 7.20 (dd, *J* = 4.3, 1.6 Hz, 1H), 6.97 (t, *J* = 2.0 Hz, 1H), 6.43 (s, 1H), 6.19 (dd, *J* = 4.3, 2.4 Hz, 1H), 3.94 (s, 3H).

13C NMR (101 MHz, $CDCl_3$) δ 191.7 (C=O), 178.1 (C) , 134.7 (C-H), 134.1(C), 129.5 (C-H), 129.1(C-H), 129.0 (C-H), 127.1(C), 125.6 (C-H), 110.3 (C-H), 61.4 (C-H), 37.8 (CH_3).

IR: $\upsilon max/cm^{-1}$ 1734.4 (C=O).

HRMS (APCI) calcd for $C_{14}H_{12}ClNO_2$ $[M+H]^+$: 262.0629, observed: 262.028.

(2-chloro-3-(4-methoxyphenyl)oxiran-2-yl)(1-methyl-1H-pyrrol-2-yl)methanone (4.3)



4.3
$C_{15}H_{14}ClNO_3$
MW: 291.73 g mol^{-1}

Procedure 1: Under nitrogen, NaH, 60% dispersion in mineral oil (44 mg, 1.1 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (192 mg, 1mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes

and allowed to stir for a further one hour. The mixture was added to *p*-methoxybenzalaldehyde (136 mg, 1mmol / 1 mL of dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1). The product (**4.3**) was obtained as yellow solid (110 mg, 38% yield).

Procedure 2

Under nitrogen, NaH, 60% dispersion in mineral oil (30 mg, 0.756 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one (226 mg, 0.687 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for 3 hour. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1) to give **4.3** as yellow solid (34% yield). R_f = 0.10 (petrol / diethyl ether 8:2).

MP: 58-59˚C,

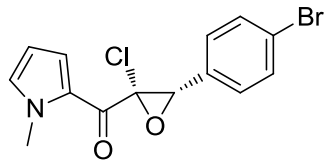
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.37 (m, 2H), 7.20 (dd, *J* = 4.3, 1.7 Hz, 1H), 6.96 (t, *J* = 2.1 Hz, 1H), 6.91 – 6.89 (m, 2H), 6.41(s, 1H), 6.19 (dd, *J* = 4.3, 2.4 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.6 (C=O), 178.4 (C) , 160.4 (C), 134.6 (C-H), 130.4 (C-H), 127.1 (C), 125.8 (C), 125.5 (C-H), 114.6 (C-H), 110.2 (C-H), 61.4 (C-H), 55.4 (CH_3), 37.7 (CH_3).

IR: υ_{max}/cm^{-1} 1727.0 (C=O).

HRMS (APCI) calcd for $C_{15}H_{14}ClNO_3$ $[M]^+$: 291.0657, observed: 291.0652.

(3-(4-bromophenyl)-2-chlorooxiran-2-yl)(1-methyl-1H-pyrrol-2-yl) methanone (4.4)



4.4
$C_{14}H_{11}BrClNO_2$
MW: 340.60 g mol-1

Under nitrogen, NaH, 60% dispersion in mineral oil (14 mg, 0.34 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (60 mg, 0.31 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to *p*-bromobenzalaldehyde (57 mg, 0.31 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1). The product (**4.4**) was obtained as white solid (75 mg, 71% yield). R_f = 0.19 (petrol / diethyl ether 8:2).

MP: 66-68˚C,

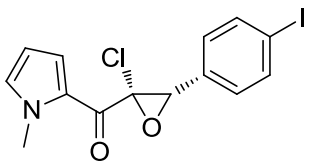
^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.58 – 7.51 (m, 2H), 7.37 – 7.34 (m, 2H), 7.23 – 7.22 (m, 1H), 6.99 (t, *J* = 2.0 Hz, 1H), 6.39 (s, 1H), 6.22 – 6.20 (m, 1H), 3.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 191.1 (C=O), 177.6 (C) , 135.0 (C-H), 133.2 (C), 132.3 (C-H), 130.6 (C-H), 127.0 (C), 125.7 (C-H), 123.8 (C), 110.4 (C-H), 60.4 (C-H), 37.8 (CH_3).

IR: υ_{max}/cm^{-1} 1731.3 (C=O).

HRMS (APCI) calcd for $C_{14}H_{11}BrClNO_2$ $[M+H]^+$: 341.9712; observed: 341.9709.

(2-chloro-3-(4-iodophenyl)oxiran-2-yl)(1-methyl-1H-pyrrol-2-yl)methanone (4.5)



4.5
$C_{14}H_{11}ClINO_2$
MW: 387.60 g mol-1

Under nitrogen, NaH, 60% dispersion in mineral oil (22 mg, 0.55 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (96 mg, 0.50 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to *p*-iodobenzalaldehyde (116 mg, 0.50 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under

reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1). The product (**4.5**) was obtained as yellow solid (170 mg, 88% yield). R_f = 0.18 (petrol / diethyl ether 9:1).

MP: 76-77˚C,

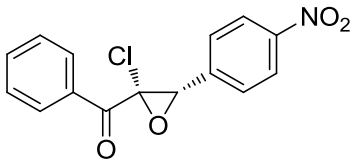
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 2H), 7.30 – 7.20 (m, 2H), 7.00 (t, *J* = 1.9 Hz, 1H), 6.36 (s, 1H), 6.22 (dd, *J* = 4.3, 2.4 Hz, 1H), 3.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.1 (C=O), 177.6 (C) , 138.3 (C-H), 135.0 (C-H), 133.9 (C), 130.7 (C-H), 127.0 (C), 125.7 (C-H), 110.4 (C-H), 95.7 (C), 60.6 (C-H), 37.8 (CH_3).

IR: υ_{max}/cm^{-1} 1730.4 (C=O).

HRMS (NSI) calcd for $C_{14}H_{11}ClINO_2$ $[M+H]^+$: 387.9596; observed: 387.9597.

(2-chloro-3-(4-nitrophenyl)oxiran-2-yl)(phenyl)methanone (4.6)



4.6
$C_{15}H_{10}ClNO_4$
MW: 303.70 g mol-1

Under nitrogen, NaH, 60% in mineral oil (220 mg, 5.5 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-phenylethan-1-one (945 mg, 5 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzalaldehyde (551 mg, 5 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 8:2). The product (**4.6**) was obtained as white oil (512 mg, 34% yield). R_f = 0.34 (petrol / diethyl ether 8:2).

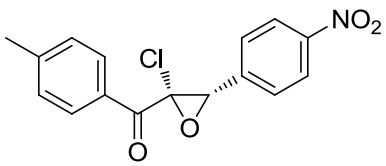
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 – 8.32 (m, 2H), 8.17 – 8.13 (m, 2H), 7.73 – 7.68 (m, 3H), 7.61 – 7.55 (m, 2H), 4.56 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.8 (C=O), 148.6 (C), 138.3 (C), 135.0 (C-H), 131.7 (C), 130.1(C-H), 129.1 (C), 128.5 (C-H), 123.6 (C-H), 80.4 (C), 61.0 (C-H).

IR: υ_{max}/cm^{-1} 1694.0 (C=O).

HRMS (NSI) calcd for $C_{15}H_{10}ClNO_4$ $[M+Na]^+$: 326.0191; observed: 326.0194.

(2-chloro-3-(4-nitrophenyl)oxiran-2-yl)(p-tolyl)methanone (4.7)



4.7
$C_{16}H_{12}ClNO_4$
MW: 317.72 g mol-1

Under nitrogen, NaH, 60% dispersion in mineral oil (22 mg, 0.55 mmol) was added to a 25 mL round bottomed flask. The 2,2-dichloro-1-(p-tolyl)ethan-1-one (102 mg, 0.5 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzalaldehyde (76 mg, 0.5 mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9.5:0.5). The product (**4.7**) was obtained as white solid (146 mg, 92% yield). R_f = 0.44 (petrol / diethyl ether 8:2).

MP: 111-112˚C,

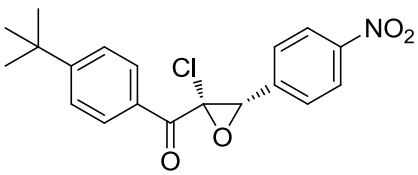
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 6.8, 1.9 Hz, 2H), 8.05 (d, *J* = 7.9 Hz, 2H), 7.70 (dd, *J* = 6.8, 1.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 4.53 (s, 1H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.5 (C=O), 148.6 (C), 146.3 (C), 138.5 (C), 130.2 (C-H), 129.8 (C-H), 129.2 (C), 128.4 (C-H), 123.6 (C-H), 80.5 (C), 61.0 (C-H), 22.1 (CH_3).

IR: υ_{max}/cm^{-1} 1694.7 (C=O).

HRMS (APCI) calcd for $C_{16}H_{12}ClNO_4$ $[M+H]^+$: 318.0528; observed: 318.0528.

(4-(tert-butyl)phenyl)(2-chloro-3-(4-nitrophenyl)oxiran-2-yl)methanone (4.8)



4.8
$C_{19}H_{18}ClNO_4$
MW: 359.80 g mol^{-1}

Under nitrogen, NaH, 60% dispersion in mineral oil (18 mg, 0.458 mmol) was added to a 25 mL round bottomed flask. The 1-(4-(*tert*-butyl)phenyl)-2,2-dichloroethan-1-one (117 mg, 0.417 mmol) was dissolved in dry THF (1 mL) and then added to the NaH dropwise over 5 minutes and allowed to stir for a further one hour. The mixture was added to *p*-nitrobenzalaldehyde (63 mg, 0.417mmol / 1 mL dry THF) and left to stir for 1h. The mixture was quenched by adding to NH_4Cl (20 mL), and the product was

extracted using ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1). The product (**4.8**) was obtained as white solid (110 mg, 74% yield). R_f = 0.43 (petrol / diethyl ether 9:1).

MP: 151-152˚C,

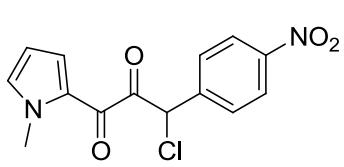
^{1}H NMR (300 MHz, CDCl3) δ 8.37 – 8.34 (m, 2H), 8.11 – 8.08 (m, 2H), 7.72 – 7.69 (m, 2H), 7.61 – 7.58 (m, 2H), 4.53 (s, 1H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4 (C=O), 158.2 (C), 148.6 (C), 138.5 (C), 130.1 (C-H), 129.0 (C), 128.4 (C-H), 126.1 (C-H), 123.6 (C-H), 80.5 (C), 61.0 (C-H), 35.5 (C), 31.1 (CH_3).

IR: υ_{max}/cm^{-1} 1683.8 (C=O).

HRMS (APCI) calcd for $C_{19}H_{18}ClNO_4$ $[M+H]^+$: 360.0997; observed: 360.0996.

3-chloro-1-(1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl)propane-1,2-dione (4.9)



4.9

$C_{14}H_{11}ClN_2O_4$

MW: 306.70 gmol^{-1}

A solution of (3-chloro-3-(4-nitrophenyl)oxiran-2-yl)(1-methyl-1*H*-pyrrol-2-yl)methanone (153 mg, 0.5 mmol) in 4 ml of toluene was refluxed for 24h. Petrol (10 mL) was added and the solvents were removed *in vacuo*. The product was obtained as yellow solid (150 mg, 98% yield). R_f = 0.27 (petrol / diethyl ether 7:3).

MP: 101-102˚C,

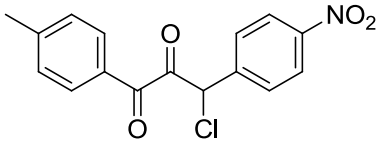
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.24(m, 2H), 7.71 – 7.67 (m, 2H), 7.29 – 7.27 (m, 1H), 7.03 (t, *J* = 2.1 Hz, 1H), 6.48 (s, 1H), 6.24 (dd, *J* = 4.4, 2.4 Hz, 1H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5(C=O), 176.8 (C=O), 148.3 (C), 141.3 (C), 135.4 (C-H), 129.9 (C-H), 126.9 (C), 126.0 (C-H), 124.1 (C-H), 110.6 (C-H), 59.4 (C-H), 37.8 (CH_3).

IR: υ_{max}/cm^{-1} 1729.0 (C=O), 1623.9 (C=O).

HRMS (NSI) calcd for $C_{14}H_{11}ClN_2O_4$ $[M+H]^+$: 307.0480; observed: 307.0484.

3-chloro-3-(4-nitrophenyl)-1-(p-tolyl)propane-1,2-dione (4.10)



4.10
$C_{16}H_{12}ClNO_4$
MW: 317.72 g mol^{-1}

A solution of (2-chloro-3-(4-nitrophenyl) oxiran-2-yl) (*p*-tolyl) methanone (106 mg, 0.33 mmol) in 4 ml of toluene was refluxed for 6h. Petrol (4mL) was added and the solvents were removed *in vacuo*. The product (**4.10**) was obtained as yellow solid (104 mg, 98% yield). R_f = 0.29 (petrol / diethyl ether 8:2).

MP: 96-98˚C,

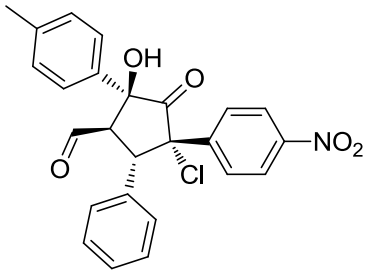
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.38 (s, 1H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4 (C=O), 189.8 (C=O), 148.5 (C), 147.2 (C), 140.3 (C), 130.5 (C-H), 130.0 (C-H), 129.9 (C-H), 129.4 (C), 124.2 (C-H), 59.5 (C-H), 22.1(CH_3).

IR: υ_{max}/cm^{-1} 1720.3 (C=O), 1662.5 (C=O).

HRMS (NSI) calcd for $C_{16}H_{12}ClNO_4$ $[M+H]^+$: 318.0528; observed: 318.0526.

4-chloro-2-hydroxy-4-(4-nitrophenyl)-3-oxo-5-phenyl-2-(p-tolyl)cyclopentane-1-carbaldehyde (4.11)



4.11
$C_{25}H_{20}ClNO_5$
MW: 449.88 g mol^{-1}

To a solution of cinnamaldehyde (26 mg, 0.2 mmol, 2 equiv.) in toluene were added successively the (*S*)-α,α-Bis[3,5-bis (trifluoromethyl) phenyl]-2-pyrrolidinemethanol trimethylsilyl ether catalyst (12 mg, 0.02mmol) and the 3-chloro-3-(4-nitrophenyl)-1-(*p*-tolyl)propane-1,2-dione (32 mg, 0.1 mol). The mixture was stirred at room temperature for 3h. Then mixture was quenched with 10 mL of 1M HCl solution and extracted three times with 20 mL of DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (SiO_2) (petrol / diethyl ether, 9:1 then 6:4). The product (**4.11**) was obtained as white solid (33 mg, 73% yield). R_f = 0.4 (petrol / diethyl ether 6:4).

MP: 134-135 °C.

$[\alpha]^{22}_D$ = -38.4 (c = 1.25 in MeOH)

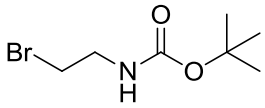
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 1.8Hz, 1H), 8.25 (d, *J* = 8.5Hz, 2H), 7.51 (d, *J* = 9.1Hz, 2H), 7.47 (d,*J* = 8.5Hz, 2H), 7.32-7.21 (m, 5H), 6.85 (d, *J* = 7.3Hz, 2H), 4.48 (d, *J* = 12.4Hz, 1H), 4.01 (d,t, *J* = 12.4Hz , 1.8Hz, 1H), 3.29 (d, *J* = 1.8Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8 (C=O), 198.1 (C=O), 148.0 (C), 143.2 (C) , 139.5 (C), 135.6 (C), 131.8 (C), 129.9 (C-H), 129.2 (C-H), 129.1 (C-H), 128.6 (C-H), 128.4 (C-H), 125.7 (C-H), 123.6 (C-H), 81.8 (C), 77.3 (C), 60.0 (C-H), 53.9 (C-H), 21.3 (CH_3).

IR: υ_{max}/cm^{-1} 3485.3 (OH), 1763.6 and 1724.5 (C=O).

HRMS (NSI) calcd for $C_{25}H_{20}ClNO_5$ $[M+NH_4]^+$: 467.1368; observed: 467.1366.

N-(tert.-butoxycarbonyl)-2-bromoethylamine (6.4)



6.4

$C_7H_{14}BrNO_2$

MW:224.10 gmol^{-1}

2.05 g (10 mmol) of 2-bromoethylamine hydrobromide are dissolved in 20 ml of THF/water 1/1 (v/v) and 3.03 g (4.12 mL) of triethylamine are added. The mixture is then cooled to 0 ˚C and a solution of 2.18 g (10 mmol) of di-*tert*.-butyldicarbonate in 3 ml of THF are added dropwise under stirring. The reaction mixture is allowed to slowly reach room temperature and stirring is continued for 20 h. The solvent is removed on the rotary evaporator and the remainder is taken up in 40 ml of ethyl acetate. It is then washed three times with 20 ml of saturated sodium bicarbonate and then with 20 ml of water. The organic solution is dried with $MgSO_4$, the solvent is removed on the rotary evaporator and the oily product (**6.4**) is dried for 3 h at 40˚C. in a high vacuum. 1.65 g (74% yield), yellow viscous oil. R_f =0.44 (petrol / diethyl ether 7:3).

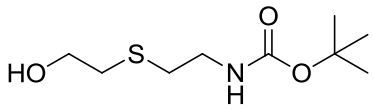
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 1H), 3.47 (t, *J* = 4.9 Hz, 2H), 3.40 (t, *J* = 5.2 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.68 (CO), 79.81 ($C(CH_3)_3$), 42.40 (CH_2), 32.80(CH_2), 28.41(CH_3).

IR: υ_{max}/cm^{-1} 3339 (N-H), 2975 (C-H), 1690 (C=O).

HRMS (APCI) $[M+H]^+$ calcd for $C_7H_{14}BrNO_2$: 224.0281 observed: 224.0283.

tert-butyl (2-((2-hydroxyethyl)thio)ethyl)carbamate (6.3)



6.3
$C_9H_{19}NO_3S$
MW: 221.32 $gmol^{-1}$

To a solution of *tert*-butyl (2- bromoethyl) carbamate (0.448 g) and 2-mercaptoethanol (0.156 g) in ethanol (2 mL) was added a solution of sodium methoxide in methanol (28percent, 0.388 g) at room temperature. The mixture was stirred for 3 days and concentrated under reduced pressure. Water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was separated and purified by column chromatography (petrol / diethyl ether 9:1) to give the title compound (**6.3**) (0.39 g) as a colourless oil, yield = 88%. R_f = 0.23 (petrol / diethyl ether 9:1).

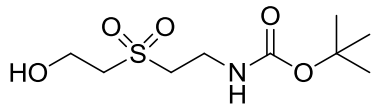
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (s, 1H), 3.74 (q, *J* = 6.0 Hz, 2H), 3.32 (q, *J* = 6.7 Hz, 2H), 2.74 (t, *J* = 5.9 Hz, 3H), 2.66 (t, *J* = 6.6 Hz, 2H), 1.44 (s, 9H).

^{13} C NMR (100 MHz, $CDCl_3$) δ 155.90 (CO), 79.30 ($C(CH_3)_3$), 60.74 (C-H), 3978(C-H), 34.55 (C-H), 32.00(CH_2), 28.17(CH_3).

IR: υ_{max}/cm^{-1} 3350(N-H), 2927 (C-H), 1688 (C=O).

HRMS (NSI) $[M+H]^+$ calcd for $C_9H_{19}NO_3S$: 222.1158; observed: 222.1158.

tert-butyl (2-((2-hydroxyethyl)sulfonyl)ethyl)carbamate (6.2)



6.2
$C_9H_{19}NO_5S$
MW: 253.32 $gmol^{-1}$

tert-butyl (2-((2-hydroxyethyl) thio) ethyl) carbamate (0.221g, 1 mmol) was dissolved in DCM (1mL) in a 25 mL round bottom flask under N_2 and cooled in an icebath (0 ˚C). 3-chlorobenzoperoxoic acid (mCPBA) (0.345 g, 2 mmol) in DCM (1 mL) was added. The reaction mixture was removed from the ice-bath and stirred at ambient temperature for 3 hr.

20 mL of sat. Sodium thiosulfate was added and the organic layer was washed with 30 mL of $NaHCO_3$. The reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extractions were washed with brine solution (1 x 20 ml) and dried over $MgSO_4$. Volatiles were removed *in vacuo* to give 0.150g as crude. The crude was separated

and purified by column chromatography (petrol / diethyl ether 9:1) then wash with only ethyl acetate to give (0.088g, 40% yield) of *tert*-butyl (2-((2-hydroxyethyl) sulfonyl) ethyl) carbamate (**6.2**) as a clear, colorless oil. R_f = 0.68 (petrol / diethyl ether 9:1).

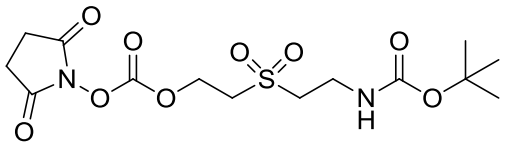
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (t, *J* = 6.1 Hz, 1H), 4.27 – 3.91 (m, 2H), 3.75 – 3.50 (m, 2H), 3.40 (t, *J* = 6.1 Hz, 3H), 3.25 (t, *J* = 5.2 Hz, 2H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.90 (CO), 77.31($C(CH_3)_3$), 56.16 (C-H), 55.96(C-H), 54.33 (C-H), 34.22(C-H), 28.25(CH_3).

IR: υ_{max}/cm^{-1} 3363(N-H), 2978 (C-H), 1689 (C=O).

HRMS (NSI) $[M+H]^+$ calcd for $C_9H_{19}NO_5S$: 254.1057; observed: 254.1053.

tert-butyl (2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy) carbonyl) oxy) ethyl) sulfonyl) ethyl) carbamate (6.1)



6.1
$C_{14}H_{22}N_2O_9S$
MW: 394.40 gmol^{-1}

tert-butyl (2-((2-hydroxyethyl)sulfonyl) ethyl) carbamate (0.253 g, 1 mmol) was dissolved in dry THF (1mL) in a 100 mL round bottom flask under N_2 at room temperature. 0.026 g, 1.1 mmol of sodium hydride was added. *bis(2,5-dioxopyrrolidin-1-yl) carbonate* (0.281 g, 1.1 mmol / 10 mL dry THF) *was* added to the mixture. The reaction mixture is stirred at room temperature for 6 hr. The reaction mixture was quenched with ammonium chloride (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extractions were washed with brine solution (1 x 20 ml) and dried over $NaSO_4$. The organic solvent was removed *in vacuo* to give 0.23g as crude. The crude was separated and purified by column chromatography (ethyl acetate: petrol 6/4) then wash with only ethyl acetate to give (21 mg, 5% yield) of tert-butyl (2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy) carbonyl) oxy) ethyl) sulfonyl) ethyl) carbamate (**6.1**) as a clear, colorless oil R_f = 0.21(ethyl acetate/petrol 6:4) .

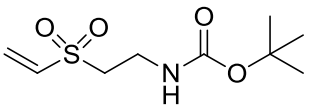
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.78 (t, *J* = 5.7 Hz, 2H), 3.80 – 3.60 (m, 2H), 3.46 (t, *J* = 5.7 Hz, 2H), 3.32 (t, *J* = 7.0, 5.7 Hz, 2H), 2.88 (s, 4H), 1.46 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.37 (CO), 155.79 (CO), 151.04 (CO), 81.83 ($C(CH_3)_3$), 63.95 (C-H), 54.79(C-H), 52.55 (C-H), 34.38 (C-H), 28.39 (C-H), 25.53 (C-H).

IR: υ_{max}/cm^{-1} 3383(N-H), 2979, 2936 (C-H), 1815, 1791, and 1740 (C=O).

HRMS (NSI) $[M+Na]^+$ calcd for $C_{14}H_{22}N_2O_9S$: 417.038; observed: 417.0930 .

tert-butyl (2-((2-((((2,5-dioxopyrrolidin-1-yl) oxy) carbonyl)oxy) ethyl) sulfonyl) ethyl) carbamate (6.12)



6.12
$C_9H_{17}NO_4S$
MW: 235.30 $gmol^{-1}$

tert-butyl (2-((2-hydroxyethyl)sulfonyl)ethyl)carbamate (51 mg, 0.2 mmol) was dissolved in DCM (1mL) in a 25 mL round bottom flask under N_2 at room temperature. *bis(2,5-dioxopyrrolidin-1-yl) carbonate* (77 mg, 0.3 mmol / 1 mL DCM), and triethylamine (40 mg, 0.4 mmol / 1 mL DCM) *was* added. The reaction mixture is stirred at ambient temperature for 6 hr. The reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extractions were washed with 30 mL of $NaHCO_3$ then with brine solution (1 x 20 ml). The organic solvent was removed *in vacuo* to give 55 mg as crude. The crude was separated and purified by column chromatography (ethyl acetate / petrol 7:3) then wash to give (25 mg, 37% yield) of *tert-butyl (2-(vinylsulfonyl)ethyl)carbamate* as a clear, colorless oil. R_f = 0.59 (ethyl acetate / petrol 7:3)

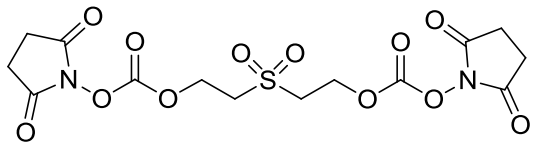
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 9.6 Hz, 1H), 6.48 (d, *J* = 16.8 Hz 1H), 6.22 (d, *J* = 9.8 Hz, 1H), 5.20 (s, 1H), 3.59 (q, *J* = 6.1 Hz, 2H), 3.23 (t, *J* = 6.0 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.70 (CO), 136.10 (C-H), 131.00 (C-H), 77.31($C(CH_3)_3$), 53.95 (C-H), 34.47(C-H), 28.29 (CH_3).

IR: υ_{max}/cm^{-1} 3377(N-H), 2978 (C-H), 1703 (C=O).

MS (ES^+) calcd for $C_9H_{17}NO_4S$: 258; observed: 258

bis(2,5-dioxopyrrolidin-1-yl) (sulfonylbis(ethane-2,1-diyl)) dicarbonate (6.15)



6.15

$C_{14}H_{16}N_2O_{12}S$

MW: 436.35 $gmol^{-1}$

Procedure1:*bis(2,5-dioxopyrrolidin-1-yl) carbonate* (0.512 g, 2 mmol / 1mL dry MeCN) was added to a solution of 2,2'-sulfonyldiethanol (0.154 g, 1 mmol), and pyridine (0.161 mL, 2 mmol) in MeCN (2 ml) under N_2 in a 25 mL Round-bottom flasks. The suspension was stirred at room temperature for 1h or until all precipitates is disappeared. The solvent was evaporated under reduced pressure and the crude was used directly in the next step.

Procedure 2 (Ammonium salt)

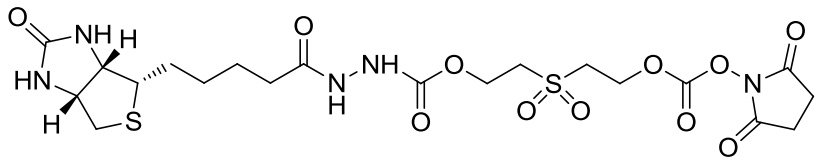
bis(2,5-dioxopyrrolidin-1-yl) carbonate (0.512 g, 2 mmol / 1mL dry MeCN) was added to a solution of 2,2'-sulfonyldiethanol (0.154 g, 1 mmol), and pyridine (0.161 mL, 2 mmol) in MeCN (2 ml) under N_2 in a 25 mL Round-bottom flasks. The suspension was stirred at room temperature for 1h or until all precipitates is disappeared. Saturated solution of NH_4Cl (15 mL) was added and the white precipitate for the products was appeared. Filtered the precipitate and washed with ethyl acetate. 0.35g (80% yields).

^{1}H NMR (400 MHz, DMSO) δ 4.76 – 4.69 (t, *J* = 5.4 Hz, 4H), 3.81 – 3.72 (t, *J* = 5.6 Hz, 4H), 2.84 – 2.79 (s, 8H).

^{13}C NMR (100 MHz, DMSO) δ 170.30 (CO), 151.34 (CO), 64.44 (C-H), 52.35 (C-H), 25.90 (C-H).

HRMS (ES^+) $[M+Na]^+$ calcd for $C_{14}H_{16}N_2O_{12}S$: 459.0322; observed: 459.0325.

2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 2-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)hydrazinecarboxylate (6.13)

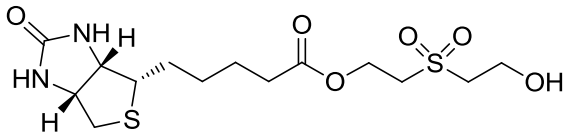


6.13
$C_{20}H_{29}N_5O_{11}S_2$
MW: 579.60 $gmol^{-1}$

5-((3aS,4S,6aR)-2-oxohexahydro- 1*H*-thieno [3,4-d]imidazol-4-yl) pentanehydrazide (0.041 g, 0.16 mmol / 1mL dry MeCN) was added to bis(2,5-dioxopyrrolidin-1-yl) (sulfonylbis(ethane-2,1-diyl)) dicarbonate (0.069 g, 0.16 mmol, 1mL dry MeCN) under N_2 in a 25 mL Round-bottom flasks. The suspension was stirred at room temperature for 1h. The reaction mixture was filtered and kept under N_2 in the freezer.

HRMS (ES^+) $[M+Na]^+$ calcd for $C_{20}H_{29}N_5O_{11}S_2$: 602.1203; observed: 602.1232.

2-((2-hydroxyethyl)sulfonyl)ethyl-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d] imidazol-4-yl)pentanoate (6.19)



6.19
$C_{14}H_{24}N_2O_6S_2$
MW: 380.48 $gmol^{-1}$

Biotin (0.391 g, 1.6 mmol), DCC (0.391 g, 1.9 mmol), and DMAP (0.028 g, 0.23 mmol) were added to a solution of 2,2'-sulfonyldiethanol (0.247 g, 1.6 mmol) in dry dichloromethane (12 ml) under N_2 in a 250 mL Round-bottom flasks. The suspension was stirred at room temperature for 9 days. After distilling off the solvent the remainder was purified by column chromatography (silica gel; dichloromethane/MeOH 9:1), 0.444 g, 73% yield) to give **6.19** as white solid. R_f = 0.5 (dichloromethane/MeOH 9:1)

MP: 134-136˚C

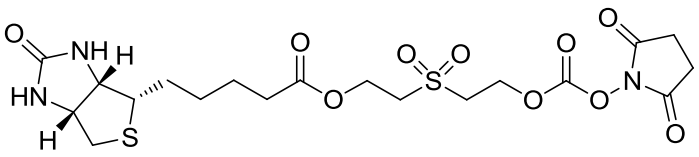
^{1}H NMR (300 MHz, DMSO) δ 6.44 (s, 1H), 6.38 (s, 1H), 4.38 (t, *J* = 5.9 Hz, 2H), 4.34 – 4.09 (m, 2H), 3.84 – 3.73 (m, 4H), 3.51 (t, *J* = 5.9 Hz, 1H), 3.30 – 3.21 (m, 3H), 3.14 – 2.77 (m, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.68 – 1.27 (m, 6H).

^{13}C NMR (100 MHz, DMSO) δ 173.00 (CO), 163.25 (CO), 61.53 (C-H), 59.71 (CH), 57.68 (C-H), 56.92(C-H), 56.61 (C-H), 55.85 (C-H), 55.52 (C-H), 55.41 (C-H), 53.44 (C-H), 33.68 (C-H), 28.47 (C-H), 24.81 (C-H).

IR: υ_{max}/cm^{-1} 3264(N-H), 2937 (C-H), 1686 (C=O).

HRMS (NSI)$[M+H]^+$ calcd for $C_{14}H_{24}N_2O_6S_2$: 381.1149; observed: 381.1151.

2-((2-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)oxy)ethyl)sulfonyl)ethyl 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoate (6.17)



6.17

$C_{19}H_{27}N_3O_{10}S_2$

MW: 521.56 gmol^{-1}

bis(2,5-dioxopyrrolidin-1-yl) carbonate (0.074 g, 0.281 mmol / 1mL dry MeCN) was added to a solution of 2-((2-hydroxyethyl)sulfonyl)ethyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-d]imidazol-4-yl)pentanoate (0.100 g, 0.263 mmol), and pyridine (0.080 mL, 0.263 mmol) in MeCN (2 ml) under N_2 in a 25 mL Round-bottom flasks. The suspension was stirred at room temperature for 30 minutes. After distilling off the solvent under reduces pressure, the crude was isolated as a white solid precipitate.

HRMS (ES$^+$) $[M+H]^+$ calcd for $C_{19}H_{27}N_3O_{10}S_2$: 522.1211; observed: 522.1208

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Appendix 1

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Reduction of 2,2,2-trichloro-1-arylethanones by RMgX: mechanistic investigation and the synthesis of substituted α,α-dichloroketones†

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2,2,2-Trichloro-1-arylethanones undergo high yielding reductions to the corresponding 2,2-dichloro-1-arylethanones in the presence of RMgX. A single electron transfer mechanism for the reaction is proposed based on trapping experiments. Reaction of the intermediate enolates with a range of electrophiles is described, providing a convenient route to substituted α,α-dichloro-β-hydroxyketones and related molecules.

α,α-Dichlorocarbonyls are versatile synthetic intermediates, typically formed by α-chlorination of carbonyls,[1] chlorination of silyl enolates,[2] electrochemical or metal mediated reductions,[3] aldol reactions[4] or cycloadditions with dichloroketene.[5] α,α-Dichlorocarbonyl groups have been employed in intramolecular radical cyclisations,[6] have been converted to chloroalkenes,[7] chlorooxiranes allowing access to α-keto esters[8] and heteroaromatics,[9] have been used as chlorinating agents[10] and were found in the natural product chlorotonil A.[11] In designing new routes to functionalised α,α-dichlorocarbonyls, we decided to investigate conditions for the reduction of 2,2,2-trichloro-1-arylethanones. We envisaged that 2,2,2-trichloro-1-arylethanones being sterically hindered and electron-deficient aromatic ketones, would form reactive ketyl radical anions in the presence of a suitable single electron donor such as a Grignard reagent.[12] Further reaction of the intermediate ketyl radical anion would then provide a new route towards substituted α,α-dichloroketones.

Our initial investigations involved the addition of commercially available 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone (**1a**) to PhMgBr, followed by quenching with excess aqueous NH_4Cl.

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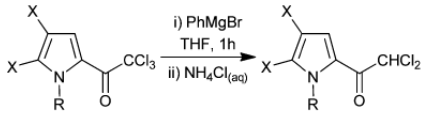
† Electronic supplementary information (ESI) available: Experimental procedures, ^1H and ^{13}C spectra and X-ray structures. Crystallographic data for **1d**, **3a**, **3b**, **3f**, **3g** and **3h**, have been deposited with the CCDC, deposition nos: CCDC 916095–916100. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc39147g

Table 1 Reaction of PhMgBr with substituted 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanones[a]



1(a-e) 2(a-e)

Entry	R	X	PhMgBr	Temp.	Product	Yield[b] (%)
1	H	H	1.1 eq.	0 °C	**2a**	50
2	H	H	1.1 eq.	r.t.	**2a**	55
3	H	H	2.2 eq.	r.t.	**2a**	90
4	Me	H	1.0 eq.	r.t.	**2b**	94
5	H	Cl	2.0 eq.	r.t.	**2c**	87
6	H	Br	2.0 eq.	r.t.	**2d**	95
7	H	I	2.0 eq.	r.t.	**2e**	93

[a] The reactions were performed by reverse addition of 1 mmol of ketone in 1 mL of THF to a 2 M solution of PhMgBr in THF. [b] Isolated yields.

With the use of 1.1 equivalents of PhMgBr, at either 0 °C or r.t., the reaction resulted in the isolation of 2,2-dichloro-1-(1*H*-pyrrol-2-yl)ethanone (**2a**) in 50–55% yield (Table 1, entries 1 and 2), formally a C–Cl to C–H reduction.

We postulated that the reaction may not go to completion due to competing deprotonation of the pyrrolic NH. Thus we re-examined the reaction of compound **1a** with 2.2 equivalents PhMgBr at r.t., and the reaction of compound **1b** (an analogous *N*-methylated compound) with 1.0 equivalents of PhMgBr (Table 1, entries 3 and 4). In both cases near-quantitative yields of the corresponding reduced compounds **2a** and **2b** were isolated after quenching of the reaction. In addition three di-halogenated pyrrole derivatives (**1c–e**) were also submitted to the optimised reaction conditions, again yielding the corresponding reduced products (**2c–e**) in high yield. Observation of this C–Cl to C–H reduction prompted us to investigate the mechanism in more detail.

After the reaction of **1a–e** with PhMgBr and quenching with aqueous NH_4Cl, a major by-product was observed by ^1H NMR spectroscopy of the crude reaction mixtures, which on isolation by silica gel chromatography was identified as 1,1′-biphenyl.

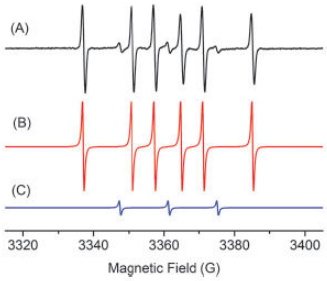


Fig. 1 (A) X-band EPR spectrum at 270 K of a THF solution resulting from the reaction of PhMgBr with ketone **1b**, in the presence of DMPO; (B) simulated spectrum of the Ph–DMPO adduct with the parameters: g = 2.0096; $a(^1H)$ = 20.3 G and $a(^{14}N)$ = 13.87 G; (C) simulated spectrum of the Ph_2–DMPO adduct, with g = 2.0095 and $a(^{14}N)$ = 13.87 G. (100 kHz modulation frequency, 1 G modulation amplitude, 0.27 mW incident microwave power).

In the case of entry 3, 40 mg of 1,1′-biphenyl could be isolated, corresponding to approximately 50% of the total added PhMgBr. The formation of significant quantities of 1,1′-biphenyl is most likely to arise from the dimerisation of phenyl radicals generated during the reaction.[13,14]

To examine this supposition further we carried out an *in situ* EPR experiment. Solutions containing ketone **1b** and PhMgBr in THF were added sequentially to an EPR tube cooled in liquid N_2. Further addition of the spin trap 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and subsequent warming to 270 K of the reaction mixture produced a species with a well-resolved, 6-line EPR spectrum (Fig. 1), corresponding to a Ph–DMPO adduct (2,2-dimethyl-5-phenylpyrrolidin-1-olate radical) with distinctive ^1H and ^{14}N hyperfine coupling constants: $a(^1H)$ = 20.3 G and $a(^{14}N)$ = 13.87 G. A minor product, the 2,2-dimethyl-5,5-diphenylpyrrolidin-1-olate radical, was also observed in the EPR spectrum (3 lines, $a(^{14}N)$ = 13.87 G). In the absence of ketone **1b** neither adduct was observed, indicating that the Ph radical is generated under the reaction conditions.

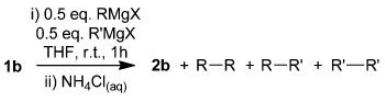
To further probe 1,1′-biphenyl formation we examined the reaction between ketone **1b** and a number of other RMgX species, where R was a *para*-substituted phenyl group (Table 2).

Reaction of 4-Me(C_6H_4)MgI with ketone **1b** (Table 2, entry 1) gave 4,4′-dimethyl-1,1′-biphenyl as a single regioisomer. One to one mixtures of *para*-substituted phenyl Grignard regents (Table 2, entries 2–4) gave in each case a mixture of 4,4′-disubstituted-1,1′-biphenyl products. This suggests that the aryl–aryl bond is being formed at the position of the original C–Mg bond, supporting the formation 1,1′-biphenyl products *via* a radical coupling mechanism. This suggests that the RMgX is donating a single electron from the R–Mg bond to the substrate.

We postulated that the overall reaction involves a late stage enolate intermediate, which is quenched by aqueous NH_4Cl to give the observed reduction product. To confirm this, ketones **1b**, **1f** and **1g** were reacted with PhMgBr and quenched with D_2O to give, in 50–96% yield, the corresponding deuterated products **2b**, **2f**, and **2g** with high levels of D incorporation (Table 3).

We then investigated the influence of the R (aryl, alkyl) and X (halogen) groups of the Grignard reagent (Table 4).

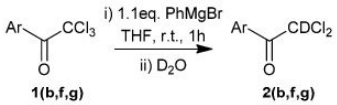
Table 2 Reaction of RMgX/R′MgX with ketone **1b**



Entry	RMgX	R′MgX	Yields[a] (%) R–R	R–R′	R′–R′
1	4-Me(C_6H_4)MgI	4-Me(C_6H_4)MgI	66	—	—
2	4-Me(C_6H_4)MgI	PhMgI	14[b]	24[b]	23
3	4-MeO(C_6H_4)MgI	4-Me(C_6H_4)MgI	43	0	16
4	4-MeO(C_6H_4)MgBr	PhMgBr	0	43	20

[a] Isolated yields. [b] Products not separable, yield determined by GC-MS.

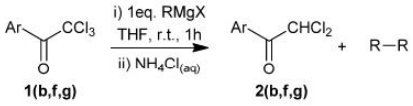
Table 3 Reaction trapping with D_2O



Ar	Product	Yield of 2[a] (%)	% D[b]
1-Methyl-1*H*-pyrrol-2-yl	(2-*d*)-**2b**	86	89
p-Tolyl	(2-*d*)-**2f**	50	>95
1-(4-(*tert*-Butyl)phenyl)	(2-*d*)-**2g**	96	93

[a] Isolated yields. [b] % Deuterium incorporation estimated by ^1H NMR.

Table 4 Influence of R and X substituents



Entry	R	X	Ar	Yield/2[a] (%)	Yield/R_2[b] (%)
1	Et	Br	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	50	nd
2	i-Pr	Cl	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	42	nd
3	Ph	Cl	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	61	45
4	Ph	Br	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	94	52
5	Ph	I	1-Methyl-1*H*-pyrrol-2-yl (**1b**)	94	62
6	Et	Br	*p*-Tolyl (**1f**)	33	nd
7	i-Pr	Cl	*p*-Tolyl (**1f**)	33	nd
8	Ph	Cl	*p*-Tolyl (**1f**)	47	35
9	Ph	Br	*p*-Tolyl (**1f**)	68	38
10	Ph	I	*p*-Tolyl (**1f**)	96	71
11	Ph	Br	1-(4-(*tert*-Butyl)phenyl) (**1g**)	71	39
12	Ph	I	1-(4-(*tert*-Butyl)phenyl) (**1g**)	98	58

[a] Isolated yields. [b] Yield based on total RMgX added.

A comparison of Et, i-Pr and Ph groups (Table 4) showed that the highest yields resulted from the use of aryl Grignards.[15] In addition, reaction yields showed the trend: X = I > Br > Cl.

Variation of solvent (THF, Et_2O and hexane) and concentration had little effect on reaction outcomes. Only with extreme dilution was any influence noticeable (see ESI†).

Therefore we propose a potential mechanism for the Grignard-mediated reduction of trichloroacetyl-substituted aromatics. We suggest that the first step of the reaction is a single electron transfer from the Grignard reagent to the ketone. This intermediate radical anion then either: (a) loses

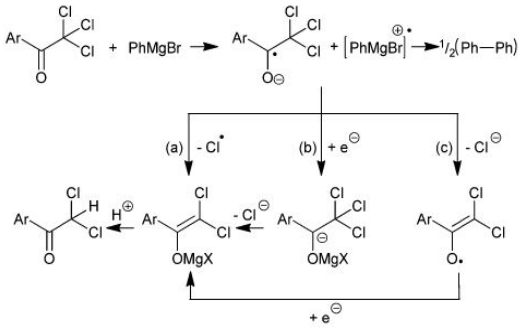
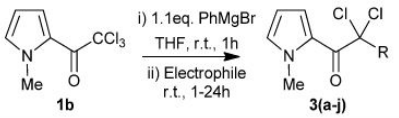


Fig. 2 Proposed reaction pathways.

Table 5 RMgX mediated reduction/functionalisation of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone



Product[a]	Electrophile	R	Yield[b] (%)
3a	PhCHO	PhCH(OH)	81[c]
3b	4-MeO(C_6H_4)CHO	4-MeO(C_6H_4)CH(OH)	85[c]
3c	4-I(C_6H_4)CHO	4-I(C_6H_4)CH(OH)	94
3d	5-Me(C_4H_2O)CHO	5-Me(C_4H_2O)CH(OH)	70
3e	C_6F_5CHO	C_6F_5CH(OH)	70
3f	4-NO_2(C_6H_4)CHO	4-NO_2(C_6H_4)CH(OH)	96[c]
3g	4-NO_2(C_6H_4)CH_2Cl	4-NO_2(C_6H_4)CH_2	37[c]
3h	4-NO_2(C_6H_4)COCl	4-NO_2(C_6H_4)C(O)	95[c]
3i	$(EtO_2C)_2CO$	$(EtO_2C)_2C(OH)$	75
3j	C_6H_5COCl	C_6H_5C(O)	50

[a] **1b** was reacted in THF with PhMgBr at r.t. for 1 h, after which a suitable electrophile was added and the mixture stirred at r.t. until TLC analysis showed that the reaction was complete. [b] Isolated yields. [c] Structures confirmed by single-crystal X-ray analysis.

a chlorine atom, (b) accepts a second electron and subsequently loses chloride or (c) loses chloride followed by addition of a second electron, to give the corresponding magnesium enolate (Fig. 2).[16]

Since the intermediate magnesium enolates can be intercepted by electrophiles, we have exploited this chemistry as a convenient "one-pot" reductive-functionalisation of 2,2,2-trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (**1b**) to give substituted α,α-dichloroketones. Reaction with 1-(chloromethyl)-4-nitrobenzene gave only a moderate yield of the expected product. Good yields were however obtained on reaction with diethyl 2-oxomalonate, aryl acid chlorides or aryl aldehydes (Table 5).[17]

In conclusion we have demonstrated a new approach to functionalised α,α-dichloroketones, *via* the reaction of commercially available RMgX reagents with 2,2,2-trichloro-1-arylethanones. Additional examination of the substrate scope and investigations into subsequent synthetic modification of the α,α-dichloroketones formed will be discussed in future publications.

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13 Trace 2-phenyltetrahydrofuran could also be detected by ^{1}H NMR and GCMS, when reactions were carried out in THF. We postulate that this is formed through radical H abstraction from the α-position of THF, followed by coupling of resulting THF derived radical with a phenyl radical.
14 Commercial PhMgBr was shown to contain <2 mg of Ph_2 per mmol.
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16 No evidence of atomic chlorine or bromine was observed by EPR. Neither C_6H_5Cl nor C_6H_5Br (the coupling products of phenyl radical and atomic halogen) could be detected by GCMS of the crude reaction mixture leading to **2b**.
17 The corresponding magnesium enolate can be prepared from **2b** through deprotonation with NaH in THF, followed by ion exchange with $MgCl_2$. The enolate was reacted with D_2O to give a 78% yield (84% deuterium incorporation by ^{1}H NMR) of (2-*d*)-**2b** or 4-NO_2(C_6H_4)CHO to give a 47% yield of **3f**.

Appendix 2

X-ray Crystallography Data

2,2-dichloro-1-(1-methyl-1H-pyrrol-2-yl)ethanone (2.16)

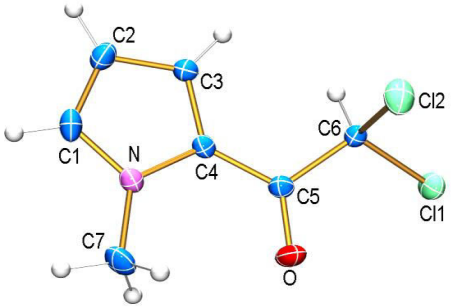

Table 1: Crystal data and structure refinement for mjh91.

Identification code	mjh91	
Chemical formula (moiety)	$C_7H_7Cl_2NO$	
Chemical formula (total)	$C_7H_7Cl_2NO$	
Formula weight	192.04	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 5.9311(3) Å	□ = 90°
	b = 10.5722(4) Å	□ = 90°
	c = 13.4606(6) Å	□ = 90°
Cell volume	844.04(7) $Å^3$	
Z	4	
Calculated density	1.511 g/cm^3	
Absorption coefficient □	0.708 mm^{-1}	
F(000)	392	
Crystal colour and size	colourless, 0.40 × 0.40 × 0.30 mm^3	
Reflections for cell refinement	4380 (□ range 3.0 to 28.6°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice □ scans	
□ range for data collection	3.0 to 28.7°	
Index ranges	h –7 to 7, k –14 to 13, l –18 to 16	
Completeness to □ = 25.0°	99.9 %	
Reflections collected	6723	
Independent reflections	1892 (R_{int} = 0.0211)	
Reflections with F^2>2□	1837	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.7650 and 0.8158	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	

Weighting parameters a, b	0.0239, 0.1694
Data / restraints / parameters	1892 / 0 / 103
Final R indices [F^2>2□]	R1 = 0.0202, wR2 = 0.0493
R indices (all data)	R1 = 0.0211, wR2 = 0.0499
Goodness-of-fit on F^2	1.075
Absolute structure parameter	0.00(5)
Extinction coefficient	0.0233(16)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.23 and −0.24 e $Å^{-3}$

2, 2-dichloro-3-hydroxy-1-(1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl) propan-1-one (2.30)

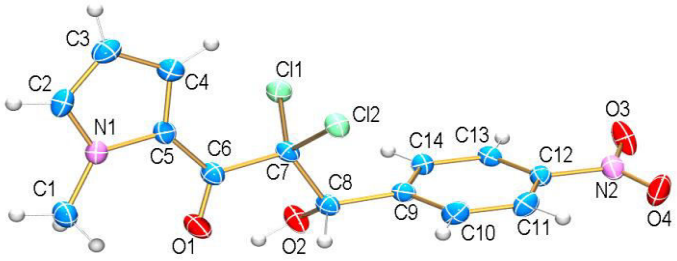

Table 1: Crystal data and structure refinement for mjh75.

Identification code	mjh75	
Chemical formula (moiety)	$C_{14}H_{12}Cl_2N_2O_4$	
Chemical formula (total)	$C_{14}H_{12}Cl_2N_2O_4$	
Formula weight	343.16	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/c1$	
Unit cell parameters	a = 8.4490(5) Å	□ = 90°
	b = 21.9722(12) Å	□ = 112.479(7)°
	c = 8.5158(6) Å	□ = 90°
Cell volume	1460.78(16) $Å^3$	
Z	4	
Calculated density	1.560 g/cm^3	
Absorption coefficient □	0.464 mm^{-1}	
F(000)	704	
Reflections for cell refinement	3678 (□ range 3.0 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice □ scans	
□ range for data collection	3.0 to 28.6°	
Index ranges	h –11 to 11, k –26 to 23, l –11 to 10	
Completeness to □ = 25.0°	98.3 %	
Reflections collected	9235	
Independent reflections	3125 (R_{int} = 0.0288)	
Reflections with F^2>2□	2589	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.98895 and 1.00000	

Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0233, 0.7057
Data / restraints / parameters	3125 / 0 / 205
Final R indices [F^2>2□]	R1 = 0.0335, wR2 = 0.0681
R indices (all data)	R1 = 0.0467, wR2 = 0.0753
Goodness-of-fit on F^2	1.067
Extinction coefficient	0.0018(7)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.31 and –0.24 e $Å^{-3}$

2, 2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(1-methyl-1H-pyrrol-2-yl) propan-1-one (2.31)

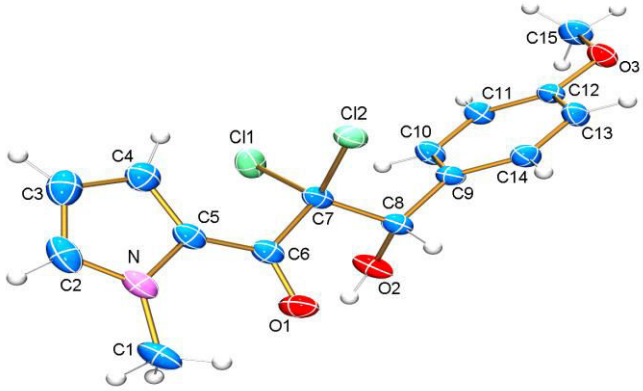

Table 1: Crystal data and structure refinement for mjh76.

Identification code	mjh76	
Chemical formula (moiety)	$C_{15}H_{15}Cl_2NO_3$	
Chemical formula (total)	$C_{15}H_{15}Cl_2NO_3$	
Formula weight	328.18	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 8.9648(6) Å	□ = 90°
	b = 12.0920(7) Å	□ = 106.344(8)°
	c = 14.0270(11) Å	□ = 90°
Cell volume	1459.11(17) $Å^3$	
Z	4	
Calculated density	1.494 g/cm^3	
Absorption coefficient □	0.454 mm^{-1}	
F(000)	680	
Crystal colour and size	colourless, 0.40 × 0.30 × 0.30 mm^3	
Reflections for cell refinement	3062 (□ range 2.9 to 28.4°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice □ scans	
□ range for data collection	2.9 to 28.4°	
Index ranges	h –11 to 10, k –15 to 13, l –18 to 18	
Completeness to □ = 25.0°	99.9 %	
Reflections collected	9278	
Independent reflections	3145 (R_{int} = 0.0284)	

Reflections with $F^2>2\square$	2539
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.8394 and 0.8759
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0342, 0.6168
Data / restraints / parameters	3145 / 0 / 196
Final R indices [$F^2>2\square$]	R1 = 0.0369, wR2 = 0.0784
R indices (all data)	R1 = 0.0509, wR2 = 0.0868
Goodness-of-fit on F^2	1.041
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.32 and –0.21 e $Å^{-3}$

2,2-dichloro-1-(1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl) propan-1-one (2.34)

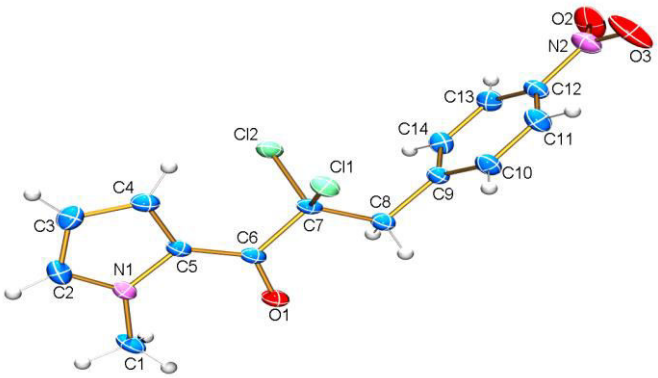

Table 1: Crystal data and structure refinement for mjh79.

Identification code	mjh79	
Chemical formula (moiety)	$C_{14}H_{12}Cl_2N_2O_3$	
Chemical formula (total)	$C_{14}H_{12}Cl_2N_2O_3$	
Formula weight	327.16	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	triclinic, $P\bar{1}$	
Unit cell parameters	a = 8.8490(11) Å	□ = 88.060(6)°
	b = 8.8572(6) Å	□ = 72.636(10)°
	c = 9.6786(9) Å	□ = 80.267(8)°
Cell volume	713.48(12) $Å^3$	
Z	2	
Calculated density	1.523 g/cm^3	
Absorption coefficient □	0.466 mm^{-1}	
F(000)	336	
Crystal colour and size	colourless, 0.30 × 0.30 × 0.10 mm^3	
Reflections for cell refinement	2302 (□ range 3.1 to 28.7°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice □ scans	
□ range for data collection	3.1 to 28.7°	
Index ranges	h –9 to 10, k –11 to 10, l –10 to 12	
Completeness to □ = 25.0°	99.8 %	
Reflections collected	5166	
Independent reflections	2967 (R_{int} = 0.0211)	
Reflections with F^2>2□	2526	
Absorption correction	semi-empirical from equivalents	

Min. and max. transmission	0.8729 and 0.9549
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0249, 0.3136
Data / restraints / parameters	2967 / 0 / 210
Final R indices [F^2>2□]	R1 = 0.0331, wR2 = 0.0711
R indices (all data)	R1 = 0.0422, wR2 = 0.0768
Goodness-of-fit on F^2	1.055
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.34 and –0.29 e $Å^{-3}$

2, 2-dichloro-3-hydroxy-1-(1-methyl-1H-pyrrol-2-yl)-3-phenylpropan-1-one (2.37)

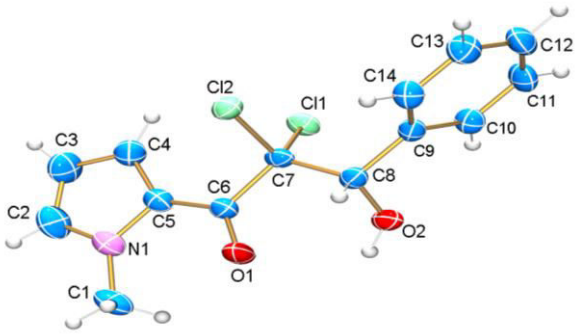

Table 1: Crystal data and structure refinement for mjh78.

Identification code	mjh78	
Chemical formula (moiety)	$C_{14}H_{13}Cl_2NO_2$	
Chemical formula (total)	$C_{14}H_{13}Cl_2NO_2$	
Formula weight	298.15	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	orthorhombic, Pbcn	
Unit cell parameters	a = 21.1956(11) Å	□ = 90°
	b = 7.5271(4) Å	□ = 90°
	c = 17.1302(14) Å	□ = 90°
Cell volume	2733.0(3) $Å^3$	
Z	8	
Calculated density	1.449 g/cm^3	
Absorption coefficient □	0.471 mm^{-1}	
F(000)	1232	
Reflections for cell refinement	3920 (□ range 2.9 to 28.6°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice □ scans	
□ range for data collection	2.9 to 28.6°	
Index ranges	h –27 to 24, k –8 to 10, l –20 to 13	
Completeness to □ = 28.6°	84.7 %	
Reflections collected	9986	
Independent reflections	2977 (R_{int} = 0.0337)	
Reflections with F^2>2□	2347	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.88578 and 1.00000	

Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0457, 1.9659
Data / restraints / parameters	2977 / 0 / 177
Final R indices [F^2>2□]	R1 = 0.0429, wR2 = 0.0981
R indices (all data)	R1 = 0.0606, wR2 = 0.1091
Goodness-of-fit on F^2	1.046
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.49 and –0.24 e $Å^{-3}$

2, 2-dichloro-1- (1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl) propane-1,3- dione (2.38)

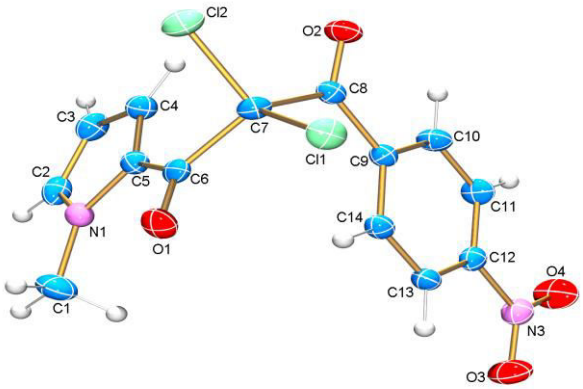

Table 1: Crystal data and structure refinement for mjh77.

Identification code	mjh77	
Chemical formula (moiety)	$C_{14}H_{10}Cl_2N_2O_4$	
Chemical formula (total)	$C_{14}H_{10}Cl_2N_2O_4$	
Formula weight	341.14	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	orthorhombic, Pbca	
Unit cell parameters	a = 12.4615(6) Å	□ = 90°
	b = 13.4977(5) Å	□ = 90°
	c = 17.2015(7) Å	□ = 90°
Cell volume	2893.3(2) $Å^3$	
Z	8	
Calculated density	1.566 g/cm^3	
Absorption coefficient □	0.468 mm^{-1}	
F(000)	1392	
Crystal colour and size	colourless, 0.30 × 0.30 × 0.10 mm^3	
Reflections for cell refinement	5529 (□ range 3.0 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice □ scans	
□ range for data collection	3.0 to 28.6°	
Index ranges	h –13 to 16, k –17 to 17, l –22 to 22	
Completeness to □ = 25.0°	99.9 %	
Reflections collected	13352	
Independent reflections	3223 (R_{int} = 0.0326)	
Reflections with F^2>2□	2709	

Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.8724 and 0.9547
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0258, 1.7441
Data / restraints / parameters	3223 / 0 / 201
Final R indices [F^2>2□]	R1 = 0.0323, wR2 = 0.0693
R indices (all data)	R1 = 0.0426, wR2 = 0.0753
Goodness-of-fit on F^2	1.036
Extinction coefficient	0.0011(2)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.34 and –0.27 e $Å^{-3}$

2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(p-tolyl)propan-1-one (3.9)

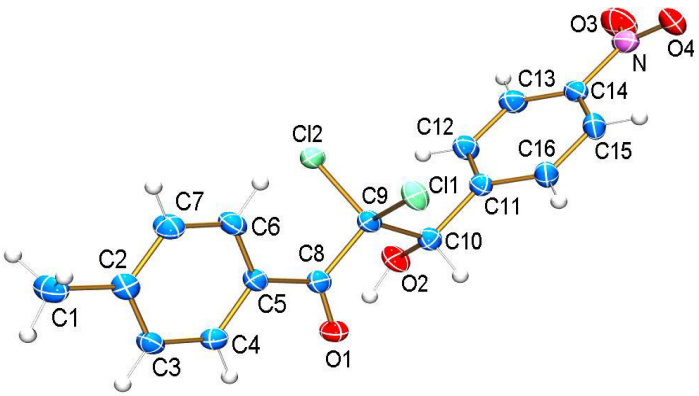

Table 1: Crystal data and structure refinement for mjh86.

Identification code	mjh86	
Chemical formula (moiety)	$C_{16}H_{13}Cl_2NO_4$	
Chemical formula (total)	$C_{16}H_{13}Cl_2NO_4$	
Formula weight	354.17	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	triclinic, $P\bar{1}$	
Unit cell parameters	a = 8.4691(5) Å	□ = 87.037(4)°
	b = 9.8694(6) Å	□ = 87.379(4)°
	c = 10.0248(5) Å	□ = 65.674(5)°
Cell volume	762.23(7) $Å^3$	
Z	2	
Calculated density	1.543 g/cm^3	
Absorption coefficient □	0.445 mm^{-1}	
F(000)	364	
Reflections for cell refinement	4864 (□ range 3.0 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice □ scans	
□ range for data collection	3.0 to 28.6°	
Index ranges	h –11 to 10, k –13 to 12, l –12 to 12	
Completeness to □ = 25.0°	99.9 %	
Reflections collected	11888	
Independent reflections	3394 (R_{int} = 0.0356)	
Reflections with F^2>2□	2819	

Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.93694 and 1.00000
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0576, 0.2993
Data / restraints / parameters	3394 / 0 / 212
Final R indices [F^2>2□]	R1 = 0.0389, wR2 = 0.1015
R indices (all data)	R1 = 0.0504, wR2 = 0.1105
Goodness-of-fit on F^2	1.057
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.50 and –0.29 e $Å^{-3}$

2,2-dichloro-3-hydroxy-3-(4-nitrophenyl)-1-(p-tolyl)propyl 4-nitrobenzoate(3.10)

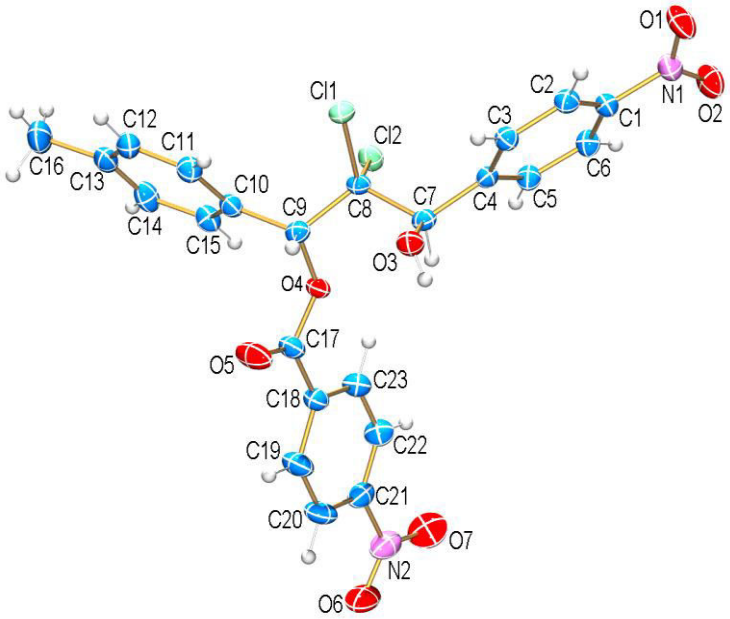

Table 1: Crystal data and structure refinement for mjh87.

Identification code	mjh87	
Chemical formula (moiety)	$C_{23}H_{18}Cl_2N_2O_7$	
Chemical formula (total)	$C_{23}H_{18}Cl_2N_2O_7$	
Formula weight	505.29	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 8.4445(4) Å	□ = 90°
	b = 15.4187(7) Å	□ = 90°
	c = 17.2259(8) Å	□ = 90°
Cell volume	2242.87(18) $Å^3$	
Z	4	
Calculated density	1.496 g/cm^3	
Absorption coefficient □	0.339 mm^{-1}	
F(000)	1040	
Crystal colour and size	colourless, 0.40 × 0.30 × 0.30 mm^3	
Reflections for cell refinement	3883 (□ range 2.9 to 28.6°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice □ scans	

□ range for data collection	2.9 to 28.7°
Index ranges	h −8 to 11, k −18 to 20, l −20 to 21
Completeness to □ = 25.0°	99.7 %
Reflections collected	10321
Independent reflections	4711 (R_{int} = 0.0338)
Reflections with F^2>2□	4157
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.8765 and 0.9052
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0349, 0.5123
Data / restraints / parameters	4711 / 0 / 313
Final R indices [F^2>2□]	R1 = 0.0401, wR2 = 0.0821
R indices (all data)	R1 = 0.0493, wR2 = 0.0881
Goodness-of-fit on F^2	1.055
Absolute structure parameter	0.02(5)
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.28 and −0.20 e $Å^{-3}$

2,2-dichloro-3-hydroxy-3-(4-methoxyphenyl)-1-(p-tolyl)propan-1-one (3.16)

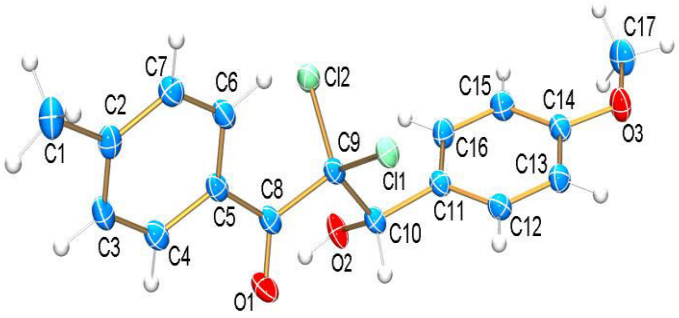

Table 1: Crystal data and structure refinement for mjh96.

Identification code	mjh96	
Chemical formula (moiety)	$C_{17}H_{16}Cl_2O_3$	
Chemical formula (total)	$C_{17}H_{16}Cl_2O_3$	
Formula weight	339.20	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 8.0789(3) Å	□ = 90°
	b = 21.5576(9) Å	□ = 95.369(4)°
	c = 8.9968(4) Å	□ = 90°
Cell volume	1560.02(11) $Å^3$	
Z	4	
Calculated density	1.444 g/cm^3	
Absorption coefficient □	0.425 mm^{-1}	
F(000)	704	
Reflections for cell refinement	6011 (□ range 3.0 to 28.4°)	
Data collection method	Xcalibur, Atlas, Gemini ultra thick-slice □ scans	
□ range for data collection	3.0 to 28.5°	
Index ranges	h –10 to 9, k –28 to 25, l –11 to 10	
Completeness to □ = 25.0°	99.8 %	
Reflections collected	13999	
Independent reflections	3396 (R_{int} = 0.0229)	
Reflections with F^2>2□	2996	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.90534 and 1.00000	

Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0302, 0.7218
Data / restraints / parameters	3396 / 2 / 215
Final R indices [F^2>2□]	R1 = 0.0290, wR2 = 0.0684
R indices (all data)	R1 = 0.0360, wR2 = 0.0726
Goodness-of-fit on F^2	1.049
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.31 and –0.19 e $Å^{-3}$

2-chloro-3-(4-nitrophenyl)oxiran-2-yl)(1-methyl-1H-pyrrol-2-yl)methanone (4.1)

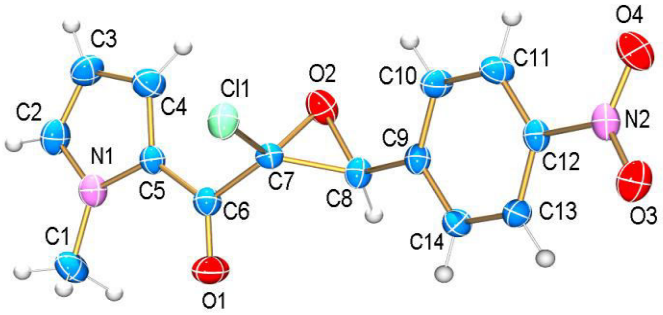

Table 1: Crystal data and structure refinement for mjh130005.

Identification code	mjh130005	
Chemical formula (moiety)	$C_{14}H_{11}ClN_2O_4$	
Chemical formula (total)	$C_{14}H_{11}ClN_2O_4$	
Formula weight	306.70	
Temperature	150(2) K	
Radiation, wavelength	MoK□, 0.71073 Å	
Crystal system, space group	monoclinic, $P12_1/n1$	
Unit cell parameters	a = 8.4142(4) Å	□ = 90°
	b = 21.2032(8) Å	□ = 116.111(6)°
	c = 8.5672(4) Å	□ = 90°
Cell volume	1372.47(11) $Å^3$	
Z	4	
Calculated density	1.484 g/cm^3	
Absorption coefficient □	0.296 mm^{-1}	
F(000)	632	
Crystal colour and size	colourless, 0.34 × 0.30 × 0.03 mm^3	
Reflections for cell refinement	5809 (□ range 2.9 to 28.5°)	
Data collection method	Xcalibur, Atlas, Gemini ultra	
	thick-slice □ scans	
□ range for data collection	2.9 to 28.6°	
Index ranges	h –11 to 10, k –25 to 28, l –11 to 11	
Completeness to □ = 25.0°	99.8 %	
Reflections collected	14096	
Independent reflections	3057 (R_{int} = 0.0232)	
Reflections with F^2>2□	2727	
Absorption correction	semi-empirical from equivalents	

Min. and max. transmission	0.9061 and 0.9912
Structure solution	direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting parameters a, b	0.0560, 1.6151
Data / restraints / parameters	3057 / 0 / 191
Final R indices [F^2>2□]	R1 = 0.0487, wR2 = 0.1230
R indices (all data)	R1 = 0.0551, wR2 = 0.1279
Goodness-of-fit on F^2	1.049
Largest and mean shift/su	0.000 and 0.000
Largest diff. peak and hole	0.95 and –0.23 e $Å^{-3}$

(2-chloro-3-(4-nitrophenyl)oxiran-2-yl)(phenyl)methanone (4.6)

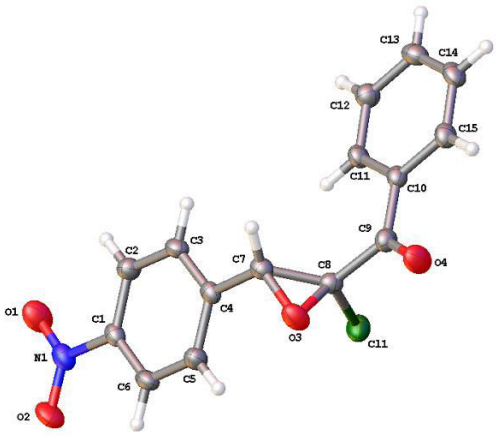

Table 1: Crystal data and structure refinement for mjh140034_fa.

Identification code	mjh140034_fa
Empirical formula	$C_{15}H_{10}NO_4Cl$
Formula weight	303.69
Temperature/K	150.01(10)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.32300(9)
b/Å	12.09364(16)
c/Å	15.09304(16)
α/°	90
β/°	96.2048(10)
γ/°	90
Volume/Å^3	1328.83(3)
Z	4
ρ_{calc}g/cm^3	1.518
μ/mm^{-1}	0.303
F(000)	624.0
Crystal size/mm^3	0.3 × 0.23 × 0.14
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.532 to 55.77
Index ranges	$-9 \leq h \leq 9$, $-15 \leq k \leq 15$, $-19 \leq l \leq 19$
Reflections collected	40662
Independent reflections	3041 [R_{int} = 0.0486, R_{sigma} = 0.0222]
Data/restraints/parameters	3041/0/190
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0328, wR_2 = 0.0724
Final R indexes [all data]	R_1 = 0.0447, wR_2 = 0.0779
Largest diff. peak/hole / e Å^{-3}	0.30/-0.28

2-chloro-3-(4-nitrophenyl)oxiran-2-yl)(p-tolyl)methanone (4.7)

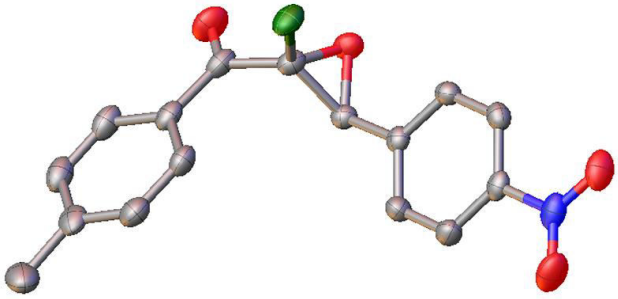

Table 1: Crystal data and structure refinement for mjh130018

Identification code	mjh130018
Empirical formula	C16H12NO4Cl
Formula weight	317.72
Temperature/K	120.0
Crystal system	monoclinic
Space group	Cc
a/Å	15.660(2)
b/Å	7.1579(10)
c/Å	14.548(2)
α/°	90
β/°	113.366(4)
γ/°	90
Volume/Å^3	1497.0(4)
Z	4
ρcalcmg/mm^3	1.410
m/mm-1	0.272
F(000)	656.0
Crystal size/mm^3	0.49 × 0.44 × 0.41
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection	5.668 to 55.174°
Index ranges	-20 ≤ h ≤ 20, -9 ≤ k ≤ 9, -18 ≤ l ≤ 18
Reflections collected	9693
Independent reflections	3415[R(int) = 0.0244]
Data/restraints/parameters	3415/2/200
Goodness-of-fit on F2	1.074
Final R indexes [I>=2σ (I)]	R1 = 0.0302, wR2 = 0.0752

Final R indexes [all data]	R1 = 0.0321, wR2 = 0.0770
Largest diff. peak/hole / e $Å^{-3}$	0.23/-0.20
Flack parameter	0.00(6)