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Phase-tag assisted synthesis of *N*-heterocycles using the Pummerer cyclisation

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Abstract

Phase-tag assisted synthesis of *N*-heterocycles using the Pummerer cyclisation

Linker strategies lie at the heart of solid phase organic synthesis and combinatorial chemistry. A new class of traceless linker cleaved using SmI_2 has been developed previously within the group. This linker system was based on an oxygen link to resin. A novel multi-functional sulfur based linker which not only links the substrate to resin and allows traceless cleavage but also enables Pummerer cyclisation chemistry to be carried out at the point of attachment has been developed.

Pummerer cyclisations are a powerful method for constructing carbocycles and heterocycles. The first Pummerer cyclisations on solid phase have been carried out in a convenient route to oxindoles which utilises a traceless sulfur link to resin. α-Bromoacetamides are immobilised using a benzyl thiol resin. Oxidation of the linking sulfur atom followed by Pummerer cyclisation and traceless cleavage using SmI_2 gives the desired oxindole products in good yield and high purity. A variety of oxindoles bearing neutral, electron rich and electron deficient aromatic systems have been synthesised using our approach. Crucially, the sulfur link to resin remains intact throughout the cyclisation leaving the heterocyclic products immobilised. The link can therefore be used again to assist further on-resin modification of the product heterocyclic framework prior to cleavage.

Fluorous thiols can be applied in a similar manner to solid supported thiols. Fluorous thiols can be used to introduce fluorous phase-tags, which when incorporated allow easy, convenient purification of the tagged compound using fluorous solid phase extraction (FSPE). Fluorous thiols have been applied in a new strategy for the fluorous phase synthesis of *N*-heterocycles. The sequence involves a fluorous phase, Pummerer cyclative capture strategy for rapid, one-pot construction of tagged, heterocyclic frameworks. The fluorous tagged heterocyclic frameworks can be modified using a variety of approaches including palladium catalysed cross-coupling reactions. Traceless removal of the phase tag with SmI_2 leads to the desired heterocycle in high purity. FSPE is applied throughout the synthetic sequence to assist purification.

Contents

Preface

The research described in this thesis was carried out under the supervision of Dr David J. Procter in the Loudon laboratory at the University of Glasgow between October 2001 and September 2004, and Dr Stephen Brand at Celltech R & D, Slough, UK (June-August 2003). Part of this thesis has been published previously:

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Finally, sincere thanks to David Edmonds for sharing the past few years and above all, for always being there for me.

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Abbreviations

Å	Ångstrom
Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Allyl	2-propenyl
aq.	aqueous
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bpoc	(2-(*p*-biphenylyl)-2-propyloxy carbonyl
Bz	benzoyl
n-BuLi	*n*-butyllithium
s-BuLi	*s*-butyllithiun
t-BuLi	*t*-butyllithium
CI	chemical ionisation
CSA	camphor sulfonic acid
d	doublet (NMR)
de	diastereoisomeric excess
dr	diastereoisomeric ratio
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DCC	dicyclohexyl carbodiimide
DDO	dimethyldioxirane
DIBAL	di*iso*-butylaluminium hydride
DIC	1,3-di*iso*-propylcarbodiimide
DIAD	diisopropylazodicarboxylate
DIPEA	di*iso*-propylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC)
EI	electron impact
eq	equivalents
Et	ethyl
EWG	electron-withdrawing group
FAB	fast atom bombardment
Fmoc	*N*-(9-fluorenylmethoxycarbonyl)
FSPE	fluorous solid phase extraction
g	gram
GC	gas chromatography
h	hour

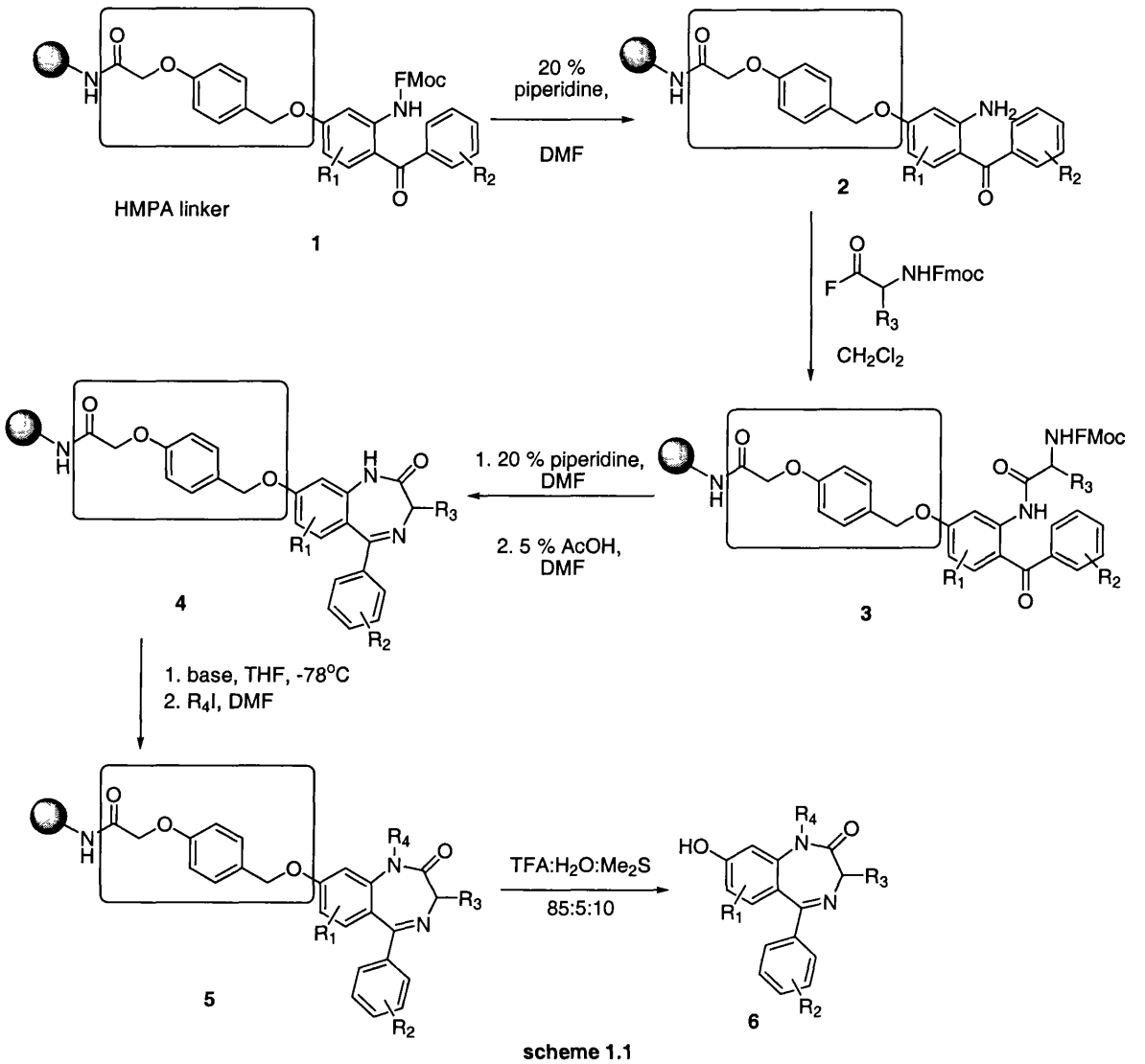
i	iso
IBX	2-iodoxybenzoic acid
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
Hz	hertz
IR	infrared
KHMDS	potassium hexamethyldisilazide
LDA	lithium di*iso*-propylamide
LHMDS	lithium hexamethyldisilazide
m	meta
M	molar
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram
min	minute
ml	millilitre
mmol	millimole
mp	melting point
Ms	methanesulfonyl
MS	molecular sieves
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NMM	*N*-methyl morpholine
NMP	*N*-methyl pyrrolidine
o	ortho
p	para
PEG	polyethylene glycol
Ph	phenyl
PMB	*para*-methoxybenzyl
Pr	propyl
*p*TSA	*para*-toluene sulfonic acid
PyBop	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
py	pyridine
q	quartet (NMR)
s	singlet (NMR)
s	secondary
sat.	saturated
rt	room temperature
t	tertiary
t	triplet (NMR)
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethyl sulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride

TLC	thin layer chromatography
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
tol	tolyl
Ts	*para*-toluenesulfonyl
TPAP	tetrapropylammonium perruthenate
µl	microlitre

1.0 Linkers in solid phase organic synthesis

In the early work on solid phase synthesis, linkers were designed for the attachment of specific functional groups, e.g. amines, alcohols, acids etc. Linkers were essentially solid supported protecting groups for these functional groups. When products were cleaved from linkers the cleaved products often contained residual functional groups such as alcohols, acids, amines and amides which were a consequence of the linker system that had been used for their attachment to solid support. Ellman was among the first to apply solid phase to the synthesis of small organic molecules.[1,2] Previously, solid phase had only been used in peptide synthesis. He carried out the solid phase synthesis of a library of 1,4-benzodiazepines as shown in scheme **1.1**.

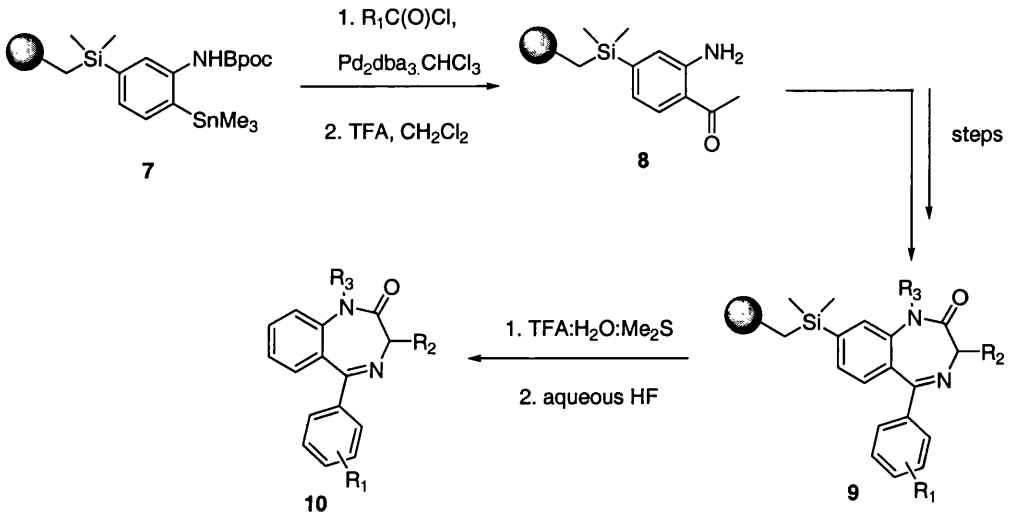
He used a polyethylene support with a hydroxymethyl phenoxyacetic acid (HMPA) linker to immobilise the substrate. In this linker system it is necessary that the benzophenone starting material bears a phenol group in order that it can be attached to the support. Upon cleavage of the 1,4-benzodiazepine **6** at the end of the synthesis, the product contains a residual phenol functional group which may or may not be desired. This is particularly significant if one desires to produce a library of compounds for biological testing as the presence of unnecessary functionality can have a dramatic effect on biological activity.



scheme 1.1

If solid phase combinatorial synthesis was to realise its full potential then it was necessary to be able to apply the technology to the synthesis of compounds which did not contain residual functional groups resulting from attachment to solid support. This prompted the development of "traceless linkers". A traceless linker is defined as a linker, which upon cleavage leads to the formation of a C-H bond and which enables the preparation of pure hydrocarbons. [3]

The linker system refers to protocols for both attachment to and cleavage from resin. Traceless linker systems usually consist of a carbon-heteroatom link between the attached organic molecule and the resin. The choice of heteroatom is important; the carbon heteroatom bond must be labile to heterolytic cleavage. Ellman has developed a traceless silicon linker and applied it to 1,4-benzodiazepine synthesis (scheme **1.2**).[4]



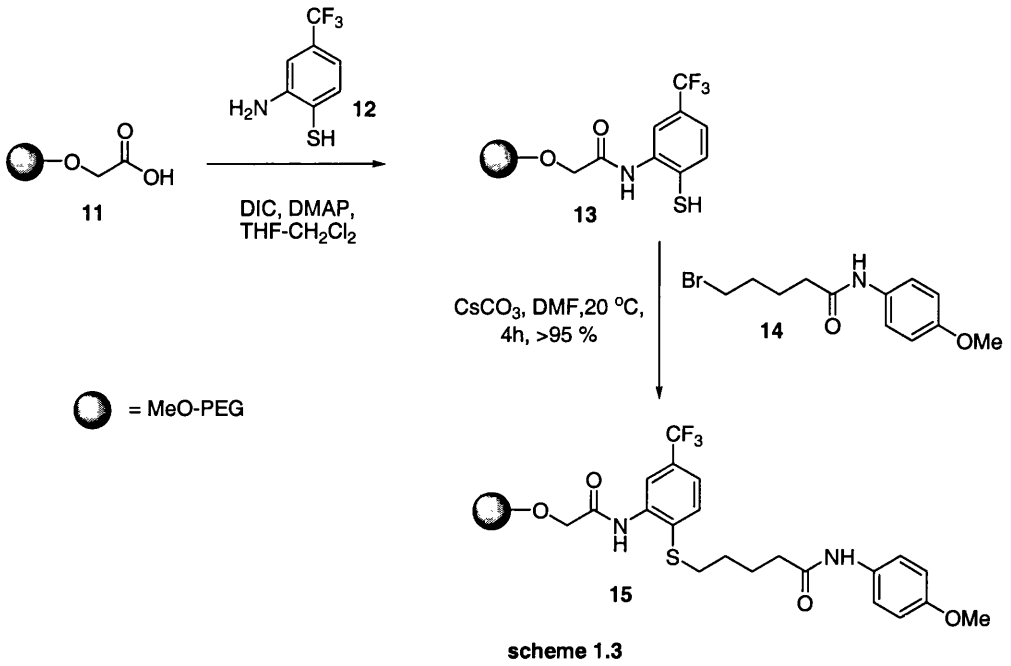
scheme 1.2

In this linker system the organic molecule is attached to resin via an aryl silicon bond. After several synthetic steps have been carried out on resin, the 1,4-benzodiazepine can be cleaved in a traceless manner by *ipso* substitution of the silicon to form an aryl C-H bond. The linker therefore does not leave any residual functionality in the product. An analogous germanium linker was also developed by Ellman.[5] Since these early traceless linker systems many other carbon-heteroatom traceless linker systems have been developed. Amongst these new linker systems sulfur and selenium based linkers have proved to be very effective for solid phase organic synthesis.

1.1 Sulfur Linkers

1.1.1 Early Sulfur linker systems

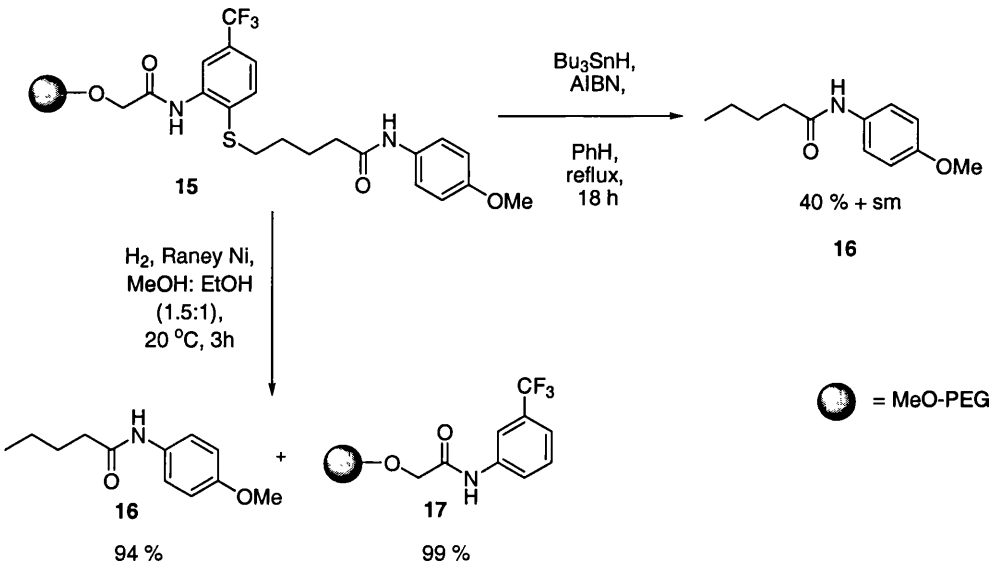
Janda was one of the pioneers of the use of sulfur linkers in traceless solid phase synthesis. Janda developed a traceless sulfur linker for the cleavage of aliphatic molecules from a soluble polymer support.[6] MeO-PEG acid soluble polymer **11** was coupled with amino thiol **12** to form thiol resin **13** which underwent alkylation with various alkyl halides, such as **14** to form a sulfide linkage to the substrate (scheme **1.3**).



scheme 1.3

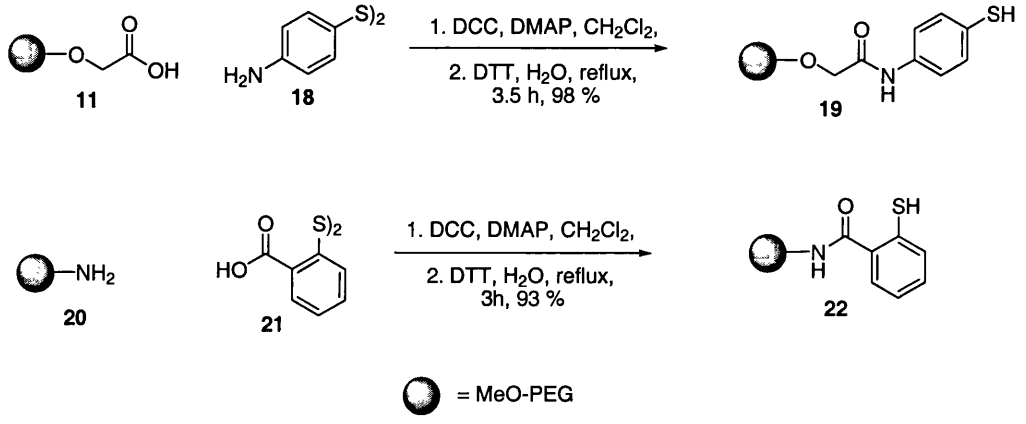
Release of the tethered molecule was achieved using Bu_3SnH and AIBN to cleave the carbon sulfur bond giving the desired aliphatic product **16** in a moderate 40 % yield together with unreacted starting material **15**. A more efficient cleavage strategy involved the use of hydrogen and Raney nickel which allowed traceless cleavage of **16** in 94 % yield after only three hours (scheme **1.4**).

Use of soluble polymers allowed easy isolation and purification of the cleaved product; precipitation of desulfurized MeO-PEG resin with ether then concentration of the filtrate gave the product in high purity by ^1H NMR.



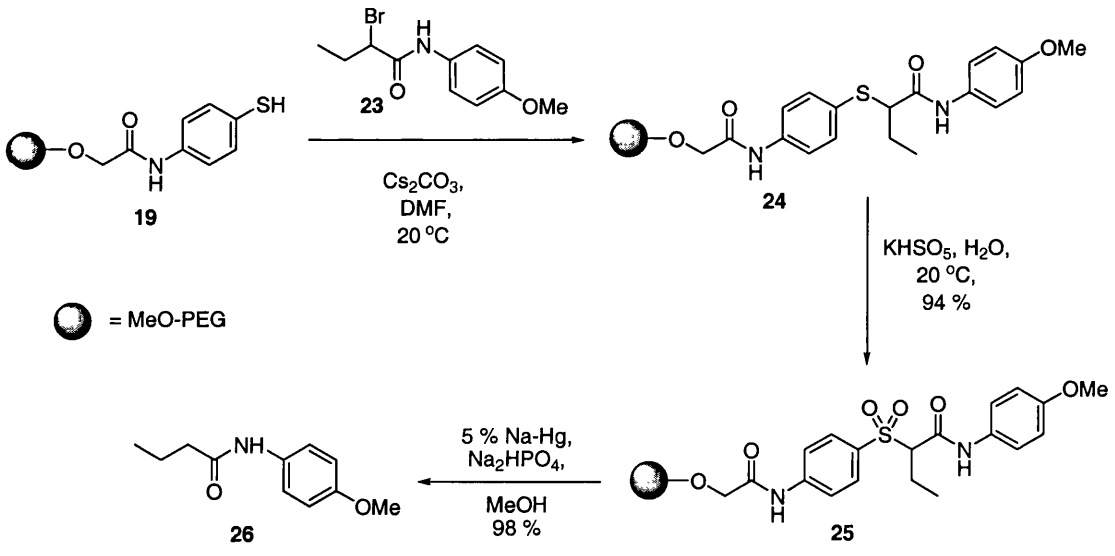
scheme 1.4

The preparation of the original sulfur linker system by Janda had some disadvantages. Firstly, aromatic thiols have a tendency to form disulfides thus reducing available thiol functionality to react with the alkyl halide. Secondly, there is competing thioester formation in the amide coupling step. Two improved traceless linker systems **19** and **22** were therefore prepared by Janda.[7] In the synthesis of both linkers, the linking thiol unit was introduced in the form of a disulfide and then reduced to the corresponding thiol using Cleland's reagent (dithiothreitol). Both polymers were prepared in high yield using this route. Alkylation and cleavage using the Raney nickel method, previously described, gave the aliphatic product in 99 % yield for both linker systems (scheme **1.5**).



scheme 1. 5

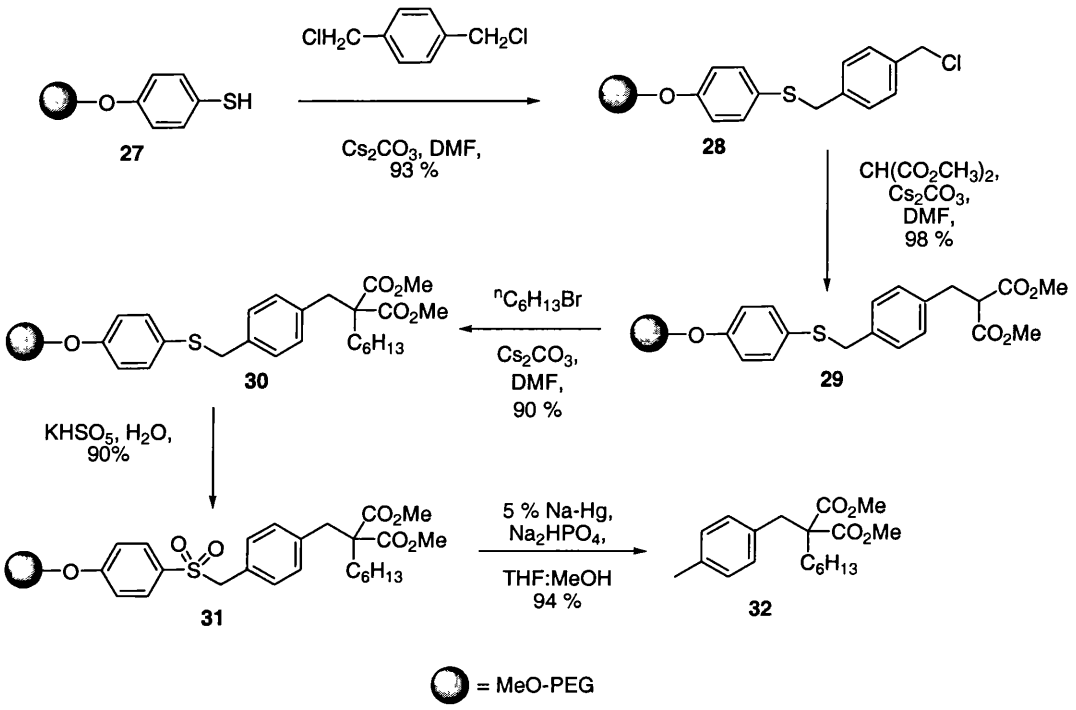
Janda's original sulfur linker can be cleaved most effectively using Raney nickel, however, this method limits the functional groups that can be tolerated in the molecule that is being prepared on the polymer support. For example, alkenes, alkynes, epoxides and sulfur-containing groups will all be reduced by Raney nickel in the cleavage step. This problem may be overcome by using a reducing agent which is more selective for the carbon-sulfur bond of the linkage. A Na-Hg reducing system will reduce the carbon-sulfur bond of an aliphatic sulfone selectively in the presence of many other reducible functionalities and was employed in an improved cleavage strategy for Janda's linker system (scheme **1.6**).[8] After attachment of the substrate **23** to the thiol polymer **19** via sulfide formation, the sulfur link was oxidised to the sulfone **25** using $KHSO_5$ (Oxone®). Oxone® will oxidise sulfides to sulfones without epoxidising double bonds or oxidising ketones to esters, and is therefore superior to *m*CPBA due to this enhanced chemoselectivity. Reduction with Na/Hg cleaved the sulfone link to resin and released the aliphatic product **26** which was isolated in high yield.



scheme 1.6

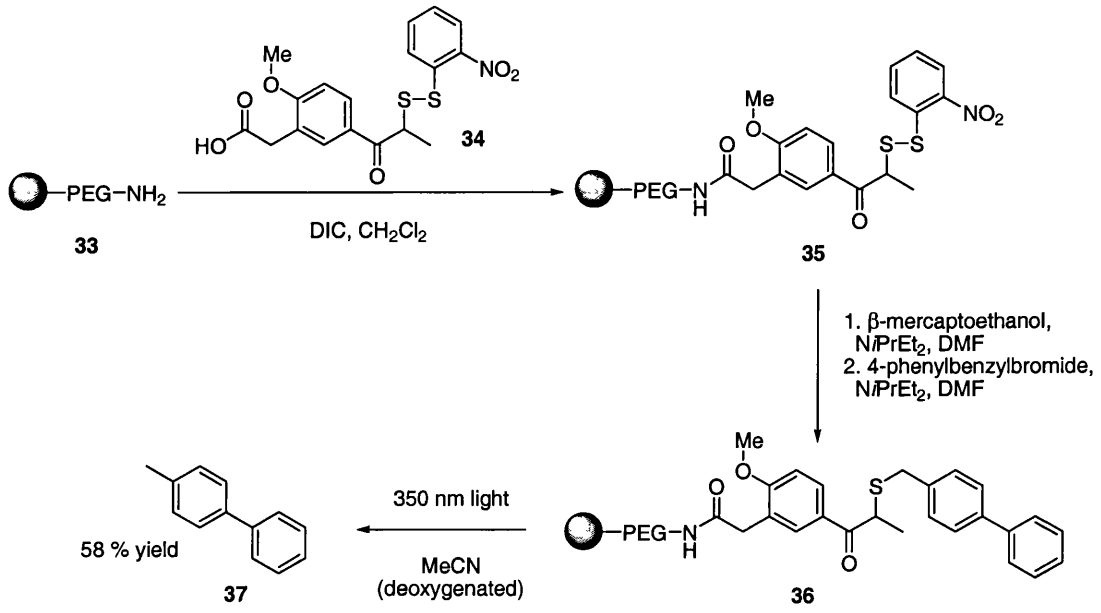
The traceless sulfur linker systems developed by Janda discussed so far, have amide functionality in the linking unit. Although amides tolerate most reaction conditions, reagents such as $LiAlH_4$, very strong base or acid would destroy the linker. In order to further expand the generality of this series of traceless sulfur linkers, ether-containing linking unit **27** was synthesised. Ether linkers are stable to very harsh reaction conditions. In order to demonstrate the use of this linker it was applied to the synthesis of alkylated

malonate derivatives (scheme **1.7**).[9] Monoalkylation of the thiol resin **27** with a dialkyl halide was followed by addition of a malonate anion. The resulting polymer supported malonate **29** was alkylated once more and following oxidation of the sulfide linker to the sulfone **31**, a malonate derivative **32** was reductively cleaved from the polymer in excellent yield. This strategy has also been applied in the synthesis of 3,5-pyrazolidinediones.[10]



scheme 1.7

Suchoeiki has developed the photocleavable (+)-2-methoxy-5-[2(2-nitrophenyl)dithiol]-1-oxopropyl)phenyl acetic acid (NpSSMpact) linker **34** for the cleavage of aliphatic molecules from solid support.[11,12] This was also one of the earliest linker systems designed for cleavage of non-peptide molecules from solid support (scheme **1.8**). The linking unit **35** was constructed by immobilisation of disulfide **34** on amine resin **33**. Treatment with β-mercaptoethanol gave polymer supported thiol which could be alkylated with benzylic halides to give sulfide linked biaryl **36**. The benzylic carbon sulfur bond was cleaved selectively under photochemical conditions to give **37** in 58 % yield.

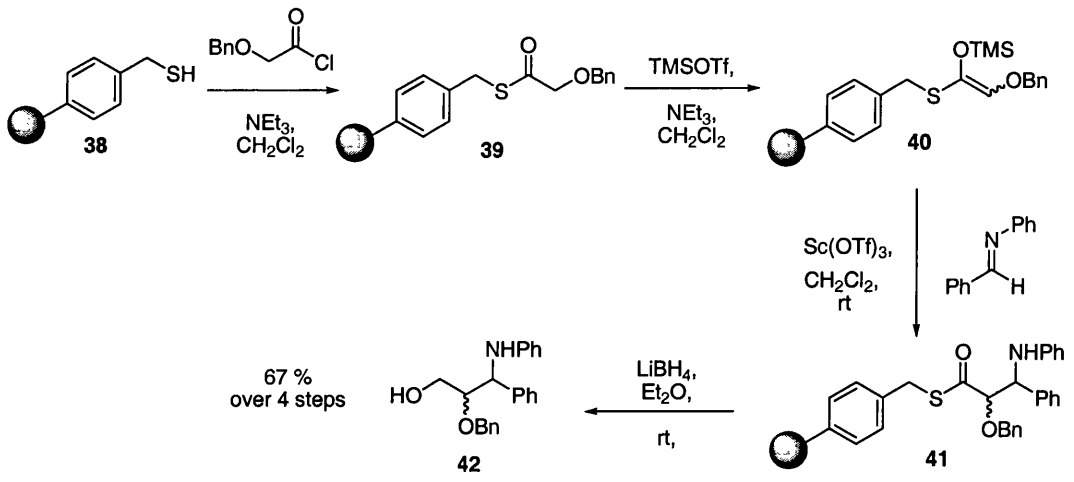


scheme 1.8

Since the development of these early linker systems, the use of sulfur linkers in solid phase synthesis has become widely exploited. Sulfur can be used as a linking atom in varying oxidation states. In these oxidation states the link can be used to facilitate a wide variety of chemistry whilst enabling traceless cleavage of products from the solid-support.

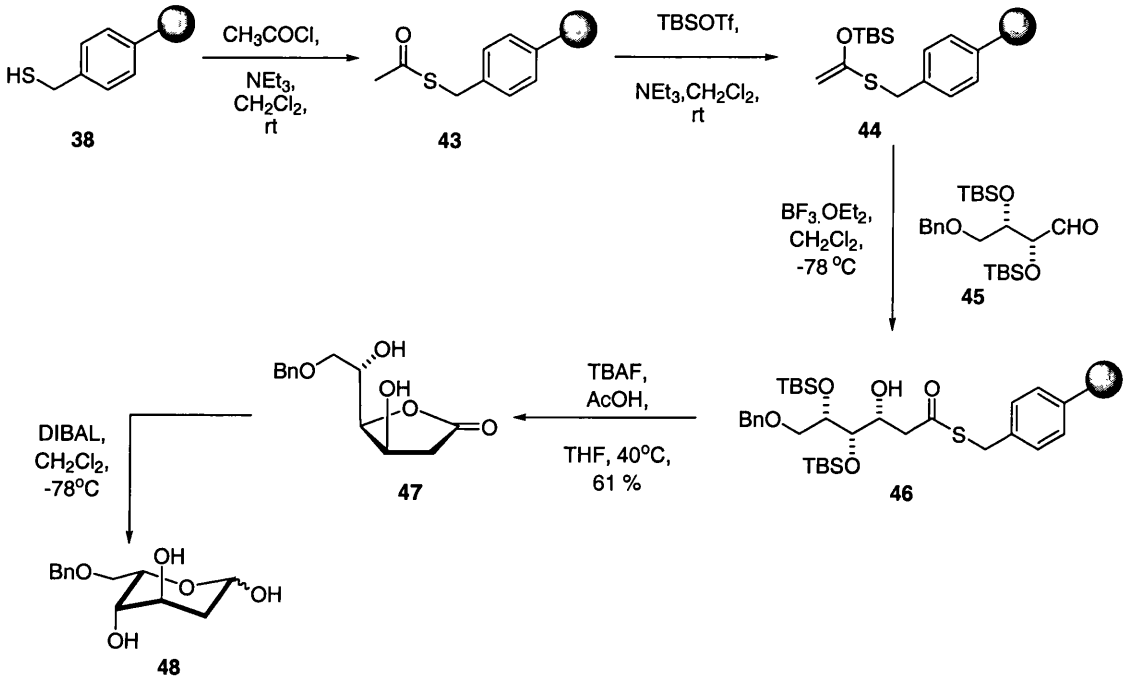
1.1.2 Thioester linkers

Kobayashi has used a sulfur linker for the solid phase preparation of amino alcohols.[13] Thiol resin **38** was acylated with benzoyl acetyl chloride to give thioester resin **39** (scheme **1.9**). Silyl enol ether **40** was then generated from **39** by treatment with trimethylsilyl triflate. Since Lewis acids are required to effect the addition of silyl enol ethers to imines, a range of Lewis acids were screened. Catalytic scandium triflate was found to be most effective in promoting the addition of the resin bound silyl enol ethers **40** to imines to give β-amino thioesters **41**. Reduction of the thioester linkage with lithium borohydride resulted in cleavage of an amino alcohol **42** from resin in good yield. A range of different acylating agents and imines were used in the sequence and a small library of amino alcohols was prepared using this methodology in yields ranging from 42-79 %.



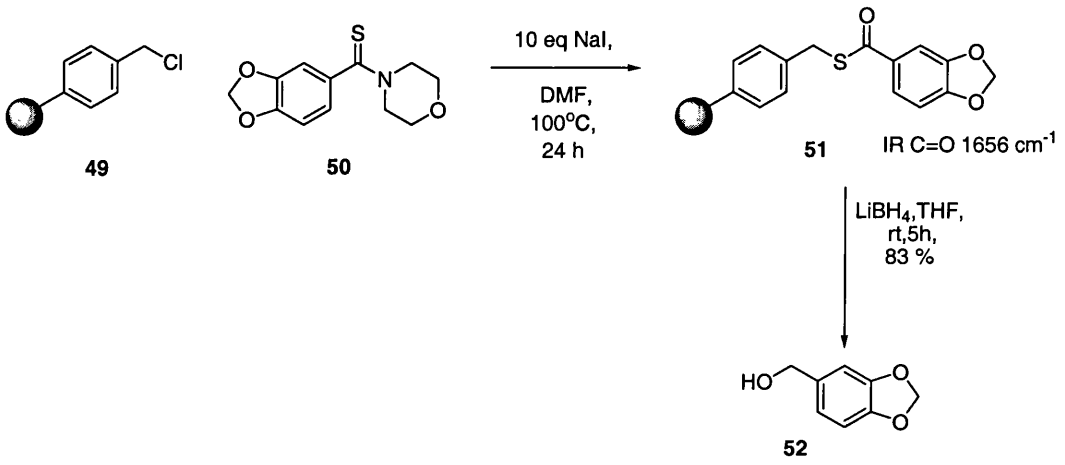
scheme 1.9

Kobayashi has applied polymer supported silyl enol ether **44** to the solid phase synthesis of monosaccharides (scheme **1.10**).[14] Resin bound silyl enol ether **44** was treated with chiral aldehyde **45** and BF_3 OEt_2 to give aldol adduct **46** in a > 98/2 dr. After deprotection of the TBS groups in **46**, spontaneous lactone formation with concomitant cleavage occurred to give lactone **47** in 61 % yield. Reduction of lactone **48** with DIBAL gave 6-*O*-benzyl-2-deoxy-L-gulose.



scheme 1.10

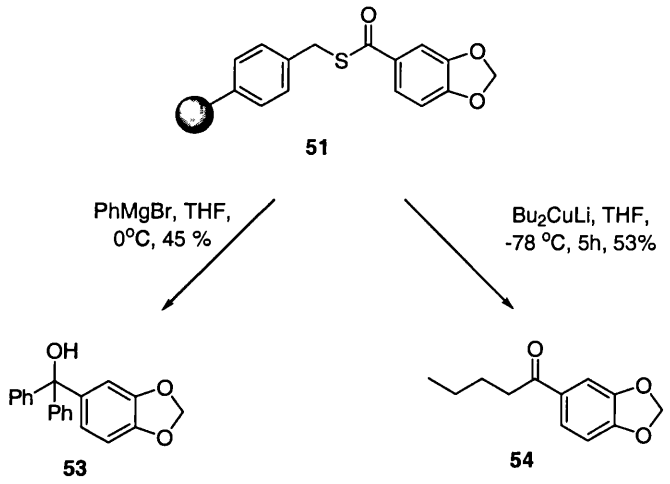
A traceless solid phase synthesis of alcohols and ketones using a sulfur link has been described by Bradley.[15] Resin bound thioesters such as **51** can be prepared by treatment of Merrifield resin **49** with thioamide **50** and NaI in DMF. The success of this reaction can be conveniently monitored by observing the appearance of a C=O stretch in the IR spectrum. Reduction of **51** with $LiBH_4$ results in cleavage of 1° alcohol **52** from resin in good yield (scheme **1.11**).



49 **50** **51** IR C=O 1656 cm^{-1} **52**

scheme 1.11

3° Alcohols and ketones such as **53** and **54**, can also be cleaved from the thioamide resin upon treatment with Grignard reagents or cuprates, respectively (scheme **1.12**).[15]



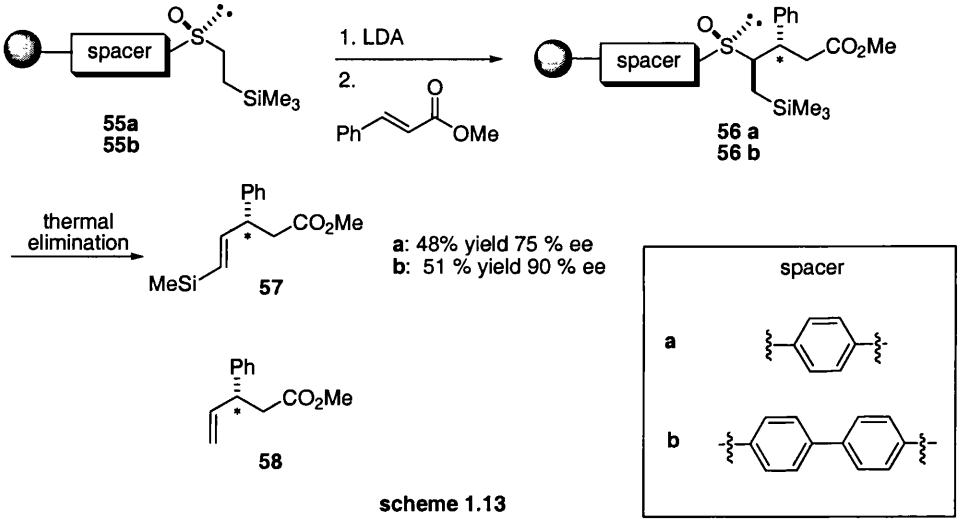
51

53 **54**

scheme 1.12

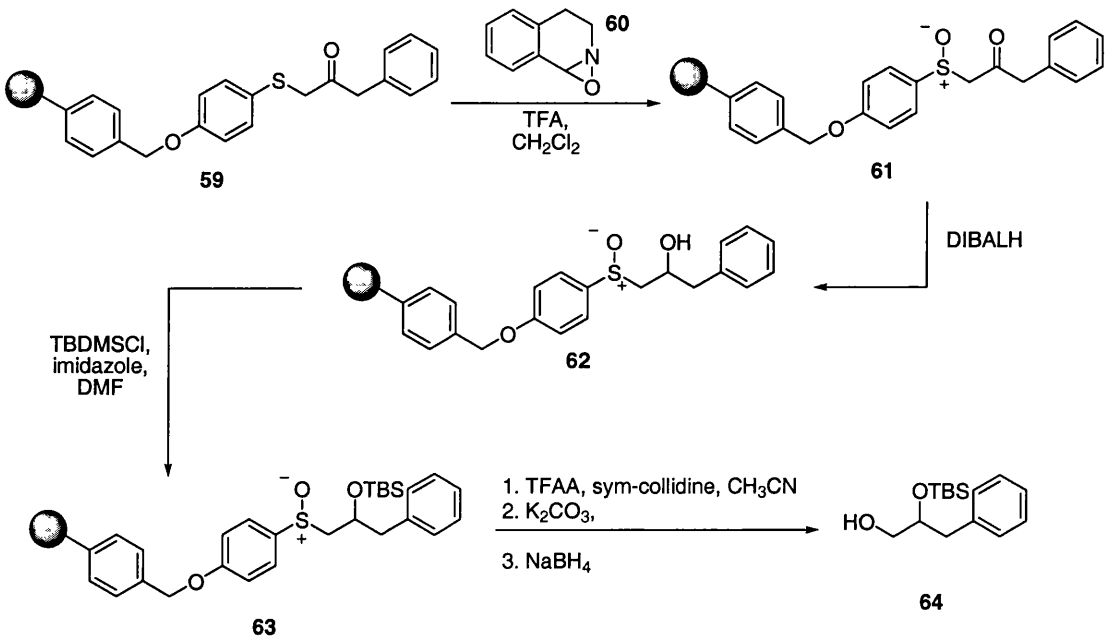
1.1.3 Sulfoxide linkers

Toru has used polymer supported chiral sulfoxides such as **55** in asymmetric conjugate additions to methyl cinnamate (scheme **1.13**).[16] Thermal elimination then occured regioselectively, to give alkene product **57** in good yield and enantiomeric excess. Stereoselectivity was found to be dependant on the nature of the spacer group. Where the spacer was a simple phenyl group **a** the product was obtained in 48 % yield and 75 % ee, however, if a biphenyl spacer **b** was used, a 51% yield and a signficantly improved 90 % ee was obtained. In an alternative cleavage strategy, treatment of **56b** with TBAF yields desilylated alkene product **58** in 56 % yield and 90 % ee. Additions to other Michael acceptors were not reported.



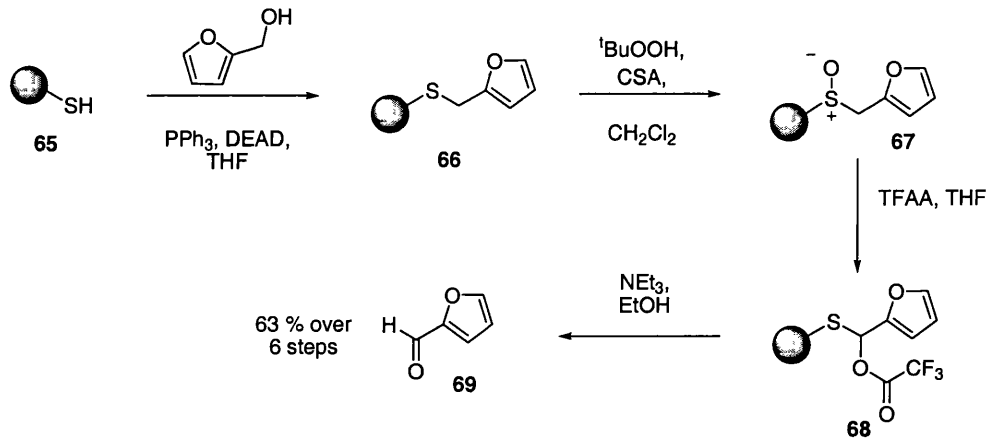
scheme 1.13

Solladié has employed a sulfoxide linker for the synthesis of 1,2-diols employing a Pummerer rearrangement cleavage strategy (scheme **1.14**).[17] *p*-Hydroxyphenyl-α-ketosulfides were constructed in solution phase and attached to the Wang based resin via the oxygen atom. Selective oxidation of the sulfide **59** to sulfoxide **61** was carried out using oxaziridine **60**. The sulfoxide link was then used to control the diastereoselectivity of DIBAL reduction of the ketone group. Two diastereoisomers were obtained and a 95 % de was reported although the relative stereochemistry of the diastereoisomers obtained was not reported. The resin bound alcohol **62** was protected as a silyl ether prior to cleavage of monoprotected diol **64** by Pummerer rearrangement followed by hydrolysis and reduction. Specific yields are not given although the cleavage was described as being almost quantitiative.



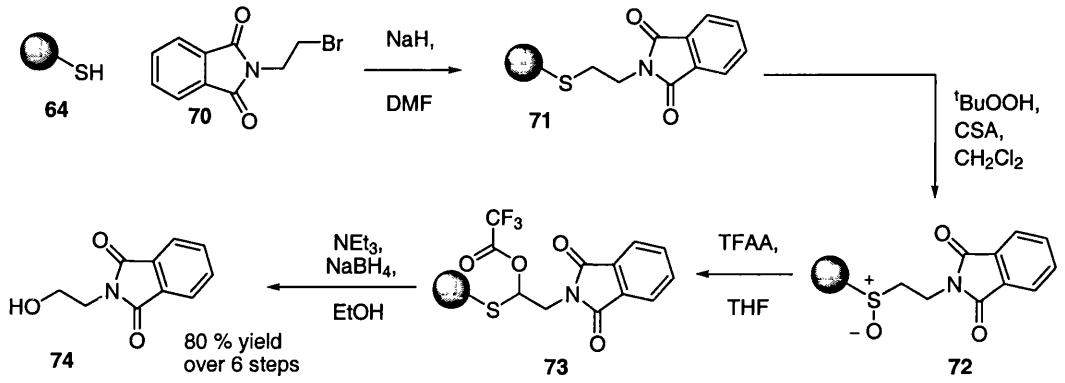
scheme 1.14

Li has also applied the Pummerer rearrangement strategy in the synthesis of aldehydes and alcohols (scheme **1.15**).[18] Furfuryl alcohol was immobilised on thiol resin **65**. The sulfide linker atom was oxidised to the sulfoxide. A range of oxidants were tested in this transformation, and the ^{t}BuOOH/CSA system was shown to give the best yield, reaction rate and the best selectivity with respect to forming sulfoxide over sulfone. The resin bound sulfoxide was treated with TFAA to give Pummerer rearrangement product **68**. Aldehyde **69** was cleaved from resin upon treatment of the Pummerer rearrangement product with NEt_3.



scheme 1.15

Alternatively, alcohols can be cleaved from resin simply by changing the reagents employed in the cleavage step (scheme **1.16**).[18] Thiol resin **64** can undergo alkylation with base and an alkyl halide **70** to give **71**. After oxidation and Pummerer rearrangement resin **73** was exposed to a one-pot cleavage reduction strategy to give alcohol **74** in 80 % yield over 6 steps which include the two step preparation of the thiol resin.



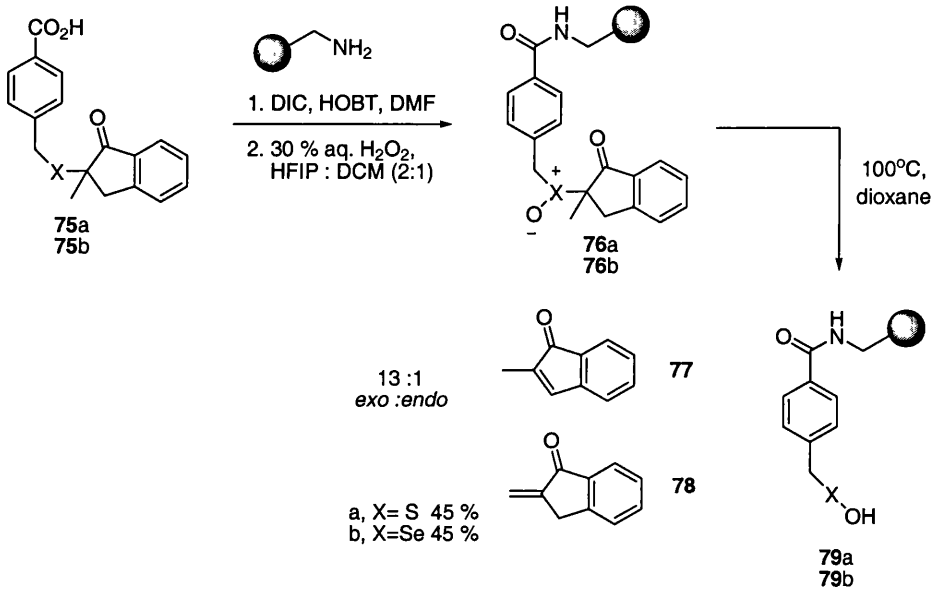
scheme 1.16

Safety catch linkers are linker systems which require activation before the final compound can be cleaved from solid support. Since cleavage cannot occur until the link has been activated, reaction conditions applied prior to this step need not be orthogonal to the final cleavage conditions.

Bradley has developed sulfoxide and selenoxide based thermally cleavable safety catch linkers and applied these in the solid phase synthesis of indenones.[19] Indanone precursors **75a** and **75b** with sulfur or selenium linking atoms α- to the carbonyl group were prepared in solution phase and attached to amino methyl polystyrene resin via an amide coupling reaction (scheme **1.17**). At this stage the linking sulfur or selenium atoms are unactivated and cleavage cannot be affected thermally. Selective oxidation conditions were then applied in order to selectively oxidise the sulfide to sulfoxide **76a** without over oxidation to the sulfone. The conditions employed were hydrogen peroxide in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and dichloromethane (2:1). These conditions allow a vast excess of hydrogen peroxide to be used without over oxidation to the sulfone. This is due to HFIP acting as an acid catalyst, enhancing the rate of the first oxidation to the sulfoxide then co-ordinating to the sulfoxide and making it unreactive in any further oxidation by

withdrawing electron density from the lone pairs on sulfur. Similar conditions were employed to prepare selenoxide **76b**.

After oxidation to sulfoxide **76a** or selenoxide **76b,** thermal elimination occurred readily to release exo **78** and endo **77** indenone from resin in greater than 95 % HPLC purity and 45 % yield based on the initial resin loading. Using the sulfur linkage it was found that thermal elimination only occurred in activated systems. The selenium linker was found to be more efficient with cleavage occurring at much lower temperature and with much less activated substrates.

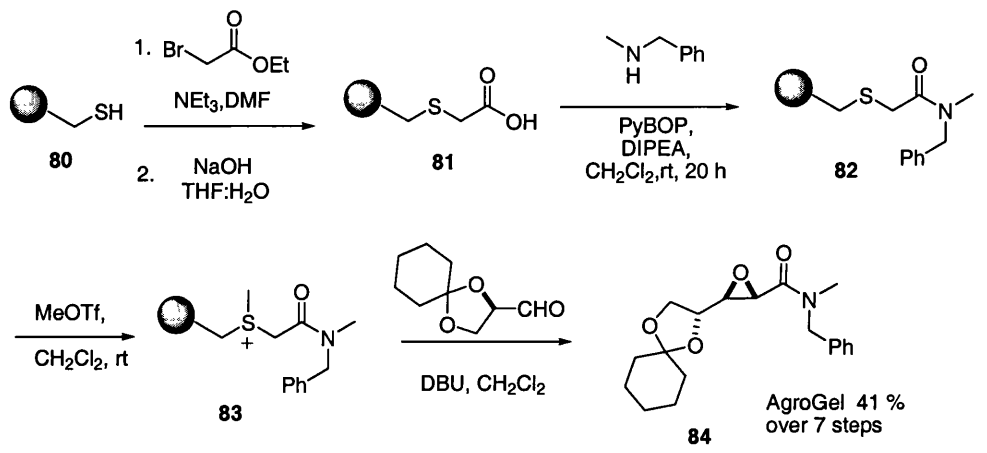


scheme 1.17

1.1.4 Sulfonium linkers

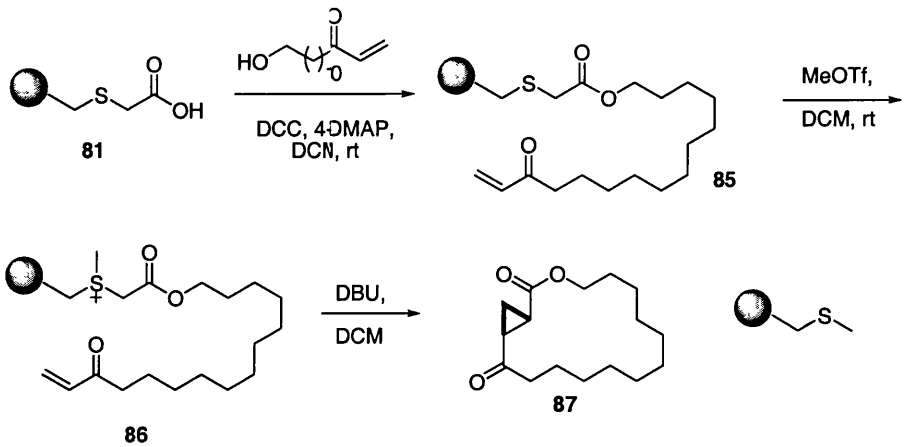
Gennari has reported the use of polymer supported sulfonium ylides for the synthesis of epoxides and cyclopropanes via an elegant cyclative cleavage strategy.[20] A thiol resin prepared from an AgroGel based polymer was used to synthesise supported sulfonium ion linked amide **83** (scheme **1.18**). Sulfur ylides were generated under mild reaction conditions from this sulfonium ion due to the stabilising, electron withdrawing effect of the sulfur-group. Treatment of the sulfonium salt with base generates a sulfur ylide, which reacts readily with an aldehyde to release an epoxide **84** from the solid support.

A major advantage of the cyclative cleavage strategy is that only the desired cyclised product is released into solution, any by-products or unreacted components remain attached to the polymer, thus products are obtained in high purity.



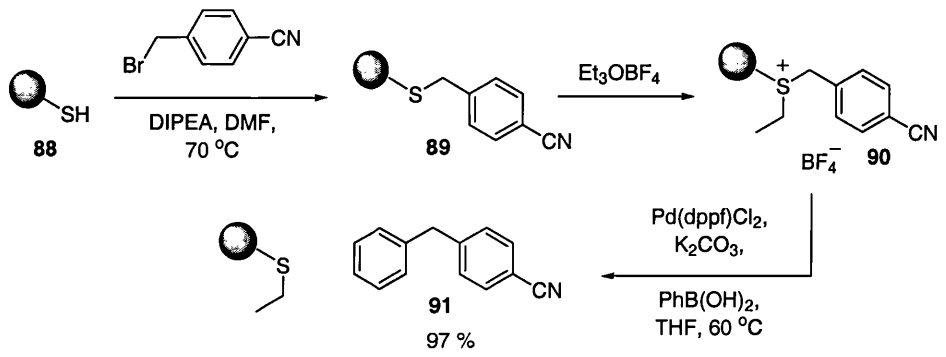
scheme 1.18

This methodology has also been successfully applied to the synthesis of macrocyclic lactones bearing a cyclopropane moiety (scheme **1.19**).[20] Resin bound sulfonium ion **86** bearing a tethered Michael acceptor group was constructed. Treatment with base, promoted sulfur ylide formation and subsequent 1,4-addition of the ylide to the Michael acceptor followed by cleavage of the macrocycle from resin with concomitant cyclopropane **87** formation. An advantage of carrying out this type of macrocyclisation reaction on solid support is that it mimics the high dilution conditions that would normally be necessary in solution phase in order to avoid competing intermolecular reaction. The yield of macrocycle is better when an AgroGel based thiol resin is used in place of a Merrifield based resin.



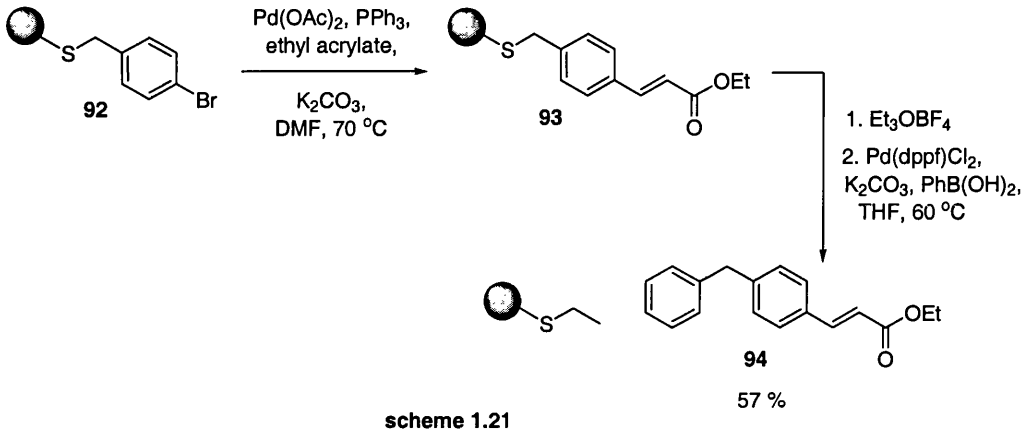
scheme 1.19

Wagner and Mioskowski have developed a safety catch sulfur linker strategy in which a new carbon carbon bond was formed upon cleavage thus introducing further diversity to the molecule in the cleavage step (scheme **1.20**).[21] An alkyl thiol resin **88** prepared from Merrifield resin was alkylated with a benzyl bromide to give benzyl sulfide resin **89**. The carbon sulfur bond formed is stable to a wide range of reactions involving nucleophiles, electrophiles, acids and bases. Activation of the link was achieved upon treatment with triethyloxonium tetrafluoroborate to give a sulfonium salt **90**. The sulfonium salt readily underwent palladium catalysed cross coupling reactions with a variety of boronic acids. The benzylic carbon sulfur bond couples selectively in preference to the alkyl carbon sulfur bonds therefore cleaving the compound from the polymer support whilst simultaneously constructing a new carbon carbon bond. Numerous biarylmethane compounds bearing electron donating groups, electron withdrawing groups and heterocycles were synthesised in yields ranging between 24 and 99 %.



scheme 1.20

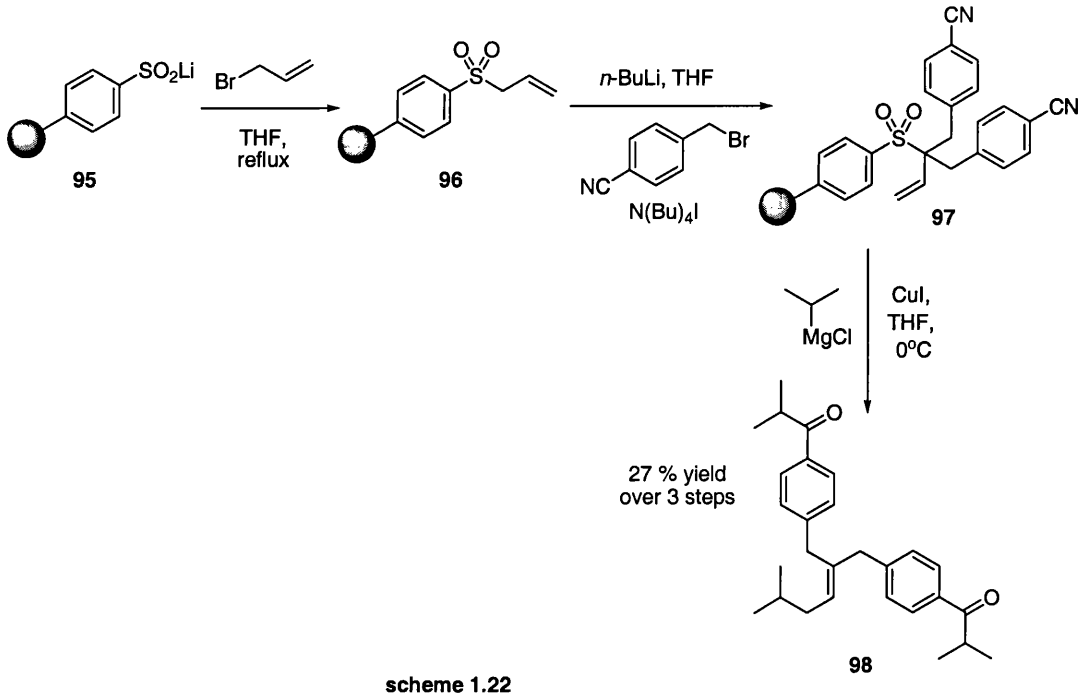
In order to demonstrate that the linker was stable to palladium catalysed coupling conditions prior to activation, a Heck reaction was carried out on the polymer supported aryl bromide **92** (scheme **1.21**). No cleavage was observed during the Heck reaction. Upon activation and palladium cross coupling the biarylmethane cinnamate derivative **94** was obtained in 57 % yield.[21]



scheme 1.21

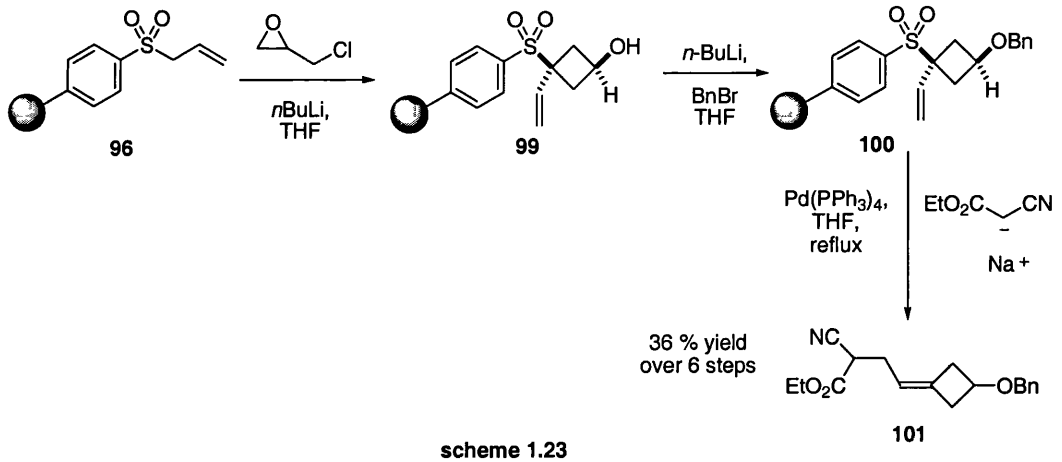
1.1.5 Sulfone Linkers

In 1997 Kurth reported a sulfone linker for the solid phase synthesis of trisubstituted olefins.[22] This was the first in a series of publications on the numerous applications of this new type of linker system. Sulfinate resin **95** was prepared from polystyrene resin by lithiation followed by treatment with sulfur dioxide (scheme **1.22**). Allylation with allyl bromide gave allyl phenyl sulfone resin **96** which underwent dialkylation upon treatment with *n*-butyllithium and alkylating agents to give α,α-dialkylated sulfone **97**. In the example shown, addition of organocopper species derived from isopropyl magnesium chloride and copper iodide, results in S_N2' displacement of the sulfinate resin and also converts the cyano groups to isopropyl ketones. Thus trisubstituted olefin **98** was released from the resin. Alkylation with different alkylating agents and displacement with various dialkyl cuprates or Grignard reagents gave a range of different trisubstituted olefins in 20-30 % yield after 3 solid phase steps.



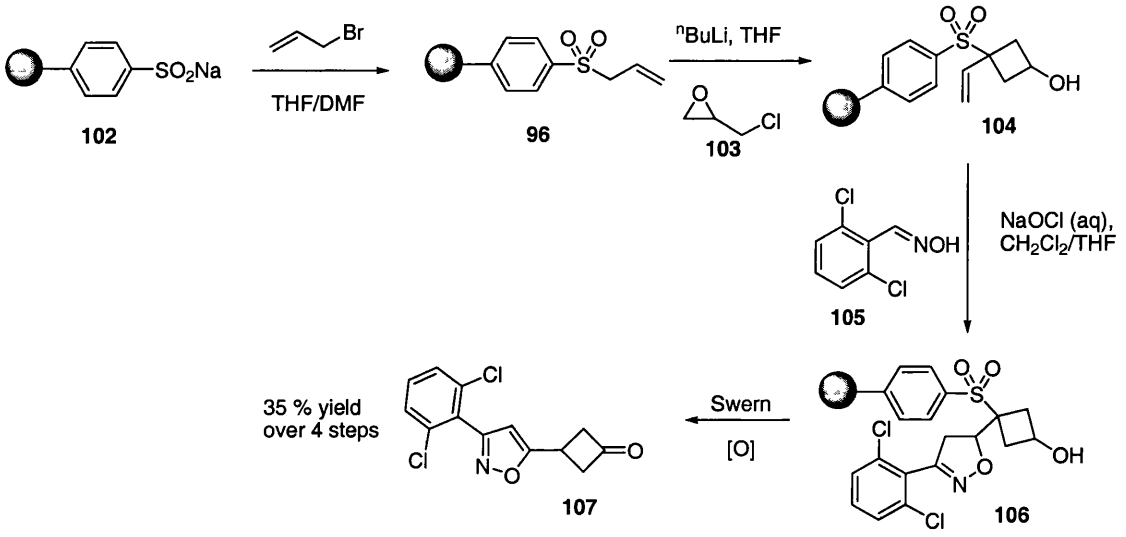
scheme 1.22

Kurth also employed the allyl sulfone resin in a synthesis of cyclobutylidenes (scheme **1.23**).[23] Allyl sulfone resin **96** was alkylated with epichlorohydrin to give resin bound cyclobutanol **99**. S_N2' displacement with a Grignard or cuprate to release the cyclobutanol from resin at this stage was not successful. Alternative methods of cleavage were therefore investigated. Protection of the hydroxyl group as the benzyl ether gave resin **100**. It was discovered that cyclobutylidene **101** could be cleaved from solid phase by palladium catalysed S_N2' displacement with a nucleophile. Purification after cleavage was necessary to remove excess nucleophile and triphenylphosphine. Several cyclobutylidenes were synthesised in 30-38 % yields using the allyl sulfone linker, two different alkyl halides were used in the *O*-alkylation step and three different nucleophiles were used in the cleavage step.



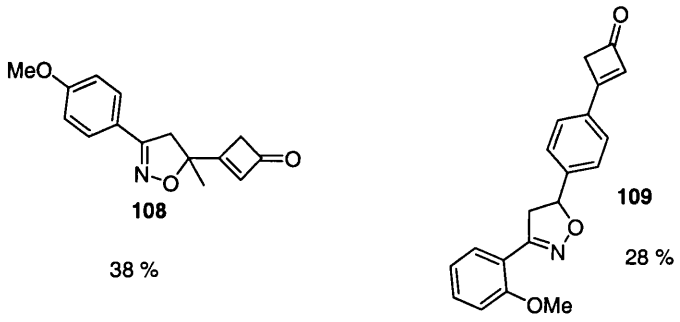
scheme 1.23

Kurth has also applied the sulfone linker in the preparation of isoxazolocyclobutanones and isoxazolinocyclobutenones.[24] Treatment of polymer supported allyl sulfone **96** with *n*-butyl lithium and 3-chloro-propylene oxide **103** led to an immobilised cyclobutanol moiety (scheme **1.24**). 1,3 Dipolar cycloaddition on the pendant double bond of **104** occurs upon treatment with oxime **105** and NaOCl. Exposure of the resultant resin **106** to Swern oxidation conditions performs several functions; the cyclobutanol was converted to the cyclobutanone, the basic reaction conditions affected the release of the compound from resin by sulfinate elimination leading to an isoxazolinocyclobutenone which finally undergoes an isomerisation to give an isoxazolocyclobutanone **107**.



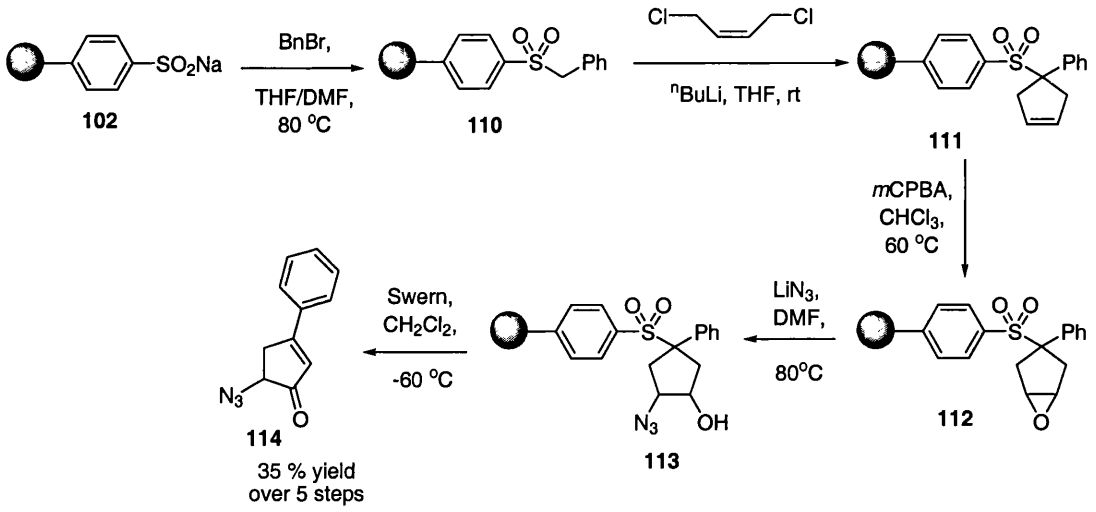
scheme 1.24

Isoxazolinocyclobutenones **108** and **109** were synthesised by *S*-alkylation with 3-chloro-2-methylpropene or 4-vinyl benzyl chloride in the initial alkylation step. In these examples the final isomerisation was not possible and sulfinate elimination yields isoxazolinocyclobutenones as the final products (scheme **1.25**).[24] Yields range between 27 and 38 % for the four solid phase steps.



scheme 1.25

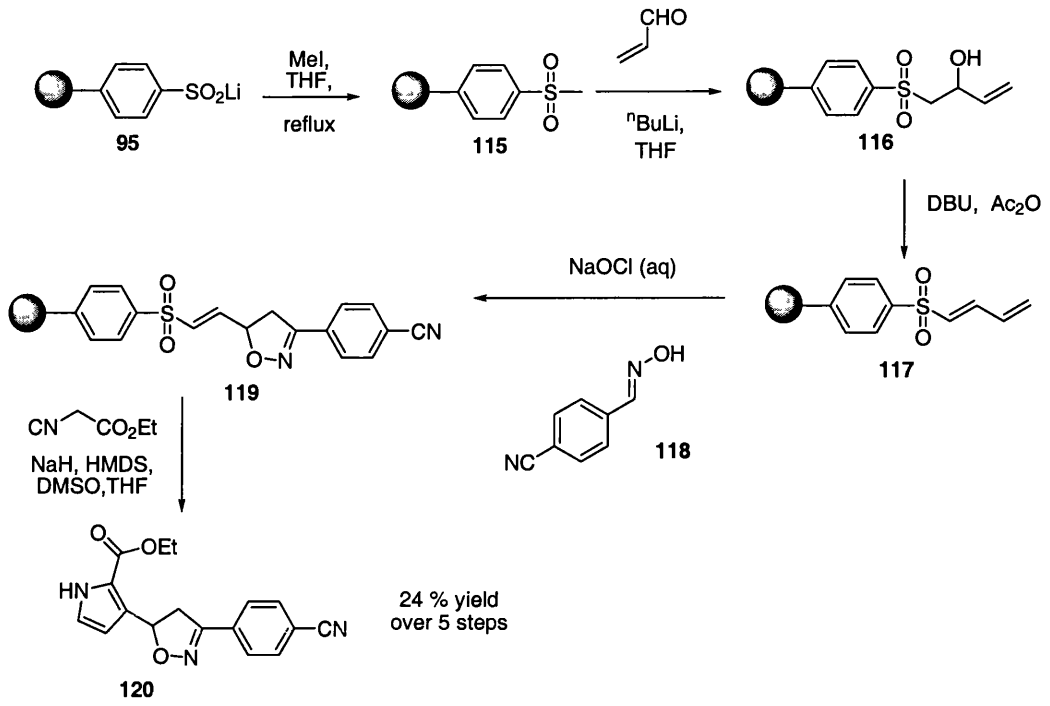
Kurth further applied the sulfone linker in a synthesis of cyclopentenones.[25] There are several points in this route at which diversity can be introduced thus making the approach highly suitable for the construction of small libraries (scheme **1.26**). *S*-Alkylation of the sulfinate resin **102** was then followed by dialkylation of sulfone **110** with 1,4-dichloro-2-butene to give a cyclopentene **111**. Oxidation of the double bond with *m*CPBA leads to an epoxide **112** which can undergo ring opening with a variety of nucleophiles. Ring opening with azide, Grignard reagents, cuprates and piperidines was demonstrated. Kurth's standard Swern oxidation/elimination strategy was employed to release cyclopentenones such as **114** in yields ranging between 18 and 40 %. This five step cyclopentenone synthesis further illustrates the utility of Kurth's sulfone linker system.



102 110 111 112 113 114

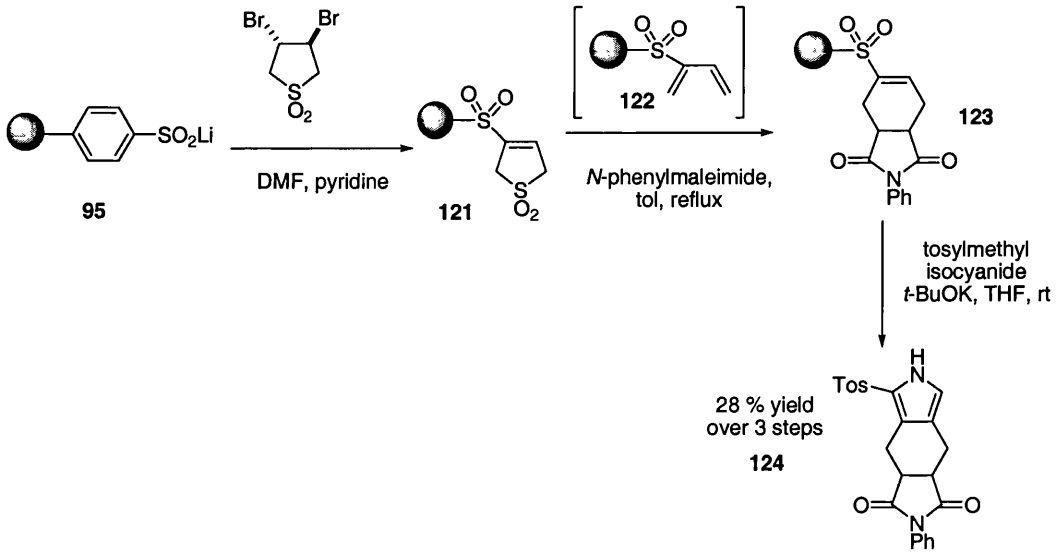
scheme 1.26

Isoxazolinopyrroles were also synthesised by Kurth using the traceless sulfone linker.[26] A polymer supported diene **117** was synthesised by 1,2-addition of the anion of sulfone resin **115** to an α-β-unsaturated aldehyde followed by elimination of water (scheme **1.27**). A regioselective 1,3-dipolar cycloaddition of diene **117** and the nitrile oxide derived from oxime **118** was then performed to give isoxazoline **119**. Upon treatment with ethyl isocyanoacetates, traceless release and cyclisation occurred to give pyrrole **120**. A small library of isoxazolinopyrrole 2-carboxylates was made in this way. Yields for the sequence were low in some cases (6-24 %) although purity of the products was high.



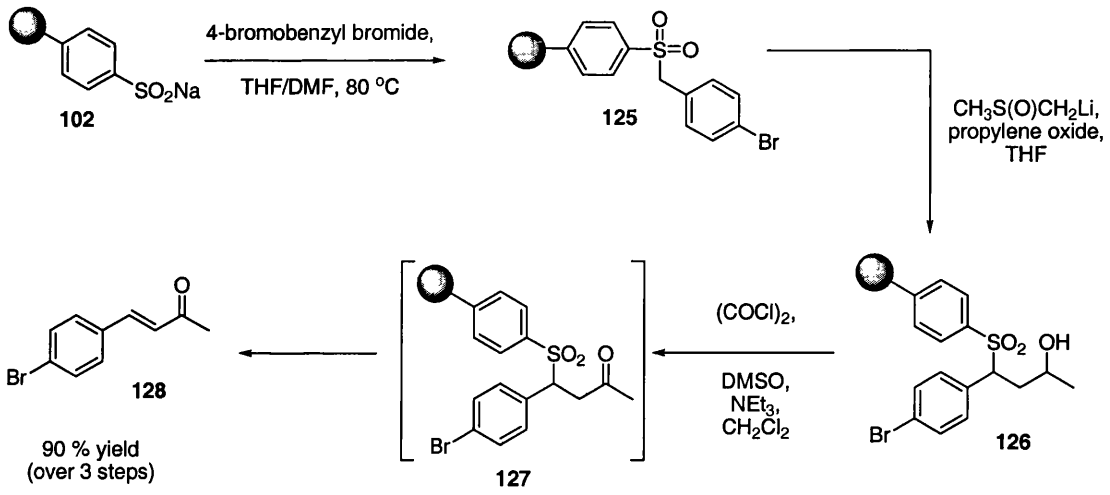
scheme 1. 27

A solid phase synthesis of 4,5,6,7-tetrahydroisoindole derivatives has also been carried out using Kurth's sulfone linker.[27] Sulfinate *S*-alkylation with trans-3,4-dibromosulfolane gave a resin bound sulfolene **121** which extruded SO_2 upon refluxing in toluene (scheme **1.28**). The resulting resin bound 1,3-butadiene **122** underwent a cycloaddition with *N*-phenylmaleimide and other dienophiles to give cycloadducts such as **123**. Treatment with tosylmethyl isocyanide (TOSMIC™) under basic conditions resulted in traceless cleavage of the product from resin with concomitant generation of a pyrrole ring. The cleaved 4,5,6,7-tetrahydroisoindole **124** was obtained in 28 % overall yield. The cycloaddition was monitored using the amide C=O stretch in the FTIR. For different dienophile examples it was necessary to heat the sulfolene resin in xylene at 145 °C for aproximately 36 hours for successful extrusion of SO_2 and cycloaddition. A range of functionalised 4,5,6,7-tetrahydroisoindoles was produced in yields of 32-41 %.



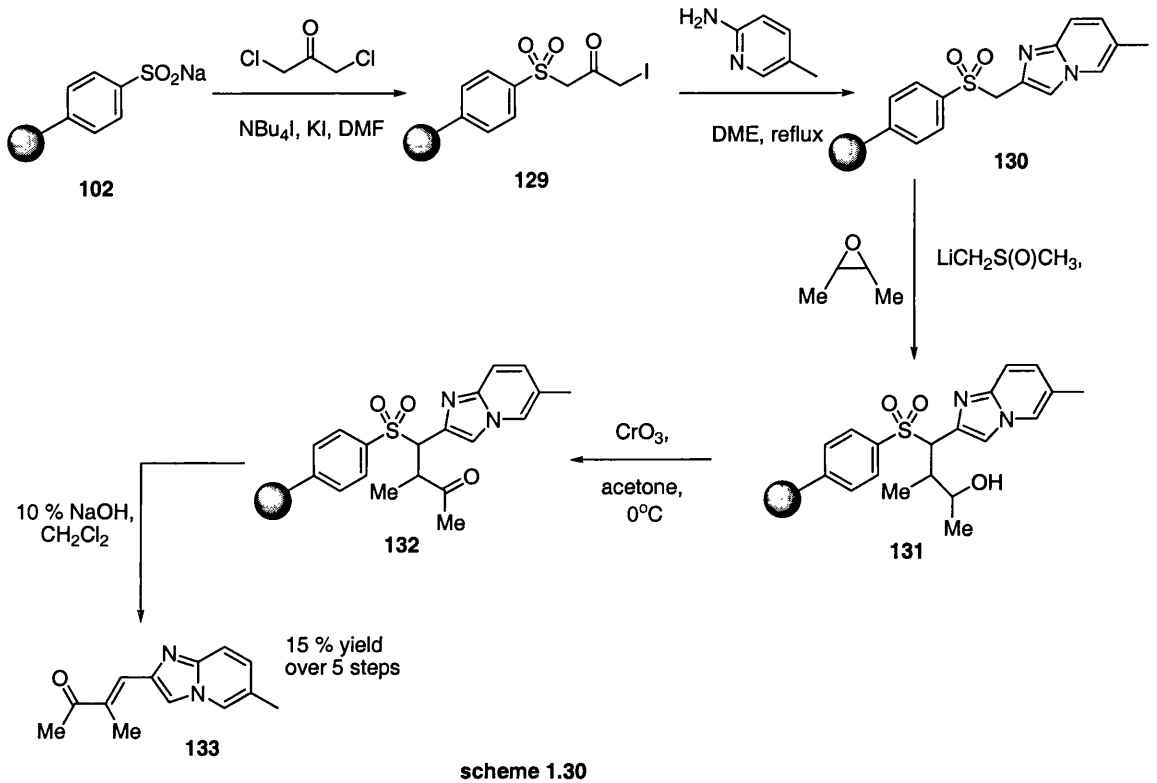
scheme 1.28

The alkylation of sulfones is usually achieved using bases such as *n*-butyllithium or LDA at low temperature. There are problems, however, in applying these bases to the deprotonation of polymer supported sulfones; since excess reagent can lead to dialkylation and it is very difficult to achieve accurate stoichiometry in polymer supported systems. Kurth has reported a solid phase synthesis of enones using a sulfone linker (scheme **1.29**).[28] The approach is based on the use of dimsyl anion (methylsulfinyl carbanion) as a base for the monoalkylation of polymer supported sulfones. Crucially no dialkylation was observed even when an excess of base was employed. The fact that this base can be used at room temperature also makes it much more convenient for use in combinatorial chemistry. A small library of enones was synthesised by a sequence involving the opening of epoxides by an α-lithiated sulfone, Swern oxidation and elimination to release enones from the polymer. Yields are excellent, ranging from 82-90 % for three steps.



scheme 1.29

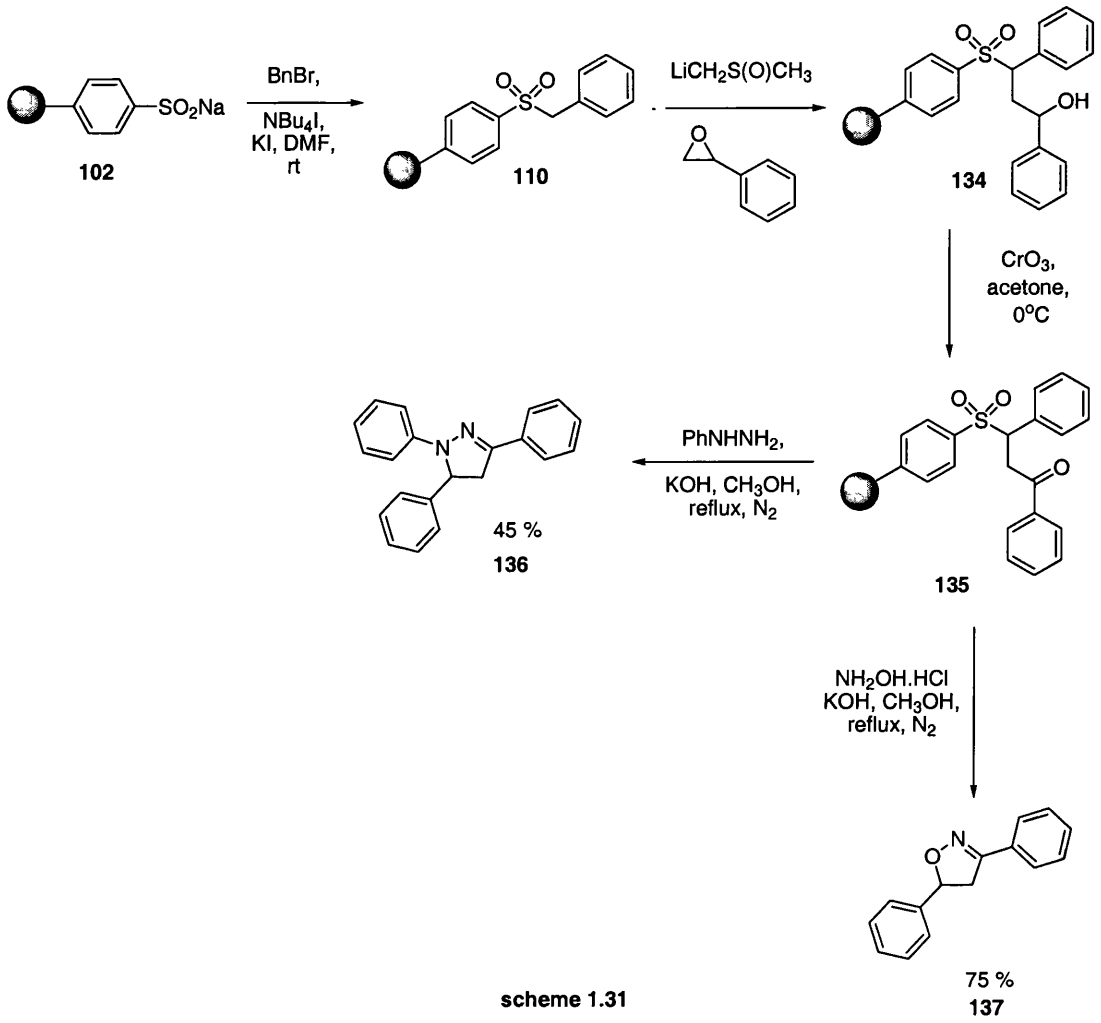
In a related study, Lam has used a sulfone linker for the traceless synthesis of a library of imidazo[1,2-a]pyridines.[29] Following alkylation of sulfinate resin **102** with 1,3-dichloro-propan-2-one, α-halo ketone resin **129** was reacted with an amino pyridine to give heterocyclic sulfone **130** (scheme **1.30**). Dimsyl anion was used to ensure that dialkylation did not occur in subsequent reactions with epoxides. Jones oxidation followed by base promoted elimination of the sulfinate resin gave imidazo[1,2-a]pyridine **133** in 15 % yield. A small library of imidazo[1,2-a]pyridines was synthesised in yields of 15-26 %.



102 129 130 131 132 133

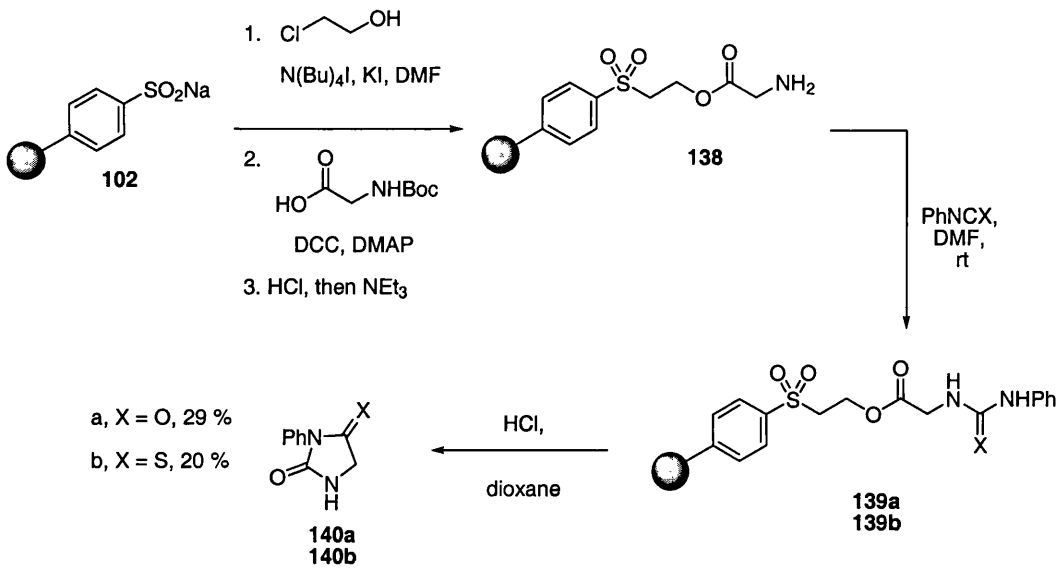
scheme 1.30

Lam also used a traceless sulfone linker for the synthesis of pyrazolines and isoxazolines (scheme **1.31**).[30] *S*-alkylation of sulfinate resin **102** yields resin bound sulfone **110**. Monoalkylation of sulfone **110** with an epoxide again using dimsyl anion as a base gave γ-hydroxy sulfone **134**. Subsequent Jones oxidation and treatment with a hydrazine or hydroxylamine leads to cyclisation and release of pyrazolines **136** and isoxazolines **137** respectively. This route offers three points at which diversity can be introduced. Several examples of pyrazolines and isoxazolines were synthesised in good yields ranging from 25-45 % over four solid phase steps and with >95 % purity by NMR.



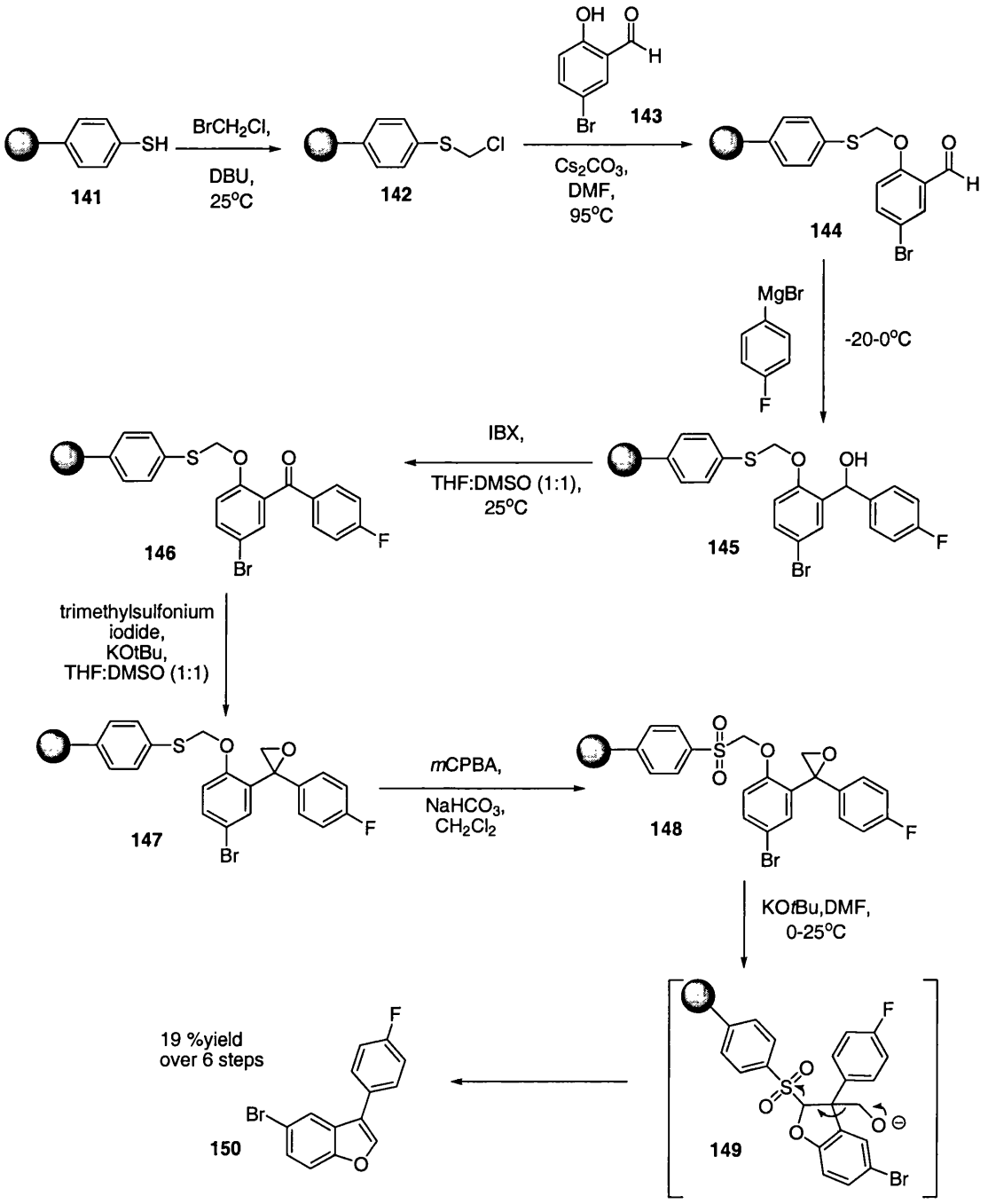
scheme 1.31

Huang has reported a solid phase route to hydantoin **140a** and thiohydantoin **140b** using a sulfone linker (scheme **1.32**).[31] Alkylation of sulfinate resin **102** with 2-chloroethanol followed by coupling with *N*-Boc protected glycine and deprotection gave resin **138**. Treatment with phenyl isocyanate or phenyl isothiocyanate gave polymer supported ureas **139a** and **139b** respectively. Treatment with acid gave hydantoin **140a** in 29 % yield or thiohydantoin **140b** in 20 % yield. No further examples were reported.



scheme 1.32

Nicolaou has employed a traceless sulfur link in the solid phase synthesis of 3-arylbenzofurans via a novel cyclofragmentation-release pathway.[32] Thiophenol resin **141** was alkylated with bromo-chloro methane in the presence of DBU to give **142** (scheme **1.33**). Chloromethylsulfide resin **142** was then alkylated with a salicyl aldehyde derivative **143** to give resin bound aldehyde **144**. Addition of a functionalised aryl magnesium bromide to aldehyde **144** gave benzhydrol **145**, which was then oxidised using IBX to give benzophenone **146**. Treatment of benzophenone **146** with trimethylsulfonium iodide gave epoxide **147**, which, after oxidation of the sulfur link to the sulfone **148**, was ready for application in the cyclofragmentation-release strategy. Treatment of sulfone **148** with base results in deprotonation at the methylene group adjacent to the sulfone followed by a 5-*exo* tet epoxide opening which triggered loss of formaldehyde and the elimination of phenylsulfinate anion thus releasing 3-arylbenzofuran **150** from the solid support in good yield. A range of 3-arylbenzofurans were synthesised via this route using a variety of salicyl aldehydes and aryl Grignard reagents in yields ranging from 6-29 % for 6 solid phase steps.

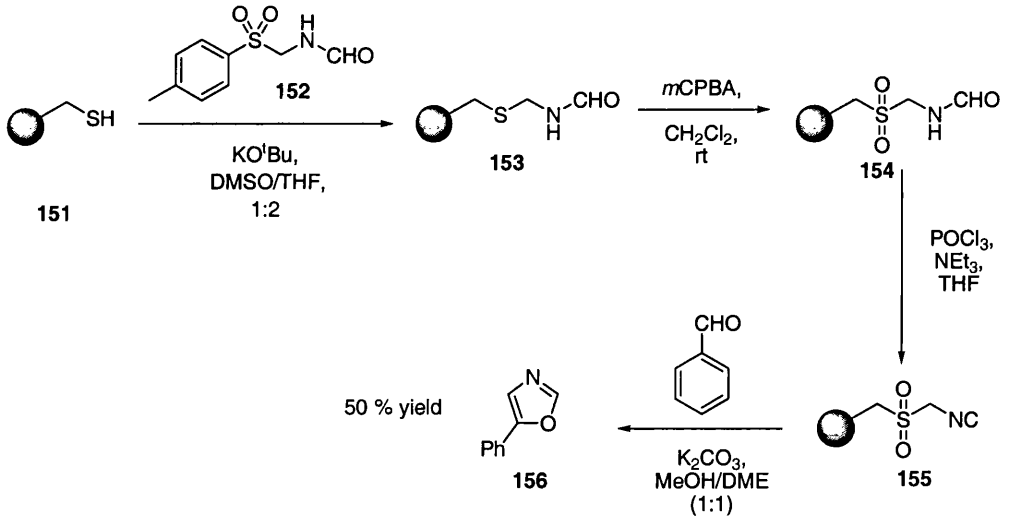


scheme 1.33

There are several advantages in applying this route to solid phase synthesis. Firstly, by varying the salicyl aldehyde derivative and the aryl Grignard reagent there are two points at which diversity can be introduced into the system. Secondly, products undergo traceless cleavage from resin during the cyclisation step. Finally, cleaved products are obtained in high purity as only the desired benzofuran product can undergo release from resin. For example, if any side reactions such as 6-*endo* cyclisation occur, then the resulting cyclised

product cannot undergo the fragmentation-release pathway and therefore remain bound to resin.

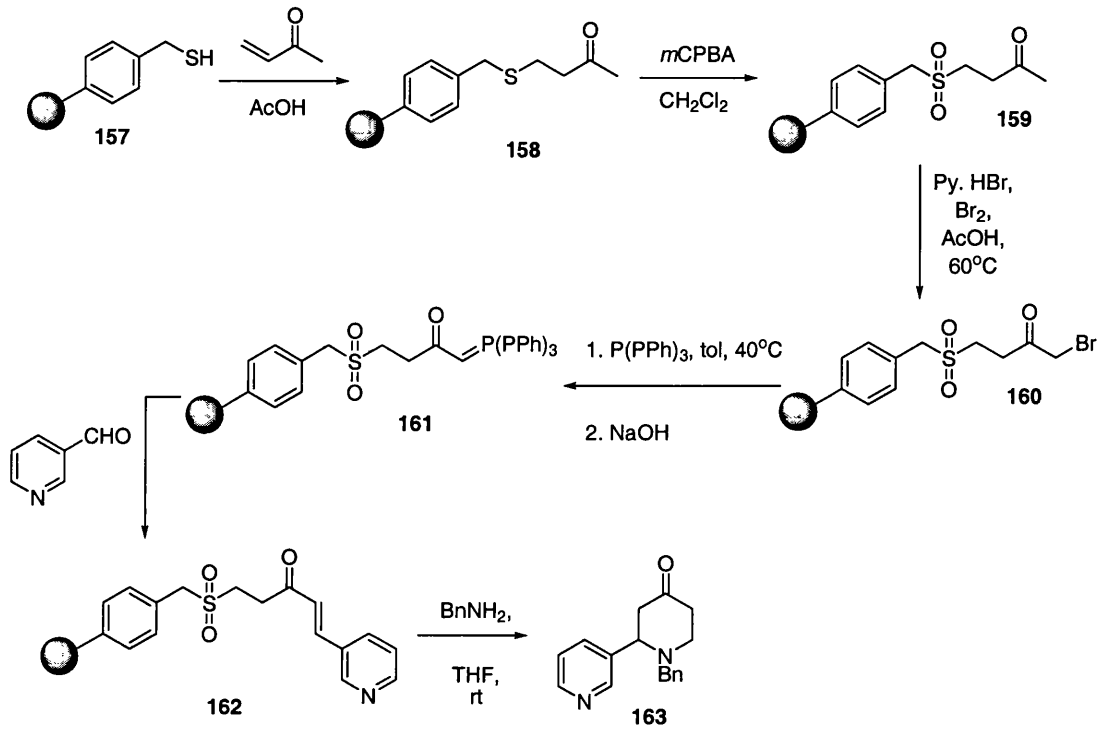
Ganesan has developed a solid phase equivalent of *p*-tolylsulfonylmethylisocyanide (TosMIC™) for the synthesis of oxazoles (scheme **1.34**).[33] Thiol resin **151** was treated with **152** to give sulfide **153**. Oxidation of the sulfide to the sulfone was followed by dehydration and reduction of the formamide to give TosMIC resin **155**. Treatment with benzaldehyde or other aromatic aldehydes and base gave 5-aryloxazole **156** in 50 %. When a Tentagel thiol resin was used the desired product was obtained in 49 % yield although impurities resulting from the breakdown of the PEG linker by K_2CO_3 were observed. TosMIC resin was treated with a range of aromatic aldehydes to give 5-aryloxazoles in yields between 25 and 50 %.



scheme 1.34

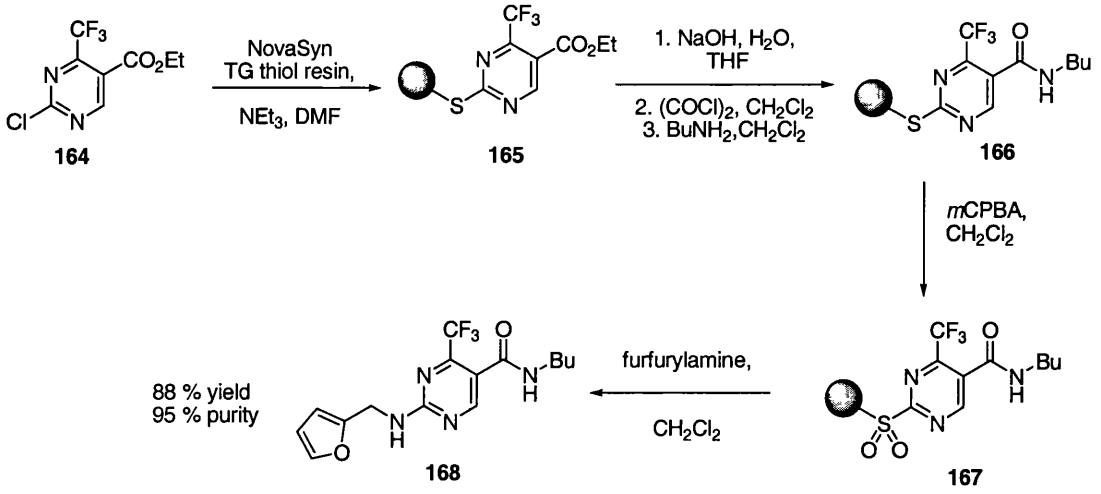
Barco has developed a solid phase route to substituted piperidin-4-one derivatives which utilises 4-benzylsulfonyl-1-triphenylphosphoranylidene resin **161** (scheme **1.35**).[34] Michael addition of thiol resin **157** to 3-butenone gave sulfide **158**. Oxidation of the sulfide link to the sulfone, α-bromination and treatment with triphenylphosphane then base gave the key resin bound ylide **161**. The ylide underwent Wittig reaction with various aldehydes to give enones such as **162**. Subsequent treatment with benzyl amine resulted in cleavage of substituted piperidin-4-one **163**. The amine has two roles in this reaction. It undergoes 1,4-addition to the enone **162** and also acts as a base to promote the elimination of the sulfone resin. Finally, 1,4-addition to the newly generated enone gave the piperidin-4-one

skeleton. Five different piperidin-4-ones were synthesised by varying the aldehyde used in the Wittig reaction however, yields were not given.



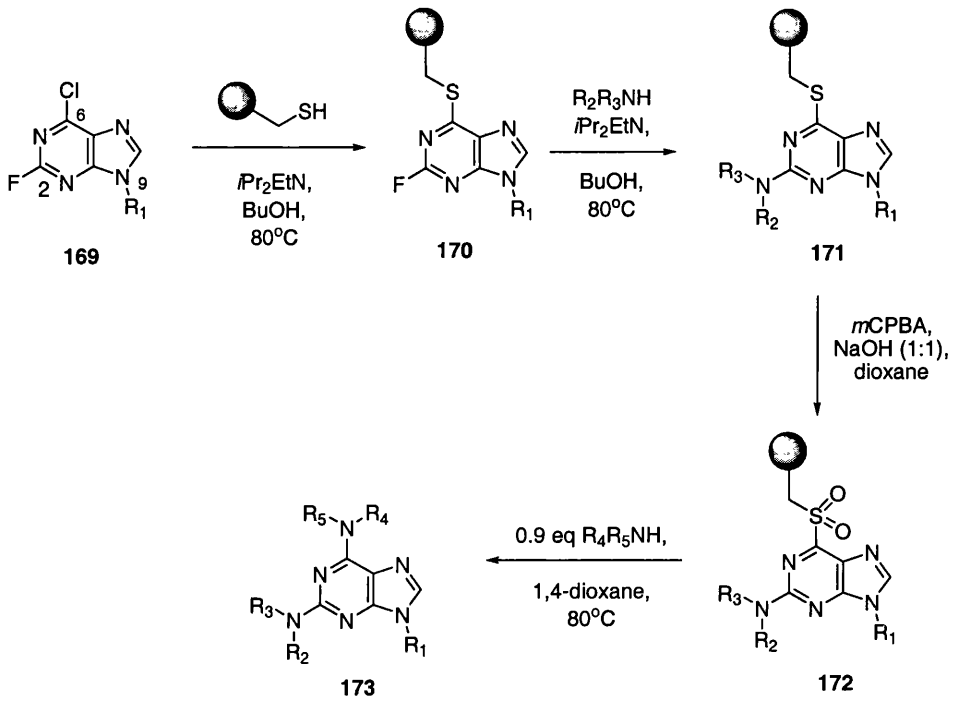
scheme 1.35

Suto has applied a traceless sulfur-based safety catch linker in the synthesis of a small pyrimidine library (scheme **1.36**).[35] 2-Chloro-4-trifluoromethylpyrimidine-5-carboxylate **164** was immobilised using tentagel thiol resin to give a resin bound pyrimidine **165**. The sulfide link was stable to a variety of reaction conditions, remaining intact through ester hydrolysis, conversion of the resultant acid to the acid chloride and subsequent amide formation. The link was activated by oxidation with *m*CPBA to give sulfone **167**. Treatment with a nucleophilic amine such as furfurylamine results in nucleophilic cleavage of the highly functionalised pyrimidine **168** from resin. Pyrimidines are obtained in high yield and purity (determined by GC/MS and HPLC).



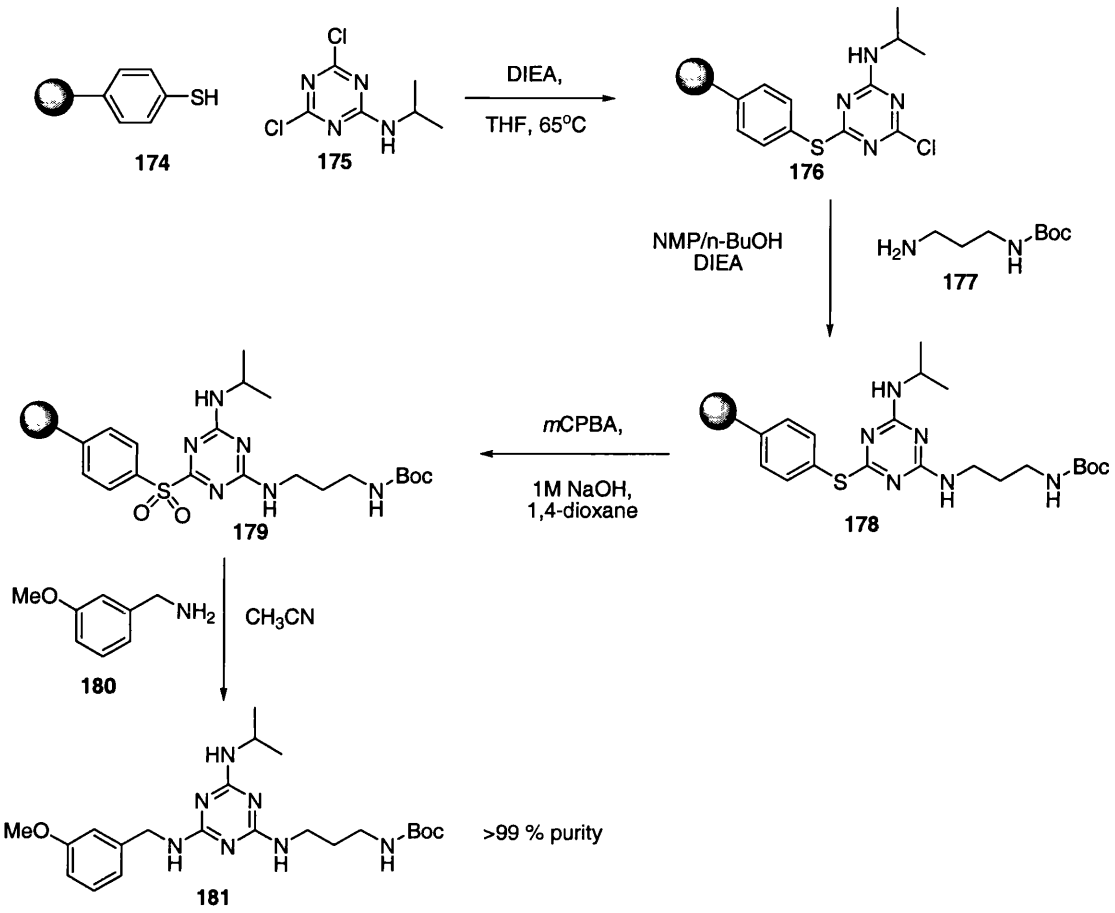
scheme 1.36

Schultz has developed a similar combinatorial based, resin-capture and release strategy for the synthesis of 2,6,9-trisubstituted purines in which a sulfur linker plays a crucial role (scheme **1.37**).[36] N9 substituted purine **169** was attached to a polymer support at the C6 position using a sulfide link to resin. Nucleophilic substitution at the C2 position of the purine occurred by treatment of resin **170** with an amine and base to give **171**. This nucleophilic substitution at C2 is not possible if the linker at C6 is amino based rather than sulfur-based. Further derivatisation of the purine can be achieved by oxidation of the thioether link to give sulfone **172**, thus, activating the C6 position to nucleophilic substitution. Treatment of **172** with a limiting amount of amine results in release of 2,6,9-substituted purines such as **173** from resin. This route has been shown to tolerate the introduction of a broad range of substituents on the purine ring. A variety of sterically hindered primary and secondary amines can be added at the C2 position. Substitution at C6 can also be carried out with a wide range of primary and secondary amines and also electron rich anilines. A library of substituted purines was produced, with an average yield of 80 % and an average >85 % purity by HPLC.



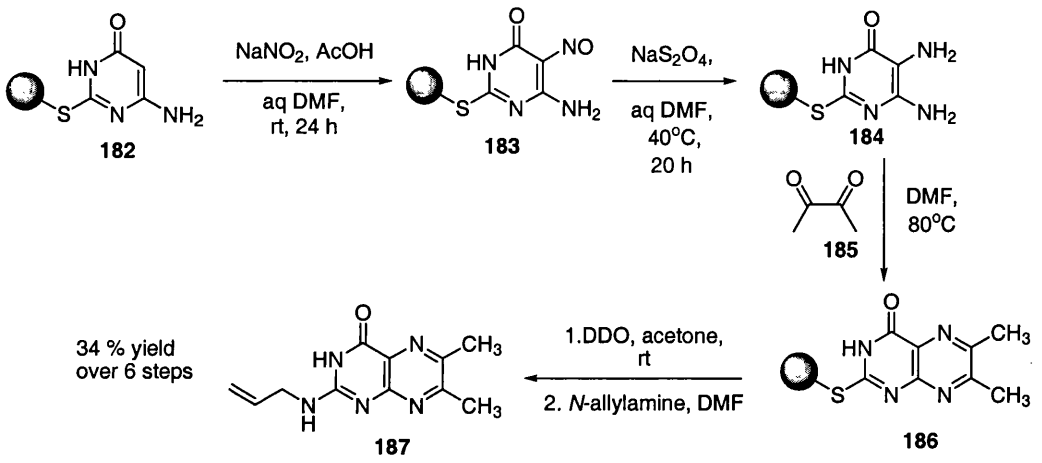
scheme 1.37

Chang has developed a safety catch method for the orthogonal synthesis of trisubstituted triazines (scheme **1.38**).[37] Monosubstituted triazine **175** was immobilised onto thiophenol resin **174**. The second chlorine atom was substituted with an amine nucleophile **177** to give resin bound disubstituted triazine **178**. Activation of the thioether link by oxidation was followed by nucleophilic displacement from resin with a nucleophilic amine **180** to give trisubstituted triazine **181** in very high purity. A range of amines, anilines and alcohol nucleophiles were tested in the sulfone displacement step. Unactivated anilines were not successful in affecting cleavage, resulting in only a trace of triazine product. Phenol and sterically hindered amines such as dibenzyl amine were also ineffective in the cleavage step. Unhindered primary and secondary amines gave the best results.



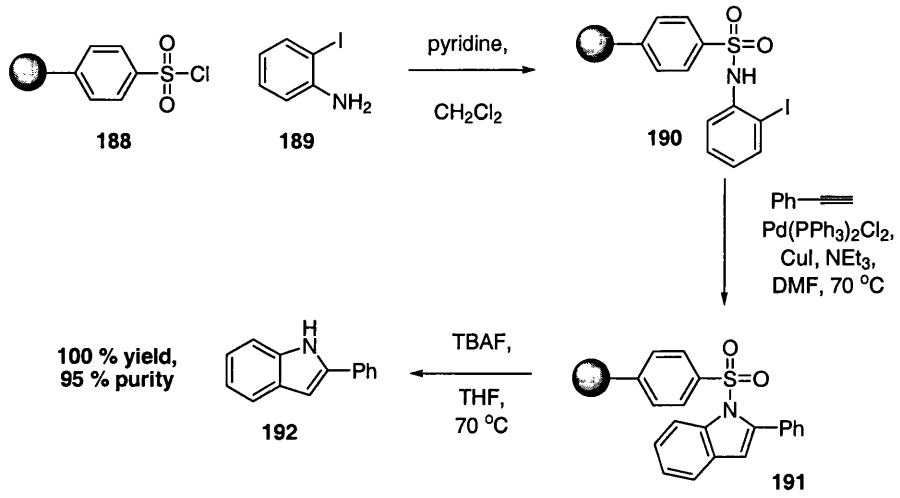
scheme 1.38

Suckling has developed a solid phase route to pteridines using the same sulfone safety-catch linker approach (scheme **1.39**).[38] Merrifield resin bound 6-amino-2-sulfanylpyrimidin-4(3H)-one **182** underwent nitration and subsequent reduction to give diamino pyrimidine resin **184**. Treatment with biacetyl **185** gave resin bound pteridine resin **186**. Activation of the thioether link was achieved by oxidation with dimethyl dioxirane. Treatment with a nucleophile such as allylamine resulted in cleavage of pteridine **187** from solid support in 34 % yield. Other nucleophiles such as azide and pyrrolidine were used in the cleavage step successfully.



scheme 1.39

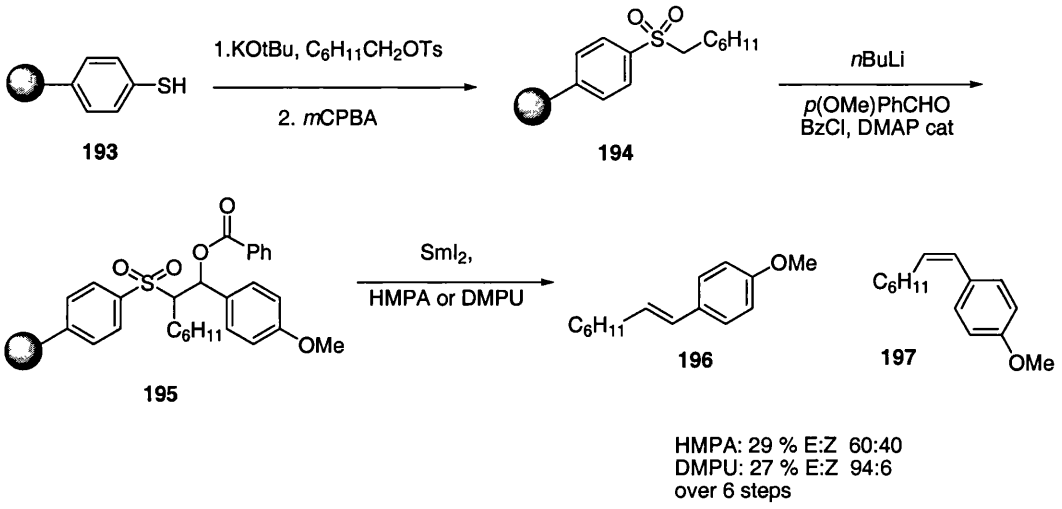
Zhang has constructed 2-substituted indoles using a traceless sulfonyl linker (scheme **1.40**).[39] The sulfonyl link has a dual role in the synthesis; it facilitates the indole cyclisation by providing activation and its activated nature also allows cleavage to be affected under mild reaction conditions. 2-Iodoaniline was loaded onto the commercially available polystyrene sulfonyl chloride resin **188**. Treatment of resin **189** with alkyne, catalytic Pd (0), catalytic Cu(I) and NEt_3 results in a Sonagashira coupling between the aryl iodide and the alkyne, followed by cyclisation to give indole **191**. In the absence of the activating sulfonyl link to resin, it would be necessary to carry out the coupling and cyclisation as a two-pot process, with the cyclisation requiring strong base and high temperature. In this case, the activating sulfonyl linker enables the cyclisation to occur under milder conditions, thus, the two transformations are carried out in one pot. Treatment of **191** with TBAF was found to be the most efficient cleavage strategy releasing the indole **192** from solid phase in high yield and purity. Again the linker system allows cleavage to take place under mild conditions. Bases such as KOH and KO*t*Bu can also be used to affect cleavage although their functional group compatibilities are less wide-ranging. To prepare diverse array of indoles with yields of 85 - 100 % and with 85 -100 % HPLC purities, various different substituted anilines (electron withdrawing and electron donating groups on the aryl ring are tolerated) and alkynes were employed.



scheme 1.40

De Clercq has utilised a sulfone linker in a solid phase Julia-type olefination process (scheme **1.41**).[40] Alkylation of aryl thiol resin **193** followed by *m*CPBA oxidation gave supported sulfone **194**. Successive treatment of the resin with *n*-butyllithium and an aldehyde followed by trapping the alkoxide anion with benzoyl chloride, gave resin bound α-benzyloxyphenyl sulfone **195**. Olefins **196** and **197** were released from the solid support upon treatment with a single electron transfer reagent. Samarium diiodide proved to be the most suitable reagent for the process and was used here together with either HMPA or DMPU. The E:Z selectivity was found to be strongly dependant on the nature of the additive. Yields ranged from 25-29 % over six solid phase steps which included the preparation of the thiophenol resin. DMPU was shown to give greater *E* selectivity than HMPA for the example shown in scheme **1.41**.

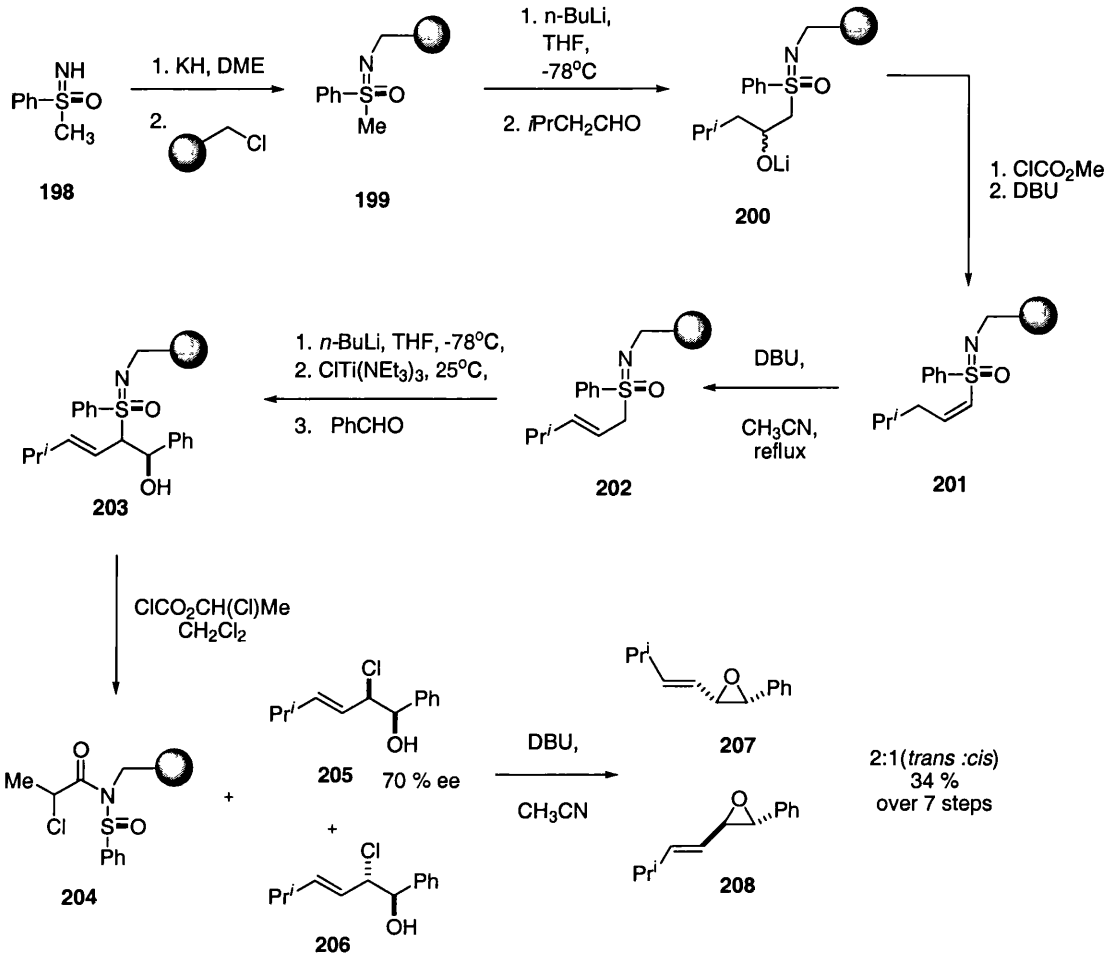
This is a potentially very useful application of a sulfone linker although the generality of the process must be explored. In addition, the stereoselectivity of the olefination process requires further study as the E:Z selectivities were seen to depend dramatically on substrate structure and, as previously mentioned, the conditions employed in the reductive cleavage.



scheme 1.41

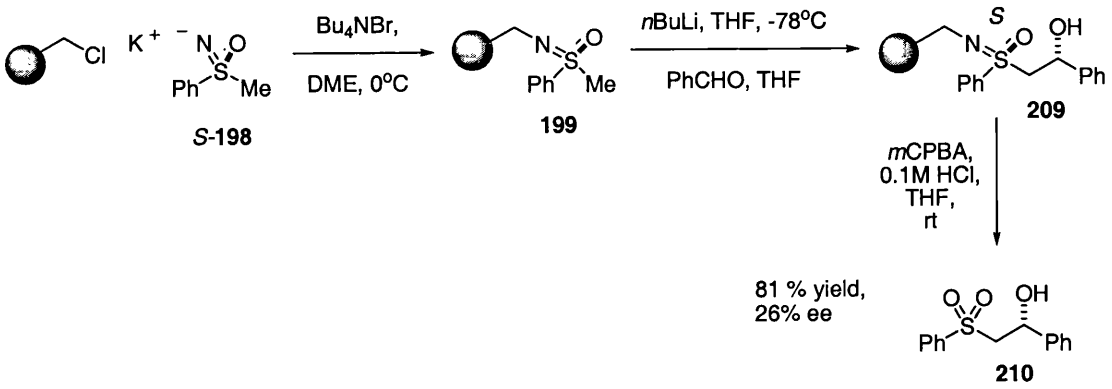
1.1.6 Sulfoximine linkers

Gais has used a chiral sulfoximine linker for the asymmetric solid phase synthesis of alkenyl oxiranes (scheme **1.42**).[41] Enantiomerically pure sulfoximine **198** was treated with potassium hydride and Merrifield resin to give resin bound chiral sulfoximine **199**. Deprotonation with *n*-butyllithium followed by addition of isovaleraldehyde gave alkoxide **200** which underwent elimination to vinyl sulfoximine **201** upon treatment with methyl chloroformate and DBU. Isomerisation to allylic sulfoximine **202** was performed by refluxing in DBU. α-Lithiation was followed by titanation and addition of the titanate to benzaldehyde to give **203**. Addition of allylic titaniums this kind to aldehyde in solution has been shown to occur diastereoselectively to give *syn* homoallylic alcohols. Cleavage of the chiral sulfoximine linker group was achieved by treatment of **203** with 2-chloroethyl chloroformate, Acylation of the sulfoximine nitrogen occurs to give an aminosulfoxonium salt and chloride ion then stereoselectively displaces the linking unit. A mixture of *syn* and *anti* chlorohydrins was obtained in a 2:1 ratio. Oxiranes **208** and **207** were obtained in a 2:1 mixture upon exposure to DBU. Low diastereoselectivity was obtained in the addition to aldehyde due to incomplete titanation of the lithiated sulfoximine. Use of a solid supported chiral sulfoximine linker for stereoselective alkenyl oxirane synthesis is promising but requires further optimisation.



scheme 1.42

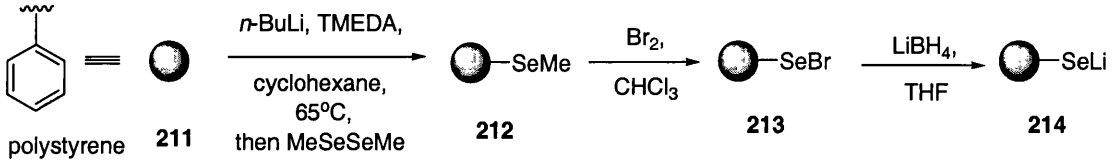
Polymer bound chiral sulfoximines have also been applied in the synthesis of chiral β-hydroxy sulfones (scheme **1.43**).[42] It was hoped that the sulfoximine moiety would control the asymmetry of reactions of the α-anion with aldehydes. Resin bound chiral sulfoximine **199** was deprotonated with *n*-butyllithium and the resulting anion quenched using benzaldehyde. Oxidative cleavage from the resin was achieved by treatment with *m*CPBA and HCl and gave sulfone **210**. Unfortunately, the released sulfone was obtained in only 26 % ee suggesting that asymmetric control by the resin bound chiral sulfoximine in the reaction with benzaldehyde was poor.


Cl
K+
N
O
S
Ph
Me
S-198
Bu4NBr,
DME, 0°C
199
nBuLi, THF, -78°C
PhCHO, THF
S
OH
209
mCPBA,
0.1M HCl,
THF,
rt
81 % yield,
26% ee
210

scheme 1.43

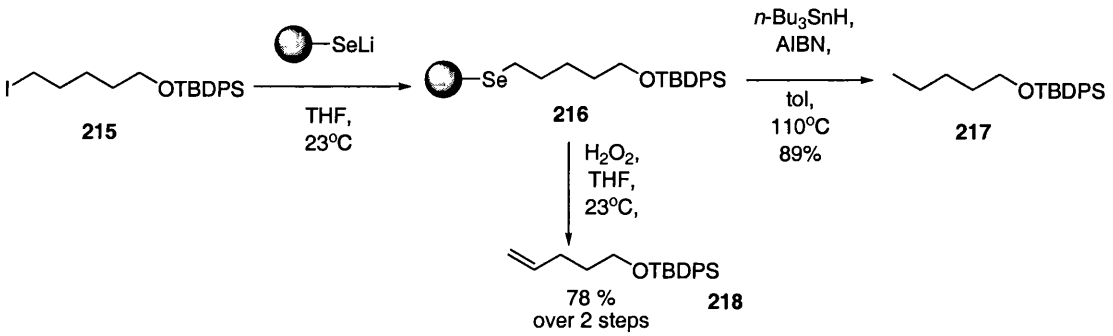
1.2 Selenium linkers

The Nicolaou group was amongst the first to prepare a series of selenium resins for linker construction.[43] Treatment of polystyrene with *n*-butyllithium followed by dimethyldiselenide gave selenoether resin **212** (scheme **1.44**). Treatment of **212** with bromine gave selenenyl bromide resin **213**. Reduction with $LiBH_4$ gave lithium selenide resin **214**.



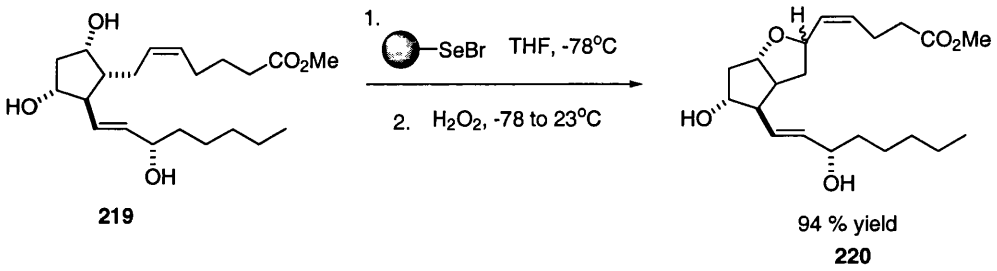
scheme 1.44

Alkyl iodide **215** was efficiently loaded onto lithium selenide resin **214** (scheme **1.45**). The compound could be released from resin in one of two ways. Radical cleavage with tributyl tin hydride resulted in release of alkyl compound **217** in 89 % yield over 2 steps.[43] Oxidation of the selenium linker to the selenoxide followed by elimination released alkene **218** in 78 % yield over 2 steps.



scheme 1.45

Selenenyl bromide resin **213** has been used in the conversion of PGI_{2a} methyl ester **219** to the PG_{I2} analogue **220** in 94 % yield (scheme **1.46**).[43] Capture of substrate **219** using selenyl bromide **213** in a selenoetherification reaction, initially gives a resin bound cyclisation product which is released into solution by oxidation of the selenium link and eliminative-cleavage to give **220**.



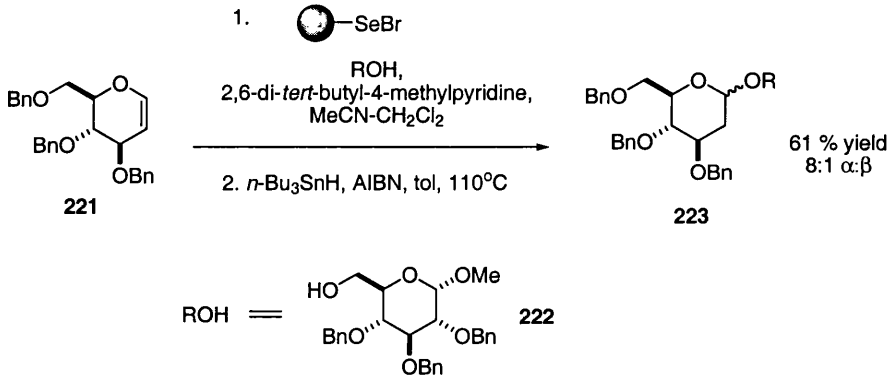
219

94 % yield

220

scheme 1.46

Selenenyl bromide resin **213** has also been used in the synthesis of 2-deoxyglycosides (scheme **1.47**).[43] Treatment of tri-*O*-benzylglucal **221** with selenenyl bromide resin **213** in the presence of an alcohol such as **222** resulted in *O*-glycosidation and immobilisation of the product through selenium at the 2-position. Radical cleavage of the C-Se bond using tributyltin hydride released the 2-deoxy glycosylated product in 61% yield as an 8:1 mixture of α and β anomers.



221

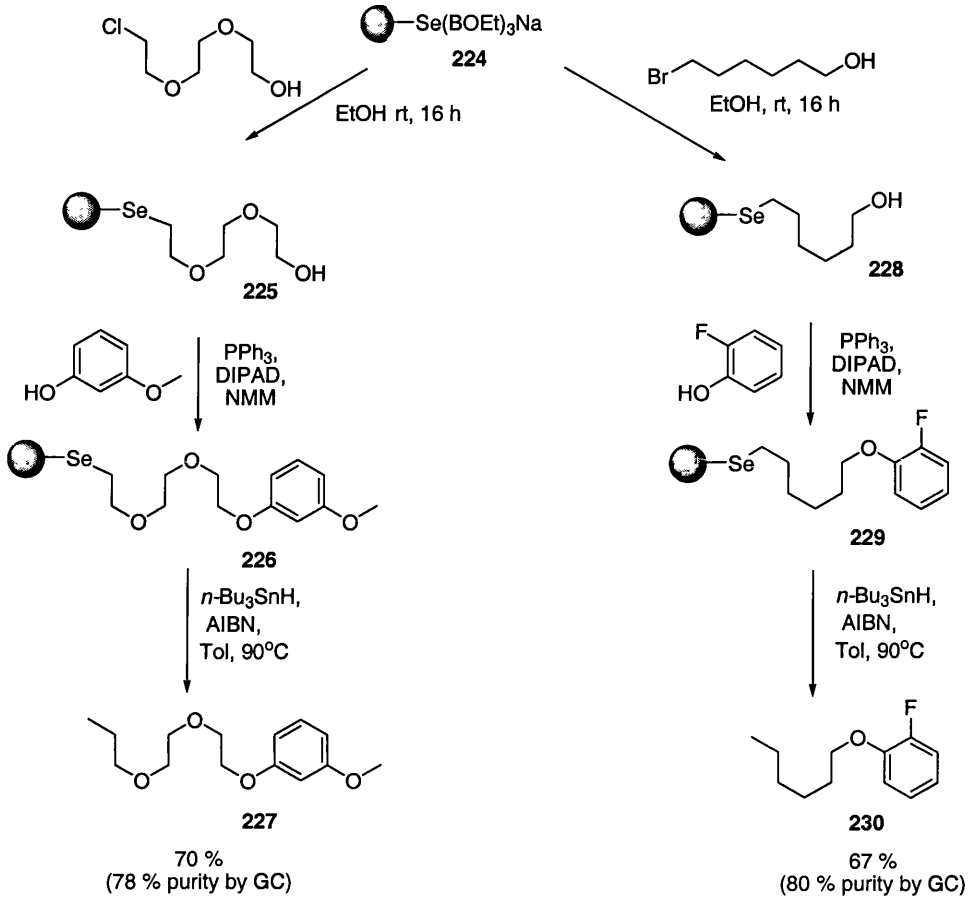
223

222

scheme 1.47

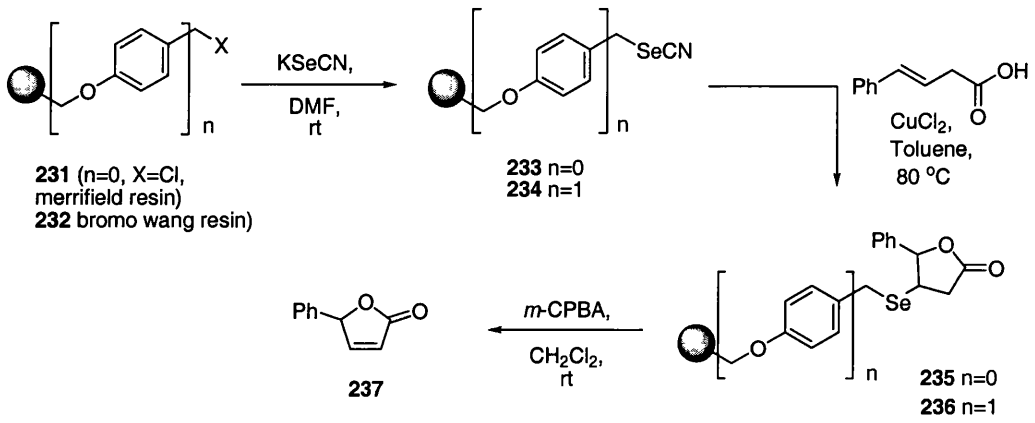
Concurrently with Nicolaou, Ruhland developed one of the first traceless selenium linkers for the formation of aliphatic C-H bonds upon cleavage (scheme **1.48**).[44] Sodium seleno(triethylborate)resin **224** was prepared from bromopolystyrene resin by lithium-bromine exchange, treatment of the resulting lithiated resin with selenium powder and finally, treatment with sodium borohydride in ethanol, thus, reducing any diselenide bonds and eliminating Se-Se crosslinking. Resin bound selenoate **224** underwent alkylation upon treatment with alkyl chlorides and alkyl bromides to give products such as **225** and **228** respectively. The resin bound alcohols were then subjected to Mitsunobu reactions with phenols to give **226** and **229**. Traceless cleavage was then carried out using tributyltin hydride. Cleavage of the aliphatic C-Se bond occurs preferentially to the aromatic C-Se bond to give aryl ethers **227** and **230** in good yields and high purity by GC. A 2 x 3 array

of alkyl aryl ethers was synthesised in yields of 57-83 % and GC purities of 78-88 % using the selenium linker system.



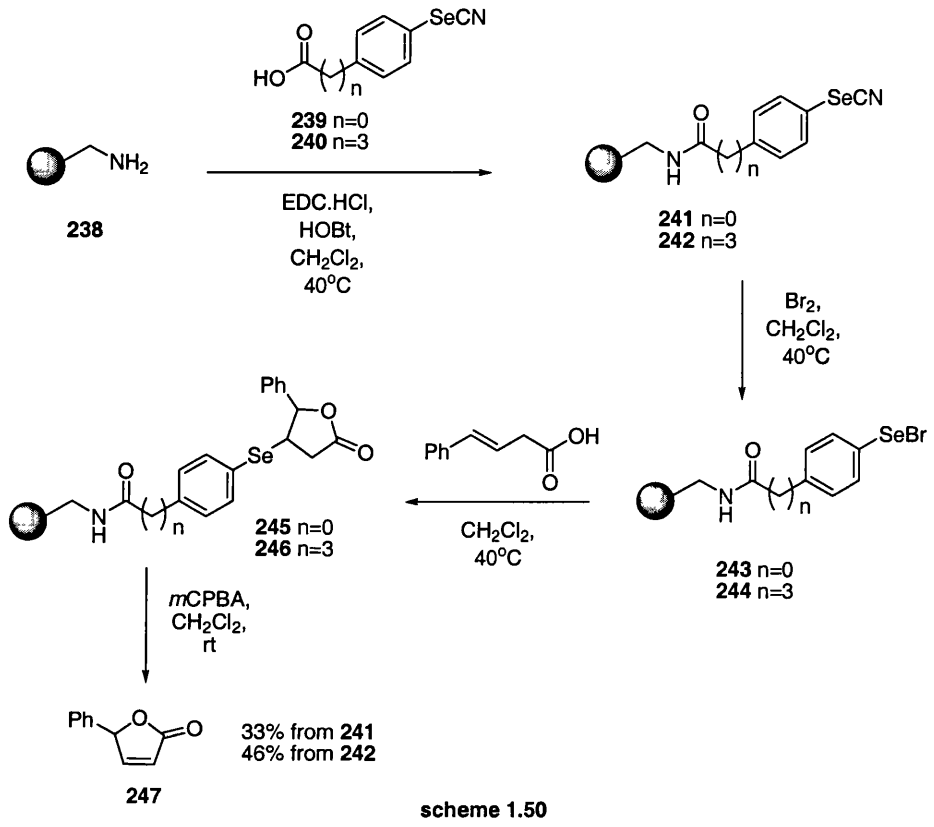
scheme 1.48

Fujita has prepared polymer supported selenocyanates for use in solid phase oxyselenenylation-deselenenylation reactions.[45] Selenocyanate resin **233** was prepared by treatment of Merrifield resin **231** with potassium selenocyanate (scheme **1.49**). A bromoWang based selenocyanate resin **234** which contains a phenoxymethyl link was also prepared in a similar manner from resin **232**. Attempts to synthesise the corresponding selenenylbromide resin from **233** were unsuccessful. Treatment of **233** with copper (II) chloride, *E*-4-phenyl-3-butenoic acid in toluene at 80°C led to intramolecular oxyselenenylation to give polymer supported selenolactone **235**. *m*CPBA oxidation to the selenoxide followed by eliminative-cleavage gave lactone **237** in 56% yield over 3 steps. The corresponding solid phase synthesis using resin **234** was less successful yielding only a trace of **237**.



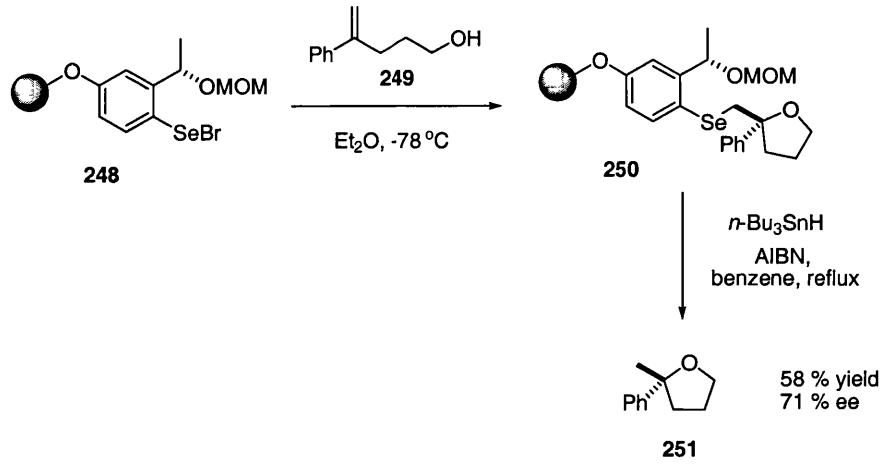
scheme 1.49

Aryl selenocyanate resins **241** and **242** were prepared from aminomethyl polystyrene resin **238** (scheme **1.50**).[45] In constrast to Fuijita's previous studies, it was possible to prepare selenenyl bromides **243** and **244** from these selenocyanates. Solid phase selenolactonisation could then be carried out simply by treating the selenenyl bromide resin with (E)-4-phenyl-3-butenoic acid in CH_2Cl_2 at 40°C to give polymer supported lactones **245** and **246**. Eliminative-cleavage was triggered by oxidation with *m*CPBA and gave **247** in 33 % yield from resin **241** and 46 % yield from resin **242**. No further examples of the selenolactonisation of enoic acids were reported.



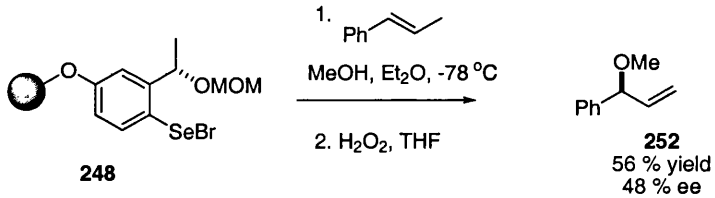
scheme 1.50

Wirth has used polymer-bound enantiomerically pure, electrophilic selenium reagents for asymmetric addition of nucleophiles to alkenes (scheme **1.51**).[46] Selenyl bromide resin **248** was prepared and applied in selenenylation reactions. The use of polystyrene, tentagel and mesoporous silica supports were investigated, however, a polystyrene support was found to give the best results in the selenylation reactions compared with tentagel resin and, although mesoporous silica gave good results in the selenenylation reactions, loadings were so low that yields could not be determined. Treatment of polystyrene based resin **248** with unsaturated alcohol **249** led to asymmetric seleniranium ion formation, followed by intramolecular nucleophilic addition of the tethered alcohol, to give polymer bound tetrahydrofuran **250** with good stereocontrol. Radical cleavage of the selenium link with tributyltin hydride gave tetrahydrofuran **251** in 58 % yield and 71 % ee. The main disadvantage of this route is that cleavage requires the use of tin reagents which are difficult to separate from the volatile products.



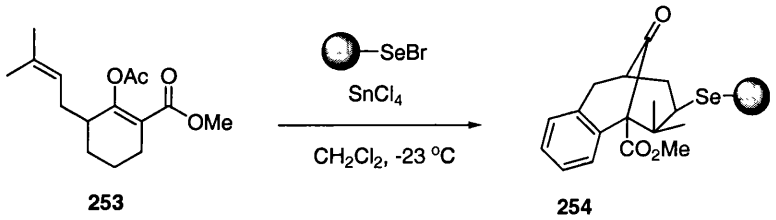
scheme 1.51

The asymmetric intermolecular addition of nucleophiles to acyclic alkenes mediated by chiral resin **248** has also been studied (scheme **1.52**).[46] In the example shown, cleavage is achieved by oxidation of the selenide link to the selenoxide followed by elimination to give chiral allylic ether **252** in 56 % yield and 48 % ee.



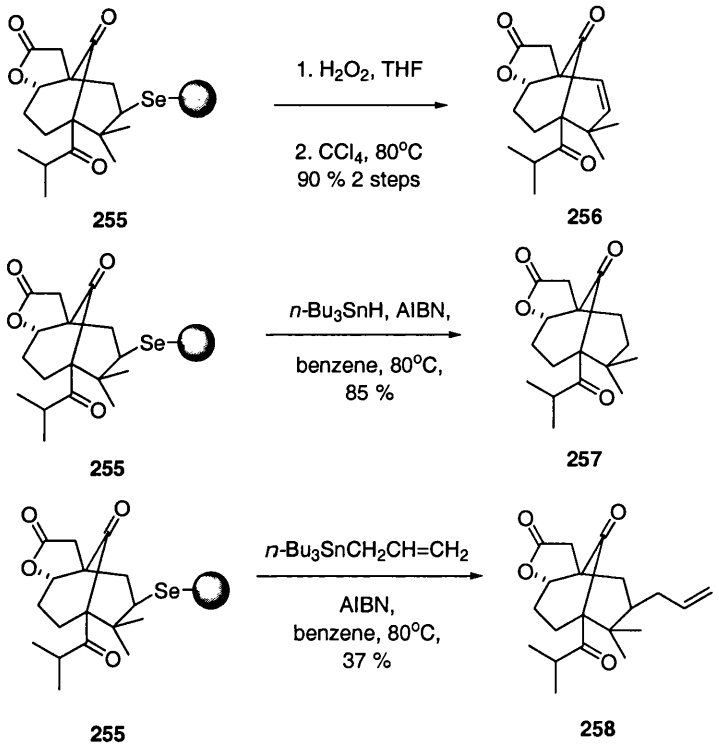
scheme 1.52

Nicolaou has applied polystyrene based selenyl bromide resins in the cyclisation of substituted cyclohexane based enol acetates such as **253** to give substituted [3.3.1] bicyclic systems (scheme **1.53**).[47] The selenyl bromide resin was reacted with an excess of enol acetate **253** and $SnCl_4$ in dichloromethane resulting in clean, capture and cyclisation to give resin bound [3.3.1] bicycle **254**.



scheme 1.53

The solid phase cyclisation reaction was carried out on a range of substrates bearing different substitution patterns around the cyclohexane scaffold. For example, resin bound cyclisation product **255** bears a 5-membered lactone ring fused to the cyclohexane system (scheme **1.54**). Several methods for the cleavage of the selenium linker were investigated and are shown in scheme **1.54**.[47] Oxidation to the selenoxide followed by elimination yields functionalised bicycle **256** in 90 % yield. Traceless cleavage to give **257** occurs upon treatment of **255** with tributyltin hydride. Finally, radical cleavage with allyltributyltin results in the introduction of an allyl group at the point of cleavage. Although this method allows further functionalisation in the cleavage step it is relatively low yielding compared with the other cleavage methods, giving **258** in only 37 % yield.



255 **256**

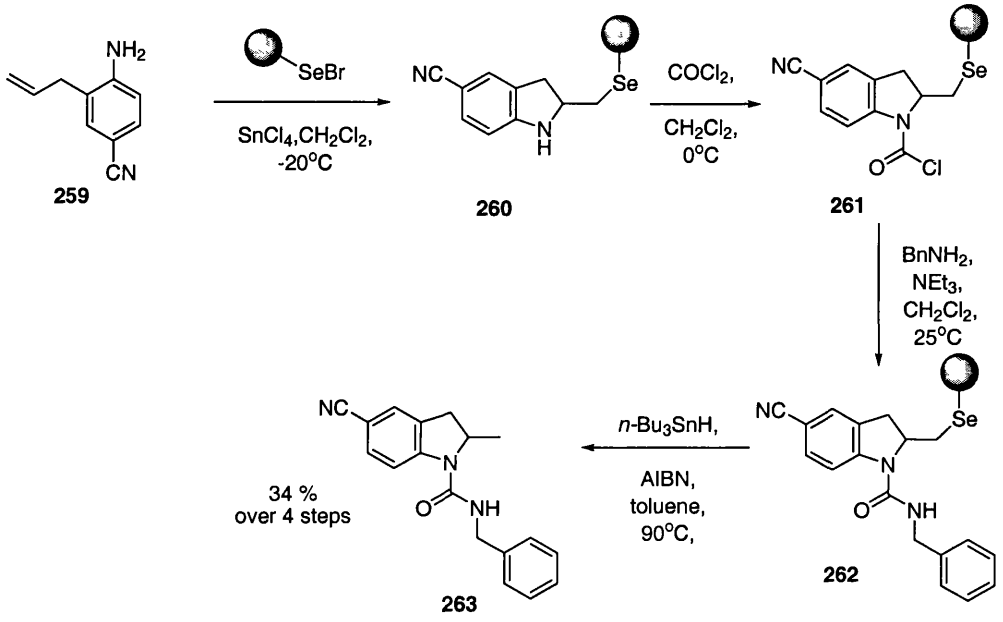
255 **257**

255 **258**

scheme 1.54

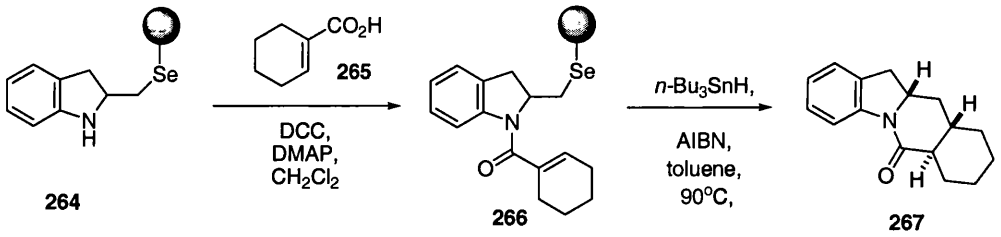
Nicolaou has also developed a selenium based cycloloading strategy for the solid phase synthesis of indolines (scheme **1.55**).[48] Treatment of *o*-allylanilines with selenyl bromide resin in the presence of a Lewis acid results in cyclative-capture to give resin bound indoline **260**. Further functionalisation on resin can be carried out prior to cleavage. Acylation of nitrogen with phosgene gave **261** which was then reacted with amines to give **262**. Traceless cleavage with tributyltin hydride gave functionalised 1-methylindoline **263**

in good yield. A range of 1-methylindolines were synthesised using this approach with yields ranging from 14-34 % for 4 steps. These compounds are of interest to the pharmaceutical industry as the 1-methylindoline structure is found in several drug candidates. For example, 1-methyl indoline derivatives act as 5-hydroxytyramine receptor antagonists and as muscarinic receptor agonists and antagonists. A disadvantage of this route lies in the use of tin reagents in the cleavage step. Purification of the products after cleavage is therefore necessary to remove tin residues.



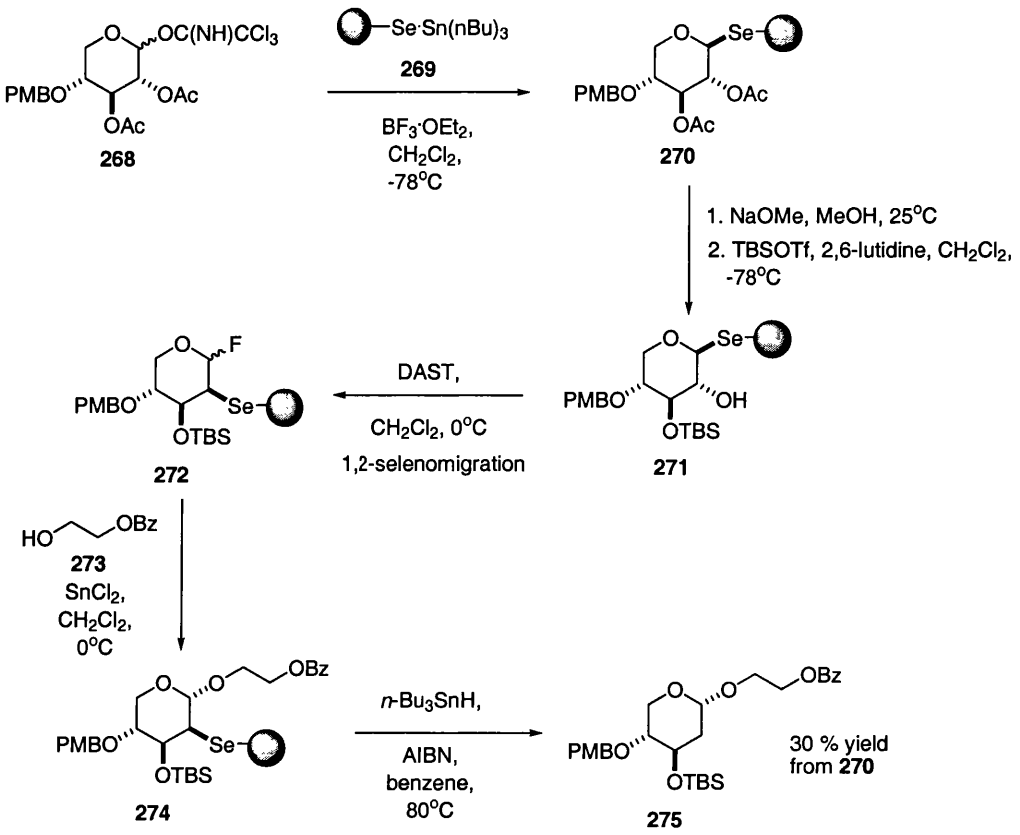
scheme 1.55

Further complexity can be introduced in the cleavage step in resin bound indolines when a suitably positioned tethered alkene is present (scheme **1.56**).[48] For example, resin bound indoline **264** was coupled with unsaturated carboxylic acid **265**. Upon treatment with tributyltin hydride a carbon centred radical was generated which underwent cyclisation onto the double bond to give polycyclic indoline **266**. Complex polycycles can therefore be generated rapidly and conveniently using this methodology.



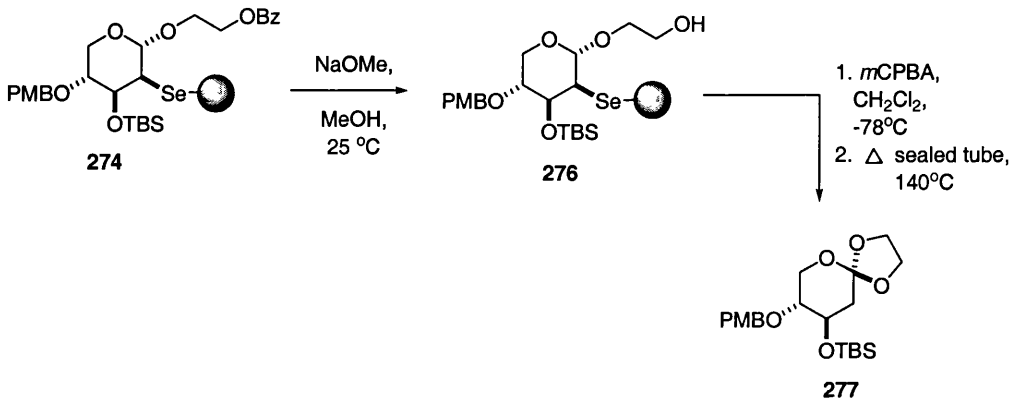
scheme 1.56

Nicolaou has exploited the 1,2-selenomigration reaction of carbohydrates in the solid supported synthesis of 2-deoxyglycosides, 2-deoxyorthoesters and 2,3-allyl orthoesters.[49] A tributyltin ether of a resin bound selenol (scheme **1.57**) was conveniently synthesised in two steps from a selenyl bromide resin. Resin **269** is more air stable than the corresponding selenol resin. Treatment of this resin with trichloroacetimidate donor **268** gave resin bound sugar **270**. Removal of the acetate protecting groups at the C2 and C3 position, and reprotection of the C3 hydroxyl gave **271** ready for the 1,2-selenomigration reaction. Treatment of **271** with DAST promotes 1,2-migration of the selenium link to resin in a stereospecific manner to give **272**, which is now linked to resin at the C2 position, whilst simultaneously generating an anomeric fluoride donor group. Resin **272** can undergo glycosylation with alcohols or sugars. Exposure to Lewis acid and monoprotected diol **273** selectively gave the α-glycoside **274**. Cleavage with tributyltin hydride gave the desired 2-deoxyglycoside **275** in excellent yield. A 3 x 3 library of 2-deoxyglycosides was synthesised using this approach in overall yields ranging from 11-32 % (from the 1-fluoro-2-seleno donor resin).



scheme 1.57

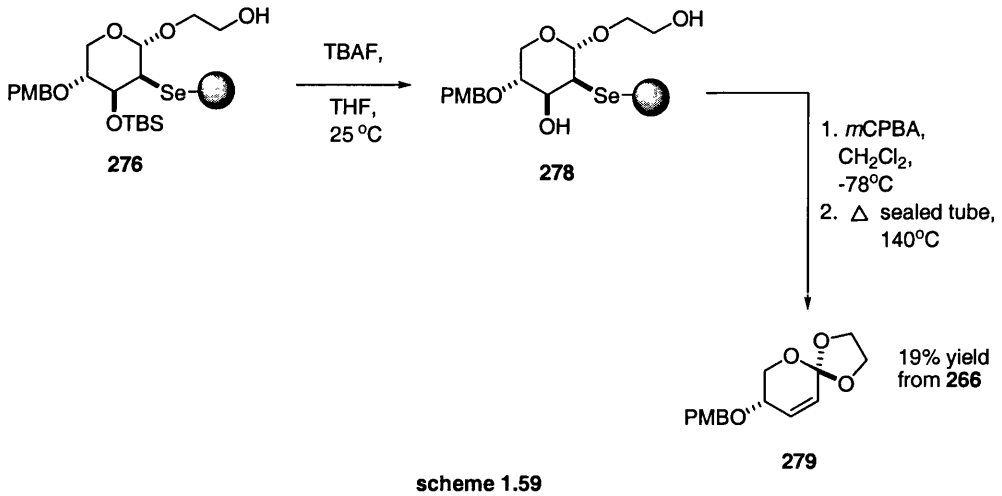
2-Deoxyorthoesters can also be synthesised using the 1,2-selenomigration methodology (scheme **1.58**).[49] Following glycosidation with monoprotected diol **273**, removal of the benzoate protection gives **276** bearing a tethered alcohol. Oxidation of the selenium link to the corresponding selenoxide followed by heating in a sealed tube gave 2-deoxyorthoester **277** in 15 % yield from resin **270**.



scheme 1.58

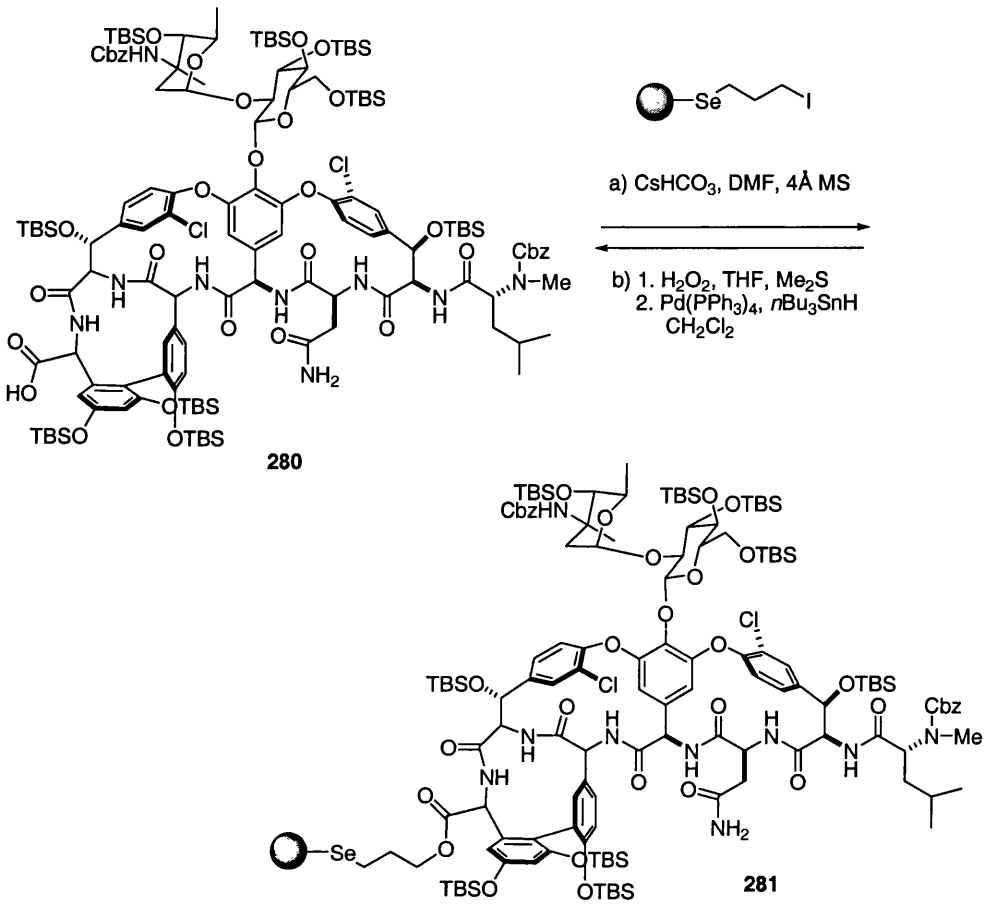
2,3-Allyl orthoesters can also be made by a slight modification of this route (scheme **1.59**).[49] Removal of the C3 silyl protecting group from resin **276** gave **278**. Oxidation to

the selenoxide followed by heating in a sealed tube triggers several events: Elimination of the C3 hydroxy group occurs with simultaneous migration of the double bond and attack of the tethered alcohol at C1 to give the 2,3-allyl orthoester **279** in 19 % yield from **270**. A small library of 2-deoxyorthoesters and 2,3-allyl orthoesters were synthesised on solid phase with overall yields ranging from 2-20 %.



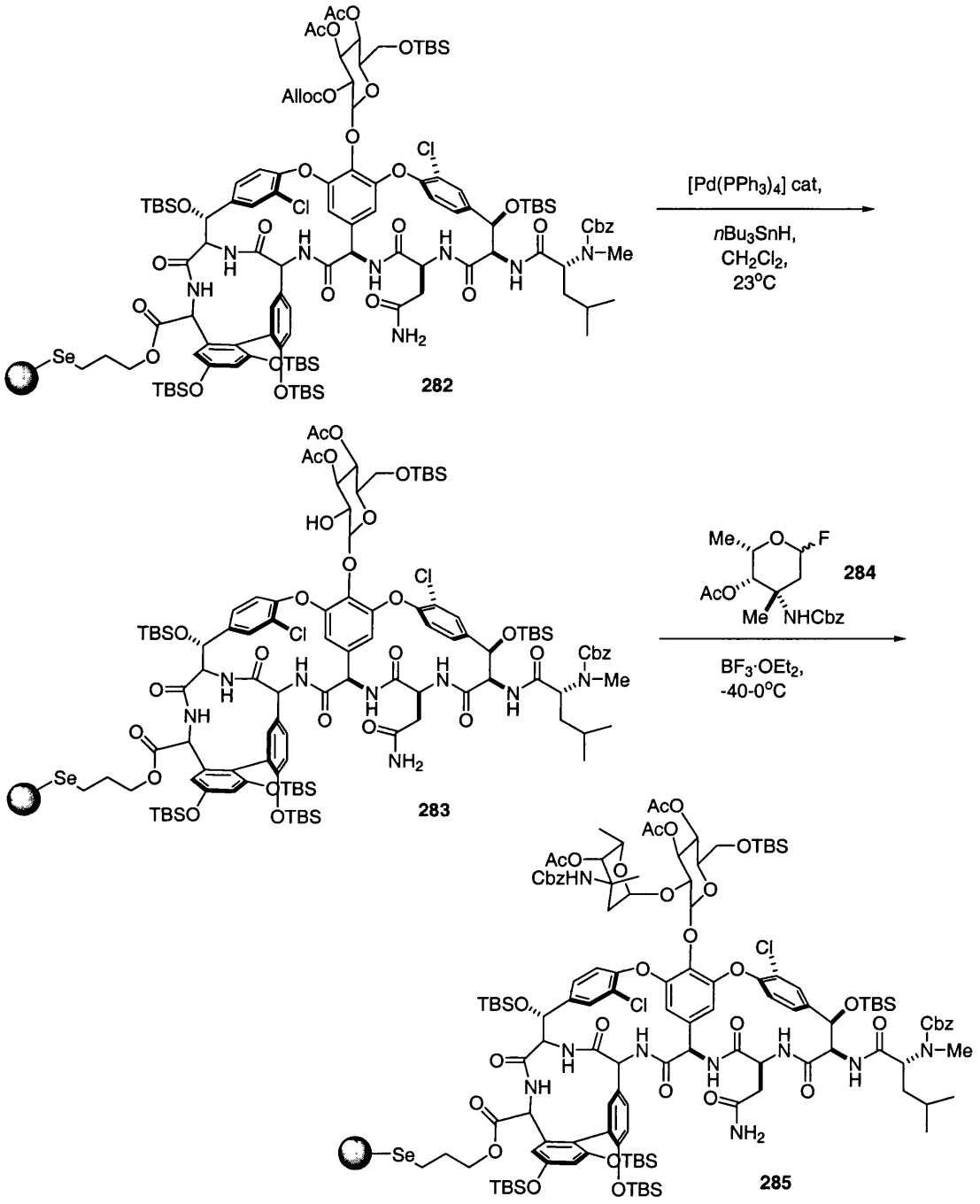
scheme 1.59

The development of new analogues of the glycopeptide antibiotic vancomycin is crucial to treat bacterial infections caused by vancomycin-resistant enterococci (VRE) strains. It is known that varying the oligosaccharide moiety can significantly increase the activity of vancomycin analogues against VRE. Production of a library of analogues of targets such as vancomycin is synthetically very challenging and solid phase synthesis has proved useful for the manipulation of this molecule. Vancomycin contains a diverse array of functionality therefore the choice of solid phase linker system is crucial. Nicoalou has utilised a selenium based safety catch linker for the solid phase semi-synthesis of vancomycin.[50] In order to demonstrate that the selenium linker allows the molecule to be efficiently loaded and cleaved from solid support, protected vancomycin derivative **280** was linked to resin through the carboxylic acid group to give a pro-allyl ester **281** (scheme **1.60**). Oxidation of selenium with H_2O_2, followed by elimination released alloc protected vancomycin. Treatment with catalytic palladium (0) and tributyl tin hydride removed the alloc group to return protected vancomycin **280**.



scheme 1.60

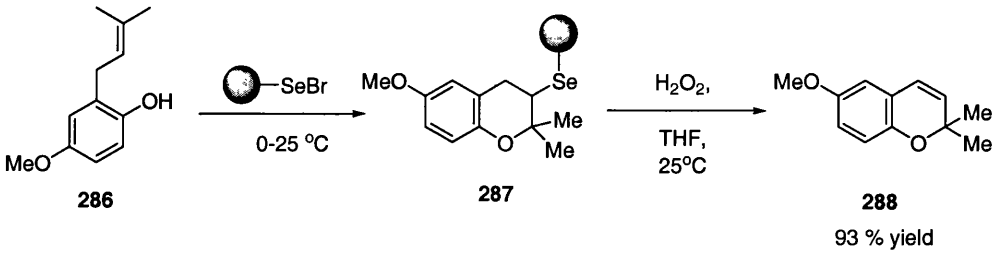
Nicoloau has demonstrated that the glycoside moiety in polymer bound vancomycin **282** can be manipulated (scheme **1.61**).[49] In the example shown, the glycoside unit of **282** bears an alloc protecting group. Deprotection with palladium (0) affords the polymer bound monosaccharide **283** leaving the selenium pro-alloc linker intact. Glycosidation with the fluoride glycosyl donor **284** then gave **285**. Performing these manipulations on solid support greatly assisted the purification of compounds en-route to vancomycin. This linker has potential as a useful tool for the construction of vancomycin libraries.



scheme 1.61

Nicolaou has also applied a selenium linker in the traceless synthesis of molecules containing the 2,2-dimethylbenzopyran moiety, a common structural motif in many natural products and biologically active compounds.[51,52] The key benzopyran forming cycloloading reaction is shown in scheme **1.62**. Treatment of selenyl bromide resin with *o*-prenylated phenols such as **286** results in cyclisation to give a resin bound 2,2-dimethylbenzopyran **287**. Traceless cleavage can be achieved by oxidation with H_2O_2 and elimination to release 2,2-dimethylbenzopyran **288** in an excellent yield of 93%. The

generality of the cyclisation was investigated using *o*-prenylated phenols bearing neutral, electron rich and electron poor substituents. Yields of cleaved products were found to be excellent ranging between 91 and 93 % regardless of the electronic nature of the aromatic ring and purities were consistently greater than 95 %.

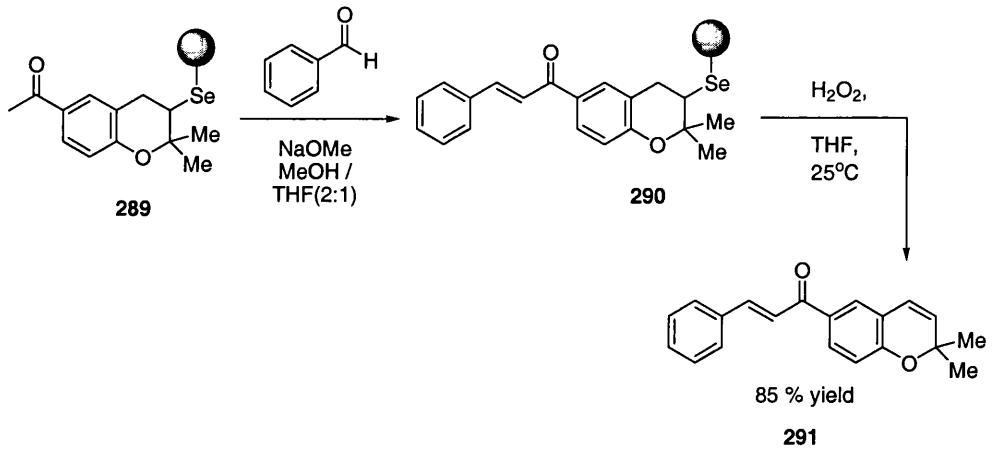


286 **287** **288**

93 % yield

scheme 1.62

Nicolaou has endeavoured to apply this methodology in the production of focused libraries of benzopyran natural products and bioactive compounds.[51,52] After cyclative-loading, further modification of the resin bound 2,2-dimethylbenzopyran core can be performed to yield a diverse array of biologically active molecules. For example, resin bound benzopyran methyl ketone **289** can undergo condensation with aldehydes followed by cleavage to give chalcone **291** in 85 % yield (scheme **1.63**). A library of 24 chalcone analogues were synthesised in yields ranging from 25-90 %.



289 **290**

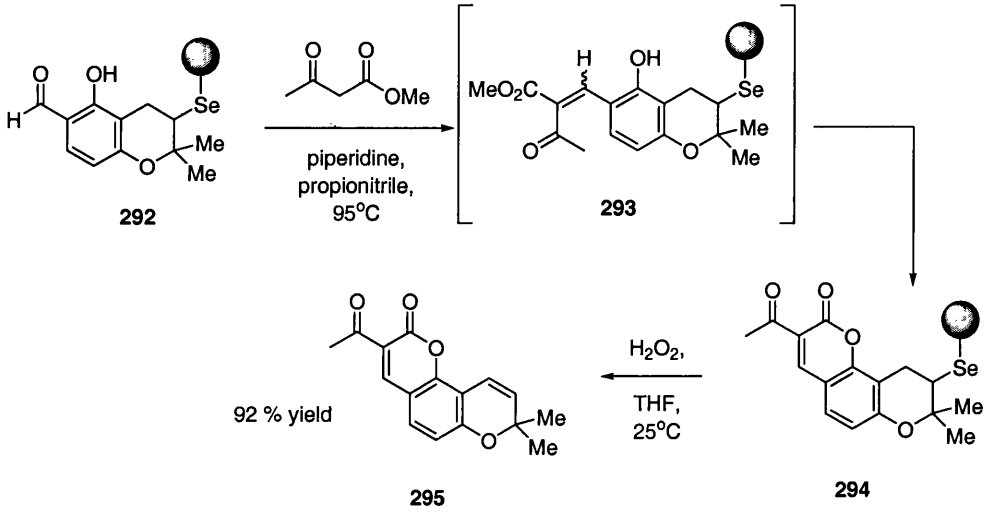
85 % yield

291

scheme 1.63

Pyranocoumarins are natural products which show anti-viral, cytotoxic and anti-platelet activity. A library of analogues of these compounds can be produced from resin bound *o*-hydroxy aldehydes **292** (scheme **1.64**).[51,52] Knoevanagel condensation with a β-ketoester

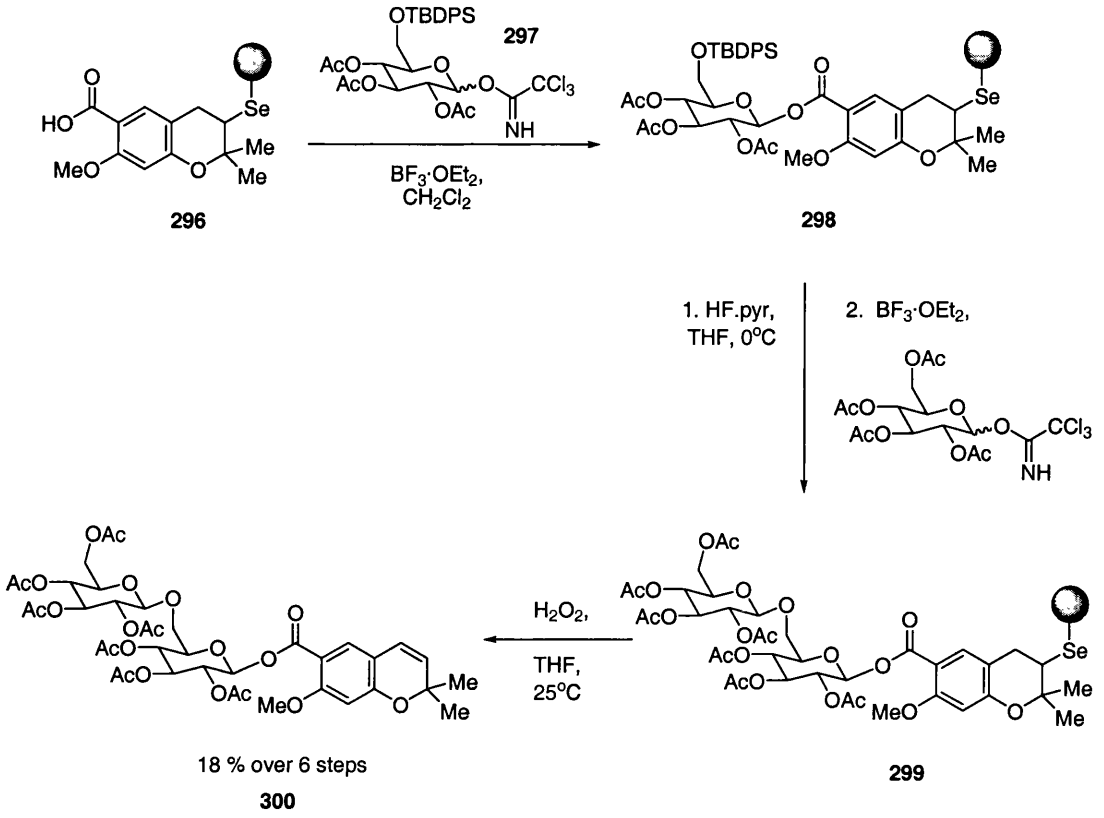
gave intermediate **293** which underwent lactonisation to give pyranocumarin **294**. Oxidation and elimination then gave **295** in 92% yield.



292 **293** **294** **295**

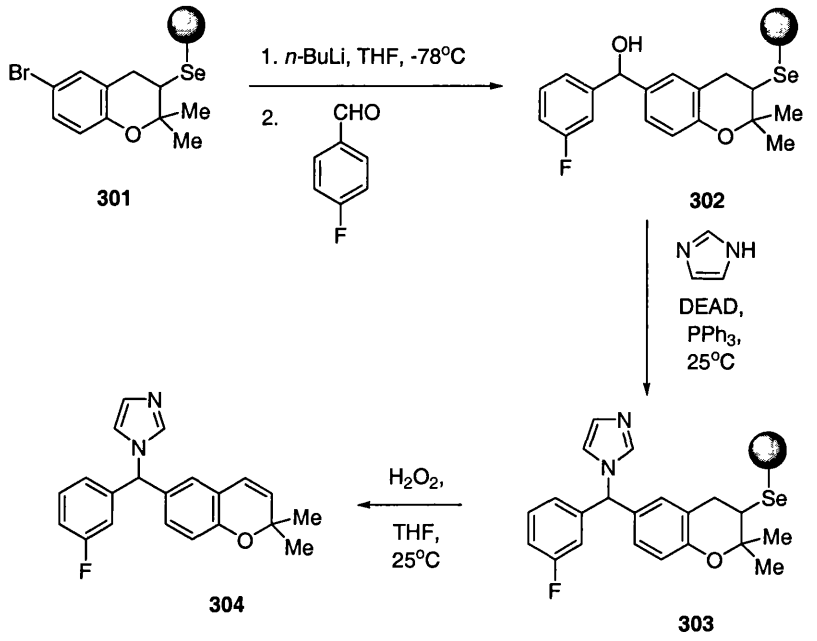
scheme 1.64

The carbohydrate containing benzopyran macrophylloside heptaacetate **300** has been synthesised from resin bound benzopyran **296** (scheme **1.65**).[51,52] Glycosidation of **296** with trichloroacetimidate **297** gave glycoside **298**. Silyl group deprotection and a second glycosidation gave **299** as a single anomer. Cleavage from resin gave heptaacetate macrophylloside **300** in 18 % yield for 6 steps.



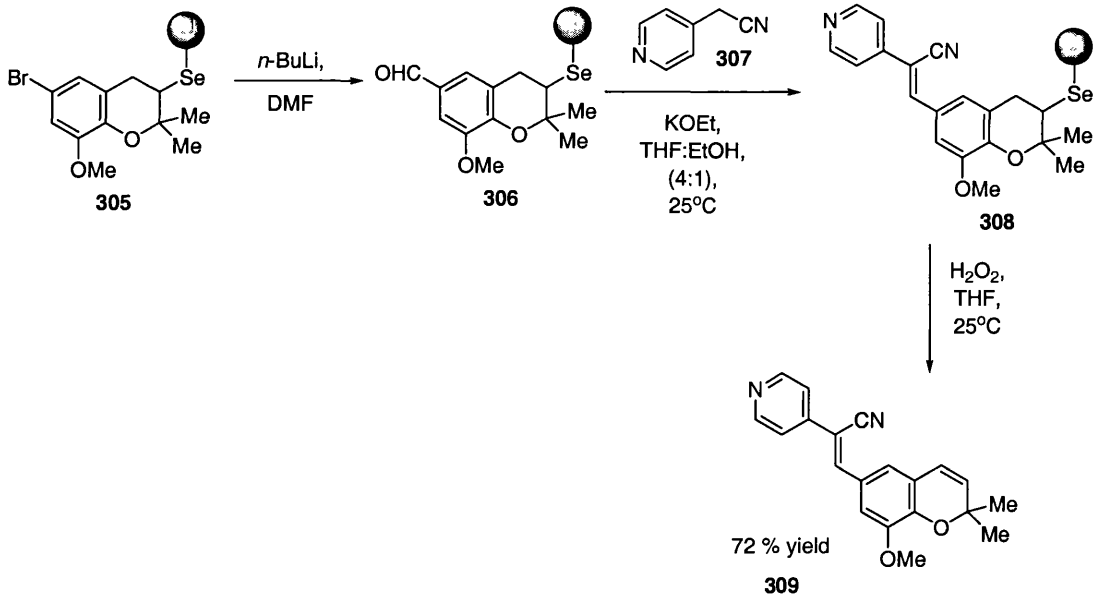
scheme 1.65

This selenium linker approach has also been used for the synthesis of a small library of aldeosterone biosynthesis inhibitors (scheme **1.66**).[52] Resin bound aryl bromide **301** underwent lithium-halogen exchange followed by addition to *p*-fluorobenzaldehyde to give benzhydrol **302**. Mitsunobu reaction with imidazole gave **303** which was oxidatively cleaved to give aldosterone biosynthesis inhibitor **304**. Various analogues of **304** were synthesised in this way by varying the aldehyde and the imidazole components.



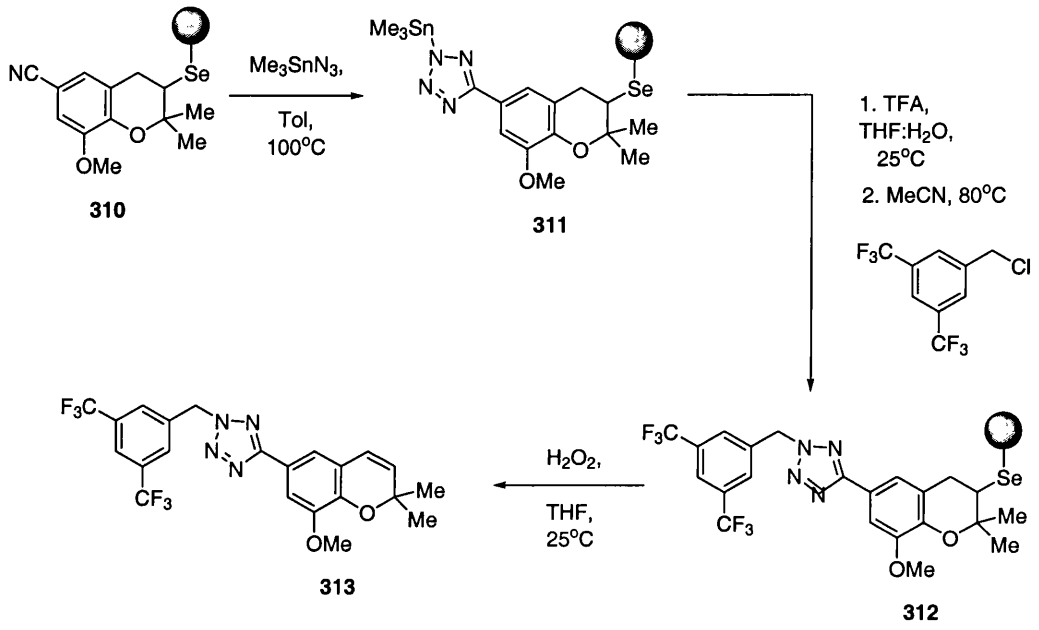
scheme 1.66

Similarly, a small library of phosphodiesterase inhibitors was synthesised from resin bound aryl bromide **305** (scheme **1.67**).[52] Lithium-halogen exchange followed by treatment with DMF gave aldehyde **306**. Condensation with nitrile **307** gave resin bound stillbene **308** which was cleaved to give phosphodiesterase inhibitor **309** in 72 % yield.



scheme 1.67

Finally, this benzopyran forming strategy has been applied in the synthesis tetrazole-containing targets such as **313** which are known to be potassium channel activators (scheme **1.68**).[52] Resin bound benzopyran **310** bearing a nitrile group was treated with azidotrimethyltin to generate tetrazole **311**. Treatment with aqueous TFA removed the trimethylstannyl group from the secondary nitrogen thus allowing alkylation to give **312**. The resin bound tetrazole was then cleaved to give substituted tetrazole **313**.



scheme 1.68

1.3 Conclusions

The emergence of solid phase and combinatorial synthesis has led to renewed interest in sulfur and selenium chemistry. Classical reactions such as selenoxide elimination, sulfone alkylation, epoxidation and cyclopropanation reactions of sulfonium ions and radical cleavage of selenides have found new roles in high-throughput chemistry.

The scope and utility of sulfur and selenium in traceless linker systems for solid phase organic synthesis has been established. These linker systems are highly effective safety catch linkers due to their ability to exist in several oxidation states each with orthogonal cleavage strategies. In addition, sulfur and selenium can mediate a diverse range of chemical transformations and can be used to enable chemistry on, and allow further diversification of, resin-bound molecules. In the case of selenium based linkers,

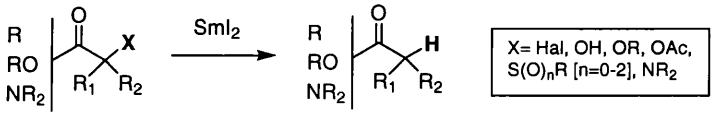
cycloloading strategies for attachment of the molecule to solid support allows complexity to be introduced in the immobilisation step. In both sulfur and selenium linker systems it has been shown that a variety of cleavage strategies exist and many of these strategies allow different types of functionality to be introduced in the cleavage step thus allowing further diversity to be introduced. Sulfur and selenium based linkers are robust and have been used in the successful synthesis of a large variety of compounds.

It seems clear that sulfur and selenium-based linker systems will continue to play a major role as the area of high throughput synthesis evolves over the coming years.

Chapter 2: The first Pummerer cyclisations on solid phase. Construction of oxindoles enabled by a sulfur link to resin

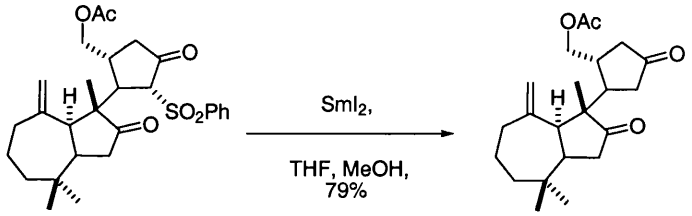
2.0 Introduction-Traceless Linkers cleaved using SmI_2

SmI_2 can reduce α-heteroatom substituted carbonyl compounds under mild neutral reaction conditions to give the parent carbonyl compounds (scheme **2.1**).[53,54] The heteroatom may be a halogen, an oxygen substituent such as an alcohol, ether or ester, or also sulfides, sulfoxides, sulfones, amides and amines. This reaction is very selective and tolerates a wide range of functionality.



scheme 2.1

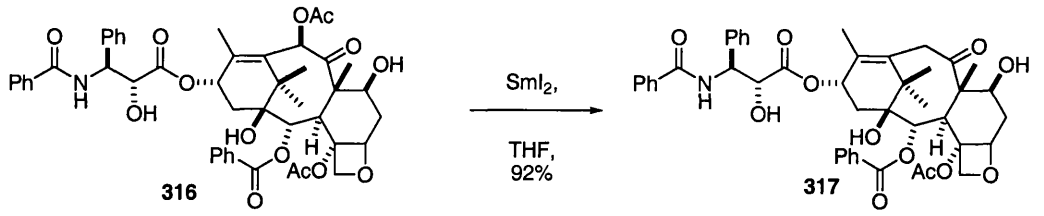
This selectivity can be observed in Overman's synthesis of the natural product shahamin K. Overman reduced the α-sulfonyl ketone moiety in **314** using SmI_2, selectively in the presence of a range of other functionality. [55]



314 **315**

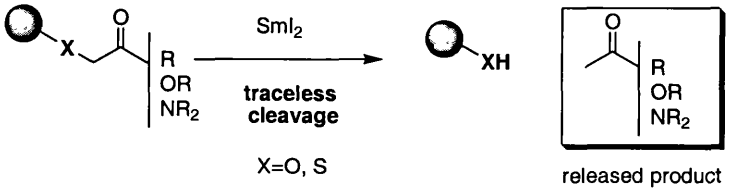
scheme 2.2

To investigate the C 10 acetate group for the biological activity of the anti-cancer agent taxol **316**, Holton has reduced the natural product with SmI_2 to give 10-deacetoxy taxol **317** in excellent yield (scheme **2.3**).[56] The α-acetoxy ketone moiety of **316** was selectively reduced to the ketone in high yield without affecting any other functionality in the sensitive molecule.



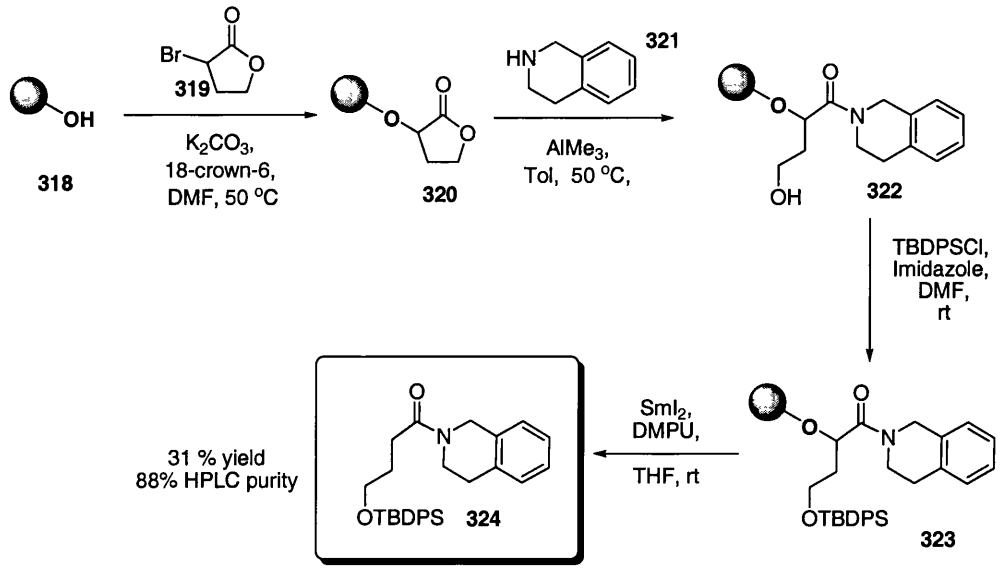
scheme 2.3

This reaction therefore has ideal properties for application to the development of a traceless linker system for solid phase organic synthesis.[57,58] If the heteroatom links the carbonyl compound to a solid support, reduction by SmI_2 would then correspond to traceless cleavage of the carbonyl compound from resin (scheme **2.4**). The term "traceless" refers to the replacement of the linking bond with an aliphatic "C-H" bond therefore cleavage leaves no trace of the original link to solid support.



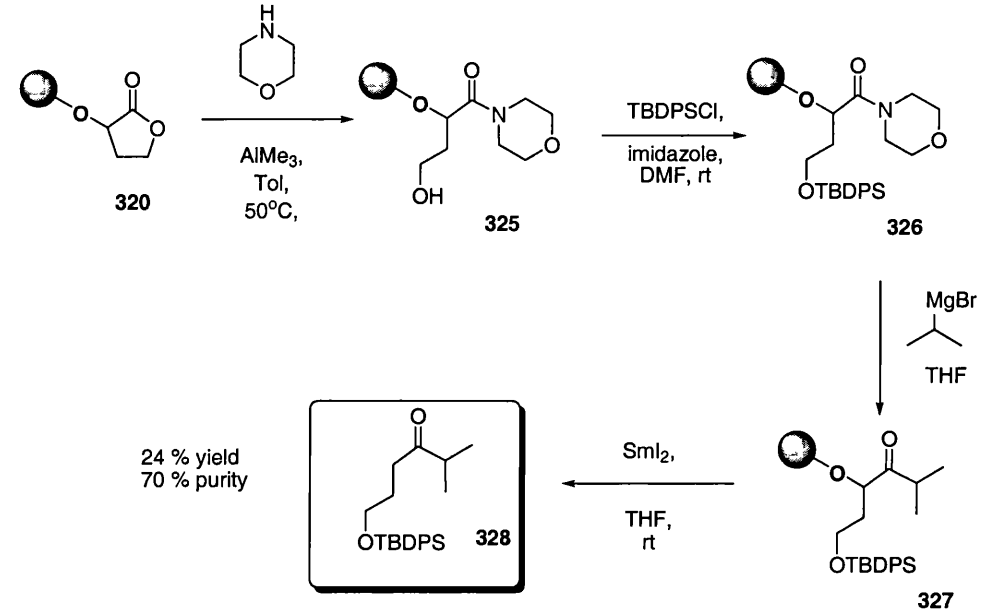
scheme 2.4

An oxygen based traceless linker system based on this idea was developed within the group.[59] We refer to this linker system as an α-heteroatom substituted carbonyl or HASC linker. This linker system was applied in the traceless synthesis of amides (scheme **2.5**) and ketones (scheme **2.6**). The linker was shown to be stable to a wide variety of reaction conditions yet was cleaved readily and selectively by SmI_2 at the end of the synthetic sequence. γ-Butyrolactone **319** was immobilised on phenol resin **318** to give resin bound lactone **320**. The lactone ring was opened upon treatment with secondary amine **321** and trimethyl aluminium to give amide **322** and the resultant alcohol was protected as the *tert*-butyl diphenylsilyl ether to give resin **323**. The release of amide **324** was achieved by cleavage of the O-link in resin **323** with SmI_2 and DMPU additive. Reduction of α-heteroatom substituted amides requires an additive such as DMPU to activate SmI_2 by increasing the reduction potential.



scheme 2.5

This linker system was also used in the synthesis of ketones as shown in scheme **2.6**.[59] Following the ring opening of resin bound lactone **320** with morpholine and silyl protection of the alcohol, resin **326** was treated with isopropylmagnesium bromide to give resin bound ketone **327**. Treatment with SmI_2 alone was sufficient for the cleavage of **328** from resin, the use of additives was not required for the reduction of α-alkoxy substituted ketones.

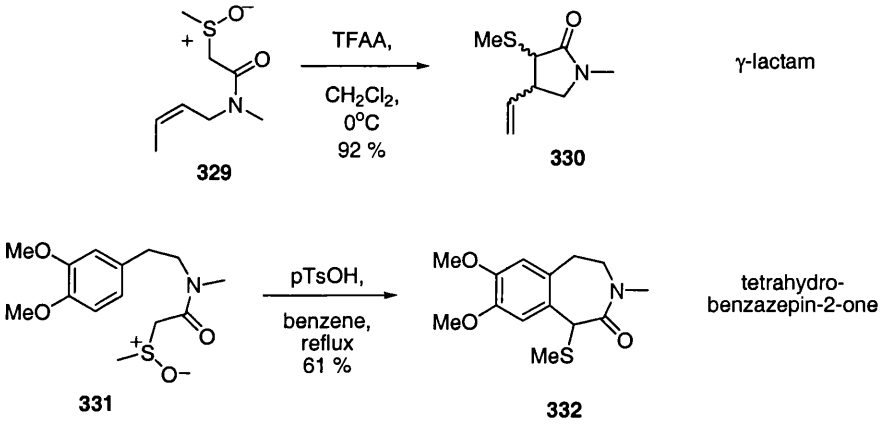


scheme 2.6

This linker system was applied in the synthesis of a range of ketones and amides in yields ranging from 16-31 % (4 or 5 steps on resin respectively) resin and in high purities.

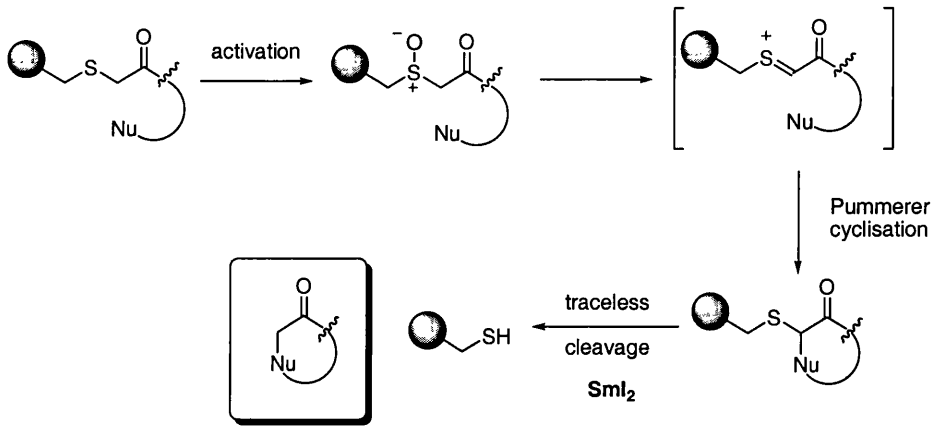
2.1 Solid phase synthesis of *N*-heterocycles using the Pummerer cyclisation

The aim of my PhD project was to develop an analogous, multifunctional sulfur HASC linker. Organosulfur compounds can exist in various oxidation states and can mediate a diverse range of reactions. The sulfur atom link would not only be used to attach the carbonyl compound to solid support but would also be used to "enable" reactions such as the Pummerer cyclisation reaction.[60,61,62] The addition of nucleophiles to sulfonium ions generated from sulfoxides is known as the Pummerer reaction. Tethered nucleophiles such as an alkene double bond or an aromatic system give rise to cyclic products. The Pummerer cyclisation reaction is a powerful method for generating heterocycles and carbocycles. Some examples of Pummerer cyclisation reactions are shown in scheme **2.7**.[63,64]



scheme 2.7

The basic idea behind our studies is shown in scheme **2.8**. A carbonyl compound bearing a tethered nucleophile can be linked to resin via an α-sulfur atom. The sulfide link can then be oxidised to the sulfoxide, from which an intermediate sulfonium ion can be generated. Attack of the tethered nucleophile onto the sulfonium ion gives a resin bound cyclic product which can at a later stage be cleaved from resin in a traceless manner using SmI_2. Use of the Pummerer cyclisation on solid support is unprecedented in the literature.



scheme 2.8

Initially, it was proposed to develop a solid phase route to oxindoles utilising the Pummerer cyclisation strategy illustrated above. Oxindoles are key heterocyclic motifs in a number of pharmaceutically important compounds and biologically active natural products. Some examples of biologically active oxindoles and oxindole based natural products are shown in Fig **2.1**.

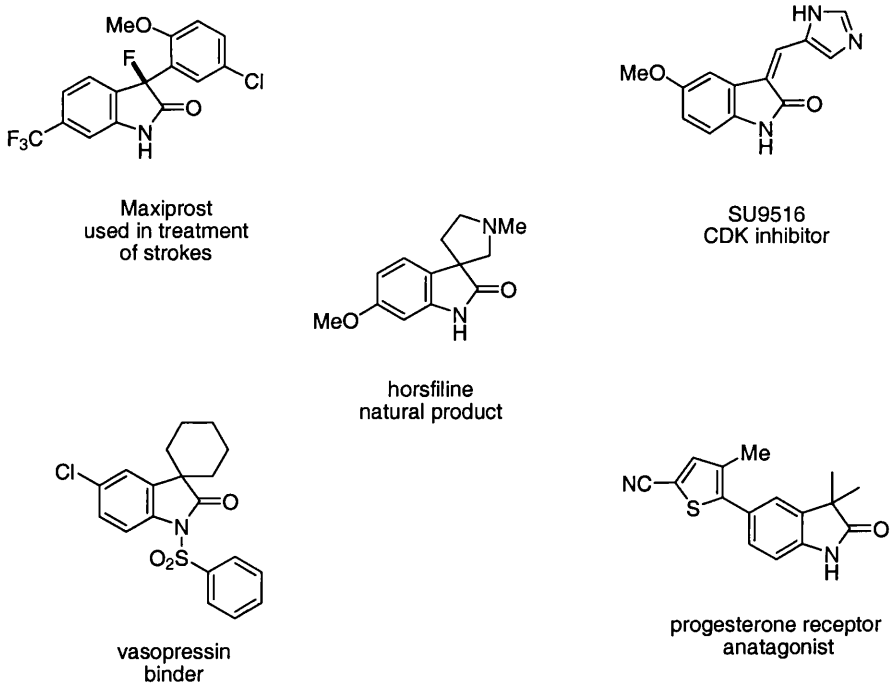
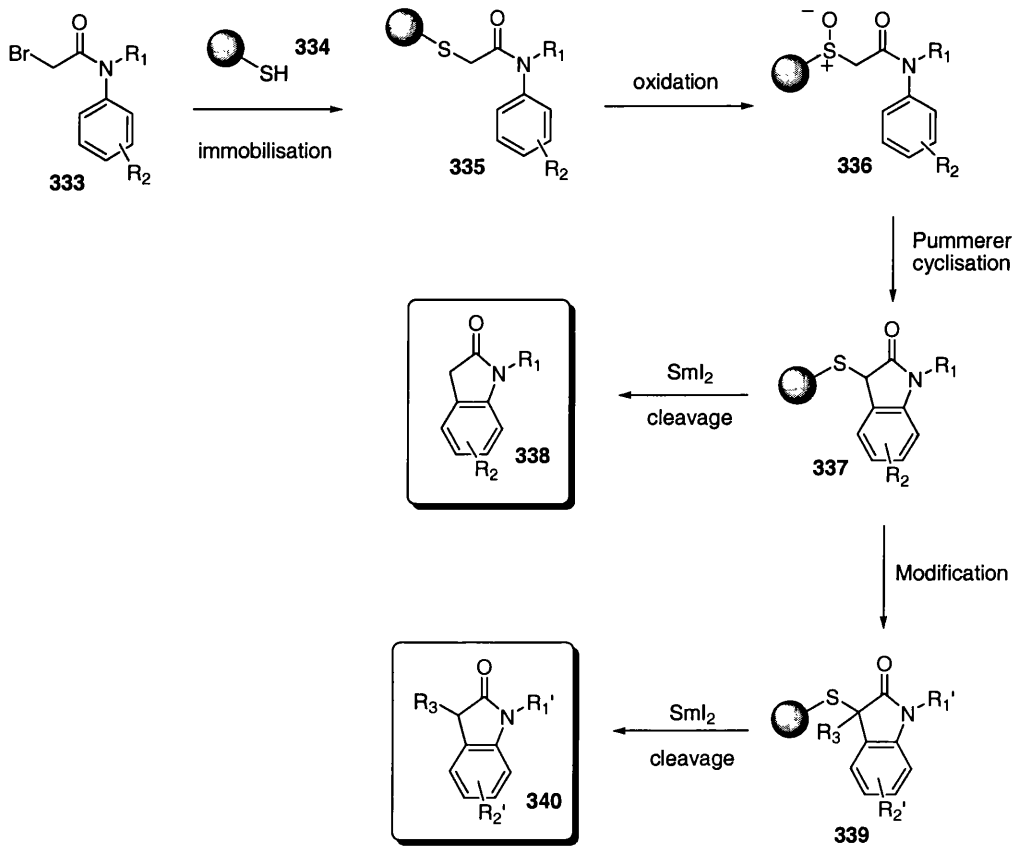


Fig 2.1

A proposed route to oxindoles using this methodology is shown in scheme **2.9**. α-Bromoacetamide substrates such as **333** will be immobilised onto thiol resin. After oxidation of the sulfide link to give resin bound sulfoxide **336**, the Pummerer cyclisation

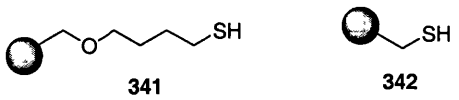
will be applied to generate a resin bound oxindole **337**. Oxindole **337** can be tracelessly cleaved to give **338** or the sulfide link can be used again to assist further modification of the heterocyclic framework to give **339**. Modified oxindole **339** can then undergo traceless cleavage to give **340**.



scheme 2.9

2.2 Choice of solid phase sulfur linker

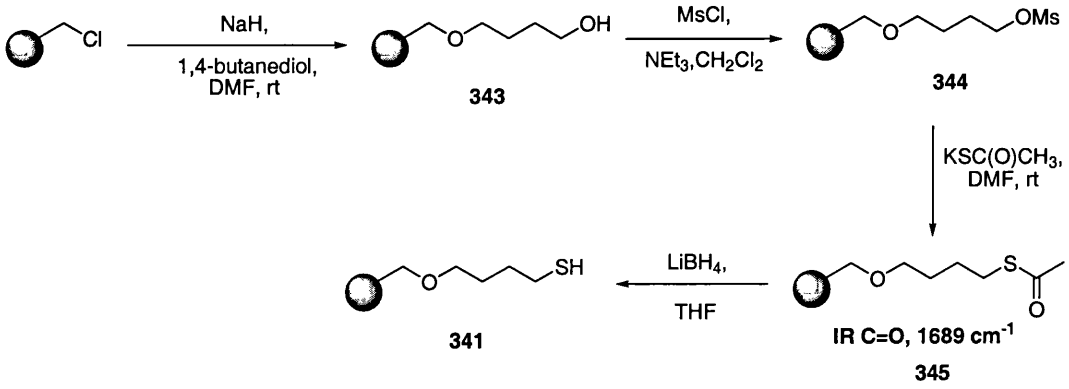
There are several existing literature methods for the preparation of polystyrene based thiol resins. Before attempting the development of a new traceless HASC sulfur linker system, it was necessary to evaluate which of these linker systems would be best suited in our route to *N*-heterocycles using the Pummerer cyclisation. Two literature thiol resins are shown in Fig **2.2**. Literature routes to both resins are short and begin from Merrifield resin.



341 342

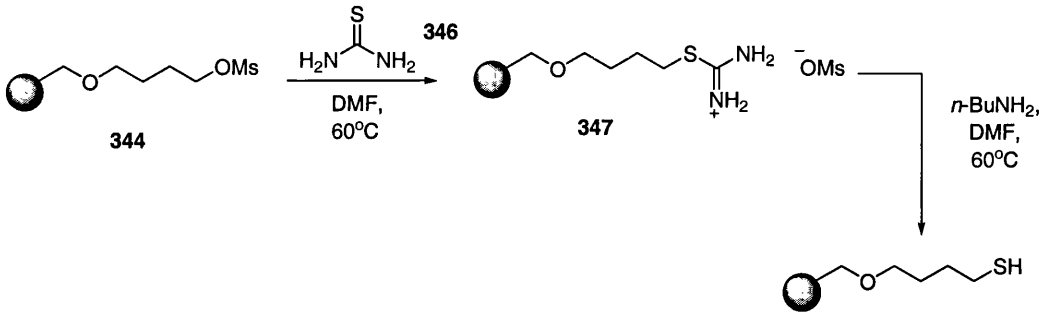
Fig 2.2

The alkyl thiol linker system of resin **341**, developed by Wagner and Mioskowski was initially considered because literature Pummerer cyclisations for the synthesis of *N*-heterocycles such as oxindoles and tetrahydroisoquinolones were carried out with alkyl sulfanyl groups.[65] Resin **341** was prepared in a similar manner to the method used by Wagner and Mioskowski (scheme **2.10**).[21] Resin bound alcohol **343** was formed by treatment of Merrifield resin with 1,4-butanediol and NaH. Mesylate formation was followed by treatment with potassium thioacetate to give thioester **345**. The presence of the thioester can be detected by the strong IR C=O stretch at 1689 cm^{-1}. The thioester group was converted to the thiol **341** by reduction with $LiBH_4$. The progress of this reaction can be monitored by the disappearance of the C=O stretch at 1689 cm^{-1}.



scheme 2.10

Wagner and Mioskowski prepared thiol resin **341** by treatment of mesylate **344** with thiourea instead of potassium thioacetate then treating the thiouronium salt with *n*-butylamine to give **341** (scheme **2.11**).

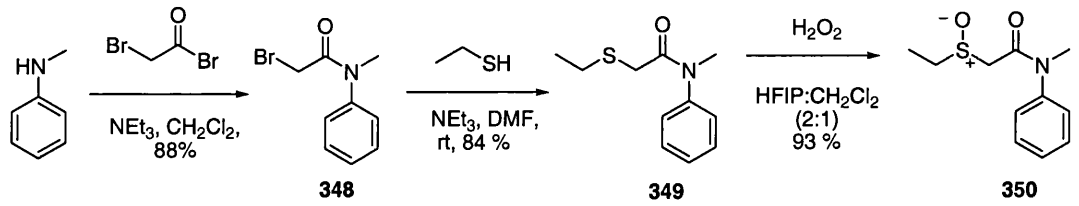


scheme 2.11

2.2.1 Solution phase model studies - using ethane thiol as a model for thiol resin

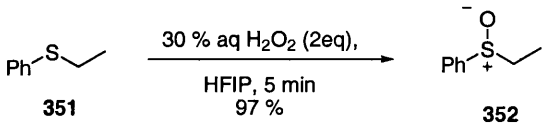
Due to the limited methods available for monitoring reactions on resin it was necessary to first develop and optimise a route to oxindoles in solution phase using a solution phase thiol to mimic the thiol resin. Initially we assumed that ethane thiol would act as an adequate model for alkyl thiol resin **341** (scheme **2.12**). α-Bromoacetamide **348** was prepared by acetylation of *N*-methyl aniline with bromoacetyl bromide. As a model for immobilisation of the α-bromoacetamide **348** onto a thiol resin **341**, **348** was treated with ethane thiol. Sulfide **349** was obtained in excellent yield indicating that the crucial immobilisation step should occur cleanly and efficiently.

It was then necessary to oxidise sulfide **349** selectively to sulfoxide **350** without over oxidation to the sulfone. Many of the usual methods for carrying out this transformation require careful control of the stoichiometry of the oxidant. This would be very difficult to achieve on resin. The oxidation step must also take place in a solvent system which is compatible with polystyrene resins. Many of the conventional reagent systems, such as $NaIO_4$, require polar solvents such as MeOH. Solvents such as MeOH cause shrinking of the resin and would therefore result in a slow, inefficient reaction. A very effective reagent system which uses H_2O_2 in the presence of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was employed.[66] Sulfide **349** was selectively oxidised to the sulfoxide **350** even in the presence of a vast excess of H_2O_2.



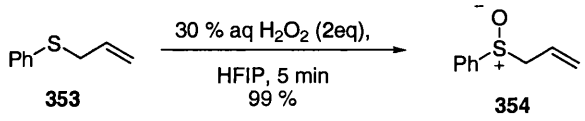
scheme 2.12

These sulfoxidation conditions were originally developed by Bégué.[66] Treatment of phenyl ethyl sulfide **351** with an excess of 30 % aqueous H_2O_2 in hexafluoroisopropanol solvent gave the desired sulfoxide **352** in excellent yield after only 5 min (scheme **2.13**). No sulfone was observed even if the reaction time was extended to 3 h. Sulfoxide **352** was treated with excess H_2O_2 for 8 h. After work-up, the starting sulfoxide was recovered unchanged.



scheme 2.13

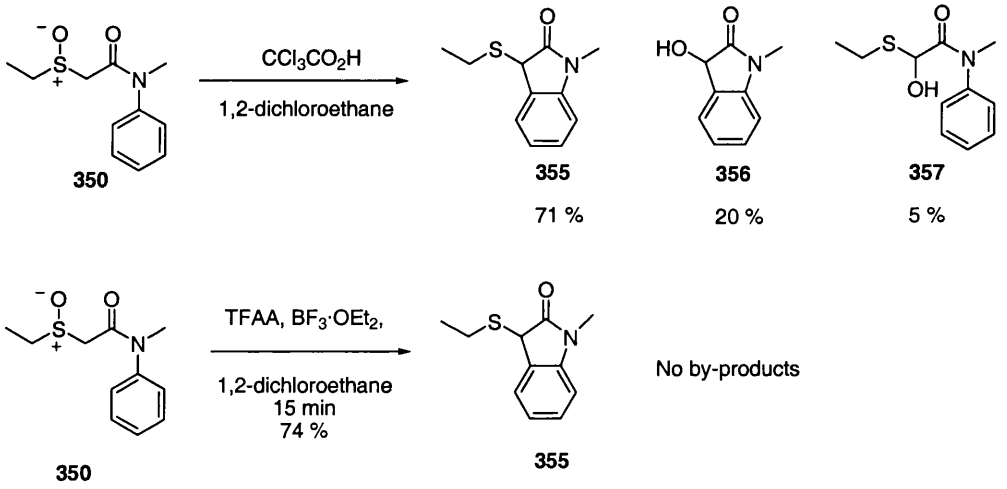
A wide range of sulfides were oxidised to the corresponding sulfoxide using these conditions. No evidence of over oxidation was observed. Allylic and vinylic sulfides could be oxidised without affecting the double bond as shown in scheme **2.14**. The rate of this oxidation reaction is rapid. Rate of oxidation of sulfur by H_2O_2 depends on the nucleophilicity of the sulfur atom. It was proposed that the HFIP solvent has two roles in this reaction. Firstly, it is thought to accelerate the sulfoxidation step by forming a hydrogen bond with the H_2O_2 thus activating the hydroxyl leaving group. After the first oxidation at sulfur, HFIP then prevents any further oxidation to the sulfone by forming a strong hydrogen bond to the oxygen of the sulfoxide. This decreases the nucleophilicity of the sulfur atom and prevents it from reacting further with H_2O_2.[66]



scheme 2.14

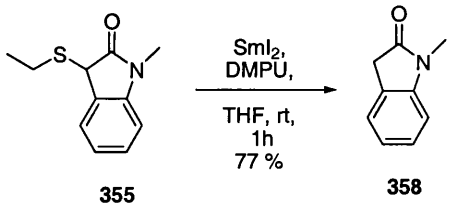
Conditions for promoting the Pummerer cyclisation of sulfoxide **350** to give oxindoles **355** were next investigated (scheme **2.15**). Initially, various organic acids such as *p*-toluene sulfonic acid, camphor sulfonic acid and trichloroacetic acid were tried. Cyclisation

product **355** was obtained as the major product however, the reactions were not clean. In the reaction promoted by trichloroacetic acid, by-products **356** and **357** were isolated. These products are formed as a result of water intercepting the sulfonium ion before cyclisation can occur. In order to avoid the production of these unwanted products, reaction conditions must be kept anhydrous. The organic acids used are very hygroscopic and extremely difficult to dry. Therefore, it would be difficult to prevent the formation of these by-products. Use of anhydrides such as acetic anhydride and trifluoroacetic anhydride did not result in Pummerer cyclisation, giving only Pummerer rearrangement product. Fortunately, it was discovered that treatment of **350** with TFAA and BF_3 OEt_2 resulted in rapid, clean Pummerer cyclisation to give **355** in 74 % yield.



scheme 2.15

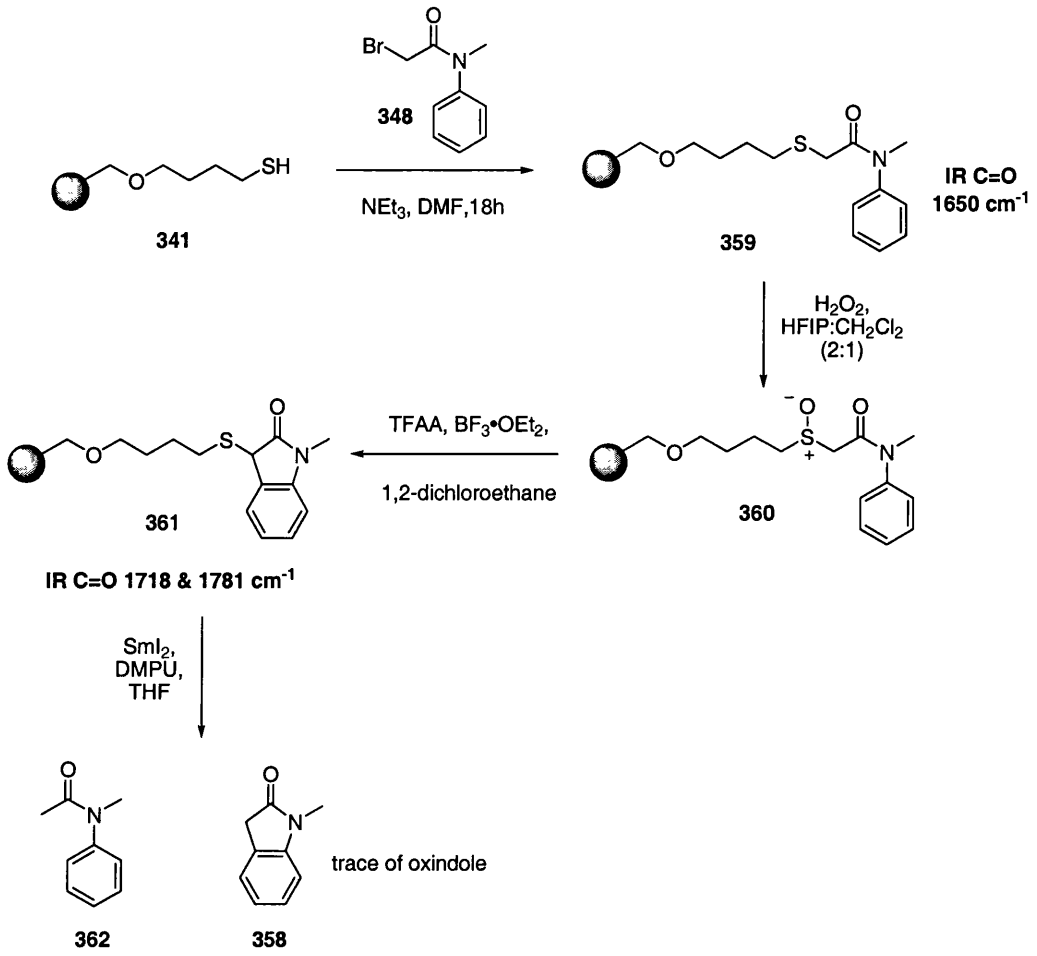
Given that an efficient route to oxindoles had been developed, it was then necessary to perform a model, traceless "cleavage" of the oxindole. Treatment of model oxindole **355** with SmI_2 in the presence of DMPU as an additive, readily resulted in the rapid cleavage of ethanethiol to give oxindole **3.58** in excellent yield (scheme **2.16**).



scheme 2.16

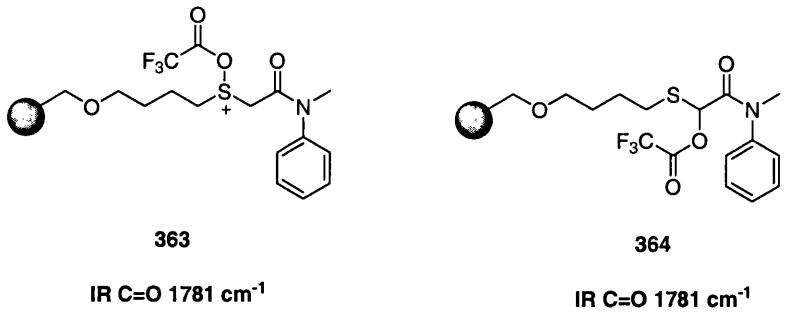
2.2.2 Solid phase studies

After successfully modelling a route to oxindoles in solution, the solid phase route was attempted using thiol resin **341** (scheme **2.17**). Thiol resin **341** was treated with α-bromoacetamide **348** and an IR carbonyl stretch at 1650 cm^{-1} was observed for the resultant resin **359**. This is a good indication that the immobilisation step occurred successfully as this value compares favourably to the IR carbonyl stretch for corresponding model amide **349**. Sulfide resin **359** was treated with H_2O_2 in HFIP: CH_2Cl_2, however, it is not possible to observe the progress of this reaction using IR spectroscopy as the characteristic sulfoxide stretch occurs at ~1020 cm^{-1} and coincides with resin signals. Exposure of sulfoxide resin **360** to Pummerer cyclisation conditions resulted in a shift in the IR C=O stretch from 1650 to give two stretches, one at 1718 cm^{-1} and another at 1781cm^{-1}. The stretch at 1718 cm^{-1} would indicate successful Pummerer cyclisation to the oxindole. However, upon SmI_2 cleavage only a trace of cyclisation product **358** was obtained together with *N*-methyl-*N*-phenylacetamide **362**. The route was repeated several times with slightly different results on each occasion. The main product, if any, was usually *N*-methyl-*N*-phenylacetamide which indicated that cyclisation had not occurred.



scheme 2.17

After the Pummerer cyclisation a significant stretch at 1781 cm^{-1} was observed in the IR spectrum (scheme **2.18**). An IR stretch in this region might be expected for the C=O of a trifluoroacetate ester. This indicated that uncyclised species such as **363** and **364** are still present and that cyclisation was incomplete.



363

IR C=O 1781 cm^{-1}

364

IR C=O 1781 cm^{-1}

scheme 2.18

In further studies, the number of equivalents of BF_3 OEt_2 was increased in an attempt to drive the cyclisation step to completion. This strategy appeared to be effective, reducing

the intensity of the C=O stretch at 1781 cm^{-1} dramatically. However, SmI_2 cleavage still only gave a very small trace of oxindole product.

This poor mass return off resin indicated that the loading of oxindole product on resin prior to cleavage was very low and that the solid phase route was not efficient. These results suggested that perhaps the use of ethane thiol as a model for alkyl thiol resin **341** was too simplistic. The main difference between the model and the resin **341** was that the model had not incorporated an oxygen atom further along the alkyl chain. The possibility that the oxygen atom in the linker could be intercepting the sulfonium ion during the Pummerer cyclisation was considered (Fig **2.3**).

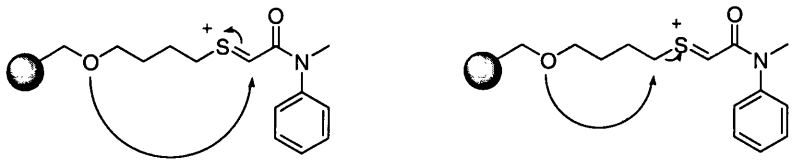
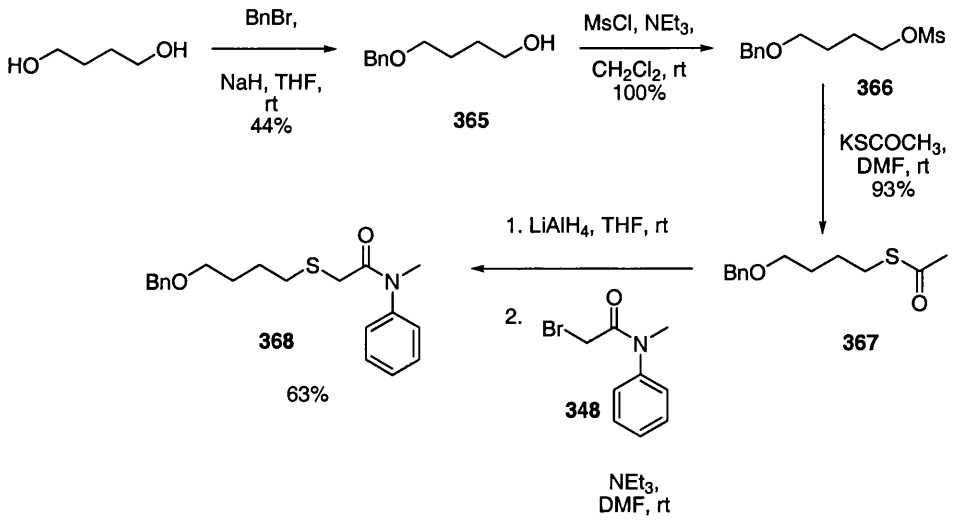


Fig 2.3

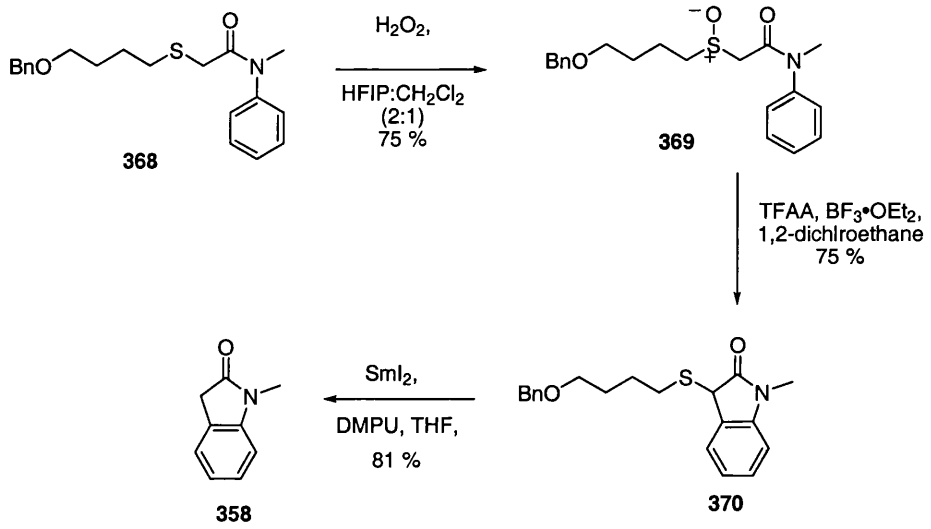
In order to investigate whether such side reactions were occurring on resin, further solution studies were carried out. On this occasion a model thiol that more closely mimicked thiol resin **341** was synthesised (scheme **2.19**).

1,4-Butanediol was monobenzylated to give **365**. In analogy to the synthesis of resin **341**, monobenzylated alcohol **365** was mesylated and then treated with potassium thioacetate to give thioester **367**. Both these reactions proceeded in excellent yields. The transformation of **367** to sulfide **368** proved slightly less efficient. Thioester **367** was reduced to the thiol and then used immediately in the reaction with **348** in order to minimise disulfide formation. Use of $LiBH_4$ in the reduction step gave the desired sulfide **368** in only 54 %. One possible explanation for the low yield obtained in this transformation is that after reduction with $LiBH_4$, thiol is obtained as a thiolate complex with boron which may be reducing the nucleophilicity of the thiol. Several methods for hydrolysing thioacetate **367** to the corresponding thiol were attempted (K_2CO_3, LiOH and MeLi) but all of these methods were found to be ineffective. Use of $LiAlH_4$ instead of $LiBH_4$ gave a slight increase in the yield of **368** to 63%. These studies identified one step in the solid phase route which may be problematic and which could be investigated more closely.



scheme 2.19

The efficiency of the Pummerer cyclisation of the model sulfide **368** was investigated (scheme **2.20**). These solution studies did not reveal any side reactions or problems associated with the use of this linker. Treatment of sulfoxide **369** with TFAA and BF_3 OEt_2 gave oxindole **370** in good yield. The crude NMR of the reaction was clean and no by-products were observed. SmI_2 cleavage of the link was also very efficient.



scheme 2.20

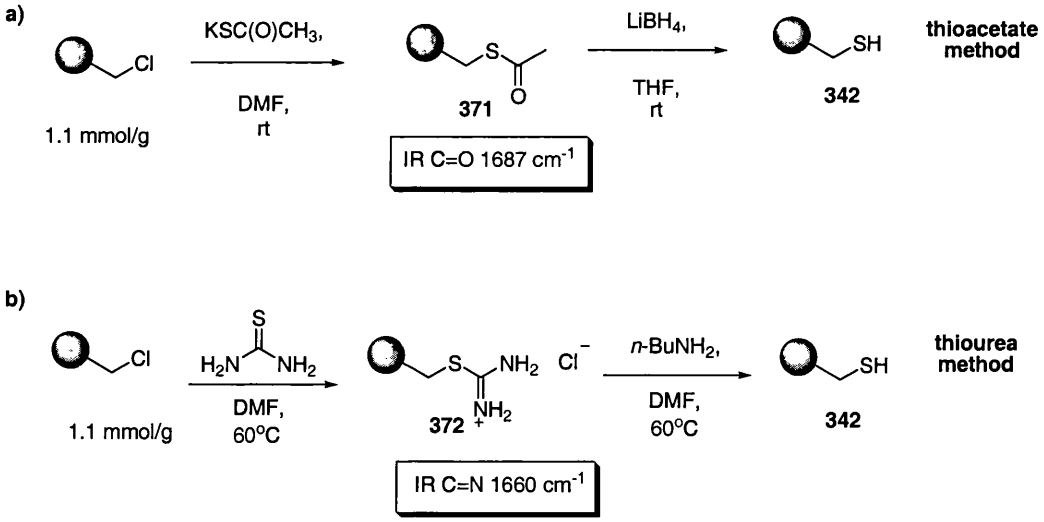
The solid phase route was attempted once again using thiol resin **341** that had been prepared via the thiourea method shown in scheme **2.21** and once using thiol resin **341** that had been prepared by reduction of thioacetate resin **345** with $LiAlH_4$. Neither of these

modifications improved the results. No significant quantity of oxindole **358** was obtained off resin. It is not clear why the attempted use of alkyl thiol resin **341** was unsuccessful. It was decided to investigate the use of the benzyl thiol resin **342**.

2.3 Benzyl thiol resin

2.3.1 Preparation of benzyl thiol resin

Benzyl thiol resin **342** was originally prepared by Kobayashi[13] from Merrifield resin in two steps by the method shown in scheme **2.21a**. In addition, we developed a thiourea-based approach to **342** (scheme **2.21b**), both methods have been used in these studies and have been found to be equally effective. The progress of these reactions can be monitored easily using IR spectroscopy.

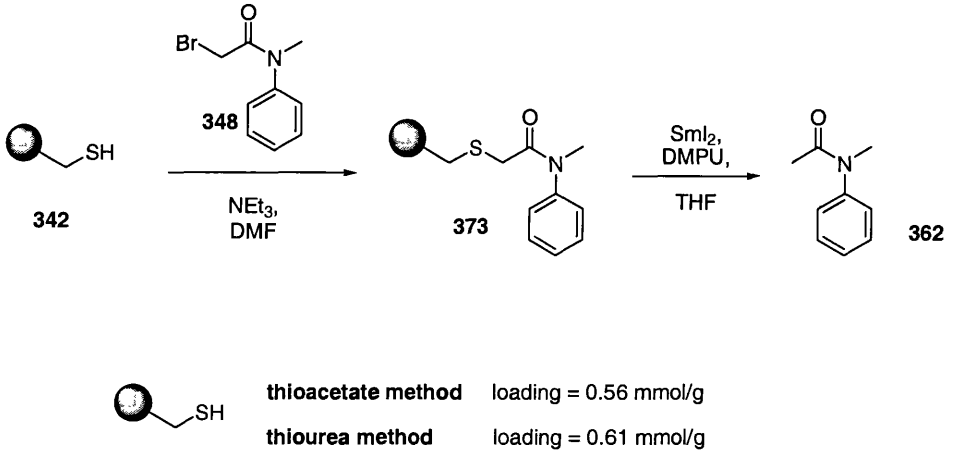


scheme 2.21

2.3.2 Determination of the loading of benzyl thiol resin

The loading of free "SH" sites on benzyl thiol **342** was determined by immobilisation of *N*-methyl-*N*-phenyl α-bromoacetamide, followed by SmI_2 cleavage and quantification of *N*-methyl-*N*-phenyl acetamide **361**. Loading of free "SH" sites for benzyl thiol resin prepared via the thioacetate method and the thiourea method were calculated. The loading

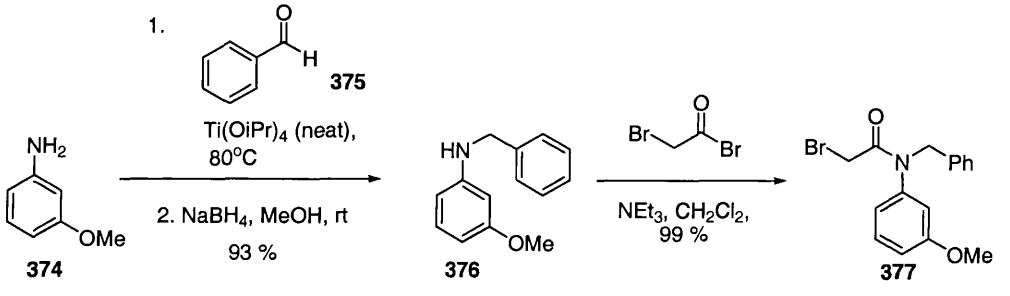
of the two resins was found to be similar at values of 0.56 mmol/g and 0.61 mmol/g (scheme **2.22**). Sulfur microanalysis results would suggest that the sulfur loading was ~ 1 mmol/g, this discrepancy is presumably due to oxidative cross-linking of the thiol functional groups.



scheme 2.22

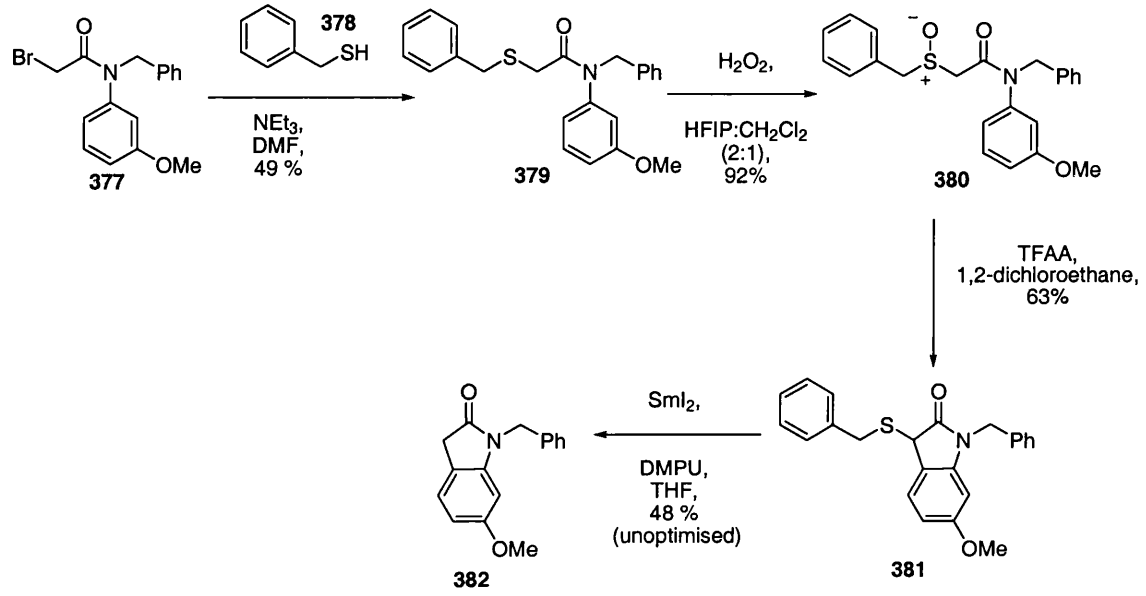
2.3.3 Solution phase model studies

Solution phase model studies were carried out using benzyl thiol as a model for the benzyl thiol resin. In order to assist the Pummerer cyclisation step, an electronically activated system was used. Secondary aniline **376** is not commercially available but can be prepared easily form *m*-anisidine and benzaldehyde by reductive amination (scheme **2.23**). Alternatively, the amine can be prepared by benzoylation of *m*-anisidine followed by reduction with $LiAlH_4$ (63% for 2 steps). α-Bromoacetamide **377** can be accessed from **376** by treatment with bromoacetyl bromide.



scheme 2.23

Reaction of α-bromoacetamide **377** with benzyl thiol **378** gave sulfide **379**. Following selective oxidation to sulfoxide **380**, treatment with TFAA gave oxindole **381** as the major regioisomer. It is interesting to note that TFAA alone is sufficient to promote Pummerer cyclisation in electronically activated systems. The minor regioisomer was separated from **381** by chromatography before the cleavage step. Cleavage of the benzylsulfanyl group was carried out using SmI_2 and DMPU to give the desired oxindole **382**.

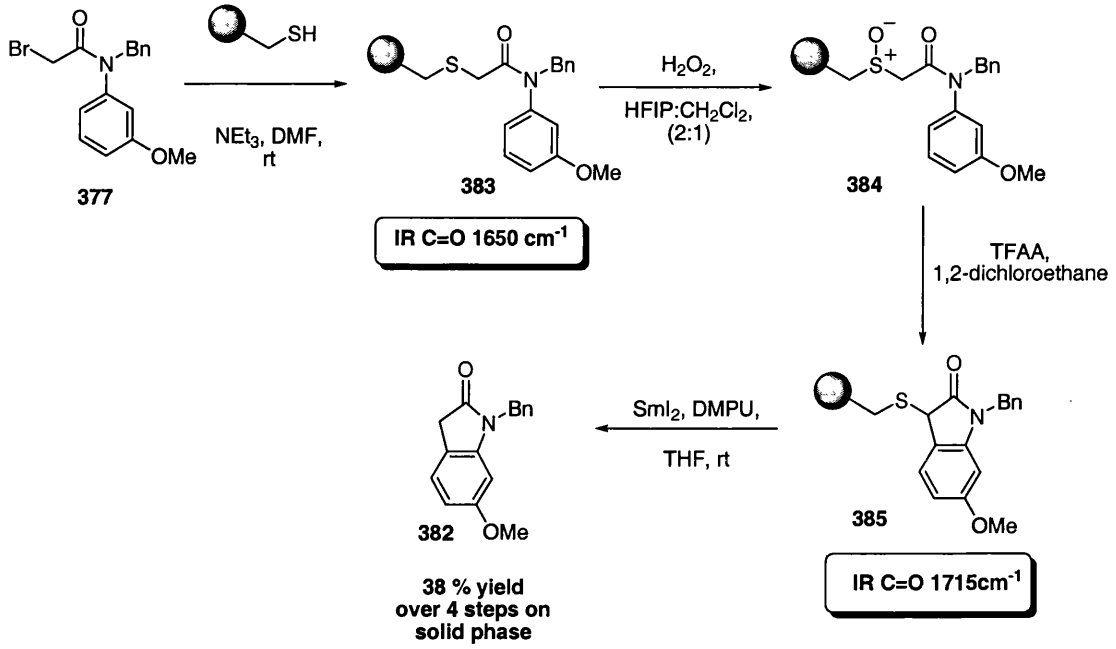


scheme 2.24

2.3.4 Solid phase studies using benzyl thiol resin

Given that the solution phase route posed no obvious problems, the sequence was then adapted to solid phase (scheme **2.25**). *N*-benzyl-2-bromo-*N*-(3-methoxy-phenyl)-acetamide **377** was immobilised using benzyl thiol resin **342**. A strong IR amide C=O stretch at 1650 cm^{-1} was observed, indicating successful loading had occurred. Following the sulfoxidation step no change in the IR can be observed, however, upon treatment of resin **384** with TFAA to give resin **385**, the IR C=O stretch shifted to 1715 cm^{-1} suggesting that cyclisation had indeed occurred. Gratifyingly, upon treatment of resin **385** with SmI_2 the desired oxindole **382** was obtained in 38 % yield over 4 solid phase steps (based on the loading of benzyl thiol resin). Oxindole **382** was obtained in high purity off resin after

filtration through a plug of silica to remove the DMPU. No other by-products were observed.



scheme 2.25

Oxindole **382** was obtained as the major isomer in a 9:1 mixture (by NMR) of regioisomers. The minor regioisomer is formed as a result of attack of the aromatic system onto the sulfonium ion at the *ortho* position to the methoxy group. The regioisomers were separated by chromatography and a crystal structure of the major isomer was obtained (Fig **2.4**).

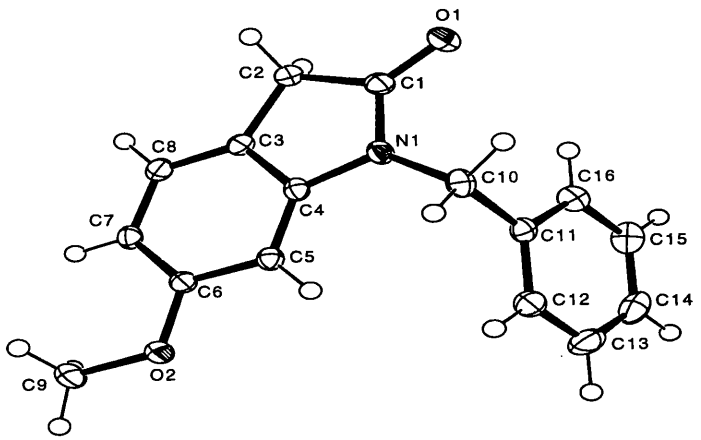
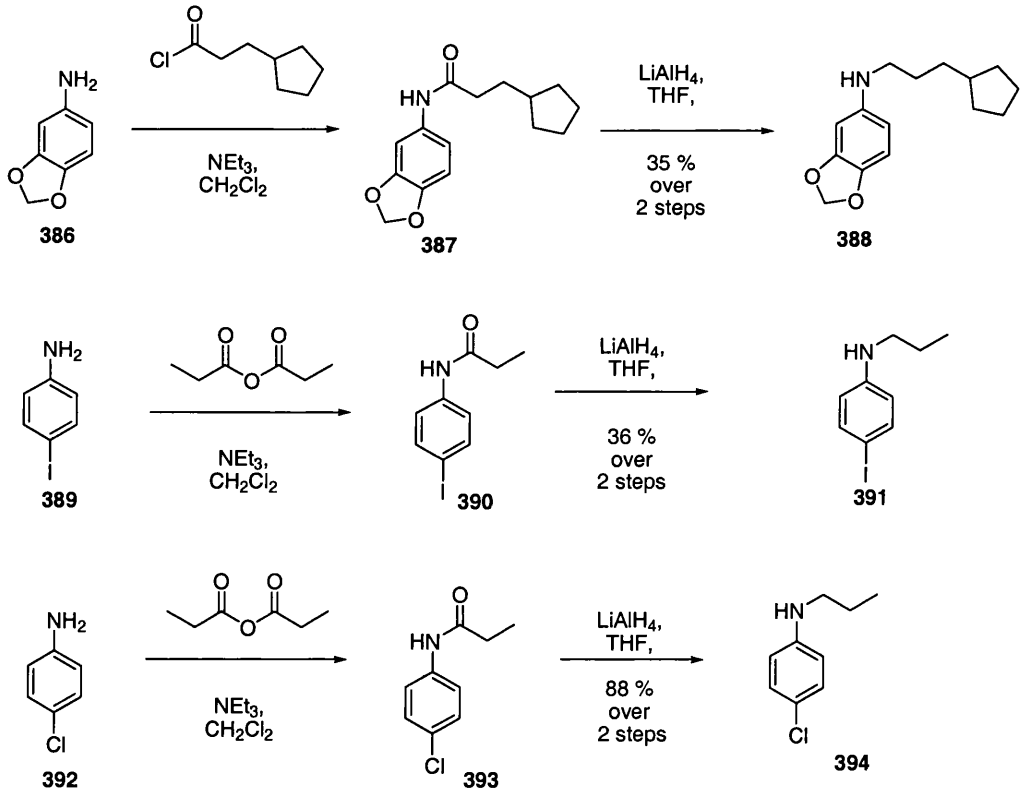


Fig 2.4

2.3.5 Preparation of anilines and α-bromoacetamides

Since a successful solid phase route to oxindoles had been developed the scope of the methodology was investigated. It was necessary to establish whether a wide range of oxindoles bearing neutral, electron rich and electron deficient aromatic rings could be synthesised using our route. As has been described previously, α-bromoacetamides can be prepared easily by acylation of the corresponding secondary aniline with bromoacetyl bromide. Unfortunately, only a limited number of secondary anilines are commercially available. In contrast, a wide range of functionalised primary anilines are available. Secondary anilines were prepared by acylation of the aniline with an acid chloride or anhydride followed by reduction of the amide with $LiAlH_4$. Selected examples of the anilines prepared are shown in scheme **2.26**.



scheme 2.26

A series of α-bromoacetamides bearing neutral, electron rich and electron deficient aryl rings were synthesised (table **2.1**).

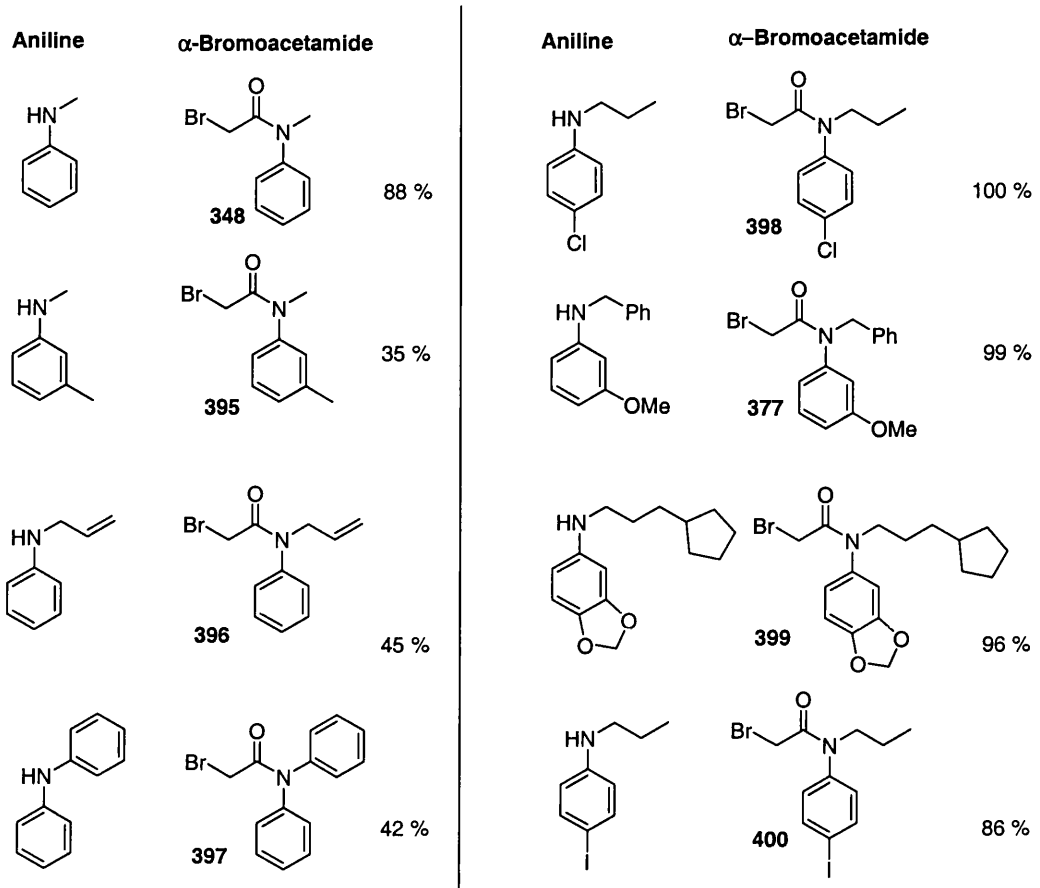
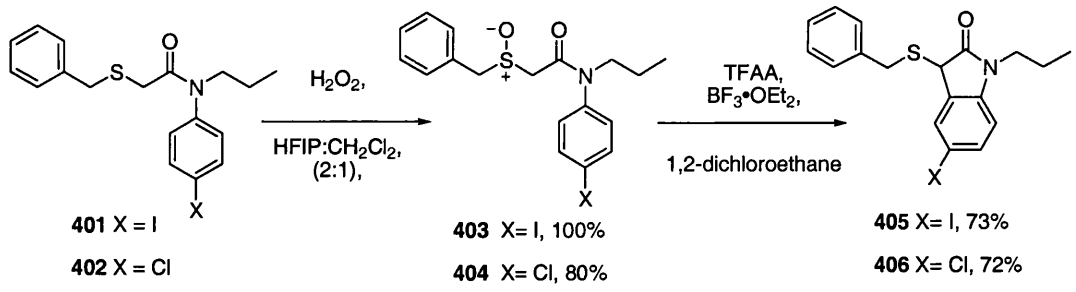


Table 2.1

2.3.6 Solution phase model studies on Pummerer cyclisation of deactivated aromatic systems

Prior to the application of this wide range of α-bromoacetamides in the solid phase synthesis of oxindoles it was necessary to establish if the Pummerer cyclisation of unactivated aromatic systems and aromatic systems bearing electron withdrawing substituents such as halogen atoms would be possible in our approach. To the best of our knowledge, the Pummerer cyclisation of aromatic systems bearing halogen atoms is unprecedented in the literature. Further solution phase model studies were therefore carried out and are shown in scheme **2.27.** Treatment of sulfoxides **403** and **404** bearing an iodine and a chlorine atom respectively, on the aromatic system, with TFAA and BF_3 OEt_2 gave the desired oxindoles. Therefore, these conditions are powerful enough to promote cyclisation of neutral and deactivated systems.



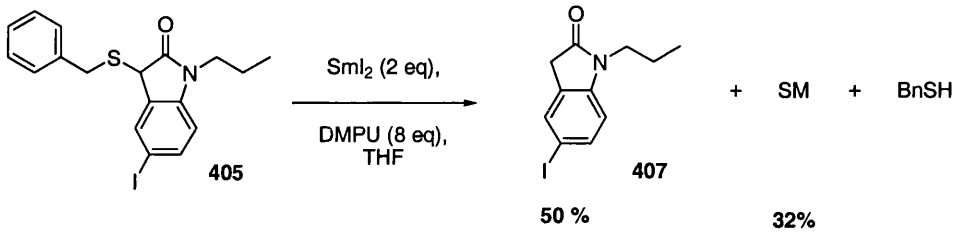
scheme 2.27

In the synthesis of 1,2,3,4-tetrahydroisoquinolines, Sano has shown that both TFAA and BF_3 OEt_2 are necessary to promote the Pummerer cyclisation where there is no electron donating group activating the reacting centre on the aromatic ring.[67] BF_3 OEt_2 will assist the reaction by promoting the formation of the sulfonium ion intermediate, however, BF_3 OEt_2 has also been shown to enhance the rate of Pummerer cyclisation regardless of whether the aromatic system is activated or not. It has been postulated that the addition of the Lewis acid promotes formation of a dicationic intermediate as shown in scheme **2.28**.[68] Such a cationic intermediate is thought to act as a super-electrophile thus promoting Pummerer cyclisation of aromatic systems which would normally be too deactivated to react.

scheme 2.28

The use of TFAA to generate oxindoles from electronically activated sulfoxide starting materials is well established. However, this is the first example of the use of this reaction on solid phase. Although Sano has applied the TFAA/BF_3 OEt_2 reaction conditions in the synthesis of 1,2,3,4-tetrahydroisoquinolines from neutral and electronically activated sulfoxides, these conditions have not been applied previously in the synthesis of oxindoles. Furthermore, there are no previous examples of application of these, or any other conditions in the Pummerer cyclisation of substrates bearing halogen atoms or other electronically deactivating groups (e.g ester groups).

In the oxindole bearing the aryl iodide moiety there is a possibility that the carbon-iodine bond will undergo reduction by SmI_2 in the cleavage step.[69] Upon treatment of the model oxindole **405** with two equivalents of SmI_2 the carbon sulfur bond underwent chemoselective cleavage to give iodo-oxindole **407** (scheme **2.29**). The halogen functionality remained intact under these conditions. Use of an excess of SmI_2 eventually does give some reduction of the carbon-iodine bond however, this excellent chemoselectivity means that our methodology should be amenable to the synthesis of halogen bearing heterocycles.



scheme 2.29

2.3.6 Solid phase synthesis of oxindoles using the Pummerer cyclisation

α-Bromoamides shown in table **2.1** were immobilised onto benzyl thiol resin and subjected to the solid phase sequence shown in scheme **2.25**. Gratifyingly, in each case the desired oxindole products were cleaved from solid support at the end of the sequence. Table **2.2** shows the neutral oxindoles prepared by Pummerer cyclisation on solid phase. Yields for the oxindoles are based on the loading of the thiol resin and are therefore for 4 solid phase steps.

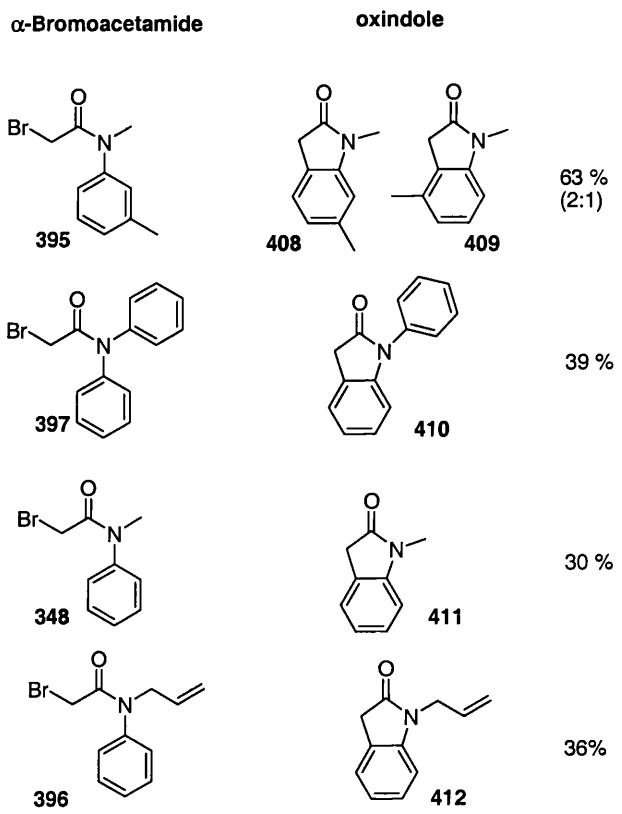


Table 2.2

Table **2.3** shows electron rich and electron deficient oxindoles prepared by Pummerer cyclisation on solid phase.

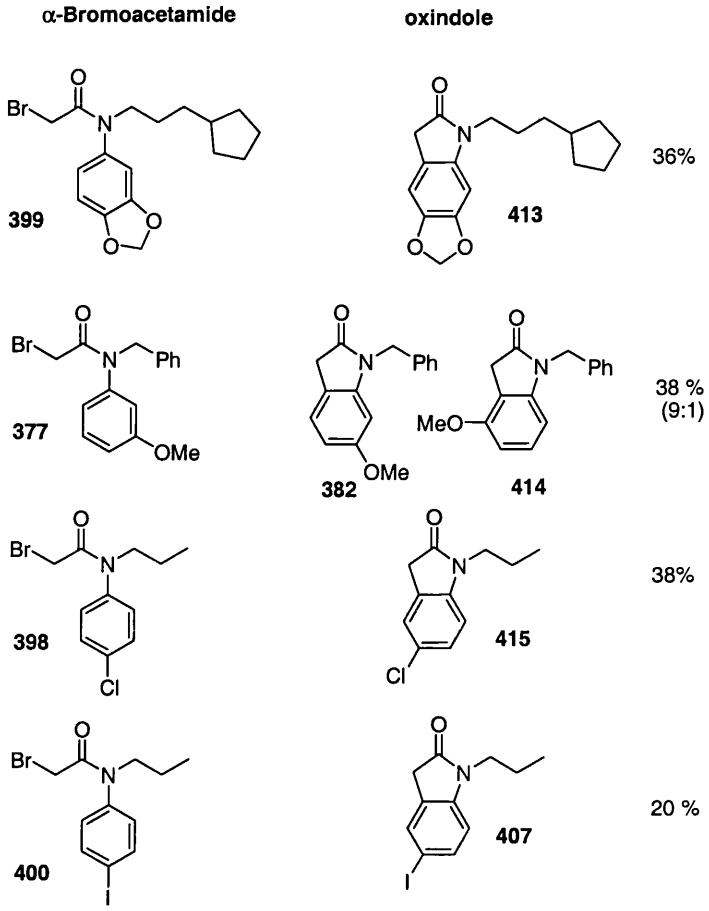
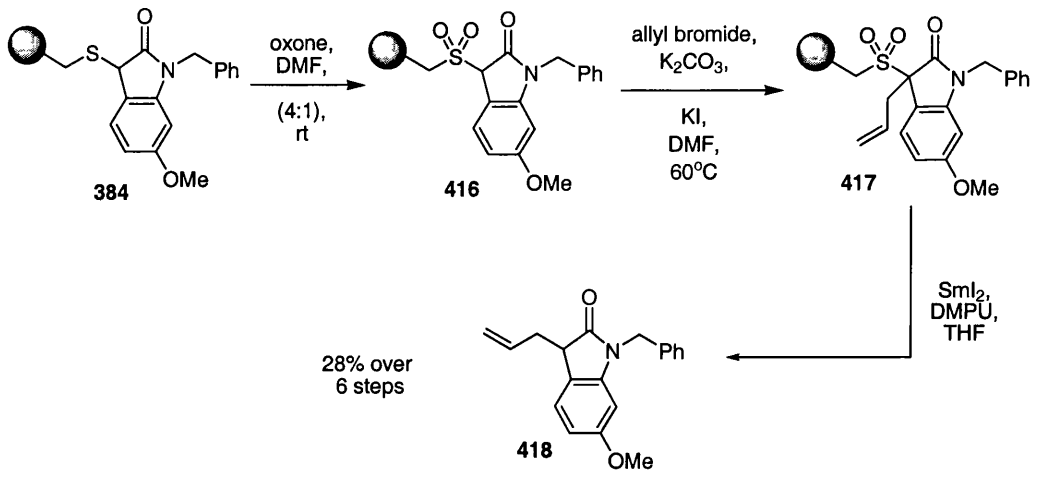


Table 2.3

2.4 Modification of the oxindole framework on resin post-cyclisation

The sulfur link to resin remains intact after the Pummerer cyclisation. Further synthetic steps on resin would allow access to elaborated oxindole frameworks. Work carried out by a project student, Rémy de Gentile, under my supervision illustrates this idea. The linking sulfur atom in resin **384** was oxidised to the sulfone **416** (scheme **2.30**). Subsequent alkylation with allyl bromide in the α-position gave modified resin bound oxindole **417** and was assisted by the increase in oxidation state of the linking sulfur atom. Finally, cleavage of the link with SmI_2 and DMPU gave 3-substituted oxindole **418** in 28 % yield over 6 solid phase steps.

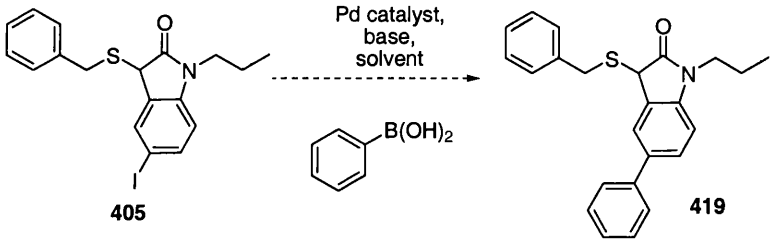


scheme 2.30

2.5 Attempted diversification of the oxindole framework through Pd-catalysed cross coupling reactions

Further diversity could be introduced into the oxindole after cyclisation through palladium catalysed cross coupling reactions of iodo-oxindoles. Solution phase model studies on aryl iodide **405** were carried out in order to find suitable conditions for the Suzuki coupling with phenyl boronic acid (scheme **2.31**).

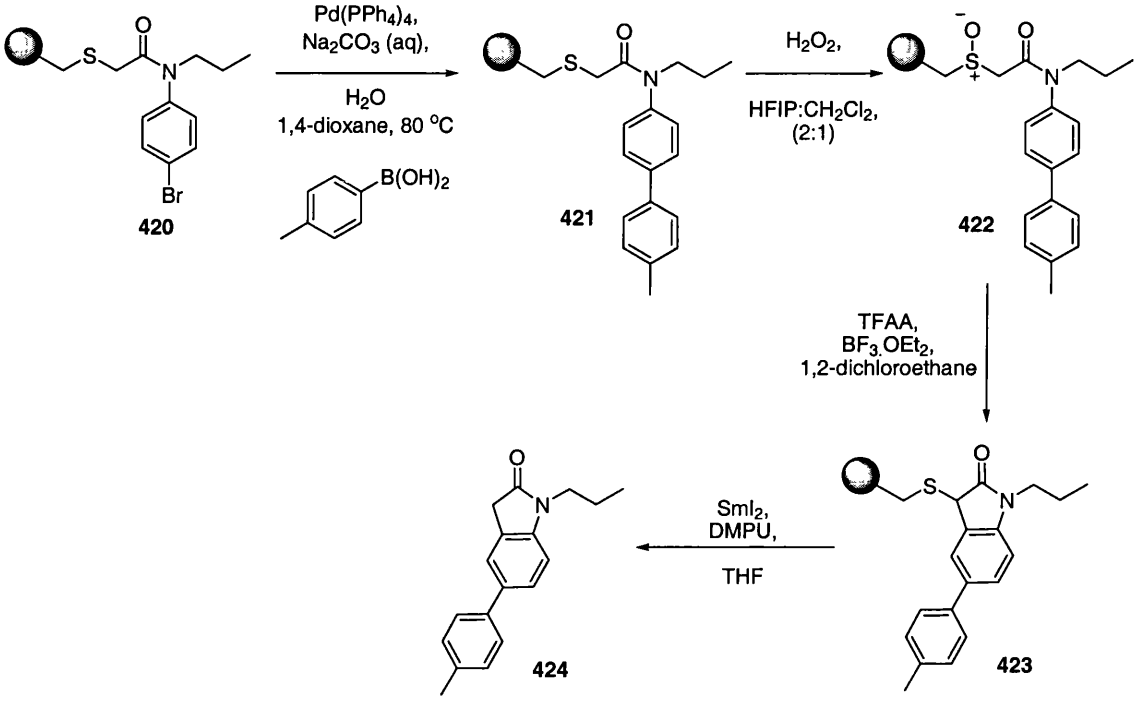
This reaction proved to be unsuccessful. Several solvents, bases, temperatures and palladium catalysts were tested; however, no product was obtained. In all cases starting material was returned unchanged from the reaction.



scheme 2.31

A possible explanation for the lack of catalytic activity in these reactions is that oxindoles bearing an α-sulfur atom such as **405** act as very good chelating ligands towards palladium thus preventing its participation in the catalytic cycle. This will be discussed in more detail in section **3.3.2**.

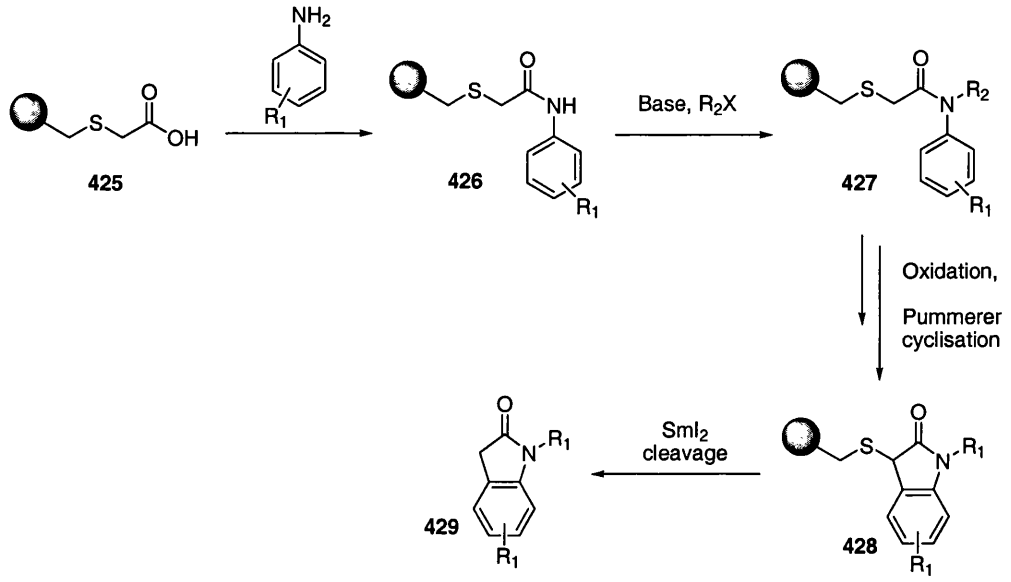
Some solution phase studies carried out on an uncyclised α-thio-*N*-arylamide substrate (see section **3.3.2**) indicate that palladium catalysed cross coupling reactions should be possible prior to cyclisation to the oxindole. On solid phase, Suzuki coupling of aryl bromide **421** with methylbenzene boronic acid was attempted prior to Pummerer cyclisation. The desired product **424** of the sequence was obtained, upon cleavage of resin **423** with SmI_2, however, it was impure and was obtained in low yield.



scheme 2.32

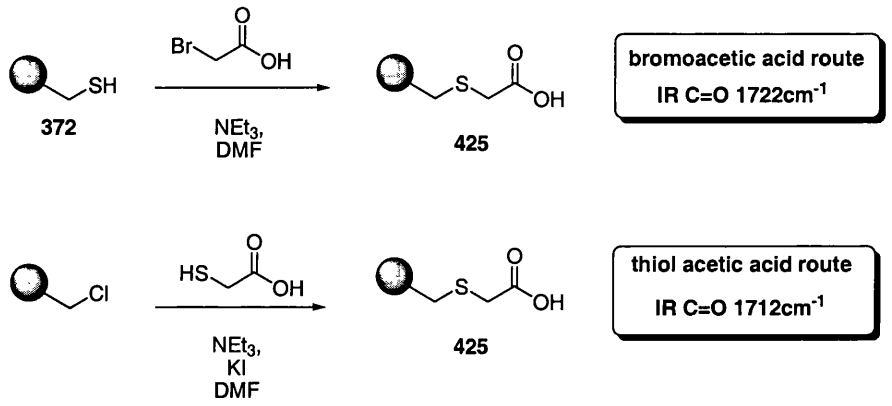
2.6 Stepwise construction of cyclisation substrates on resin

Although an efficient solid phase route to oxindoles had been developed, the methodology has some short comings. Although the preparation of α-bromoacetamides in solution phase prior to immobilisation is straightforward, it would be more convenient if the cyclisation substrates could be built-up on resin to allow diversification to be increased using solid phase rather than solution phase steps. We aimed to develop a route such as that shown in scheme **2.33**. Carboxylic acid resin **425** could be coupled to primary amine to give resin bound amide **426**. *N*-alkylation would then give a resin bound cyclisation substrate **427** which could be oxidised and cyclised as previously described.



scheme 2.33

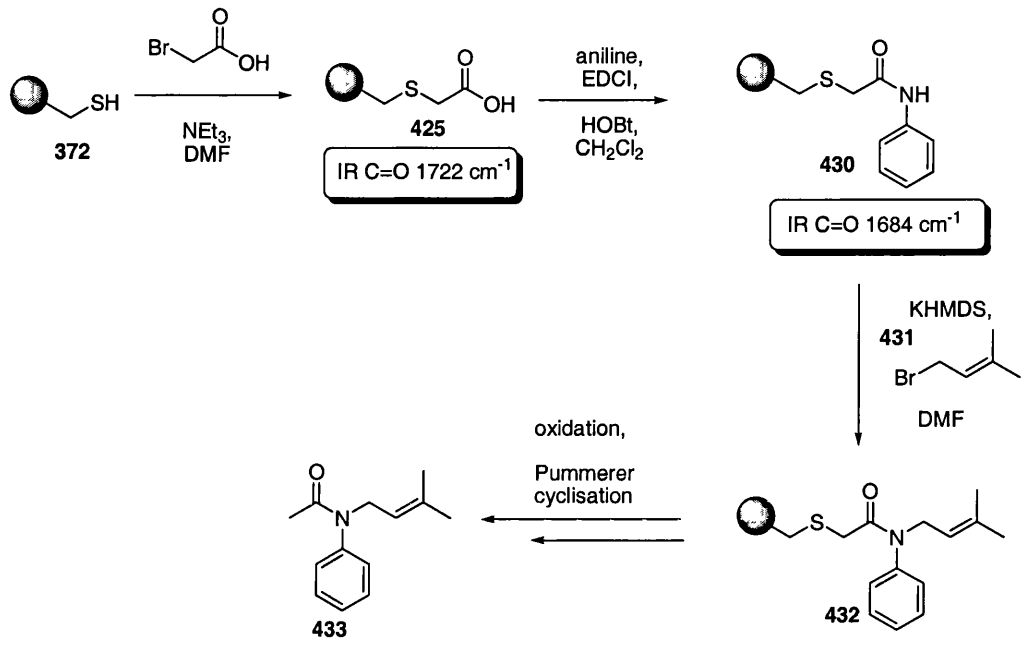
Two approaches were used to synthesise acid resin **425**. In the first method, thiol resin **372** was treated with bromoacetic acid under basic conditions. An IR carbonyl stretch at 1722 cm^{-1} was observed, apparently indicating the successful preparation of **425**. An attractive alternative method that was examined to allow **425** to be prepared directly from Merrifield resin by treatment with thiol acetic acid. This would negate the need for the preparation of a thiol resin. A broad IR carbonyl stretch at 1712cm^{-1} was obtained.



scheme 2.34

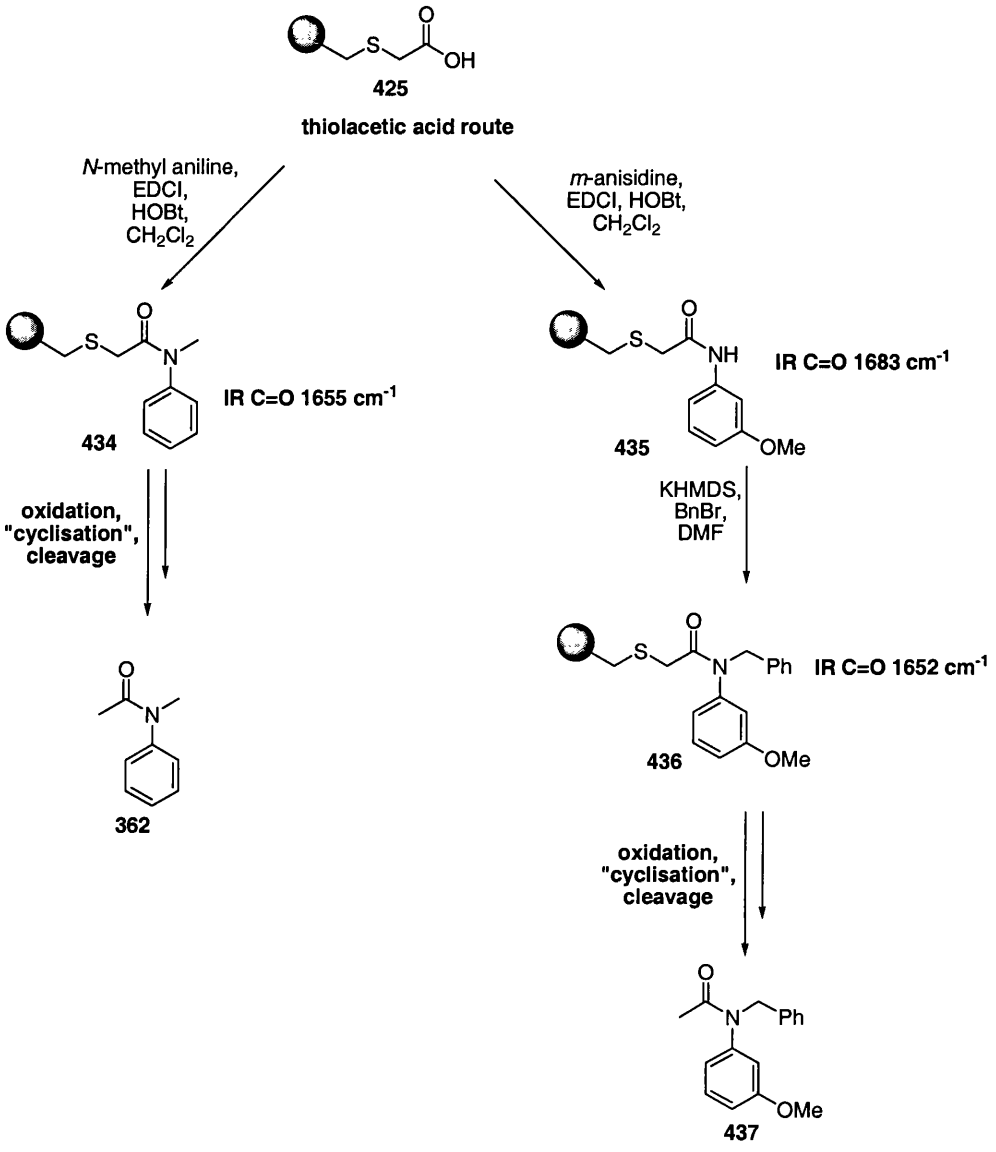
Acid resin **425** prepared by the bromoacetic acid route was coupled with aniline. A shift in the carbonyl stretch from 1722 cm^{-1} to 1684 cm^{-1} was observed, which is consistent with the formation of a secondary amide such as **430**. *N*-alkylation of amide **430** was attempted using KHMDS and prenyl bromide **431**. However, after oxidation, cyclisation and

cleavage, only acetamide **433** was obtained suggesting that cyclisation on solid phase had not occurred.



scheme 2.35

We then focused on acid resin **425** which had been prepared by the thiol acetic acid route (scheme **2.36**). Acid resin **425** was coupled with *m*-anisidine and an appropriate carbonyl stretch at 1683 cm^{-1} was observed. After treatment with base and benzyl bromide a shift in the carbonyl stretch to 1652 cm^{-1} was observed seemingly indicating successful alkylation. Unfortunately, after oxidation, cyclisation and cleavage, only acetamide **437** was obtained. In an alternative strategy, acid resin **425** was coupled with *N*-methyl aniline in order to avoid the possibly problematic *N*-alkylation step. Again, an appropriate carbonyl stretch at 1655 cm^{-1} for resin **434** seemed to indicate that coupling has occurred successfully. However, oxidation, cyclisation and cleavage gave only acetamide **362**. It was unclear why cyclisation would not occur when the cyclisation substrates were constructed in this stepwise manner.



scheme 2.36

2.7 Application of our solid phase Pummerer methodology to the synthesis of biologically active oxindoles

Analogues of generic oxindole **438** shown in fig **2.5** are of pharmaceutical interest as they may show biological activity against a kinase protein known as P38. This protein is involved in a cascade of reactions in the human inflammatory response.

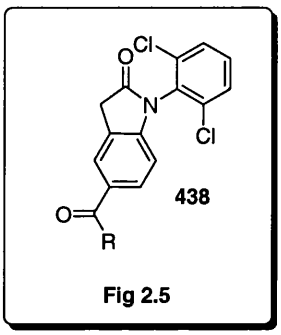


Fig 2.5

Molecules which inhibit this protein are potential drug candidates for inflammatory diseases such as rheumatoid arthritis. Some examples of known inhibitors of p38 are shown in fig **2.6**. These molecules contain core bicyclic scaffolds. VX-745 inhibits the kinase p38 by competitive binding at the ATP-binding site. The important interactions on this binding are the formation of a hydrogen bond between the carbonyl oxygen and the NH of a methionine residue (Met 109). Binding is also driven by hydrophobic interaction between the protein and the dichlorophenyl group. The rigid structure of the molecule is thought to assist effective binding. Structural similarities between these known p38 inhibitors and the oxindole **438** shown (fig **2.5**) can be observed which suggests that oxindole analogues may bind and inhibit kinase p38 in a similar manner.

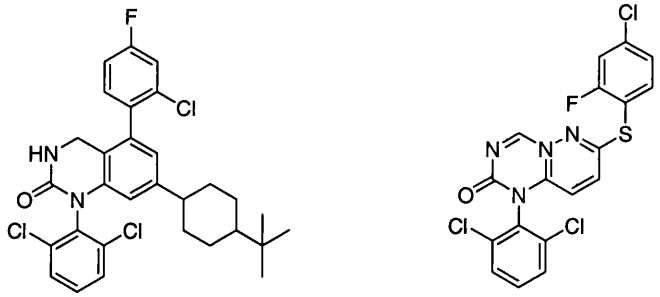
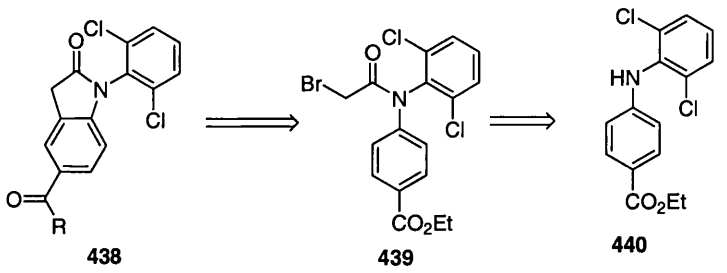


Fig 2.6

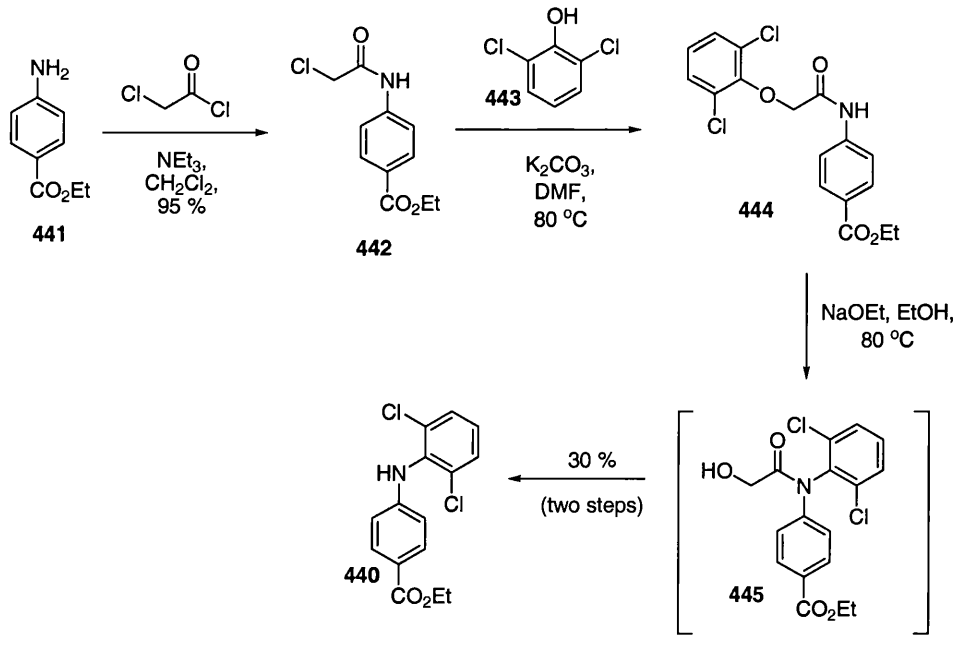
It was envisaged that a small library of analogues of this oxindole could be synthesised using the solid phase Pummerer cyclisation methodology that has been developed. Oxindoles based on core structure **438** can be derived from immobilisation of α-bromoacetamides such as **439** onto thiol resin followed by oxidation of the link and Pummerer cyclisation (scheme **3.37**). The ester group on one aromatic ring could then be modified post-cyclisation in the preparation of analogues. Finally, the desired oxindole analogue could be cleaved from resin.



scheme 2.37

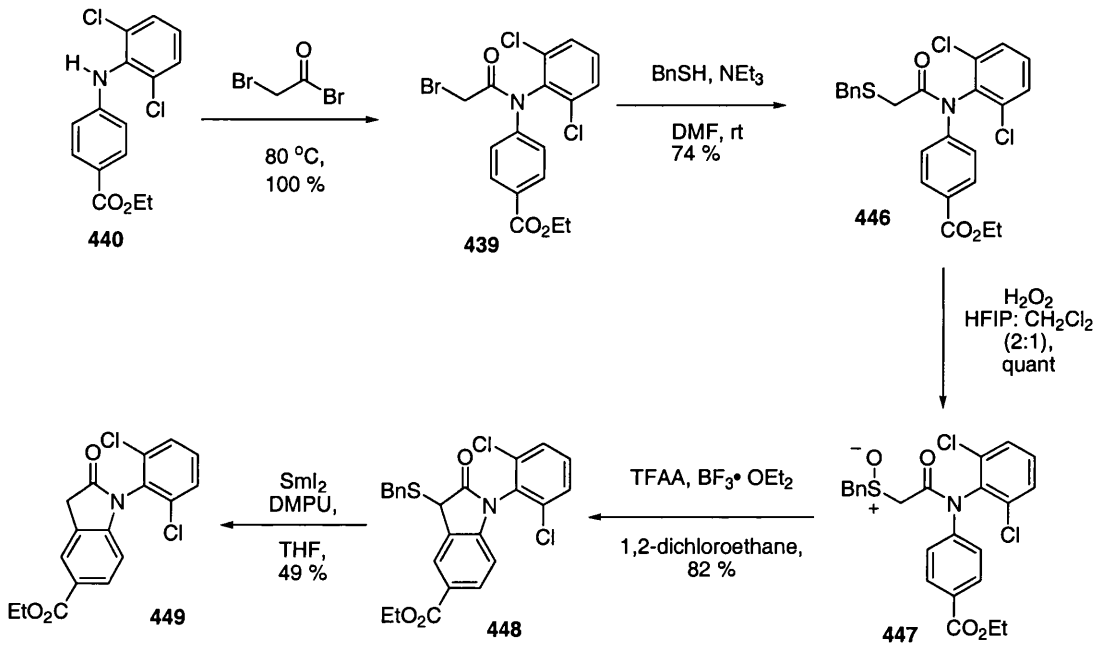
2.7.1 Synthesis of diaryl amine 440

α-Bromoacetamide **439** can be synthesised from diaryl amine **440**. Amine **440** is not commercially available and its preparation is not trivial due to the steric hindrance introduced by the two *ortho* chlorine atoms. Amine **440** can be prepared from α-chloroacetamide **442** via a Smiles rearrangement.[70] Treatment of **442** with 2,6-dichlorophenol **443** and potassium carbonate gave ether **444** which underwent Smiles rearrangement upon treatment with stronger base to give α-hydroxy acetamide **445**. Acetamide **445** was not isolated and underwent hydrolysis to the desired amine **440** *in situ*.



scheme 2.38

It was necessary to carry out solution phase model studies for the synthesis of oxindole **449** prior to attempting the solid phase route in order to establish whether our Pummerer cyclisation conditions would tolerate ester functionality on the aromatic ring. α-Bromoacetamide **439** was prepared by heating amine **440** with neat bromoacetyl bromide. Using benzyl thiol as a model for the thiol resin, reaction with **439** gave sulfide **446** in good yield. Sulfoxidation followed by treatment with Pummerer cyclisation conditions, TFAA and BF_3 OEt_2 gave the desired oxindole bearing an ester group, indicating that the route tolerates ester functionality on the aryl ring. Cleavage of the benzyl sulfanyl group using SmI_2 gave the desired oxindole albeit in modest yield.

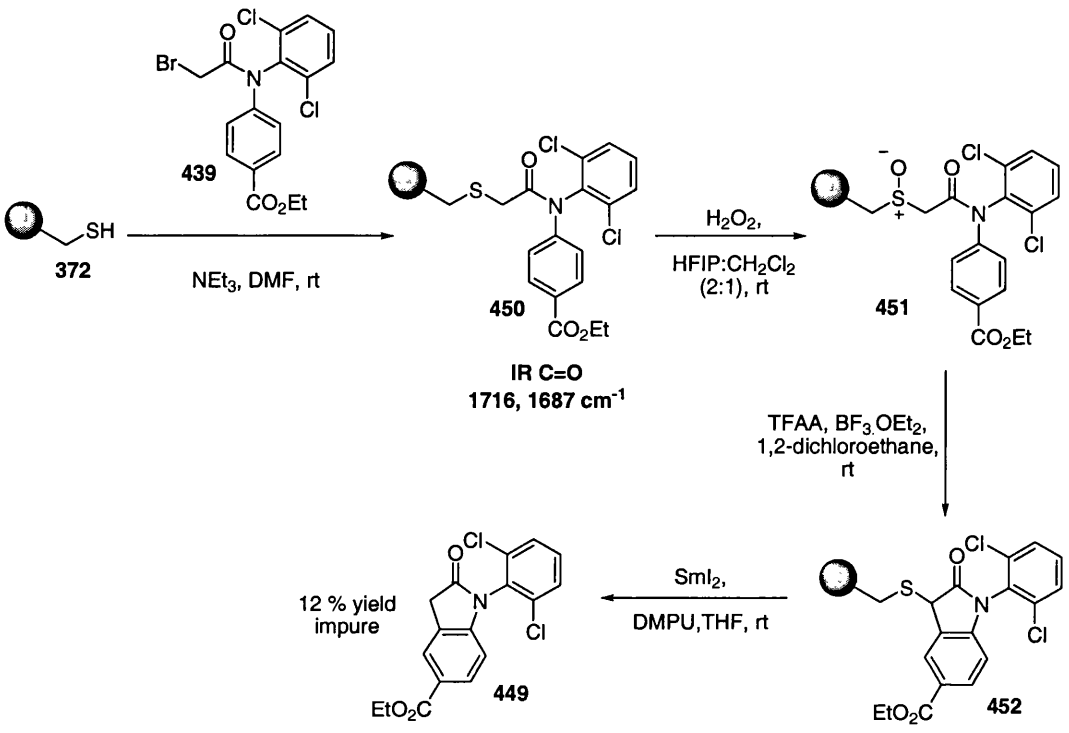


scheme 2.39

2.7.2 Solid phase studies

Given that a successful solution phase route had been developed, the sequence was attempted on solid phase (scheme **2.40**). The α-bromoacetamide **439** was immobilised using thiol resin. IR spectroscopy showed the carbonyl stretches indicating that immobilisation had occurred successfully. Solid state NMR was also used to show that immobilisation and sulfoxidation had occurred successfully. However, in contrast to the solution phase reactions, cyclisation and SmI_2 cleavage gave the desired oxindole **449** in

poor yield, low purity and the reaction proved difficult to reproduce. It is hard to explain the discrepancy between the solution and solid phase results as the progress of the solid phase reactions are difficult to monitor and it was not easy to identify at which stage the problem lay.



scheme 2.40

A possible explanation for the poor results from solid phase is that the Lewis acidic nature of the Sm (III) by-products present in the cleavage step is promoting decomposition of the product oxindole **449**. The carbonyl group of oxindole **449** is very electrophilic due to the electron withdrawing character of the aryl groups on nitrogen and is therefore succeptible to nucleophilic attack. The solid phase reaction time is longer than in solution, prolonged exposure to Lewis acid which may be resulting in decomposition of the product.

Although the solid phase route did not prove to be as effective as we had expected we believe that the problems can be attributed to the instability of the substrate. Some alternative oxindole kinase p38 inhibitor analogues could be made using this methodology by changing the dichlorophenyl group to a less electron withdrawing hydrophobic moiety such as cyclopropyl.

2.8 Conclusions

In conclusion, we have described the first Pummerer cyclisations on solid phase. The cyclisation reactions are enabled by the sulfur atom linking the substrate to the resin. Crucially, the sulfur link remains intact during the cyclisation allowing further solid phase modification of the basic heterocyclic scaffold. The generality of the approach has been investigated by preparing a range of oxindoles. The sulfur linking atom has been used a second time in a different oxidation state to assist further elaboration of the oxindole. Attempts to build up the cyclisation step stepwise on solid–phase were not successful and this will require further investigation.

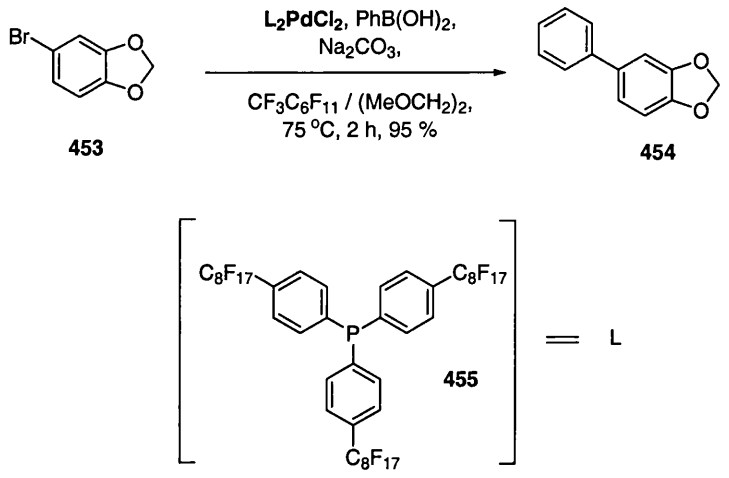
Chapter 3: A Fluorous phase, Pummerer cyclative capture strategy for the synthesis of *N*-Heterocycles

3.0 Introduction to fluorous phase synthesis

Fluorous phase synthesis has become a useful tool for organic synthesis.[71,72,73] The main advantage of using fluorous phase chemistry is in the ease with which fluorinated components of a reaction can be separated from non-fluorinated organic molecules or reagents.

3.0.1 Fluorous biphasic systems (FBS)

The earliest application of fluorous molecules was in fluorous biphasic catalytic systems. In a fluorous biphasic reaction the immiscibility of fluorous solvents with conventional organic solvents is exploited. For example, a fluorous catalyst is present in the fluorous phase and the organic phase contains the substrate to be involved in the reaction together with organic reagents. The reaction is heated and the two phases combine, becoming homogeneous and allowing the catalytic reaction to take place. After the reaction is complete, the mixture is allowed to cool and the two phases separate again. The fluorous catalyst is in the fluorous phase and can be recovered and re-used, while the desired product can be found in the organic phase. An example of a fluorous palladium-catalysed Suzuki reaction carried out by Bannwarth is shown in scheme **3.1**.[74] A fluorous bis-triphenylphosphane palladium complex was synthesised and employed in the Suzuki cross coupling of aryl bromide **453** with phenyl boronic acid to give biaryl **454**. The reaction was carried out in a mixture of PFMC (perfluoromethylcyclohexane) and dimethoxyethane. The catalyst was recovered from the fluorous phase after the reaction and re-used several times. After recycling the catalyst six times the yield had not significantly diminished.

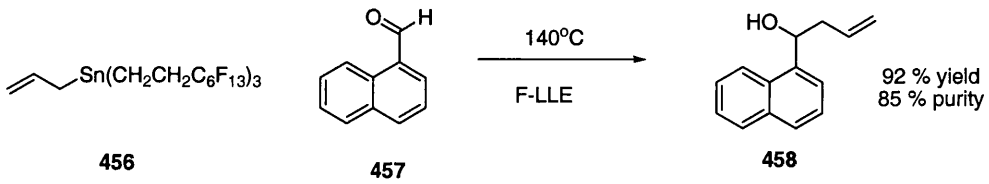


scheme 3.1

3.0.2 Fluorous liquid-liquid extraction

Following on from the idea of fluorous biphasic reactions, the technique of fluorous liquid-liquid extraction (F-LLE) for the separation of fluorous from non-fluorous organic molecules was utilised. Fluorous solvents such as perfluoroalkanes, perfluoroethers and perfluoroamines are generally immiscible with organic solvents. Fluorous molecules are soluble in fluorous solvents due to favourable fluorine-fluorine interactions. This property of fluorous solvents can be used to extract fluorous molecules from an organic phase into a fluorous solvent phase.

Curran has employed this technique in the purification of allyl alcohols prepared by the allylation of aldehydes using a fluorous allylstannane reagent (scheme **3.2**).[75] Aldehyde **457** was heated with fluorous allylstannane **456**. At the end of the reaction the crude mixture contains product alcohol **458** and fluorous tin products. The crude reaction mixture was partitioned between acetonitrile and perfluorohexanes (FC-72), fluorous tin products should partition into the fluorous layer whilst the desired alcohol **458** should remain in the acetonitrile layer. The layers were separated and the acetonitrile layer was extracted two more times with FC-72 to ensure that the fluorous tin products had been completely removed. After evaporation of the solvent from the acetonitrile layer, the desired product **458** was obtained in high purity.



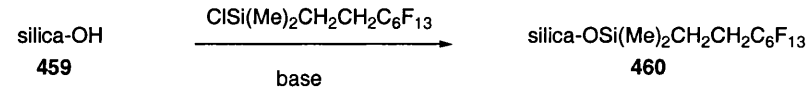
456 **457** **458**

scheme 3.2

A limitation of fluorous liquid-liquid extraction is that a high partition co-efficient in fluorous solvent is necessary if the technique is to be effective. The molecule must have a very high fluorine content to be soluble in the fluorous liquid phase. It has been estimated that the fluorine content must be approximately 60 % of the molecular weight of the molecule for effective liquid-liquid extraction. In recent years attention has turned to the technique of fluorous solid phase extraction (FSPE) for the separation of fluorinated and non-fluorinated molecules.

3.0.3 Fluorous solid phase extraction (FSPE)

Fluorous solid phase extraction is a technique which allows simple, convenient separation of fluorous tagged compounds from non-fluorous compounds using fluorous reverse phase silica gel (FRPSG).[76] Fluorous reverse phase silica **460** is prepared by treatment of normal silica gel with a silyl chloride bearing a perfluoroalkyl chain as shown in scheme **3.3**.



459 **460**

scheme 3.3

Several other fluorous reverse phase silica columns with branched fluorous chains have also been developed. Organic compounds are eluted from these columns in order of decreasing polarity. Fluorous silica was originally used by analytical chemists in standard reverse phase HPLC columns for the separation of organic compounds. Fluorous reverse phase silica gel was found to be superior to normal reverse phase silica columns in that they did not retain organic compounds as readily, and therefore gave better separation.

Fluorous reverse phase silica columns were found to show special separation properties with fluorous tagged molecules. It was found that these columns retained fluorous tagged

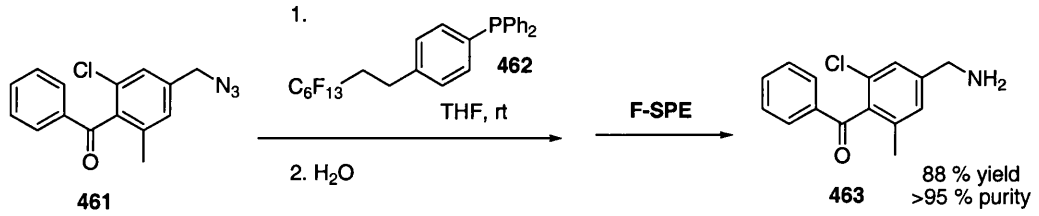
molecules to a much greater degree than one would expect based on the polarity of the molecule. Fluorous-fluorous interactions between the tagged molecule and the fluorous column cause molecules with greater fluorine content to be retained on the column longer. Fluorous molecules are eluted from these columns based on fluorous tag length instead of polarity.

A typical fluorous solid phase extraction (FSPE) procedure involves loading a crude reaction mixture containing fluorous tagged and non-fluorous organic molecules onto a fluorous silica column. Elution with a fluorophobic solvent system such as 80 % MeOH / H_2O removes non-fluorinated compounds from the column. The fluorous tagged molecules are retained due to their strong fluorous-fluorous interactions with the fluorous silica. The column is then eluted with a fluorophilic solvent system such as MeOH which removes the fluorous tagged molecule from the column in high purity.

A major advantage of FSPE over F-LLE is that a much lighter fluorous tag can be used. The fluorous tagged molecule can be 40 % or less by molecular weight and separation from non-tagged organic molecules is still highly effective. Since the development of FSPE the application of fluorous techniques in synthesis has rapidly increased in popularity. Within organic synthesis, the fluorous phase has been employed in several ways.

The utility of FSPE can be demonstrated by considering fluorous reagent systems. Fluorous versions of many reagents such as DEAD, triphenylphosphine, organotin and organoselenium reagents have been developed. Non-fluorous versions of these reagents and their by-products are often difficult to separate from the products of a reaction. Fluorous solid phase extraction (FSPE) can be used to remove these reagents at the end of a synthetic transformation. As with polymer bound reagents, an excess of fluorous reagents can be used to drive reactions to completion, these reagents can be separated easily from the product molecules at the end of the reaction. In the example shown in scheme **3.4** a fluorous phosphine was employed in the Staudinger reaction.[77] Azide **461** was treated with fluorous tagged phosphine **462** followed by water to give amine **463**. Normally, the triphenylphosphine oxide generated in this reaction is difficult to remove. However, the fluorous tagged phosphine **463** employed here can easily be separated using FSPE to give the desired amine **463** in very high purity. This example highlights how a single "light"

fluorous tag is sufficient for FSPE to be successful. F-LLE would require higher fluorine content in the fluorous triphenylphosphine.

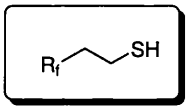


scheme 3.4

Fluorous reagents, fluorous scavengers, fluorous ligands, fluorous protecting groups and fluorous tags are just some of the ways in which fluorous technology has been employed since the development of the very useful FSPE technique.

3.0.4 Fluorous thiols

Several fluorous thiols with varying lengths of perfluoroalkyl chains are commercially available Fig **3.1**.



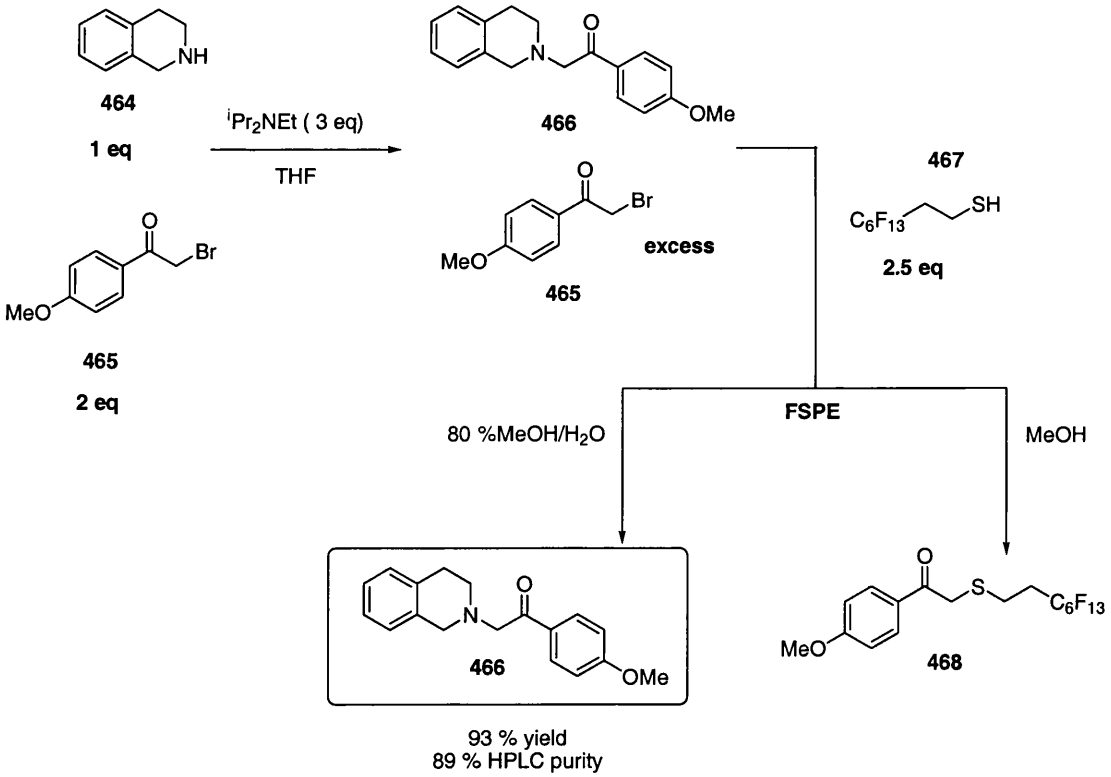
R_f = C_3F_7
C_4F_9
C_6F_{13}
$(CF_2)_4CF(CF_3)_2$
$(CF_2)_6CF(CF_3)_2$
C_8F_{17}
$C_{10}H_{21}$

Fig 3.1

These fluorous thiols each contain a two carbon spacer unit between the perfluoroalkyl chain and the thiol functional group. This spacer unit minimizes the strong electron withdrawing effect of the perfluoroalkyl group such that nucleophilicity at the sulfur is maintained. Fluorous thiols such as these have been employed in several ways in organic synthesis.

Fluorous thiol **467** has been employed by Zhang as an alkyl halide scavenger in *N*-alkylation reactions (scheme **3.5**).[78] Amine **464** was alkylated with an excess of α-bromoketone **465**. After the alkylation is complete the crude reaction mixture contains a mixture of *N*-alkylated product **466** and excess α-bromoketone **465**. 1*H*, 1*H*, 2*H*, 2*H*-

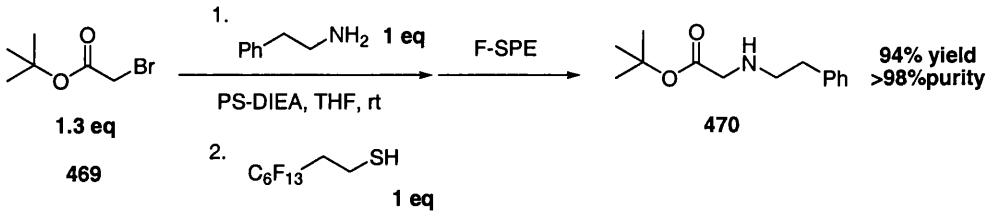
Perfluorooctanethiol **467** was added in order to scavenge the excess alkyl halide **465** by the formation of fluorous tagged sulfide **468**. The desired product **466** was then separated from sulfide **468** using FSPE. Eluting with 80 % MeOH / H_2O gave the amine **466** in good yield and high purity. Fluorous sulfide **468** was obtained by eluting with MeOH. A range of tertiary amines were synthesised in this manner using FSPE to assist purification. Products were obtained in yields ranging from 75-95 % and HPLC purities from 80-95 % demonstrating that fluorous thiols can act as effective scavenging reagents for the removal of unreacted alkylating agents from reaction mixtures. It is interesting to note that the use of a fluorous thiol scavenger is superior to the use of a polymer supported thiol scavenger since the scavenging reaction takes place much faster under the homogeneous solution phase conditions involved.



scheme 3.5

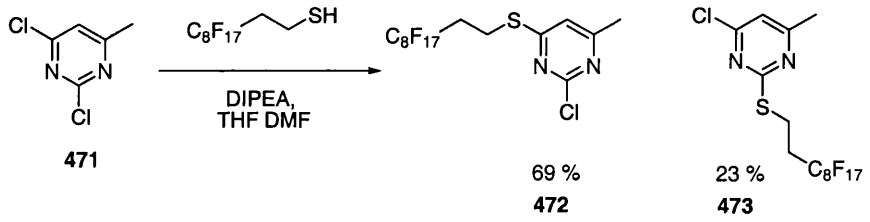
In similar work, Lindsley has employed the same fluorous thiol as a scavenger of excess alkyl halide in *N*-alkylation of a primary amine (scheme **3.6**).[79] α-Bromoester **469** was treated with phenethylamine. Excess bromide **469** was scavenged using fluorous thiol and

following FSPE, the desired *N*-alkylated product was obtained in excellent yield and purity.



scheme 3.6

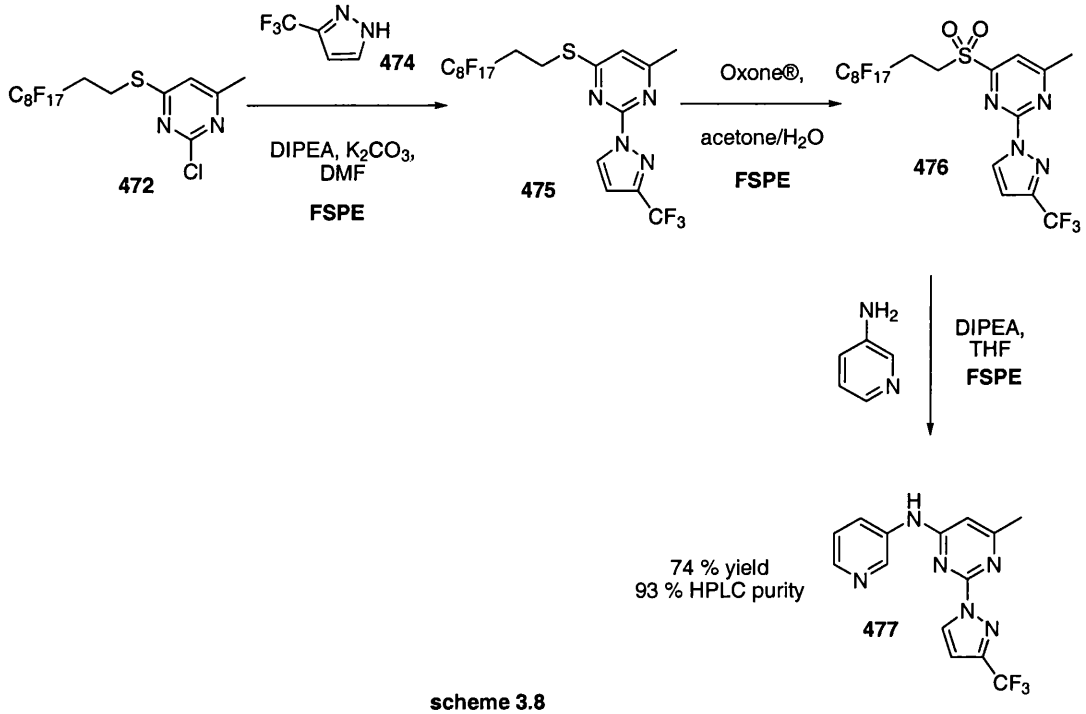
Fluorous thiols have also been used as phase tags. As in solid phase synthesis where a polymer resin is used to immobilise a substrate during a multi-step synthetic sequence and to assist the purification throughout the synthesis; functionalised fluorous chains can be linked to substrates and act as a phase tag during a synthetic sequence. Zhang has employed fluorous phase tags in the synthesis of disubstituted pyrimidines (scheme **3.7** & **3.8**).[80] 2,4-Dichloro-6-methylpyrimidine **471** was treated with 1*H*, 1*H*, 2*H*, 2*H*-perfluorodecanethiol to give a mixture of fluorous tagged chloropyrimidines **472** and **473**. Flash chromatography on normal silica gel was used to separate the isomers, the major of which was used in subsequent steps.



scheme 3.7

Fluorous tagged pyrimidine **472** was treated with pyrazole **474** under basic conditions which resulted in nucleophilic substitution at chlorine to give **475**. The sulfur atom in the fluorous tag was then activated by oxidation to the sulfone **476** using Oxone®. The fluorous tag then underwent nucleophilic displacement upon treatment with 3-amino pyridine to give disubstituted pyrimidine **477**. An important feature of this synthetic sequence is that at each stage FSPE can be used to allow convenient, easy purification. In the final cleavage step, the crude reaction mixture containing the fluorous tag, the desired product, DIPEA and excess amine were loaded onto a fluorous silica column which

contained a small amount of acidic ion-exchange resin (Amberlite CG-50) on top. Eluting with 80 % MeOH / H_2O gave the desired product **477** in high purity. The fluorous tag was retained by the fluorous silica and the excess amines were retained by the ion-exchange resin. A range of different nucleophiles were used in the cleavage step to produce a small library of disubstituted pyrimidines in yields ranging from 74-93 % with HPLC purities of 89-97 %.



scheme 3.8

3.0.5 Advantages of using fluorous phase tags

The use of fluorous phase tags in organic synthesis instead of polymer beads offers many advantages. Fluorous phase reactions are carried out in solution phase as "light" fluorous tagged molecules are very lipophilic and highly soluble in organic solvents. Since the tagged molecule and the reagents are homogeneous in organic solvent during the reaction, the kinetics of fluorous phase reactions are much faster than solid phase reactions. Reactions can be monitored by conventional methods such as NMR and TLC therefore a fluorous phase synthetic route can be developed and optimised much quicker and easier than an analogous solid phase route. Purification is made trivial by employing the FSPE technique. As with solid phase synthesis, an excess of reagents can be used to drive reactions to completion. These excess reagents can be easily removed using FSPE. The use

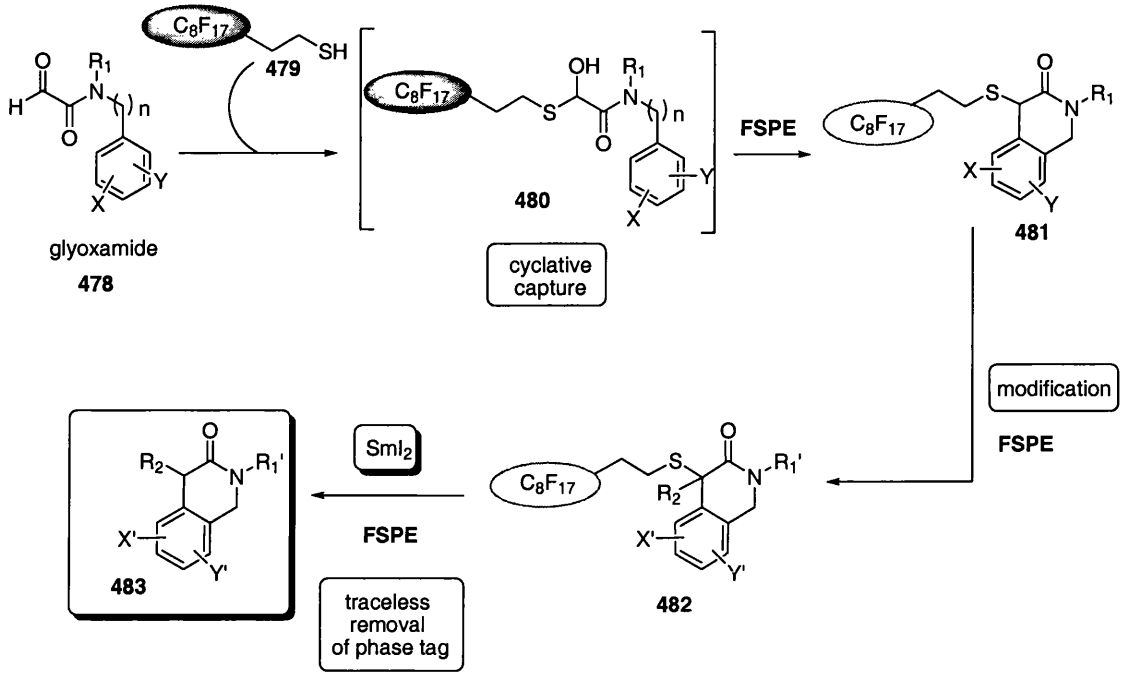
of fluorous phase tags therefore offers the advantages of solution phase synthesis whilst retaining the advantages offered by solid phase synthesis.

3.1 Fluorous phase, Pummerer cyclative capture strategy for the synthesis of *N*-heterocycles

Although a successful route to oxindoles using the first Pummerer cyclisations on solid phase has been developed, our methodology has some limitations. As with all solid phase processes, due to the limited methods available for monitoring reactions on solid support, the synthetic route took a long time to develop and optimise. In addition, several steps on resin are necessary to access the basic heterocyclic framework (i.e. immobilisation, oxidation and cyclisation). We sought to address these limitations in two ways. Firstly, by using a fluorous phase tag instead of polystyrene resin; this would overcome some of the inherent limitations of solid phase synthesis. Secondly, we proposed to develop a novel method of carrying out the Pummerer cyclisation; using a cyclative capture strategy. Our strategy involves introducing the fluorous phase tag and constructing the heterocyclic framework in a single synthetic operation (scheme **3.9**).

The approach is based upon the addition of fluorous thiols to a glyoxamide **478**, generating a hemi-thioacetal intermediate **479**, which is at the correct oxidation level for activation and Pummerer cyclisation. Therefore, in one-step, the substrate is captured by a fluorous thiol triggering cyclisation to give a heterocycle with the fluorous phase tag incorporated. The phase tag can then be used to assist in further elaboration of the heterocyclic framework. At the end of the synthesis the fluorous tag can be cleaved under mild, electron transfer conditions using SmI_2. The use of a fluorous phase tag allows reactions to be monitored conveniently and purification at each stage is simple using FSPE (scheme **3.9**).

It should be noted that this is a novel approach to the Pummerer cyclisation in which the sulfonium ion intermediate is generated from readily accessible glyoxamide substrates *via* a hemi-thioacetal, in a single synthetic operation. This is in contrast to the more conventional approaches to the Pummerer reaction in which the sulfonium ion intermediate is usually accessed from a sulfoxide substrate. In this work, this novel reaction has been applied primarily to the construction of oxindoles, however it has the potential for application in the synthesis of a range of interesting targets.

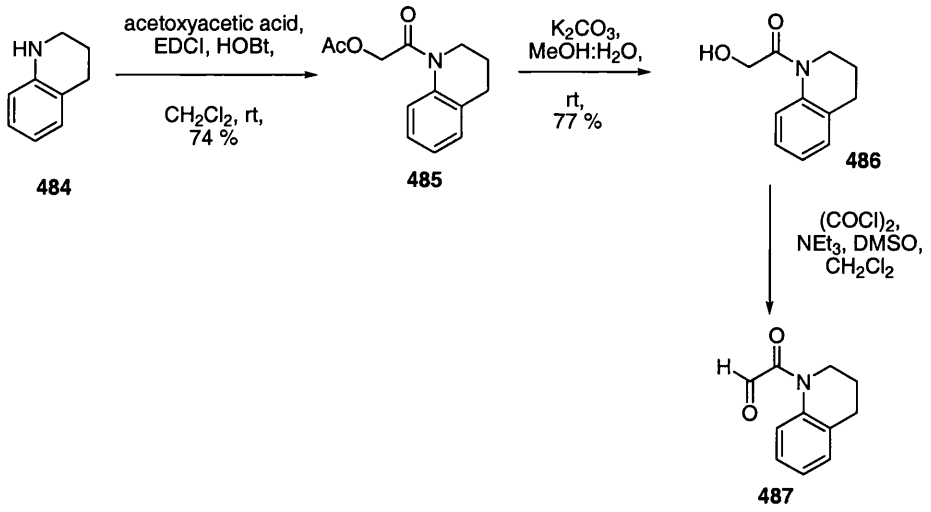


scheme 3.9

3.2 Results and discussion

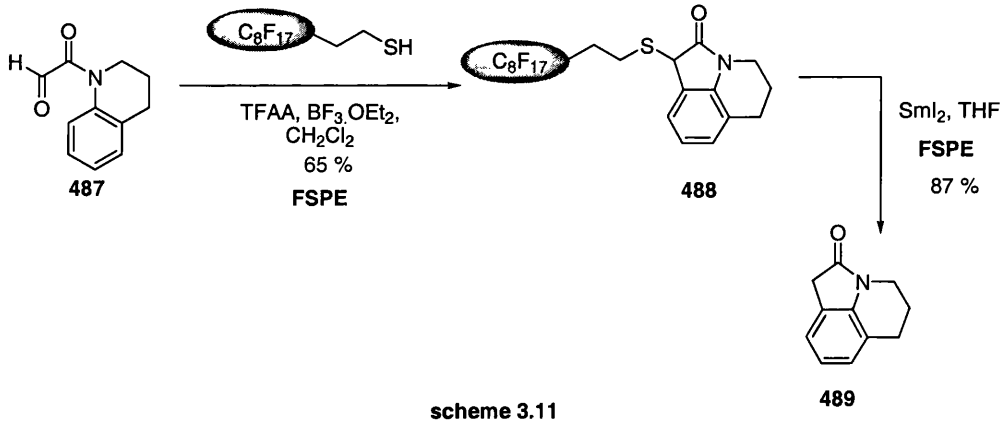
3.2.1 Synthesis of glyoxamide substrates for cyclative capture

Glyoxamides can be synthesised in three steps from secondary amines.[81] An example is shown in scheme **3.10**. Secondary amine **484** was coupled with acetoxyacetic acid using EDCI and HOBt to give α-acetoxyamide **485** in 74 % yield. Hydrolysis of the acetate group gave hydroxyamide **486** in 77 % yield. No purification was required after either of these steps. Oxidation of hydroxyamide **486** using Swern oxidation conditions gave the desired glyoxamide **487**. The crude NMR of the glyoxamide is complex as the glyoxamide exists in equilibrium with the corresponding hydrate. It is therefore difficult to determine a yield for the oxidation. The crude product was therefore used without further purification.



scheme 3.10

In practice, our Fluorous phase, Pummerer cyclative capture strategy was highly effective in the synthesis of oxindoles. As shown in scheme **3.11**, addition of fluorous thiol **479** to glyoxamide **487**, followed by successive treatment with TFAA and BF_3 OEt_2 gave the desired fluorous tagged oxindole **488** in 65 % yield after purification using FSPE. Cleavage of the fluorous tag with SmI_2 followed by FSPE gave oxindole **489** in excellent yield.



scheme 3.11

Table **3.1** summarises the glyoxamides synthesised for use in our cyclative capture approach. All glyoxamides were prepared using an analogous 3 step route to that shown in scheme **3.10**. Yields for α-acetoxy amides are based on the coupling of acetoxyacetic acid with the corresponding secondary amine.

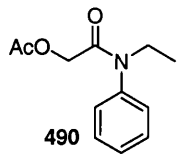
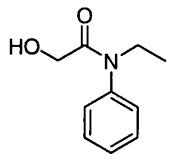
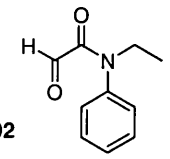
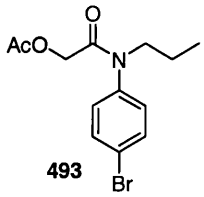
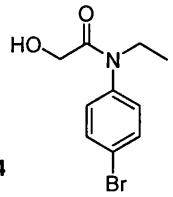
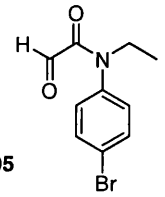
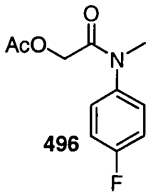
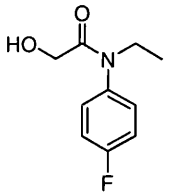
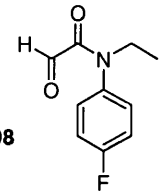
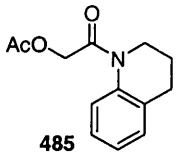
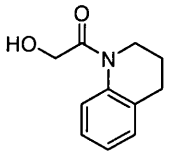
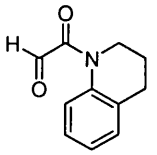
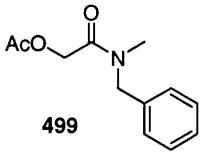
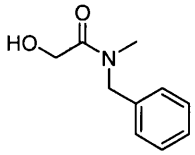
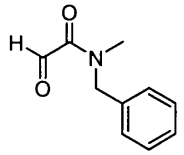
α-acetoxyamide		α-hydroxamide		glyoxamide
 **490**	74 %	 **491**	95%	 **492**
 **493**	87%	 **494**	99%	 **495**
 **496**	96%	 **497**	70%	 **498**
 **485**	74%	 **486**	77%	 **487**
 **499**	93%	 **500**	96%	 **501**

Table 3.1

3.2.2 Fluorous, Pummerer cyclative capture

The readily accessible glyoxamide substrates were treated with 1*H*, 1*H*, 2*H*, 2*H*-perfluorodecane-1-thiol ($C_8F_{17}CH_2CH_2SH$) **479** which resulted in capture of the substrate and hemi-thioacetal formation. In the same reaction pot, activation with TFAA followed by treatment with BF_3 OEt_2 gave the product heterocycles in good isolated yield after rapid purification using fluorous solid-phase extraction. The *N*-heterocycles synthesised by fluorous phase, Pummerer cyclative capture of a range of glyoxamides are shown in table **3.2**. Yields are overall isolated yields for the 2 steps from the corresponding α-hydroxyamide.

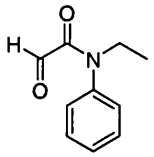
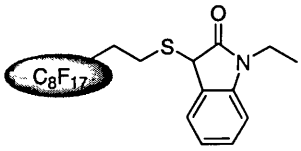
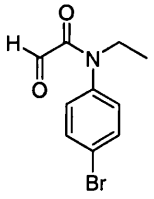
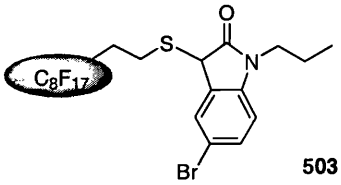
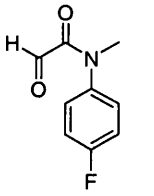
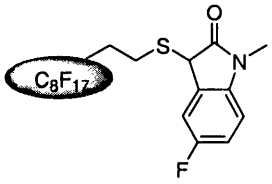
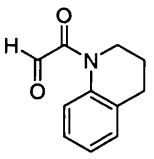
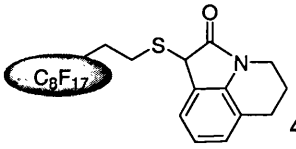
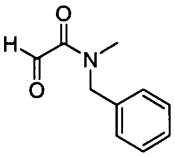
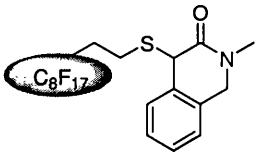
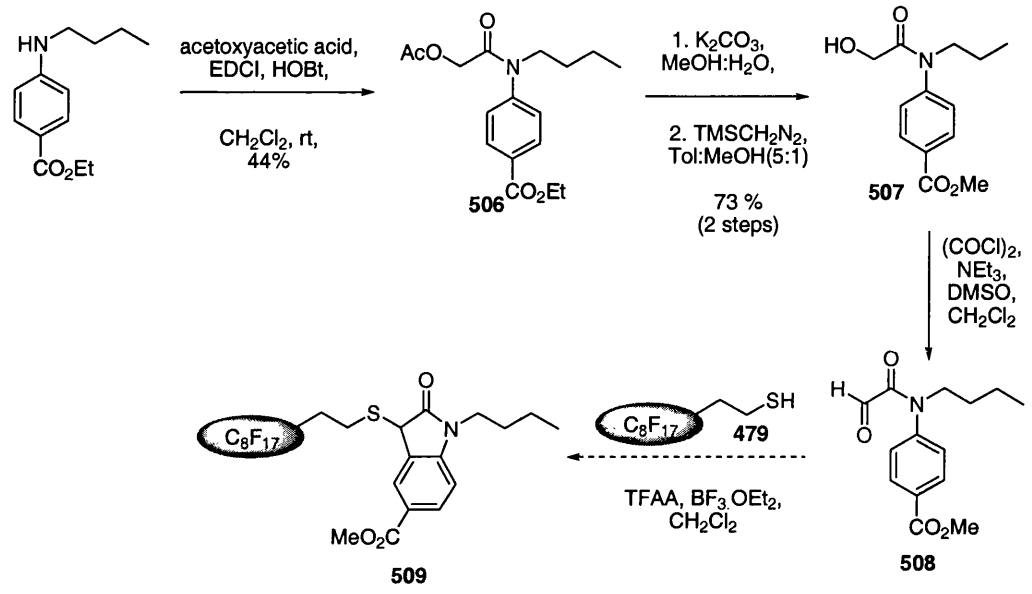
glyoxamide		tagged *N*-Heterocycle		
	**492**		**502**	59 %
	**495**		**503**	85 %
	**498**		**504**	80 %
	**487**		**488**	65%
	**501**		**505**	45 %

Table 3.2

Neutral and electron deficient fluorous tagged oxindoles were synthesised in good yield using this methodology. A tetrahydroisoquinolinone was also synthesised, demonstrating that it is possible to apply this strategy in the synthesis of heterocycles with larger ring-sizes.

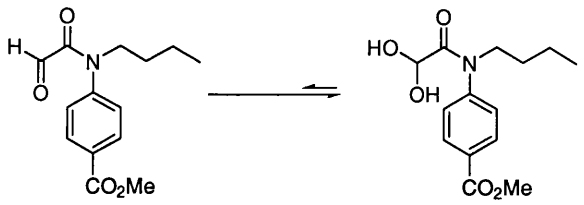
It would be useful to synthesise heterocycles bearing ester functionality on the aromatic ring as this would be amenable to further modification. Glyoxamide **508** which bears an

ethyl ester in the *para* position was synthesised with a minor modification to the normal route (scheme **3.12**). The cyclative capture strategy was applied to glyoxamide **508**, however, the desired oxindole **509** was not obtained. The crude NMR indicated that the fluorous thiol had not undergone addition to glyoxamide **508**.



scheme 3.12

A possible explanation for the lack of reactivity of the glyoxamide can be understood by considering the position of the equilibrium between the glyoxamide **508** and its hydrate (scheme **3.13**).[82] Where the aromatic ring does not bear a strongly electron withdrawing group in conjugation with the nitrogen atom, the equilibrium should lie towards the glyoxamide, however, in this substrate the ester group lies *para* to the nitrogen and therefore the hydrate should predominate as the aldehyde group of the glyoxamide is more electron deficient. In this substrate, the hydrate appears not to react with the fluorous thiol and therefore Pummerer cyclisation does not take place. The ^{1}H NMR of the crude reaction mixture after the Swern oxidation of **507** suggests that the hydrate is formed exclusively since the usual aldehyde proton is not observed. A possible solution to this problem is to synthesise a glyoxamide with the ester functionality in the *meta* position, thus avoiding direct conjugation with the lone pair on nitrogen.

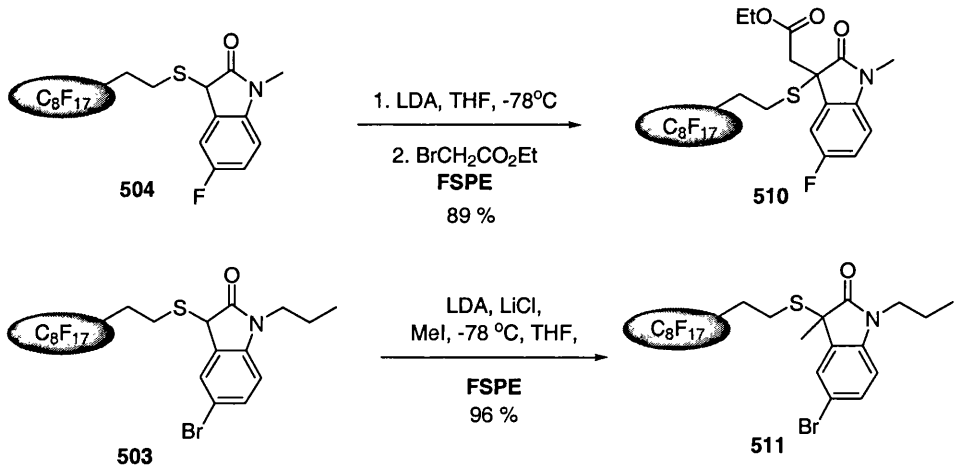


scheme 3.13

3.3 Modification of the heterocyclic framework post cyclisation

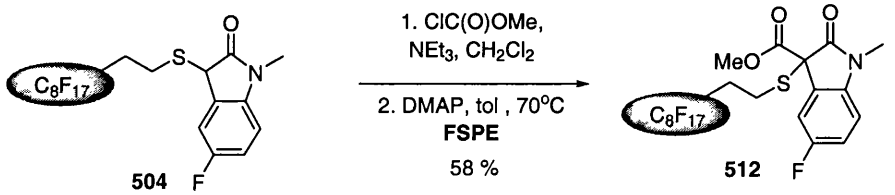
3.3.1 Modifications at the α-position

After conveniently accessing fluorous-tagged heterocycles by the Pummerer cyclative capture process, the tagged-heterocycles can be modified in a variety of ways. The sulfur atom linkage to the fluorous phase tag can be used to facilitate elaboration at the α-position. Some α-alkylations are shown in scheme **3.14**.



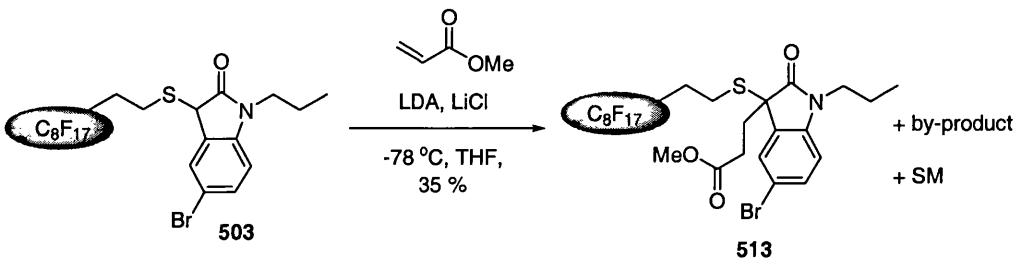
scheme 3.14

Oxindole **512** was prepared by *O*-acylation followed by DMAP catalysed rearrangement to give the *C*-acylated product (scheme **3.15**).[83]



scheme 3.15

The Michael addition of oxindole **503** to methyl acrylate was investigated. The use of LDA led to a mixture containing only 35 % yield of the desired product **513**.



scheme 3.16

The by-product(s) was thought to arise from the enolate generated after the first Michael addition (Fig **3.2**), undergoing further reaction with methyl acrylate. The use of only one equivalent of base and methyl acrylate did not prevent by-product formation or the recovery of starting material. The use of LHMDS as a base gave similar results.

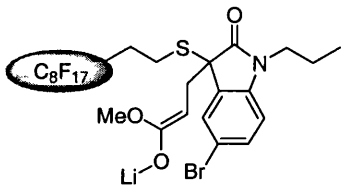
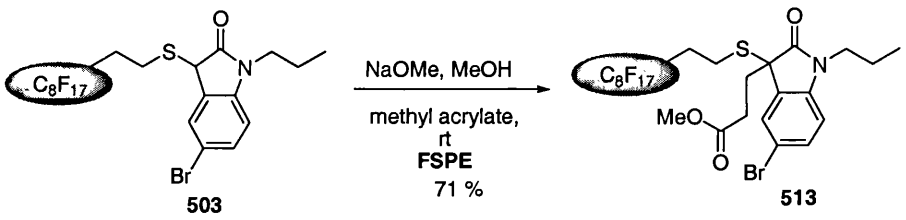


Fig 3.2

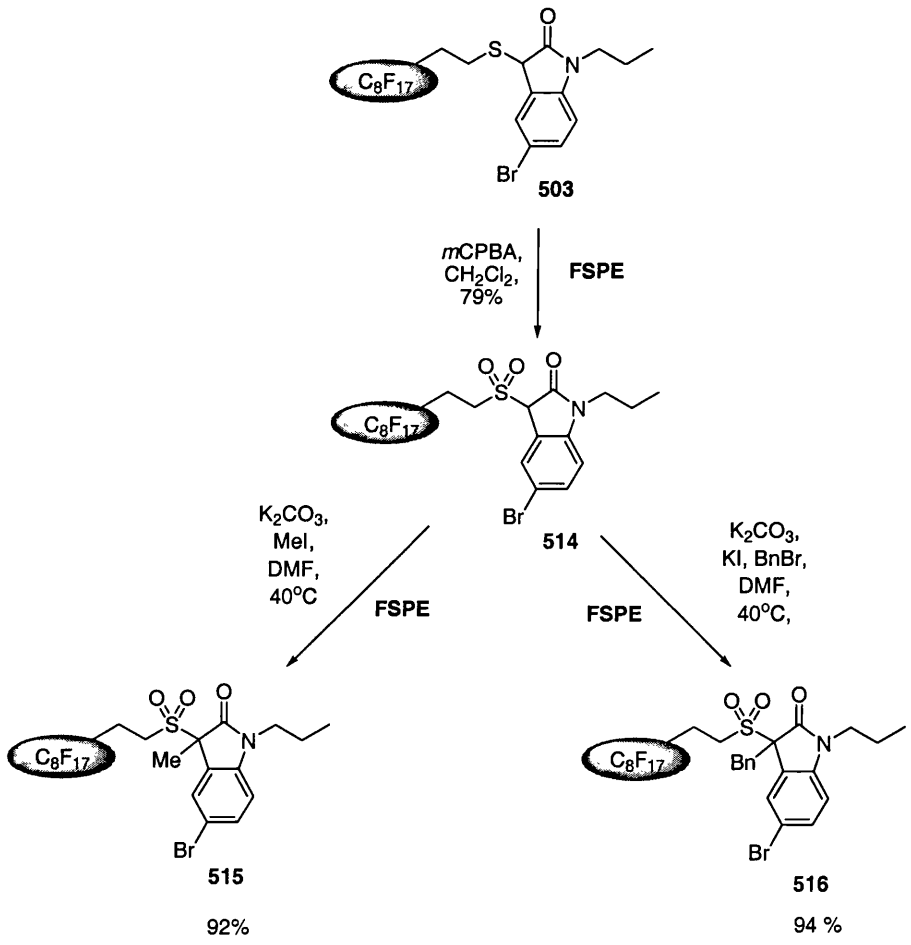
These results suggested that the enolate of the Michael adduct was more reactive than the enolate of the oxindole. The use of a protic solvent to protonate the enolate as soon as it was formed was felt to be necessary and the use of sodium methoxide in methanol gave the Michael adduct **513** in good yield. All the starting material was consumed and no by-product was observed (scheme **3.17**).



scheme 3.17

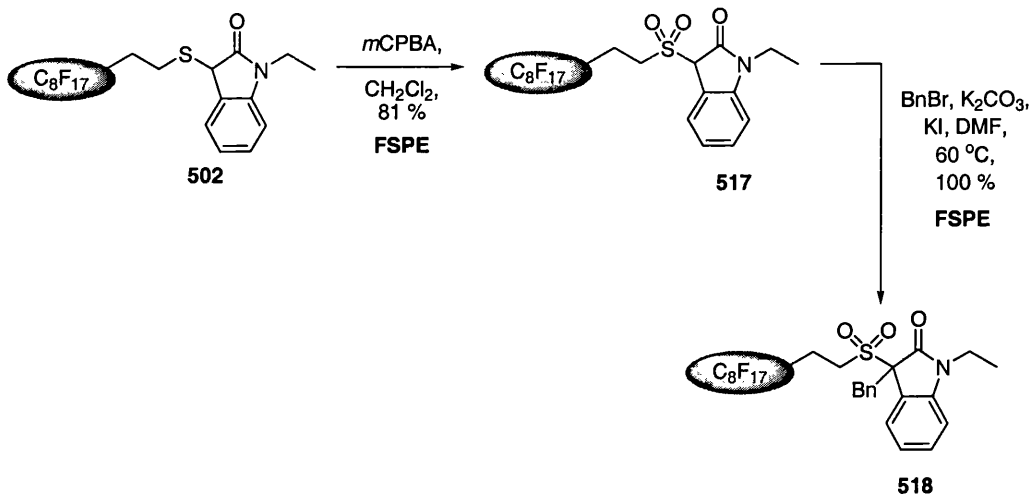
Crucially, in all of these modification reactions, excess reagents can be used to drive the reactions to completion. Purification after each modification step can be carried out conveniently using FSPE.

Oxidation of the sulfur atom linkage to the sulfone oxidation state allows modifications at the α-position to be carried out under much milder conditions. As shown in scheme **3.18**, *m*CPBA oxidation of the sulfide **514** to sulfone **515** enables α-alkylation to be carried out using mild bases such as K_2CO_3. FSPE can again be used at each stage to assist purification.



scheme 3.18

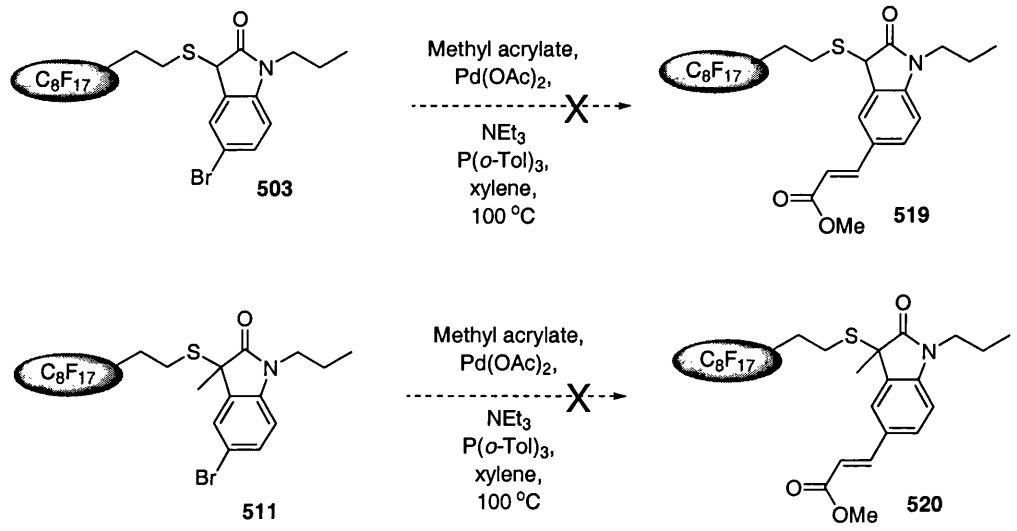
Similarly, sulfide **502** can be oxidised to the sulfone **517** in excellent yield. Sulfone assisted alkylation gave the desired modified oxindole **518** in quantitative yield (scheme **3.19**).



scheme 3.19

3.3.2 Modifications using palladium-catalysed cross couplings

We aimed to diversify the fluorous tagged heterocycles through palladium catalysed cross couplings utilising halide functionality on the aromatic ring. Initially the Heck reaction of oxindole **503** was attempted (scheme **3.20**). Unfortunately, no reaction occurred and starting material was recovered. It was considered that it might be necessary to block the enolisable α-position. Oxindole **511** bearing an α-methyl group was therefore prepared and subjected to the Heck reaction but again no palladium catalysis was observed.



scheme 3.20

Since no catalytic activity had been observed, it was postulated that the structure of fluorous tagged oxindoles such as **503** could be inhibiting catalysis. In the oxindole

substrates the carbonyl oxygen atom and the sulfur atom are locked in a *cis* conformation, this makes them potentially excellent chelating ligands for palladium. Strong chelation to palladium would prevent the metal becoming involved in the catalytic cycle (Fig **3.3**).

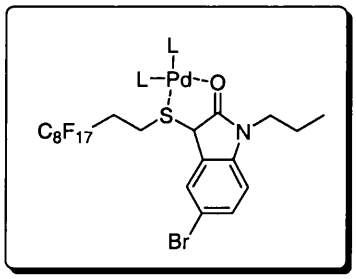
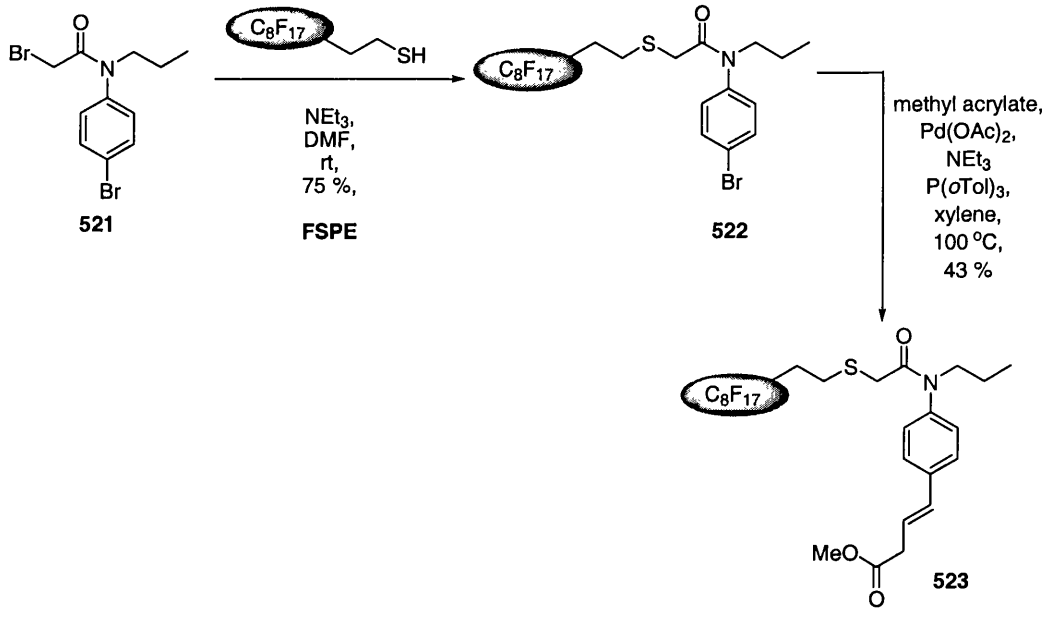


Fig 3.3

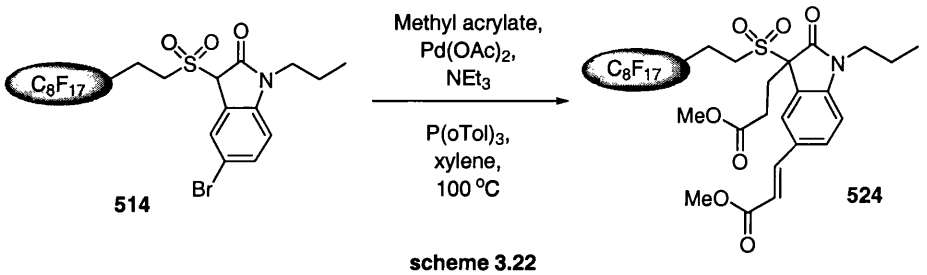
In order to further investigate this hypothesis an uncyclised α-alkylsulfanyl-*N*-arylamide **522** was synthesised (Scheme **3.21**). In substrates such as **522** there is free rotation around the C-S bond and therefore it is likely to be a less effective metal chelator. The Heck reaction on **522** was indeed successful which lends support to the idea that the tagged oxindole structure itself is inhibiting palladium catalysis.



scheme 3.21

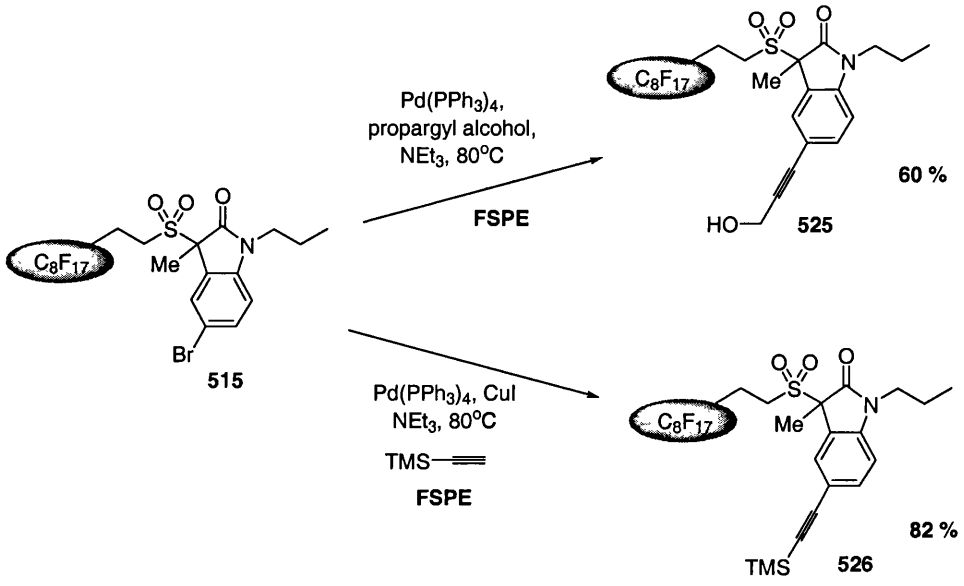
Palladium catalysed reactions on a compound such as **510** may be more successful if the sulfide is oxidised to the sulfone **514**. In the sulfone the sulfur lone pairs are no longer

available for chelation to palladium. The Heck reaction of sulfone **514** with methyl acrylate was attempted (scheme **3.22**). On this occasion some catalysis was observed. Heck reaction on the aryl ring took place, however, the increased acidity of the α-proton in the sulfone resulted in Michael addition to methyl acrylate. The major product of this reaction was **524** (impure, yield not obtained), suggesting that blocking the α-position would be necessary to prevent competing reaction occurring.



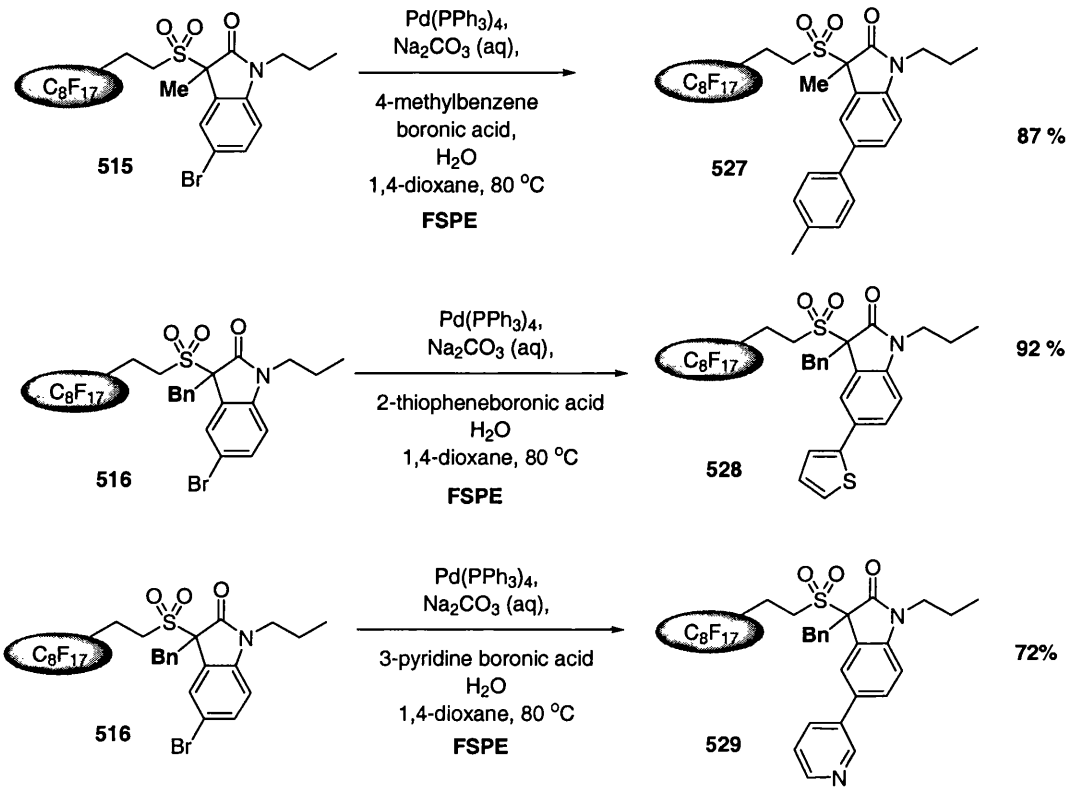
scheme 3.22

The Heck reaction of α-blocked sulfone **515** was sluggish and gave only a trace of product after 24 h. Since substrates which showed some activity in palladium catalysed reactions had been identified, we decided to test them in other palladium catalysed transformations such as Sonogashira reactions (Scheme **3.23**). These reactions proved very successful and coupled products were obtained in excellent yields. FSPE proved very useful in the purification of these modified oxindole products.



scheme 3.23

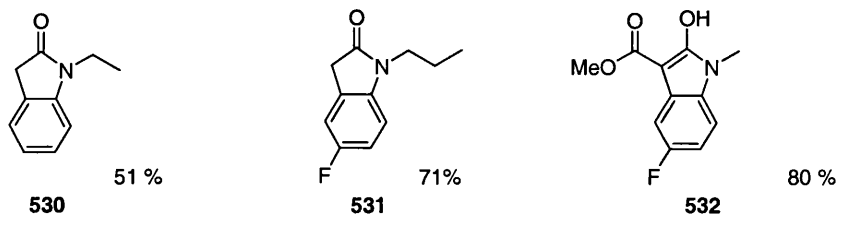
Suzuki couplings (scheme **3.24**) of tagged 5-bromo-oxindoles also proved very successful. In each case excess boronic acid could be used to drive the reactions to completion. At the end of the reaction FSPE effectively removed the excess acid together with by-products from the palladium tetrakis(triphenylphosphine), to give modified fluorous tagged oxindoles in high purity.

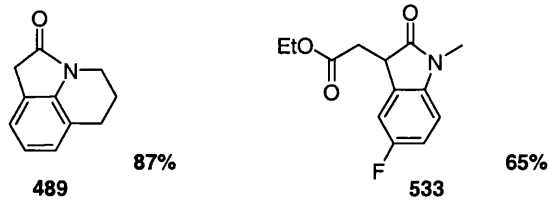


scheme 3.24

3.4 Traceless cleavage of the fluorous tag

At the end of the synthetic sequence, the fluorous phase tag can be removed in a traceless manner by reduction with SmI_2. No additives were required to activate SmI_2 regardless of whether the sulfur atom was in the sulfide or the sulfone oxidation state. Treatment of a fluorous tagged heterocycle with the linking sulfur atom in the sulfide oxidation state with SmI_2 at room temperature, gave the desired heterocycle after cleavage. FSPE can again be used to assist purification, the desired product eluting in the non-fluorous fraction, thereby separating it from the fluorous thiol tag. Fig **3.4** summarizes the heterocycles produced by SmI_2 cleavage of the fluorous phase tags at the sulfide oxidation state.





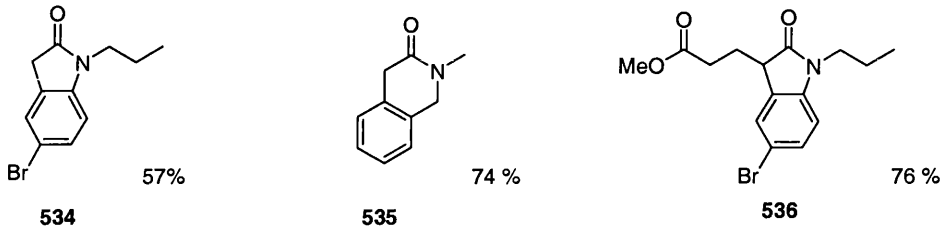


Fig 3.4

For cleavage of fluorous sulfones, treatment of the fluorous tagged heterocycles with SmI_2 at room temperature gave the desired product. No further purification was required as the fluorous component was lost to the aqueous layer during work up.

Fig **3.5** shows the heterocycles obtained by SmI_2 cleavage of the fluorous phase tag in the sulfone oxidation state.

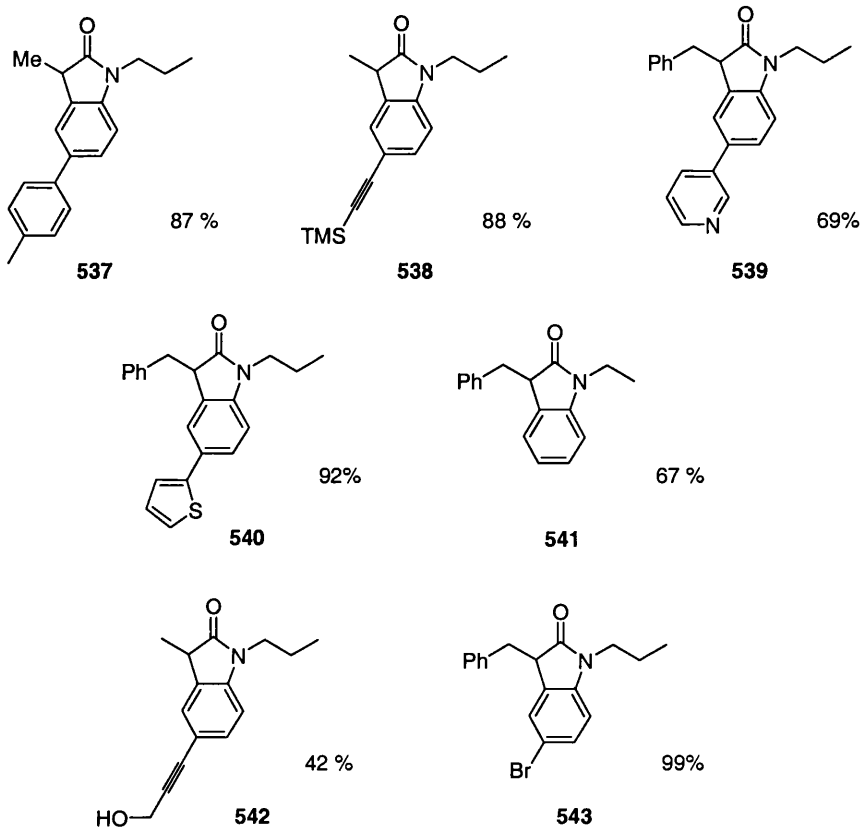


Fig 3.5

3.5 Conclusions

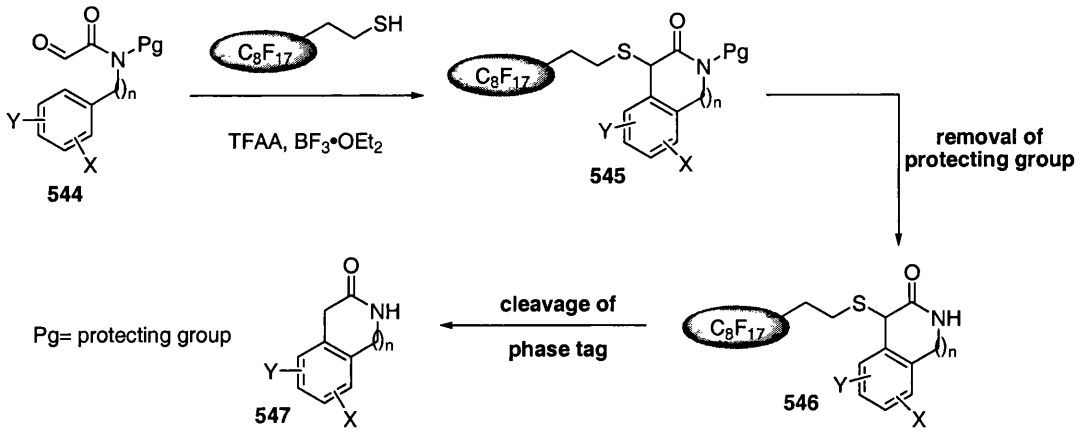
In conclusion, we have developed a new strategy for the fluorous phase synthesis of *N*-heterocycles libraries. The sequence involves several key features; a fluorous phase, Pummerer cyclative capture strategy for rapid access to tagged, heterocyclic frameworks; modification of the fluorous heterocyclic scaffolds using a variety of approaches including palladium catalysed cross couplings; traceless, reductive removal of the fluorous phase tag. The use of a fluorous phase tag has enabled us to overcome some of the limitations associated with our solid phase Pummerer sequence, allowing us to expand some of its generality.

3.6 Future work

There are several areas in which our fluorous phase Pummerer cyclative capture strategy can be further developed and applied for the high throughput synthesis of heterocycles.

3.6.1 Cyclative capture of glyoxamides bearing nitrogen protecting groups

Many biologically active nitrogen heterocycles contain a free NH group (see fig **2.1**). The preparation of heterocycles by Pummerer reaction has been shown to require a substituent on nitrogen for successful cyclisation.[84] In order to apply our Pummerer, cyclative capture approach to the synthesis of these heterocycles it is necessary to develop a protecting group strategy to temporarily mask the nitrogen atom and thus enable cyclative capture. We therefore need to identify a suitable protecting group and to find a route to a glyoxamide substrate such as **544** (scheme **3.25**). Following cyclative capture to give fluorous tagged heterocycle **545**, removal of the *N*-protecting group and cleavage of the tag will yield the desired heterocycle **547** with a free NH group. The protecting group used must be stable under the Lewis acidic conditions used in the cyclisation reaction.



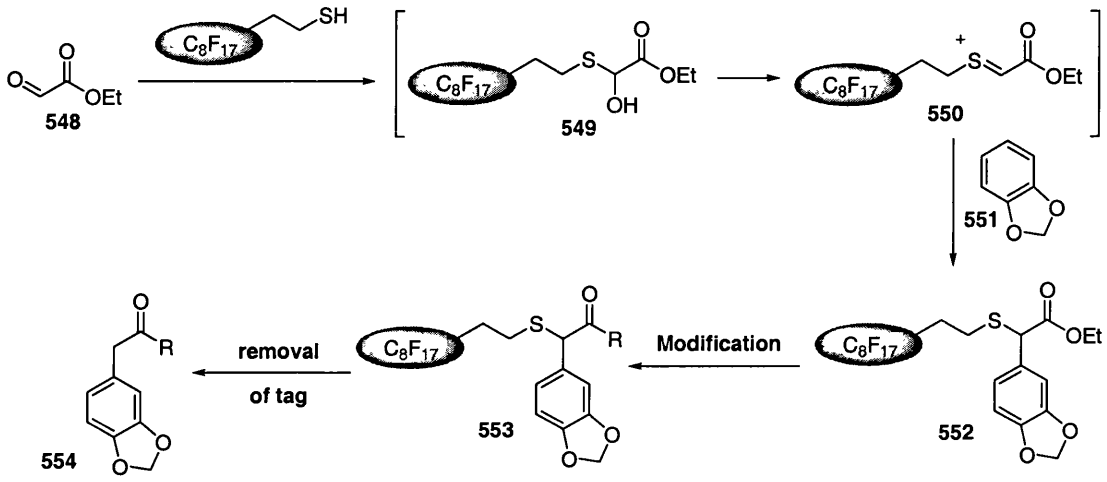
scheme 3.25

This approach will also allow us to synthesise libraries of compounds with different substituents on nitrogen.

3.6.2 Intermolecular Pummerer reactions

It would be interesting to investigate whether our one-pot approach to the Pummerer reaction could be applied in an intermolecular sense[85] (scheme **3.26**). Addition of fluorous

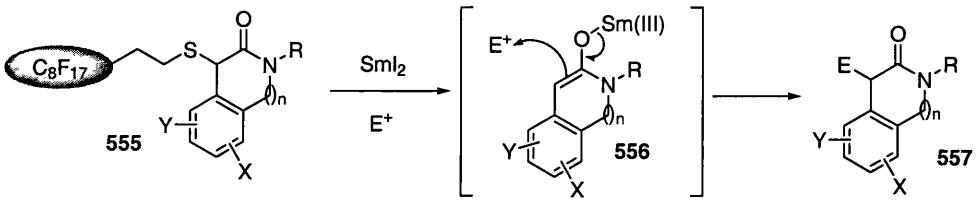
thiol to glyoxylates such as **548** (or glyoxamides) would generate an intermediate hemi-thioacetal **549** from which a sulfonium ion **550** can form. Nucleophiles such as **551** should undergo addition to sulfonium ion **550** to give **552**. The fluorous tag can be used to assist in purification after further modifications. It is necessary to explore the scope of the nucleophiles which can be used in this intermolecular Pummerer reaction. For example, the use of silyl enol ethers, allyl silanes and electron rich aromatics would be examined initially.



scheme 3.26

3.6.4 Sequential SmI_2 cleavage-diversification

SmI_2 cleavage of the phase tag may present an opportunity to introduce further diversification into the product heterocycle. Treatment of the fluorous tagged heterocycle **555** with SmI_2 results in reductive cleavage of the tag and the formation of a samarium enolate **556**. If an electrophile such as an aldehyde or ketone is present in the cleavage reaction then it may be possible to trap the enolate to give modified heterocycles such as **557**.



scheme 3.27

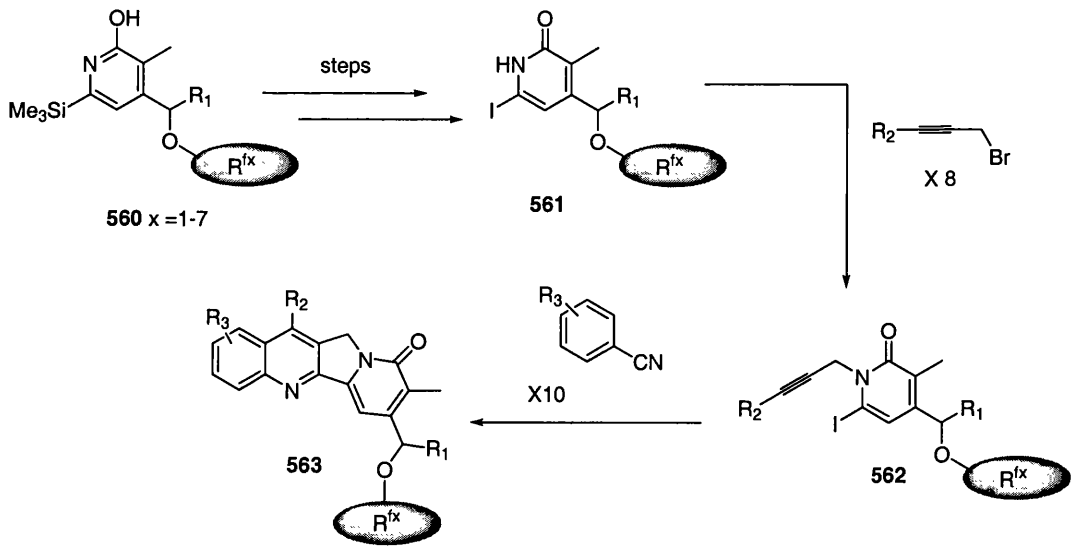
3.6.3 Fluorous mixture synthesis

To further explore the utility of our methodology in high throughput synthesis we aim to undertake the construction of a small library of heterocycles using fluorous mixture synthesis. Fluorous mixture synthesis relies upon the principal that molecules bearing fluorous tags of varying fluorine content can be separated using fluorous HPLC (F-HPLC). Curran has applied fluorous mixture synthesis in the synthesis of analogues of discodermolide[86] and in the production of a 560-member library of Mappicine analogues **559** (Fig **3.6**).[87]

(S)-mappicine **558** mappicine analogues **559**

Fig 3.6

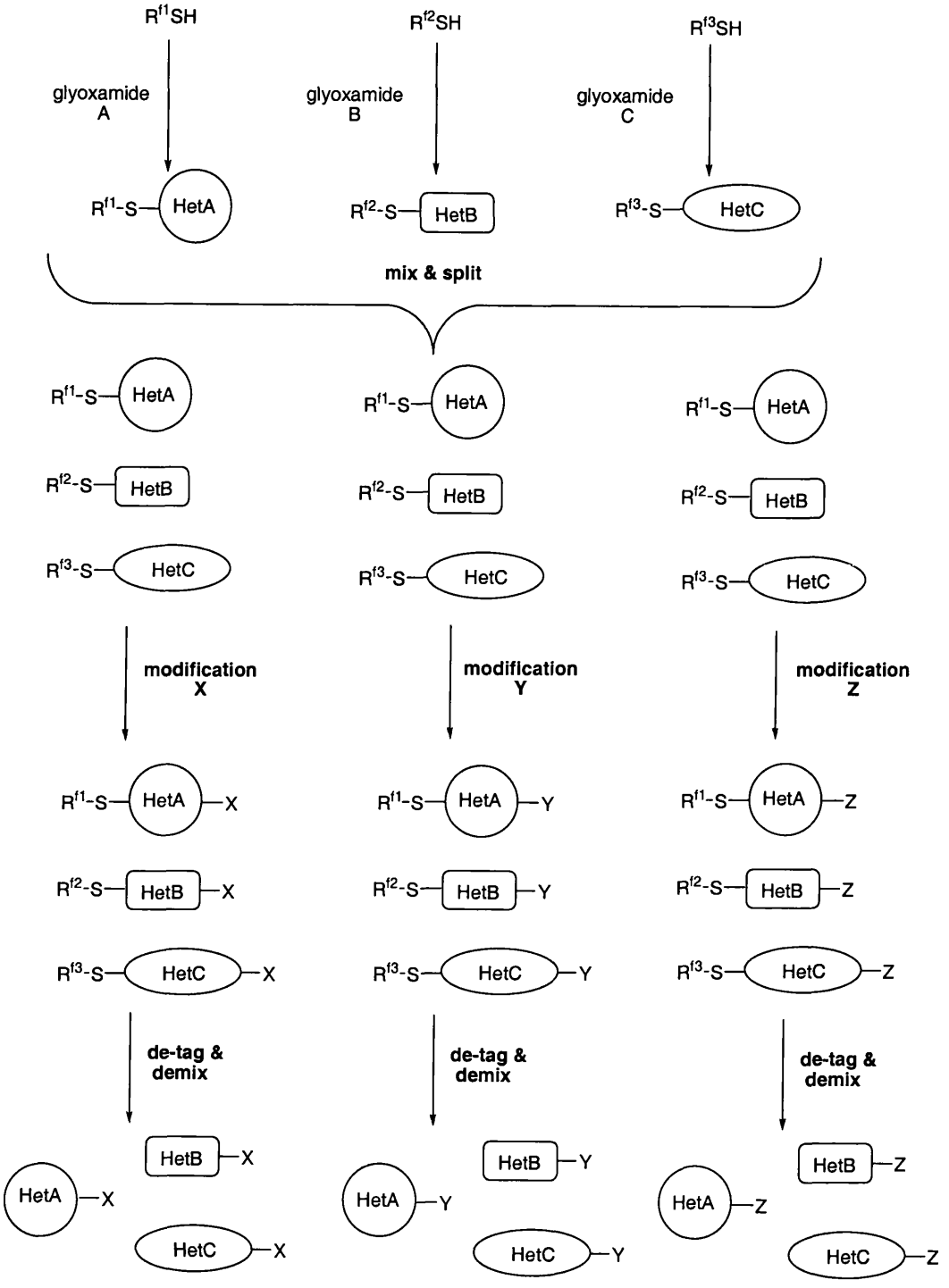
The basic outline for construction of the library is shown in scheme **3.28**. Seven different pyridinyl alcohols each bearing a different R_1 group were attached to seven different fluorous phase tags of varying fluorine content. After conversion to pyridones **561** these compounds were mixed and split into eight portions. Each of these portions was *N*-alkylated in parallel with eight different propargyl bromides. After alkylation, each portion was further split into ten portions and each portion was reacted in parallel with a ten different isonitriles. This gave eighty mixtures each containing seven different tagged heterocycles. The seven different tagged heterocycles in each mixture were separated from each other on the basis of the length of their fluorous phase tag using F-HPLC. Following separation by F-HPLC, de-tagging gave 560 different mappacine analogues in high purity.



scheme 3.28

As shown in scheme **3.29**, fluorous thiols of varying fluorine content can be added to different glyoxamides to give a range heterocycles with different fluorous tags incorporated. [Note that a range of fluorous thiols are commercially available.] The tagged heterocycles can be mixed together and split and each mixture exposed to different modification reactions. Each mixture of tagged products can then be de-mixed by F-HPLC and finally de-tagged to give a library of modified heterocycles.

It is easy to see how the simple fluorous mixture using our Pummerer cyclative capture approach shown in scheme **3.28** could be extended to make large libraries of *N*-heterocycles.


$R^{f1}SH$
$R^{f2}SH$
$R^{f3}SH$
glyoxamide A
glyoxamide B
glyoxamide C
R^{f1}-S— HetA
R^{f2}-S— HetB
R^{f3}-S— HetC
mix & split
modification X
modification Y
modification Z
—X
—Y
—Z
de-tag & demix

scheme 3.28

Chapter 4: Experimental Section

General considerations

All experiments were performed under an atmosphere of Ar or N_2, using anhydrous solvents unless otherwise stated. Reactions were carried out using oven dried glassware. THF was distilled from sodium/benzophenone, CH_2Cl_2 and $^iPrNH_2$ was distilled from CaH_2, NEt_3 was distilled from CaH_2 and stored over KOH under Ar/N_2. DMSO was distilled from CaH_2 and stored over molecular sieves and under Ar/N_2.

^1H NMR and ^{13}C NMR were recorded on a Fourier transform spectrometer, with chemical shift values being reported in ppm relative to residual chloroform ($\delta_H = 7.27$ or $\delta_C = 77.2$) as an internal standard unless otherwise stated. NMR signals were assigned using DEPT - 135, HMQC and COSY spectra. All coupling constants are reported in Hertz (Hz). Mass spectra were recorded at the University of Glasgow using a JEOL JMS-700. IR spectra were recorded using a JASCO FT/IR 410 spectrometer. Melting points were measured on a Kofler hot stage apparatus and are uncorrected.

Column chromatography was carried out using Fischer Matrex silica gel 60 and Fluoroflash silica. Macherey-Nagel aluminium backed plates, precoated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by UV or staining with alkali $KMnO_4$.

Solid phase reactions were carried out in round bottom flasks and were performed with gentle stirring. Commercially available Merrifield resin with a loading of 1.1 mmol/g [copoly(styrene-1% DVB), 200-400 mesh] was used. Solvents and soluble reagents were removed by water suction after transference of the reaction suspension into polypropylene bond elute® cartridges (25 ml or 50 ml fitted with a polyethylene porous disk). THF used for washing resin was distilled prior to use in order to remove the BHT stabiliser.

Calculation of the theoretical loading of resins was carried out according to the equation reported in the Advanced ChemTech catalogue 1998 p101 as shown below:

$$S(th) = \frac{S(s)}{1 + \left(\frac{S(s) \times Wt(add)}{1000}\right)}$$

S (th) - Theoretical substitution mmol / g

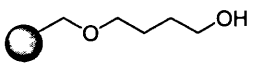
S (s) - Starting substitution mmol / g

Wt (add) - g/mol added to resin

General procedure for washing resin

After transferring the resin to a bond elute® cartridge, the resin was washed with the following solvents: H_2O, THF, THF: H_2O (3:1), THF: H_2O (3:1), THF: H_2O (1:3), THF, MeOH, CH_2Cl_2, MeOH and THF.

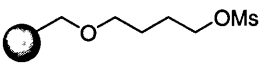
***O*-Merrifield bound 1,4-butanediol (343)** [21]



Merrifield resin (1.00 g, 1.10 mmol, 1 eq) was swollen in DMF (15 ml) for 15 min. 1,4-Butanediol (0.97 ml, 11.0 mmol, 10 eq) and NaH (132 mg, 5.50 mmol, 5 eq) were added to the suspension of resin and the reaction was allowed to stir overnight at room temperature. The resin was then washed using our standard washing protocol.

IR $\upsilon_{max}/(cm^{-1})$ 3436 (OH)

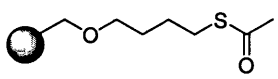
***O*-Merrifield bound methanesulfonic acid 4-hydroxy-butyl ester (344)**[21]



O-Merrifield bound 1,4-butanediol (300 mg, 0.32 mmol, 1 eq) was swollen in CH_2Cl_2 (4 ml) for 15 min. Methane sulfonyl chloride (0.12 ml, 1.59 mmol, 5 eq) and triethylamine (0.22 ml, 1.59 mmol, 5 eq) was added and the reaction allowed to stir at room temperature for 4 h. The resin was then washed using our standard washing protocol.

IR $\upsilon_{max}/(cm^{-1})$ 1355 (SO_2-O), 1172 (SO_2-O)

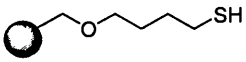
_O_-Merrifield bound _S_-(4-hydroxybutyl) thioacetate (345)



_O_-Merrifield bound methanesulfonic acid 4-hydroxy-butyl ester (300 mg, 0.294 mmol, 1 eq) was swollen in DMF (6 ml) for 15 min. Potassium thioacetate (67.2 mg, 0.59 mmol) was then added and the reaction was allowed to stir overnight at room temperature. The resin was then washed using our standard washing protocol.

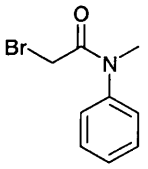
IR $\upsilon_{max}/(cm^{-1})$ 1689 (C=O)

_O_-Merrifield bound 4-mercaptobutanol (341)



_O_-Merrifield bound _S_-(4-hydroxybutyl) thioacetate (300 mg, 0.30 mmol, 1 eq) was swollen in THF for 15 min. $LiBH_4$ (0.3 ml of 2 M soln in THF, 0.60 mmol, 2 eq) was then added. The reaction was allowed to stir overnight at room temperature. The resin was then washed using our standard washing protocol.

2-Bromo-_N_-methyl-_N_-phenylacetamide (348)[88]



To a solution of _N_-methyl aniline (0.33 ml, 3.00 mmol, 1 eq) and NEt_3 (0.42 ml, 3.00 mmol, 1 eq) in CH_2Cl_2 (3.5 ml) at 0 °C was added by cannula, a solution of bromoacetyl bromide (0.26 ml, 3.00 mmol, 1 eq) in CH_2Cl_2 (5 ml). The reaction was allowed to stir at room temperature for 16 h. CH_2Cl_2 (10 ml) was then added to the reaction, the organic layer was washed with 0.5 M HCl (3 × 20 ml) and brine (3 × 20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated _in vacuo_, to give 2-bromo-_N_-methyl-

N-phenylacetamide **348** (0.60 g, 2.63 mmol, 88%) as a brown solid which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (3H, s, NC*H*$_3$), 3.65 (2H, s, C*H*$_2$Br), 7.22 (2H, d, J = 7.3 Hz, 2 × Ar*H*) and 7.31-7.41 (3H, m, 3 × Ar*H*).

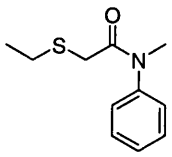
^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2 (*C*H$_2$Br), 38.5 (N*C*H$_3$), 127.4 (2 × Ar*C*H), 128.9 (Ar*C*H), 130.4 (2 × Ar*C*H), 143.5 (Ar*C*) and 166.9 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 3060, 2969, 1662 (C=O), 1594, 1496, 1382, 1226, 1118 and 701 (C-Br) .

MS *m/z* (FAB mode) 228 ($(M+H)^+$, 100%), 227 (20), 199 (5), 148 (17), 106 (11), 92 (3) and 69 (3).

$C_9H_{11}NOBr$ requires 228.0024, found 228.0023.

2-Ethylsulfanyl-*N*-methyl-*N*-phenylacetamide (349)



To a solution of 2-bromo-*N*-methyl-*N*-phenylacetamide **348** (70 mg, 0.31 mmol, 1 eq) in DMF (4 ml) was added NEt_3 (52 μl, 0.37 mmol, 1.2 eq) and ethanethiol (27 μl, 0.37 mmol, 1.2 eq). The reaction was allowed to stir at rt for 2 h. CH_2Cl_2 was added and the reaction was washed with water. The organic layer was then dried ($MgSO_4$), and concentrated *in vacuo* to give 2-ethylsulfanyl-*N*-methyl-*N*-phenyl-acetamide **349** as a yellow/orange oil (54 mg, 0.26 mmol, 84%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, t, J = 7.4 Hz, C*H*$_3$CH$_2$), 2.60 (2H, q, J = 7.4 Hz, CH$_3$C*H*$_2$), 2.99 (2H, s, CH$_2$CO), 3.22 (3H, s, NC*H*$_3$) and 7.18-7.29 (5H, m, 5 × Ar*H*).

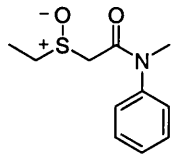
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (*C*H$_3$), 27.0 (*C*H$_2$), 33.2 (*C*H$_2$CO), 38.0 (N*C*H$_3$), 127.8 (2 × Ar*C*H), 128.4 (Ar*C*H), 130.2 (2 × Ar*C*H), 144.1 (Ar*C*) and 170.2 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 3060, 2965, 2927, 1655 (C=O), 1595 and 1117.

MS *m/z* (EI^+ mode) 209 (M^+, 11%), 149(100), 148(48), 134(22), 107(42), 77(37) and 58(13).

$C_{11}H_{15}NOS$ requires 209.0874, found 209.0873.

(±)-2-Ethylsulfinyl-*N*-methyl-*N*-phenylacetamide (350)



To a solution of 2-ethylsulfanyl-*N*-methyl-*N*-phenylacetamide **349** (40 mg, 0.19 mmol, 1 eq) in HFIP (2 ml) and CH_2Cl_2 (1ml) was added 30 % aqueous H_2O_2 (43 ml, 0.38 mmol, 2 eq). The reaction was allowed to stir at room temperature for 15 min. The reaction was then quenched with aqueous saturated Na_2SO_3 solution. The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-2-ethylsulfinyl-*N*-methyl-*N*-phenylacetamide **350** as an orange oil (39 mg, 0.18 mmol, 93%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, J = 7.5 Hz, CH_3CH_2), 2.71 (1H, m, 1H from CH_3CH_2) , 2.95 (1H, m, 1H from CH_3CH_2), 3.44 (1H, d, AB system, J = 13.9Hz, 1H from CH_2CO), 3.52 (1H, d, AB system, J = 13.9 Hz, 1H from CH_2CO), 3.24 (3H, s, NCH_3), 7.16-7.19 (2H, m, 3 × Ar*H*) and 7.30-7.41 (3H, m, 3 × Ar*H*).

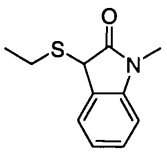
^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8 (CH_3), 37.9 (NCH_3), 46.7 (CH_3CH_2) 55.6 (CH_2CO), 127.7 (2 × Ar*C*H), 129.1 (Ar*C*H), 130.6 (2 × Ar*C*H), 143.1 (Ar*C*) and 164.7 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 3060, 2965, 2973, 2934, 2360, 1655 (C=O), 1594, 1117, 1020 (S=O).

MS *m/z* (CI+ mode) 226 ($(M+H)^+$, 57%), 200 (10), 169 (14), 149 (100), 148 (28), 120(25), 79 (39), 77 (17).

$C_{11}H_{15}NO_2S$ requires 225.0823, found 225.0824 (calculated for M^+ in EI+ mode).

(±)-1-Methyl-3-ethylsulfanyl-1,3-dihydro-indol-2-one (355)



To a solution of (±)-2-ethylsulfinyl-*N*-methyl-*N*-phenylacetamide **350** (50 mg, 0.22 mmol, 1 eq) in CCl_4 (3 ml) was added anhydrous *p*-TsOH (76 mg, 0.44 mmol, 2 eq). The reaction mixture was heated at reflux for 2 h. After cooling, CH_2Cl_2 (10 ml) was added and the organic layer was washed with water (3 × 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified using flash chromatography on silica gel using 40% ethyl acetate in petroleum ether as eluant to give (±)-1-methyl-3-ethylsulfanyl-1,3-dihydro-indol-2-one **355** (33 mg, 0.16 mmol, 71 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (3H, t, J = 7.4 Hz, C*H*$_3$CH$_2$), 2.50 (1H, m, 1H from CH$_3$C*H*$_2$) , 2.67 (1H, m, 1H from CH$_3$C*H*$_2$), 3.15 (3H, s, NC*H*$_3$), 4.23 (1H, s, C*H*CO), 6.75 (1H, d, J = 7.7 Hz, Ar*H*), 7.02 (1H, t, J = 7.4Hz, Ar*H*), 7.23 (1H, t, J = 7.7 Hz, Ar*H*), 7.31 (1H, d, J = 7.4 Hz, Ar*H*).

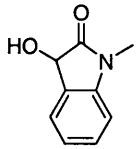
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (*C*H$_3$), 24.3 (CH$_3$*C*H$_2$) 26.8 (N*C*H$_3$), 45.0 (*C*HCO), 108.5 (Ar*C*H), 123.2 (Ar*C*H), 125.4 (Ar*C*H), 126.5 (Ar*C*), 129.3 (Ar*C*H), 144.4 (Ar*C*) and 175.9 (*C*=O).

IR υ_{max}/(cm^{-1}) 3055, 2964, 2927, 2871, 1718 (C=O), 1611, 1469, 1491 and 1371.

MS *m/z* (EI+ mode) 207 (M^+, 23%), 206 (23), 178 (18), 147 (100), 146 (55), 118 (15), 104 (15), 91(21), 83 (18), 65 (16) and 44 (21).

$C_{11}H_{13}NOS$ requires 207.0718, found 207.0717.

(±)-3-Hydroxy-1-methyl-1,3-dihydro-indol-2-one (356)[89]

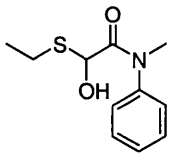


^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (3H, s, NC*H*$_3$), 4.99 (1H, s, C*H*OH), 6.76 (1H, d, J = 7.8 Hz, Ar*H*), 7.04 (1H, t, J = 7.6 Hz, Ar*H*), 7.27 (1H, t, J = 7.8 Hz, Ar*H*) and 7.39 (1H, d, J = 7.3 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6 (N*C*H$_3$), 70.2 (*C*HOH), 108.9 (Ar*C*H), 123.5 (Ar*C*H), 125.5 (Ar*C*H), 127.1 (Ar*C*), 130.3 (Ar*C*H), 144.3 (Ar*C*) and 177.0 (*C*=O).

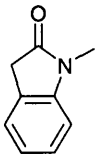
MS *m/z* (EI+ mode) 163 (M^+, 82%), 161(19), 146 (13), 134 (17), 118 (20), 106 (100), 77 (41), 63 (12), 77 (40) and 51 (21).

(±)-2-Ethylsulfanyl-2-hydroxy-*N*-methyl-*N*-phenylacetamide (357)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, t, J = 7.4 Hz, CH_3) 2.51-2.66 (2H, m, CH_2S) 3.21 (3H, s, NCH_3), 4.24 (1H, s, C*H*OH) and 7.25-7.45 (5H, m, 5 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (*C*H_3), 24.7 (CH_3*C*H_2), 38.1 (N*C*H_3), 49.3 (*C*HOH), 127.8 (2 x Ar*C*H), 128.7 (Ar*C*H), 130.2 (2 × Ar*C*H), 143.7 (Ar*C*) and 169 (C=O).
MS *m/z* (EI+ mode) 209 (M^+, 96%), 206 (21), 178 (10), 146 (80), 135 (100), 106 (18), 77 (20) and 45 (7).

1-Methyl-1,3-dihydro-indol-2-one (358)[65]



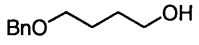
To a solution of 1-methyl-3-ethylsulfanyl-1,3-dihydro-indol-2-one **355** (26 mg, 0.13 mmol, 1 eq) in THF (1 ml) was added DMPU (0.32 ml, 2.64 mmol, 3 eq) and SmI_2 (0.1 M in THF, 6.7 ml, 0.67 mmol, 3 eq). The reaction was allowed to stir at room temperature for 1 h. The reaction was then quenched with H_2O (5 ml) and $NaHCO_3$ (5 ml) then extracted with ethyl acetate (3 × 10 ml). The organic layers were dried (Mg_2SO_4) and concentrated *in vacuo*. The crude product was purified using flash chromatography on silica gel using 30% ethyl acetate in petroleum ether as eluant to give 1-methyl-1,3-dihydro-indole-2-one **358** (24.6 mg, 0.17 mmol, 77%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (3H, s, NCH_3), 3.46 (2H, s, CH_2CO), 6.75 (1H, d, J = 7.8 Hz, Ar*H*), 6.97 (1H, t, J = 7.5 Hz, Ar*H*) and 7.17-7.24 (2H, m, 2 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1 (N*C*H_3), 34.7 (*C*H_2CO), 107.1 (Ar*C*H), 121.3 (Ar*C*H), 123.3 (Ar*C*H), 123.5 (Ar*C*), 126.9 (Ar*C*H) 144.2 (Ar*C*) and 174.0 (*C*=O).
IR υ_{max}/(cm^{-1}) 3058, 2942, 2919, 1700 (C=O), 1612, 1463, 1348 and 754

MS *m/z* (EI+ mode) 147 (M^+, 90%), 132 (10), 118 (100), 104 (7), 91 (20), 85 (24), 82 (38), 78 (16), 57 (12) and 47(11)

C_9H_9NO requires 147.0684, found 147.0684.

4-Benzyloxy-butan-1-ol (365) [90]



To a solution of butane-1,2-diol (2 ml, 22.6 mmol, 1 eq) in DMF (45 ml) at 0°C was added NaH (434 mg, 18.1 mmol, 0.8 eq). The mixture was allowed to stir at rt for 1 h. Benzyl bromide (2.15 ml, 18.1 mmol, 0.8 eq) was added and the reaction allowed to stir at rt for 22 h. H_2O (10 ml) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were washed with $NaHCO_3$ (3 × 20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil. The crude product was purified by flash chromatography using 50% ethyl acetate in petroleum ether as eluant to give 4-benzyloxy-butan-1-ol **365** as a clear oil (1.52 g, 7.96 mmol, 44%).

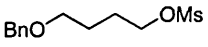
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.76 (4H, m, 2 × C*H*$_2$), 2.22 (1H, s, O*H*), 3.54 (2H, t, J = 6.0 Hz, C*H*$_2$O), 4.14 (2H, m, C*H*$_2$OH), 4.55 (2H, s, PhC*H*$_2$) and 7.28-7.36 (5H, m, 5 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1 (*C*H$_2$), 30.6 (*C*H$_2$), 63.2 (C*H*$_2$OH), 70.7 (*C*H$_2$O), 73.5 (*C*H$_2$Ph), 128.1 (2 × Ar*C*H), 128.8 (3 × Ar*C*H) and 138.5 (Ar*C*).

MS *m/z* (EI+ mode): 180 (M^+, 6%), 107 (65), 91 (100), 83 (21), 65 (17) and 43 (6).

$C_{11}H_{16}O_2$ requires 180.1150, found 180.1152.

Methanesulfonic acid 4-benzyloxy-butyl ester (366)[91]

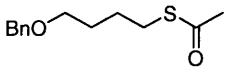


To a solution of 4-benzyloxy-butan-1-ol **365**(183 mg, 0.95 mmol, 1 eq) in CH_2Cl_2 (5 ml) was added NEt_3 (0.2 ml, 1.43 mmol, 1.5 eq) and methane sulfonyl chloride (0.11ml, 1.43 mmol, 1.5 eq). The reaction was allowed to stir at rt overnight. The reaction was then quenched with $NaHCO_3$ (5 ml) and the aqueous layer extracted with CH_2Cl_2 (3 × 5 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give

methanesulfonic acid 4-benzyloxy-butyl ester **366** as a yellow oil (245 mg, 0.95 mmol, 100%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.69 (2H, m, C*H*$_2$), 1.77-1.84 (2H, m, C*H*$_2$) 2.90 (3H, s, C*H*$_3$SO$_2$), 3.45 (2H, t, J 6.1 Hz, CH_2OMs), 4.19 (2H, t, J 6.4 Hz, CH_2O), 4.43 (2H, s, PhC*H*$_2$) and 7.20-7.31 (5H, m, 5 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (*C*H$_2$), 26.6 (*C*H$_2$), 37.7 (*C*H$_3$SO$_2$), 69.7 (*C*H$_2$OMs), 70.3 (*C*H$_2$O), 73.4 (*C*H$_2$Ph), 128.1 (3 × Ar*C*H), 128.8 (2 × Ar*C*H) and 138.7 (Ar*C*).
IR $\upsilon_{max}/(cm^{-1})$ 3029, 2938, 2859, 1454, 1353 (SO_2O), 1174 (SO_2O), 941, 740.
MS *m/z* (EI+ mode) 258 (M^+, 6%), 161 (20), 91 (100), 84 (17) and 55 (11).
$C_{12}H_{18}O_4S$ requires 258.0926, found 258.0927.

Thioacetic acid-*S*-(4-benzyloxybutyl) ester (367)

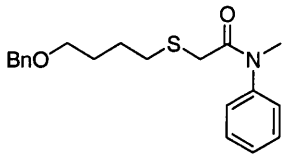


To a solution of methanesulfonic acid 4-benzyloxy-butyl ester **366** (245 mg, 0.95 mmol, 1 eq) in DMF (10 ml) was added potassium thioacetate (163 mg, 1.43 mmol, 1.5 eq). The reaction was allowed to stir at rt for 20 h. H_2O (8 ml) was added to the reaction mixture and the reaction mixture was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were washed with $NaHCO_3$ (3 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The crude product was purified by filtration through a pad of silica gel using 30 % ethyl acetate in petroleum ether as eluant to give thioacetic acid-S-(4-benzyloxybutyl) ester **367** (210 mg, 0.88 mmol, 93 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57-1.65 (4H, m, 2 × C*H*$_2$), 2.25 (3H, s, C*H*$_3$CO), 2.81 (2H, t, J = 5.9 Hz, C*H*$_2$), 3.40 (2H, t, J = 5.9 Hz, C*H*$_2$), 4.42 (2H, s, PhC*H*$_2$), 7.20-7.29 (5H, m, 5 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 26.76 (*C*H$_2$), 29.2 (*C*H$_2$), 29.3 (*C*H$_2$), 31.0 (*C*H$_3$CO), 70.0 (*C*H$_2$), 73.2 (Ph*C*H$_2$), 127.9 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 138.9 (Ar*C*), 196.3 (*C*=O).
IR $\upsilon_{max}/(cm^{-1})$ 3029, 2856, 1691 (C=O), 1454, 1355, 1105, 1027, 956.
MS (EI^+ mode): 238 (M^+, 24 %), 195 (13), 132 (30), 91 (100).

$C_{13}H_{18}O_2S$ requires 238.1028, found 238.1028.

2-(4-Benzyloxy-butylsulfanyl)-*N*-methyl-*N*-phenylacetamide (368)



To a solution of thioacetic acid-*S*-(4-benzyloxybutyl) ester **367** (153 mg, 0.64 mmol, 1 eq) in THF (7.5 ml) was added $LiAlH_4$ (49 mg, 0.32 mmol, 2 eq). The reaction was allowed to stir at rt overnight then quenched with acetone (5 ml). The organic layer was washed with water (3 × 8 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was immediately placed under an argon atmosphere then dissolved in DMF (14 ml) and NEt_3 (90 µl, 0.64 mmol, 1 eq). 2-Bromo-*N*-methyl-*N*-phenylacetamide (160 mg, 0.70 mmol, 1.1 eq) was added and the reaction was allowed to stir at rt for 12 h. CH_2Cl_2 was added and the reaction mixture was then washed with water (3 × 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5% ethyl acetate in dichloroethane as eluant to give 2-(4-benzyloxy-butylsulfanyl)-*N*-methyl-*N*-phenyl-acetamide **368** (137 mg, 0.40 mmol, 63%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.62 (4H, m, 2 × C*H*$_2$), 2.58 (2H, t, J = 6.8 Hz, C*H*$_2$S), 2.97 (2H, s, C*H*$_2$CO), 3.21 (3H, s, NC*H*$_3$), 3.38 (2H, t, J = 6.0, C*H*$_2$O), 4.41 (2H, s, PhC*H*$_2$O), 7.06-7.39 (10H, m, Ar*H*).

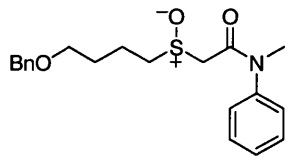
^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3 (*C*H$_2$), 29.2 (*C*H$_2$), 32.7 (*C*H$_2$S), 33.5 (*C*H$_2$CO), 38.0 (NC*H*$_3$), 70.1 (*C*H$_2$O), 73.3 (*C*H$_2$Ph), 127.6 (ArCH), 127.8 (2 × ArC*H*), 127.9 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 130.1 (2 × Ar*C*H), 130.6 (Ar*C*H), 139.0 (Ar*C*), 144.1 (Ar*C*N), 160.6 (C=O).

IR υ_{max}/(cm^{-1}) 2935, 2856, 1654 (C=O), 1594, 1373,1114.

MS *m/z* (EI+ mode) 343 (M$^+$, 25%), 252 (15), 195 (13), 149 (100), 148 (85), 134 (35), 120 (24), 107 (52), 92 (100), 91 (100), 77 (38), 65 (12).

$C_{20}H_{25}NO_2S$ requires 343.1606, found 343.1603 .

(±)-2-(4-Benzyloxy-butylsulfinyl)-*N*-methyl-*N*-phenyl-acetamide (369)



To a solution of 2-(4-benzyloxy-butylsulfanyl)-*N*-methyl-*N*-phenylacetamide **368** (27 mg, 0.08 mmol, 1 eq) in HFIP (2 ml) and CH_2Cl_2 (1 ml) was added 30 % aqueous H_2O_2 (16.5 µl, 0.16 mmol, 2 eq). The reaction was allowed to stir at rt for 2 h. The reaction was then quenched with saturated aqueous Na_2SO_3 and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-2-(4-benzyloxybutylsulfinyl)-*N*-methyl-*N*-phenylacetamide **369** (22 mg, 0.06 mmol, 75 %) as a clear oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.75 (2H, m, C*H*$_2$), 1.75-1.83 (2H, m, C*H*$_2$), 2.69-2.76 (1H, m, 1H from C*H*$_2$SO), 2.89-2.98 (1H, m, 1H from C*H*$_2$SO), 3.23 (3H, s, NC*H*$_3$), 3.34-3.53 (4H, m, C*H*$_2$CO and C*H*$_2$O) 4.42 (2H, s, PhC*H*$_2$), 7.14-7.40 (10H, m, Ar*H*).

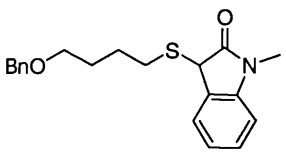
^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5 (*C*H$_2$), 27.8 (*C*H$_2$), 36.5 (N*C*H$_3$), 51.9 (*C*H$_2$S), 55.0 (*C*H$_2$CO), 68.5 (*C*H$_2$O), 72.0 (Ph*C*H$_2$), 126.3 (2 × Ar*C*H), 126.6 (Ar*C*H), 126.6 (2 × ArCH), 127.4 (2 × Ar*C*H), 127.7 (Ar*C*H), 129.2 (2 × Ar*C*H), 137.3 (Ar*C*), 141.7 (Ar*C*), 163.3 (*C*=O).

IR υ_{max}/(cm^{-1}) 2935, 2861, 1650 (C=O), 1594, 1376, 1112, 1027 (S=O).

MS *m/z* (FAB$^+$/NOBA mode): 360 ((M+H)$^+$, 19%), 281 (9), 147 (36), 73 (100).

$C_{20}H_{26}NO_3S$ requires 360.1633, found 360.1632.

(±)-3-(4-Benzyloxy-butylsulfanyl)- 1-methyl-1,3-dihydro-indol-2-one (370)



To a solution of (±)-2-(4-benzyloxy-butylsulfinyl)-*N*-methyl-*N*-phenylacetamide **369** (63.3 mg, 0.18 mmol, 1 eq) in 1,2-dichloroethane (4 ml) was added TFAA (0.15 ml, 1.08 mmol , 6 eq). The reaction was allowed to stir at room temperature for 10 min. BF_3 Et_2O (0.19 ml, 1.52 mmol, 4 eq) was then added and the reaction was allowed to stir for 1 h. The reaction was then quenched with 1 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified using flash chromatography on silica gel using 40% ethyl acetate in petroleum ether as eluant to give (±)-3-(4-benzyloxybutylsulfanyl)-1-methyl-1,3-dihydro-indol-2-one **370** (46 mg, 0.14 mmol, 75%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43-1.65 (4H, m, 2 × C*H*$_2$), 2.44-2.50 (1H, m, 1H from C*H*$_2$S), 2.66-2.73 (1H, m, 1H from C*H*$_2$S), 3.14 (3H, s, NCH_3), 3.37 (2H, t, J = 5.2 Hz, C*H*$_2$O), 4.22 (1H, s, C*H*S), 4.40 (2H, s, PhC*H*$_2$), 6.74 (1H, d, J = 7.8 Hz, Ar*H*), 7.00 (1H, t, J = 7.5 Hz, Ar*H*), 7.20-7.31 (7H, m, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2 (*C*H$_2$), 26.8 (N*C*H$_3$), 29.2 (C*H*$_2$), 29.9 (*C*H$_2$S), 45.0 (*C*HS), 70.1 (*C*H$_2$O), 73.2 (Ph*C*H$_2$), 108.6 (Ar*C*H), 123.3 (Ar*C*H), 125.4 (Ar*C*H) 126.4 (Ar*C*), 127.9 (Ar*C*H), 128.0 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 129.4 (Ar*C*H), 139.0 (Ar*C*), 144.0 (ArC), 176.0 (*C*=O).

IR υ_{max}/(cm^{-1}) 2935, 2857, 1716 (C=O), 1612, 1371, 1087.

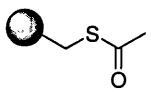
MS *m/z* (EI+ mode) 341 (M^+, 24%), 250 (9), 178 (29), 162 (33), 147 (100), 146 (85), 118 (14), 91 (89), 89 (14), 65 (10).

$C_{20}H_{23}O_2S$ requires 341.1449, found 341.1451.

Preparation of benzyl thiol resin

Method 1: Thioacetate route

***S*-Merrifield bound thioacetic acid (371)**[13]

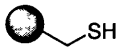


Merrifield resin (1.00 g, 1.1 mmol/g, 1.1 mmol, 1 eq) was swollen in DMF (10 ml) for 15 min. Potassium thioacetate (377 mg, 3.3 mmol, 3 eq) was added and the reaction was

allowed to stir at rt for 24 h. The resin was then washed using our standard washing protocol. The product resin **371** was then dried *in vacuo*.

IR $\upsilon_{max}/(cm^{-1})$ 1687 (C=O).

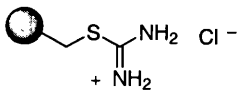
Benzyl thiol resin (342)[13]



S-Merrifield bound thioacetic acid **371**(1.05 g, 1.06 mmol / g, 1.11 mmol, 1 eq) was swollen in THF (10 ml). $LiBH_4$ (120 mg, 5.55 mmol, 5 eq) was added. The reaction was allowed to stir at rt for 20 h. The resin was then washed using our standard washing protocol. The product resin **342** was then dried *in vacuo*. Disappearance of the IR C=O stretch at 1687 cm^{-1} was observed.

Method 2: thiourea route

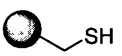
***S*-Merrifield bound isothiouronium chloride (372)**



Merrifield resin (1.00 g, 1.1 mmol / g, 1.1 mmol, 1 eq) was swollen in DMF (10 ml) for 15 min. Thiourea (419 mg, 5.5 mmol, 5 eq) was added and the reaction was heated at 60 °C for 24 h. The resin was then washed using our standard washing protocol. The product resin **372** was then dried *in vacuo*.

IR $\upsilon_{max}/(cm^{-1})$ 1648(C=N).

Benzyl thiol resin (342)



S-Merrifield bound isothiouronium chloride **372** (1.07 g, 1.02 mmol / g, 1.09 mmol, 1 eq) was swollen in DMF (10 ml). *n*-Butylamine (0.28 ml, 5.45 mmol, 5 eq) was added and the

reaction was heated at 60 °C for 18 h. The resin was then washed using our standard washing protocol. The product resin **342** was then dried *in vacuo*.
Upon IR analysis, disappearance of the C=N stretch was observed.

_S_-Merrifield bound 2-mercapto-_N_-methyl-_N_-phenylacetamide (373)

Benzyl thiol resin **342** (410 mg, 1.11 mmol/g theoretical loading based on loading of Merrifield resin, 0.46 mmol, 1 eq) was swollen in DMF (5 ml) for 15 min. NEt_3 (0.14 ml, 1.40 mmol, 3 eq) and 2-bromo-*N*-methyl-*N*-phenyl acetamide **348** (319 mg, 1.40 mmol, 3 eq) were then added and the reaction was allowed to stir at rt for 18 h. The resin was then washed using our standard washing protocol. The product resin **373** was then dried *in vacuo*.
IR $\upsilon_{max}/(cm^{-1})$ (C=O) 1654 cm^{-1}

Determination of the loading of benzyl thiol resin prepared via method 1

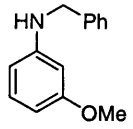
S-Merrifield bound 2-mercapto-*N*-methyl-*N*-phenylacetamide **373** (420 mg, 0.97 mmol/g (theoretical loading), 0.41 mmol, 1 eq) which was derived from benzyl thiol resin **342** prepared using the thioacetate method was swollen in THF (4 ml). DMPU (0.40 ml, 3.30 mmol, 8 eq) and a solution of SmI_2 (8 ml, 0.1 M sol in THF, 0.8 mmol, 2 eq) was added and the reaction allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated, before filtration through a short plug of silica washing with 40 % ethyl acetate in petroleum ether to give *N*-methyl-*N*-phenyl acetamide **362** (33 mg, 0.22 mmol, 53 %)
Loading of the *S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-phenylacetamide was therefore approximately 0.52 mmol /g. Loading of the benzyl thiol resin prepared via the thioacetate route was 0.56 mmol / g.

Determination of the loading of benzyl thiol resin prepared via method 2

Cleavage of *S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-phenylacetamide **373** which was derived from benzyl thiol resin prepared using the thiourea method was carried out according to the previous procedure. Loading of *S*-Merrifield bound 2-mercapto-*N*-methyl-

N-phenylacetamide **362** was approximatley 0.56 mmol / g. Loading of benzyl thiol resin prepared via the thiourea route was therefore 0.61 mmol / g.

_N_-Benzyl-3-methoxyaniline (376)[92]



To a neat mixture of *m*-methoxy aniline **374** (0.70 ml, 6.20 mmol, 1 eq) and benzaldehyde **375** (0.75 ml, 7.4 mmol, 1.2 eq) was added $Ti(O^iPr)_4$ (2.7 ml, 9.3 mmol, 1.5 eq). The reaction was heated at 80 °C for 18 h. The reaction was allowed to cool to rt, MeOH (6 ml) was added and the reaction was further cooled to 0 °C. $NaBH_4$ (235 mg, 6.2 mmol, 1 eq) was then added and the reaction was allowed to stir at rt for 5 h. Water was added and the organic layer was extracted with CH_2Cl_2 (× 3). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-benzyl-3-methoxyaniline **376** (1.23 g, 5.77 mmol, 93 %) as an orange oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s, C*H*$_3$O), 4.04 (1H, s, N*H*), 4.24 (2H, s, PhC*H*$_2$), 6.12 (1H, m, Ar*H*), 6.20 (2H, m, 2 × Ar*H*), 7.00 (1H, t, J = 8.1 Hz, Ar*H*), 7.18-7.34 (5H, m, 5 × Ar*H*).

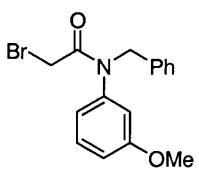
^{13}C NMR (100 MHz, $CDCl_3$) δ 48.7 (Ph*C*H$_2$), 55.5 (CH_3O), 99.3 (Ar*C*H), 103.1 (Ar*C*H), 106.4 (Ar*C*H), 128.1 (Ar*C*H), 128.3 (2 × Ar*C*H), 129.0 (2 × Ar*C*H), 130.4 (Ar*C*H), 139.7 (ArC), 150.0 (Ar*C*), 161.2 (Ar*C*).

IR υ_{max}/(cm^{-1}) 3409 (NH), 3025, 2931, 2832, 1612, 1509, 1494, 1452.

MS *m/z* (EI$^+$ mode) 213 (M$^+$, 95%), 136 (21), 91 (100), 84 (25), 65 (14).

$C_{14}H_{15}NO$ requires 213.1154, found 213.1153.

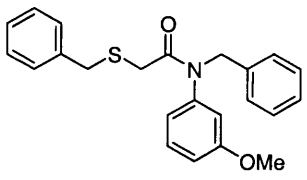
_N_-Benzyl-2-bromo-_N_-(3-methoxy-phenyl) acetamide (377)



To a solution of *N*-benzyl-3-methoxyaniline **376** (878 mg, 4.12 mmol, 1 eq) and NEt_3 (0.87 ml, 6.20 mmol, 1.5 eq) in CH_2Cl_2 (30 ml) at 0°C was added bromoacetyl bromide (0.54 ml, 6.20 mmol, 1.5 eq). The reaction was allowed to stir at rt for 7 h. The reaction mixture was then washed with 0.5 M HCl (3 × 20 ml) and brine (3 × 20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-benzyl-2-bromo-*N*-(3-methoxy-phenyl) acetamide **377** (1.34 g, 4.09 mmol, 99 %) as a brown oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (2H, s, C*H*$_2$CO), 3.65 (3H, s, C*H*$_3$O), 4.81 (2H, s, PhC*H*$_2$), 6.49 (1H, apparent triplet, J = 2.1 Hz, Ar*H*), 6.57 (1H, d, J= 7.8 Hz, Ar*H*), 6.81 (1H, dd, J= 8.3, 2.2 Hz, Ar*H*), 7.12- 7.23 (6H, m, Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7 (*C*H$_2$CO), 54.0 (Ph*C*H$_2$), 55.7 (*C*H$_3$O), 114.1 (Ar*C*H), 114.8 (Ar*C*H), 120.6 (Ar*C*H), 128.1 (Ar*C*H), 128.8 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 130.8 (Ar*C*H), 137.1 (Ar*C*), 142.6 (Ar*C*), 160.7 (Ar*C*O), 166.8 (*C*=O).
IR υ_{max}/(cm^{-1}) 3029, 1662 (C=O), 1600, 148, 1286.
MS *m/z* (EI$^+$ mode) 333 (M$^+$, 5%), 254 (82), 212 (12), 150 (80), 91 (100), 65 (12).
$C_{16}H_{16}NO_2Br$ requires 333.0364, found 333.0361.

N-Benzyl-2-benzylsulfanyl-N-(3-methoxy-phenyl)-acetamide (379)



To a solution of *N*-benzyl-2-bromo-*N*-(3-methoxyphenyl) acetamide **377** (300 mg, 0.90 mmol, 1 eq) in DMF (4ml) was added NEt_3 (0.13 ml, 0.90 mmol, 1 eq) and benzyl thiol **378** (0.11 ml, 0.90 mmol, 1 eq). The reaction was allowed to stir at rt for 4.5 h. CH_2Cl_2 (10 ml) was added and the organic layer was washed with water (3 × 10 ml) and $NaHCO_3$ (3 × 10ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified using flash chromatography on silica gel using 30% ethyl acetate in petroleum ether as eluant to give *N*-benzyl-2-benzyl sulfanyl-*N*-(3-methoxyphenyl)-acetamide **379** (160 mg, 0.44 mmol, 49%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (2H, s, CH_2CO), 3.60 (3H, s, CH_3O), 3.82 (2H, s, $PhCH_2S$), 4.80 (2H, s, $PhCH_2$), 6.43 (1H, d, J = 2.3 Hz, Ar*H*), 6.49 (1H, d, J = 7.8 Hz, Ar*H*), 6.73 (1H, dd, J = 8.3, 2.3 Hz, Ar*H*), 7.09-7.25 (11H, m, 11 × Ar*H*)

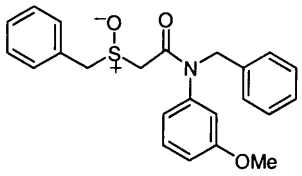
^{13}C NMR (100 MHz, $CDCl_3$) δ 32.5 (CH_2), 36.7 (CH_2), 53.5 ($PhCH_2$), 55.7 (CH_3O), 114.4 (Ar*C*H), 120.9 (Ar*C*H), 127.4 (Ar*C*H), 127.8 (Ar*C*H), 128.8 (4 × Ar*C*H), 129.1 (2 × Ar*C*H), 129.6 (2 × Ar*C*H), 130.5 (Ar*C*H), 137.7 (Ar*C*), 138.1 (Ar*C*), 143.3 (Ar*C*), 160.6 (Ar*C*O), 169.7 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 3060, 3027, 2937, 1650 (C=O), 1600, 1488, 1390.

MS *m/z* (EI^+ mode) 377 (M^+, 8%), 255 (62), 213 (16), 164 (5), 122 (10), 91 (100), 65 (10).

$C_{23}H_{23}NO_2S$ requires 377.1449, found 377.1451.

(±)-*N*-Benzyl-2-benzylsulfinyl-*N*-(3-methoxyphenyl) acetamide (380)



To a solution of *N*-benzyl-2-benzylsulfanyl-*N*-(3-methoxy-phenyl) acetamide **379** (126 mg, 0.34 mmol, 1 eq) in HFIP:CH_2Cl_2 (4ml:2ml) was added 30 % aqueous H_2O_2 (0.15 ml, 1.36 mmol, 4 eq) and the reaction allowed to stir at rt for 1 h. The reaction was then quenched with aqueous saturated Na_2SO_3 solution. The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-*N*-benzyl-2-benzylsulfinyl-*N*-(3-methoxyphenyl) acetamide **380** as a yellow oil (122 mg, 0.31 mmol, 92 %) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (1H, d, AB system, J = 14.6 Hz, 1H from $PhCH_2S$), 3.35 (1H, d, AB system, J = 14.6 Hz, 1H from $PhCH_2S$), 3.59 (3H, s, OCH_3), 4.05 (1H, d, AB system, 13.0 Hz, 1H from CH_2CO), 4.24 (1H, d, AB system, 13.0 Hz, 1H from CH_2CO), 4.75 (1H, d, AB system, J = 14.2 Hz, 1H from $PhCH_2N$), 4.85 (1H, d, AB system, J = 14.2 Hz, 1H from $PhCH_2N$), 6.33 (1H, apparent triplet, J = 2.2 Hz, Ar*H*), 6.43 (1H, dd, J= 7.8, 1.0 Hz, ArH), 6.73-6.76 (1H, multiplet, Ar*H*), 7.08 – 7.30 (11H, m, 11 × ArH).

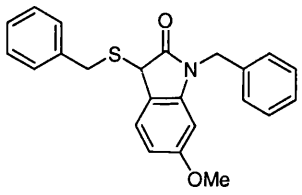
^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0 (Ph*C*H_2S), 52.7 (*C*H_2CO), 54.4 (O*C*H_3), 56.4 (Ph*C*H_2N), 112.9 (Ar*C*H), 113.5 (Ar*C*H), 119.3 (Ar*C*H), 126.7 (Ar*C*H), 127.3 (Ar*C*H), 127.5 (2 × Ar*C*H), 127.7 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 128.5 (Ar*C*), 129.5 (3 × Ar*C*H), 135.5 (Ar*C*), 140.8 (Ar*C*), 159.5 (Ar*C*O), 163.4 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 3060, 3029, 2919, 1644 (C=O), 1587, 1488, 1402, 1164.

MS *m/z* (EI^+ mode) 393 (M^+, 10%), 255 (16), 212 (6), 91 (100), 83 (24), 65 (7).

$C_{23}H_{23}NO_3S$ requires 393.1399, found 393.1400.

(±)-1-Benzyl-3-benzylsulfanyl-6-methoxy-1,3-dihydro-indol-2-one (381)



To a solution of (±)-*N*-benzyl-2-benzylsulfinyl-*N*-(3-methoxyphenyl) acetamide **380** (41.2 mg, 0.11 mmol, 1 eq) in 1,2-dichloroethane (4ml) was added TFAA (93 μl, 0.66 ml, 6 eq) and the reaction allowed to stir at rt for 2 h. The reaction was quenched with 5 % NaOH solution (5 ml) and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 (× 2) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified using flash chromatography on silica gel (20% ethyl acetate in petroleum ether) to give (±)-1-benzyl-3-benzylsulfanyl-6-methoxy-1,3-dihydro-indol-2-one **381** (26 mg, 0.07 mmol, 63%) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (3H, s, C*H*$_3$O), 3.68-3.72 (1H, m, 1H from PhC*H*$_2$), 4.04 -4.16 (2H, m, 1H from PhC*H*$_2$ and C*H*S), 4.75 (2H, s, PhC*H*$_2$N), 6.19 (1H, d, J = 2.2 Hz, Ar*H*), 6.42 (1H, dd, J = 2.2, 8.2 Hz, Ar*H*), 7.08 (1H, d, J = 8.2 Hz, Ar*H*), 7.14-7.32 (10H, m, 10 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 34.7 (Ph*C*H_2S), 43.2 (*C*HS), 44.3 (Ph*C*H_2N), 55.8 (*C*H_3O), 97.7 (Ar*C*H), 106.9 (Ar*C*H), 117.5 (Ar*C*), 126.2 (Ar*C*H), 127.6 (Ar*C*H), 127.7 (2 × Ar*C*H), 128.1 (Ar*C*H), 128.7 (2 × Ar*C*H), 129.2 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 136.0 (Ar*C*), 137.8 (Ar*C*), 144.9 (Ar*C*), 161.0 (Ar*C*O), 176.8 (*C*=O).

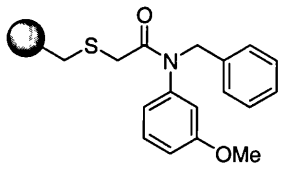
IR $\upsilon_{max}/(cm^{-1})$ 2915, 2838, 1720 (C=O), 1621, 1496, 1373, 1164.

MS *m/z* (EI^+ mode) 375 (M^+, 5%), 253 (100), 252 (82), 162 (5), 91 (85), 65 (7).

$C_{23}H_{21}NO_2S$ requires 375.1293, found 375.1292.

General procedure A: The immobilisation of α-bromo acetamides onto benzyl thiol resin

***S*-Merrifield bound *N*-benzyl-2-mercapto-*N*-(3-methoxyphenyl) acetamide (383)**

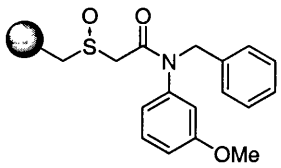


Benzyl thiol resin **342** (617 mg, 0.56 mmol / g, 0.35 mmol, 1 eq) was swollen in DMF (5 ml) for 15 mins and NEt_3 (0.22 ml, 1.56 mmol, 4.6 eq) added. A solution of *N*-benzyl-2-bromo-*N*-(3-methoxyphenyl) acetamide **377** (520 mg, 1.56 mmol, 4.6 eq) in DMF (3 ml) was then added by cannula. The reaction was allowed to stir at rt for 18 h. The resin was then washed using our standard washing protocol. The product resin **383** was then dried *in vacuo*.

IR $\upsilon_{max}/(cm^{-1})$ 1650 (C=O).

General procedure B: Oxidation of resin bound sulfides to sulfoxides

***S*-Merrifield bound *N*-benzyl-*N*-(3-methoxyphenyl)-2-sulfinyl acetamide (384)**

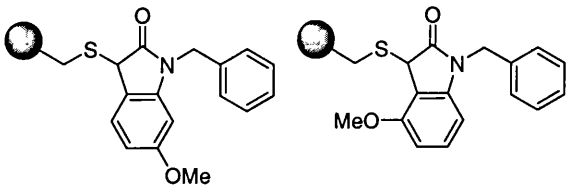


S-Merrifield bound *N*-benzyl-2-mercapto-*N*-(3-methoxyphenyl) acetamide **383** (716 mg, 0.49 mmol/g, 0.35 mmol, 1 eq) was swollen in HFIP (4 ml) and CH_2Cl_2 (2ml). 30% aqueous H_2O_2 (0.26 ml, 2.28 mmol, 6.5 eq) was then added and the reaction allowed to stir at rt overnight. The resin was then washed using our standard washing protocol. The product resin **384** was then dried *in vacuo*.

IR $\upsilon_{max}/ (cm^{-1})$ 1670 (C=O).

General procedure C: Pummerer cyclisation of electron rich aromatic systems

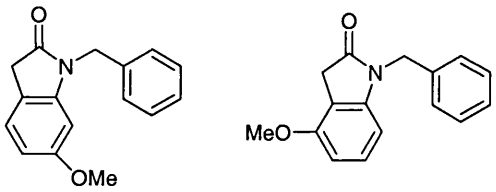
***S*-Merrifield bound 1-benzyl-3-mercapto-6-methoxy-1,3-dihydro-indol-2-one and *S*-Merrifield bound 1-benzyl-3-mercapto-4-methoxy-1,3-dihydro-indol-2-one (385)**



S-Merrifield bound *N*-benzyl-*N*-(3-methoxyphenyl)-2-sulfinyl acetamide **(384)** (671 mg, 0.49 mmol/g, 0.33 mmol, 1 eq) was swollen in 1,2-dichloroethane (6 ml) for 15 mins. Trifluoroacetic anhydride (0.75 ml, 5.3 mmol, 16 eq) was then added and the reaction was allowed to stir at rt for 18 h. The resin was then washed using our standard washing protocol. The product resin **385** was then dried *in vacuo*.

IR $\upsilon_{max}/(cm^{-1})$ 1714 (C=O).

1-Benzyl-6-methoxy-1,3-dihydro-indol-2-one (382) and 1-Benzyl-4-methoxy-1,3-dihydro-indol-2-one (414)



S-Merrifield bound 1-benzyl-3-mercapto-6-methoxy-1,3-dihydro-indol-2-one and *S*-Merrifield bound 1-benzyl-3-mercapto-4-methoxy-1,3-dihydro-indol-2-one **385** (598 mg, 0.49 mmol /g, 0.29 mmol, 1 eq) were swollen in THF (5 ml) for 15 min. DMPU (0.58 ml, 4.8 mmol, 16.5 eq) and a solution of SmI_2 (12.0 ml of 0.1 M, 1.20 mmol, 4.1 eq) were added and the reaction was allowed to stir at rt for 15 h. The resin was filtered and the solution phase was collected and concentrated before filtration through a short plug of silica washing with 30 % ethyl acetate in petroleum ether to give 1-benzyl-6-methoxy-1,3-dihydro-indol-2-one **382** and 1-benzyl-4-methoxy-1,3-dihydro-indol-2-one **414** (27.7 mg,

0.11 mmol, 38 % as a 9:1 mixture of regioisomers (by NMR). (Yield is calculated over 4 solid phase steps based on thiol resin loading of 0.48 mmol/g) as a clear oil.

The regioisomers were separated by flash chromatography using 20 % ethyl acetate in petroleum ether as eluant. 1-Benzyl-6-methoxy-1,3-dihydro-indol-2-one **382** was the major regioisomer.

For major isomer **382**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (2H, s, CH_2CO), 3.65 (3H, s, CH_3O), 4.82 (2H, s, PhCH_2) 6.25 (1H, d, J= 2.3 Hz, Ar*H*), 6.43 (1H, dd, J= 8.2, 2.3 Hz, Ar*H*), 7.05 (1H, d, J = 8.2 Hz, Ar*H*), 7.16-7.26 (5H, m, 5 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5 (*C*H_2CO) 44.2 (Ph*C*H_2), 55.8 (*C*H_3O), 97.7 (Ar*C*H), 106.4 (Ar*C*H), 116.8 (Ar*C*), 125.2 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.0 (Ar*C*H), 129.2 (2 × Ar*C*H), 136.2 (Ar*C*), 145.9 (Ar*C*), 160.2 (Ar*C*O), 176.3 (*C*=O).

IR υ_{max}/(cm^{-1}) 3002, 2937, 1700 (C=O), 1623, 1594,1496.

MS *m/z* (EI$^+$ mode) 253 (M^+, 97%), 224 (8), 162 (144), 149 (13), 91 (100), 83 (18), 57 (10).

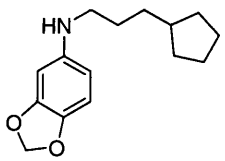
$C_{16}H_{15}NO_2$ requires 253.1103, found 253.1103.

For minor isomer **414**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (2H, s, CH_2CO), 3.78 (3H, s, CH_3O), 4.82 (2H, s, PhCH_2), 6.32 (1H, d, J= 7.8 Hz, Ar*H*), 6.51 (1H, d, J = 8.1 Hz, Ar*H*), 7.07 (1H, apparent t, J = 8.1 Hz, Ar*H*), 7.16-7.26 (5H, m, 5 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9 (*C*H_2CO) 44.3 (Ph*C*H_2), 55.8 (*C*H_3O), 102.9 (Ar*C*H), 105.8 (Ar*C*H), 111.4 (Ar*C*), 127.8 (2 × Ar*C*H), 127.9 (Ar*C*H), 129.1 (2 × Ar*C*H), 129.5 (Ar*C*H) 136.5 (Ar*C*), 145.9 (Ar*C*), 155.8 (Ar*C*O), 175.9 (*C*=O).

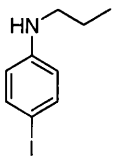
Benzo[1,3]dioxol-5-yl-(3-cyclopentyl-propyl)-amine (388)



To a solution of 3,4-(methylenedioxy) aniline **386** (1.72 g, 12.5 mmol, 1 eq) in CH_2Cl_2 (20ml) was added NEt_3 (1.94 ml, 13.8 mmol, 1.1 eq) and 3-cyclopentyl propionyl chloride (1.94 ml, 13.8 mmol, 1.1 eq). The reaction was allowed to stir at room temperature for 3 h before EtOAc was added to the reaction mixture. After separation, The organic layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated to give a white solid. To a solution of the crude amide (3.20 g, 12.2 mmol, 1 eq) in THF (45 ml) at 0 °C was added $LiAlH_4$ (972 mg, 25.6 mmol, 2.1 eq). The reaction was allowed to stir at room temperature for 18 h. The reaction was quenched with H_2O. The aqueous and organic layers were separated and the aqueous layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 50 % petroleum ether in CH_2Cl_2 as eluant to give benzo[1,3]dioxol-5-yl-(3-cyclopentyl-propyl)-amine **388** (1.07 g, 4.38 mmol, 35 %) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07-1.12 (2H, m, 2H from 2 × CH_2), 1.37-1.49 (2H, m, CH_2), 1.50-1.67 (6H, m, 3 × CH_2), 1.73-1.87 (3H, m, CH and 2H from 2 × CH_2), 3.07 (2H, t, J = 7.3 Hz, C*H*$_2$N), 5.89 (2H, s, C*H*$_2$O$_2$), 6.18 (1H, dd, J = 2.3, 8.3 Hz, Ar*H*), 6.36 (1H, d, J = 2.3 Hz, Ar*H*), 6.69 (1H, d, J = 8.3 Hz, Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (2 × *C*H_2), 28.7 (*C*H_2), 33.1 (2 × *C*H_2), 33.9 (*C*H_2), 40.3 (*C*H), 46.6 (*C*H_2), 97.2 (Ar*C*H), 101.1 (*C*H_2O$_2$), 106.1 (ArCH), 109.0 (Ar*C*H), 141.0 (Ar*C*O), 143.0 (Ar*C*O), 148.7 (*C*=O).
IR υ_{max}/(cm^{-1}) 3399 (NH), 2857, 1633, 1504, 1199.
MS *m/z* (EI$^+$ mode) 247 (M$^+$, 68%), 150 (100), 137 (8), 65(5).
$C_{15}H_{21}NO_2$ requires 247.1572, found 247.1572.

4-Iodo-*N*-propyl aniline (391)

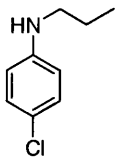


To a solution of 4-iodoaniline **389** (3.00 g, 13.7 mmol, 1 eq) in CH_2Cl_2 (60 ml) was added and NEt_3 (5.78 ml, 41.1 mmol, 3 eq) and propionic anhydride (3.51 ml, 27.4 mmol, 3 eq). The reaction was allowed to stir at room temperature for 3 h. The reaction mixture was

washed with $NaHCO_3$, and 1 M HCl, dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. THF (100ml) was added the solution cooled to 0 °C. $LiAlH_4$ (1.09 g, 28.8 mmol, 2.1 eq) was added slowly. The reaction was allowed to stir at room temperature for 18 h. The reaction was quenched with H_2O. The aqueous and organic layers were separated and the aqueous layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The crude reaction mixture was purified by flash chromatography using 50 % petroleum ether in CH_2Cl_2 as eluant to give 4-iodo-*N*-propyl aniline **391** (1.31 g, 4.93 mmol, 36 %) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.60-1.69 (2H, m, C*H*$_2$CH$_3$), 3.07 (2H, t, J = 7.1 Hz, C*H*$_2$N), 3.75 (1H, broad s, N*H*), 6.34-6.40 (2H, apparent dt, J= 3.0, 9.8 Hz, 2 × Ar*H*), 7.41-7.45 (2H, apparent dt, J = 3.0, 9.8 Hz, 2 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9 (*C*H$_3$), 22.9 (*C*H$_2$), 46.1 (CH$_2$N), 77.9 (Ar*C*I), 115.3 (2 × Ar*C*H), 138.1 (2 × Ar*C*H), 148.3 (Ar*C*).
IR $\upsilon_{max}/(cm^{-1})$ 2962, 1604, 1506, 1321.
MS *m/z* (EI^+ mode) 261 (M^+, 62%), 232 (92), 105 (36), 84 (100), 47 (17).
$C_9H_{12}NI$ requires 261.0015, found 261.0014.

4-Chloro-*N*-propyl-aniline (394)[93]

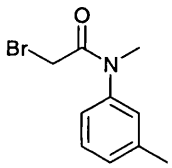


To a solution of 4-chloroaniline **392** (1.18 g, 14.2 mmol, 1 eq) in CH_2Cl_2 (40ml) was added NEt_3 (4.00 ml, 28.4 mmol, 2 eq) and propionic anhydride (2.00 ml, 15.6 mmol, 1.1 eq). The reaction was allowed to stir at room temperature for 3 h. The reaction mixture was washed with $NaHCO_3$ and 1 M HCl, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid. THF (100 ml) was added and the solution was cooled to 0 °C before the addition of $LiAlH_4$ (1.02 g, 26.8 mmol, 2 eq). The reaction was then allowed to stir at room temperature for 18 h before being quenched with H_2O. The aqueous and organic layers were separated and the aqueous layer was washed with $NaHCO_3$, dried ($MgSO_4$) and

concentrated *in vacuo* to give 4-chloro-*N*-propyl aniline **394** (2.12 g, 24.9 mmol, 93 %) as a yellow oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, J = 7.4 Hz, CH_3CH_2), 1.62-1.72 (2H, m, CH_2), 3.08 (2H, t, J= 7.1 Hz, CH_2N), 3.67 (1H, broad singlet, NH), 6.55 (2H, apparent doublet, J = 8.8 Hz, 2 × ArH), 7.14 (2H, apparent doublet, J = 8.9 Hz, 2 × ArH).
^{13}C NMR (100 MHz, $CDCl_3$) δ 12.01 (CH_3), 23.0 (CH_2), 46.3 (CH_2N), 114.1 (2 × ArCH), 121.9 (ArCCl), 129.6 (2 × ArCH), 147.5 (ArCN)
IR $\upsilon_{max}/(cm^{-1})$ 3413 (NH), 1598, 1496, 1317, 1176.
MS *m/z* (EI$^+$ mode) 169 (M^+, 70%), 143 (25), 140 (100), 111 (26), 82 (45), 77 (14), 46 (7).
$C_9H_{12}NCl$ requires 169.0658, found 169.0657.

2-Bromo-*N*-methyl-*N*-(3-methylphenyl)-acetamide (395)

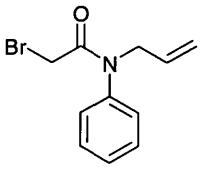


To a solution of *N*-methyl toluidine (1 ml, 7.80 mmol, 1 eq) and NEt_3 (1.20 ml, 8.60 mmol, 1.1 eq) in CH_2Cl_2 (30 ml) at 0 °C was added bromoacetyl bromide (0.74 ml, 8.60 mmol, 1.1 eq), the reaction was allowed to stir at rt for 1.5 h. The reaction mixture was then washed with 0.5 M HCl (3 × 20 ml) and brine (3 × 20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give 2-bromo-*N*-methyl-*N*-(3-methylphenyl) acetamide **395** (660 mg, 2.73 mmol, 35 %) as a red/brown solid which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (3H, s, CH_3-Ar), 3.22 (3H, s, NCH_3), 3.60 (2H, s, CH_2Br), 7.00 (2H, overlapping singlet and doublet, 2 × ArH), 7.13 (1H, d, J= 8.0 Hz, ArH), 7.25 (1H apparent t, J= 7.6 Hz, ArH).
^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (CH_3Ar), 27.3 (CH_2Br), 38.4 (CH_3N), 124.3 (ArCH), 127.9 (ArCH), 129.7 (ArCH), 130.1 (ArCH), 140.6 (ArC), 143.4 (ArC), 166.9 (C=O).
IR $\upsilon_{max}/(cm^{-1})$: 3045, 2962, 1664 (C=O), 1376, 1114.
MS *m/z* (EI$^+$ mode) 241 (M^+, 7%), 162 (9), 121 (13), 83 (100), 47 (17).

$C_{10}H_{12}BrNO$ requires 241.0102, found 241.0104.

2-Bromo-*N*-allyl-*N*-phenylacetamide (396)



To a solution of *N*-allylaniline (1.0 g, 7.50 mmol, 1 eq) and NEt_3 (1.05 ml, 7.50 mmol, 1 eq) in CH_2Cl_2 (15 ml) at 0 °C was added a solution of bromoacetyl bromide (1.96 ml, 22.5 mmol, 3 eq) in CH_2Cl_2 (5 ml) and the reaction allowed to stir at rt for 18 h. The reaction mixture was then washed with 0.5 M HCl (3 × 20 ml) and brine (3 × 20 ml). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The crude reaction was purified by flash chromatography on alumina using 40 % ethyl acetate in petroleum ether as eluant to give 2-bromo-*N*-allyl-*N*-phenylacetamide **396** (868 mg, 3.38 mmol, 45%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (2H, s, C*H*$_2$Br), 4.32 (2H, d, J = 6.1 Hz, C*H*$_2$N), 5.15 (2H, apparent t J = 7.5 Hz, C*H*$_2$=CH), 5.83-5.93 (1H, m, C*H*=CH$_2$), 7.22-7.28 (2H, m, Ar*H*), 7.39-7.48 (3H, m, Ar*H*).

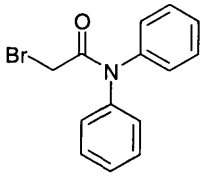
^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6 (*C*H$_2$Br), 53.3 (*C*H$_2$N), 119.0 (*C*H$_2$=CH), 128.5 (2 × ArCH), 129.1 (Ar*C*H), 130.2 (2 × Ar*C*H), 132.5 (*C*H=CH$_2$), 141.8 (Ar*C*), 166.5 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 1666 (C=O), 1594, 1494, 1394, 1276.

MS *m/z* (EI$^+$ mode) 253 (M$^+$, 8%), 212 (7), 174 (100), 132 (25), 106 (28), 83 (65), 77 (35), 41 (19).

$C_{11}H_{12}BrNO$ requires 253.0102, found 253.0107.

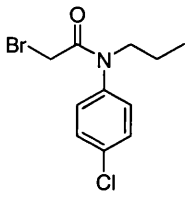
2-Bromo-*N*,*N*-diphenylacetamide (397)[94]



To a solution of *N*,*N*-diphenylamine (0.68 g, 4.00 mmol, 1 eq) and NEt_3 (0.56 ml, 4.00 mmol, 1 eq) in CH_2Cl_2 (10 ml) at 0 °C was added by cannula, a solution of bromoacetyl bromide (1.05 ml, 12.0 mmol, 3.0 eq) in CH_2Cl_2 (5 ml) and the reaction was allowed to stir at room temperature for 16 h. CH_2Cl_2 (10 ml) was added to the reaction, the organic layer was washed with 0.5 M HCl (3 × 20 ml) and brine (3 × 20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by recrystallisation from petroleum ether / methanol to give 2-bromo-*N*,*N*-diphenylacetamide **397** (0.49 g, 1.68 mmol, 42%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (2H, s, C*H*$_2$CO), 7.18-7.59 (10H, broad signal, Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3 (*C*H_2Br), 125-131 (10 × Ar*C*H).
MS *m/z* (EI$^+$ mode) 289 (M+, 32%), 222 (4), 196 (14)), 169 (100), 167 (53), 86 (30), 84 (48), 49 (25)
$C_{14}H_{12}BrNO$ requires 289.0102, found 289.0103.

2-Bromo-*N*-(4-chlorophenyl)-*N*-propylacetamide (398)



To a solution of *N*-propyl-4-chloroaniline (1.18 g, 10.7 mmol, 1 eq) and NEt_3 (4.5 ml, 32.1 mmol, 3 eq) in CH_2Cl_2 (40 ml) at 0 °C was added bromoacetyl bromide (1.23 ml, 13.9 mmol, 1.3 eq) and the reaction allowed to stir at rt for 16 h. The reaction mixture was washed with 0.5 M HCl and 1 M NaOH. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give 2-bromo-*N*-(4-chlorophenyl)-*N*-propylacetamide **398** (3.11 g, 10.7 mmol, 100 %) as a brown oil which was used without further purification.

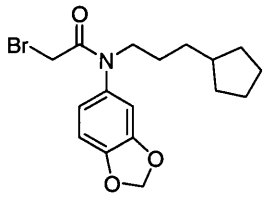
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.36-1.51 (2H, m, C*H*$_2$), 3.51-3.61 (4H, m, C*H*$_2$N and C*H*$_2$CO), 7.16 (2H, apparent d, J =8.7 Hz, 2 × Ar*H*), 7.39 (2H, apparent d, J = 8.7 Hz, 2 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H_3), 21.1 (*C*H_2), 27.4 (*C*H_2CO), 51.9 (*C*H_2N), 129.8 (2 × Ar*C*H), 130.9 (2 × Ar*C*H), 134.9 (Ar*C*), 140.4 (Ar*C*), 166.6 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 2962, 2931, 1658 (C=O), 1488.

MS *m/z* (EI^+ mode) 289 (M^+, 7%), 249 (11), 140 (52), 84 (100), 47 (15).

$C_{11}H_{13}NOClBr$ requires 288.9869, found 288.9875.

_N_-Benzo[1,3]dioxol-5-yl-2-bromo-_N_-(3-cyclopentyl-propyl)acetamide (399)



To a solution of benzo[1,3]dioxol-5-yl-(3-cyclopentyl-propyl)amine (1.07 g, 4.30 mmol, 1 eq) in CH_2Cl_2 (50 ml) at 0 °C was added NEt_3 (1.20 ml, 8.60 mmol, 2 eq) and bromoacetyl bromide (0.45 ml, 5.20 mmol, 1.2 eq) and the reaction was allowed to stir at room temperature for 14 h. The reaction mixture was washed with 0.5 M HCl, $NaHCO_3$, dried ($MgSO_4$) and concentrated to give *N*-benzo[1,3]dioxol-5-yl-2-bromo-*N*-(3-cyclopentyl-propyl) acetamide **399** as a brown oil (1.53 g, 4.13 mmol, 96 %) which was used without further purification.

^1H NMR (400 MHz, $CDCl_3$) δ 0.97-.099 (2H, m, 2H from 2 × CH_2), 1.19-1.28 (2H, m, CH_2), 1.35-1.52 (6H, m, 3 × CH_2), 1.62-1.65 (3H, m, CH and 2H from 2 × CH_2), 3.56 (2H, t, J = 7.7 Hz, C*H*$_2$N), 3.60 (2H, s, C*H*$_2$Br), 5.98 (2H, s, C*H*$_2$O$_2$), 6.65 (2H, m, 2 × Ar*H*), 6.76 (1H, d, J = 8.7 Hz, Ar*H*).

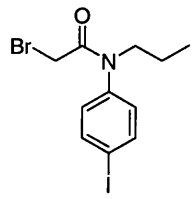
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (*C*H_2), 27.0 (*C*H_2), 27.8 (*C*H_2CO), 33.0 (2 × *C*H_2), 33.4 (2 × *C*H_2), 40.3 (*C*H), 50.6 (*C*H_2N), 102.4 (*C*H_2O$_2$), 209.0 (Ar*C*H), 109.1 (Ar*C*H), 122.0 (Ar*C*H), 135.64 (Ar*C*N), 148.1 (Ar*C*O), 148.9 (Ar*C*O), 166.8 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 1661 (C=O), 1623, 1504, 1484, 1228.

MS *m/z* (EI^+ mode) 367 (M^+, 57%), 288 (23), 257 (25), 192 (14), 150 (100), 111(29), 69 (30), 41 (15).

$C_{17}H_{22}NO_3Br$ requires 367.0783, found 367.0788.

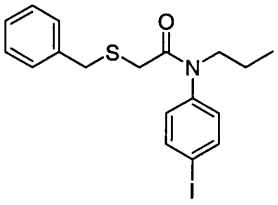
2-Bromo-*N*-(4-iodophenyl)-*N*-propylacetamide (400)



To a solution of 4-iodo-*N*-propyl aniline (813 mg, 3.11 mmol, 1 eq) and NEt_3 (0.87 ml, 6.22 mmol, 2 eq) in CH_2Cl_2 (20 ml) at 0 °C was added bromoacetyl bromide (0.35 ml, 4.04 mmol, 1.3 eq) and the reaction allowed to stir at rt for 1.5 h. The reaction mixture was then washed with 0.5 M HCl (3 × 20 ml) and brine (3 × 20 ml). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give 2-bromo-*N*-(4-iodophenyl)-*N*-propylacetamide **400** (1.02 g, 2.67 mmol, 86%) as a brown oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz, C*H*$_3$), 1.41-1.51 (2H, m, C*H*$_2$), 3.53 (2H, s, C*H*$_2$CO), 3.57 (2H, t, J = 7.6 Hz, C*H*$_2$N), 6.95 (2H, apparent d, J = 8.4 Hz, 2 × Ar*H*), 7.71 (2H, apparent d, J = 8.4 Hz, 2 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2 (*C*H$_3$), 20.7 (*C*H$_2$), 27.2 (*C*H$_2$), 51.5 (*C*H$_2$N), 94.1 (Ar*C*I), 130.1 (2 × Ar*C*H), 139.5 (2 × Ar*C*H), 141.3 (Ar*C*), 165.7 (*C*=O).
IR υ_{max}/(cm^{-1}) 2961, 2930, 1655 (C=O), 1481, 1211.
MS *m/z* (CI$^+$ mode) 384 ((M+H)$^+$, 43%), 382 ((M+H)$^+$, 43%), 302 (45), 256 (40), 218 (27), 176 (100), 136 (20).
$C_{11}H_{14}NOBrI$ requires 381.9304, found 381.9305.

2-Benzylsulfanyl-*N*-(4-iodophenyl)-*N*-propylacetamide (401)



To a solution of 2-bromo-*N*-(4-iodophenyl)-*N*-propylacetamide **400** (386 mg, 1.01 mmol, 1 eq) and NEt_3 (0.21 ml, 1.52 mmol, 1.5 eq) in DMF (10 ml) was added benzyl thiol (0.12

ml, 1.01 mmol, 1 eq) and the reaction allowed to stir at rt for 2 h. 40 % EtOAc in petroleum ether was added to the reaction mixture and the organic layer separated and washed with $NaHCO_3$ and H_2O. The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 20 % EtOAc in petroleum ether as eluant to give 2-benzylsulfanyl-*N*-(4-iodophenyl)-*N*-propyl acetamide **401** (268 mg, 0.63 mmol, 62 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.9 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.58-1.49 (2H, m, C*H*$_2$CH$_3$), 2.86 (2H, s, C*H*$_2$CO), 3.65 (2H, t, 7.6 Hz, C*H*$_2$N), 3.86 (2H, s, PhC*H*$_2$S), 6.92 (2H, apparent d, J = 8.5 Hz, 2 × Ar*H*), 7.25-7.93 (5H, m, 5 × Ar*H*), 7.71 (2H, apparent d, J = 8.5 Hz, 2 × Ar*H*).

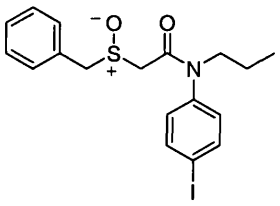
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H$_3$), 21.3 (*C*H$_2$), 32.5 (*C*H$_2$), 36.6 (*C*H$_2$), 51.4 (*C*H$_2$), 93.7 (Ar*C*I), 127.4 (Ar*C*H), 128.8 (2 × Ar*C*H), 129.6 (2 × Ar*C*H), 130.7 (2 × Ar*C*H), 138.0 (Ar*C*), 139.3 (2 × Ar*C*H), 142.3 (Ar*C*), 169.3 (*C*=O)

IR $\upsilon_{max}/(cm^{-1})$ 1643 (C=O), 1481, 1396, 1305.

MS *m/z* (EI$^+$ mode) 425 (M$^+$, 15%), 303 (73), 260 (100), 219 (19), 91 (79).

$C_{18}H_{20}NOSI$ requires 425.0310, found 425.0311.

(±)-2-(Benzylsulfinyl)-*N*-(4-iodophenyl)-*N*-propylacetamide (403)



To a solution of 2-benzylsulfanyl-*N*-(4-iodophenyl)-*N*-propyl acetamide **401** (290 mg, 0.68 mmol, 1 eq) in HFIP: CH_2Cl_2 (4 ml: 2 ml) was added 30 % aqueous H_2O_2 (0.31 ml, 2.72 mmol, 4 eq) and the reaction allowed to stir at rt for 1 h. The reaction was then quenched with aqueous saturated Na_2SO_3 solution. The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-2-(benzylsulfinyl)-*N*-(4-iodophenyl)-*N*-propylacetamide **403** (300 mg, 0.68 mmol, 100 %) as a yellow oil. The crude product was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.4 Hz, CH_3), 1.39-1.50 (2H, m, CH_2), 3.18 (1H, d, AB system, J = 14.3 Hz, 1H from CH_2CO), 3.23 (1H, d, AB system, J = 14.3 Hz, 1H from CH_2CO), 3.52-3.63 (2H, m, CH_2N), 3.99 (1H, d, AB system, J = 13.1 Hz, 1H from PhCH_2S), 4.18 (1H, d, AB system, J = 13.1 Hz, 1H from PhCH_2S), 6.77 (2H, apparent doublet, J = 8.6 Hz, 2 × Ar*H*), 7.19-7.22 (2H, m, 2 × ArH), 7.27-7.31 (3H, m, 3 × Ar*H*), 7.61 (2H, apparent doublet, J = 9.3 Hz, 2 × Ar*H*).

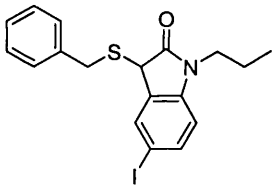
^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1 (*C*H_3), 19.8 (CH_2CH$_3$), 50.0 (CH_2), 52.2 (*C*H_2), 56.3 (*C*H_2), 93.1 (Ar*C*I), 127.5 (Ar*C*H), 127.8 (2 × Ar*C*H), 128.3 (Ar*C*), 129.1 (2 × Ar*C*H), 129.4 (2 × Ar*C*H), 138.2 (2 × Ar*C*H), 139.8 (Ar*C*N), 162.9 (*C*=O).

IR υ_{max}/(cm^{-1}) 2965, 2875, 1644 (C=O), 1482, 1410, 1129.

MS *m/z* (EI$^+$ mode) 441 (M$^+$, 10%), 303 (6), 91 (100), 43 (8).

$C_{18}H_{20}O_2NSI$ requires 441.0260, found 441.0258.

(±)-3-Benzylsulfanyl-5-iodo-1-propyl-1,3-dihydro-indol-2-one (405)



To a solution of (±)-2-(benzylsulfinyl)-*N*-(4-iodophenyl)-*N*-propylacetamide **403** (166.5 mg, 0.38 mmol, 1 eq) in 1,2-dichloroethane (4 ml) was added TFAA (0.43 ml, 3.04 mmol, 8 eq), and the reaction allowed to stir at room temperature for 10 min. BF_3 Et_2O (0.19 ml, 1.52 mmol, 4 eq) was then added and the reaction was allowed to stir for a further hour. The reaction was then quenched with 1 M NaOH solution and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 40 % EtOAc in petroleum ether as eluant to give (±)-3-benzylsulfanyl-5-iodo-1-propyl-1,3-dihydro-indol-2-one **405** (117 mg, 0.28 mmol, 73 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.4 Hz, CH_3), 1.54 -1.64 (2H, m, CH_2), 3.50 (2H, t, J = 7.3 Hz, CH_2N), 3.68 (1H, d, J = 13.2 Hz, 1H from PhCH_2S), 4.04 (1H, s, C*H*S),

4.11 (1H, d, J = 13.2 Hz, 1H from PhCH_2S), 6.49 (1H, d, J = 8.2 Hz, Ar*H*), 7.14-7.29 (5H, m, 5 × Ar*H*), 7.43 (1H, s, Ar*H*), 7.49 (1H, dd, J = 8.2, 1.1 Hz, Ar*H*).

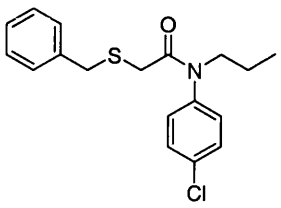
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (*C*H_3), 21.0 (*C*H_2), 34.8 (*C*H_2), 42.2 (Ph*C*H_2S), 43.1 (*C*HS), 85.1 (Ar*C*I), 110.8 (Ar*C*H), 127.8 (Ar*C*H), 128.4 (Ar*C*), 128.9 (2 × Ar*C*H), 129.6 (2 × Ar*C*H), 134.4 (Ar*C*H), 137.4 (Ar*C*), 138.1 (Ar*C*H), 143.7 (Ar*C*), 175.2 (*C*=O)

IR $\upsilon_{max}/(cm^{-1})$ 1704(C=O), 1600, 1477, 1332, 1103.

MS *m/z* (EI$^+$ mode) 423 (M^+, 19%), 301 (100), 272 (30), 258 (25), 116 (24), 91 (61).

$C_{18}H_{18}NOIS$ requires 423.0154, found 423.0155.

2-Benzylsulfanyl-*N*-(4-chlorophenyl)-*N*-propylacetamide (402)

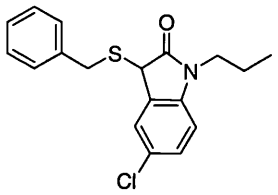


To a solution of 2-bromo-*N*-(4-chlorophenyl)-*N*-propylacetamide **398** (249 mg, 0.86 mmol, 1 eq) in DMF (5 ml) were added NEt_3 (0.18 ml, 1.29 mmol, 1.5 eq) and benzyl thiol (0.11 ml, 0.95 mmol, 1.1 eq) and the reaction was allowed to stir at rt for 45 min. H_2O was added and the reaction mixture was extracted with 40 % ethyl acetate in petroleum ether. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 20 % ethyl acetate in petroleum ether as eluant to give 2-benzylsulfanyl-*N*-(4-chlorophenyl)-*N*-propylacetamide **402** (158 mg, 0.47 mmol, 55 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.4 Hz, CH_3CH_2), 1.40-1.55 (2H, m, CH_2), 2.76 (2H, s s, CH_2CO), 3.55 (2H, t, J = 7.6 Hz, CH_2N), 3.77 (2H, s, PhCH_2S), 7.0 (2H, m, 2 × Ar*H*), 7.08-7.31 (7H, m, 7 × Ar*H*)

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H_3), 21.3 (*C*H_2), 32.5 (*C*H_2), 36.6 (*C*H_2), 51.4 (*C*H_2), 127.4 (Ar*C*H), 128.8 (2 × Ar*C*H), 129.6 (2 × Ar*C*H), 130.2 (4 × Ar*C*H), 134.3 (Ar*C*), 138.0 (Ar*C*), 141.0 (Ar*C*), 169.4 (*C*=O).

3-Benzylsulfanyl-5-Chloro-1-propyl-1,3-dihydro-indol-2-one (406)



To a solution of 2-benzylsulfanyl-*N*-(4-chloro phenyl)-*N*-propylacetamide **402** (46.8 mg, 0.14 mmol, 1 eq) in HFIP (3 ml) was added 30 % aqueous H_2O_2 (0.06 ml, 0.56 mmol, 4 eq) and the reaction allowed to stir at rt for 15 min. The reaction was then quenched with aqueous saturated Na_2SO_3 solution. The aqueous and organic layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-2-benzylsulfinyl-*N*-(4-chlorophenyl)-*N*-propylacetamide **404** (39 mg, 0.11 mmol, 80 %).

To a solution of (±)-2-benzylsulfinyl-*N*-(4-chlorophenyl)-*N*-propylacetamide **404** (39 mg, 0.11 mmol, 1 eq) in 1,2-dichloroethane (5 ml) was added TFAA (0.13 ml, 0.90 mmol, 8 eq) and the reaction was allowed to stir for 1 h. BF_3 OEt_2 (0.06 ml, 0.45 mmol, 4 eq) was then added and the reaction was allowed to stir for a further 1 h. The reaction was then quenched with 1 M NaOH solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 20 % EtOAc in petroleum ether as eluant to give (±)-3-benzylsulfanyl-5-chloro-1-propyl-1,3-dihydro-indol-2-one **406** (26 mg, 0.28 mmol, 72%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 6.6 Hz, C*H*$_3$), 1.55-1.65 (2H, m, C*H*$_2$), 3.53 (2H, t, J = 7.3 Hz, C*H*$_2$N), 3.89 (1H, d, J = 15.9 Hz, 1H from PhC*H*$_2$S), 4.06 (1H, s, C*H*S), 4.11 (1H, d, J= 13.2 Hz, 1H from PhC*H*$_2$S), 6.63 (1H, dd, J = 3.4, 5.4 Hz, Ar*H*), 7.06-7.44 (7H, m, 7 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3 (*C*H$_3$), 19.7 (*C*H$_2$), 33.4 (Ph*C*H$_2$S), 40.9 (*C*H$_2$N), 42.0 (*C*HS), 108.3 (Ar*C*H), 124.6 (Ar*C*H), 126.3 (Ar*C*), 126.4 (Ar*C*H), 126.8 (Ar*C*), 127.5 (2 × Ar*C*H), 127.8 (Ar*C*H), 128.2 (2 × Ar*C*H), 135.9 (Ar*C*), 141.1 (Ar*C*), 174.0 (*C*=O).

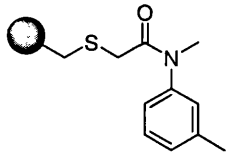
IR $\upsilon_{max}/(cm^{-1})$ 1708 (C=O), 1608, 1481, 1334, 1106.

MS (EI+ mode) 331 (M^+, 3 %), 209 (100), 108 (15), 91 (25).

$C_{18}H_{18}NOClS$ requires 331.0798, found 331.0793.

Solid phase route to oxindoles

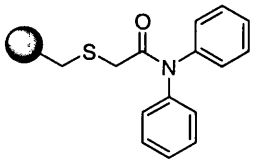
***S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-(3-methylphenyl)acetamide**



As for general procedure A. Thiol resin **342**, on treatment with 2-bromo-*N*-methyl-*N*-(3-methylphenyl) acetamide **395** gave *S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-(3-methylphenyl)acetamide.

IR υ_{max}/ (cm^{-1}) 1650 (C=O).

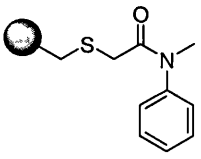
***S*-Merrifield bound 2-mercapto-*N*,*N*-diphenylacetamide**



As for general procedure A. Thiol resin **342**, on treatment with 2-bromo-*N*,*N*-diphenyl acetamide **397** gave *S*-Merrifield bound 2-mercapto-*N*,*N*-diphenylacetamide.

IR υ_{max}/ (cm^{-1}) 1664 (C=O).

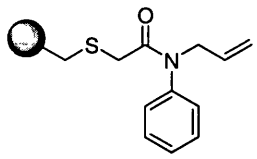
***S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-phenylacetamide**



As for general procedure A. Thiol resin **342**, on treatment with 2-bromo-*N*-methyl-*N*-phenyl acetamide **348** gave *S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-phenylacetamide.

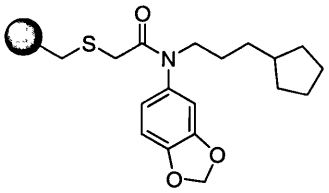
IR υ_{max}/ (cm^{-1}) 1654 (C=O).

S-Merrifield bound *N*-allyl-2-mercapto-*N*-phenylacetamide



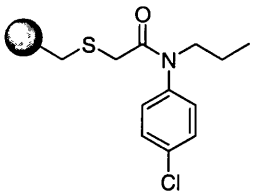
As for general procedure A. Thiol resin **342**, on treatment with 2-bromo-*N*-allyl-*N*-phenyl acetamide **396** gave *S*-Merrifield bound *N*-allyl-2-mercapto-*N*-phenylacetamide.
IR $\upsilon_{max}/(cm^{-1})$ 1652 (C=O).

S-Merrifield bound *N*-(benzo[d][1,3]dioxol-5-yl)-*N*-(3-cyclopentylpropyl)-2-mercaptoacetamide



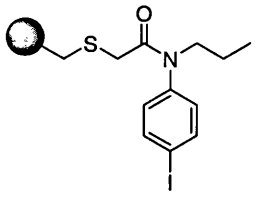
As for general procedure A. Thiol resin **342**, on treatment with *N*-benzo[1,3]dioxol-5-yl-2-bromo-*N*-(3-cyclopentyl-propyl) acetamide **399** gave *S*-Merrifield bound *N*-(benzo[d][1,3]dioxol-5-yl)-*N*-(3-cyclopentylpropyl)-2- mercaptoacetamide.
IR $\upsilon_{max}/(cm^{-1})$ 1650 (C=O).

S-Merrifield bound *N*-(4-chlorophenyl)-2-mercapto-*N*-propylacetamide



As for general procedure A. Thiol resin **342**, on treatment with 2-bromo-*N*-(4-chlorophenyl)-*N*-propylacetamide **398** gave product resin *S*-Merrifield bound *N*-(4-chlorophenyl)-2-mercapto-*N*-propylacetamide.
IR $\upsilon_{max}/(cm^{-1})$ 1652 (C=O).

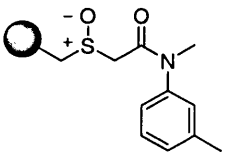
S-Merrifield bound *N*-(4-iodophenyl)-2-mercapto-*N*-propylacetamide



As for general procedure A. Thiol resin **342**, on treatment with 2-bromo-*N*-(4-iodophenyl)-*N*-propylacetamide **400** gave *S*-Merrifield bound *N*-(4-iodophenyl)-2-mercapto-*N*-propylacetamide.

IR $\upsilon_{max}/(cm^{-1})$ 1650 (C=O).

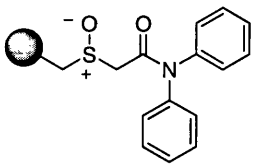
S-Merrifield bound *N*-methyl-*N*-(3-methylphenyl)-2-(sulfinyl) acetamide



As for general procedure B. Upon oxidation, *S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-(3-methylphenyl)acetamide gave *S*-Merrifield bound *N*-methyl-*N*-(3-methylphenyl)-2-(sulfinyl) acetamide.

IR $\upsilon_{max}/ (cm^{-1})$ 1650 (C=O).

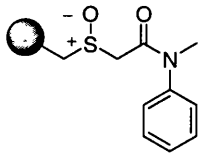
S-Merrifield *N*,*N*-diphenyl 2-(sulfinyl) acetamide



As for general procedure B. Upon oxidation, *S*-Merrifield bound 2-mercapto-*N*,*N*-diphenylacetamide gave product resin *S*-Merrifield *N*,*N*-diphenyl 2-(sulfinyl) acetamide.

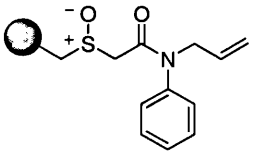
IR $\upsilon_{max}/ (cm^{-1})$ 1660 (C=O).

S-Merrifield bound *N*-methyl-*N*-phenyl 2-(sulfinyl) acetamide



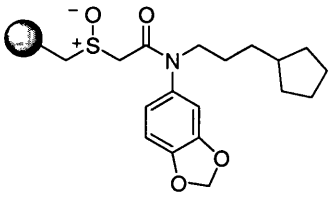
As for general procedure B. Upon oxidation, *S*-Merrifield bound 2-mercapto-*N*-methyl-*N*-phenylacetamide gave *S*-Merrifield bound *N*-methyl-*N*-phenyl 2-(sulfinyl) acetamide.
IR υ_{max}/ (cm^{-1}) 1650 (C=O).

S-Merrifield bound *N*-allyl-*N*-Phenyl-2-sulfinyl acetamide



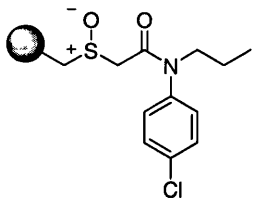
As for general procedure B. Upon oxidation, *S*-Merrifield bound *N*-allyl-2-mercapto-*N*-phenylacetamide gave *S*-Merrifield bound *N*-allyl-*N*-Phenyl-2-sulfinyl acetamide.
IR υ_{max}/(cm^{-1}) 1648 (C=O).

S-Merrifield bound *N*-(benzo[d][1,3]dioxol-5-yl)-*N*-(3-cyclopentylpropyl)-2-sulfinyl acetamide



As for general procedure B. Upon oxidation, *S*-Merrifield bound *N*-(benzo[d][1,3]dioxol-5-yl)-*N*-(3-cyclopentylpropyl)-2- mercaptoacetamide gave *S*-Merrifield bound *N*-(benzo[d][1,3]dioxol-5-yl)-*N*-(3-cyclopentylpropyl)-2-sulfinyl acetamide.
IR υ_{max}/ (cm^{-1}) 1648 (C=O)

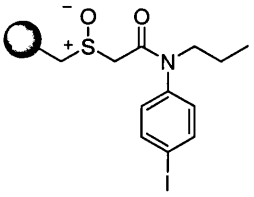
_S_-Merrifield bound _N_-(4-chlorophenyl)-_N_-propyl-2-sulfinyl acetamide



As for general procedure B. Upon oxidation, _S_-Merrifield bound _N_-(4-chlorophenyl)-2-mercapto-_N_-propylacetamide gave _S_-Merrifield bound _N_-(4-chlorophenyl)-_N_-propyl-2-sulfinyl acetamide.

IR $\upsilon_{max}/(cm^{-1})$ 1644 (C=O).

_S_-Merrifield bound _N_-(4-iodophenyl)-_N_-propyl-2-sulfinyl acetamide

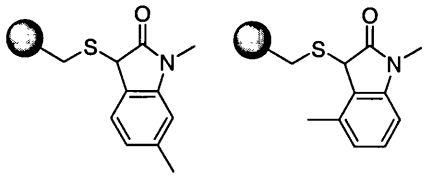


As for general procedure B. Upon oxidation, _S_-Merrifield bound _N_-(4-iodophenyl)-2-mercapto-_N_-propylacetamide gave _S_-Merrifield bound _N_-(4-iodophenyl)-_N_-propyl-2-sulfinyl acetamide.

IR $\upsilon_{max}/(cm^{-1})$ 1648 (C=O).

General procedure D: Pummerer cyclisation of neutral and electron deficient aromatic systems

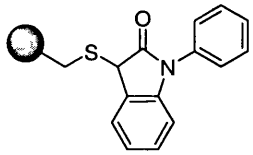
***S*-Merrifield bound 3-mercapto-1,6-dimethyl-1,3-dihydro-indol-2-one and *S*-Merrifield bound 3-mercapto-1,4-dimethyl-1,3-dihydro-indol-2-one**



S-Merrifield bound *N*-methyl-*N*-(3-methylphenyl)-2-(sulfinyl) acetamide and *S*-Merrifield bound *N*-methyl-*N*-(5-methylphenyl)-2-(sulfinyl) acetamide (647 mg, 0.55 mmol/g, 0.36 mmol, 1 eq) was swollen in 1,2-dichloroethane (6 ml) for 15 min. Trifluoroacetic anhydride (0.85 ml, 0.60 mmol, 17 eq) was added and the reaction allowed to stir at rt for 3 h. BF_3 OEt_2 (1.14 ml, 9 mmol, 25 eq) was added and the reaction was allowed to stir at rt for a further 18h. The resin was then washed using our standard washing protocol.The product resin was then dried *in vacuo*.

IR υ_{max}/ (cm^{-1}) 1714 (C=O).

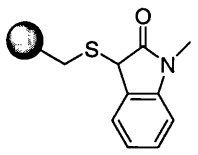
***S*-Merrifield bound 3-mercapto-1-phenyl-1,3-dihydro-indol-2-one**



As for general procedure D. Upon cyclisation, *S*-Merrifield *N*,*N*-diphenyl 2-(sulfinyl) acetamide gave *S*-Merrifield bound 3-mercapto-1-phenyl-1,3-dihydro-indol-2-one.

IR υ_{max}/ (cm^{-1}) 1722 (C=O).

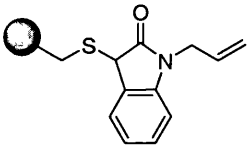
_S_-Merrifield bound 3-mercapto-1-methyl-1,2-dihydro-indol-2-one



As for general procedure D. Upon cyclisation, _S_-Merrifield bound _N_-methyl-_N_-phenyl 2-(sulfinyl) acetamide gave _S_-Merrifield bound 3-mercapto-1-methyl-1,2-dihydro-indol-2-one.

IR υ_{max}/ (cm^{-1}) 1716 (C=O).

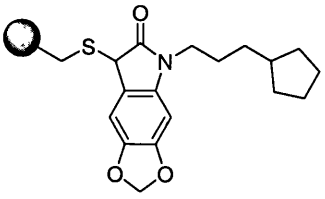
_S_-Merrifield bound 1-allyl-3-mercapto-1,3-dihydro-indol-2-one



As for general procedure D. Upon cyclisation, _S_-Merrifield bound _N_-allyl-_N_-Phenyl-2-sulfinyl acetamide gave product resin _S_-Merrifield bound 1-allyl-3-mercapto-1,3-dihydro-indol-2-one.

IR υ_{max}/(cm^{-1}) 1714 (C=O).

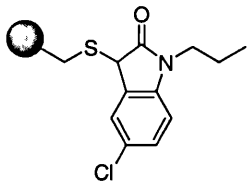
_S_-Merrifield bound 5-(3-cyclopentylpropyl)-7-mercapto-5H-[1,3]dioxolo[4,5-f]indol-6(7H)-one



As for general procedure C. Upon cyclisation, _S_-Merrifield bound _N_-(benzo[d][1,3]dioxol-5-yl)-_N_-(3-cyclopentylpropyl)-2-sulfinyl acetamide gave _S_-Merrifield bound 5-(3-cyclopentylpropyl)-7-mercapto-5H-[1,3]dioxolo[4,5-f]indol-6(7H)-one.

IR (cm^{-1}) 1710 (C=O)

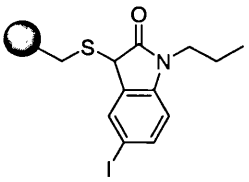
S-Merrifield bound 5-chloro-3-mercapto-1-propyl-1,3-dihydro-indol-2-one



As for general procedure D. Upon cyclisation, *S*-Merrifield bound *N*-(4-chlorophenyl)-*N*-propyl-2-sulfinyl acetamide gave *S*-Merrifield bound 5-chloro-3-mercapto-1-propyl-1,3-dihydro-indol-2-one.

IR $\upsilon_{max}/(cm^{-1})$ 1716 (C=O).

S-Merrifield bound 5-iodo-3-mercapto-1-propyl-1,3-dihydro-indol-2-one

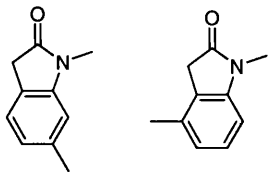


As for general procedure D. Upon cyclisation, *S*-Merrifield bound *N*-(4-iodophenyl)-*N*-propyl-2-sulfinyl acetamide gave *S*-Merrifield bound 5-iodo-3-mercapto-1-propyl-1,3-dihydro-indol-2-one.

IR $\upsilon_{max}/(cm^{-1})$ 1714 (C=O).

SmI_2 cleavage of oxindoles from resin

1,6-Dimethyl-1,3-dihydro-indol-2-one (408) and 1,4-Dimethyl-1,3-dihydro-indol-2-one (409)



S-Merrifield bound 3-mercapto-1,6-dimethyl-1,3-dihydro-indol-2-one and *S*-Merrifield bound 3-mercapto-1,4-dimethyl-1,3-dihydro-indol-2-one (584 mg, 0.55 mmol / g, 0.32 mmol, 1 eq) was swollen in THF (7 ml) for 15 min. DMPU (0.51 ml, 4.20 mmol, 13 eq) and a solution of SmI_2 (10.4 ml of 0.1 M sol in THF, 1.04 mmol, 3.3 eq) were then added and the reaction allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated *in vacuo*. Filtration through a short plug of silica washing with 30 % ethyl acetate in petroleum ether to gave 1,6-dimethyl-1,3-dihydro-indol-2-one **408** and 1,4-dimethyl-1,3-dihydro-indol-2-one **409** (32.4 mg, 0.20 mmol, 63 %) as a 2:1 mixture by NMR and as a clear oil. (yield over 4 solid phase steps based on thiol resin of loading 0.61 mmol/g).

For the major isomer **408**[95]:

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s, C*H*$_3$Ar), 3.11 (3H, s, NC*H*$_3$), 3.40 (2H, s, C*H*$_2$), 6.57 (1H, s, Ar*H*), 6.77 (1H, d, J = 8.2 Hz, Ar*H*), 6.79 (1H, d, J = 8.2 Hz, Ar*H*),

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (*C*H$_3$Ar), 25.1 (N*C*H$_3$), 34.5 (*C*H$_2$CO), 108.0 (Ar*C*H), 120.4 (Ar*C*), 121.7 (Ar*C*H), 123.0 (Ar*C*H), 136.9 (Ar*C*), 144.3 (Ar*C*), 174.5 (*C*=O).

IR υ_{max}/(cm^{-1}) 3052, 2937, 1695 (C=O), 1619, 1606, 1467, 1097, 948.

MS *m/z* (EI$^+$ mode) 161 (M$^+$, 100%), 132 (83), 117 (24), 91 (19), 83 (34), 57 (18), 55 (10).

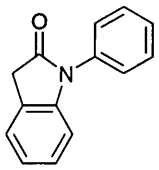
$C_{10}H_{11}NO$ requires 161.0841, found 161.0840.

For the minor isomer **409**[96]:

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (3H, s, C*H*$_3$Ar), 3.12 (3H, s, NC*H*$_3$), 3.33 (2H, s, C*H*$_2$), 6.57 (1H, d, J = 9.8 Hz, Ar*H*), 7.03 (1H, d, J = 7.5 Hz, Ar*H*), 7.13 (1H, apparent t, J = 7.8 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (*C*H_3Ar), 25.3 (N*C*H_3), 33.7 (*C*H_2CO), 104.6 (Ar*C*H), 122.2 (Ar*C*), 122.7 (Ar*C*H), 126.8 (Ar*C*H), 133.0 (Ar*C*), 143.9 (Ar*C*), 174.1 (*C*=O).

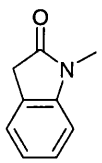
1-Phenyl-1,3-dihydro-indol-2-one (410)[65]



S-Merrifield bound 3-mercapto-1-phenyl-1,3-dihydro-indol-2-one (577 mg, 0.50 mmol /g, 0.29 mmol, 1 eq) was swollen in THF (6 ml) for 15 min. DMPU (0.51 ml, 4.2 mmol, 8.4 eq) and a solution of SmI_2 (10.6 ml of 0.1 M solution in THF, 1.06 mmol, 3.7 eq) were added and the reaction allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated *in vacuo*. Filtration through a short plug of silica washing with 40 % ethyl acetate in petroleum ether to gave 1-phenyl-1,3-dihydro-indol-2-one **410** (24 mg, 0.11 mmol, 39 %) as a clear oil. (Yield over 4 solid phase steps based on thiol resin of loading 0.56 mmol/g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (2H, s, CH_2), 6.71 (1H, d, J = 7.9 Hz, Ar*H*), 7.0 (1H, t, J = 7.3 Hz, Ar*H*), 7.13 (1H, t, J = 7.5 Hz, Ar*H*), 7.24 (1H, d, J = 7.4 Hz, Ar*H*), 7.32-7.36 (3H, m, 3 × Ar*H*), 7.44-7.57 (2H, m, 2 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 36.5 (*C*H_2CO), 109.8 (Ar*C*H), 123.2 (Ar*C*H), 124.7 (Ar*C*), 125.0 (Ar*C*H), 127.0 (2 × Ar*C*H), 128.2 (Ar*C*H), 128.5 (Ar*C*H), 130.1 (2 × Ar*C*H), 134.9 (Ar*C*), 145.6 (Ar*C*), 174.8 (*C*=O).
IR υ_{max}/(cm^{-1}) 3056, 2948, 2919, 1706 (C=O), 1610, 1590, 1500, 1479, 1365.
MS *m/z* (EI^+ mode) 209 (M^+, 50%), 209 (54), 180 (100), 82 (25), 77 (11), 46 (8)/
$C_{14}H_{14}NO$ requires 209.0841, found 209.0840.

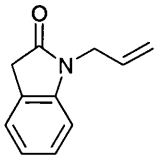
1-Methyl-1,3-dihydro-indole-2-one (411)[65]



S-Merrifield bound 3-mercapto-1-methyl-1,2-dihydro-indol-2-one (315 mg, 0.52 mmol /g, 0.16 mmol, 1 eq) was swollen in THF (4 ml) for 15 min. DMPU (0.30 ml, 2.48 mmol, 15.5 eq) and a solution of SmI_2 (6.20 ml of 0.1 M solution in THF, 0.62 mmol, 3.9 eq) were added and the reaction allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated *in vacuo*. Filtration through a short plug of silica washing with 50 % ethyl acetate in petroleum ether to gave 1-methyl-1,3-dihydro-indole-2-one **411** (10 mg, 0.07 mmol, 43 %) as a clear oil. (Yield over 4 solid phase steps based on thiol resin of loading 0.56 mmol/g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (3H, s, NC*H*$_3$), 3.46 (2H, s, C*H*$_2$CO), 6.75 (1H, d, J = 7.8 Hz, Ar*H*), 6.97 (1H, t, J = 7.5 Hz, Ar*H*) and 7.17-7.24 (2H, m, 2 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1 (N*C*H$_3$), 34.7 (*C*H$_2$CO), 107.1 (Ar*C*H), 121.3 (Ar*C*H), 123.3 (Ar*C*H), 123.5 (Ar*C*), 126.9 (Ar*C*H) 144.2 (Ar*C*) and 174.0 (*C*=O).
IR υ_{max}/(cm^{-1}) 3058, 2942, 2919, 1700 (C=O), 1612, 1463, 1348 and 754.
MS *m/z* (EI$^+$ mode) 147 (M$^+$, 90%), 132 (10), 118 (100), 104 (7), 91 (20), 85 (24), 82 (38), 78 (16), 57 (12) and 47(11).
C_9H_9NO requires 147.0684, found 147.0684.

1-Allyl-1,3-dihydro-indol-2-one (412)[97]



S-Merrifield bound 1-allyl-3-mercapto-1,3-dihydro-indol-2-one (641 mg, 0.55 mmol /g, 0.35 mmol, 1 eq) was swollen in THF (6 ml) for 15 min. DMPU (0.57 ml, 4.70 mmol, 13.4 eq) and a solution of SmI_2 (11.8 ml of 0.1 M solution in THF, 1.18 mmol, 3.4 eq) were added and the reaction allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated. It was then filtered through a short plug of silica washing with 40 % ethyl acetate in petroleum ether to give 1-allyl-1,3-dihydro-indol-2-one **412** (18 mg, 0.10 mmol, 30 %) as a clear oil. (Yield over 4 solid phase steps based on thiol resin of loading 0.61 mmol/g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.5 (2H, s, CH_2CO), 4.27-4.29 (2H, m, CH_2N), 5.14-5.19 (2H, m, CH_2=CH), 5.73-5.82 (1H, m, C*H*=CH_2), 6.75 (1H, d, J = 7.8 Hz, Ar*H*), 6.96 (1H, t, J = 7.3 Hz, Ar*H*), 7.15 – 7.19 (2H, m, 2 × Ar*H*).

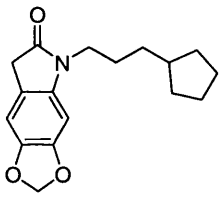
^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1 (*C*H_2CO), 42.7 (*C*H_2N), 109.3 (*C*H=CH_2), 117.9 (*C*H_2=), 122.7 (Ar*C*H), 124.8 (Ar*C*H), 124.9 (Ar*C*), 128.2 (Ar*C*H), 131.8 (Ar*C*H), 144.8 (Ar*C*), 175.2 (*C*=O).

IR υ_{max}/(cm^{-1}) 3054, 2917, 1702 (C=O), 1612, 1486, 1465, 1349, 1197.

MS *m/z* (EI$^+$ mode) 173 (M^+, 85%), 144 (31), 130 (51), 118 (26), 84 (100), 77 (17), 47 (20).

$C_{11}H_{11}NO$ requires 173.0841, found 173.0841.

5-(3-cyclopentylpropyl)-5H-[1,3]dioxolo[4,5-f]indol-6(7H)-one (413)



S-Merrifield bound 5-(3-cyclopentylpropyl)-7-mercapto-5H-[1,3]dioxolo[4,5-f]indol-6(7H)-one (620 mg, 0.48 mmol/g, 0.30 mmol, 1 eq) was swollen in THF (5 ml) for 15 min. DMPU (0.46 ml, 3.8 mmol, 12.7 eq) and a solution of SmI_2 (9.6 ml of 0.1 M solution in THF, 0.96 mmol, 3.2 eq) were added and the reaction was allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated *in vacuo*. Filtration through a short plug of silica washing with 30 % ethyl acetate in petroleum ether to give 5-(3-cyclopentylpropyl)-5H-[1,3]dioxolo[4,5-f]indol-6(7H)-one **413** (31 mg, 0.11 mmol, 36 %) as a clear oil. (Yield over 4 solid phase steps based on thiol resin of loading 0.56 mmol/g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98-1.02 (2H, m, 2H from 2 × CH_2), 1.26-1.32 (2H, m, CH_2), 1.42-1.60 (6H, m, 3 × CH_2), 1.65-1.70 (3H, m, CH and 2H from 2 × CH_2), 3.37 (2H, s, CH_2CO), 3.56 (2H, t, J = 7.5 Hz, CH_2N), 5.86 (2H, s, CH_2O_2), 6.37 (1H, s, Ar*H*), 6.7 (1H, s, Ar*H*).

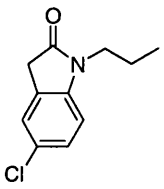
^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (2 × CH_2), 27.1 (CH_2), 33.0 (2 × CH_2), 33.7 (CH_2), 36.5 (CH_2CO), 40.2 (CH), 40.7 (CH_2N), 92.7 (ArCH), 101.4 (CH_2O_2), 106.5 (ArCH), 116.5 (ArC), 139.2 (ArCN), 143.2 (ArCO), 147.5 (ArCO), 175.6 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 1687 (C=O), 1616, 1500, 1473,1328.

MS *m/z* (EI^+ mode) 287(M^+, 100%), 177 (20), 162 (45), 132 (28), 104 (5), 77 (7), 41 (14).

$C_{17}H_{21}NO_3$ requires 287.1521, found 287.1520.

5-Chloro-1-propyl-1,3-dihydro-indol-2-one (415)[98]



S-Merrifield bound 5-chloro-3-mercapto-1-propyl-1,3-dihydro-indol-2-one (0.99 g, 0.50 mmol/g, 0.50 mmol, 1 eq) was swollen in THF (10 ml) for 15 min. DMPU (0.99 ml, 8.20 mmol, 16.4 eq) and a solution of SmI_2 (20.5 ml of 0.1 M solution in THF, 2.05 mmol, 4.1 eq) were added and the reaction was allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated *in vacuo*. Filtration through a short plug of silica washing with 30 % ethyl acetate in petroleum ether to give 5-chloro-1-propyl-1,3-dihydro-indol-2-one **415** (39.7 mg, 0.19 mmol, 38 %) as a clear oil. (Yield over 4 solid phase steps based on thiol resin of loading 0.56 mmol/g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz, CH_3), 1.57-1.67 (2H, m, CH_2), 3.45 (2H, s, CH_2CO), 3.59 (2H, t, J = 7.4 Hz, CH_2N), 6.76 (1H, d, J = 7.9 Hz, ArH), 7.15-7.18 (2H, m, 2 × ArH).

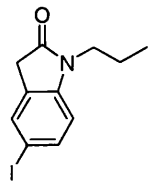
^{13}C NMR (100 MHz, $CDCl_3$) δ 10.4 (CH_3), 19.7 (CH_2), 34.6 (CH_2CO), 40.7 (CH_2N), 108.1 (ArCH), 123.9 (ArCH), 125.2 (ArC), 126.4 (ArC), 126.7 (ArCH), 142.3 (ArC), 173.4 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 1695 (C=O), 1610, 1486, 1342.

MS *m/z* (EI+ mode) 209 (M^+, 64%), 180 (36), 152 (58), 117 (32), 85 (65), 84 (100), 47 (17).

$C_{11}H_{12}NOCl$ requires 209.0607, found 209.0605.

5-Iodo-1-propyl-1,3-dihydro-indol-2-one (407)



S-Merrifield bound 5-iodo-3-mercapto-1-propyl-1,3-dihydro-indol-2-one (845 mg, 0.48 mmol/g, 0.41 mmol, 1 eq) was swollen in THF (7 ml) for 15 min. DMPU (0.44 ml, 3.65 mmol, 8.9 eq) and a solution of SmI_2 (9.10 ml of 0.1 M solution in THF, 0.91 mmol, 2.2 eq) were added and the reaction allowed to stir at rt for 18 h. The resin was filtered and the solution phase was collected and concentrated *in vacuo*. Filtration through a short plug of silica washing with 30 % ethyl acetate in petroleum ether to give 5-iodo-1-propyl-1,3-dihydro-indol-2-one **407** (24 mg, 0.08 mmol, 20 %) as a clear oil. (Yield over 4 solid phase steps based on thiol resin of loading 0.56 mmol/g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.56 -1.66 (2H, m, C*H*$_2$), 3.43 (2H, s, C*H*$_2$CO), 3.57 (2H, t, J = 7.3 Hz, C*H*$_2$N), 6.44 (1H, d, J = 8.2 Hz, Ar*H*), 7.47 (1H, s, Ar*H*), 7.52 (1H, d, J = 8.2 Hz, Ar*H*).

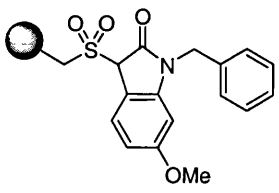
^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3 (*C*H$_3$), 19.6 (*C*H$_2$), 34.3 (*C*H$_2$CO), 40.6 (*C*H$_2$N), 83.4 (Ar*C*I), 109.3 (Ar*C*H), 126.0 (Ar*C*), 132.2 (Ar*C*H), 135.6 (Ar*C*H), 143.5(Ar*C*), 173.1 (*C*=O).

IR (υ_{max}/(cm^{-1}) 2960, 2917, 2848, 1698 (C=O), 1600, 1481.

MS *m/z* (EI$^+$ mode) 301 (M$^+$, 100%), 272 (36), 259 (19), 244 (19), 177 (70), 83 (29).

$C_{11}H_{12}NOI$ requires 300.9964, found 300.9964.

***S*-Merrifield bound 1-benzyl-6-methoxy-3-sulfonyl-1,3-dihydro-indol-2-one (416)**

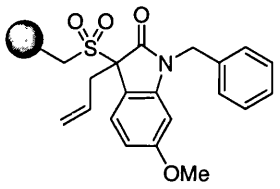


S-Merrifield bound 1-benzyl-3-mercapto-6-methoxy-1,3-dihydro-indol-2-one **384** (2.51 g, 0.49 mmol/g, 1.23 mmol, 1 eq) was swollen in DMF:H_2O (20 ml: 5 ml) for 15 min.

Oxone® (11.4 g, 18.6 mmol, 15.1 eq) was then added and the reaction allowed to stir at rt for 18 h. The resin was then washed using our standard washing protocol and the product resin, *S*- Merrifield bound 1-benzyl-6-methoxy-3-sulfonyl-1,3-dihydro-indol-2-one **416** was then dried *in vacuo*.

IR $\upsilon_{max}/(cm^{-1})$ 1712 (C=O), 1166 (S=O).

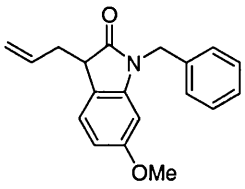
S-Merrifield bound 3-allyl-1-benzyl-6-methoxy-3-sulfonyl-1,3-dihydro-indol-2-one (417)



S-Merrifield bound 1-benzyl-6-methoxy-3-sulfonyl-1,2-dihydro-indol-2-one **416** (2.06 g, 0.48 mmol/g, 0.98 mmol, 1 eq) was swollen in DMF (20 ml) for 15 min. K_2CO_3 (2.56 g, 18.5 mmol, 18.9 eq), KI (123 mg, 0.74 mmol, 0.76 eq) and allyl bromide (1.28 ml, 14.8 mmol, 15.1 eq) were then added and the reaction was heated at 60 °C for 16 h. The resin was then washed using our standard washing protocol and the product resin, *S*-Merrifield bound 3-allyl-1-benzyl-6-methoxy-3-sulfonyl-1,3-dihydro-indol-2-one **417** was then dried *in vacuo*.

IR $\upsilon_{max}/(cm^{-1})$ 1714 (C=O), 1180 (S=O).

3-Allyl-1-benzyl-6-methoxy-1,3-dihydro-indol-2-one (418)



S Merrifield bound 3-allyl-1-benzyl-6-methoxy-3-sulfonyl-1,3-dihydro-indol-2-one **417** (1.0 g, 0.47 mmol/g, 0.47 mmol, 1 eq) was swollen in THF (10 ml) for 15 min. DMPU (1.68 ml, 13.9 mmol, 30 eq) and a solution of SmI_2 (34.7 ml of 0.1 M solution in THF, 3.47 mmol, 7.4 eq) were added and the reaction was allowed to stir at rt for 18 h. The resin

was filtered and the solution phase was collected and concentrated *in vacuo*. Filtration through a short plug of silica washing with 20% ethyl acetate in petroleum ether to gave 3-allyl-1-benzyl-6-methoxy-1,3-dihydro-indol-2-one **418** (38.7 mg, 0.13 mmol, 28 %) as a clear oil. (Yield over 4 solid phase steps based on thiol resin of loading 0.56 mmol/g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48-2.56 (1H, m, 1H from C*H*$_2$CH=CH$_2$), 2.71-2.81 (1H, m, 1H from C*H*$_2$CH=CH$_2$), 3.47 (1H, t, J = 6.1 Hz, C*H*), 3.65 (3H, s, C*H*$_3$O), 4.72 (1H, d, J = 15.6 Hz, 1H from C*H*$_2$N), 4.88 (1H, d, J = 15.6 Hz, 1H from C*H*$_2$N), 4.98 (1H, d, J = 10.1 Hz, 1H from C*H*$_2$=CH), 5.05 (1H, dd, J = 17.0 Hz, 1.1 Hz, 1H from C*H*$_2$=CH), 5.62-5.72 (1H, m, C*H*=CH$_2$), 6.22 (1H, d,. J = 2.2 Hz, Ar*H*), 6.44 (1H, dd, J = 8.1, 2.2 Hz, Ar*H*), 7.10 (1H, d, J = 8.1 Hz, *ArH*), 7.16-7.27 (5H, m, 5 × Ar*H*).

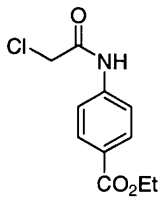
^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3 (*C*H$_2$CH=CH$_2$), 43.8 (NCH$_2$Ph), 44.7 (*C*H), 55.4 (*C*H$_3$O), 97.2 (Ar*C*H), 105.9 (Ar*C*H), 118.1 (*C*H$_2$=CH), 120.5 (Ar*C*), 124.7 (Ar*C*H), 127.3 (2 × Ar*C*H), 127.6 (Ar*C*H), 128.6 (2 × Ar*C*H), 134.1 (*C*H=CH$_2$), 135.9 (Ar*C*), 144.7 (Ar*C*), 159.9 (Ar*C*), 178.0 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 1710 (C=O), 1624, 1503, 1382, 1165.

MS *m/z* (EI$^+$ mode) 293 (M^+, 28%), 252 (100), 91 (75), 83 (39), 47 (8).

$C_{19}H_{19}NO_2$ requires 293.1416, found 293.1415.

Ethyl-4-(2-chloroacetamido) benzoate (442)



To a solution of 4-ethylamino benzoic acid **441** (6.04 g, 36.6 mmol, 1 eq) in CH_2Cl_2 (100 ml) was added NEt_3 (10.2 ml, 73.2 mmol, 2 eq). The reaction was cooled to 0 °C and chloroacetyl chloride (3.2 ml, 40.3 mmol, 1.1 eq) was slowly added. The reaction was allowed to stir at rt for 3 h. The reaction mixture was then washed with 0.5M HCl, saturated aqueous $NaHCO_3$ then dried ($MgSO_4$) and concentrated *in vacuo* to give ethyl 4-(2-chloroacetamido)benzoate **442** (8.42 g, 34.8 mmol, 95 %) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, t, J = 7.1 Hz, C*H*$_3$), 4.34 (2H, s, C*H*$_2$Cl), 4.49 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 7.77 (2H, m, 2 × Ar*H*), 8.17 (2H, m, 2 × Ar*H*), 8.50 (1H, s, N*H*).

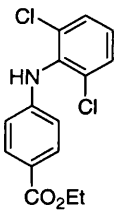
^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (*C*H$_3$), 41.9 (*C*H$_2$), 60.0 (*C*H$_2$), 118.3 (2 × Ar*C*H), 125.7 (Ar*C*), 129.7 (2 × Ar*C*H), 140.0 (Ar*C*), 163.5 (*C*=O), 165.0 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 3389 (NH), 2359, 2340, 1716 (C=O, ester), 1682 (C=O, amide), 1599, 1530, 1408, 1173, 1107.

MS *m/z* (EI^+ mode) 241 (63), 213 (20), 196 (70), 165 918), 137 (24), 120 (500), 83 (100), 65 (16), 47 (20).

$C_{11}H_{12}NO_3Cl$ requires 241.0506, found 241.0504

Ethyl 4-(2,6-dichlorophenylamino)benzoate (440)



To a solution of ethyl 4-(2-chloroacetamido) benzoate **442** (7.69 g, 31.8 mmol, 1 eq) in DMF (140 ml) was added K_2CO_3 (17.6 g, 127.4 mmol, 4 eq) and 2,6-dichlorophenol (5.18 g, 31.8 mmol, 1 eq) and the reaction was heated at 85 °C for 16 h. The reaction was allowed to cool and a solution of NaOEt (21.6g, 318 mmol, 10 eq) in ethanol (80 ml) was added. The reaction was heated at 80 °C for 4 h. After cooling, water (150 ml) was added to the reaction. The water / DMF layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a brown solid. The crude product mixture was purified by flash chromatography using 10 % EtOAc in petroleum ether as eluant to give ethyl 4-(2,6-dichlorophenylamino)benzoate **440** (3.03 g, 9.45 mmol, 30 %) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J = 7.1 Hz, C*H*$_3$), 4.35 (2H, q, J = 7.1 Hz, C*H*$_2$CH$_3$), 5.98 (1H, s, N*H*), 6.67 (2H, apparent dt, J = 9.3, 2.2 Hz, 2 × Ar*H*), 7.16 (1H, t, J = 8.1 Hz, Ar*H*), 7.43 (2H, d, J = 8.1 Hz, 2 × Ar*H*), 7.94 (2H, d, J = 9.3 Hz, 2 × Ar*H*).

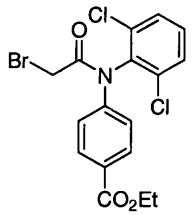
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8 (*C*H_3), 60.8 (*C*H_2), 114.8 (2 × Ar*C*H), 122.6 (Ar*C*), 127.1 (Ar*C*H), 129.3 (2 × Ar*C*H), 131.5 (2 × Ar*C*H), 132.9 (2 × Ar*C*), 135.6 (ArC), 148.0 (Ar*C*), 166.8 (*C*=O).

IR υ_{max}/(cm^{-1}) 3317 (NH), 2357, 1667 (C=O), 1602, 1515, 1287, 1171.

MS *m/z* (EI$^+$ mode) 309 (100), 264 (93), 201 (39), 167 (22), 132 (10), 83 (20), 65 (10).

$C_{15}H_{13}NO_2Cl_2$ requires 309.0323, found 309.0321.

Ethyl 4-(2-bromo-*N*-(2,6-dichlorophenyl)acetamido)benzoate (439)



Ethyl 4-(2,6-dichlorophenylamino)benzoate **440** (1.18 g, 3.8 mmol, 1 eq) was heated in neat bromoacetyl bromide (6 ml) at 90 °C for 1 h. The reaction was allowed to cool and CH_2Cl_2 (100 ml) was added. The CH_2Cl_2 layer was washed with 0.5 M NaOH, dried ($MgSO_4$) and concentrated *in vacuo* to give ethyl 4-(2-bromo-*N*-(2,6-dichlorophenyl)acetamido)benzoate **439** (1.63 g, 3.80 mmol, 100 %) as a brown solid which was used without further purification (~2:1 mixture of rotamers).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (6H, t, J = 7.1 Hz, C*H*$_3$ of both rotamers), 3.83 (2H, s, C*H*$_2$CO of one rotamer), 4.03 (2H, s, C*H*$_2$CO of one rotamer), 4.38 (4H, q, J = 7.0 Hz, C*H*$_2$O of both rotamers), 7.38 (6H, broad signal, 3 × Ar*H* of both rotamers), 7.38 (4H, broad signal, 2 × Ar*H* of both rotamers), 7.75 (4H, broad signal, 2 × Ar*H* of both rotamers).

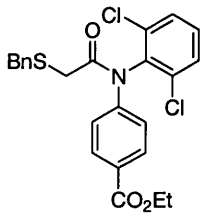
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (*C*H_3), 28.6 (*C*H_2CO), 61.5 (*C*H_2O), 124.7 (2 × Ar*C*H), 130.2 (2 × Ar*C*H), 130.6 (2 × Ar*C*H), 131.5 (Ar*C*H), 166.2 (*C*=O), signals for quaternary aromatic carbons not observed.

IR υ_{max}/(cm^{-1}) 2953, 1686 (C=O), 1602, 1271, 1107.

MS *m/z* (EI$^+$ mode) 431 (M^+, 36%), 429 (M+, 26%), 396 (72), 309 (100), 264 (45), 201 (35).

$C_{17}H_{14}NO_3BrCl_2$ requires 428.9534, found 428.9532.

Ethyl 4-(2-(benzylthio)-*N*-(2,6-dichlorophenyl)acetamido)benzoate (446)



To a solution of ethyl 4-(2-bromo-*N*-(2,6-dichlorophenyl)acetamido)benzoate **439** (260 mg, 0.6 mmol, 1 eq) in DMF (10 ml) was added NEt_3 (0.16 ml, 1.2 mmol, 2 eq) and benzyl thiol (0.07 ml, 0.6 mmol, 1 eq) and the reaction allowed to stir at rt for 1 h. 30 % Ethyl acetate in petroleum ether was added to the reaction mixture and the mixture was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by by flash chromatography using 10 % EtOAc in petroleum ether as eluant to give ethyl 4-(2-(benzylthio)-*N*-(2,6-dichlorophenyl)acetamido)benzoate **446** (212 mg, 0.44 mmol, 74 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J = 7.1 Hz, C*H*$_3$), 3.06 (2H, s, one rotamer of C*H*$_2$CO), 3.27 (2H, s, one rotamer of C*H*$_2$CO), 3.94 (2H, s, PhC*H*$_2$), 4.39 (2H, q, J = 7.1 Hz, C*H*$_2$O), 7.16-7.37 (10H, m, 10 × Ar*H*), 7.55 (2H, d, J = 7.2 Hz, 2 × Ar*H*).

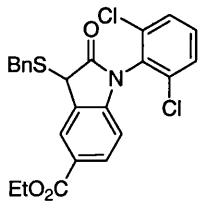
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (*C*H$_3$), 34.3 (*C*H$_2$CO), 36.7 (Ph*C*H$_2$), 61.4 (*C*H$_2$O), 124.7 (2 × Ar*C*H), 127.6 (2 × Ar*C*H), 128.9 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 130.0 (2 × Ar*C*H), 130.5 (Ar*C*H), 131.1 (Ar*C*H), 166.3 (*C*=O), 169.3 (*C*=O), quaternary aromatic carbons not detected.

IR υ_{max}/(cm^{-1}) 2981, 1714 (C=O), 1681 (C=O), 1604, 1274, 1105.

MS *m/z* (EI$^+$ mode) 473 (5), 351 (50), 316 (95), 309 (15), 264 (11), 91 (100), 65 (12).

$C_{24}H_{21}NO_3BrCl_2S$ requires 473.0619, found 473.0620.

Ethyl 3-(benzylthio)-1-(2,6-dichlorophenyl)-2-oxo-2,3-dihydro-1H-indol-5-yl carboxylate (448)



To a solution of ethyl 4-(2-(benzylthio)-*N*-(2,6-dichlorophenyl)acetamido)benzoate **446** (165 mg, 0.35 mmol, 1 eq) in hexafluoroisopropanol (5 ml) and CH_2Cl_2 (2.5 ml). H_2O_2 (0.14 ml of 35 % aq sol, 1.4 mmol, 4 eq) was added and the reaction was allowed to stir at room temperature for 20 min. The reaction was quenched with $NaHCO_3$. CH_2Cl_2 was added and the organic layer washed with water, dried ($MgSO_4$) and concentrated to give ethyl 4-(2-(benzylsulfinyl)-*N*-(2,6-dichlorophenyl)acetamido)benzoate **447** (172 mg, 0.35 mmol, 100 %) as a clear oil which was used without further purification. To a solution of ethyl 4-(2-(benzylsulfinyl)-*N*-(2,6-dichlorophenyl)acetamido)benzoate **447** (61mg, 0.12 mmol, 1 eq) in 1,2-dichloroethane (8 ml) was added TFAA (70 µl, 0.5 mmol, 4 eq) and the reaction allowed to stir at room temperature for 15 min. BF_3 OEt_2 (0.13 ml, 1.0 mmol, 8 eq) was added and the reaction was allowed to stir at room temperature for a further 20 min. The reaction was quenched with 0.1 M NaOH. The aqueous and organic layers were separated and the organic layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography using 10 % ethyl acetate in petroleum ether as eluant to give Ethyl 3-(benzylthio)-1-(2,6-dichlorophenyl)-2-oxo-2,3-dihydro-1H-indol-5-yl carboxylate **448** 47 mg, 0.29 mmol, 82 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, J = 7.1 Hz, CH_3), 3.75 (1H, d, J = 12.9 Hz, 1H from PhCH_2), 4.22-4.34 (3H, m, CH_2O and 1H from PhCH_2), 4.36 (1H, s, C*H*), 6.37 (1H, d, J = 8.2 Hz, Ar*H*), 7.17-7.47 (8H, m, 8 × Ar*H*), 7.88 (1H, d, J = 8.2 Hz, Ar*H*), 7.95 (1H, s, Ar*H*).

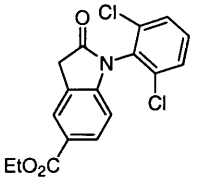
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (*C*H_3), 34.9 (Ph*C*H_2), 43.4 (*C*H), 61.4 (*C*H_2O), 109.2 (Ar*C*H), 125.7 (Ar*C*), 126.4 (Ar*C*), 127.4 (Ar*C*H), 127.8 (Ar*C*H), 129.0 (2 × Ar*C*H), 129.5

(Ar*C*H), 129.6 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 131.6 (Ar*C*H), 131.9 (Ar*C*H), 135.8 (2 × Ar*C*), 137.3 (Ar*C*), 146.4 (Ar*C*), 166.3 (*C*=O), 174.5 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 3062, 2981, 1735 (C=O), 1710 (C=O), 1616, 1494, 1263, 1166, 1108.

MS *m/z* (FAB^+ mode) 472 (M^+, 64%), 349 (100), 348 (88), 91 (70).

Ethyl (1-(2,6-dichlorophenyl)-2-oxo-1,3-dihydro-indol-5-yl) carboxylate (449)



To a solution of ethyl 3-(benzylthio)-1-(2,6-dichlorophenyl)-2-oxo-2,3-dihydro-1*H*-indol-5-yl carboxylate **448** (70.3 mg, 0.14 mmol, 1 eq) in THF (5 ml) was added DMPU (0.14 ml, 1.12 mmol, 8 eq) and a solution of SmI_2 (2.97 ml of 0.1 M soln in THF, 0.30 mmol, 2 eq) and the reaction allowed to stir at rt for 2.5 h. $CHCl_3$ was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated. The crude product mixture was purified by flash chromatography using 10 % ethyl acetate in petroleum ether as eluant to give ethyl (1-(2,6-dichlorophenyl)-2-oxo-1,3-dihydro-indol-5-yl) carboxylate **449** (19 mg, 0.05 mmol, 49 % based on 20 % recovered starting material).

^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (3H, t, J= 7.1 Hz, C*H*$_3$), 3.75 (2H, s, C*H*$_2$CO), 4.29 (2H, q, J= 7.1Hz, C*H*$_2$O), 6.26 (1H, d, J = 8.3 Hz, Ar*H*), 7.33 (1H, t, J = 7.5 Hz, Ar*H*), 7.44 (2H, m, 2 × Ar*H*), 7.88 (1H, d, J= 8.3 Hz, Ar*H*), 7.97 (1H, s, Ar*H*).

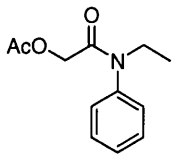
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (*C*H$_3$), 34.7 (*C*H$_2$CO), 61.4 (*C*H$_2$O), 109.5 (Ar*C*H), 124.5 (Ar*C*), 125.9 (Ar*C*), 126.6 (Ar*C*H), 129.5 (Ar*C*H), 129.7 (2 × Ar*C*H), 130.4 (2 × ArC), 131.1 (Ar*C*H), 137.4 (Ar*C*), 147.6 (ArC), 166.6 (C=O), 173.9 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 2959, 2916, 1730 (C=O), 1711 (C=O), 1613, 1492, 1262, 1162.

MS *m/z* (EI^+ mode) 349 (M^+, 45 %), 304 (27), 286 (15), 214 (20), 120 (24), 84 (100), 47 (27).

$C_{17}H_{13}NO_3Cl_2$ requires 349.0272, found 349.0270.

_N_-ethyl-2-acetoxy-_N_-phenylacetamide (490)



To a solution of acetoxy acetic acid (1.29 g, 10.9 mmol, 1 eq), _N_-ethyl aniline (1.65 ml, 13.1 mmol, 1.2 eq) and 1-hydroxybenzotriazole (283 mg, 2.20 mmol, 0.2 eq) in CH_2Cl_2 (40 ml) was added EDCI (2.50 g, 13.1 mmol, 1.2 eq) and the reaction was allowed to stir at room temperature for 18 h. The reaction mixture was washed with 1M HCl and water then dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil. The crude product mixture was purified by flash chromatography using 50 % ethyl acetate in petroleum ether as eluant to give _N_-ethyl-2-acetoxy-_N_-phenylacetamide **490** (1.79 g, 8.01 mmol, 74 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, t, J = 7.1 Hz, C*H*$_3$), 2.04 (3H, s, C*H*$_3$), 3.69 (2H, t, J = 7.2 Hz, C*H*$_2$), 4.26 (2H, s, C*H*$_2$CO), 7.18 (2H, apparent d, J = 9.1 Hz, 2 × Ar*H*), 7.27-7.41 (3H, m, 3 × Ar*H*).

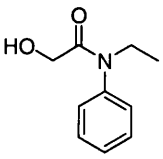
^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2 (*C*H$_3$), 20.6 (*C*H$_3$), 44.6 (*C*H$_2$N), 62.7 (*C*H$_2$CO), 128.6 (2 × Ar*C*H), 129.1 (Ar*C*H), 130.4 (2 × Ar*C*H), 143.2 (Ar*C*), 165.4 (*C*=O, amide), 170.8 (*C*=O, ester).

IR υ_{max}/(cm^{-1}) 2973, 2937, 1745 (C=O), 1671 (C=O), 1594, 1494, 1224.

MS *m/z* (EI$^+$ mode) 221 (M$^+$, 20%), 148 (62), 121 (100), 83 (58), 43 (55).

$C_{12}H_{15}NO_3$ requires 221.1052, found 221.1058.

_N_-Ethyl-2-hydroxy-_N_-phenylacetamide (491)



To a solution of _N_-ethyl-2-acetoxy-_N_-phenylacetamide **490** (1.78 g, 8.05 mmol, 1 eq) in MeOH (30 ml) and water (15 ml) was added K_2CO_3 (4.45 g, 32.2 mmol, 4 eq) and the

reaction was allowed to stir at room temperature for 24 h. H_2O (30 ml) was added to the reaction and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-ethyl-2-hydroxy-*N*-phenylacetamide **491** (1.37 g, 7.65 mmol, 95 %) as a clear oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, J= 7.2 Hz, C*H*$_3$), 3.45 (1H, s, O*H*), 3.63 (2H, s, C*H*$_2$CO), 3.70 (2H, q, J = 7.2 Hz, C*H*$_2$), 7.07 (2H, dd, J= 8.4, 0.84 Hz, 2 × Ar*H*), 7.23-7.37 (3H, m, 3 × Ar*H*).

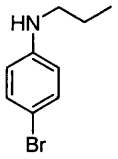
^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (*C*H$_3$), 44.8 (*C*H$_2$), 60.9 (*C*H$_2$), 128.6 (2 × Ar*C*H), 129.1 (Ar*C*H), 130.3 (2 × Ar*C*H), 139.7 (Ar*C*), 171.7 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 3444 (OH), 1658 (C=O), 1594, 1496, 1386.

MS *m/z* (EI$^+$ mode) 179 (M^+, 72%), 148 (64), 120 (100), 106 (75), 77 (52).

$C_{10}H_{13}NO_2$ requires 179.0946, found 179.0944.

4-Bromo-*N*-propyl aniline



To a solution of 4-bromoaniline (6.00 g, 35.0 mmol, 1 eq) in CH_2Cl_2 (150 ml) was added NEt_3 (7.38 ml, 52.5 mmol, 1.5 eq) and propionic anhydride (9.0 ml, 70.0 mmol, 2 eq) and the reaction allowed to stir at room temperature for 3 h. The reaction mixture was then washed with aqueous saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. THF (120 ml) was then added and the reaction was cooled to 0 °C. $LiAlH_4$ (3.05g, 80.5 mmol, 2.3 eq) was added slowly and the reaction was allowed to stir at room temperature for 16 h. The reaction was cooled to 0 °C and quenched slowly with H_2O. CH_2Cl_2 was added and the aqueous and organic layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) concentrated *in vacuo*. The crude product was purified by flash chromatography using 20 % EtOAc in petroleum ether to give 4-bromo-*N*-propyl aniline (4.97 g, 23.1 mmol, 66 % over 2 steps) as a dark orange oil.

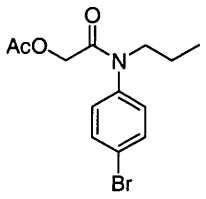
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.66 (2H, m, C*H*$_2$), 3.07 (2H, t, J = 7.1 Hz, C*H*$_2$N), 3.87 (1H, broad singlet, N*H*), 6.49-6.53 (2H, m, 2 × Ar*H*), 7.24-7.28 (2H, m, 2 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0 (*C*H$_3$), 22.9 (*C*H$_2$), 46.2 (*C*H$_2$N), 109.1 (Ar*C*), 114.7 (2 × Ar*C*H), 132.3 (2 × Ar*C*H), 147.7 (Ar*C*).

MS *m/z* (EI$^+$ mode) 213 (M$^+$, 32%), 184 (100), 105 (22), 84 (34), 47 (7).

$C_9H_{12}NBr$ requires 213.0153, found 213.0151.

_N_-(4-Bromophenyl)-_N_-propyl 2-acetoxyacetamide (493)



To a solution of acetoxy acetic acid (2.64 g, 22.4 mmol, 1 eq), 4-bromo-*N*-propyl aniline (4.97, 22.4 mmol, 1.2 eq) and 1-hydroxybenzotriazole (605 mg, 4.48 mmol, 0.2 eq) in CH_2Cl_2 (40 ml) was added EDCI (5.14g, 26.9 mmol, 1.2 eq) and the reaction allowed to stir at room temperature for 18 h. The reaction mixture was washed with 1M HCl and water then dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil. The crude product mixture was purified by flash chromatography using 30 % ethyl acetate in petroleum ether as eluant to give *N*-(4-bromophenyl)-*N*-propyl 2-acetoxyacetamide **493** (6.16 g, 19.5 mmol, 87 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.40-1.49 (2H, m C*H*$_2$), 2.06 (3H, s, C*H*$_3$CO), 3.56 (2H, t, J = 8.2 Hz, C*H*$_2$N), 4.24 (2H, s, C*H*$_2$CO), 7.04- 7.08 (2H, m, 2 × Ar*H*), 7.47-7.52 (2H, m, 2 × Ar*H*).

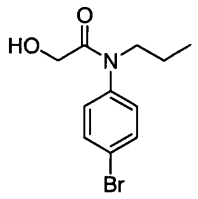
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H$_3$), 20.9 (*C*H$_3$CO), 21.2 (*C*H$_2$), 51.4 (*C*H$_2$N), 62.1 (*C*H$_2$CO), 123.0 (Ar*C*), 130.3 (2 × Ar*C*H), 133.7 (2 × Ar*C*H), 140.0 (Ar*C*), 166.4 (*C*=O amide), 170.1 (*C*=O, ester).

IR υ_{max}/(cm^{-1}) 2962, 2933, 2873, 1747 (C=O), 1679, 1486, 1423, 1224.

MS *m/z* (EI$^+$ mode) 315 (M$^+$, 35%), 213 (50), 184 (56), 86 (65), 84 (100), 43 (67).

$C_{13}H_{16}O_3NBr$ requires 313.0314, found 313.0318.

_N_-(4-Bromophenyl)-_N_-propyl-2-hydroxyacetamide (494)



To a solution of _N_-(4-bromophenyl)-_N_-propyl 2-acetoxyacetamide **493** (748 mg, 2.38 mmol, 1 eq) in MeOH (20 ml) and water (10 ml) was added K_2CO_3 (1.31g, 9.52 mmol, 4 eq) and the reaction allowed to stir at room temperature for 24 h. H_2O (20ml) was added to the reaction and the aqueous layer was extracted with EtOAc. Combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give _N_-(4-bromophenyl)-_N_-propyl-2-hydroxyacetamide **494** (646 mg, 2.36 mmol, 99 %) as an orange oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.40-1.51 (2H, m, C*H*$_2$), 3.23 (1H, t, J = 4.5 Hz, O*H*), 3.61 (2H, t, J = 7.6 Hz, C*H*$_2$N), 3.67 (2H, d, J = 4.5 Hz, C*H*$_2$CO), 6.98 (2H, d, J = 8.5 Hz, 2 × Ar*H*), 7.50 (2H, d, J = 8.5 Hz, 2 × Ar*H*).

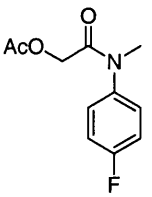
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H$_3$), 21.2 (*C*H$_2$), 51.6 (*C*H$_2$N), 60.9 (*C*H$_2$CO), 123.2 (Ar*C*), 130.2 (2 × Ar*C*H), 133.7 (2 × Ar*C*H), 139.0 (Ar*C*), 171.7 (*C*=O).

IR υ_{max}/(cm^{-1}) 3436 (OH), 2962, 2931, 2873, 1658 (C=O), 1488, 1384, 1286, 1097.

MS *m/z* (EI$^+$ mode) 271 (M$^+$, 35%), 229 (35), 184 (100), 155 (15), 105 (27), 84 (64), 43 (68).

$C_{11}H_{14}O_2NBr$ requires 271.0208, found 271.0207.

_N_-(4-Fluorophenyl)-_N_-methyl 2-acetoxyacetamide (496)



To a solution of acetoxy acetic acid (2.64 g, 22.1 mmol, 1 eq), 4-fluoro-_N_-methyl aniline (2.5 ml, 22.1 mmol, 1 eq) and 1-hydroxybenzotriazole (597 mg, 4.48 mmol, 0.2 eq) in CH_2Cl_2 (40 ml) was added EDCI (5.06 g , 26.5 mmol, 1.2 eq) and the reaction allowed to

stir at room temperature for 18 h. The reaction mixture was washed with 1M HCl and water then dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-(4-fluorophenyl)-*N*-methyl 2-acetoxyacetamide **496** (4.79 g, 21.2 mmol, 96 %) as a brown solid which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (3H, s, C*H*$_3$CO), 3.19 (3H, s, C*H*$_3$N), 4.28 (2H, s, C*H*$_2$O), 7.05-7.20 (5H, m, 5 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (*C*H$_3$CO), 38.0 (*C*H$_3$N), 61.9 (*C*H$_2$O), 117.5 (d, J = 22.7 Hz, 2 × Ar*C*H), 129.5 (d, J = 8.7 Hz, 2 × Ar*C*H), 138.4 (Ar*C*N), 163.1 (d, J = 247.8 Hz, Ar*C*F), 167.0 (*C*=O), 171.0 (*C*=O).

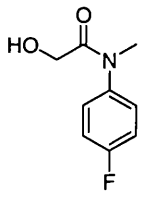
IR $\upsilon_{max}/(cm^{-1})$ 2952, 1745 (C=O, ester), 1666 (C=O, amide), 1508, 1423, 1218, 1079.

MS (CI^+ mode) 226 ($(M+H)^+$, 100%),184 (9), 174 (8).

$C_{11}H_{13}NO_3F$ requires 226.0879 found 226.0855.

Mpt : 65-67 °C

N-(4-Fluorophenyl)-N-methyl-2-hydroxyacetamide (497)



To a solution of *N*-(4-fluorophenyl)-*N*-methyl 2-acetoxyacetamide **496** (4.73g, 21.0 mmol, 1 eq) in MeOH (60 ml) and H_2O (30 ml) was added K_2CO_3 (11.6 g, 84.0 mmol, 4 eq) and the reaction allowed to stir at room temperature for 24 h. H_2O (20 ml) was added to the reaction and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-(4-fluorophenyl)-*N*-methyl-2-hydroxyacetamide **497** (2.68 g, 14.7 mmol, 70 %) as a brown solid which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (3H, s, C*H*$_3$N), 3.72 (2H, s, C*H*$_2$CO), 7.01-7.16 (5H, m, 5 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0 (CH_3N), 60.8 (CH_2O), 117.5 (d, J = 22.8 Hz, 2 × ArCH), 129.4 (d, J = 8.7 Hz, 2 × ArCH), 137.4 (ArCN), 162.6 (d, J = 248.1 Hz, ArCF), 172.3 (C=O).

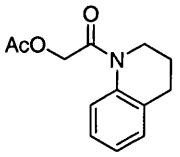
IR $\upsilon_{max}/(cm^{-1})$ 3436 (OH), 1650 (C=O), 1500, 1353, 1216, 1097.

MS *m/z* (EI^+ mode) 183 (M^+, 68%), 152 (57), 124 (100), 95 (27), 82 (14), 75 (14).

$C_9H_{10}O_2NF$ requires 183.0696, found 183.0695.

Mpt : 95 -97 °C

_N_-(3,4-Dihydroquinolin-1(2H)-yl) 2-acetoxyacetamide (485)



To a solution of acetoxy acetic acid (602 mg, 5.10 mmol, 1 eq), 1,2,3,4-tetrahydroquinolone (0.70 ml, 5.60 mmol, 1.1 eq) and 1-hydroxy benzotriazole (138 mg, 1.02 mmol, 0.2 eq) in CH_2Cl_2 (40 ml) was added EDCI (2.50 g, 13.1 mmol, 1.2 eq) and the reaction allowed to stir at room temperature for 4 h. The reaction mixture was washed with 1M HCl and water then dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil. The crude product mixture was purified by flash chromatography using 80 % ethyl acetate in petroleum ether as eluant to give *N*-(3,4-dihydroquinolin-1(2H)-yl) 2-acetoxyacetamide **485** (880 mg, 3.77 mmol, 74 %) as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.77-2.02 (2H, m, CH_2), 2.11 (3H, s CH_3CO), 2.72 (2H, t, J = 8.0 Hz, CH_2Ph), 3.92 (2H, t, J = 7.2 Hz, CH_2N), 4.78 (2H, s, CH_2CO), 7.11-7.29 (4H, m, 4 × ArH).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH_3CO), 23.7 (CH_2), 26.6 (CH_2), 43.1 (CH_2N), 62.2 (CH_2CO), 123.8 (ArCH), 125.9 (ArCH), 126.4 (ArCH), 128.4 (ArC), 128.8 (ArCH), 137.7 (ArC), 166.4 (C=O, amide), 170.6 (C=O, ester).

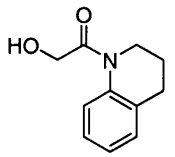
IR $\upsilon_{max}/(cm^{-1})$ 3056, 2934, 1732 (C=O, ester), 1644 (C=O, amide), 1492, 1401, 1230.

MS *m/z* (EI^+ mode) 223 (M^+, 25%), 133 (100), 177 (10), 77 (12), 43 (41).

$C_{13}H_{15}NO_3$ requires 223.1052, found 223.1052.

Mpt: 86-88 °C.

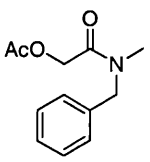
2-Hydroxy-*N*-(3,4-dihydroquinolin-1(2H)-yl)acetamide (486)



To a solution of *N*-(3,4-dihydroquinolin-1(2H)-yl) 2-acetoxyacetamide **485** (880 mg, 3.77 mmol, 1 eq) in MeOH (20 ml) and H_2O (10 ml) was added K_2CO_3 (2.18 g, 15.8 mmol, 4 eq) and the reaction allowed to stir at room temperature for 24 h. H_2O (30 ml) was added to the reaction and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give 2-Hydroxy-*N*-(3,4-dihydroquinolin-1(2H)-yl)acetamide **486** (583 mg, 2.90 mmol, 77 %) as a yellow solid which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95-2.06 (2H, m, C*H*$_2$), 2.73-2.78 (2H, broad signal, C*H*$_2$Ar), 3.62 (2H, broad signal, C*H*$_2$N), 3.81 (1H, t, J= 6.5 Hz, O*H*), 4.31 (2H, broad singlet, C*H*$_2$OH), 7.19-7.25 (4H, m, 4 × Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9 (*C*H$_2$), 27.1 (*C*H$_2$), 43.6 (*C*H$_2$N), 61.4 (*C*H$_2$O), 123.9 (Ar*C*H), 126.8 (Ar*C*H), 128.8 (Ar*C*), 129.3 (2 × Ar*C*H), 137.6 (Ar*C*), C=O not detected.
IR υ_{max}/(cm^{-1}) 3371 (OH), 3059, 2940, 1647 (C=O), 1487, 1421, 1093.
MS *m/z* (EI$^+$ mode) 191 (M$^+$, 92%), 160 (45), 132 (100), 117 (20), 77 (25).
$C_{11}H_{13}NO_2$ requires 191.0946, found 191.0947.
Mpt: 78 °C.

***N*-(Benzyl)-*N*-methyl 2-acetoxyacetamide (499)**



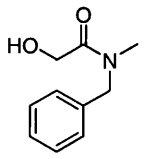
To a solution of acetoxy acetic acid (0.83 g, 7.05 mmol, 1 eq), *N*-benzylmethyl amine (1.0 ml, 121.2 mmol, 1.1 eq) and 1-hydroxy benzotriazole (209 mg, 1.55 mmol, 0.2 eq) in CH_2Cl_2 (40 ml) was added EDCI (5.14 g, 26.9 mmol, 1.2 eq) and the reaction was allowed

to stir at room temperature for 18 h. The reaction mixture was washed with 1M HCl and H_2O then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography using 30 % ethyl acetate in petroleum ether as eluant to give *N*-(benzyl)-*N*-methyl 2-acetoxyacetamide **499** (1.59 g, 6.56 mmol, 93 %) as clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (3H, s, C*H*$_3$CO of one rotamer), 2.33 (3H, s, C*H*$_3$CO of one rotamer), 2.89 (3H, s, C*H*$_3$N of one rotamer), 2.99 (3H, s, C*H*$_3$N of one rotamer), 4.49 (2 H, s, C*H*$_2$N of one rotamer), 4.61 (2H, s, C*H*$_2$N of one rotamer), 4.78 (4H, s, C*H*$_2$CO of both rotamers) 7.21-7.42 (10H, m, 5 × Ar*H* of both rotamers).

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (*C*H$_3$CO of one rotamer), 21.1 (*C*H$_3$CO of one rotamer), 33.7 (*C*H$_3$N of one rotamer) 34.4 (*C*H$_3$N of one rotamer), 51.5 (*C*H$_2$N of one rotamer), 52.7 (*C*H$_2$N of one rotamer), 61.7 (*C*H$_2$O of one rotamer), 61.8 (*C*H$_2$O of one rotamer), 126.4 (2 ×Ar*C*H of one rotamer), 127.6 (2 × Ar*C*H of one rotamer), 127.9 (Ar*C*H of one rotamer), 128.2 (2 × Ar*C*H of one rotamer), 128.7 (2 × Ar*C*H of one rotamer), 129.1 (Ar*C*H of one rotamer) 135.9 (Ar*C* of one rotamer), 136.9 (Ar*C* of one rotamer), 166.9 (C=O of amide, one rotamer), 167.2 (C=O of amide, one rotamer), 171.1 (C=O).
IR $\upsilon_{max}/(cm^{-1})$ 1746 (C=O of ester), 1665 (C=O of amide), 1495, 1232, 1067.
MS *m/z* (EI$^+$ mode) 221 (M^+, 2%), 161 (50), 118 (48), 91 (100), 65 (15), 43 (34).
$C_{12}H_{15}O_3N$ requires 221.1052, found 221.1050.

N-Benzyl-2-hydroxy-N-methylacetamide (500)[99]



To a solution of *N*-(benzyl)-*N*-methyl 2-acetoxyacetamide **499** (1.19 g, 5.38 mmol, 1 eq) in MeOH (20 ml) and H_2O (10 ml) was added K_2CO_3 (2.97 g, 21.5 mmol, 4 eq) and The reaction allowed to stir at room temperature for 24 h. H_2O (20 ml) was added to the reaction and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give *N*-benzyl-2-hydroxy-*N*-

methylacetamide **500** (0.92 g, 5.16 mmol, 96 %) as clear which was used without further purification.

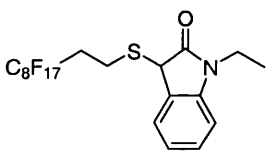
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (3H, s, C*H*$_3$N of one rotamer), 2.96 (3H, C*H*$_3$N of one rotamer), 3.71 (2H, broad s, O*H* of both rotamers), 4.21 (2H, s, C*H*$_2$N of one rotamer), 4.26 (2H, s, C*H*$_2$N of one rotamer), 4.55 (2H, s, C*H*$_2$O of one rotamer), 4.31 (2H, s, C*H*$_2$O of one rotamer), 6.91-7.49 (10 H, m, 5 × Ar*H* of both rotamers).
^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4 (*C*H$_3$N of one rotamer), 33.9 (*C*H$_3$N of one rotamer), 51.2 (*C*H$_2$N of one rotamer), 51.4 (*C*H$_2$N of one rotamer), 59.9 (*C*H$_2$O of one rotamer), 60.3 (*C*H$_2$O of one rotamer), 126.0 (2 × Ar*C*H of one rotamer), 127.3 (2 × Ar*C*H of one rotamer), 127.6 (Ar*C*H of one rotamer), 127.9 (2 × Ar*C*H of one rotamer), 128.7 (2 × Ar*C*H of one rotamer), 129.1 (Ar*C*H of one rotamer) 132.9 (Ar*C* of one rotamer) 133.9 (Ar*C* of one rotamer), 169.5 (C=O of one rotamer), 169.6 (C=O of one rotamer).
IR $\upsilon_{max}/(cm^{-1})$ 3398 (OH), 1639 (C=O), 1494, 1453, 1384, 1069.
MS *m/z* (EI^+mode) 179 (M^+, 33%), 118 (10), 91 (100), 88 (17), 65 (16).
$C_{10}H_{13}O_2N$ require 179.0946, found 179.0946.

Fluorous tagged oxindoles

General procedure for purification using Fluorous solid phase extraction (FSPE)

Crude reaction mixtures were loaded onto a fluorous silica gel column using 80 % MeCN / H_2O. Non-fluorous tagged components were eluted from the column with 80 % MeCN/H_2O (fluorophobic solvent). Fluorous-tagged components were then eluted using MeCN (fluorophilic solvent).

1-Ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1,3-dihydro-indol-2-one (502)



To a solution of oxalyl chloride (70 µl, 0.77 mmol, 1.1 eq) in CH_2Cl_2 (5 ml) at – 78 °C was added DMSO (0.1 ml, 1.40 mmol, 2 eq). After stirring for 35 min a solution of *N*-ethyl-2-hydroxy-*N*-phenylacetamide **491** (125 mg, 0.70 mmol, 1 eq) in CH_2Cl_2 (5 ml) was added. After stirring for a further 1 h at – 78 °C, NEt_3 (0.49 ml, 3.48 mmol, 5 eq) was added and the reaction was allowed to stir at room temperature for 1 h 30 min. CH_2Cl_2 was added to the reaction mixture and the organic layer was washed with $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude glyoxamide which was used without further purification. CH_2Cl_2 (10 ml) was added to the crude glyoxamide **492** followed by 1H, 1H,2H, 2H-perfluorodecane-1-thiol (0.14 ml, 0.49 mmol, 0.7 eq) and the reaction was allowed to stir at room temperature for 20 h. TFAA (0.89 ml, 6.26 mmol, 9 eq) was then added and after 1 h, $BF_3 \cdot OEt_2$ (0.44 ml, 3.48, 5 eq) was added. After stirring for 1 h the reaction was quenched with $NaHCO_3$, the organic layer was washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude reaction mixture was purified by fluorous chromatography to give 1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1,3-dihydro-indol-2-one **502** (182 mg, 0.28 mmol, 59 % over 2 steps) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (3H, t, J = 7.2 Hz, C*H*$_3$), 2.31-2.44 (2H, m, CF_2CH_2), 2.73-2.82 (1H, m 1H from CH_2S), 2.87-2.97 (1H, m, 1H from CH_2S), 3.71-3.87 (2H, m, CH_2N), 4.33 (1H, s, CH), 6.87 (1H, d, J = 7.8 Hz, Ar*H*), 7.10 (1H, t, J = 7.5 Hz, Ar*H*), 7.33 (1H, t, J = 7.8 Hz, Ar*H*), 7.40 (1H, d, J= 7.5 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (*C*H$_3$), 21.2 (*C*H_2S), 32.4 (CF_2CH_2, t, J = 21.9 Hz), 35.4 (*C*H_2N), 45.3 (*C*H), 108.9 (Ar*C*H), 123.3 (Ar*C*H), 125.7 (Ar*C*H), 125.8 (Ar*C*), 129.8 (Ar*C*H), 143.5 (Ar*C*), 174.9 (*C*=O).

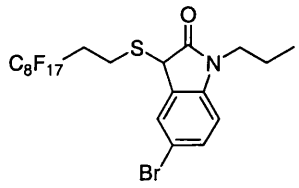
IR υ_{max}/(cm^{-1}) 3060, 2979, 1712 (C=O), 1612, 1353, 1236, 1201.

MS *m/z* (EI$^+$ mode) 639 (M$^+$, 10%), 161 (100), 83 (11).

$C_{20}H_{14}NOF_{17}S$ requires 639.0525, found 639.0527.

Mpt 41- 44 °C

5-Bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-propyl-1,3-dihydro-indol-2-one (503)



To a solution of oxalyl chloride (0.39 ml, 4.5 mmol, 1.1 eq) in CH_2Cl_2 (30 ml) at – 78 °C was added DMSO (0.58 ml, 8.2 mmol, 2 eq). After stirring for 35 min a solution of *N*-(4-bromophenyl)-*N*-propyl-2-hydroxyacetamide **494** (1.10 g, 4.1 mmol, 1 eq) in CH_2Cl_2 (30 ml) was added. After stirring for a further 1 h at – 78 °C, NEt_3 (2.88 ml, 20.5 mmol, 5 eq) was added and the reaction was allowed to stir at room temperature for 18 h. CH_2Cl_2 was added to the reaction mixture and the organic layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude glyoxamide **495** (684 mg, 2.54 mmol, 62 %) which was used without further purification. CH_2Cl_2 (10 ml) was added to the crude glyoxamide followed by 1H, 1H,2H, 2H-perfluorodecane-1-thiol (0.52 ml, 1.77 mmol, 0.7 eq) and the reaction allowed to stir at room temperature for 20 h. TFAA (3.36 ml, 2.27 mmol, 9 eq) was added. After 1 h $BF_3 \cdot OEt_2$ (1.61 ml, 12.7 mmol, 5 eq) was added. After stirring for 1h the reaction was quenched with $NaHCO_3$, the organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo.* The crude reaction mixture was purified by fluorous chromatography to give 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-propyl-1,3-dihydro-indol-2-one **503** (1.10 g, 1.51 mmol, 85 % from glyoxamide) as an orange solid.

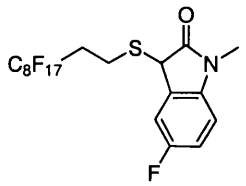
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.58-1.67 (2H, m, C*H*$_2$), 2.28-2.42 (2H, m, CF_2CH_2), 2.78-2.78 (1H, m, 1H from C*H*$_2$S), 2.87-2.94 (1H, m, 1H from C*H*$_2$S), 3.52-3.66 (2H, m, C*H*$_2$N), 4.24 (1H, s, C*H*S), 6.66 (1H, d, J = 8.3 Hz, Ar*H*), 7.37 (1H, dd, J = 8.3, 1.9 Hz, Ar*H*), 7.44 (1H, s, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (*C*H$_3$), 21.0 (*C*H$_2$), 21.5 (*C*H$_2$S), 32.3 (CF_2CH_2, t, J = 22.0 Hz), 42.4 (*C*H$_2$N), 44.9 (*C*H), 110.5 (Ar*C*H), 115.8 (Ar*C*), 127.7 (Ar*C*), 128.8 (Ar*C*H), 132.7 (ArCH), 142.9 (Ar*C*), 174.7 (*C*=O).

IR υ_{max}/(cm^{-1}) 2967, 2935, 2877, 1714 (C=O), 1606, 1481, 1238, 1203, 1145.

MS *m/z* (EI^+ mode) 733 (M^+, 18%), 731 (M^+, 18%), 253 (100), 210 (11).
$C_{21}H_{15}ONBrF_{17}S$ requires 730.9786, found 730.9781.

5-Fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1,3-dihydro-indol-2-one (504)



To a solution of oxalyl chloride (0.53 ml, 6.02 mmol, 1.1 eq) in CH_2Cl_2 (20 ml) at – 78 °C was added DMSO (0.77 ml, 10.9 mmol, 2 eq). After stirring for 35 min a solution of *N*-(4-fluorophenyl)-*N*-methyl-2-hydroxyacetamide **497** (1.00 g, 5.47 mmol, 1 eq) in CH_2Cl_2 (10 ml) was added. After stirring for a further 1 h at – 78 °C, NEt_3 (3.85 ml, 27.4 mmol, 5 eq) was added and the reaction was allowed to stir at room temperature for 18 h. CH_2Cl_2 was added to the reaction mixture and the organic layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude glyoxamide which was used without further purification. CH_2Cl_2 (10 ml) was added to the crude glyoxamide **498** followed by 1H, 1H,2H, 2H-perfluorodecane-1-thiol (0.89 ml, 3.05 mmol, 0.7 eq) and the reaction was allowed to stir at room temperature for 20 h. TFAA (5.80 ml, 39.2 mmol, 9 eq) was added, then, after 1 h BF_3 OEt_2 (2.75 ml, 21.8 mmol, 5 eq) was added. After stirring for 1h the reaction was quenched with $NaHCO_3$, the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by fluorous chromatography to give 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1,3-dihydro-indol-2-one **504** (1.96 g, 2.44 mmol, 80 % from glyoxamide) as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 2.37-2.48 (2H, m, CF_2CH_2), 2.80-2.90 (1H, m, 1H from CH_2S), 2.95-3.00 (1H, m, 1H from CH_2S), 3.24 (3H, s, CH_3N), 4.30 (1H, s, C*H*), 6.79 (1H, dd, J = 8.5, 4.0 Hz, Ar*H*), 7.07 (1H, apparent td, J = 6.7, 2.0 Hz, Ar*H*), 7.16 (1H, dq, J = 7.7, 0.8 Hz, Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_2S), 26.9 (CH_3N), 32.2 (CF_2CH_2, t, J =21.8 Hz), 45.4 (*C*H), 109.3 (Ar*C*H, d, J = 7.9 Hz), 113.6 (Ar*C*H, d, J = 25.1 Hz), 116.2 (Ar*C*H, d, J =

23.4 Hz), 127.1 (Ar*C* , d, J = 8.6 Hz), 140.3 (Ar*C*N), 159.8 (Ar*C*F , d, J = 240.4 Hz), 175.0 (*C*=O).

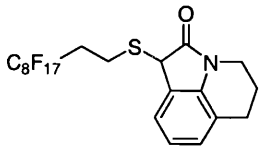
IR $\upsilon_{max}/(cm^{-1})$ 2932, 1714 (C=O), 1494, 1265, 1240, 1211, 1149.

MS *m/z* (EI^+ mode) 643 (M^+, 10%), 165 (100), 164 (62), 109 (10).

$C_{19}H_{11}ONF_{18}S$ requires 643.0274, found 643.0265.

Mpt : 85 °C

1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one (488)



To a solution of oxalyl chloride (0.18 ml, 2.10 mmol, 1.1 eq) in CH_2Cl_2 (10 ml) at – 78 °C was added DMSO (0.27 ml, 3.78 mmol, 2 eq). After stirring for 35 min a solution of 2-hydroxy-*N*-(3,4-dihydroquinolin-1(2H)-yl)acetamide **486** (361 mg, 1.89 mmol, 1 eq) in CH_2Cl_2 (10 ml) was added. After stirring for a further 1 h at – 78 °C, NEt_3 (1.32 ml, 9.45 mmol, 5 eq) was added and the reaction was allowed to stir at room temperature for 1 h 30 min. CH_2Cl_2 was added to the reaction mixture and the organic layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude glyoxamide **487** which was used without further purification. CH_2Cl_2 (10 ml) was added to the crude glyoxamide followed by 1H,1H,2H,2H-perfluorodecane-1-thiol (0.39ml, 1.32 mmol, 0.7 eq) and the reaction was allowed to stir at room temperature for 20 h. TFAA (2.50 ml, 17.0 mmol, 9 eq) was then added and after 1 h, BF_3 OEt_2 (1.19 ml, 9.45, 5 eq) was added. After stirring for 1h the reaction was quenched with $NaHCO_3$, the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The crude reaction mixture was purified by fluorous chromatography to give 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one **488** (559 mg, 0.86 mmol, 65 % over 2 steps) as a yellow solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.89-1.99 (2H, m, CH_2), 2.25-2.39 (2H, m, CF_2CH_2), 2.68-2.79 (3H, m, $ArCH_2$ and 1H from CH_2S), 2.81-2.90 (1H, m, 1H from CH_2S), 3.60- 3.71

(2H, m CH_2N), 4.43 (1H, s, C*H*), 6.91 (1H, t, J = 7.6 Hz, Ar*H*), 7.00 (1H, d, J = 7.6 Hz, Ar*H*), 7.12 (1H, d, J = 7.6 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (*C*H_2 and *C*H_2S), 24.3 (*C*H_2), 32.0 (CF_2*C*H_2, t, J = 21.5 Hz), 39.1 (*C*H_2N), 46.0 (*C*H), 120.7 (Ar*C*), 122.6 (Ar*C*H), 122.7 (Ar*C*H), 123.8 (Ar*C*), 128.2 (Ar*C*H), 139.8 (Ar*C*), 173.8 (*C*=O).

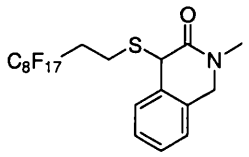
IR $\upsilon_{max}/(cm^{-1})$ 3055, 2942, 1703 (C=O), 1626, 1479, 1194, 1143.

MS *m/z* (EI^+ mode) 651 (M^+, 11%), 173 (100), 144 (14).

$C_{21}H_{14}F_{17}NOS$ requires 651.0525, found 651.0526.

Mpt: 71°C

4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfanyl)-2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (505)



To a solution of oxalyl chloride (0.27 ml, 3.10 mmol, 1.1 eq) in CH_2Cl_2 (2 ml) at – 78 °C was added DMSO (0.40 ml, 5.60 mmol, 2 eq). After stirring for 35 min a solution of *N*-benzyl-*N*-methyl-2-hydroxacetamide **500** (500 mg, 2.80 mmol, 1 eq) in CH_2Cl_2 (10 ml) was added. After stirring for a further 1 h at – 78 °C, NEt_3 (2.20 ml, 15.5 mmol, 5 eq) was added and the reaction was allowed to stir at room temperature for 18 h. CH_2Cl_2 was added to the reaction mixture and the organic layer was washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give the glyoxamide (353 mg, 2.02 mmol, 72 %) which was used without further purification. CH_2Cl_2 (16 ml) was added to the crude glyoxamide **501**. followed by 1H, 1H, 2H, 2H-perfluorodecane-1-thiol (0.41 ml, 1.40 mmol, 0.7 eq) and the reaction was allowed to stir at room temperature for 20 h. TFAA (2.70 ml, 18.0 mmol, 9 eq) was added, then, after 1 h BF_3 OEt_2 (1.27 ml, 10 mmol, 5 eq) was added. After stirring for 1h the reaction was quenched with $NaHCO_3$, the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using CH_2Cl_2 as eluant to give 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-2-methyl-1,2-dihydroisoquinolin-3(4H)-one **505** (402 mg, 0.64 mmol, 45 % from glyoxamide) as a yellow oil.

^{1}H NMR δ 2.30-2.50 (2H, m, CF_2CH_2), 2.78-2.88 (1H, m, 1H from CH_2S), 2.97-3.06 (1H, m, 1H from CH_2S), 3.06 (3H, s, NCH_3), 4.15 (1H, d, J = 15.8 Hz, 1H from CH_2N), 4.49 (1H, s, CHCO), 4.78 (1H, d, J = 15.8 Hz, 1H from CH_2N), 7.09-7.30 (4H, m, 4 x ArH).

^{13}C NMR δ 23.5 (CH_2S), 32.0 (t, J = 21.8 Hz, CF_2CH_2), 35.2 (NCH_3), 46.9 (CH), 52.6 (CH_2N), 125.9 (ArCH), 128.3 (ArCH), 128.4 (ArCH), 128.6 (ArCH), 132.5 (ArC), 132.8 (ArC), 167.7 (C=O).

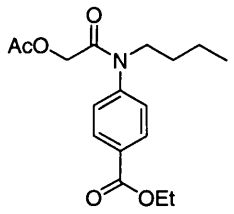
IR $\upsilon_{max}/(cm^{-1})$ 1654 (C=O), 1195, 1143.

MS *m/z* (CI^+ mode) 640 ($(M+H^+)$, 100%), 178 (15), 162 (45), 107 (5).

$C_{20}H_{15}NOF_{17}S$ requires 640.0603, found 640.0604.

Mpt 55-58 °C.

Ethyl 4-(2-acetoxy-*N*-butylacetamido)benzoate (506)



To a solution of acetoxy acetic acid (339 mg, 2.87 mmol, 1 eq), ethyl-4-(*N*-butylamino)benzoate **505** (0.70 g, 3.16 mmol, 1.1eq) and 1-hydroxy benzotriazole (78 mg, 0.57 mmol, 0.2 eq) in CH_2Cl_2 (40 ml) was added EDCI (658 mg, 3.44 mmol, 1.2 eq) and the reaction was allowed to stir at room temperature for 18 h. The reaction mixture was washed with 1M HCl and H_2O then dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 20 % ethyl acetate in petroleum ether as eluant to give ethyl 4-(2-acetoxy-*N*-butylacetamido)benzoate **506** (406 mg, 1.26 mmol, 44 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.3 Hz, CH_3), 1.18-1.37 (2H, m, CH_2), 1.41 (3H, t, J = 7.1 Hz, CH_3CH_2O) 1.47-1.53 (2H, m, CH_2), 2.14 (3H, s, CH_3CO), 3.75 (2H, t J = 7.6 Hz, CH_2N), 4.35 (2H, s, CH_2CO), 4.42 (2H, q, J = 7.1 Hz, CH_2O), 7.32-7.35 (2H, m, 2 × ArH), 8.14 (2H, apparent dd, J = 6.6, 1.8 Hz, 2 × ArH).

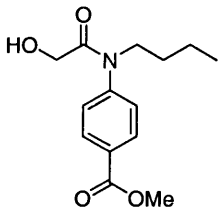
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (*C*H_3), 14.7 (*C*H_3), 20.7 (*C*H_2), 20.9 (*C*H_3CO), 30.1 (*C*H_2), 49.7 (*C*H_2N), 61.8 (*C*H_2O), 62.1 (*C*H_2CO), 182.5 (2 × Ar*C*H), 131.0 (Ar*C*), 131.7 (2 × Ar*C*H), 144.9 (Ar*C*), 165.9 (C=O), 166.3 (C=O), 170.9 (C=O).

IR υ_{max}/(cm^{-1}) 2928, 1748 (C=O, ester), 1715 (C=O, ester), 1680 (C=O, amide), 1604, 1508, 1367, 1271, 1100.

MS *m/z* (EI^+ mode) 321 (M^+, 55%), 265 (35), 221 (55), 178 (100), 165 (53), 132 (25), 101 (83), 73 (44).

$C_{17}H_{23}O_5N$ requires 321.1576, found 321.1577.

Methyl 4-(*N*-butyl-2-hydroxyacetamido)benzoate (507)



To a solution of ethyl 4-(2-acetoxy-*N*-butylacetamido)benzoate **506** (298 mg, 0.93 mmol, 1 eq) in MeOH (20 ml) and H_2O (10 ml) was added K_2CO_3 (0.65 g , 4.70 mmol, 5 eq) and the reaction allowed to stir at room temperature for 24 h. H_2O (20 ml) was added to the reaction and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give 4-(*N*-butyl-2-hydroxyacetamido)benzoic acid (170 mg, 0.68 mmol, 73 %) as a clear oil which was used without further purification. To a solution of 4-(*N*-butyl-2-hydroxyacetamido)benzoic acid (170 mg, 0.68 mmol, 1 eq) in MeOH : Toluene (1 ml : 5 ml) was added trimethylsilyldiazomethane (0.69 ml of 2M soln in hexane, 1.38 mmol, 2 eq) and the reaction allowed to stir at rt for 5 min. The reaction was then concentrated *in vacuo* to give methyl 4-(*N*-butyl-2-hydroxyacetamido)benzoate **507** (183 mg, 0.68 mmol, 100 %) as a yellow oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.2 Hz, C*H*$_3$), 1.19-1.30 (2H, m, C*H*$_2$), 1.19-1.46 (2H, m, C*H*$_2$), 3.34 (1H, s, O*H*), 3.77 (4H, apparent singlet, C*H*$_2$N and C*H*$_2$OH), 3.87 (3H, s, C*H*$_3$O), 7.18 (2H, apparent d, J = 8.0 Hz, 2 × Ar*H*), 8.05 (2H, apparent d, 2 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7 (*C*H_3), 18.9 (*C*H_2), 28.7 (*C*H_2), 48.4 (*C*H_2N), 51.4 (O*C*H_3), 59.6 (*C*H_2O), 119.2 (Ar*C*), 127.1 (2 × Ar*C*H), 130.3 (2 × Ar*C*H), 142.8 (Ar*C*), 165.0 (*C*=O), 170.0 (*C*=O).

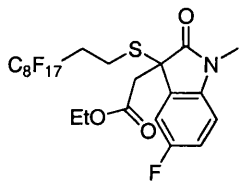
IR υ_{max}/(cm^{-1}) 3427 (OH), 2955, 2930, 1719 (C=O, ester), 1658 (C=O, amide), 1435, 1274, 1100.

MS *m/z* (EI$^+$ mode) 265 (M$^+$, 40%), 209 (65), 164 (100), 132 (19), 57 (28).

$C_{14}H_{19}O_4N$ requires 265.1314, found 265.1314.

Modifications α-to the oxindole carbonyl

Ethyl 2-(5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorosulfanyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetate (510)



To a solution of diisopropylamine (0.05 ml, 0.34 mmol, 1.2 eq) in THF (3 ml) at –78°C was added *n*-BuLi (0.14 ml of 2.46 M soln in THF, 0.34 mmol, 1.2 eq) and the reaction was allowed to stir for 45 min. A solution of 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1,3-dihydro-indol-2-one **504** (178 mg, 0.28 mmol, 1 eq) in THF (5 ml) was added by cannula. After stirring for 1 h at –78 °C, ethyl bromoacetate (0.09 ml, 0.84 mmol, 1.1 eq) was added and the reaction allowed to stir for 2.5 h gradually warming up to room temperature. The reaction was quenched with aqueous saturated NH_4Cl solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by fluorous chromatography to give ethyl 2-(5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-2-oxo-2,3-dihydo-1*H*-indol-3-yl)acetate **510** (181 mg, 0.25 mmol, 89 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.1 Hz, C*H*$_3$), 2.07-2.20 (2H, m, C*H*$_2$CF$_2$), 2.57-2.65 (1H, m, 1H from C*H*$_2$S), 2.68-2.76 (1H, m, 1H from C*H*$_2$S), 3.02 (1H, d, J =

16.6 Hz, 1H from CH_2CO), 3.20 (3H, s, NCH_3), 3.27 (1H, d, J = 16.6 Hz, 1H from CH_2CO), 3.80-3.93 (2H, m, CH_2O), 6.73 (1H, m, Ar*H*), 6.97 (2H, m, Ar*H*).

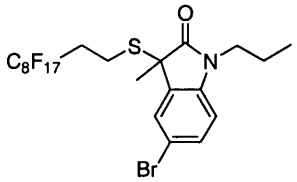
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3CH_2), 19.9 (CH_2S), 27.1 (CH_3N), 31.8 (CH_2CF_2, t, J = 21.9 Hz), 40.3 (CH_2CO), 50.9 (CCH_2), 61.5 (CH_2O), 109.4 (Ar*C*H, d, J = 7.8 Hz), 111.9 (Ar*C*H, d, J = 25.1 Hz), 116.3 (Ar*C*H, d, J = 23.7 Hz), 130.2 (Ar*C*, d, J = 8.0 Hz), 140.0 (Ar*C*, d, J = 1.8 Hz), 159.7 (Ar*C*F, d, J = 240.5 Hz), 168.6 (*C*=O amide), 176.1 (*C*=O ester).

IR $\upsilon_{max}/(cm^{-1})$ 1715 (C=O amide and ester), 1613, 1496, 1194, 1144.

MS *m/z* (EI^+ mode) 729 (M^+, 27%), 251 (65), 178 (100), 177 (55), 148 (20).

$C_{23}H_{17}NO_3SF_{18}$ requires 729.0642, found 729.0639.

5-Bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one (511)



To a solution of diisopropylamine (0.05 ml, 0.35 mmol, 1.2 eq) and LiCl (62 mg, 1.45 mmol, 5 eq) in THF (5 ml) at –78 °C was added *n*-BuLi (0.17 ml of a 2.05 M soln in THF, 0.35 mmol, 1.2 eq) and the reaction allowed to stir for 45 min. A solution of 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-propyl-1,3-dihydro-indol-2-one **503** (211 mg, 0.29 mmol, 1 eq) in THF (4 ml) was added by cannula. After stirring for 1 h at – 78 °C, MeI (24 μl, 0.39 mmol, 1.1 eq) was added and the reaction allowed to stir for 18 h gradually warming up to room temperature. The reaction was quenched with aqueous saturated NH_4Cl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-3-methyl-1-propyl1,3-dihydro-indol-2-one **511** (208 mg, 0.28 mmol, 96 %) as a brown oil which was used without further purification.

^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz, CH_3), 1.59 (3H, s, CH_3), 1.55-1.67 (2H, m CH_2), 2.06-2.21 (2H, m, CF_2CH_2), 2.53-2.65 (2H, m, CH_2S), 3.51-3.68 (2H, m,

C*H*$_2$N), 6.68 (1H, d, J = 8.3 Hz, Ar*H*), 7.36 (1H, dd, J = 8.3, 2.0 Hz, Ar*H*), 7.39 (1H, d, J = 2.0 Hz, Ar*H*).

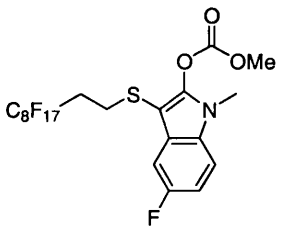
^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2 (*C*H$_3$), 19.0 (*C*H$_2$S), 19.7 (*C*H$_2$), 21.4 (*C*H$_3$C*quat*), 30.6 (CF$_2$*C*H$_2$, t, J = 21.9 Hz), 40.9 (*C*H$_2$N), 49.1 (*C*Me), 109.1 (Ar*C*H), 114.6 (Ar*C*), 126.1 (Ar*C*H), 131.0 (Ar*C*H), 132.1 (Ar*C*), 140.1 (Ar*C*), 175.7 (*C*=O).

IR υ_{max}/(cm^{-1}) 2965, 1714 (C=O), 1604, 1481, 1238. 1195, 1145.

MS *m/z* (EI$^+$ mode) 747 (M$^+$, 3%), 745 (M$^+$, 32%), 405 (20), 337 (10), 299 (35), 268 (35), 91 (45), 44 (100).

$C_{22}H_{17}NOBrF_{17}S$ requires 744.9943, found 744.9954.

5-Fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1*H*-indol-2-yl methyl carbonate



To a solution of 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1,3-dihydro-indol-2-one **504** (146 mg, 0.23 mmol, 1 eq) was added NEt_3 (0.13 ml, 0.92 mmol, 4 eq) and methyl chloroformate (0.07 mml, 0.92 mmol, 4 eq) in CH_2Cl_2 (8 ml) and the reaction was allowed to stir at rt for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1H-indol-2-yl methyl carbonate (154 mg, 0.22 mmol, 96 %) as an orange oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (2H, m, C*H*$_2$CF$_2$), 2.76 (2H, t, J = 8.1 Hz, C*H*$_2$S), 3.56 (3H, s, NC*H*$_3$), 3.93 (3H, s, C*H*$_3$O), 6.95 (1H, apparent td, J = 6.9, 2.5 Hz, Ar*H*), 7.16 (1H, m, Ar*H*), 7.28 (1H, dd, J = 9.1, 2.4 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 26.8 (*C*H$_2$S), 29.4 (N*C*H$_3$), 32.7 (*C*H$_2$CF$_2$, t, J = 21.7 Hz), 56.9 (*C*H$_3$O), 104.7 (Ar*C*H, d, J = 24.6 Hz), 111.1 (Ar*C*H, d, J = 9.3 Hz), 111.4 (Ar*C*H, d,

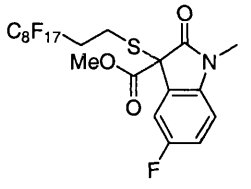
J = 26.0 Hz), 128.8 (Ar*C*), 129.6 (2 × Ar*C*), 146.6 (Ar*C*), 152.9 (*C*=O), 159.3 (Ar*C*F, d, J = 235.7 Hz).

IR $\upsilon_{max}/(cm^{-1})$ 2941, 1780 (C=O), 1652, 1487, 1241, 1200, 1149.

MS *m/z* (EI^+ mode) 701 (M^+, 42%), 642 (27), 210 (100), 177 (20), 83 (15), 59 (15).

$C_{21}H_{13}NO_3F_{18}S$ requires 701.0329, found 701.0330.

Methyl 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylthio)-1-methyl-2-oxo-2,3-dihydro-1H-indole-3-carboxylate (512)



To a solution of 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1H-indol-2-yl methyl carbonate (154 mg, 0.22 mmol, 1 eq) in toluene (6 ml) was added dimethylaminopyridine (9 mg, 0.07 mmol, 30 mol %) and the reaction was heated at 70 °C for 3 h. After cooling, CH_2Cl_2 (10 ml) was added and the organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified using fluorous chromatography to give methyl 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate **512** (92 mg, 0.13 mmol, 60 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26-2.39 (2H, m, CH_2CF$_2$), 3.00 (2H, t, J = 8.1 Hz, CH_2S), 3.20 (3H, s, NCH_3), 3.72 (3H, s, CH_3O), 6.74 (1H, dd, J = 8.6, 4.0 Hz, Ar*H*), 6.99-7.10 (2H, m, 2 × Ar*H*).

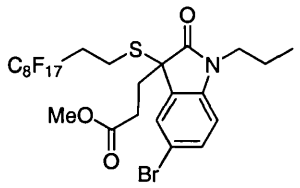
^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (*C*H$_2$S), 27.3 (*C*H$_3$N), 31.8 (*C*H$_2$CF$_2$, d, J = 21.7 Hz), 54.4 (*C*H$_3$O), 58.0 (*C*CO), 109.8 (Ar*C*H, d, J = 8.0 Hz), 113.5 (Ar*C*H, d, J = 25.3 Hz), 117.2 (Ar*C*H, d, J = 23.3 Hz), 126.8 (Ar*C*, d, J = 8.5 Hz), 139.6 (Ar*C*), 159.7 (Ar*C*F, d, J = 241.4 Hz), 167.1 (*C*=O), 171.9 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 1746 (C=O), 1716 (C=O), 1495, 1198, 1144.

MS *m/z* (EI^+ mode) 701 (M^+, 10%), 642 (20), 191 (100), 135 (10).

$C_{21}H_{13}NO_3F_{18}S$ requires 701.0329, found 701.0328.

Methyl-3-(5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10 heptadecafluorodecylsulfanyl)-2-oxo-1-propyl-2,3-dihydro-1*H*-indol-3-yl)propanoate (513)



To a solution of 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-propyl-1,3-dihydro-indol-2-one **504** (84 mg, 0.11 mmol, 1 eq) in MeOH (5 ml) was added NaOMe (15 mg, 0.28 mmol, 2.5 eq) and methyl acrylate (13 μl, 0.14 mmol, 1.3 eq) was added and the reaction allowed to stir for 18 h gradually warming up to room temperature. The reaction was quenched with aqueous saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by fluorous chromatography to give methyl-3-(5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-2-oxo-1-propyl-2,3-dihydro-1*H*-indol-3-yl)propanoate **513** (64 mg, 0.08 mmol, 71 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.58-1.67 (2H, m, C*H*$_2$CO), 1.95-2.03 (1H, m, one CH of C*H*$_2$CS), 2.08-2.21 (3H, m, one CH of C*H*$_2$CS and R_fCH_2), 2.28-2.43 (2H, m, C*H*$_2$CH$_3$), 2.56-2.71 (2H, m, C*H*$_2$S), 3.52 (3H, s, OC*H*$_3$), 3.60 (2H, t, J = 7.3 Hz, C*H*$_2$N), 6.69 (1H, d, J = 8.3 Hz, Ar*H*), 7.35 (1H, d, J = 2.0 Hz, Ar*H*), 7.38 (1H, dd, J = 8.3, 2.0 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (*C*H$_3$), 20.0 (*C*H$_2$S), 21.1 (*C*H$_2$CH$_3$), 29.7 (*C*H$_2$CS), 31.1 (*C*H$_2$CO), 31.8 (CF_2CH_2, t, J = 21.7 Hz), 42.4 (*C*H$_2$N), 52.2 (O*C*H$_3$), 53.6 (*C*S), 110.6 (Ar*C*H), 116.1 (Ar*C*), 127.9 (Ar*C*H), 130.7 (Ar*C*), 132.9 (Ar*C*H), 142.1 (Ar*C*), 172.5 (*C*=O), 175.7 (*C*=O).

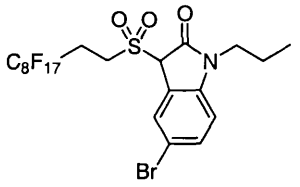
IR $\upsilon_{max}/(cm^{-1})$ 2938, 1735 (C=O), 1708 (C=O), 1604, 1481, 1195, 1143.

MS (FAB$^+$ mode) 818 (M$^+$, 60%), 340 (85), 340 (85), 306 (100), 278 (83), 236 (20), 70 (28).

$C_{25}H_{22}NO_3S_{17}FBr$ requires 818.0232, found 818.0213.

Mpt 53 °C

5-Bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one (514)



To a solution of 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-propyl-1,3-dihydro-indol-2-one **503** (564 mg, 0.77 mmol, 1 eq) in CH_2Cl_2 (15 ml) was added *m*CPBA (709 mg of 57-86 % *m*CPBA, ~3.08 mmol, ~4 eq) and the reaction allowed to stir at room temperature for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified using fluorous phase chromatography to give 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **514** (463 mg, 0.61 mmol, 79 %) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.59-1.68 (2H, m, C*H*$_2$), 2.63-2.76 (2H, m, C*H*$_2$CF$_2$), 3.52-3.74 (3H, m, C*H*$_2$N and 1H from C*H*$_2$SO$_2$), 3.79-3.86 (1H, m, 1H from C*H*$_2$SO$_2$), 4.76 (1H, s, C*H*), 6.71 (1H, d, J = 8.4 Hz, Ar*H*), 7.49 (1H, dd, J = 8.4, 1.5 Hz, Ar*H*), 7.69 (1H, d, J = 1.5 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H$_3$), 20.9 (*C*H$_2$), 24.7 (CF$_2$*C*H$_2$, t, J = 22.6 Hz), 42.7 (*C*H$_2$N), 44.4 (*C*H$_2$SO$_2$), 65.6 (*C*H), 111.1 (ArCH), 116.5 (Ar*C*), 118.9 (Ar*C*), 130.6 (Ar*C*H), 134.4 (Ar*C*H), 144.2 (ArC), 167.0 (*C*=O).

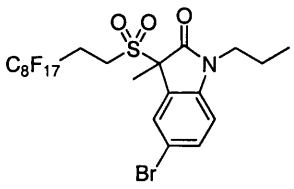
IR υ_{max}/(cm^{-1}) 2971, 2922, 1731 (C=O), 1482, 1197, 1138.

MS *m/z* (EI$^+$ mode) 763 (M$^+$, 8%), 252 (100), 210 (10), 173 (11), 116 (10).

$C_{21}H_{15}O_3NBrF_{17}S$ requires 762.9685, found 762.9683.

Mpt: 132 °C.

5-Bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one (515)



To a solution of 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **514** (321 mg, 0.41 mmol, 1 eq) in DMF (8 ml) was added K_2CO_3 (0.57 g, 4.1 mmol, 10 eq), and methyl iodide (0.25 ml, 4.10 mmol, 10 eq) and the reaction was heated at 40 °C for 2 h. EtOAc (10 ml) was added to the reaction and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction was purified using fluorous chromatography to give 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **515** (292 mg, 0.38 mmol, 92 %) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.61-1.70 (2H, m, C*H*$_2$), 1.84 (3H, s, C*H*$_3$C), 2.54-2.66 (3H, m, C*H*$_2$CF$_2$), 3.30-3.38 (1H, m, 1H from C*H*$_2$SO$_2$), 3.51-3.58 (1H, m, 1H from C*H*$_2$N), 3.69-3.80 (2H, m, 1H from C*H*$_2$N and 1H from C*H*$_2$SO$_2$), 6.75 (1H, d, J = 8.4 Hz, Ar*H*), 7.49 (1H, dd, J = 8.4, 2.0 Hz, Ar*H*), 7.62 (1H, d, J = 2.0 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H$_3$), 18.8 (*C*H$_3$C), 20.9 (C*H*$_2$), 24.2 (CF$_2$*C*H$_2$, t, J = 24.0 Hz), 40.4 (*C*H$_2$SO$_2$), 42.8 (*C*H$_2$N), 70.3 (*C*CH$_3$), 111.0 (Ar*C*H), 116.5 (Ar*C*), 125.0 (Ar*C*), 129.8 (Ar*C*H), 134.3 (Ar*C*H), 143.2 (Ar*C*), 171.2 (*C*=O).

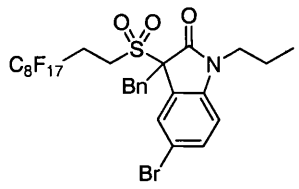
IR υ_{max}/(cm^{-1}) 2976, 2943, 1707 (C=O), 1482, 1197, 1145.

MS *m/z* (FAB$^+$ mode) 778 ((M+H)$^+$, 14%), 266 (100), 188 (27), 69 (28).

$C_{22}H_{18}O_3NBrF_{17}S$ requires 777.9919, found 777.9904.

Mpt: 106 °C.

3-Benzyl-5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propylindol-2-one (516)



To a solution of 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **514** (472 mg, 0.62 mmol, 1 eq) in DMF (15 ml) was added K_2CO_3 (856 mg, 6.20 mmol, 10 eq), KI (103 mg, 0.62 mmol, 1 eq) and benzyl bromide (0.37ml, 3.10 mmol, 5 eq) and the reaction heated at 60 °C for 3 h. EtOAc (10 ml) was added to the reaction and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The crude reaction was purified using fluorous chromatography to give 3-benzyl-5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **516** (481 mg, 0.58 mmol, 94 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.25-1.34 (2H, m, *C*H$_2$), 2.57-2.70 (2H, m, C*H*$_2$CF$_2$), 3.27-3.53 (3H, m, C*H*$_2$N and 1H from C*H*$_2$SO$_2$), 3.54 (1H, d, J = 12.8 Hz, 1H from PhC*H*$_2$), 3.67 (1H, d, J = 12.8 Hz, 1H from PhC*H*$_2$), 3.80-3.90 (1H, m, 1H from C*H*$_2$SO$_2$), 6.48 (1H, d, J = 8.4 Hz, Ar*H*), 6.84 (2H, apparent dd, J = 7.7, 1.4 Hz, 2 × Ar*H*), 6.96-7.09 (3H, m, 3 × Ar*H*), 7.37 (1H, dd, J = 8.4, 2.0 Hz, Ar*H*), 7.77 (1H, d, J = 2.0 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$), 20.6 (*C*H$_2$), 24.2 (CF$_2$*C*H$_2$, t, J = 22.5 Hz), 37.7 (Ph*C*H$_2$), 41.0 (*C*H$_2$SO$_2$), 42.6 (*C*H$_2$N), 75.4 (*C*CH$_2$Ph), 110.9 (Ar*C*H), 116.1 (Ar*C*), 122.7 (Ar*C*), 128.1 (Ar*C*H), 128.7 (2 × Ar*C*H), 130.2 (Ar*C*H), 130.4 (2 × Ar*C*H), 132.0 (Ar*C*), 134.2 (Ar*C*H), 143.7 (Ar*C*), 169.8 (*C*=O).

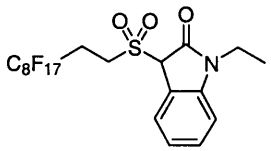
IR υ_{max}/(cm^{-1}) 2949, 2874, 1710 (C=O), 1605, 1485, 1197, 1133.

MS *m/z* (FAB$^+$ mode) 854 ((M+H)$^+$, 17%), 342 (100), 314 (35), 264 (20), 69 (27).

$C_{28}H_{22}O_3NBrF_{17}S$ requires 854.0232, found 854.0223.

Mpt: 124-126 °C.

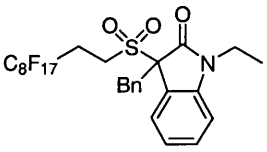
1-Ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10 heptadecafluorodecylsulfonyl)-1,3-dihydro-indol-2-one (517)



To a solution of 1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1,3-dihydro-indol-2-one **502** (118 mg, 0.18 mmol, 1 eq) in CH_2Cl_2 (10 ml) was added *m*CPBA (182 mg of 57-86 % *m*CPBA, ~0.74 mmol,~4 eq) and the reaction allowed to stir at room temperature for 45 min. The reaction mixture was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified using fluorous phase chromatography to give 1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1,3-dihydro-indol-2-one **517** (99 mg, 0.15 mmol, 81 %) as an orange-brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.24 Hz, C*H*$_3$), 2.61-2.75 (2H, m, CF_2CH_2), 3.57-3.85 (4H, m, CH_2S and CH_2N), 4.76 (1H, s, C*H*), 6.87 (1H, d, J = 7.9 Hz, Ar*H*), 7.11 (1H, t, J = 8.0 Hz, Ar*H*), 7.41 (1H, t, J = 7.8 Hz, Ar*H*), 7.58 (1H, d, J = 7.6 Hz, Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (*C*H$_3$), 24.7 (CF_2CH_2, t, J = 22.7 Hz), 35.9 (CH_2S), 44.2 (CH_2), 66.0 (*C*H), 109.6 (Ar*C*H), 116.7 (Ar*C*), 123.9 (Ar*C*H), 127.7 (Ar*C*H), 131.5 (Ar*C*H), 144.7 Ar*C*), 166.9 (*C*=O).
IR υ_{max}/(cm^{-1}) 2887, 2944, 2886, 1708 (C=O), 1610, 1195, 1143.

3-Benzyl-1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1,3-dihydro-indol-2-one (518)



To a solution of 1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1,3-dihydro-indol-2-one **517** (29.3 mg, 0.04 mmol, 1 eq) in

DMF (5 ml) was added K_2CO_3 (55 mg, 0.4 mmol, 10 eq), KI (3 mg, 0.02 mmol, 0.5 eq) and benzyl bromide (0.05ml, 0.4 mmol, 10 eq) and the reaction heated at 60 °C for 18 h. EtOAc (10 ml) was added to the reaction and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude prodict mixture was purified using fluorous chromatography to give 3-benzyl-1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1,3-dihydro-indol-2-one **518** (30 mg, 0.04 mmol, 100 %) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.2 Hz, CH_3), 2.52-2.65 (2H, m, CF_2CH_2), 3.32-3.43 (2H, m, 1H from CH_2N and 1H from CH_2S), 3.56-3.80 (4H, m, 1H from CH_2N and 1H from CH_2S and $PhCH_2$) 6.61 (1H, d, J = 7.8 Hz, Ar*H*), 6.83 (2H, apparent dd, J = 7.7, 1.2 Hz, 2 × Ar*H*), 6.94- 7.03 (3H, m, 3 × Ar*H*), 7.10 (1H, t, J = 8.1 Hz, Ar*H*), 7.26 (1H, t, J = 8.4 Hz, Ar*H*), 7.76 (1H, d, J = 7.6 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1 (CH_3), 24.3 (CF_2CH_2, t, J = 22.3 Hz), 35.5 (CH_2N), 37.6 (CH_2Ph), 41.1 (CH_2SO_2), 109.3 (Ar*C*H), 120.9 (Ar*C*), 123.6 (Ar*C*H), 127.4 (Ar*C*H), 127.8 (Ar*C*H), 128.4 (2 × Ar*C*H), 130.5 (2 × Ar*C*H), 131.4 (Ar*C*H), 132.3 (Ar*C*), 143.9 (Ar*C*), 169.7 (*C*=O).

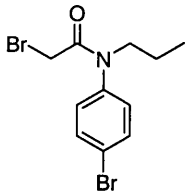
IR $\upsilon_{max}/(cm^{-1})$ 3066, 2979, 2929, 1700 (C=O), 1610, 1488, 1369, 1195, 1133.

MS *m/z* (EI^+ mode) 761 (M^+, 11%), 250 (100), 222 (100), 193 (15), 91 (24)

$C_{27}H_{20}O_3NF_{17}S$ requires 761.0892, found 761.0895.

Mpt 96 – 98 °C.

2-Bromo-*N*-(4-bromophenyl)-*N*-propylacetamide (521)



To a solution of 4-bromo-*N*-propyl aniline (379 mg, 1.77 mmol, 1 eq) in CH_2Cl_2 (80 ml) was added NEt_3 (0.5 ml, 3.54 mmol, 2 eq) and bromoacetyl bromide (0.23 ml, 2.66 mmol, 1.5 eq) and the reaction allowed to stir at room temperature for 3 h. The reaction mixture was then washed with 2M NaOH, dried ($MgSO_4$) and concentrated *in vacuo* to give 2-

bromo-*N*-(4-bromophenyl)-*N*-propylacetamide **521** (522 mg,1.65 mmol, 93 %) as an orange oil which was used without further purification.

^{1}H NMR(400 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.41-1.51 (2H, m, C*H*$_2$), 3.53-3.63 (4H, m, C*H*$_2$N and C*H*$_2$CO), 7.10 (2H, apparent d, J = 8.6 Hz, 2 × Ar*H*), 7.46 (2H, apparent d, J = 8.6 Hz, 2 × Ar*H*).

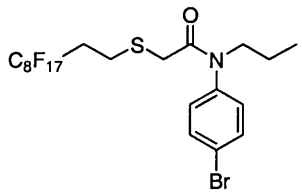
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (*C*H$_3$), 21.1 (*C*H$_2$), 27.4 (*C*H$_2$), 51.9 (*C*H$_2$CO), 122.9 (Ar*C*), 130.2 (2 × Ar*C*H), 133.5 (2 × Ar*C*H), 141.0 (Ar*C*), 166.4 (*C*=O).

IR υ_{max}/(cm^{-1}) 2962, 2931, 2873, 1656 (C=O), 1484, 1211, 1118, 1010.

MS *m/z* (EI$^+$ mode) 334 (M$^+$, 39%), 292 (40), 254 (40), 184 (100), 155 (14).

$C_{11}H_{13}NOBr_2$ requires 332.9364, found 332.9362.

_N_-(4-Bromophenyl)-2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-_N_-propylacetamide (522)



To a solution of 2-bromo-*N*-(4-bromophenyl)-*N*-propylacetamide **521** (548 mg, 1.60 mmol, 1 eq) in DMF (5 ml) was added NEt_3 (0.45 ml, 3.20 mmol, 2 eq) and 1H,1H,2H,2H-perfluorodecane-1-thiol (0.47 ml, 1.60 mmol, 1 eq) and the reaction allowed to stir at rt for 1 h. 30% EtOAc in petroleum ether was added and the organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by fluorous chromatography to give *N*-(4-bromophenyl)-2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-*N*-propylacetamide **522** (874 mg, 1.20 mmol, 75 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.41-1.50 (2H, m, C*H*$_2$), 2.27-2.30 (2H, m, CF_2CH_2), 2.81 (2H, t, J = 8.0 Hz, C*H*$_2$S), 2.95 (2H, s, C*H*$_2$CO), 3.56 (2H, t, J = 7.6 Hz, C*H*$_2$N), 7.05 (2H, apparent d, J = 8.4 Hz, 2 × Ar*H*), 7.49 (2H, apparent d, J = 8.8 Hz, 2 × Ar*H*).

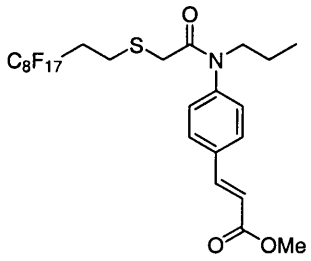
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (*C*H_3), 20.8 (*C*H_2), 23.3 (CH_2S), 31.6 (CF_2CH_2, t, J = 21.5 Hz), 33.4 (*C*H_2CO), 51.1 (*C*H_2N), 122.2 (Ar*C*), 130.1 (2 × Ar*C*H), 133.0 (2 × Ar*C*H), 141.0 (Ar*C*), 168.4 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 2969, 1654 (C=O), 1486, 1241, 1213.

MS *m/z* (EI^+ mode) 733 (M^+, 4%), 654 (3), 493 (35), 255 (62), 213 (100), 184 (28), 43 (32).

$C_{21}H_{17}NOBrF_{17}S$ requires 732.9943, found 732.9938.

(*E*)-Methyl 3-(4-(2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-*N*-propylacetamido)phenyl)acrylate (523)



A flask containing *N*-(4-bromophenyl)-2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-*N*-propylacetamide **522** (208 mg, 0.28 mmol, 1 eq), $Pd(OAc)_2$ (18 mg, 0.08 mmol, 30 mol %), P(*o*-Tol)$_3$ (26 mg, 0.08 mmol, 30 mol %) was flushed with argon. Methyl acrylate (0.50 ml, 5.60 mmol, 20 eq), NEt_3 (0.04 ml, 0.31 mmol, 1.1 eq) and *o*-xylene (3ml) were added and the reaction was heated at 100 °C for 18 h. The reaction was allowed to cool, CH_2Cl_2 was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 20 % EtOAc in petroleum ether as eluant to give (*E*)-methyl 3-(4-(2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-*N*-propylacetamido)phenyl)acrylate **533** (88 mg, 0.12 mmol, 43 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz, C*H*$_3$), 1.43-1.53 (2H, m, *C*H_2), 2.27-2.43 (2H, m, C*H*$_2CF_2$), 2.82 (2H, t, J = 8.0 Hz, C*H*$_2S$), 2.98 (2H, s, *C*H_2CO), 3.63 (2H, t, J = 6.3 Hz, C*H*$_2N$), 3.75 (3H, s, OC*H*$_3$), 6.38 (1H, d, J = 16.0 Hz, C*H*=CHCO$_2$Me), 7.18-7.20 (2H, m, 2 × Ar*H*), 7.51 (2H, apparent d, J = 8.4 Hz, 2 × Ar*H*), 7.61 (1H, apparent d, J = 16.0 Hz, CH=C*H*CO$_2$Me).

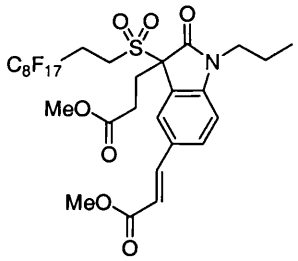
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H_3), 21.3 (*C*H_2), 23.7 (*C*H_2S), 32.0 (CF_2CH_2, t, J = 21.9 Hz), 33.8 (*C*H_2CO), 51.6 (*C*H_2N), 52.2 (*C*H_3O), 119.6 (*C*H=CHCO$_2$Me), 129.3 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 134.8 (Ar*C*), 143.5 (CH=*C*HCO$_2$Me), 143.9 (Ar*C*), 167.4 (C=O), 168.8 (C=O).

IR υ_{max}/(cm^{-1}) 1715 (C=O, ester), 1638 (C=O, amide), 1509, 1236, 1200.

MS *m/z* (EI$^+$ mode) 739 (M$^+$, 10%), 493 (18), 219 (100), 190 (25), 176 (14), 43 (13).

$C_{25}H_{22}O_3NF_{17}S$ requires 739.1049, found 739.1046.

(*E*)-Methyl 3-(3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-(3-methoxy-3-oxopropyl)-2-oxo-1-propyl-2,3-dihydro-1H-indol-5-yl)acrylate (524)



A flask containing 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **514** (76 mg, 0.10 mmol, 1 eq), $Pd(OAc)_2$ (7 mg, 0.03 mmol, 30 mol %), P(*o*-Tol)$_3$ (9 mg, 0.03 mmol, 30 mol %) was flushed with argon. Methyl acrylate (0.05 ml, 0.5 mmol, 5 eq), NEt_3 (0.02 ml, 0.11 mmol, 1.1 eq) and *o*-xylene (5 ml) were added and the reaction was heated at 100 °C for 18 h. The reaction was allowed to cool, CH_2Cl_2 was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography using 30 % EtOAc in petroleum ether as eluant to give (*E*)-methyl 3-(3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-(3-methoxy-3-oxopropyl)-2-oxo-1-propyl-2,3-dihydro-1H-indol-5-yl)acrylate **524** as a yellow oil (impure, yield not determined).

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz, C*H*$_3$), 1.62-1.72 (2H, m, C*H*$_2$), 1.85-1.93 (1H, m, 1H from C*H*$_2$C(quat)), 2.00-2.10 (1H, m, 1H from C*H*$_2$C(quat)), 2.54-2.81 (4H, m C*H*$_2$CF$_2$ and C*H*$_2$CO), 3.32-3.38 (1H, m, 1H from C*H*$_2$SO$_2$), 3.50 (3H, s, C*H*$_3$O), 3.58-3.92 (6H, m, C*H*$_2$N, C*H*$_3$O and 1H from C*H*$_2$SO$_2$), 6.34 (1H, d, J = 15.8 Hz,

CH=C*H*CO_2Me), 6.90 (1H, d, J = 8.2 Hz, Ar*H*), 7.53 (1H, dd, J = 8.2, 1.6 Hz, Ar*H*), 7.59 (1H, d, J = 16.0 Hz, C*H*=CHCO$_2$Me), 7.63 (1H, d, J = 1.5 Hz, Ar*H*).

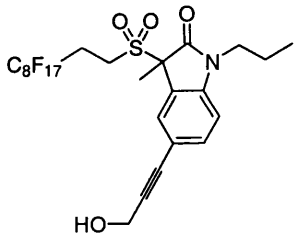
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (*C*H$_3$), 21.1 (*C*H$_2$), 24.2 (CF$_2$*C*H$_2$), 26.9 (*C*H$_2$C(quat)), 29.2 (*C*H$_2$CO), 40.7 (*C*H$_2$N), 43.0 (*C*H$_2$SO$_2$), 52.2 (*C*H$_3$O), 52.4 (*C*H$_3$O), 73.8 (C(quat)), 110.1 (Ar*C*H), 117.9 (CH=*C*HCO$_2$Me), 120.1 (Ar*C*), 126.1 (Ar*C*H), 130.7 (Ar*C*), 132.4 (Ar*C*H), 143.7 (*C*H=CHCO$_2$Me), 146.2 (Ar*C*), 167.6 (*C*=O), 170.5 (*C*=O), 171.7 (*C*=O).

IR υ_{max}/(cm^{-1}) 1737 (C=O), 1708 (C=O), 1636, 1608, 1196, 1136.

MS *m/z* (FAB$^+$ mode, NaI) 878 ((M + Na)$^+$,100%), 856 (15), 367 (74), 344 (66), 312 (47), 271 (17).

$C_{29}H_{26}NO_7SF_{17}Na$ requires 878.1056, found 878.1060.

3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-5-(3-hydroxyprop-1-ynyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one (525)



A flask containing 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **515** (66 mg, 0.08 mmol, 1 eq) and palladium (0) tetrakis(triphenylphosphine) (18 mg, 0.02 mmol, 20 mol %) was flushed with argon. Propargyl alcohol (14 μl, 0.16 mmol, 3 eq) and triethylamine (3 ml) was added and the reaction was heated at 80 °C. The reaction was allowed to cool, CH_2Cl_2 was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The crude product mixture was purified using fluorous chromatography to give 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-5-(3-hydroxyprop-1-ynyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **525** (33 mg, 0.05 mmol, 59 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 8.1 Hz, C*H*$_3$), 1.61-1.70 (2H, m, C*H*$_2$), 1.83 (3H, s, C*H*$_3$C), 2.53-2.66 (2H, m, C*H*$_2$CF$_2$), 3.30-3.37 (1H, m, 1H from C*H*$_2$SO$_2$), 3.52-

3.60 (1H, m, 1H from CH_2N), 3.70-3.79 (2H, m, 1H from CH_2N and 1H from CH_2SO_2), 4.42 (2H, s, CH_2OH), 6.82 (1H, d, J = 8.2 Hz, Ar*H*), 7.44 (1H, dd, J = 8.2, 1.6 Hz, Ar*H*), 7.57 (1H, d, J = 1.6 Hz, Ar*H*).

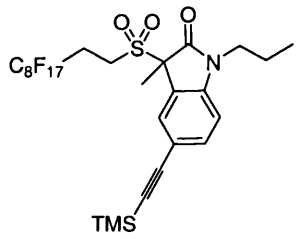
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 18.7 (CH_3C), 21.0 (CH_2), 24.2 (CH_2CF_2, t, J = 22.0 Hz), 40.4 (CH_2SO_2), 42.8 (CH_2N), 52.0 (CH_2OH), 70.1 (CCH_3), 85.2 (C_{alkyne}), 87.9 (C_{alkyne}), 109.6 (ArCH), 118.3 (ArC), 123.4 (ArC), 130.0 (ArCH), 135.1 (ArCH), 144.1 (ArC), 171.6 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 2938, 2359 (C≡C), 1711 (C=O), 1490, 1197, 1142, 1089.

MS *m/z* (EI^+ mode) 753 (M^+, 5%), 242 (100), 200(3), 77 (2).

$C_{25}H_{20}O_4NF_{17}S$ requires 753.0842, found 753.0845.

3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-5-(2-(trimethylsilyl)ethynyl)-1,3-dihydro-indol-2-one (526)



A flask containing 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **515** (49 mg, 0.06 mmol, 1 eq) and palladium (0) tetrakis(triphenylphosphine) (15 mg, 0.02 mmol, 20 mol %) and copper (I) iodide (2 mg, 0.01 mmol, 20 mol %) was flushed with Argon. Trimethyl silylacetylene (0.09 ml, 0.63 mmol, 10 eq) and triethylamine (3 ml) was added and the reaction was heated at 60 °C. The reaction was allowed to cool, CH_2Cl_2 was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The crude product mixture was purified using fluorous chromatography to give 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-5-(2-(trimethylsilyl)ethynyl)-1,3-dihydro-indol-2-one **526** (41 mg, 0.05 mmol, 82 %) as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ 0.26 (9H, s, $(CH_3)_3Si$), 0.97 (3H, t, J = 7.4 Hz, CH_3), 1.69-1.78 (2H, m, CH_2), 1.91 (3H, s, CH_3C), 2.60-2.73 (2H, m, CH_2CF_2), 3.36-3.43 (1H, m, 1H

from CH_2SO_2), 3.60-3.66 (1H, m, 1H from CH_2SO_2), 3.77-3.85 (2H, m, CH_2N), 6.87 (1H, d, J = 8.2 Hz, Ar*H*), 7.55 (1H, dd, J = 8.2, 1.5 Hz, Ar*H*), 7.67 (1H, d, J = 1.5 Hz, Ar*H*).

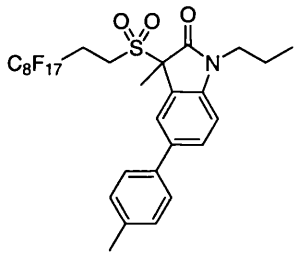
^{13}C NMR (100 MHz, $CDCl_3$) δ 0.00 ($(CH_3)_3Si$), 11.2 (CH_3), 18.3 (CH_3C), 20.7 (CH_2) 23.9 (CH_2CF_2, t, J = 22.0 Hz), 40.1 (CH_2SO_2), 42.9 (CH_2N), 69.8 (*C*Me), 94.7 (C_{alkyne}), 104.1 (C_{alkyne}), 109.1 (Ar*C*H), 118.7 (Ar*C*), 123.0 (Ar*C*), 129.8 (Ar*C*H), 135.0 (Ar*C*H), 143.7 (ArC), 171.3 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 2969, 2882, 2155 (C≡C), 1716 (C=O), 1614, 1489, 1199, 1143.

MS *m/z* (FAB mode, NaI) 818 ($(M+Na)^+$, 2%), 796 (9), 284 (100), 212 (32), 73 (30).

$C_{27}H_{26}NO_3SF_{17}SiNa$ requires 818.1029, found 818.1016.

3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-5-*p*-tolyl-1,3-dihydro-indol-2-one (527)



A flask containing 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **515** (106 mg, 0.14 mmol, 1 eq), palladium (0) tetrakis(triphenylphosphine) (35 mg, 0.03 mmol, 20 mol %) and methylbenzene boronic acid (57 mg, 0.42 mmol, 3 eq) was flushed with argon. Na_2CO_3 (0.21 ml of 2M aqueous solution, 0.42 mmol, 3 eq), H_2O (1 ml) and 1,4-dioxane (5 ml) were added and the reaction was heated at 80 °C for 3.5 h. The reaction was allowed to cool, CH_2Cl_2 was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified using fluorous chromatography to give 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-5-*p*-tolyl-1,3-dihydro-indol-2-one **527** (95 mg, 0.12 mmol, 87 %) as a white solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, t, J = 7.4 Hz, CH_3), 1.75-1.84 (2H, m, CH_2), 1.98 (3H, s, CH_3C), 2.42 (3H, s, CH_3Ar), 2.63-2.76 (2H, m, CH_2CF_2), 3.41-3.51 (1H, m, 1H from CH_2SO_2), 3.67-3.74 (1H, m, 1H from CH_2N), 3.86-3.90 (2H, m, 1H from CH_2N and

1H from CH_2SO_2), 7.01 (1H, d, J = 8.2 Hz, Ar*H*), 7.26 (2H, apparent d, J = 8.0 Hz, 2 × Ar*H*), 7.46 (2H, apparent d, J = 8.1 Hz, 2 × Ar*H*), 7.65 (1H, dd, J = 8.2, 1.8 Hz, Ar*H*), 7.79 (1H, d, J = 1.8 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 18.8 (CH_3C), 21.0 (CH_2), 21.5 (CH_3Ar), 24.1 (CF_2CH_2, t, J = 22.7 Hz), 40.4 (CH_2SO_2), 42.8 (CH_2N), 70.4 (CCH_3), 109.8 (ArCH), 123.7 (Ar*C*), 125.4 (ArCH), 127.2 (2 × ArCH), 129.9 (ArCH), 130.0 (2 × ArCH), 137.5 (Ar*C*), 137.6 (Ar*C*), 137.7 (Ar*C*), 143.0 (Ar*C*), 171.6 (*C*=O).

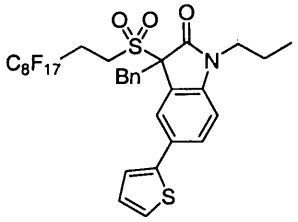
IR $\upsilon_{max}/(cm^{-1})$ 2972, 2941, 1721 (C=O), 1488, 1198, 1143.

MS *m/z* (FAB^+ mode, NaI) 812 ($(M + Na)^+$, 100%), 301 (55), 278 (100), 220 (20), 69 (20).

$C_{29}H_{24}NO_3SF_{17}Na$ requires 812.1103, found 812.1101.

Mpt: 143-145 °C

3-benzyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-1-propyl-5-(thiophen-2-yl)-1,3-dihydro-indol-2-one (528)



A flask containing 3-benzyl-5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **516** (123 mg, 0.14 mmol, 1 eq), palladium (0) tetrakis(triphenylphosphine) (35 mg, 0.03 mmol, 20 mol %) and thiophene-2-boronic acid (54 mg, 0.42 mmol, 3 eq) was flushed with argon. Na_2CO_3 (0.21 ml of 2M aqueous solution, 0.42 mmol, 3 eq), H_2O (1 ml) and 1,4-dioxane (5 ml) were added and the reaction was heated at 80 °C for 3.5 h. The reaction was allowed to cool, CH_2Cl_2 was added and the organic layer was washed with water, dried (Mg SO_4) and concentrated *in vacuo.* The crude product mixture was purified using fluorous chromatography to give 3-benzyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-5-(thiophene-2-yl)1,3-dihydro-indol-2-one **528** (110 mg, 0.13 mmol, 92 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.28-1.37 (2H, m, C*H*$_2$), 2.59-2.69 (2H, m, C*H*$_2$CF$_2$), 3.31-3.45 (2H, m, 1H from C*H*$_2$N and 1H from C*H*$_2$SO$_2$), 3.49-3.58 (1H, m, C*H*$_2$N), 3.63 (1H, d, J = 12.8 Hz, 1H from PhC*H*$_2$), 3.70 (1H, d, J = 12.8 Hz, 1H from PhC*H*$_2$), 3.80-3.88 (1H, m, 1H from C*H*$_2$SO$_2$), 6.61 (1H, d, J = 8.2 Hz, Ar*H*), 6.85 (1H, d, J = 1.7 Hz, Ar*H*), 6.87 (1H, d, J = 1.2 Hz, Ar*H*), 6.95-7.04 (4H, m, 4 × Ar*H*), 7.22-7.25 (2H, m, 2 × Ar*H*), 7.49 (1H, dd, J = 8.2, 1.8 Hz, Ar*H*), 7.88 (1H, d, J = 1.8 Hz, Ar*H*).

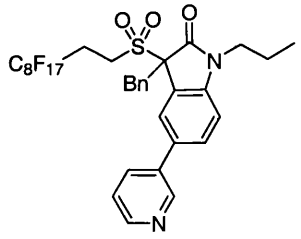
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H$_3$), 20.8 (*C*H$_2$), 24.3 (CF$_2$*C*H$_2$, t, J = 22.3 Hz), 37.7 (Ph*C*H$_2$), 41.1 (*C*H$_2$SO$_2$), 42.6 (*C*H$_2$N), 75.5 (*C*CH$_2$Ph), 109.8 (Ar*C*H), 121.5 (Ar*C*), 123.5 (Ar*C*H), 124.8 (Ar*C*H), 125.2 (Ar*C*H), 128.0 (Ar*C*H), 128.5 (Ar*C*H), 128.6 (2 × Ar*C*H), 129.1 (Ar*C*H), 130.4 (Ar*C*), 130.5 (2 × Ar*C*H), 132.3 (Ar*C*), 143.7 (Ar*C*), 143.8 (Ar*C*), 170.0 (*C*=O).

IR υ_{max}/(cm^{-1}) 1710 (C=O), 1489, 1200, 1136.

MS *m/z* (FAB$^+$ mode) 858 ((M+H)$^+$, 16%), 346 (100), 318 (26), 288 (10), 69 (20).

$C_{32}H_{25}NO_3SF_{17}$ requires 858.1004, found 858.1007.

3-benzyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecylsulfonyl)-1-propyl-5-(pyridin-3-yl)-1,3-dihydro-indol-2-one (529)



A flask containing 3-benzyl-5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **516** (82 mg, 0.10 mmol, 1 eq), palladium (0) tetrakis(triphenylphosphine) (23mg, 0.02 mmol, 20 mol %) and pyridine-3-boronic acid (37 mg, 0.30 mmol, 3 eq) was flushed with argon. Na_2CO_3 (0.15 ml of 2M aqueous solution, 0.30 mmol, 3 eq), H_2O (1 ml) and 1,4-dioxane (5 ml) were added. The reaction was heated at 80 °C for 3.5 h. The reaction was allowed to cool, CH_2Cl_2 was added and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo.* The crude product mixture was purified using fluorous chromatography to give 3-benzyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-

heptadecafluorodecylsulfonyl)-1-propyl-5-(pyridin-3-yl)-1,3-dihydro-indol-2-one **529** (59 mg, 0.07 mmol, 72 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.42-1.51 (2H, m, C*H*$_2$), 2.70-2.81 (2H, m, C*H*$_2$CF$_2$), 3.46-3.55 (2H, m, 1H from C*H*$_2$N and 1H from C*H*$_2$SO$_2$), 3.62-3.69 (1H, m, 1H from C*H*$_2$N), 3.74 (1H, d, J = 12.8 Hz, 1H from PhC*H*$_2$), 3.82 (1H, d, J = 12.8 Hz, 1H from PhC*H*$_2$), 3.98-4.03 (1H, m, 1H from C*H*$_2$SO$_2$), 6.82 (1H, d, J = 8.2 Hz, Ar*H*), 6.91 (1H, s, Ar*H*), 6.96 (1H, s, Ar*H*), 7.06-7.14 (3H, m, 3 × Ar*H*), 7.41-7.44 (1H, m, Ar*H*), 7.57 (1H, dd, J = 8.2, 1.8 Hz, Ar*H*), 7.90-7.94 (2H, m, 2 × Ar*H*), 8.66 (1H, s, Ar*H* of pyridine ring), 8.89 (1H, s, Ar*H* of pyridine ring).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*H$_3$), 20.8 (*C*H$_2$), 24.2 (CF$_2$*C*H$_2$, t, J = 21.9 Hz), 37.8 (Ph*C*H$_2$), 41.0 (*C*H$_2$SO$_2$), 42.7 (*C*H$_2$N), 75.5 (*C*CH$_2$Ph), 110.0 (Ar*C*H), 121.7 (ArC), 124.1 (Ar*C*H), 126.0 (Ar*C*H), 128.0 (Ar*C*H), 128.7 (2 × Ar*C*H), 130.3 (Ar*C*H), 130.4 (2 × Ar*C*H), 132.3 (Ar*C*), 133.5 (Ar*C*), 134.6 (Ar*C*H), 136.1 (Ar*C*), 144.7 (Ar*C*), 148.5 (Ar*C*H), 149.0 (Ar*C*H), 170.2 (*C*=O).

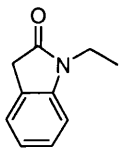
IR υ_{max}/(cm^{-1}) 2935, 1713 (C=O), 1617, 1199, 1135.

MS *m/z* (FAB$^+$ mode) 853 ((M+H)$^+$, 85%), 342 (100), 265 (14), 91 (5).

$C_{33}H_{26}O_3N_2F_{17}S$ requires 835.1393, found 853.1396.

Mpt: 51-53 °C.

1-Ethyl-1,3-dihydro-indol-2-one (530)[100]



To a solution of 1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)indolin-2-one **502** (131 mg, 0.21 mmol, 1 eq) in THF (3.5 ml) was added SmI_2 (6.9 ml of a 0.1 M soln in THF, 0.69 mmol, 3.3 eq) and the reaction was allowed to stir at room temperature for 24 h. CH_2Cl_2 (10 ml) was added to the reaction and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 1-ethyl-1,3-dihydro-indol-2-one **530** (19 mg, 0.12 mmol, 55 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, J = 7.2 Hz, C*H*$_3$), 3.45 (2H, s, C*H*$_2$CO), 3.70 (2H, q, J = 7.2 Hz, C*H*$_2$), 6.77 (1H, d, J = 7.9 Hz, Ar*H*), 6.96 (1H, t, J = 7.9 Hz, Ar*H*), 7.19 (2H, apparent t, J = 6.3 Hz, 2 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (*C*H$_3$), 35.0 (*C*H$_2$N), 36.3 (*C*H$_2$CO), 108.6 (Ar*C*H), 122.5 (Ar*C*H), 124.9 (Ar*C*H), 125.2 (Ar*C*), 128.2 (A*r*CH), 144.7 (Ar*C*), 175.1 (*C*=O).

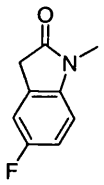
IR υ_{max}/(cm^{-1}) 3052, 2942, 1697 (C=O), 1612, 1492, 1463, 1348, 1241, 1241.

MS *m/z* (EI$^+$ mode) 161 (M$^+$, 76%), 146 (20), 132 (20), 118 (90), 91 (20), 84 (100), 47 (20).

$C_{10}H_{11}NO$ requires 161.0841, found 161.0841.

Mpt 92 – 94 °C.

5-Fluoro-1-methyl-1,3-dihydro-indol-2-one (531)[98]



To a solution of 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-1,3-dihydro-indol-2-one **504** (170 mg, 0.26 mmol, 1 eq) in THF (3 ml) was added SmI_2 (6.5 ml of a 0.1 M soln in THF, 0.65 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 24 h. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 5-fluoro-1-methyl-1,3-dihydro-indol-2-one **531** (31 mg, 0.19 mmol, 71 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (3H, s, C*H*$_3$N), 3.45 (2H, s, C*H*$_2$CO), 6.65 (1H, dd, J = 8.4, 4.4 Hz, Ar*H*), 6.89-6.94 (2H, m, 2 × Ar*H*).

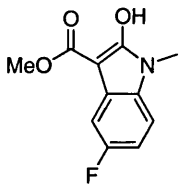
^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7 (*C*H$_3$N), 36.4 (*C*H$_2$CO), 108.7 (Ar*C*H, d, J = 7.9 Hz), 112.9 (Ar*C*H, d, J = 24.8 Hz), 114.4 (Ar*C*H, d, J = 23.1 Hz), 126.4 (d, J = 9.1 Hz, Ar*C*), 138.5 (Ar*C*N), 159.5 (Ar*C*F, d, J = 238.6 Hz), 175.0 (C=O).

IR υ_{max}/(cm^{-1}) 1695 (C=O), 1621, 1494, 1348, 1222, 1133.

MS *m/z* (EI$^+$ mode) 165 (M$^+$, 100%), 150 (10), 136 (99), 109 (20), 96 (10).

C_9H_8NOF requires 165.1670, found 165.1676.

Methyl 5-fluoro-1-methyl-2-hydroxy-indole-3-carboxylate (532)



To a solution of methyl 5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylate **512** (114 mg, 0.16 mmol, 1 eq) in THF (5 ml) was added SmI_2 (4.0 ml of a 0.1 M soln in THF, 0.40 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 15 min. EtOAc was added to the reaction and the organic layer was washed with 1M HCl. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. 80 % MeCN / H_2O was added and the precipated fluorous thiol was removed by filtration to give methyl 5-fluoro-1-methyl-2-hydroxy-indole-3-carboxylate **532** (33 mg, 0.15 mmol, 92 %) as a clear oil and as a 1:1 mixture of tautomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (3H, s, NC*H*$_3$, one tautomer), 3.53 (3H, s, NC*H*$_3$, one tautomer), 3.73 (3H, s, C*H*$_3$O, one tautomer), 3.89 (3H, s, C*H*$_3$O, one tautomer), 4.37 (1H, s, CH), 6.70 (1H, dd, J = 8.4, 4.4 Hz, Ar*H*), 6.79 (1H, td, J = 9.2, 2.4 Hz, Ar*H*), 6.92-7.06 (3H, m, 3 × Ar*H*), 7.31 (1H, d, J = 48.0 Hz, Ar*H*).

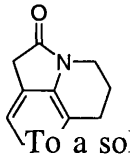
^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7 (N*C*H$_3$ of one tautomer), 27.5 (N*C*H$_3$ of one tautomer), 51.3 (*C*H$_3$O of one tautomer), 52.3 (C*H*), 53.2 (*C*H$_3$O of one tautomer), 84.6 (*C*S), 105.6 (Ar*C*H of one tautomer, d, J = 26.0 Hz), 108.5 (Ar*C*H of one tautomer, d, J = 25.0 Hz), 108.9 (Ar*C*H of one tautomer, d, J = 8.0 Hz), 109.3 (Ar*C*H of one tautomer, d, J = 9.0 Hz), 113.0 (Ar*C*H of one tautomer, d, J = 25.0 Hz), 115.6 (Ar*C*H of one tautomer, d, J = 23.0 Hz), 124.5 (Ar*C* of one tautomer), 124.6 (Ar*C* of one tautomer), 128.4 (Ar*C* of one tautomer), 140.6 (Ar*C* of one tautomer), 159.2 (Ar*C*F of one tautomer, d, J = 240 Hz), 159.7 (Ar*C*F of one tautomer, J = 235 Hz), 166.8 (*C*=O), 170.1 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 3229 (OH), 1650 (broad C=O of ester & amide), 1541, 1458, 1214.

MS *m/z* (EI$^+$ mode) 223 (M^+, 50%), 191 (100), 164 (45), 135 (35), 109 (19), 84 (35).

$C_{11}H_{10}O_3NF$ requires 223.0645, found 223.0646.

5,6-Dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one (489)[101]



To a solution of 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-5,6-

To a solution of 1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one **488** (118 mg, 0.18 mmol, 1 eq) in THF (5 ml) was added SmI_2 (4.5 ml of a 0.1 M soln in THF, 0.45 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 24 h. $NaHCO_3$ was added to the reaction and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one **489** (27 mg, 0.16 mmol, 87 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00-2.06 (2H, apparent pentet, J = 5.9 Hz, CH_2), 2.79 (2H, t, J = 6.1 Hz, ArCH_2), 3.52 (2H, s, CH_2CO), 3.74 (2H, t, J = 5.9 Hz, CH_2N), 6.95 (1H, t, 7.8 Hz, Ar*H*), 7.05 (1H, d, J = 7.7 Hz, Ar*H*), 7.09 (1H, d, J = 7.3 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (*C*H_2), 24.8 (*C*H_2), 36.9 (*C*H_2), 39.9 (*C*H_2), 120.5 (Ar*C*), 122.1 (Ar*C*H), 122.5 (Ar*C*H), 123.6 (Ar*C*), 126.9 (Ar*C*H), 141.5 (Ar*C*), 174.5 (*C*=O).

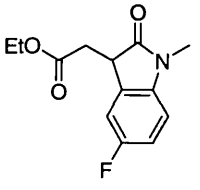
IR υ_{max}/(cm^{-1}) 3041, 2924, 1691 (C=O), 1600, 1479, 1345.

MS *m/z* (EI$^+$ mode) 173 (M^+, 100%), 144 (67), 117 (15), 83 (65), 47 (13).

$C_{11}H_{11}NO$ requires 173.0841, found 173.0840.

Mpt: 89-90°C.

Ethyl 2-(5-fluoro-1-methyl-2-oxo-1,3-dihydro-indol-3-yl)acetate (533)



To a solution of ethyl 2-(5-fluoro-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-methyl-2-oxo-2,3-dihydo-1*H*-indol-3-yl)acetate **510** (115 mg, 0.16 mmol, 1 eq) in THF (6 ml) was added SmI_2 (4.8 ml of 0.1 M soln in THF, 0.48 mmol, 3.0 eq) and the reaction allowed to stir at room temperature for 15 min. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give ethyl 2-(5-fluoro-1-methyl-2-oxo-1,3-dihydro-indol-3-yl)acetate **533** (26 mg, 0.10 mmol, 65 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, t, J = 7.1 Hz, C*H*$_3$CH$_2$), 2.69 (1H, dd, J = 17.1, 8.3 Hz, 1H from C*H*$_2$CH), 3.00 (1H, dd, J = 17.1, 4.2 Hz, 1H from C*H*$_2$CH), 3.15 (3H, s, C*H*$_3$N), 3.70 (1H, dd, J = 8.3, 4.2 Hz, C*H*), 4.13-4.11 (2H, m, C*H*$_2$O), 6.68 (1H, dd, J = 8.4, 4.2 Hz, Ar*H*), 6.89-6.98 (2H, m, 2 × Ar*H*).

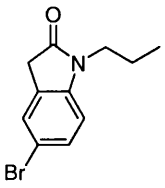
^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (*C*H$_3$), 26.8 (*C*H$_3$N), 35.2 (*C*H$_2$CH), 42.5 (*C*H), 61.4 (*C*H$_2$O), 108.7 (Ar*C*H, d, J = 8.5 Hz), 112.6 (Ar*C*H, d, J = 25 Hz), 114.8 (Ar*C*H, d, J = 23.7 Hz), 130.1 (Ar*C*, d, J = 8.6 Hz), 140.7 (Ar*C*), 159.6 (Ar*C*, d, J = 239 Hz), 171.2 (*C*=O), 176.7 (*C*=O).

IR υ_{max}/(cm^{-1}) 1705 (C=O), 1622, 1492, 1274, 1093.

MS *m/z* (EI$^+$ mode) 251(M$^+$, 25%), 177 (100), 148 (15), 135 (12), 82 (10).

$C_{13}H_{14}NO_3F$ requires 251.0958, found 251.0957.

5-Bromo-1-propyl-1,3-dihydro-indol-2-one (534)



To a solution of 5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1-propyl-1,3-dihydro-indol-2-one **503** (292 mg, 0.40 mmol, 1 eq) in THF (10 ml) was added SmI_2 (10 ml of a 0.1 M soln in THF, 1.0 mmol, 2.5 eq) and the reaction was allowed to stir at room temperature for 24 h. CH_2Cl_2 (10 ml) was added to the reaction and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous

chromatography to give 5-bromo-1-propyl-1,3-dihydro-indol-2-one **534** (57 mg, 0.22 mmol, 56 %) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.57-1.66 (2H, m, C*H*$_2$), 3.45 (2H, s, C*H*$_2$CO), 3.58 (2H, t, J = 7.4 Hz, C*H*$_2$N), 6.63 (1H, d, J = 8.2 Hz, Ar*H*), 7.30-7.33 (2H, overlapping doublet and singlet, 2 × Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (*C*H$_3$), 21.1 (*C*H$_2$), 36.0 (*C*H$_2$CO), 42.1 (*C*H$_2$N), 110.1 (Ar*C*H), 115.1 (Ar*C*), 127.0 (Ar*C*), 128.0 (Ar*C*H), 131.0 (Ar*C*H), 144.2 (Ar*C*), 174.7 (*C*=O).

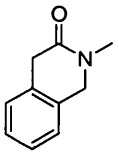
IR υ_{max}/(cm^{-1}) 2965, 2935, 2877, 1695 (C=O), 1606, 1484, 1342, 1105.

MS *m/z* (EI$^+$ mode) 253 (M$^+$, 56%), 224 (25), 196 (25), 117 (100), 84 (56), 47 (12).

$C_{11}H_{12}ONBr$ requires 253.0102, found 253.0101.

Mpt 105 – 108 °C.

2-Methyl-1,4-dihydro-2*H*-isoquinolin-3-one (535)[65]



To a solution of 4-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-2-methyl-1,2-dihydroisoquinolin-3(4H)-one **505** (153 mg, 0.24 mmol, 1 eq) in THF (5 ml) was added SmI_2 (6.0 ml of a 0.1 M soln in THF, 0.60 mmol, 2.5 eq) and the reaction allowed to stir at room tem temperature for 24 h. CH_2Cl_2 (10 ml) was added to the reaction and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 2-methyl-1,4-dihydro-2*H*-isoquinolin-3-one **535** (39 mg, 0.18 mmol, 74 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (3H, s, NC*H*$_3$), 3.55 (2H, s, C*H*$_2$N), 4.43 (2H, s, C*H*$_2$CO), 7.08-7.10 (2H, m, 2 × Ar*H*), 7.14-7.24 (2H, m, 2 × Ar*H*).

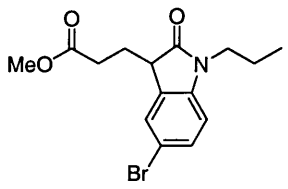
^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8 (*C*H$_3$), 37.9 (*C*H$_2$N), 53.3 (*C*H$_2$CO), 125.4 (Ar*C*H), 126.9 (Ar*C*H), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 131.3 (Ar*C*), 132.6 (Ar*C*), 169.2 (C=O).

IR υ_{max}/(cm^{-1}) 3033, 2922, 1632 (C=O), 1493, 1457, 1401, 1088.

MS *m/z* (EI$^+$ mode) 161 (M^+, 14%), 118 (10), 104 (22), 85 (100), 83 (100), 47 (46).

$C_{10}H_{11}NO$ requires 161.0841, found 161.0841.

Methyl 3-(5-bromo-2-oxo-1-propyl-1,3-dihydro-indol-3-yl)propanoate (536)



To a solution of methyl-3-(5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-2-oxo-1-propyl-2,3-dihydro-1*H*-indol-3-yl)propanoate **513** (37 mg, 0.05 mmol, 1 eq) in THF (5 ml) was added SmI_2 (1.3 ml of a 0.1 M soln in THF, 0.13 mmol, 2.5 eq) and the reaction was allowed to stir at room temperature for 18 h. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give methyl 3-(5-bromo-2-oxo-1-propyl-1,3-dihydro-indol-3-yl)propanoate **536** (13 mg, 0.038 mmol, 76 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.56-1.66 (2H, m, C*H*$_2$), 2.09-2.31 (3H, m, C*H*$_2$CH and 1H from C*H*$_2$CO), 2.35-2.44 (1H, m, 1H from C*H*$_2$CO), 3.44 (1H, t, J = 6.0 Hz, C*H*CO), 3.50-3.64 (5H, m, C*H*$_2$N and OC*H*$_3$), 6.64 (1H, d, J = 8.2 Hz, Ar*H*), 7.30-7.33 (2H, m, 2 × Ar*H*).

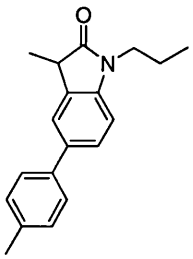
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (*C*H$_3$), 21.1 (*C*H$_2$CH$_3$), 26.0 (C*H*$_2$CH), 30.3 (*C*H$_2$CO$_2$Me), 42.0 (*C*H$_2$N), 44.7 (*C*H), 52.0 (O*C*H$_3$), 110.1 (Ar*C*H), 115.3 (Ar*C*), 127.7 (Ar*C*H), 130.7 (Ar*C*), 131.3 (Ar*C*H), 143.3 (Ar*C*), 173.5 (C=O, amide), 176.9 (C=O, ester).

IR υ_{max}/(cm^{-1}) 2963, 2930, 1734 (C=O, ester), 1701 (C=O, amide), 1605, 1482, 1339.

MS *m/z* (EI$^+$mode) 339 (M^+, 36%), 309 (44), 267 (100), 265 (99), 238 (33), 210 (20), 116 (20).

$C_{15}H_{18}O_3NBr$ requires 339.0470, found 339.0476.

3-Methyl-1-propyl-5-*p*-tolyl-1,3-dihydro-indol-2-one (537)



To a solution of 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-5-*p*-tolyl-1,3-dihydro-indol-2-one **527** (75 mg, 0.09 mmol, 1 eq) in THF (5 ml) was added SmI_2 (2.3 ml of a 0.1 M soln in THF, 0.23 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 15 min. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 3-methyl-1-propyl-5-*p*-tolyl-1,3-dihydro-indol-2-one **537** (24 mg, 0.085 mmol, 94 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.44 (3H, d, J = 7.6 Hz, C*H*$_3$CH), 1.60-1.70 (2H, m, C*H*$_2$), 2.32 (3H, s, C*H*$_3$Ar), 3.41 (1H, q, J = 7.6 Hz, C*H*), 3.63 (2H, t, J = 7.0 Hz, C*H*$_2$N), 6.81 (1H, d, J = 8.2 Hz, Ar*H*), 7.16 (2H, apparent d, J = 8.0 Hz, 2 × Ar*H*), 7.38-7.40 (4H, m, 4 × Ar*H*).

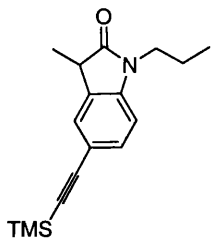
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (*C*H$_3$), 16.0 (*C*H$_3$CH), 21.2 (*C*H$_2$), 21.5 (*C*H$_3$Ar), 41.1 (*C*HCO), 41.9 (*C*H$_2$N), 108.9 (Ar*C*H), 122.8 (Ar*C*H), 126.8 (Ar*C*H), 127.1 (2 × Ar*C*H), 129.9 (2 × Ar*C*H), 131.7 (Ar*C*), 136.0 (Ar*C*), 137.2 (Ar*C*), 138.6 (Ar*C*), 140.0 (Ar*C*), 179.0 (C=O).

IR υ_{max}/(cm^{-1}) 2965, 2930, 2872, 1706 (C=O), 1617, 1486, 1348, 1207.

MS *m/z* (EI$^+$ mode) 279 (M$^+$, 100%), 250 (10), 222 (65), 207 (14).

$C_{19}H_{21}NO$ requires 279.1623, found 279.1625.

3-Methyl-1-propyl-5-(2-(trimethylsilyl)ethynyl)-1,3-dihydro-indol-2-one (538)



To a solution of 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-3-methyl-1-propyl-5-(2-(trimethylsilyl)ethynyl)-1,3-dihydro-indol-2-one **526** (75 mg, 0.09 mmol, 1 eq) in THF (6 ml) was added SmI_2 (2.3 ml of a 0.1 M soln in THF, 0.23 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 15 min. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 5-(3-hydroxyprop-1-ynyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **538** (23 mg, 0.08mmol, 88 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (9H, s, $(CH_3)_3Si$), 0.88 (3H, t, J = 7.4 Hz, CH_3), 1.38 (3H, d, J = 7.6 Hz, CH_3CH), 1.56-1.66 (2H, m, CH_2), 3.32 (1H, q, J = 7.6 Hz, CH), 3.58 (2H, t, J = 7.4 Hz, CH_2N), 6.68 (1H, d, J = 8.1 Hz, ArH), 7.27 (1H, s, ArH), 7.31 (1H, dd, J = 8.1, 1.6 Hz, ArH).

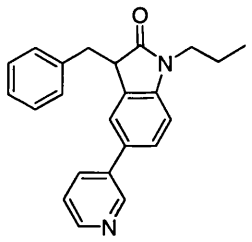
^{13}C NMR (100 MHz, $CDCl_3$) δ 0.00 ($(CH_3)_3Si$), 11.3 (CH_3), 15.4 (CH_3CH), 20.7 (CH_2), 40.2 (CH), 41.5 (CH_2N), 93.0 (*Calkyne*), 105.2 (*Calkyne*), 107.9 (ArCH), 116.7 (ArC), 127.2 (ArCH), 130.7 (ArC), 132.1 (ArCH), 143.7 (ArC), 178.5 (C=O).

IR $\upsilon_{max}/(cm^{-1})$ 2965, 2149 (C≡C), 1715 (C=O), 1615, 1488, 1347.

MS *m/z* (EI^+ mode) 285 (M^+, 100%), 270 (85), 228 (22), 106 (8), 73 (7).

$C_{17}H_{23}NOSi$ requires 285.1549, found 285.1548.

3-Benzyl-1-propyl-5-(pyridin-3-yl)-1,3-dihydro-indol-2-one (539)



To a solution of 3-benzyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-5-(pyridin-3-yl)-1,3-dihydro-indol-2-one **529** (87 mg, 0.10 mmol, 1 eq) in THF (5 ml) was added SmI_2 (2.5 ml of a 0.1 M soln in THF, 0.25 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 15 min. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 3-benzyl-1-propyl-5-(pyridin-3-yl)-1,3-dihydro-indol-2-one **539** (24 mg, 0.071 mmol, 71 %) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.49-1.60 (2H, m, C*H*$_2$), 2.87 (1H, dd, J = 13.5, 9.2 Hz, 1H from C*H*$_2$Ph), 3.46-3.55 (2H, m, 1H from C*H*$_2$Ph and 1H from C*H*$_2$N), 3.62-3.72 (2H, m, 1H from C*H*$_2$N and C*H*), 6.79 (1H, d, J = 8.1 Hz, Ar*H*), 6.85 (1H, s, Ar*H*), 7.10-7.27 (6H, m, 6 × Ar*H*), 7.36 (1H, dd, J = 8.1, 1.3 Hz, Ar*H*), 7.62-7.65 (1H, m, Ar*H*), 8.47 (1H, s, Ar*H*), 8.61 (1H, s, Ar*H*).

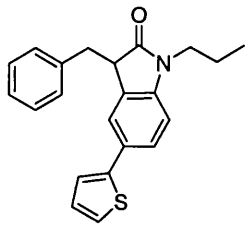
^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3 (*C*H$_3$), 19.7 (*C*H$_2$), 35.9 (Ph*C*H$_2$), 40.6 (*C*H$_2$N), 40.1 (*C*H), 107.7 (Ar*C*H), 122.5 (Ar*C*H), 122.6 (Ar*C*H), 125.8 (Ar*C*H), 125.6 (Ar*C*H), 127.3 (Ar*C*H), 128.4 (Ar*C*), 128.5 (2 × Ar*C*H), 130.3 (Ar*C*), 132.9 (2 × Ar*C*H), 136.6 (2 × Ar*C*), 143.0 (Ar*C*), 146.7(Ar*C*H), 146.8 (Ar*C*H), 175.8 (*C*=O).

IR υ_{max}/(cm^{-1}) 2965, 2930, 1702 (*C*=O), 1617, 1475, 1350.

MS *m/z* (EI$^+$ mode) 342 (M$^+$, 100%), 251 (83), 209 (18), 194 (15), 91 (32), 84 (31), 47 (5).

$C_{23}H_{22}NO_2$ requires 342.1732, found 342.1733.

3-Benzyl-1-propyl-5-(thiophen-2-yl)-indolin-2-one (540)



To a solution of 3-benzyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-5-(thiophene-2-yl)-1,3-dihydro-indol-2-one **528** (82 mg, 0.10 mmol, 1 eq) in THF (5 ml) was added SmI_2 (2.4 ml of a 0.1 M soln in THF, 0.24 mmol, 2.5 eq) and the reaction was allowed to stir at room temperature for 15 min. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 3-benzyl-1-propyl-5-(thiophen-2-yl)-1,3-dihydro-indol-2-one **540** (27 mg, 0.075 mmol, 75 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.43-1.56 (2H, m, C*H*$_2$), 2.85-2.95 (1H, m, 1H from PhC*H*$_2$), 3.43-3.50 (2H, m, 1H from PhC*H*$_2$ and 1H from C*H*$_2$N), 3.56-3.67 (2H, m, 1H from C*H*$_2$N and C*H*), 6.67 (1H, d, J = 8.1 Hz, Ar*H*), 6.88-7.00 (3H, m , 3 × Ar*H*), 7.05-7.37 (6H, m, 6 × Ar*H*), 7.38 (1H, dd, J = 8.1, 1.2 Hz, Ar*H*).

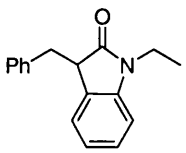
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (*C*H$_3$), 21.0 (*C*H$_2$), 37.2 (PhCH$_2$), 42.0 (*C*H$_2$N), 53.8 (*C*H), 108.8 (Ar*C*H), 122.5 (Ar*C*H), 122.9 (Ar*C*H), 124.4 (Ar*C*H), 126.0 (Ar*C*H), 127.1 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (2 × Ar*C*H), 128.8 (Ar*C*), 129.5 (Ar*C*), 130.0 (2 × Ar*C*H), 138.0 (Ar*C*), 143.7 (Ar*C*), 144.8 (Ar*C*), 177.1 (*C*=O).

IR υ_{max}/(cm^{-1}) 2961, 2924, 2873, 1701 (C=O), 1486, 1339, 1103.

MS (CI$^+$ mode, isobutane) 348 ((M+H)$^+$, 100%).

$C_{22}H_{22}NOS$ requires 348.1422, found 348.1423.

3-Benzyl-1-ethyl-1,3-dihydro-indol-2-one (541)



To a solution of 3-benzyl-1-ethyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfanyl)-1,3-dihydro-indol-2-one **518** (141 mg, 0.19 mmol, 1 eq) in THF (5 ml) was added SmI_2 (4.7 ml of a 0.1 M soln in THF, 0.47 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 3 h. CH_2Cl_2 (10 ml) was added to the reaction and the organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 3-benzyl-1-ethyl-1,3-dihydro-indol-2-one **541** (30.0 mg, 0.13 mmol, 67 %) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.2 Hz, C*H*$_3$), 2.88 (1H, dd, J = 13.6, 8.8 Hz, 1H from PhC*H*$_2$), 3.38 (1H, dd, J = 13.6, 4.4 Hz, 1H from PhC*H*$_2$), 3.54 (1H, m, 1H from C*H*$_2$N), 3.61-3.74 (2H, m, C*H* and 1H from C*H*$_2$N), 6.67 (1H, d, J = 7.8 Hz, Ar*H*), 6.75 (1H, d, J = 7.4 Hz, Ar*H*), 6.85 (1H, td, J = 7.5, 0.9 Hz, Ar*H*), 7.04-7.18 (6H, m, 6 × Ar*H*).

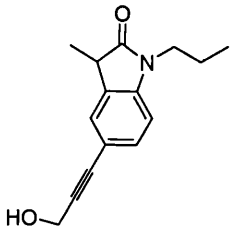
^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8 (*C*H$_3$), 34.9 (*C*H$_2$N), 37.2 (PhCH$_2$), 47.4 (*C*H), 108.4 (ArCH), 122.2 (Ar*C*H), 125.0 (Ar*C*H), 126.9 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.0 (Ar*C*), 129.9 (2 × Ar*C*H), 138.0 (Ar*C*), 143.7 (Ar*C*), 177.0 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 2923, 1710 (C=O), 1612, 1488, 1467, 1363, 1230.

MS *m/z* (EI$^+$ mode) 251 (M$^+$, 80%), 160 (100), 132 (12), 91 (89).

$C_{17}H_{17}NO$ requires 251.1310, found 251.1311.

5-(3-Hydroxyprop-1-ynyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one (542)

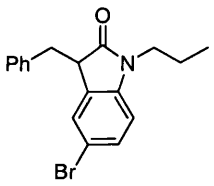


To a solution of 3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-5-(3-hydroxyprop-1-ynyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **525** (63 mg, 0.08 mmol, 1 eq) in THF (5 ml) was added SmI_2 (2.0 ml of a 0.1 M soln in THF, 0.20 mmol, 2.5 eq) and the reaction allowed to stir at room temperature for 15 min. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined

organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product mixture was purified by fluorous chromatography to give 5-(3-hydroxyprop-1-ynyl)-3-methyl-1-propyl-1,3-dihydro-indol-2-one **542** (8 mg, 0.033 mmol, 42 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.39 (3H, d, J = 7.6 Hz, C*H*$_3$CH), 1.56-1.67 (2H, m, C*H*$_2$), 3.34 (1H, q, J = 7.6 Hz, C*H*), 3.53-3.62 (2H, m, C*H*$_2$N), 4.29 (2H, s, C*H*$_2$OH), 6.70 (1H, d, J = 8.1 Hz, Ar*H*), 7.23 (1H, s, Ar*H*), 7.28 (1H, d, J = 8.1 Hz, Ar*H*).
^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (*C*H$_3$), 15.8 (*C*H$_3$CH), 21.1 (*C*H$_2$), 40.7 (*C*H), 42.0 (*C*H$_2$N), 52.1 (*C*H$_2$OH), 86.1 (*C alkyne*), 86.7 (*C alkyne*), 108.5 (Ar*C*H), 116.5 (Ar*C*), 127.3 (Ar*C*H), 131.3 (Ar*C*), 132.3 (Ar*C*H), 144.1 (Ar*C*), 178.9 (*C*=O).
IR $\upsilon_{max}/(cm^{-1})$ 3381 (OH), 2965, 2930, 2873, 1685 (C=O), 1615, 1487, 1348.
MS *m/z* (EI$^+$ mode) 243 (M^+, 100%), 214 (23), 186 (45), 168 (10), 84 (21).
$C_{15}H_{17}O_2N$ requires 243.1259, found 243.1259.

3-Benzyl-5-bromo-1-propyl-1,3-dihydro-indol-2-one (543)



To a solution of 3-benzyl-5-bromo-3-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecylsulfonyl)-1-propyl-1,3-dihydro-indol-2-one **516** (140 mg, 0.16 mmol, 1 eq) in THF (5 ml) was added SmI_2 (3.5 ml of a 0.1 M soln in THF, 0.35 mmol, 2.2 eq) and the reaction was allowed to stir at room temperature for 15 min. $NaHCO_3$ was added to the reaction and the organic layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by filtration through a short pad of silica washing with 30 % EtOAc / petroleum ether to give 3-benzyl-5-bromo-1-propyl-1,3-dihydro-indol-2-one **543** (54 mg, 0.16 mmol, 98 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (3H, t, J = 7.4 Hz, C*H*$_3$), 1.41-1.53 (2H, m, C*H*$_2$), 2.90 (1H, dd, J = 13.7, 8.5 Hz, 1H from PhC*H*$_2$), 3.33-3.43 (2H, m, 1H from PhC*H*$_2$N and 1H

from C*H*$_2$N), 3.54-3.64 (2H, m, 1H from C*H*$_2$N and C*H*), 6.53 (1H, d, J = 8.3 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 7.03-7.07 (2H, m, 2 × Ar*H*), 7.10-7.19 (3H, m, 3 × Ar*H*), 7.24 (1H, d, J = 8.3 Hz, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (*C*H$_3$), 20.9 (*C*H$_2$), 36.9 (Ph*C*H$_2$), 41.9 (*C*H$_2$N), 47.3 (*C*H), 109.9 (ArC*H*), 114.8 (Ar*C*), 127.2 (Ar*C*H), 128.1 (Ar*C*H), 128.7 (2 × Ar*C*H), 129.8 (2 × Ar*C*H), 130.9 (Ar*C*), 131.1 (Ar*C*H), 137.4 (Ar*C*), 143.3 (Ar*C*), 176.6 (*C*=O).

IR $\upsilon_{max}/(cm^{-1})$ 1697 (C=O), 1604, 1482, 1350, 1102.

MS *m/z* (EI$^+$mode) 343 (M^+, 32%), 252 (22), 91 (100), 65 (5).

$C_{18}H_{18}ONBr$ requires 343.0572 found 343.0560

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Appendix I

Crystal structure of oxindole **382**

Table 1. Crystal data and structure refinement for km3402.

Identification code	km3402	
Empirical formula	$C_{16}H_{15}NO_2$	
Formula weight	253.29	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 2_1/a 1	
Unit cell dimensions	a = 8.3006(2) Å	α= 90°.
	b = 10.7427(2) Å	β= 95.137(1)°.
	c = 14.3728(4) Å	γ = 90°.
Volume	1276.49(5) Å^3	
Z	4	
Density (calculated)	1.318 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	536	
Crystal size	0.50 x 0.13 x 0.12 mm^3	
Theta range for data collection	2.85 to 29.93°.	
Index ranges	-11<=h<=11, -13<=k<=15, -20<=l<=20	
Reflections collected	11672	
Independent reflections	3652 [R(int) = 0.030]	
Completeness to theta = 29.93°	99.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3652 / 0 / 173	
Goodness-of-fit on F^2	1.002	
Final R indices [I>2sigma(I)]	R1 = 0.043, wR2 = 0.106	
R indices (all data)	R1 = 0.056, wR2 = 0.115	
Largest diff. peak and hole	0.32 and -0.19 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for km3402. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	891(1)	14353(1)	6330(1)	20(1)
C(2)	1589(1)	13500(1)	5623(1)	20(1)
C(3)	1292(1)	12221(1)	5991(1)	17(1)
C(4)	506(1)	12344(1)	6813(1)	16(1)
C(5)	38(1)	11334(1)	7318(1)	17(1)
C(6)	380(1)	10145(1)	6978(1)	17(1)
C(7)	1170(1)	9998(1)	6167(1)	19(1)
C(8)	1626(1)	11048(1)	5674(1)	19(1)
C(9)	116(2)	7948(1)	7153(1)	27(1)
C(10)	-510(1)	14089(1)	7793(1)	20(1)
C(11)	584(1)	14081(1)	8692(1)	18(1)
C(12)	260(2)	13328(1)	9436(1)	25(1)
C(13)	1271(2)	13363(1)	10266(1)	32(1)
C(14)	2592(2)	14151(1)	10356(1)	31(1)
C(15)	2916(1)	14905(1)	9612(1)	28(1)
C(16)	1924(1)	14870(1)	8781(1)	22(1)
N(1)	286(1)	13613(1)	7001(1)	18(1)
O(1)	849(1)	15491(1)	6321(1)	27(1)
O(2)	-96(1)	9174(1)	7507(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for km3402.

C(1)-O(1)	1.2228(14)	C(9)-H(9A)	0.9800
C(1)-N(1)	1.3793(14)	C(9)-H(9B)	0.9800
C(1)-C(2)	1.5204(15)	C(9)-H(9C)	0.9800
C(2)-C(3)	1.5006(15)	C(10)-N(1)	1.4592(14)
C(2)-H(2A)	0.9900	C(10)-C(11)	1.5108(15)
C(2)-H(2B)	0.9900	C(10)-H(10A)	0.9900
C(3)-C(8)	1.3771(15)	C(10)-H(10B)	0.9900
C(3)-C(4)	1.4063(14)	C(11)-C(12)	1.3875(16)
C(4)-C(5)	1.3801(15)	C(11)-C(16)	1.3947(16)
C(4)-N(1)	1.4045(13)	C(12)-C(13)	1.3967(18)
C(5)-C(6)	1.4062(15)	C(12)-H(12)	0.9500
C(5)-H(5)	0.9500	C(13)-C(14)	1.382(2)
C(6)-O(2)	1.3694(13)	C(13)-H(13)	0.9500
C(6)-C(7)	1.3965(15)	C(14)-C(15)	1.3858(19)
C(7)-C(8)	1.4021(15)	C(14)-H(14)	0.9500
C(7)-H(7)	0.9500	C(15)-C(16)	1.3892(16)
C(8)-H(8)	0.9500	C(15)-H(15)	0.9500
C(9)-O(2)	1.4288(14)	C(16)-H(16)	0.9500
O(1)-C(1)-N(1)	124.90(10)	H(9A)-C(9)-H(9C)	109.5
O(1)-C(1)-C(2)	127.37(10)	H(9B)-C(9)-H(9C)	109.5
N(1)-C(1)-C(2)	107.73(9)	N(1)-C(10)-C(11)	112.69(8)
C(3)-C(2)-C(1)	103.39(9)	N(1)-C(10)-H(10A)	109.1
C(3)-C(2)-H(2A)	111.1	C(11)-C(10)-H(10A)	109.1
C(1)-C(2)-H(2A)	111.1	N(1)-C(10)-H(10B)	109.1
C(3)-C(2)-H(2B)	111.1	C(11)-C(10)-H(10B)	109.1
C(1)-C(2)-H(2B)	111.1	H(10A)-C(10)-H(10B)	107.8
H(2A)-C(2)-H(2B)	109.0	C(12)-C(11)-C(16)	119.46(11)
C(8)-C(3)-C(4)	119.08(10)	C(12)-C(11)-C(10)	121.26(10)
C(8)-C(3)-C(2)	132.63(9)	C(16)-C(11)-C(10)	119.27(10)
C(4)-C(3)-C(2)	108.29(9)	C(11)-C(12)-C(13)	119.95(12)
C(5)-C(4)-N(1)	127.88(9)	C(11)-C(12)-H(12)	120.0
C(5)-C(4)-C(3)	122.82(10)	C(13)-C(12)-H(12)	120.0
N(1)-C(4)-C(3)	109.30(9)	C(14)-C(13)-C(12)	120.51(12)
C(4)-C(5)-C(6)	117.14(9)	C(14)-C(13)-H(13)	119.7
C(4)-C(5)-H(5)	121.4	C(12)-C(13)-H(13)	119.7
C(6)-C(5)-H(5)	121.4	C(13)-C(14)-C(15)	119.54(12)
O(2)-C(6)-C(7)	123.90(10)	C(13)-C(14)-H(14)	120.2
O(2)-C(6)-C(5)	114.93(9)	C(15)-C(14)-H(14)	120.2
C(7)-C(6)-C(5)	121.17(10)	C(14)-C(15)-C(16)	120.42(12)
C(6)-C(7)-C(8)	119.94(10)	C(14)-C(15)-H(15)	119.8
C(6)-C(7)-H(7)	120.0	C(16)-C(15)-H(15)	119.8
C(8)-C(7)-H(7)	120.0	C(15)-C(16)-C(11)	120.13(11)
C(3)-C(8)-C(7)	119.85(10)	C(15)-C(16)-H(16)	119.9
C(3)-C(8)-H(8)	120.1	C(11)-C(16)-H(16)	119.9
C(7)-C(8)-H(8)	120.1	C(1)-N(1)-C(4)	111.30(9)
O(2)-C(9)-H(9A)	109.5	C(1)-N(1)-C(10)	124.22(9)
O(2)-C(9)-H(9B)	109.5	C(4)-N(1)-C(10)	124.46(9)
H(9A)-C(9)-H(9B)	109.5	C(6)-O(2)-C(9)	116.96(8)
O(2)-C(9)-H(9C)	109.5		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for km3402. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	21(1)	18(1)	19(1)	2(1)	-4(1)	0(1)
C(2)	25(1)	19(1)	16(1)	1(1)	-1(1)	0(1)
C(3)	18(1)	19(1)	15(1)	0(1)	-2(1)	-1(1)
C(4)	14(1)	16(1)	17(1)	-2(1)	-2(1)	1(1)
C(5)	16(1)	16(1)	16(1)	-1(1)	0(1)	1(1)
C(6)	17(1)	16(1)	16(1)	1(1)	-1(1)	0(1)
C(7)	22(1)	16(1)	18(1)	-3(1)	1(1)	2(1)
C(8)	22(1)	21(1)	16(1)	-2(1)	1(1)	0(1)
C(9)	39(1)	15(1)	27(1)	-1(1)	7(1)	-1(1)
C(10)	16(1)	19(1)	24(1)	-4(1)	2(1)	2(1)
C(11)	17(1)	17(1)	21(1)	-3(1)	5(1)	3(1)
C(12)	30(1)	23(1)	25(1)	-1(1)	11(1)	-1(1)
C(13)	45(1)	33(1)	20(1)	2(1)	11(1)	10(1)
C(14)	32(1)	38(1)	22(1)	-8(1)	-1(1)	14(1)
C(15)	19(1)	32(1)	32(1)	-7(1)	-2(1)	3(1)
C(16)	18(1)	21(1)	25(1)	-1(1)	2(1)	1(1)
N(1)	19(1)	14(1)	19(1)	-2(1)	0(1)	2(1)
O(1)	35(1)	16(1)	27(1)	2(1)	-2(1)	0(1)
O(2)	29(1)	15(1)	20(1)	0(1)	5(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x\ 10^3$) for km3402.

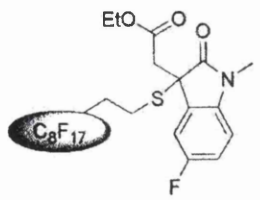
	x	y	z	U(eq)
H(2A)	1028	13616	4992	24
H(2B)	2760	13654	5596	24
H(5)	-493	11438	7872	20
H(7)	1398	9187	5950	22
H(8)	2165	10950	5123	23
H(9A)	-468	7873	6532	40
H(9B)	-308	7338	7576	40
H(9C)	1270	7792	7109	40
H(10A)	-1477	13575	7876	24
H(10B)	-879	14951	7656	24
H(12)	-650	12787	9382	30
H(13)	1050	12842	10774	39
H(14)	3273	14177	10923	37
H(15)	3822	15448	9671	33
H(16)	2159	15383	8273	26

Table 6. Torsion angles [°] for km3402.

O(1)-C(1)-C(2)-C(3)	-179.75(11)	C(10)-C(11)-C(12)-C(13)	-178.44(10)
N(1)-C(1)-C(2)-C(3)	-0.02(11)	C(11)-C(12)-C(13)-C(14)	0.42(18)
C(1)-C(2)-C(3)-C(8)	179.59(11)	C(12)-C(13)-C(14)-C(15)	-0.40(19)
C(1)-C(2)-C(3)-C(4)	0.21(11)	C(13)-C(14)-C(15)-C(16)	-0.07(19)
C(8)-C(3)-C(4)-C(5)	-0.51(15)	C(14)-C(15)-C(16)-C(11)	0.53(18)
C(2)-C(3)-C(4)-C(5)	178.96(9)	C(12)-C(11)-C(16)-C(15)	-0.51(17)
C(8)-C(3)-C(4)-N(1)	-179.81(9)	C(10)-C(11)-C(16)-C(15)	178.00(10)
C(2)-C(3)-C(4)-N(1)	-0.33(11)	O(1)-C(1)-N(1)-C(4)	179.56(10)
N(1)-C(4)-C(5)-C(6)	179.20(9)	C(2)-C(1)-N(1)-C(4)	-0.18(11)
C(3)-C(4)-C(5)-C(6)	0.04(15)	O(1)-C(1)-N(1)-C(10)	0.78(17)
C(4)-C(5)-C(6)-O(2)	179.48(9)	C(2)-C(1)-N(1)-C(10)	-178.96(9)
C(4)-C(5)-C(6)-C(7)	0.43(15)	C(5)-C(4)-N(1)-C(1)	-178.92(10)
O(2)-C(6)-C(7)-C(8)	-179.39(9)	C(3)-C(4)-N(1)-C(1)	0.33(12)
C(5)-C(6)-C(7)-C(8)	-0.43(16)	C(5)-C(4)-N(1)-C(10)	-0.14(16)
C(4)-C(3)-C(8)-C(7)	0.51(15)	C(3)-C(4)-N(1)-C(10)	179.10(9)
C(2)-C(3)-C(8)-C(7)	-178.81(11)	C(11)-C(10)-N(1)-C(1)	-101.78(12)
C(6)-C(7)-C(8)-C(3)	-0.05(16)	C(11)-C(10)-N(1)-C(4)	79.60(13)
N(1)-C(10)-C(11)-C(12)	-114.72(12)	C(7)-C(6)-O(2)-C(9)	-5.53(15)
N(1)-C(10)-C(11)-C(16)	66.79(13)	C(5)-C(6)-O(2)-C(9)	175.46(9)
C(16)-C(11)-C(12)-C(13)	0.04(17)		

Appendix II

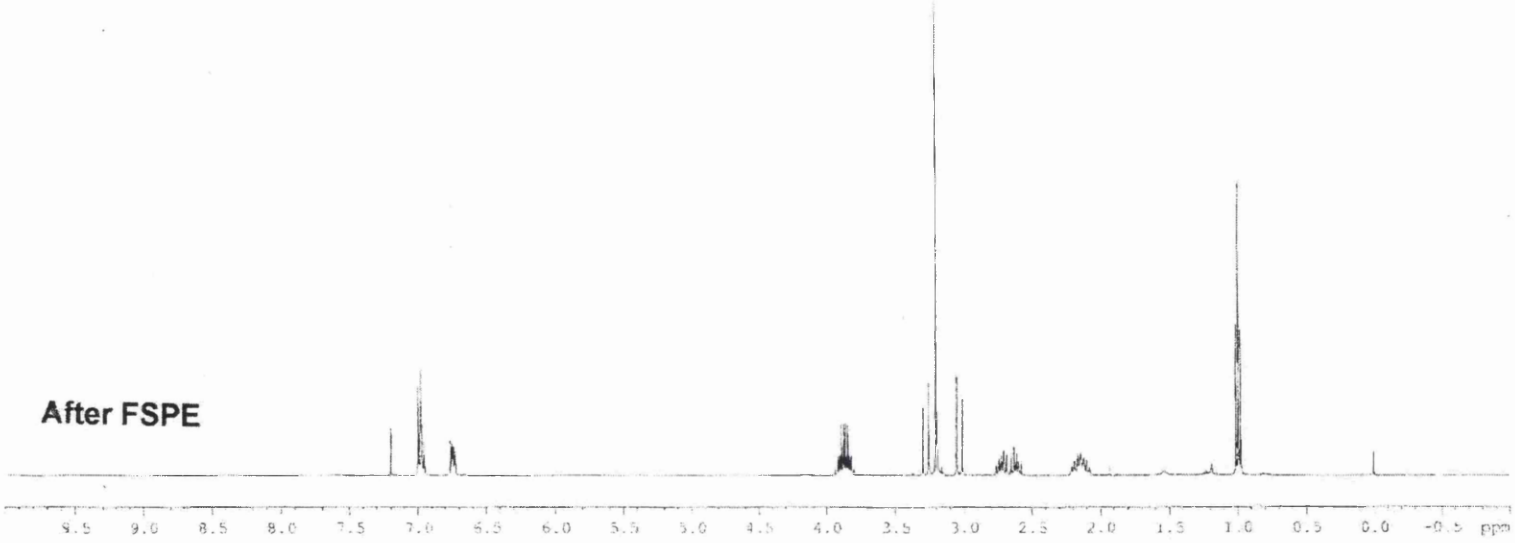
Sample NMR spectra of modified heterocycles before and after FSPE

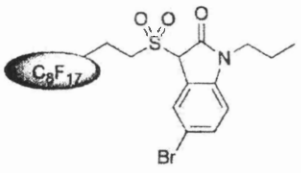


510

Before FSPE

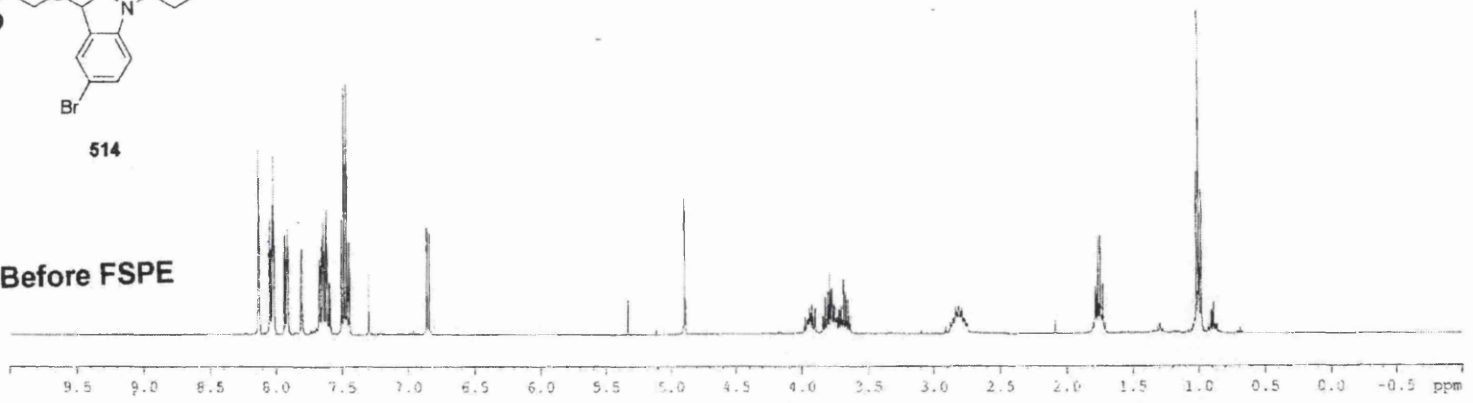
After FSPE



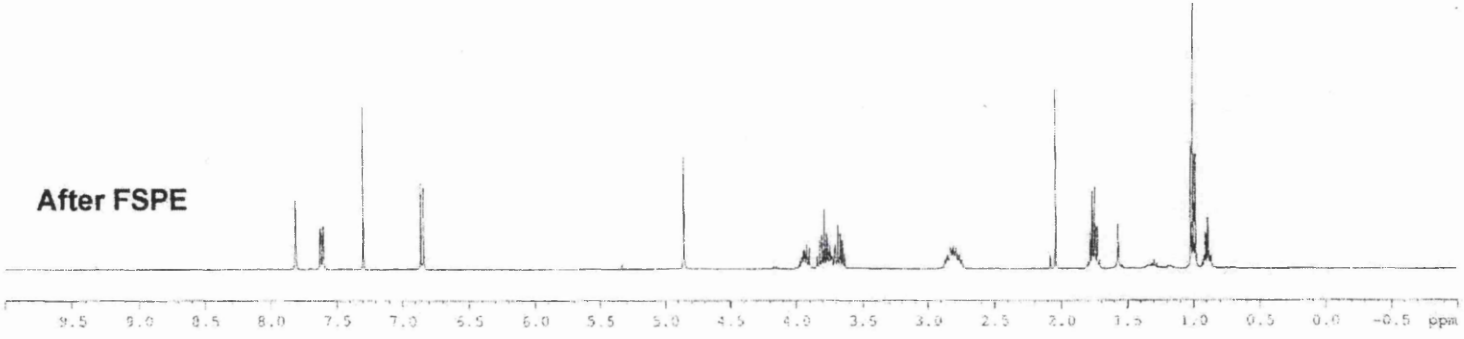


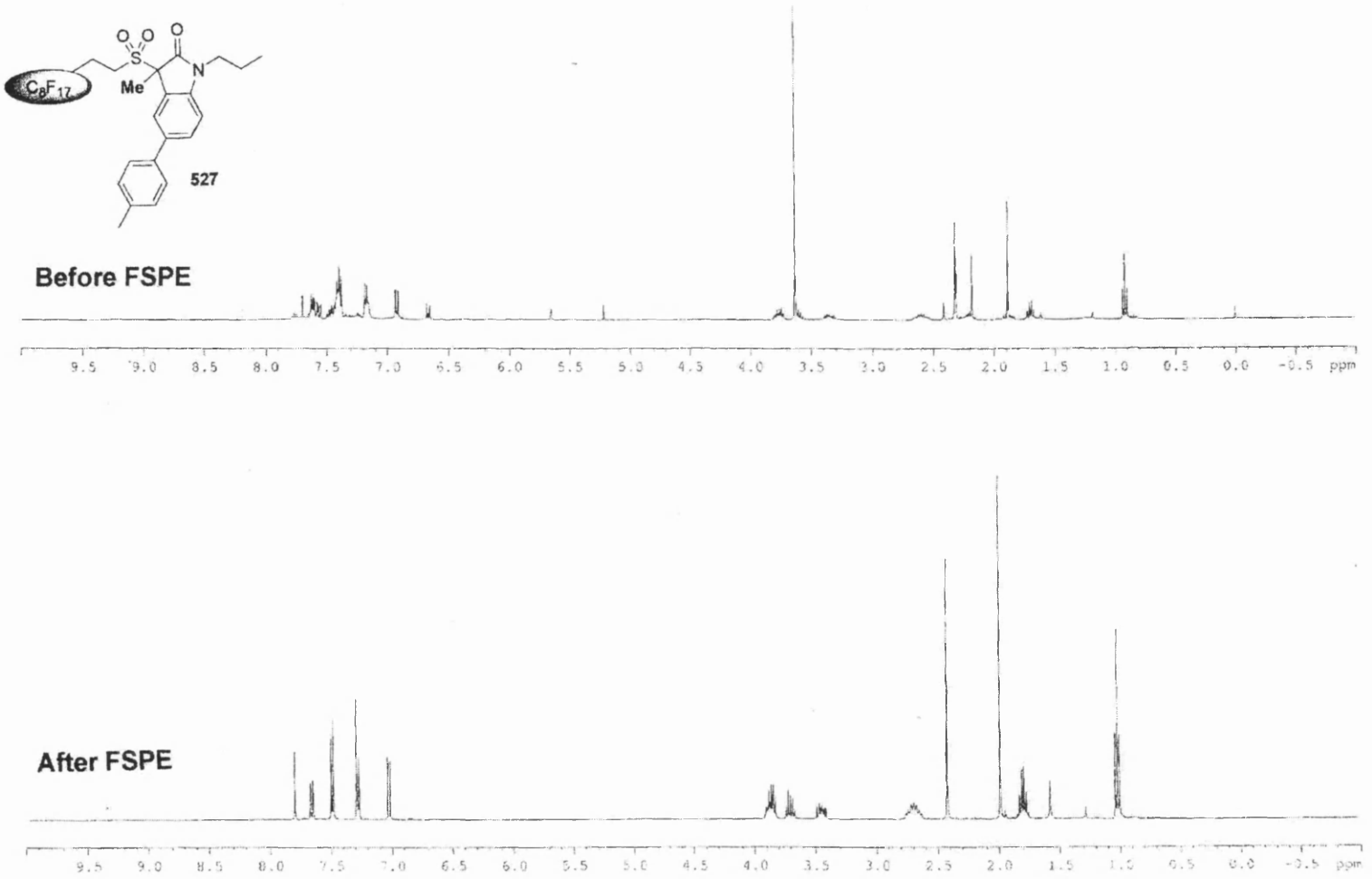
514

Before FSPE



After FSPE




C8F17
Me
527
Before FSPE
After FSPE
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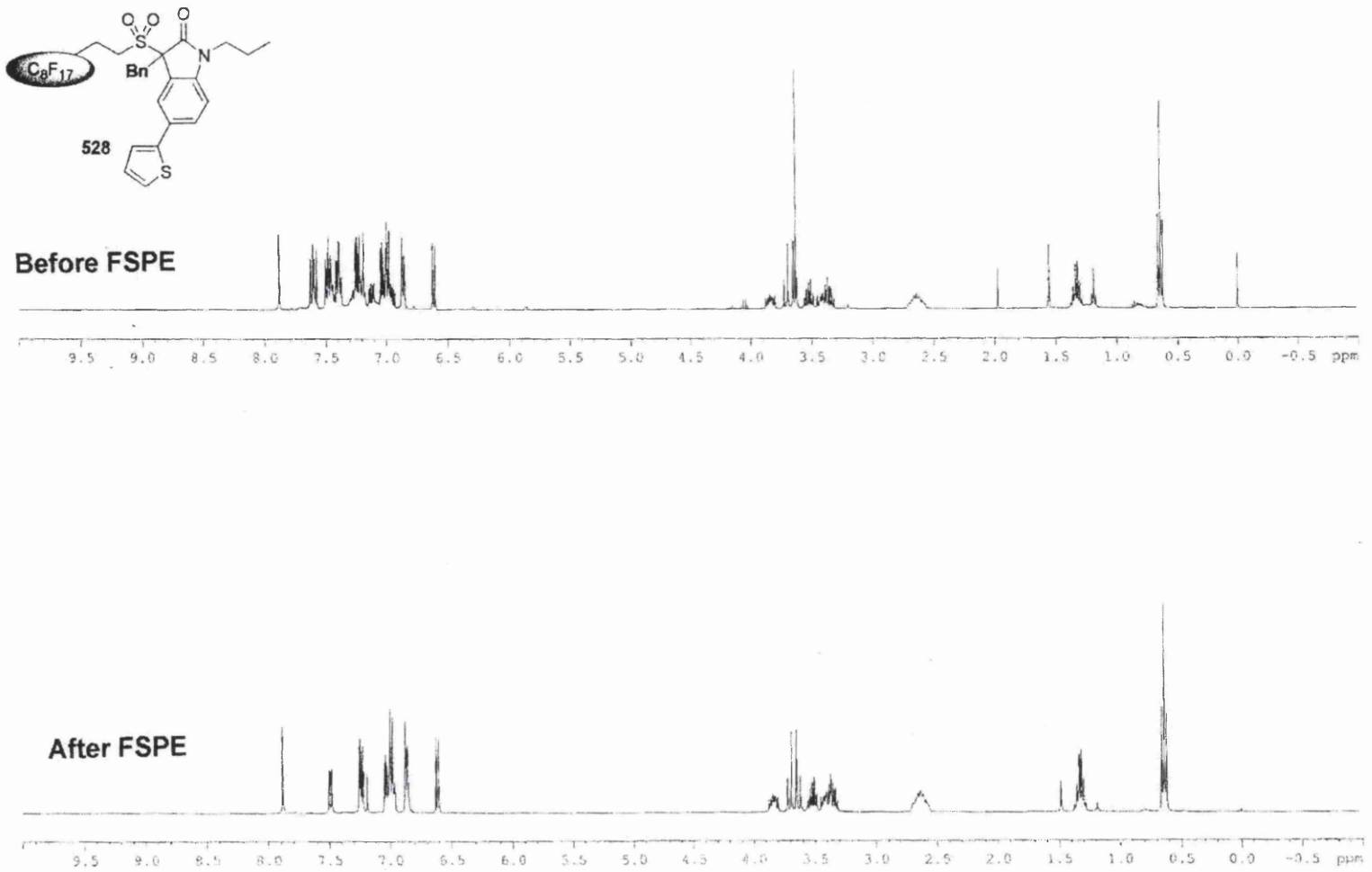
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Bn
528
Before FSPE
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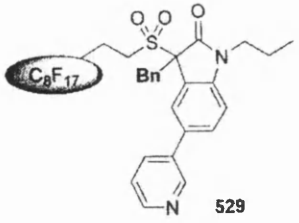

529

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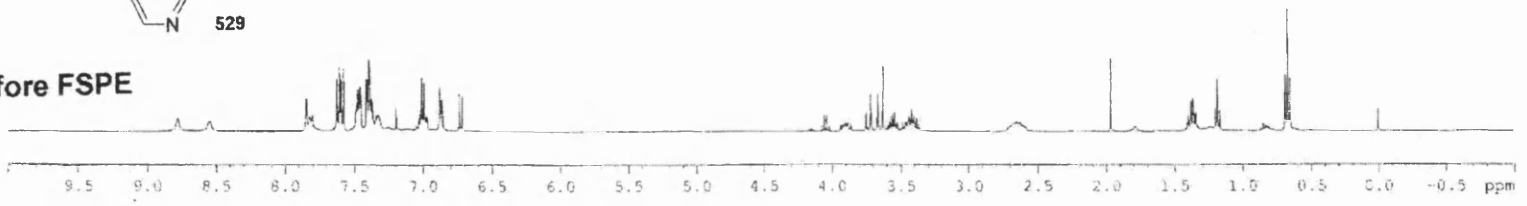

After FSPE