Regioselective C–H Thioarylation of Arenes Using Iron Catalysis

Amy C. Dodds, MSci

A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

School of Chemistry

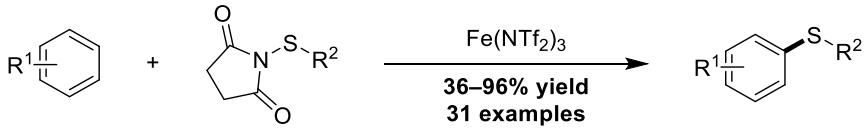
College of Science and Engineering

University of Glasgow

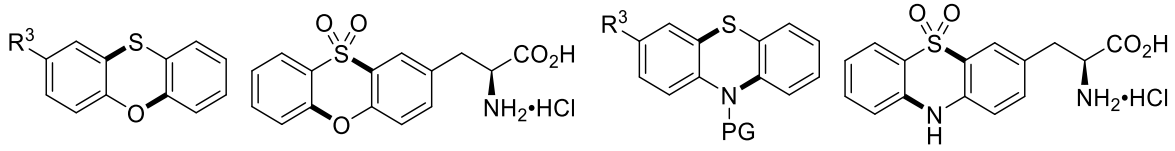
May 2023

Abstract

The aim of this PhD was to develop novel methods of C–S bond formation using earth abundant transition metal catalysis. The first project focused on the development of a regioselective, iron(III) triflimide-catalysed C–H thioarylation of electron-rich arenes. The methodology was used to synthesise pharmaceutically relevant aryl sulfur-containing compounds, as well as for the late-stage thioarylation of amino acid derivatives. Kinetic studies were undertaken, demonstrating that *N*-thiosuccinimides bearing electron deficient arenes undergo thioarylation catalysed by the iron(III) triflimide catalyst, whereas, electron-rich *N*-(arylthio)succinimides react *via* an autocatalytic mechanism partly promoted by the Lewis basic product.



The second and third projects describe the extension of this methodology for the synthesis of sulfur containing heterocycles. In particular, further optimisation studies identified that the iron(III) triflimide-catalysed thioarylation reaction could be accelerated upon addition of a Lewis base catalyst, resulting in a dual Lewis acid/Lewis base catalytic system. Subsequent copper or palladium mediated C–O or C–N cross-coupling reactions were then employed to synthesise small libraries of phenoxathiins and phenothiazines, respectively.



The final project details the development of a synthetic route towards a new class of fluorescent α-amino acids derived from L-tryptophan, which used the iron(III) triflimide/diphenyl selenide dual-catalysed thioarylation reaction as the key step. A small library of compounds was synthesised, which all displayed promising photophysical properties.

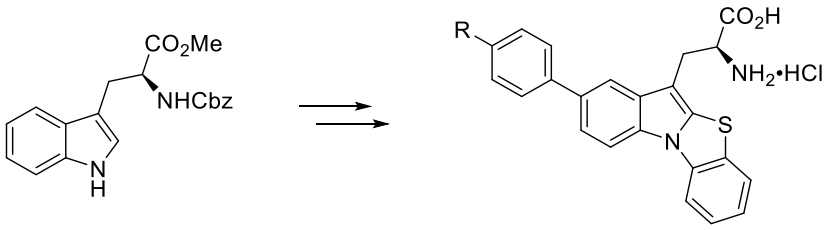


Table of Contents

Acknowledgements

Firstly, I would like to thank Professor Andrew Sutherland for allowing me to undertake my PhD within his research group. Andy has been a fantastic supervisor and there is no doubt in my mind that his help and guidance over the years has shaped me into the chemist I am today. He has always been on hand to provide suggestions and advice from way back in my early undergraduate years, until now looking forward to my career beyond my PhD, and for this I will be eternally grateful. Thank you, Andy!

I would like to express my gratitude to the technical staff of the Joseph Black building for their help and assistance throughout my PhD including Karen and Finlay (stores), Andy and Jess (mass spec) and Dr. David Adam (NMR).

Thank you to all members of the Sutherland group past and present – Martyn, Holly, Leanne, Nina, Lachlan, Valeria, Olivia, Beckie, Euan and Liyao – for making my PhD such an enjoyable experience. Thanks also to the Hartley group for making the Loudon lab a brilliant place to work. To Joe and Becca, you are amazing people and I feel so lucky to have worked alongside you both. Our time in the Loudon lab was filled with laughter and we have so many memories that I will look back on with great fondness. Thank you for getting on board with the 7's!! To Rochelle, thank you for being a great friend. I could not have wished to go through this experience with anyone better. Hopefully the Bratz Tweevil twins will be reunited in the chemistry world soon.

To my mum Tracy and dad Sandy, thank you for your infinite love and support throughout my entire life. I could not have achieved half of what I have so far without your guidance. Thank you for taking an interest in all I do chemistry wise, despite not being able to understand a word of it! To my best friends – Lorraine, Emma, Chloe, Louise, Sophie, Amy and Emily – thank you for all the fun times and for keeping me sane. You guys are the best. To Catherine, John and Jake, thank you for welcoming me into your family and getting me drunk all the time!

Finally, thanks to Josh for being by my side through this whole journey. My life is a whole lot brighter with you in it. And to my baby girl Nelly, you are the best thing that has ever happened to me. I can't wait to see what the future holds for our trio.

Authors Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis represents the original work of Amy C. Dodds and has not been submitted for any other degree at the University of Glasgow or any other institution. The research was carried out at the University of Glasgow in the Loudon Laboratory under the supervision of Professor Andrew Sutherland between October 2019 to March 2023. Aspects of the work described herein have been published elsewhere as listed below.

A. C. Dodds, A. Sutherland, Regioselective C–H Thioarylation of Electron-Rich Arenes by Iron(III) Triflimide Catalysis, *J. Org. Chem.*, 2021, **86**, 5922–5932.

A. C. Dodds, A. Sutherland, Synthesis of Phenoxathiins Using an Iron-Catalysed C–H Thioarylation, *Org. Biomol. Chem.*, 2022, **20**, 1738–1748.

A. C. Dodds, S. Puddu, A. Sutherland, Thioarylation of Anilines Using Dual Catalysis: Two-Step Synthesis of Phenothiazines, *Org. Biomol. Chem.*, 2022, **20**, 5602–5614.

A. C. Dodds, L. J. N. Waddell, A. Sutherland, Regioselective Functionalisation of Arenes using Iron Triflimide Catalysis, *Synlett.*, 2023, DOI: 10.1055/s-0042-1751445.

Abbreviations

Abs	Absorbance
Ac	Acetyl
Ar	Aromatic
AzAla	*β*-(1-azulenyl)-L-alanine
[BMIM]NTf_2	1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide
Bn	Benzyl
br	Broad
Bz	Benzoyl
Cbz	Carboxybenzyl
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMA	*N,N*-Dimethylacetamide
DMC	Dimethylcarbonate
DME	Dimethoxyethane
DMEDA	1,2-Dimethylethylenediamine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EC	Ethyl crotonate
EDG	Electron donating group
EI	Electron impact
equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl

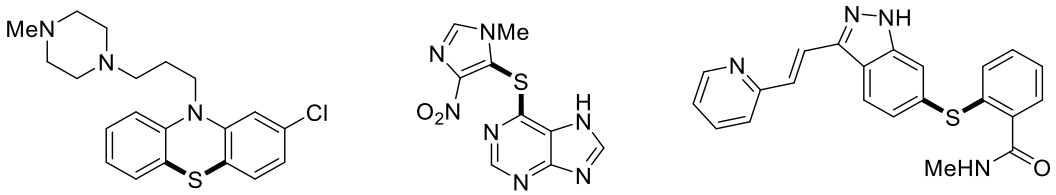
EWG	Electron withdrawing group
FDA	Food and drug administration
Fmoc	Fluorenylmethyloxycarbonyl
g	Gram(s)
h	Hour(s)
HRMS	High-resolution mass spectrometry
Hz	Hertz
IR	Infrared spectroscopy
J	Coupling Constant
lit.	Literature
M	Molar
m	Multiplet
m-	*Meta*-
Me	Methyl
min	Minutes
mol	Mole(s)
Mp	Melting point
Ms	Mesyl
m/z	Mass to charge ratio
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
NSAID	Nonsteroidal anti-inflammatory drug
NTf_2	Bis(trifluoromethylsulfonyl)imide

o-	*Ortho*-
OAc	Acetate
p-	*Para*-
PET	Positron Emission Tomography
Ph	Phenyl
PPh_3	Triphenylphosphine
ppm	Parts per million
q	Quartet
rt	Room temperature
s	Singlet
S_N2	Bimolecular nucleophilic substitution
SPECT	Single photon emission computed tomography
t	Triplet
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
Ts	Tosyl
UV	Ultraviolet
Vis	Visible
λ_{abs}	Absorbance maximum
°C	Degrees Celsius
λ_{em}	Emission maximum
ϕ	Fluorescence quantum yield
ε	Molar attenuation coefficient

1.0 Introduction

1.1 Introduction to C–S Bonds

Aryl sulfides represent a common motif found in a wide range of biologically active natural products and pharmaceuticals.[1] For example, this scaffold is found in drug molecules such as prochlorperazine **1**, an anti-psychotic agent, azathioprine **2**, an immunosuppressant drug and axitinib **3**, a compound used in the treatment of advanced kidney cancer (Figure 1).[2] Aryl sulfides have also been used in polymer and synthetic chemistry,[3,4] as well as serving as useful precursors to more highly oxidised sulfur-based functional groups such as sulfoxides and sulfones.[5] Thus, the development of mild, selective and sustainable methods for the preparation of carbon-sulfur bonds are of some importance.



1 **2** **3**

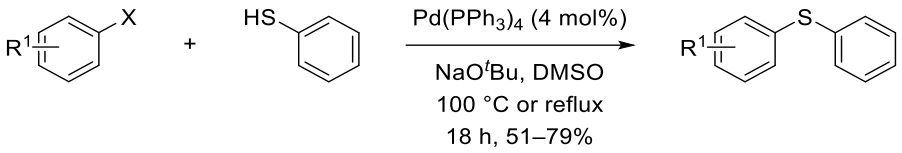
Figure 1: Examples of biologically active molecules containing an aryl sulfide moiety.

Whereas alkyl thioethers can be easily prepared through S_N2 displacements, the construction of aryl sulfides is somewhat less trivial, and this is typically achieved through cross-coupling reactions of aryl halides/pseudohalides and thiols/thiol derivatives. These are often catalysed by transition metals such as palladium, copper and nickel,[1,6,7] and are limited by the tendency of organic sulfur compounds to coordinate to these metals and readily poison the catalysts. As such, most of the known methods to form C–S bonds rely on harsh conditions such as high reaction temperatures, the use of strong bases and high loadings of catalyst and ligands.[8,9,10] Additionally, the use of thiols or thiophenols as sulfur sources can introduce difficulties such as unpleasant smells, easy oxidation and toxicity.[11] Therefore, efforts have focused on identifying thiol surrogates amenable to C–S bond forming reactions.

1.2 Transition Metal-Catalysed Aromatic C–S Bond Formation

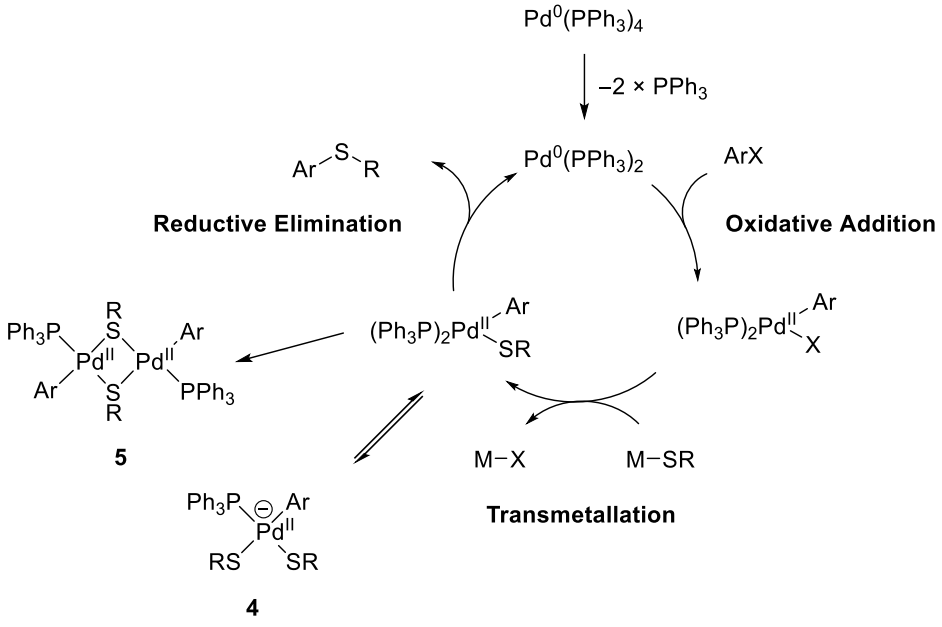
1.2.1 Palladium-Catalysed C–S Bond Formation

The first successful cross-coupling reaction for the synthesis of aryl C–S bonds was reported by Migita and co-workers in 1978.[12,13] Aryl sulfides were obtained in moderate to good yields from aryl halides (bromides and iodides) and thiols using $Pd(PPh_3)_4$ as a catalyst (Scheme 1).[10] Whilst providing an invaluable starting point, this protocol exhibits several major drawbacks, including the short lifetime of the catalyst and limited substrate scope.[13] Additionally, aryl chlorides were poor substrates for the coupling reaction, which is a major disadvantage due to their wide availability and low cost.[14]



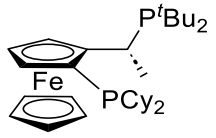
Scheme 1: Palladium catalysed aryl C–S bond formation, R_1 = H, *p*-Me, *p*-MeO, *p*-Cl, X = Br, I.

It was hypothesised that the short lifetime of the palladium catalyst could be limited by the facile displacement of the dative triphenylphosphine ligands by thiolate anions to form complexes such as **4**, or the tendency to form bridging thiolate complexes (**5**). These have a slow rate of reductive elimination and result in slower catalysis (Scheme 2).[15,16]



Scheme 2: General mechanism for the palladium-catalysed C–S bond-forming reactions.

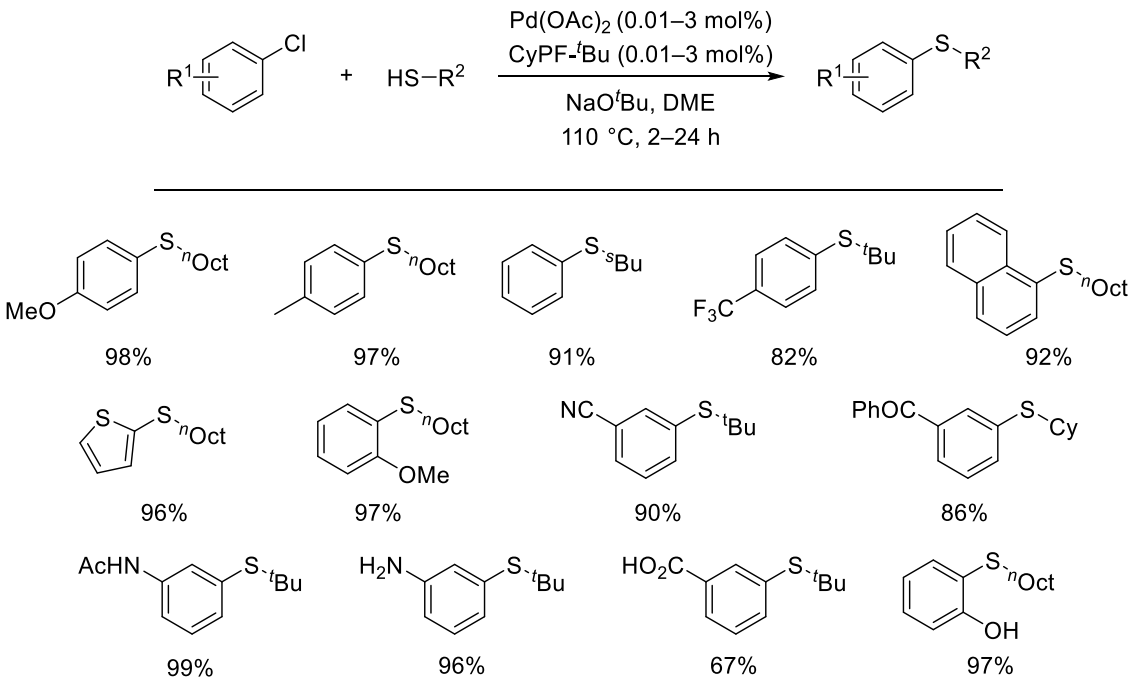
To overcome the issue of short catalyst lifetime, it was proposed that more efficient catalysts would result from the use of bidentate ligands, which could bind more strongly to the metal centre. This would minimise the formation of unreactive complexes **4** and **5**, whilst simultaneously promoting oxidative addition and reductive elimination.[1,14,15] In 2006, Hartwig and co-workers reported the general and highly efficient coupling of aryl chlorides with thiols, catalysed by palladium complexes of the ferrocene-based Josiphos ligand CyPF-*t*Bu (**6**) (Figure 2).[14] The restricted backbone conformation allowed the ligand to operate efficiently as a bidentate ligand, whilst the strong electron donating ability encourages oxidative addition. This, in combination with the large steric bulk, which drives reductive elimination, deemed **6** a good candidate for the generation of practical palladium catalysts.[17]



6

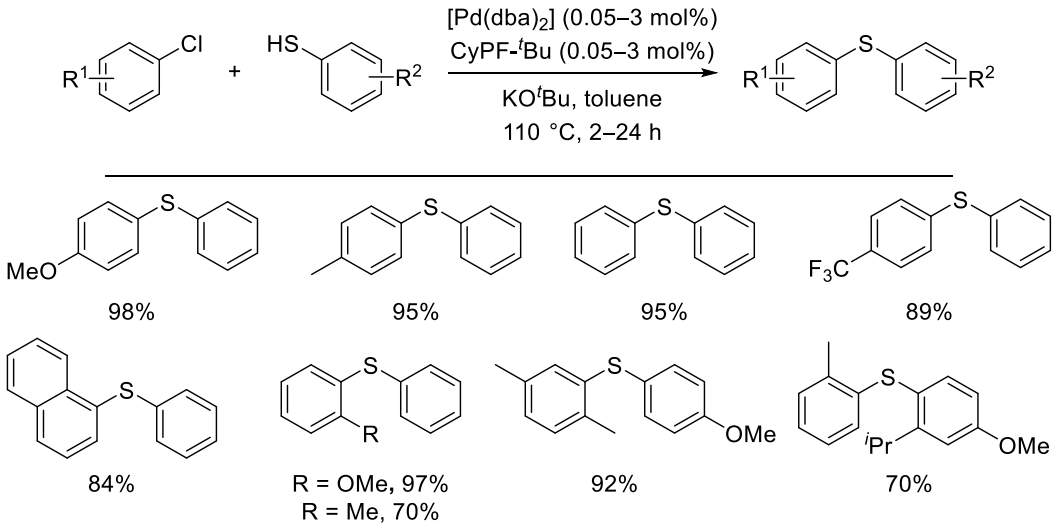
Figure 2: Josiphos ligand CyPF-*t*Bu (**6**).

Optimisation studies revealed that the use of $Pd(OAc)_2$ in combination with Josiphos ligand **6** and sodium *tert*-butoxide, using 1,2-dimethoxyethane as a solvent, allowed the most efficient coupling of aryl chlorides with aliphatic thiols (Scheme 3). With the optimised conditions established, the substrate scope was then explored. It was found that primary, secondary and tertiary aliphatic thiols coupled with ease to give the desired aryl thioethers in excellent yields. Additionally, the cross-coupling reaction was amenable to both electron rich and electron deficient chloroarenes, furnishing the desired products in high yields. Sterically hindered *ortho*-substituted chloroarenes also coupled successfully, and the methodology was shown to be tolerant of a wide range of functional groups such as protected and free amino groups, ketones, nitriles, carboxylic acids and phenols.[14]



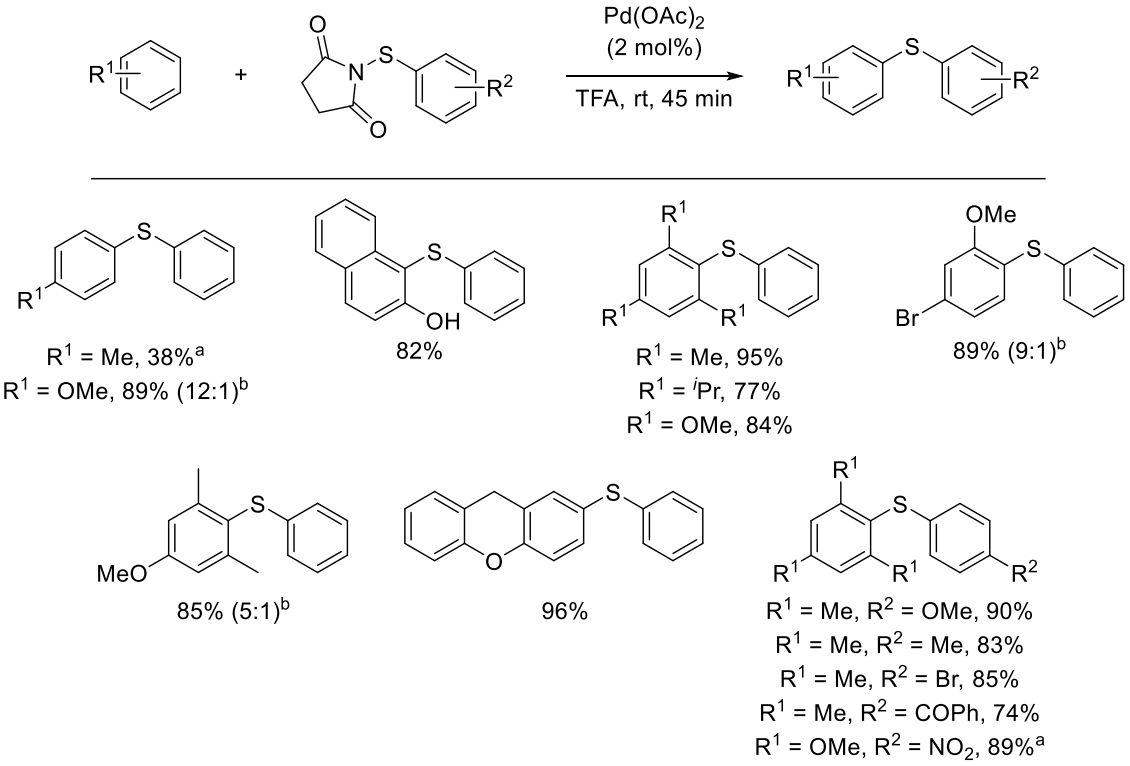
Scheme 3: Substrate scope of functionalised aryl chlorides with aliphatic thiols.

For the cross-coupling of aromatic thiols, studies found that the combination of [Pd(dba)$_2$], Josiphos ligand **6** and sodium *tert*-butoxide, using toluene as a solvent, gave the best results (Scheme 4). The use of these conditions allowed for the successful cross-coupling of electron rich, electron neutral and electron deficient chloroarenes with electron rich and electron neutral aromatic thiols. Chloroarenes and thiophenols with *ortho*-substituents were well tolerated, with the desired products being isolated in good to excellent yields.



Scheme 4: Substrate scope of functionalised aryl chlorides with aromatic thiols.

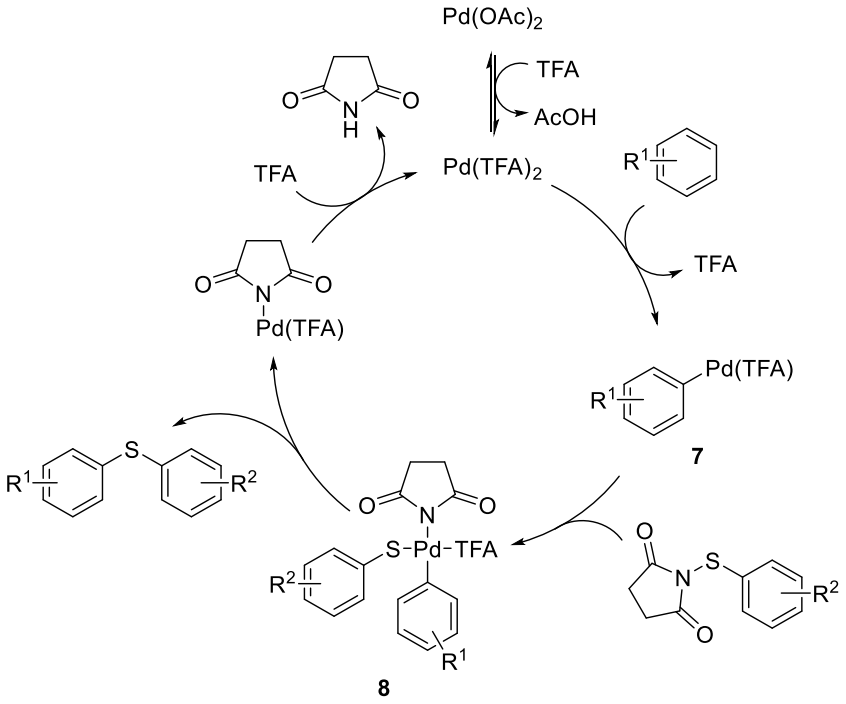
Carbon-sulfur bonds have also successfully been constructed *via* the direct thioarylation of C–H bonds using electrophilic thioarylating reagents. A palladium-catalysed thioarylation of arenes using *N*-thiosuccinimides was reported by Anbarasan and co-workers in 2014.[18] Optimisation studies highlighted that, the use of $Pd(OAc)_2$ as the catalyst and trifluoroacetic acid (TFA) as a solvent, allowed for the direct construction of biaryl sulfides in good yields with high regioselectivity (Scheme 5). Investigation of the substrate scope revealed that arenes bearing at least one directing group were amenable to the methodology. This process was efficient for a range of biaryl sulfides, however, some limitations were noted, including the use of TFA as a solvent, which is highly harmful and corrosive. The coupling of toluene resulted in a moderate yield of 38%, and in some cases e.g. the coupling of 3,5-dimethylanisole and 3-bromoanisole, a mixture of *ortho*- and *para*-thioarylated products were obtained.



Scheme 5: Palladium(II)-catalysed C–H thioarylation of arenes with *N*-thiosuccinimides. [a]4 h; [b]Mixture of *para*- and *ortho*- isomers.

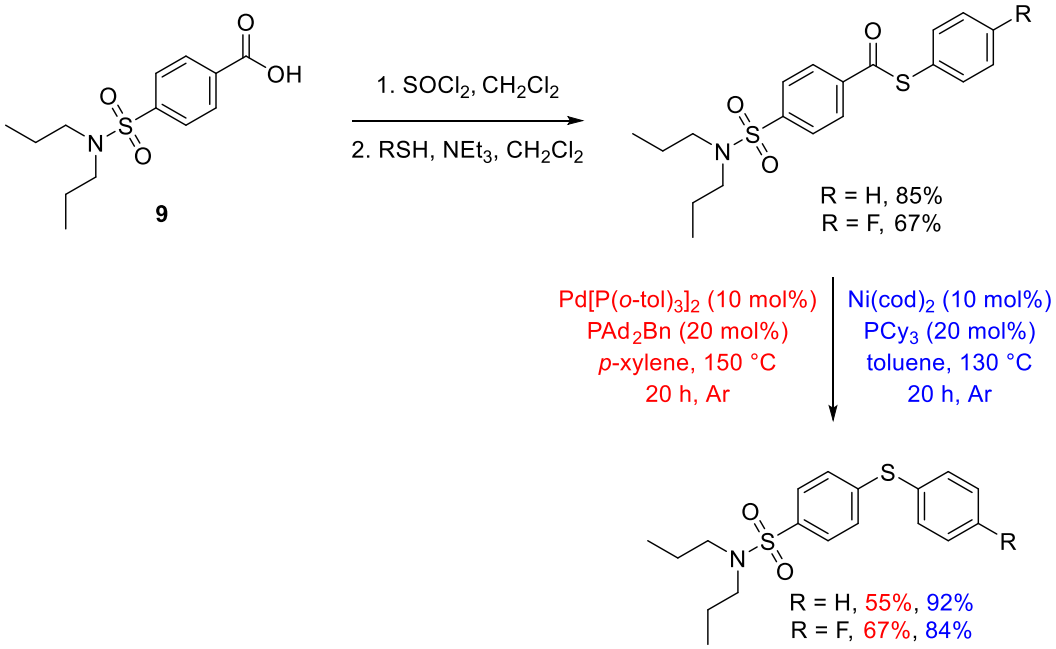
The proposed reaction mechanism for the transformation is outlined in Scheme 6. Initially, the combination of $Pd(OAc)_2$ and TFA result in the formation of highly electrophilic palladium trifluoroacetate, which reacts with arenes *via* an electrophilic aromatic substitution reaction to afford the arylpalladium(II) species **7**. Oxidative

addition of the the N–S bond ensues to give palladium(IV) intermediate **8**, which undergoes subsequent reductive elimination to provide the desired product. Ligand exchange allows for the regeneration of the catalytically active palladium species.[18]



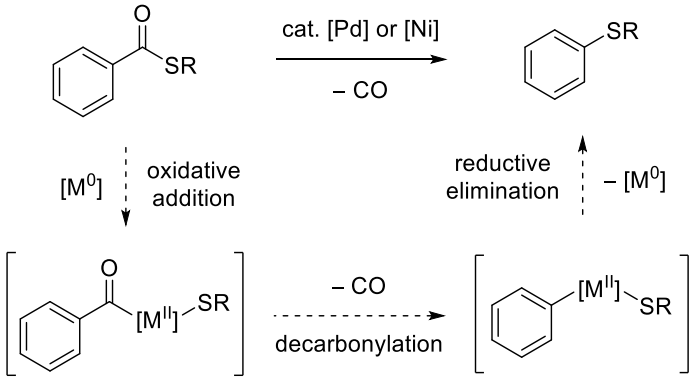
Scheme 6: Proposed reaction mechanism for the Pd-catalysed thioarylation of arenes.

In 2018, Sanford and co-workers reported the development of a palladium- or nickel-catalysed decarbonylative C–S coupling reaction that converts thioesters into thioethers.[19] This method provides access to biaryl, heteroaryl and aryl alkyl thioethers, under base and thiol free conditions. The substrate scope was broad, with a wide variety of functional groups being well tolerated on the carboxylic acid component such as benzylic groups, ester functionalities and boronic acids. The synthetic utility of the transformation was demonstrated with the late-stage functionalisation of the carboxylic acid-containing drug probenecid (**9**) (Scheme 7), which is used to treat gout and hyperuricemia.[20] Treatment of **9** with thionyl chloride, and subsequent reaction with thiophenols, allowed for the preparation of a small series of probenecid thioesters. These were then subjected to the optimised Pd- or Ni-catalysed decarbonylation reaction conditions. Both sets of conditions provided the desired aryl thioethers in moderate to good yields, highlighting the potential of this transformation for the late stage thioarylation of complex molecules containing carboxylic acid functionalities.



Scheme 7: Late-stage thioarylation of probenecid (**9**).

It is proposed that the reaction follows the traditional mechanism for Pd- or Ni-catalysed intramolecular decarbonylation (Scheme 8). The first step involves oxidative addition of the thioester to form an acylmetal thiolate. Next, an arylthiolate intermediate results from the decarbonylation step and then the desired product is obtained following reductive elimination.[19]



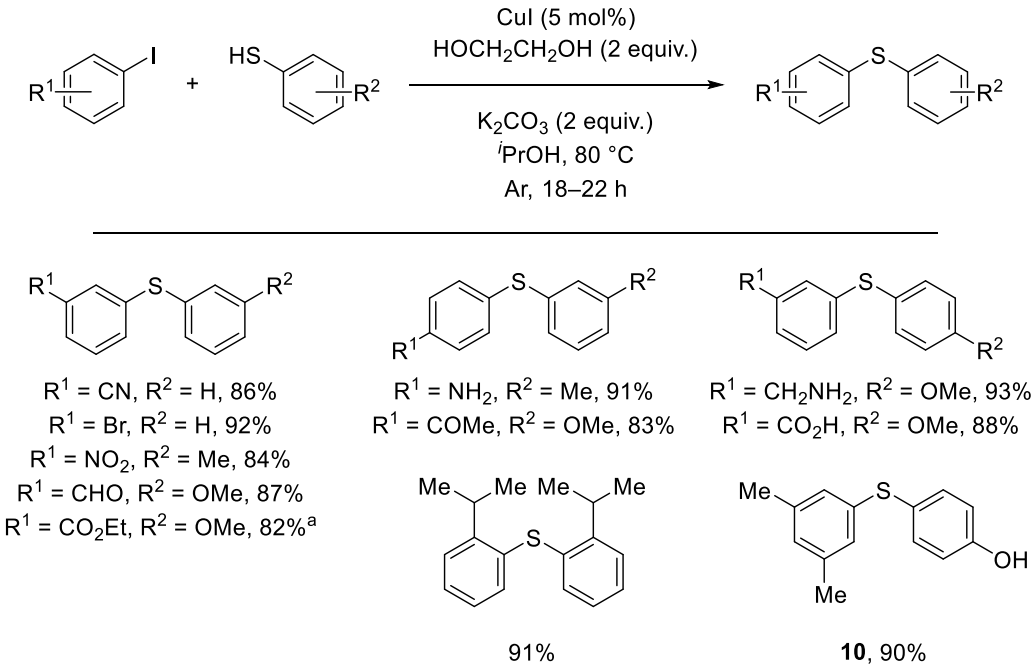
Scheme 8: Proposed reaction mechanism for the decarbonylation of thioesters.

1.2.2 Copper-Catalysed C–S Bond Formation

The Ullman reaction has proven especially useful for the formation of carbon-heteroatom bonds under mild conditions. However, in contrast to the volume of literature which exists for the formation of C–O and C–N bonds, the analogous C–

S bond forming reaction is less well reported. In general, the use of copper-catalysis in cross-coupling reactions results in operationally simple and practical procedures due to the low-cost, low-toxicity and high stability of readily available copper catalysts.[21]

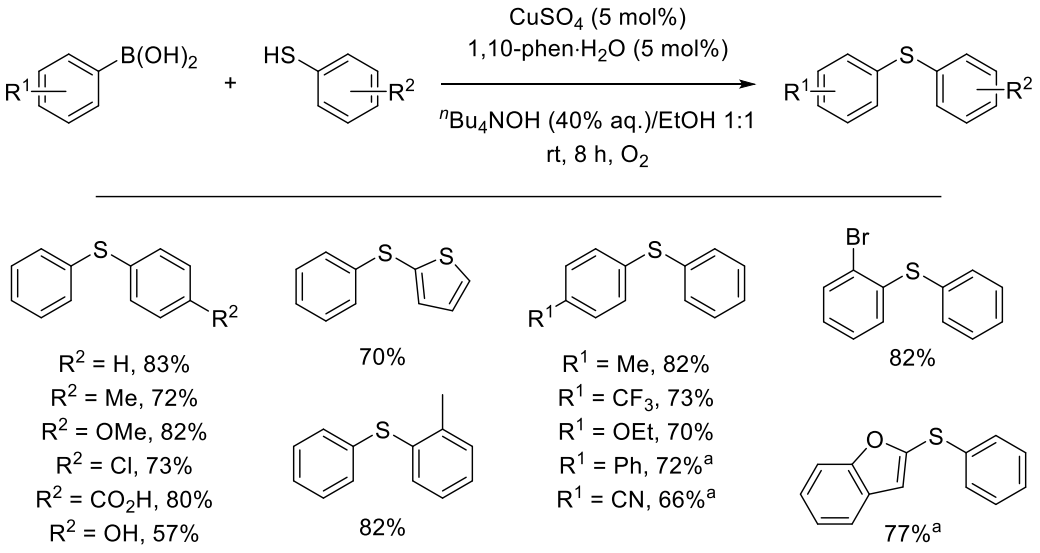
In 2002, Buchwald and co-workers reported a copper-catalysed C–S bond forming reaction of aryl iodides with thiophenols under mild conditions (Scheme 9).[22] Optimisation studies identified that the combination of CuI (5 mol%), K_2CO_3 and ethylene glycol in 2-propanol allowed the most efficient coupling. The use of a mild base at a moderate temperature (80 °C) resulted in a transformation tolerant of both acid- and base- sensitive functional groups. Aryl iodides possessing nitriles and nitro groups, ketones, carboxylic acids, aldehydes and unprotected hydroxyl and amino groups were all cross-coupled efficiently, giving the desired aryl thioethers in good to excellent yields. Aryl iodide and thiophenol components with *ortho*-substituents were also well tolerated. One interesting result is the successful reaction between 5-iodo-*m*-xylene and 4-hydroxythiophenol to give **10**, where chemoselective C–S bond formation occurs in the presence of a phenolic OH group.



Scheme 9: CuI-catalysed cross-coupling reaction of aryl iodides and thiophenols. [a]DME used as a solvent.

Whilst this protocol demonstrates significant progress with respect to developing copper-catalysed C–S sulfenylations, its scope is limited to the coupling of aryl iodides. The Chan–Lam reaction offers an alternative to traditional cross-coupling

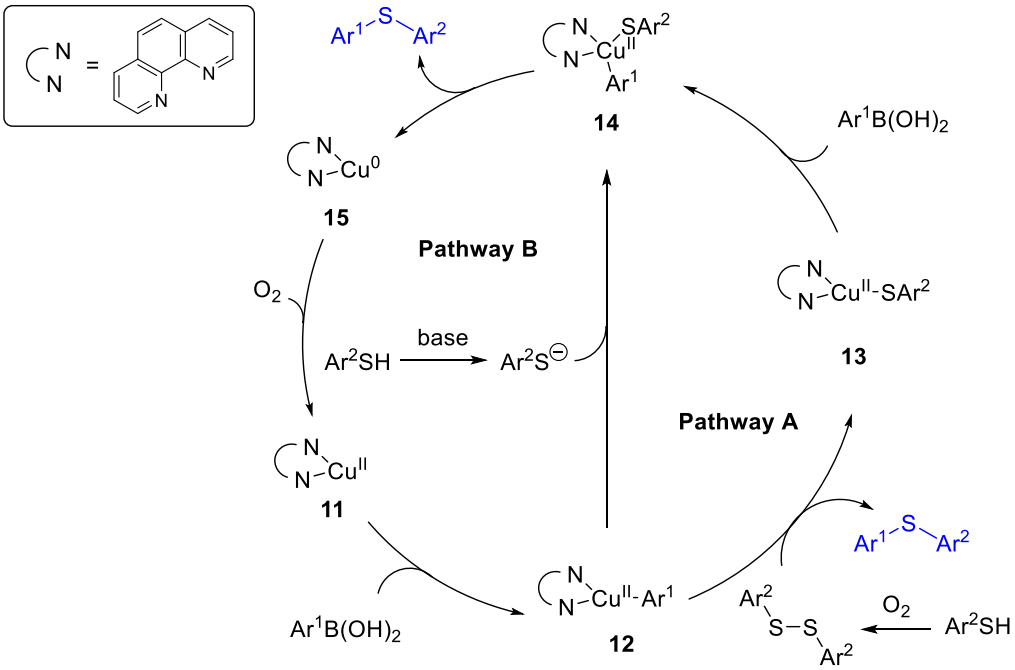
reactions employed to construct carbon-heteroatom bonds and makes use of accessible boronic acids and derivatives. In 2012, Feng and co-workers reported a novel and efficient method of copper-catalysed C–S bond formation involving the reaction of aromatic thiols with aryl and heteroaryl boronic acids at room temperature (Scheme 10).[23] The reaction makes use of the readily available copper salt, copper sulfate ($CuSO_4$) as a catalyst, accompanied by the inexpensive 1,10-phenanthroline monohydrate as a ligand. Additionally, the use of environmentally-friendly solvent, ethanol, further compliments the methodology. Investigation of the substrate scope demonstrated that both electron-rich and electron-deficient thiophenols and boronic acids functioned as effective substrates for the transformation, with the coupling appearing to be insensitive to the electronic properties of the substrates. Boronic acids bearing bromo and chloro substituents reacted to give the desired aryl thioethers in good yields, offering functional handles for further transformations. The successful cross-coupling of 4-hydroxythiophenol demonstrated that this approach also avoids oxidative C–O coupling.



Scheme 10: Cu-catalysed Chan–Lam-type *S*-arylation of thiophenols with boronic acids at room temperature. [a]24 h.

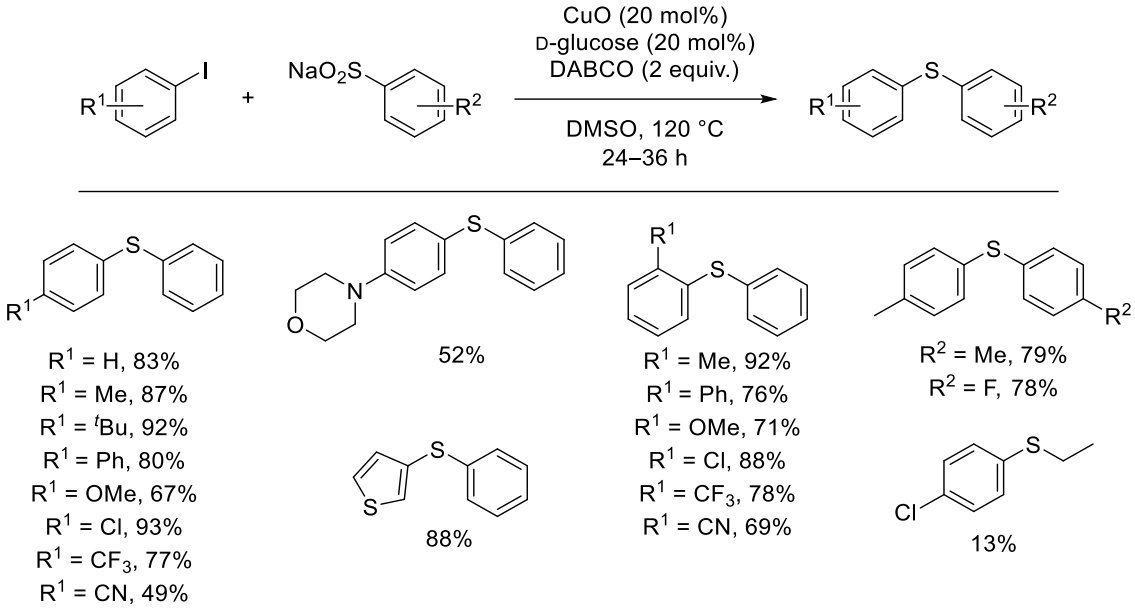
The proposed mechanism for the transformation is detailed in Scheme 11. Initial coordination of 1,10-phenanthroline monohydrate to $CuSO_4$ results in the formation of Cu(II) intermediate **11**. This subsequently undergoes transmetallation with the boronic acid to form **12**. From here, there are two possible pathways which can complete the catalytic cycle. In pathway A, 1,2-diphenyldisulfanes (formed from the Cu(II) catalysed oxidation of the thiol starting material) can react with **12** to give the

desired product and intermediate **13**. Intermediate **13** can then undergo transmetallation with the boronic acid to give **14**. The other pathway – pathway B – involves reaction of **12** with the thiolate anion directly to achieve **14**. In both cases, reductive elimination follows, providing the desired product and a Cu(0) species **15**, which is oxidised by O_2 to regenerate the Cu(II) catalyst and complete the cycle.[23]



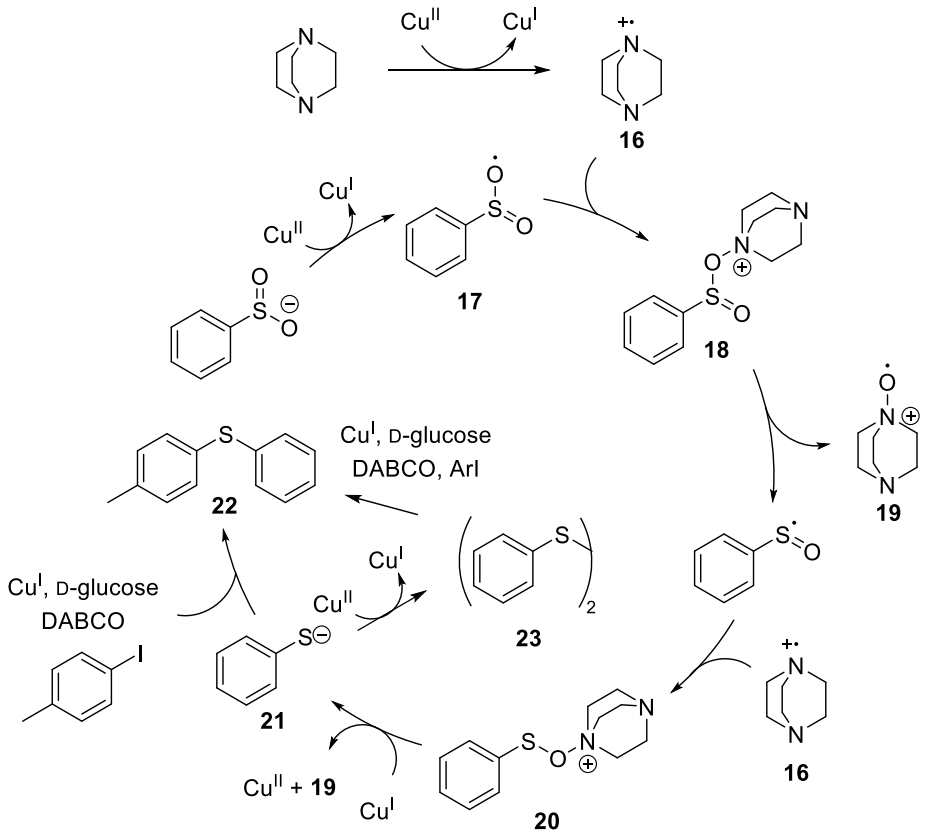
Scheme 11: Proposed mechanism of the Chan–Lam-type *S*-arylation.

Whilst this methodology is useful, the disadvantages of using free thiols such as unpleasant odours and toxicity, requires the development of new methods for C–S bond formation that do not rely on thiols being employed as reagents. In 2020, Ma and co-workers reported an alternative method for the synthesis of aryl thioethers from sodium arylsulfinates and iodoarenes (Scheme 12).[24] Arylsulfinates represent promising thiol surrogates in the construction of aryl thioethers due to their high stability and non-volatile nature. The substrate scope verified the compatibility of a variety of aryl iodides with a range of electronic natures. Whilst the copper(II) catalyst and D-glucose ligand are both inexpensive and readily available, this methodology is limited by the high temperature and long reaction times required. Additionally, the use of 2 equivalents of DABCO as a base, renders the reaction atom inefficient.



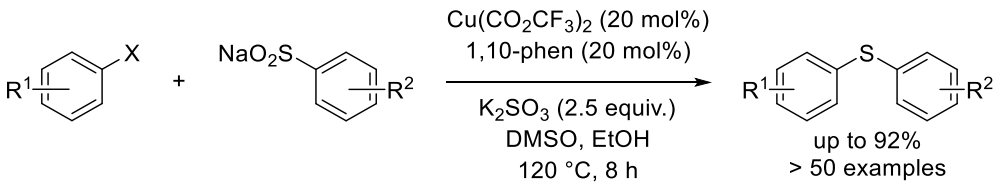
Scheme 12: Cu(II)-catalysed cross-coupling of sodium sulfinates and aryl iodides to form aryl thioethers.

The group performed a series of control experiments to support the hypothesised mechanism for the reaction outlined in Scheme 13.[24] Firstly, copper(II) oxidation of DABCO results in the formation of DABCO radical cation **16**. Copper(II) oxidation is also responsible for the generation of benzenesulfinate radical **17**, from sodium benzenesulfinate. Next, the two radical species combine to give DABCO-sulfinate **18**. Liberation of a DABCO *N*-oxide radical, **19**, allows the resulting reduced sulfinyl radical to react with **16**, furnishing DABCO-sulfanolate **20**. Thiolate **21** is obtained *via* Cu(I) oxidation, which can undergo a cross-coupling reaction with 4-iodotoluene to provide the desired aryl thioether product **22**. Alternatively, Cu(II) can promote the oxidation of thiolate **21** to give disulfide **23**, which can also react with 4-iodotoluene under the optimised conditions to give desired product **22**.



Scheme 13: Proposed mechanism of the Cu-catalysed, DABCO-promoted diaryl thioether formation.

Encouraged by these results, Ma and co-workers sought to develop other novel methods for C–S bond formation, which used alternative reagents to aryl halides. In 2021, the group described a Chan–Lam-type C–S coupling reaction for aryl thioether formation which uses aryl boronic acids/esters/borates and sodium aryl sulfinates (Scheme 14).[25] The substrate scope was broad with a diverse range of sodium aryl sulfinates and organoboron compounds being well tolerated.



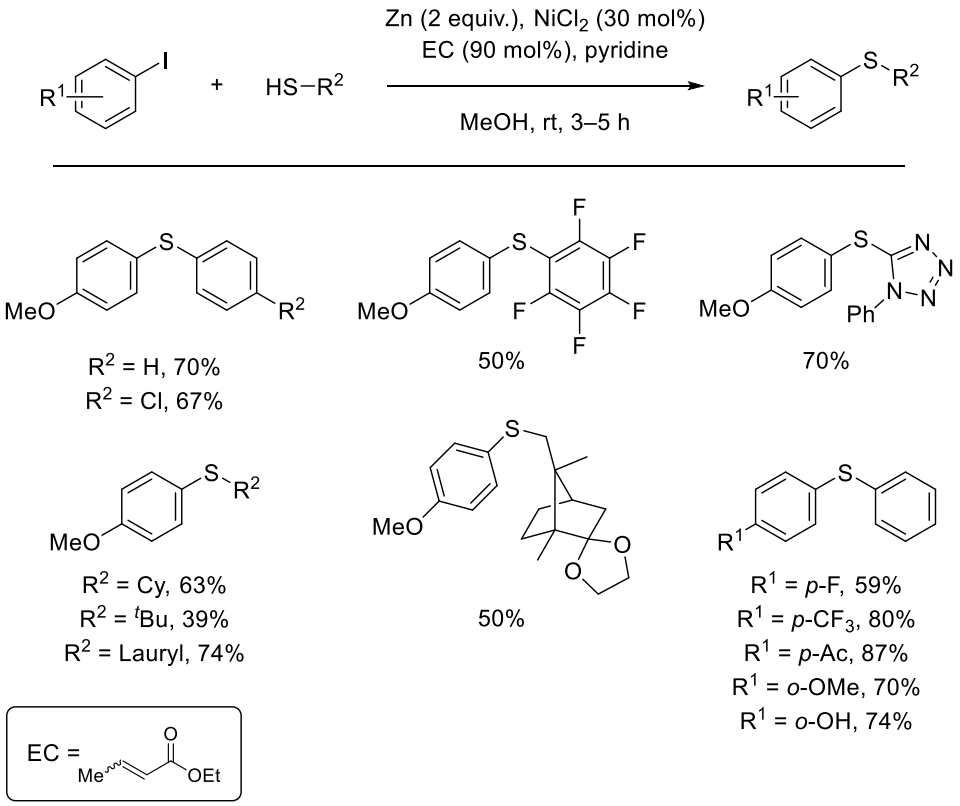
Scheme 14: Chan–Lam-type C–S coupling reaction of sodium aryl sulfinates and organoboron compounds. X = $B(OH)_2$, boroxine, B(pin), BF_3K.

1.2.3 Nickel-Catalysed C–S Bond Formation

Another transition metal which is frequently used in cross-coupling reactions for C–S bond formation is nickel. The use of nickel as a catalyst is generally preferred

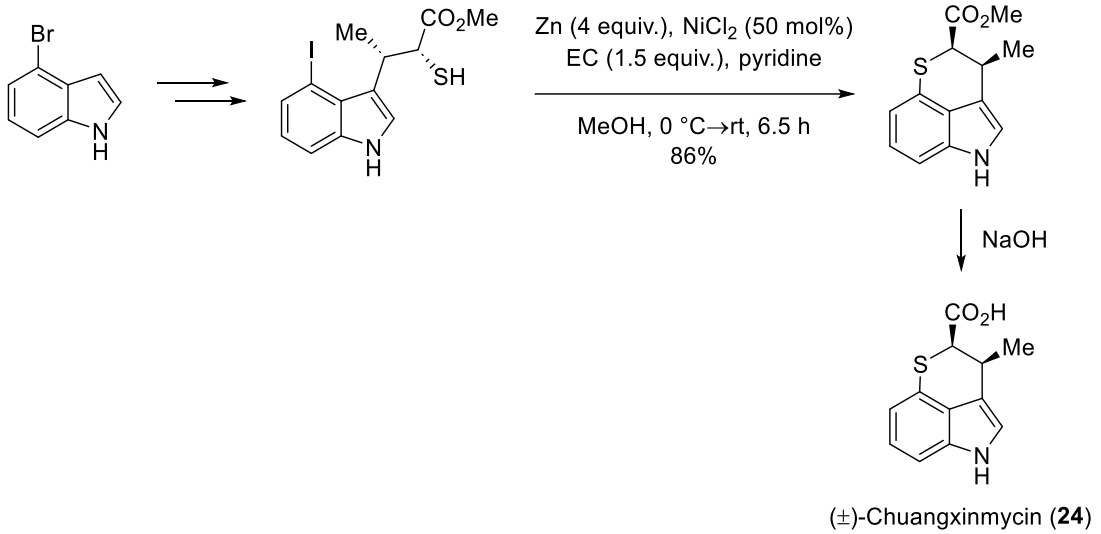
nowadays over transformations employing transition metals such as Pd, Rh and Ir, due to its commercial availability, ease of operation and facile oxidative addition.[8]

In 2013, Peng and co-workers reported the use of an inexpensive and readily available Ni(0) complex to achieve both inter- and intramolecular cross-coupling of thiols and iodoarenes (Scheme 15).[26] In this reaction, the active catalyst Ni(0).2EC.Py is formed *in situ* by heating a mixture of Zn/$NiCl_2$/pyridine/ethyl crotonate (EC) at 55 °C for 15 min.[27] A variety of electron rich and electron deficient aryl iodides underwent C–S bond construction with both aryl and alkyl thiols to furnish the desired aryl thioethers in moderate to good yields.



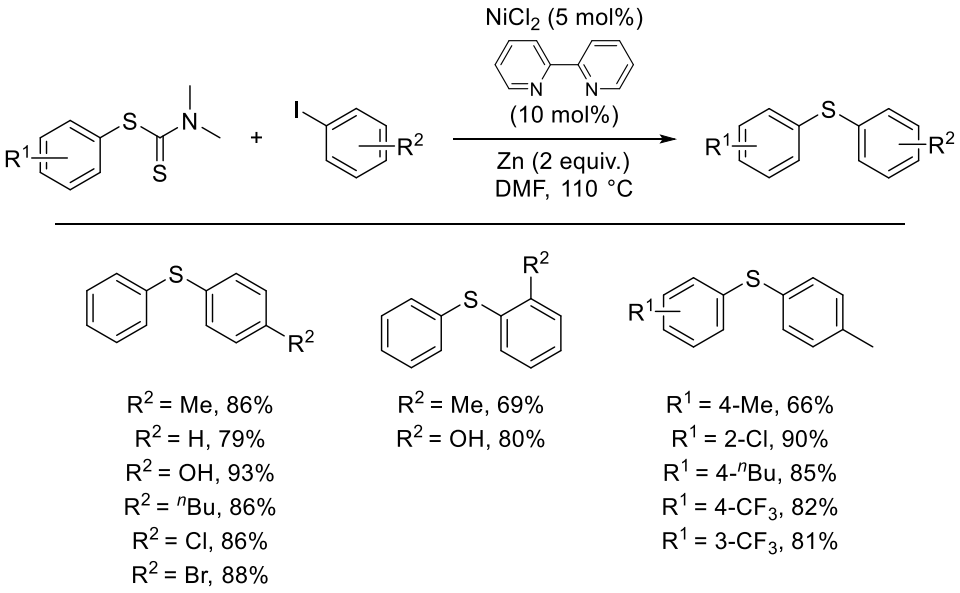
Scheme 15: Substrate scope of intermolecular nickel-catalysed C–S coupling reaction.

Extension of the intermolecular C–S cross-coupling reaction allowed for the development of an intramolecular version.[26] The synthetic utility of the transformation was demonstrated when the C–S bond forming method was used as a key step in the synthesis of (±)-chuangxinmycin (**24**), an effective treatment for *Escherichia coli* infection (Scheme 16).[28] Whilst these conditions provide a broad substrate scope, and permit access to both aryl and alkyl thioethers as well as sulfur-containing heterocycles at low temperatures, this methodology requires high catalyst loadings and uses super-stoichiometric quantities of zinc.



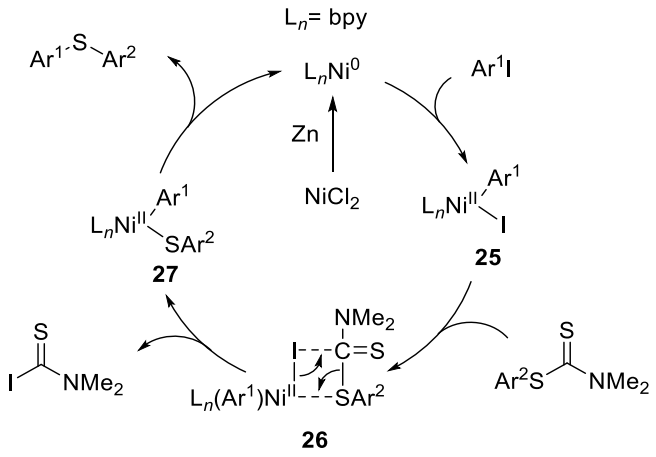
Scheme 16: Intramolecular C–S cross-coupling for the preparation of (±)-Chuangxinmycin.

An example of a nickel-catalysed C–S cross-coupling reaction employing a thiol surrogate as a coupling partner, was detailed by Dong and co-workers in 2017.[29] Here, the group report the use of inexpensive $NiCl_2$ as a catalyst for the reaction between phenyldithiocarbamates and aryl iodides (Scheme 17). The success of the substrate scope highlights that the electronic nature of both the phenyldithiocarbamates and aryl iodides had little effect on the reaction. Although catalyst loading is low, the necessity of stoichiometric amounts of zinc (2 equiv.) and high temperatures is unfavourable.



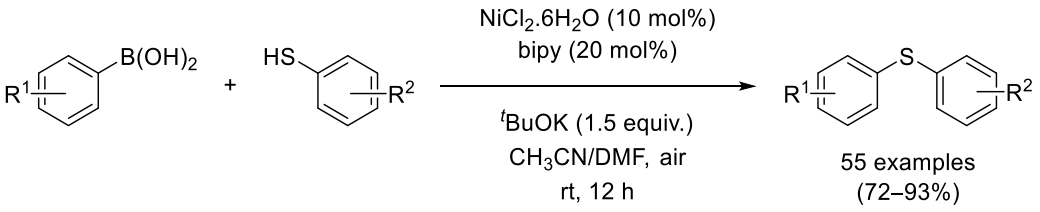
Scheme 17: Nickel-catalysed cross-coupling of phenyldithiocarbamates and aryl iodides.

A plausible mechanism for the reaction is summarised in Scheme 18. Firstly, nickel chloride ($NiCl_2$) is reduced by the zinc to Ni(0), to which the bipyridine (bpy) ligand coordinates. Oxidative addition then occurs with the aryl iodide to give intermediate **25**, which reacts with the phenyldithiocarbamate in a metathesis type reaction (**26** represents the transition state) forming transmetallated intermediate **27**. This undergoes a subsequent reductive elimination to furnish the desired product and regenerate the Ni(0) catalyst.



Scheme 18: Proposed mechanism for the nickel(0)-catalysed C–S coupling.

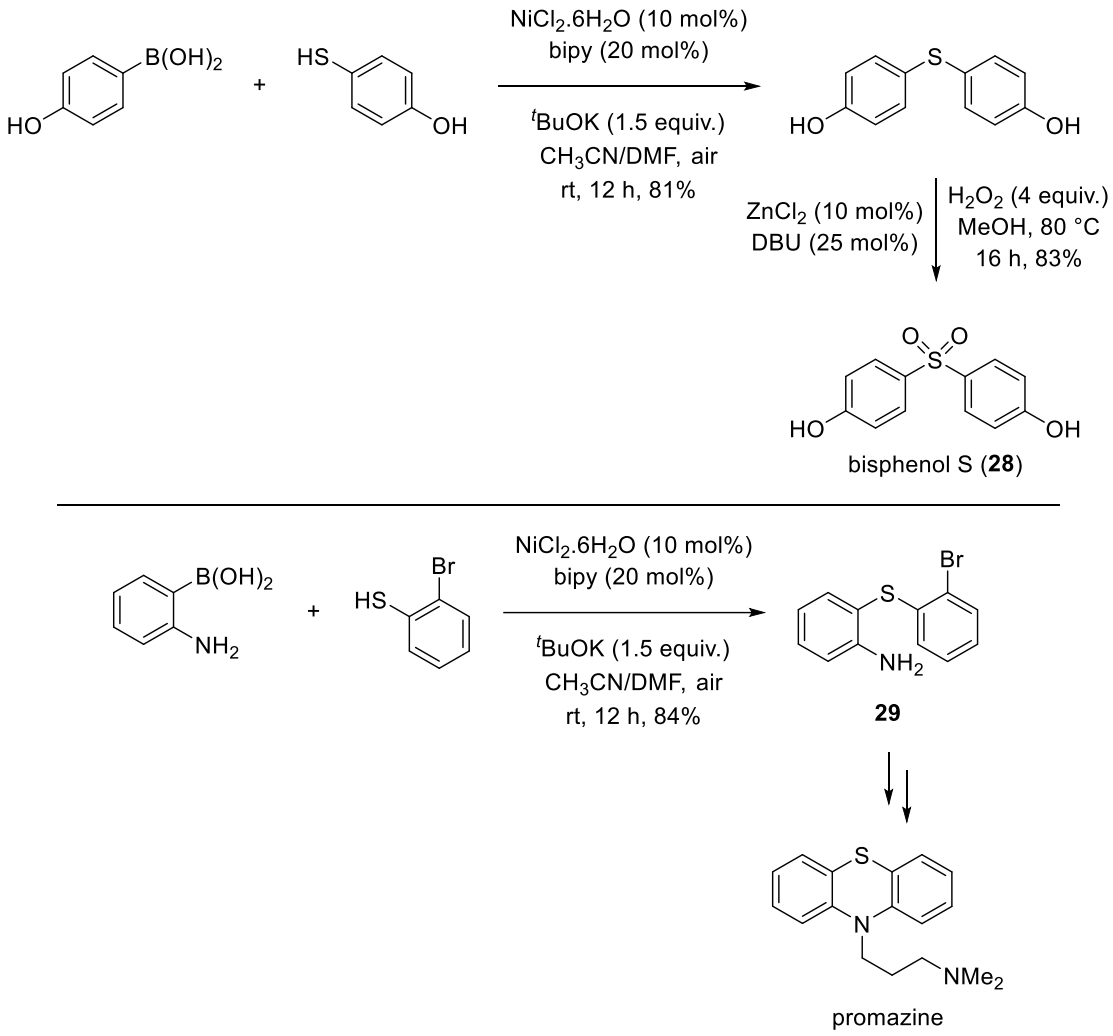
More recently, Fernandes and co-workers have developed a room temperature nickel-catalysed cross-coupling reaction of aryl-boronic acids with thiophenols to synthesise aryl thioethers (Scheme 19).[8] The catalyst system for the reaction is similar to the one reported by Dong and co-workers ($NiCl_2.6H_2O$ and 2,2'-bipyridine), but does not require any zinc additives and occurs at a much milder temperature (room temperature). The methodology displayed a wide substrate scope, with 55 aryl thioethers being successfully synthesised in good to excellent yields.



Scheme 19: Nickel-catalysed cross-coupling of aryl boronic acids with thiophenols.

The synthetic utility of the nickel(II)-catalysed cross-coupling method was exemplified with the synthesis of useful scaffolds outlined in Scheme 20. The

reaction was employed as a key step in the construction of bisphenol S (**28**), an epoxy resin monomer which is a component of a plastic substitute used to make baby bottles,[30] as well as for the synthesis of aryl thioether **29**, which is a precursor of the anti-psychotic drug promazine.[31] It is hypothesised that the reaction mechanism is analogous to the Chan–Lam type coupling. Since this method avoids the use of expensive transition-metal catalysts and complex ligands, as well as being operationally simple and making use of readily available starting materials, this offers an attractive approach towards C–S bond formation.



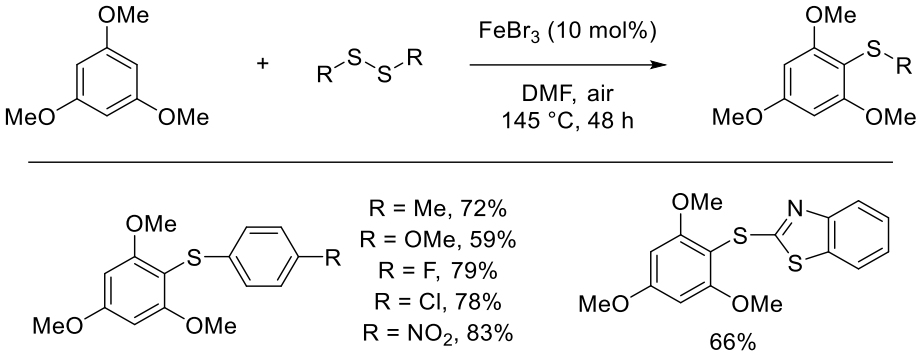
Scheme 20: Synthesis of useful scaffolds, bisphenol S and promazine precursor **29**.

1.3 Other Methods of C–S Bond Formation

In addition to cross-coupling reactions catalysed by palladium, copper and nickel, there are several other methods which have been reported for the formation of C–S bonds. One such method involves the use of iron catalysis. Due to the cheap,

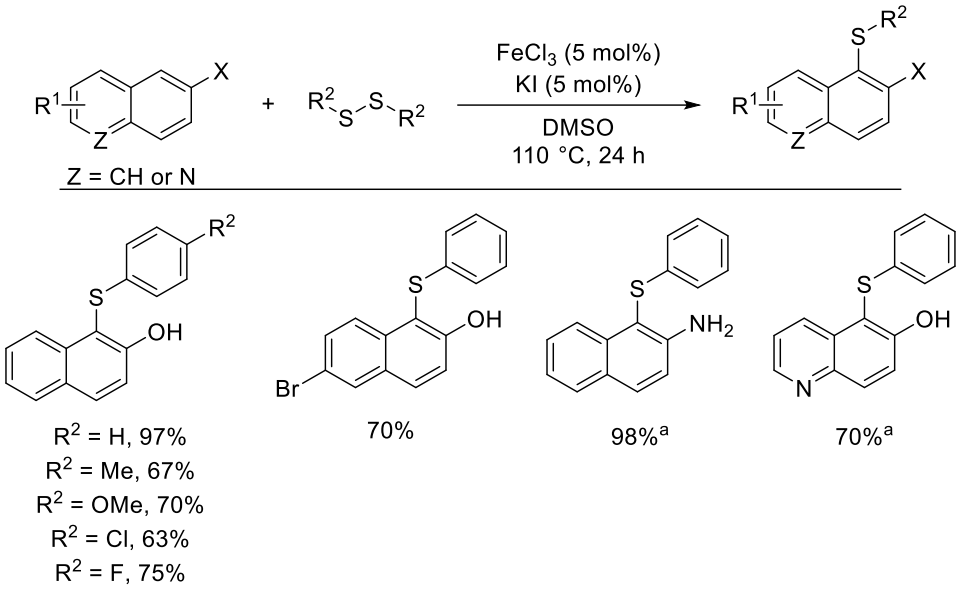
readily available and non-toxic nature of iron, the use of iron salts as catalysts is highly attractive.[1]

In 2012, Chen and co-workers described an iron(III)-catalysed direct C–H sulfenylation of 1,3,5-trimethoxybenzene with aryl disulfides (Scheme 21).[32] Investigation of the substrate scope confirmed a broad functional group tolerance, with the desired aryl thioethers being obtained in moderate to good yields. The use of dialkyl, diallyl and dibenzyl disulfides resulted in lower product yields. The employment of cheap iron salt, $FeBr_3$, as the catalyst is advantageous, however, the high temperatures and long reaction times are unfavourable. Additionally, the methodology is limited to the cross-coupling of 1,3,5-trimethoxybenzene, with a stark drop in yield being observed with other arenes such as 1,3-dimethoxybenzene and 1,2,4-trimethoxybenzene.



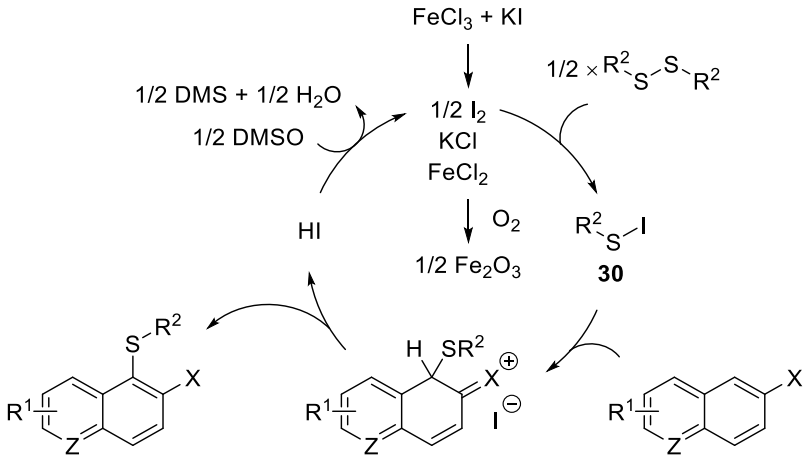
Scheme 21: Iron(III)-catalysed C–H sulfenylation of 1,3,5-trimethoxybenzene.

More recently, Seckler and co-workers have reported the C-1 sulfenylation (and selenation) of 2-naphthols and 2-naphthylamines, catalysed by iron(III) chloride and potassium iodide (Scheme 22).[33] This methodology allows access to biaryl sulfides using low catalyst loadings of $FeCl_3$ and KI, however, the substrate scope is limited to electron rich naphthalene derivatives.



Scheme 22: $FeCl_3$ and KI-catalysed sulfenylation of naphthalene derivatives. [a]$FeCl_3$ (30 mol%), KI (30 mol%).

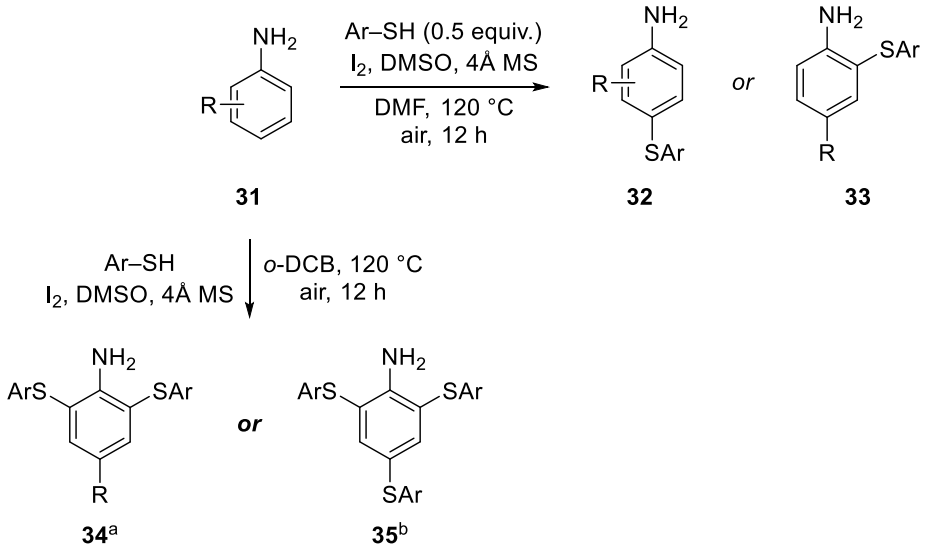
The proposed mechanism for the reaction is outlined in Scheme 23. Firstly, molecular iodine is produced from a redox reaction between $FeCl_3$ and KI. This then oxidises the disulfide to form an electrophilic intermediate (**30**), which undergoes an electrophilic aromatic substitution reaction to give the desired product. The HI generated in the reaction reacts with DMSO to restore the iodine catalyst and completes the catalytic cycle.



Scheme 23: Proposed mechanism for the $FeCl_3$ and KI-catalysed C–S coupling.

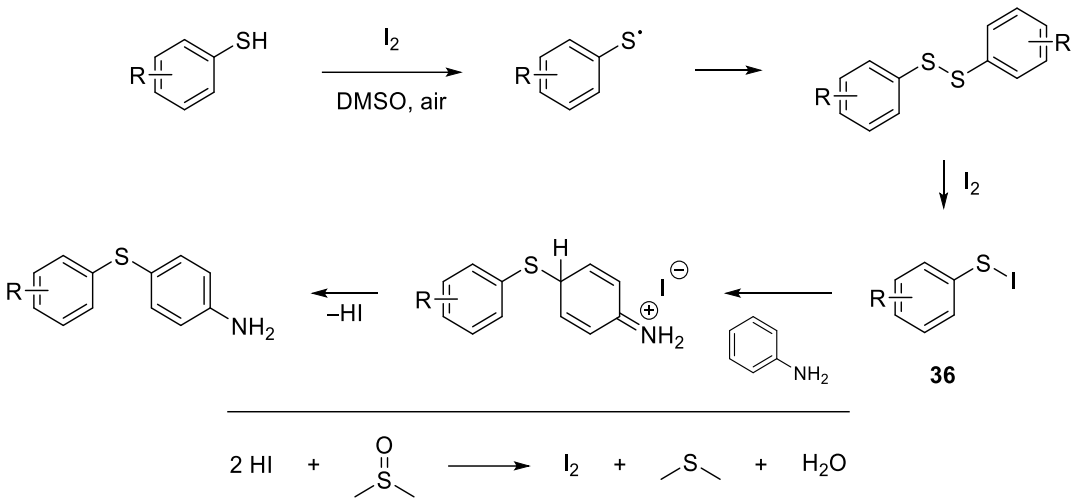
Deng and co-workers have also reported the use of iodine and DMSO to achieve the direct thioarylation of unprotected anilines with aryl thiols, under metal-free conditions.[34] Careful alteration of the reaction conditions allowed for the selective formation of mono-, di- and tri-sulfenylated products (Scheme 24). When an excess

of aniline **31** was used (2.0 equiv.) in DMF, the major product of the reaction was the 4-substituted aniline **32**. Since *para*-substitution was found to be most favourable, 4-substituted anilines had to be employed as starting materials to prepare mono-*ortho*-substituted products **33**. Both di- (**34**) and tri-sulfenylated products (**35**) could be cleanly prepared in *ortho*-dichlorobenzene (*o*-DCB), depending on the number of equivalents of thiol added. Whilst this methodology permits the formation of C–S bonds directly from C–H bonds under metal-free conditions, the substrate scope is limited to anilines bearing alkyl and halo substituents. No reactions were observed using aliphatic thiols or electron deficient anilines. Additionally, lower yields of desired products were observed for electron rich anilines such as 4-methoxyaniline, which is likely due to competition between the two directing groups leading to a mixture of regioisomers.



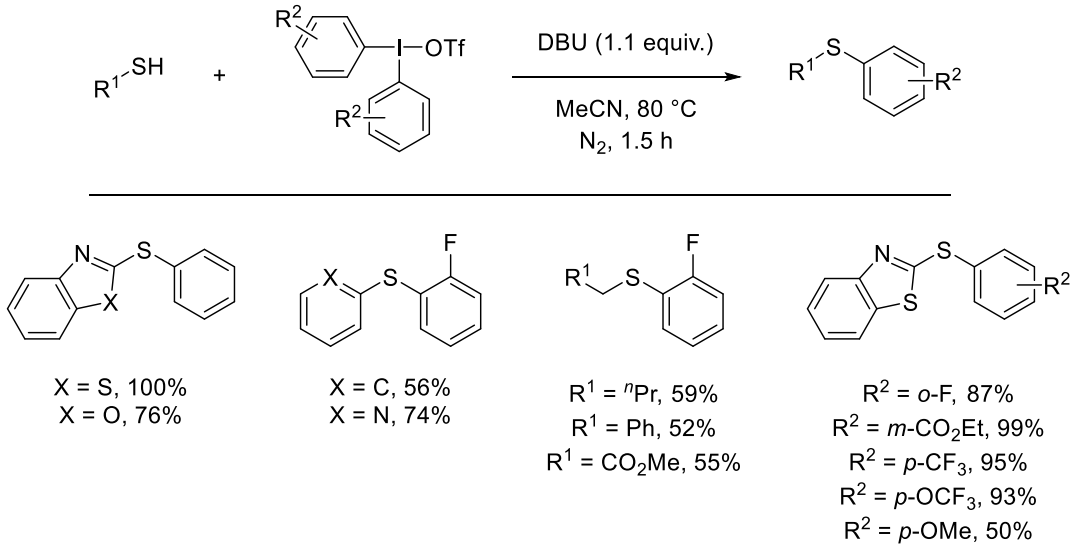
Scheme 24: Iodine/DMSO promoted sulfenylation of anilines with thiols. [a]2.5 equiv. ArSH; [b]5.0 equiv. ArSH.

It is hypothesised that the reaction proceeds *via* the reaction mechanism illustrated in Scheme 25. Initially, iodine promotes oxidation of the thiol, generating a thiyl radical. This combines with another thiyl radical to give a disulfide intermediate, which reacts with iodine to form 2 equivalents of the electrophilic species **36**. An electrophilic aromatic substitution reaction ensues, with subsequent deprotonation resulting in formation of the desired product. As previously discussed in the reaction developed by Seckler and co-workers, reaction of the liberated HI with DMSO results in regeneration of I_2.



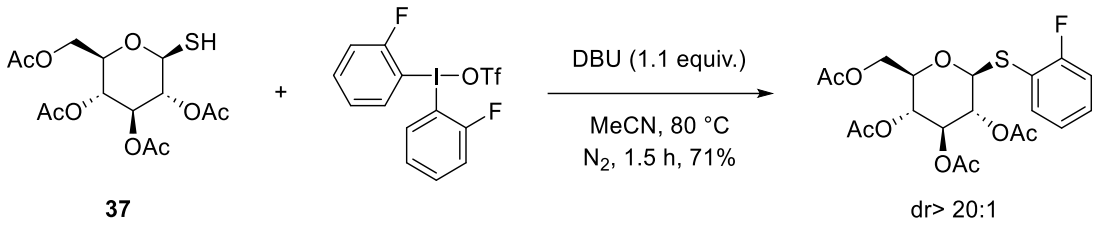
Scheme 25: Proposed mechanism for the iodine and DMSO promoted C–H sulfenylation reaction.

Another metal-free protocol for the arylation of thiols has recently been described by Kalek and co-workers (Scheme 26).[35] The group successfully managed to react thiols with diaryliodonium salts under basic conditions, utilising the favourable reduction of I(III) to I(I) as a thermodynamic driving force. The substrate scope was broad, with aryl, heteroaryl and alkyl thiols all being well tolerated. Electron deficient and moderately electron rich diaryliodonium salts reacted to give the desired aryl thioethers in good to excellent yields, however, lower efficiency was observed with the use of strongly electron-donating groups.



Scheme 26: Substrate scope of metal-free arylation of thiols with diaryliodonium salts.

The methodology was found to be amenable for the *S*-arylation of 1-thio-β-D-glucose derivative (**37**), highlighting its potential for the synthesis of complex, biologically-relevant aryl sulfides (Scheme 27). Whilst this methodology shows good potential in the context of pharmaceutical applications (avoiding the risk of possible contamination of products with trace metal residues), stoichiometric quantities of aryl iodide by-products are generated, resulting in a process with poor atom economy.

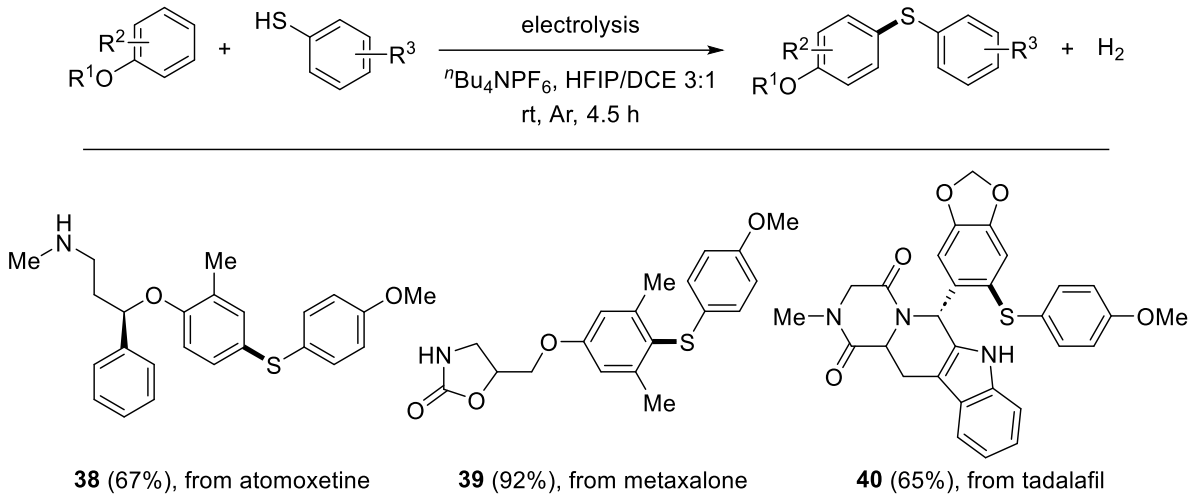


37 dr> 20:1

Scheme 27: *S*-arylation of 1-thio-β-D-glucose derivative **37**.

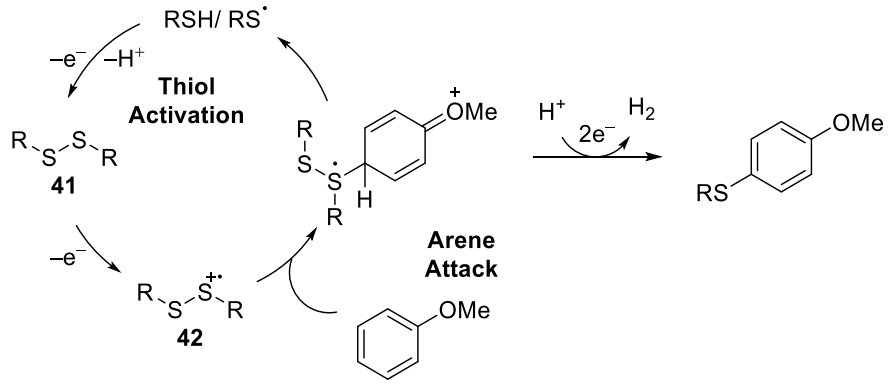
Electrocatalysis is another technique which can be used to construct C–S bonds. The use of sustainable electricity can allow for cleaner and more highly atom-economical methods of thioarylation to be developed, relative to the methods outlined previously which employ pre-functionalised starting materials such as stoichiometric quantities of hypervalent iodine.[35] In 2020, Wu and co-workers reported a protocol for the regioselective thiolation of anisole derivatives using electrochemistry (Scheme 28).[36] The group recognised the preferable oxidative tendency of thiols relative to common arenes, and proposed that aryl sulfenylation could be achieved by activation of thiols. Electrochemistry was used to precisely monitor the oxidation potential, guaranteeing the selective oxidation of the thiol to a highly active disulfide radical cation. This was then coupled to anisole substrates to afford the desired aryl thioethers in a highly regioselective manner. This reaction allowed for successful late-stage functionalisation of FDA approved drug molecules such as atomoxetine (treatment for attention-deficit hyperactivity disorder), metaxalone (muscle relaxant and pain relief) and tadalafil (treatment for erectile dysfunction) to give **38**, **39**, and **40**, respectively, exemplifying the applicability of the reaction for the thioarylation of highly complex structures. Whilst this methodology marks significant progress in developing a mild technique for aryl thiolation, the use of electrochemistry requires specialist equipment for the transformation.

Additionally, pyrophoric hydrogen gas is released as a by-product, which could cause safety concerns for large scale reactions.



Scheme 28: Selective thiolation of aryl C–H bonds using electrochemistry and late-stage functionalisation of FDA approved drug molecules.

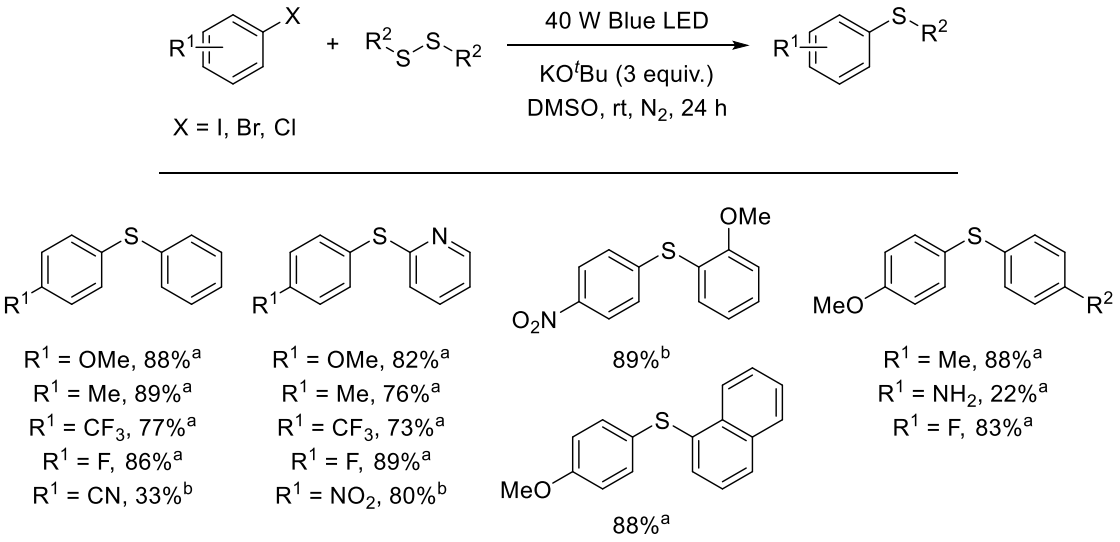
The proposed mechanism for this transformation is outlined in Scheme 29. The thiophenol starting material undergoes a single electron transfer to give the corresponding radical, which rapidly dimerises to disulfide **41**. Oxidation of the disulfide results in the formation of radical cation **42**, which is highly electrophilic. An electrophilic aromatic substitution reaction with anisole ensues and the final product is achieved with subsequent deprotonation and release of a thiyl radical.



Scheme 29: Proposed reaction mechanism.

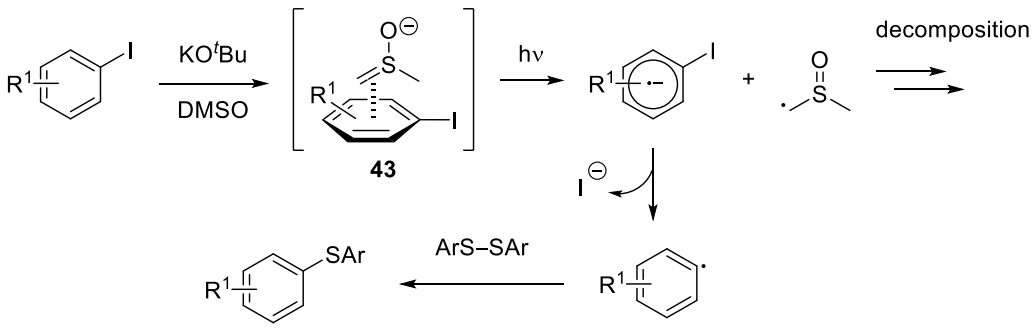
In addition to electrochemistry, photoredox strategies have also been employed for the synthesis of C–S bonds,[37,38] although these methods generally require the use of expensive photocatalysts. However, Laulhé and co-workers have recently developed a visible-light-induced cross-coupling reaction between aryl halides and

diaryl disulfides, which does not require any metal catalysts, ligands or photocatalysts (Scheme 30).[39] The reaction proceeds under mild conditions and allowed for the isolation of a range of products in moderate to excellent yields. Whilst the methodology was tolerant of a range of functional groups including heterocyclic aryl halides, acidic or easily hydrolysable moieties were unsuitable.



Scheme 30: Visible-light-induced cross-coupling reaction between aryl halides and diaryl disulfides. ^{a}X = I; ^{b}X = Br.

The group performed several control experiments and carried out time dependent-density functional theory (TD-DFT) calculations in order to formulate a plausible mechanism (Scheme 31). Firstly, potassium *tert*-butoxide is used to generate dimsyl anions from DMSO. These then form an electron-donor-acceptor complex (**43**) with the aryl halide. Irradiation with blue light then permits a charge-transfer from the dimsyl anion to the aryl halide to form an aryl radical anion and dimsyl radical. Loss of iodide ensues, resulting in an aryl radical which couples with the disulfide or thiyl radical to give the desired product.



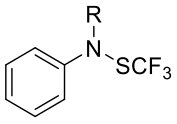
Scheme 31: Proposed mechanism for the visible-light-induced cross-coupling reaction between aryl halides and diaryl disulfides.

1.4 Lewis and Brønsted Acid-Catalysed Aryl C–H Sulfenylation

In recent years, the development of mild and selective methods for the functionalisation of unactivated C–H bonds has become particularly topical. Obviously, the development of protocols which can construct C–S bonds *via* direct C–H bond activation is likely to be more practical and economical than the aforementioned methods, negating the need for pre-functionalised starting materials such as aryl halides and boronic acids and, thus, improving atom economy and waste treatment (e.g. of halide salts).

An important transformation involves the incorporation of the trifluoromethylthio (SCF_3) group, since this generally contributes to better physiochemical properties. This is largely due to its high lipophilicity (Hansch parameter π_R = 1.44) favouring transmembrane permeation and increasing bioavailability.[40,41] Whilst there have been several methods described to install the SCF_3 group – similarly to other C–S bond forming techniques – these tend to be indirect and usually require harsh reagents/conditions.[42]

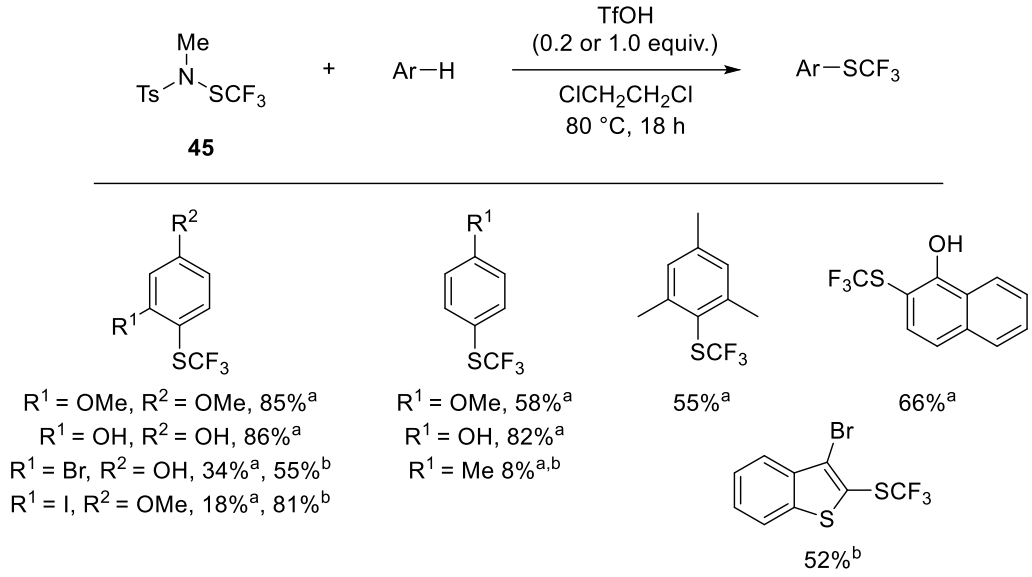
Excluding the use of CF_3SCl due to its high toxicity, Langlois and co-workers were first to report the use of trifluoromethanesulfenamides (Figure 3) as regents to install SCF_3 groups *via* a 'Friedel-Crafts-like' reaction.[43] However, these reactions were limited to electron rich compounds such as indoles.



44a, R = H
44b, R = Me

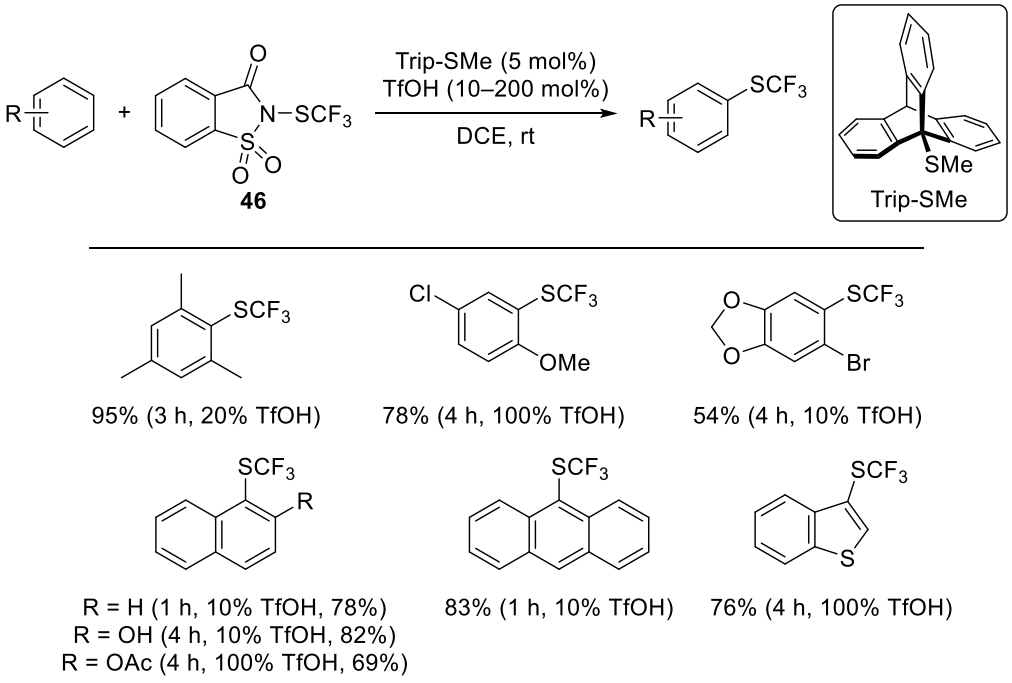
Figure 3: Trifluoromethanesulfenamides.

In 2015, Billard and co-workers subsequently developed a second generation of trifluoromethanesulfenamide, **45**, which replaces the phenyl ring of **44b** with a tosyl group. This reagent is more reactive and has been used successfully to carry out reactions previously unsuccessful with **44**. The optimised reaction conditions and substrate scope is outlined in Scheme 32.[44] Whilst this methodology marks significant progress in developing a mild technique of trifluoromethylthiolation, the substrate scope is limited and cannot be used with acid sensitive compounds.



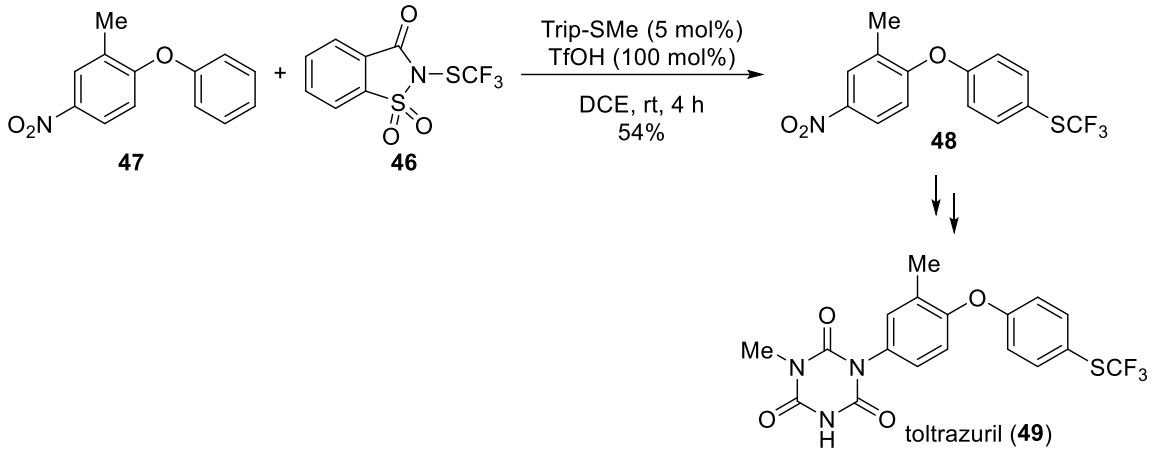
Scheme 32: Electrophilic aromatic trifluoromethylthiolation with **45** and subsequent substrate scope. [a]Reaction carried out with 0.2 equiv. of TfOH, [b]Reaction carried out with 1.0 equiv. of TfOH.

Another recent advance in the construction of C–S bonds has been achieved by Miura and co-workers, who have reported a metal-free, direct trifluoromethylthiolation of arenes using triptycenyl sulfide (Trip-SMe) as a catalyst (Scheme 33).[45] Whilst the substitution methods reported by Langlois and Billard were generally limited to highly activated arenes, this method enabled the substitution of a range of arenes with the SCF_3 group at room temperature, some of which were unactivated such as alkylbenzenes and haloanisoles.



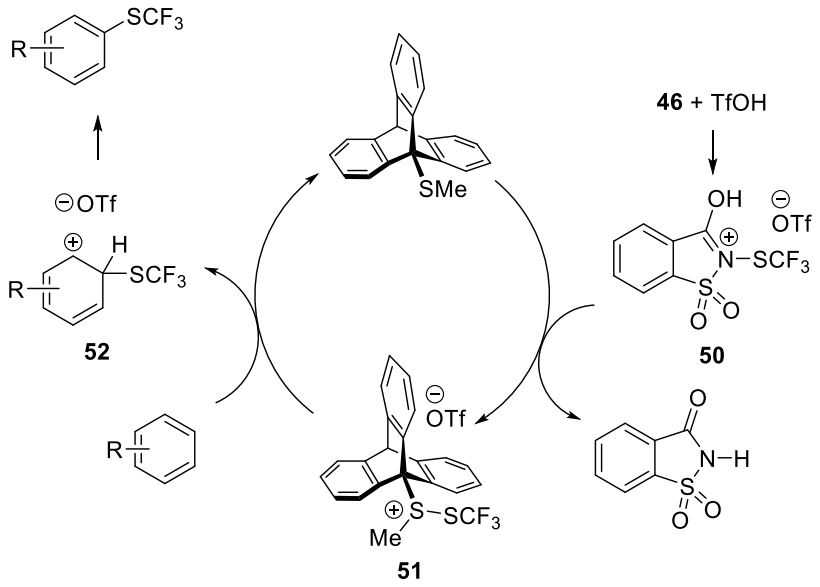
Scheme 33: Trifluoromethylthiolation of arenes using triptycenyl sulfide.

The methodology was also used for the effective trifluoromethylthiolation of diaryl ether **47** (Scheme 34). The product of this reaction (**48**) is a precursor of the potent anticoccidial agent, toltrazuril (**49**),[46] demonstrating the potential application of this protocol for the synthesis of biologically relevant molecules containing the SCF_3 moiety.



Scheme 34: Trifluoromethylthiolation of **47** to synthesise toltrazuril precursor **48**.

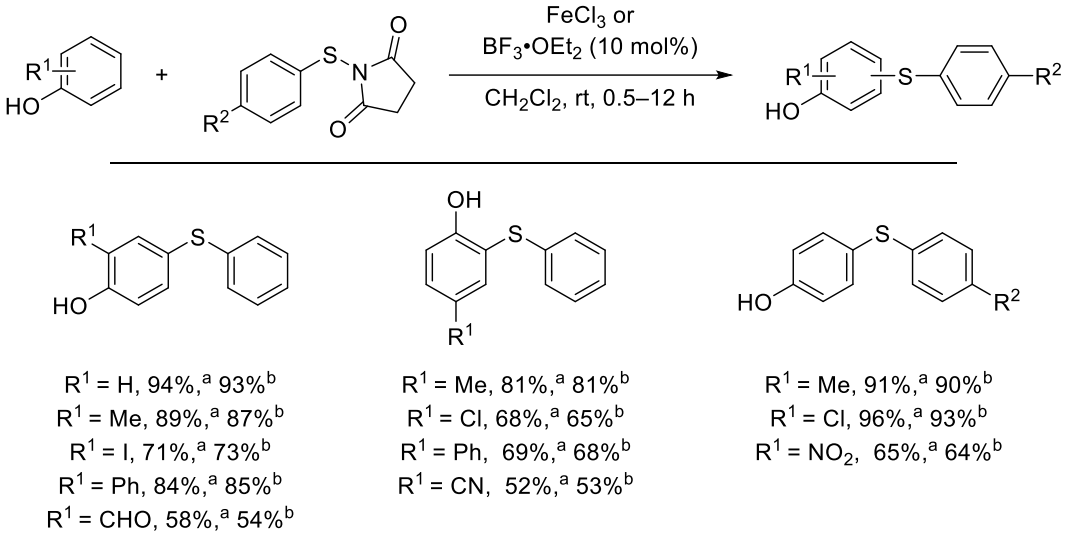
The proposed reaction mechanism involves initial protonation of the SCF_3-saccharin **46** with TfOH to give intermediate **50**, which reacts with Trip-SMe to form a catalytically active sulfonium complex (**51**) (Scheme 35).[45] The arene then reacts to form an arenium ion intermediate (**52**) *via* electrophilic addition of the SCF_3 functionality. Deprotonation follows, generating the desired product.



Scheme 35: Proposed reaction mechanism for the direct trifluoromethylthiolation of arenes using Trip-SMe.

This methodology represents a significant advance in trifluoromethylthiolation strategies, which is not limited to highly nucleophilic arenes, however, this technique is still unsuitable for compounds bearing acid sensitive functionalities. Additionally, like the methods reported by Langlois and Billard, some substrates required stoichiometric amounts of triflic acid (TfOH) for efficient reaction. Triflic acid is a harmful reagent which causes eye damage and severe burns/tissue damage in contact with skin. Furthermore, the Trip-SMe catalyst is not commercially available and thus, must be synthesised prior to its use. The method of preparation adopted by the group involved the reaction of 9-bromotriptycene with *n*-BuLi at –78 °C, followed by the addition of sulfur and then methyl iodide to give the desired product in 40% yield.

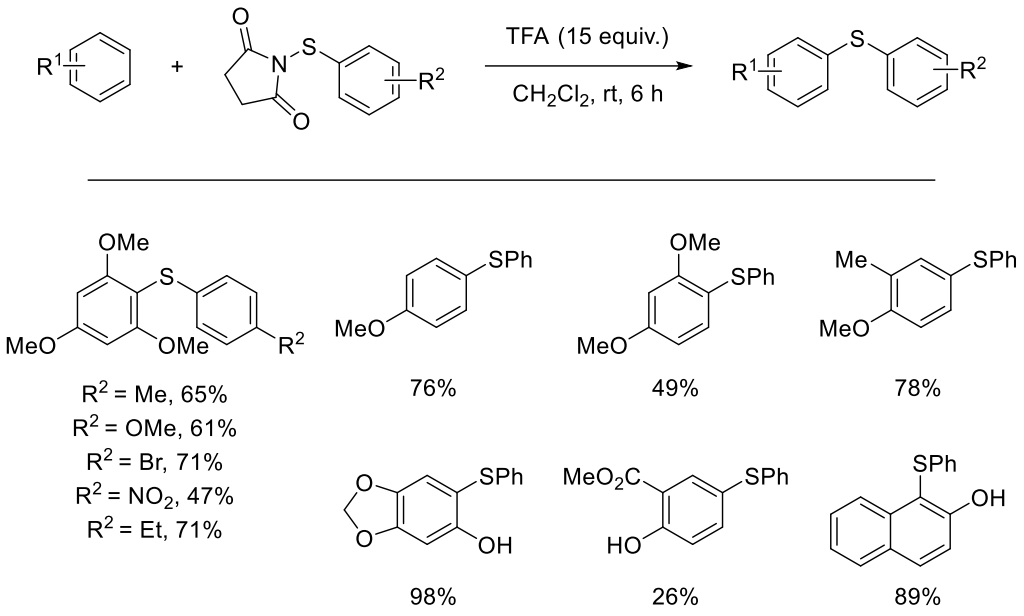
In 2014, Fu and co-workers reported the C–H sulfenylation of substituted phenols at room temperature using $FeCl_3$ or BF_3•OEt_2 as the catalyst (Scheme 36).[47] The approach involves the coupling of phenols with *N*-(arylthio)succinimides without the need for any ligands or air extrusion. The substrate scope highlights that a number of different functional groups could be tolerated such as halides, ethers, ketones, aldehydes, carboxylic acids and nitro groups. However, this procedure was only investigated using phenolic starting materials.



Scheme 36: Iron or boron catalysed C–H sulfenylation of substituted phenols at room temperature. [a]Using $FeCl_3$ as the catalyst. [b]Using BF_3•OEt_2 as the catalyst.

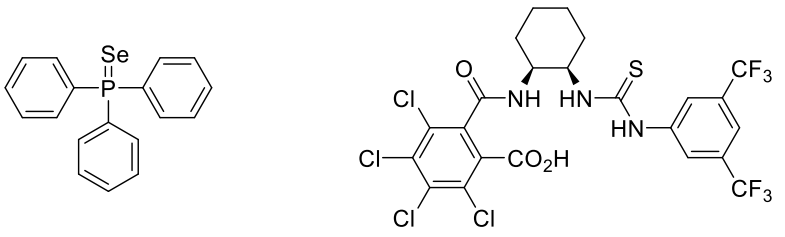
Further to this, Cossy and co-workers reported a method for the metal-free, regioselective C–H sulfenylation of electron rich arenes from *N*-(arylthio)succinimides using trifluoroacetic acid (TFA) at room temperature (Scheme

37).[48] The substrate scope outlines that the reaction was successful for electron-rich arenes and that some electron-withdrawing groups can be tolerated. Whilst the transformation shows high regioselectivity, the use of superstoichiometric quantities of the extremely harmful and corrosive reagent TFA is unfavourable.



Scheme 37: Metal-free C–H sulfenylation of electron rich arenes with TFA.

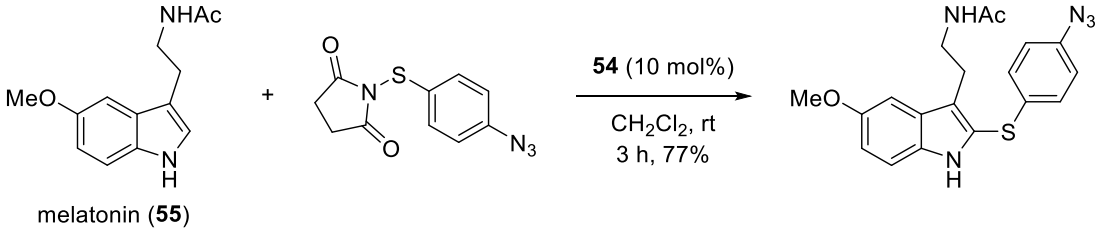
Gustafson and co-workers demonstrated that Lewis bases such as triphenylphosphine sulfide and selenide (**53**) can act as catalysts to achieve halogenation of arenes using *N*-halosuccinimides (Figure 4).[49,50] As such, the group set out to determine if Lewis base catalysis could also be used to achieve aryl C–S bond formation. Whilst Lewis bases proved ineffective on their own, the combination of **53** (10 mol%) and TFA (1 equiv.) resulted in rapid C–H sulfenylation on the minute timescale.[51] This synergy between Bronsted acids and Lewis bases was first observed by Denmark and co-workers in the study of olefin sulfenylations.[52,53] With this information in hand, the group incorporated both of these characteristics into a single catalyst, developing **54**, which was able to effect the sulfenylation of electron rich aza-heterocycles, at room temperature, using a 10 mol% loading.[51]



53 **54** (racemic)

Figure 4: Triphenylphosphine selenide **53** and conjugate Lewis base-Bronsted acid catalyst **54**.

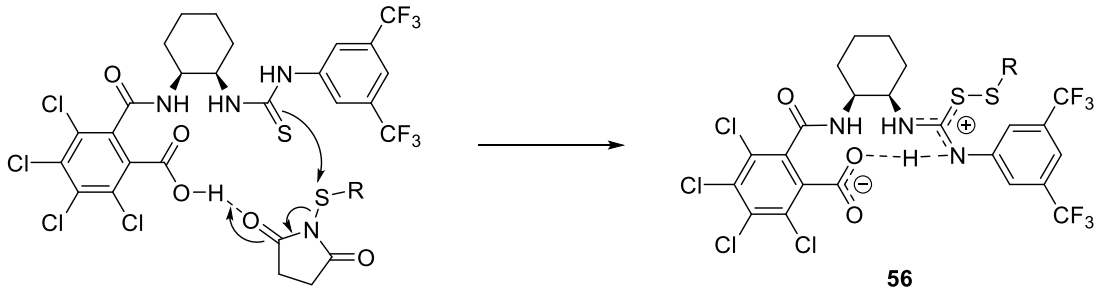
The group employed the developed methodology to achieve the late-stage functionalisation of biologically active small molecules such as melatonin (**55**) (Scheme 38). In particular, the group utilised an *N*-(arylthio)succinimide containing an azide tag. In addition to new melatonin analogues, this provides a functional handle to insert linkers for the preparation of chimeric molecules such as PROTACS,[54] or affinity labelled analogues to identify target proteins.[55]



melatonin (**55**)

Scheme 38: Sulfenylation of melatonin catalysed by **54**.

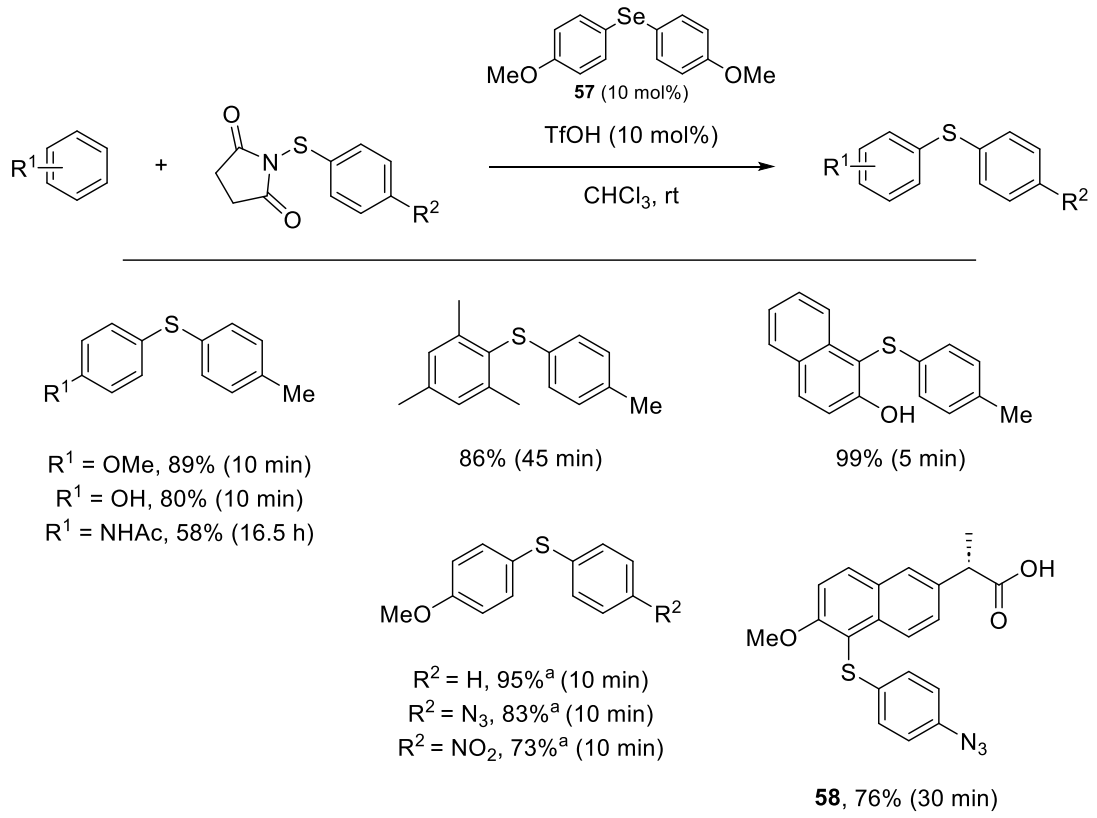
It is proposed that this catalytic sulfenylation operates through a mechanism whereby the carboxylic acid moiety activates the *N*-(arylthio)succinimide *via* protonation (Scheme 39). Subsequent attack from the Lewis-basic thiourea results in thiouronium adduct **56**, which acts as an electrophilic sulfenium source which can combine with an aza-heterocycle in an electrophilic aromatic substitution reaction.[51]



56

Scheme 39: Proposed mechanism for the catalytic activation of *N*-(arylthio)succinimides by conjugate Lewis base-Bronsted acid catalyst **54** giving activated sulfenium **56**.

Based on this work, Gustafson and co-workers hypothesised that selenide ethers (which have been used for the sulfenofunctionalisation of alkenes)[56] could potentially function as better catalysts since there would be no mechanism to stabilise the Lewis base/sulfenium adducts. As such, these destabilised products would likely be more electrophilic, ideally resulting in reactions with less electron-rich aromatics. In 2018, the group reported the use of selenide ether **57** in combination with TfOH (10 mol%) to achieve C–S sulfenylation at room temperature (Scheme 40).[57] This methodology shows tolerance to a variety of different functional groups such as phenols, carboxylic acids, heterocycles and protected amines. FDA approved drug molecule, naproxen, was also cleanly thioarylated under the optimised conditions to give the desired product **58**, in good yield. Additionally, as previously discussed, the successful incorporation of the azido functional group is of particular interest since this group possesses a number of applications, especially in bioorthogonal conjugation chemistry.[58] Limitations of this approach include, the incompatibility of free amino groups, which tended to furnish *N*-sulfenylated products and the use again of triflic acid.



Scheme 40: Lewis base/Bronsted acid dual-catalytic C–H sulfenylation of aromatics. [a]Conversion determined by ^{1}H NMR spectroscopy.

1.5 Conclusions

In conclusion, due to the widespread presence of aryl thioether moieties in natural products and drug candidates, significant effort has focused on developing robust methods of C–S bond formation. Here, a variety of the reported transformations have been discussed, with earlier work laying the groundwork for more recent advances. Whilst all the work discussed has proved effective for the construction of aryl thioethers, methods involving the direct functionalisation of unreactive C–H bonds offer the most promise in terms of efficiency and atom economy (Scheme 41).

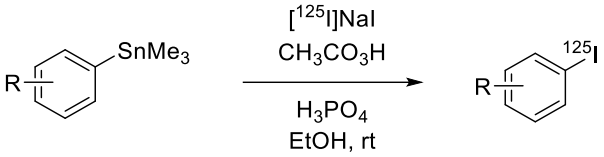
Scheme 41: Direct C–H sulfenylation.

To avoid the use of pre-functionalised arenes, some methods of C–H sulfenylation have been developed, however, these generally require the use of precious transition metal catalysts or employ harmful Brønsted acids such as triflic acid and TFA. Development of novel, mild and regioselective methods of C–H thioarylation remains an area of high demand. In particular, it would be highly advantageous to develop direct sulfenylation reactions that are catalysed by Earth-abundant first row transition metals such as iron and, demonstrate a wider scope than phenols as substrates.[47] Given the inexpensive, sustainable and non-toxic nature of these elements, their use as catalysts would contribute to the innovation of environmentally friendly and economically attractive reactions.[59]

2.0 Development of a Regioselective C–H Thioarylation of Electron-Rich Arenes

2.1 Previous Work in the Sutherland Group

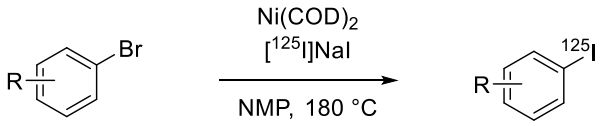
Previous work done in the group has focused on developing mild and regioselective methods of halogenation due to the high importance of aryl halides as intermediates in synthetic chemistry. These scaffolds have a wide range of applications e.g. in cross-coupling reactions and in the formation of organometallic reagents.[60] In particular – as a group that specialises in molecular imaging of diseases – developing methodologies to efficiently synthesise radio-iodinated aryl compounds for use in single photon emission computed tomography (SPECT) is vital. Traditionally, the radioiodination of arenes was achieved through the oxidative iodination of aryl stannanes (Scheme 42).[61]



Scheme 42: Radioiodination of arenes *via* oxidative iodination of aryl stannanes.

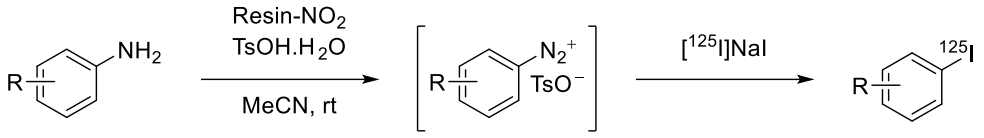
This method has its limitations, including the use of stoichiometric amounts of organotin reagents which are highly toxic, unstable and problematic to remove. In order to overcome the issues associated with the synthesis and subsequent use of arylstannanes, the group sought to develop new, milder methods for the iodination of arenes.

Alternative approaches for aryl iodination reactions include nickel-catalysed Finkelstein reactions of aryl bromides (Scheme 43). Whilst this methodology has been used effectively for the preparation of SPECT tracers, high reaction temperatures are required.[62,63]



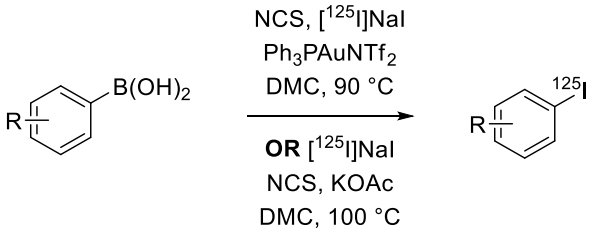
Scheme 43: Nickel(0)-catalysed Finkelstein reaction of aryl bromides.

The group have also developed an efficient method for the radioiodination of anilines (Scheme 44). Here, anilines were converted into stable diazonium salts using a polymer-supported nitrite reagent, followed by Sandmeyer-type reactions in a one-pot process.[64,65]



Scheme 44: Radioiodination reaction of anilines.

Furthermore, the group have successfully developed procedures for the synthesis of aryl iodides *via* substitution reactions of (pseudo)halides such as boronic acids. (Scheme 45).[66,67]

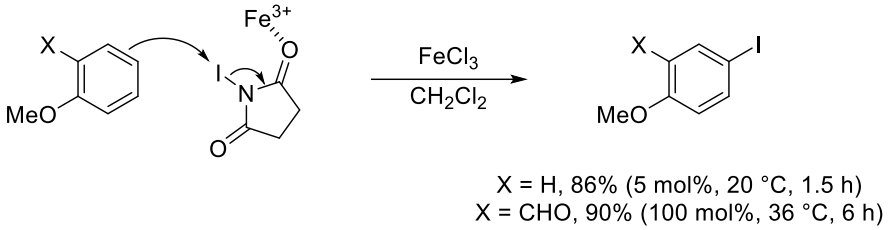


Scheme 45: Gold(I) and base-mediated iododeboronation of aryl bronic acids.

Whilst these novel methodologies have proved invaluable for the preparation of SPECT agents,[64–67] they are limited by the requirement of a pre-functionalised handle on the arene component. As such, the group began to investigate methods for the radioiodination of arenes *via* C–H functionalisation.

In 2015, the Sutherland group reported a method for the Lewis acid activation of *N*-iodosuccinimide (NIS) for rapid and regioselective aryl iodination *via* an electrophilic aromatic substitution reaction.[68] Optimisation studies focused on the iodination of anisole with NIS and the study began with an activity screen of a range of transition metal Lewis acid cataysts. Iron(III) chloride (5 mol%) was found to be the best catalyst for the reaction, giving the desired *p*-iodinated arene in 86% yield after 1.5 h (Scheme 46). Despite iron(III) chloride (5 mol%) proving to be an effective catalyst for electron rich arenes, aromatic compounds bearing electron withdrawing groups e.g. 2-methoxybenzaldehyde required much higher catalyst loadings (sometimes

stoichiometric amounts of iron(III) chloride) and slightly higher temperatures to achieve full conversion.



Scheme 46: Iron(III) chloride-catalysed iodination of anisole and 2-methoxybenzaldehyde.

It became evident that, a more active form of Fe(III) was required. It has been reported that metal triflimides can be used as super Lewis acids for a range of transformations. The Lewis acidic nature of the metal can be enhanced upon formation of the triflimide salt, since the highly delocalised nature of the triflimide counterion coupled with its steric bulk generates a metal centre with higher positive charge character.[69] With this in mind, it was proposed that iron(III) triflimide could act as a superior catalyst for the regioselective iodination of arenes relative to $FeCl_3$. It was reported in the literature that iron(III) triflimide could be generated from the combination of iron(III) chloride with the readily available and inexpensive ionic liquid, 1-butyl-3-methylimidazolium *bis*(trifluoromethylsulfonyl)imide ([BMIM]NTf_2) (Figure 5).[70]

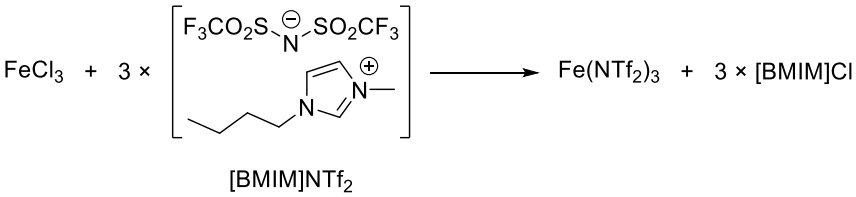
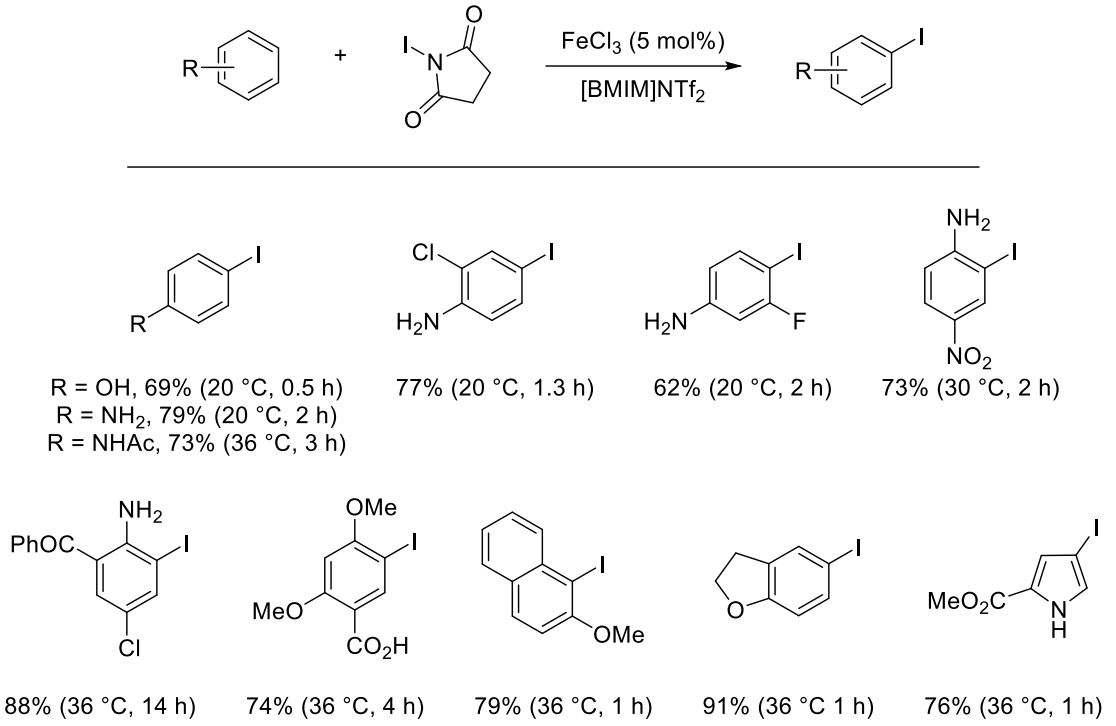


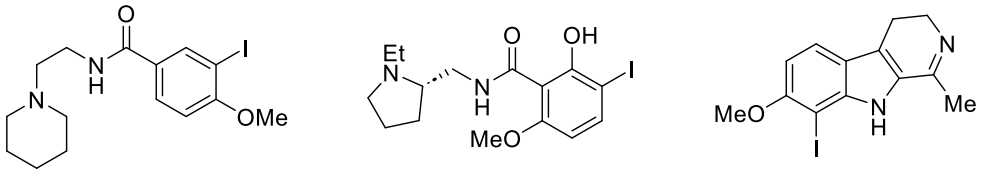
Figure 5: Formation of iron(III) triflimide from $FeCl_3$ and [BMIM]NTf_2.

Iodination of 2-methoxybenzaldehyde using $FeCl_3$ (5 mol%) and [BMIM]NTf_2 as the solvent resulted in a significant increase in reaction rate, giving the desired product in 88% yield after 2.5 h at 36 °C. The transformation was found to be successful for a wide variety of substrates including phenols, anilines, naphthalene, 2,3-dihydrobenzofuran and a C1-substituted pyrrole as well as compounds bearing more electron withdrawing groups such as aldehydes, ketones and carboxylic acids (Scheme 47).



Scheme 47: Substrate scope for the iodination of arenes using $FeCl_3$ in combination with [BMIM]NTf_2.

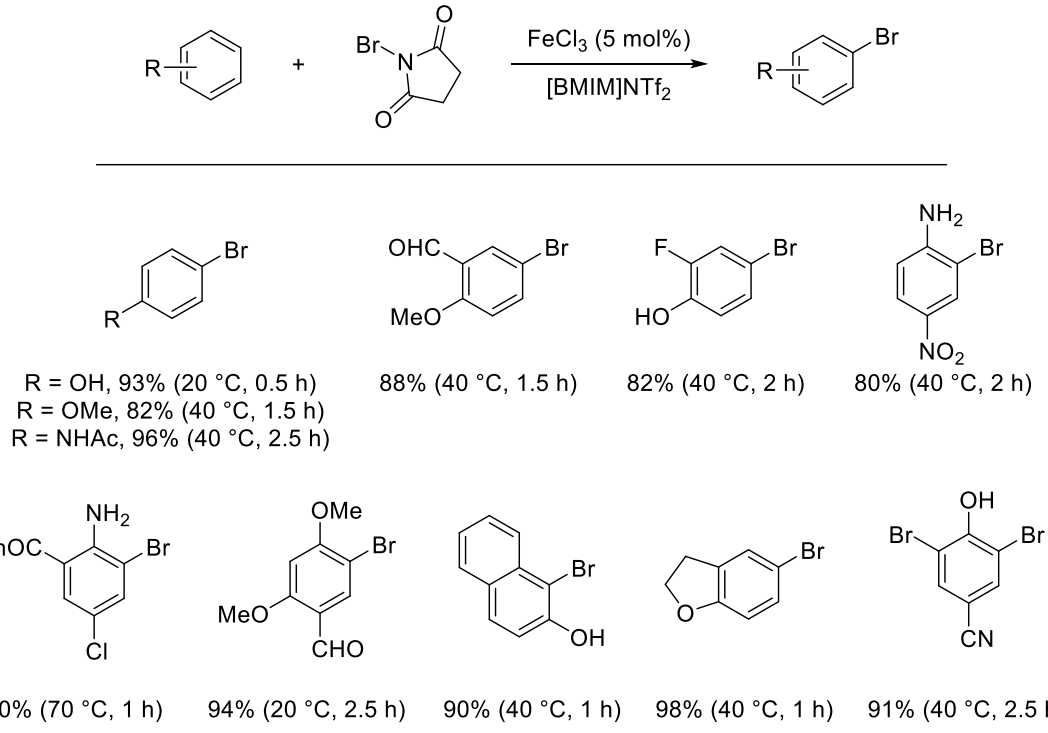
Several medicinally important compounds were subsequently synthesised, using the iron(III) triflimide-catalysed iodination reaction as a key step (Figure 6). It should be noted here that each compound was temporarily protected as the tetrafluoroborate salt *via* treatment with tetrafluoroboric acid. This was to prevent any undesired side reactions occurring with the nucleophilic functionalities within the molecules. Iodination was then carried out under the optimised conditions. The first target compound, PIMBA (**59**),[71] was isolated in an 84% yield over the two steps. PIMBA (**59**) is a SPECT compound which, in its [^{123}I]-form is used for the imaging of breast cancer tumours. The second target (–)-IBZM (**60**), is another SPECT agent and an antagonist of the human dopamine D_2 receptor.[72] The final target molecule was 8-iodoharmaline (**61**), which is a potent monoamine oxidase inhibitor.[73] For these compounds, formation of the tetrafluoroborate salts, followed by the reaction with NIS catalysed by $Fe(NTf_2)_3$ gave the desired products in 47% and 73%, respectively.



PIMBA (**59**) (–)-IBZM (**60**) 8-iodoharmaline (**61**)

Figure 6: Synthetic utility of iron(III) triflimide-catalysed iodination reaction.

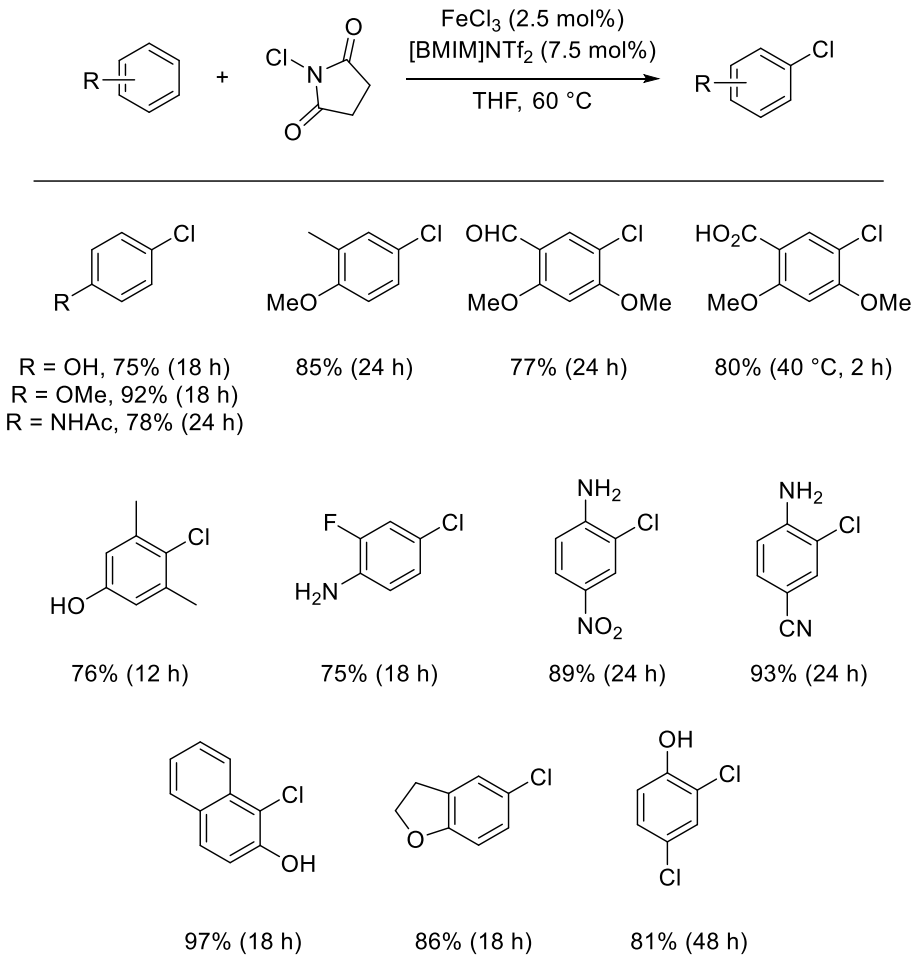
The group then proceeded to investigate the viability of $Fe(NTf_2)_3$ as a catalyst for other halogenations. Despite having no success with fluorinations, bromination and chlorination reactions were achieved using the corresponding *N*-halosuccinimides. The bromination reactions furnished similar results to the analogous iodinations. Electron-rich arenes coupled with ease under mild conditions to give the desired products in good yield, and arenes with electron-withdrawing groups required slightly elevated temperatures (Scheme 48). The use of two equivalents of *N*-bromosuccinimide (NBS) for the reaction of 4-cyanophenol allowed for the direct synthesis of herbicide bromoxynil.[74,75]



Scheme 48: Substrate scope for the bromination of arenes using $FeCl_3$ in combination with $[BMIM]NTf_2$.

The group found that chlorination reactions using *N*-chlorosuccinimide required more forcing conditions (Scheme 49).[76] A reaction temperature of 60 °C was

necessary, and reaction times usually exceeded 12 h. Undoubtedly, the most significant finding from the $Fe(NTf_2)_3$-catalysed chlorination protocol was the realisation that the reaction could proceed using catalytic amounts of both iron(III) chloride and $[BMIM]NTf_2$, negating the need for $[BMIM]NTf_2$ as the solvent. It was proposed that using catalytic quantities of $[BMIM]NTf_2$ would allow for a broader substrate scope and easier workup and isolation procedures.

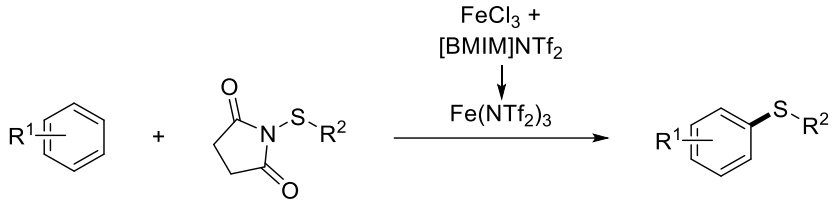


Scheme 49: Substrate scope for the chlorination of arenes using $FeCl_3$ in combination with $[BMIM]NTf_2$.

2.2 Project Aims

The first aim of this PhD was to build upon previous work done in the group and investigate iron(III) triflimide as a catalyst for the mild, efficient and regioselective formation of aryl C–S bonds using *N*-thiosuccinimides. Since the group have reported the use of the super Lewis acid iron(III) triflimide as a catalyst for the activation of *N*-halosuccinimides and the subsequent regioselective halogenation of arenes, it was proposed that the same catalyst could be used as an effective Lewis acidic catalyst for the thioarylation of arenes (Scheme 50). Following initial

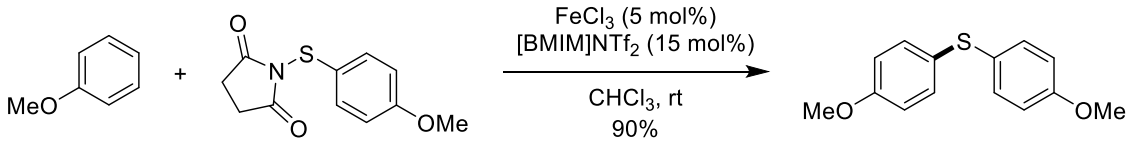
optimisation studies, the scope of the transformation was explored by varying both the arene and *N*-thiosuccinimide components. One of the main goals of this project was to demonstrate the synthetic utility of the methodology by using it as a key step in the synthesis of pharmaceutically relevant aryl sulfur-containing compounds, as well as the late-stage functionalisation of amino acids and drug compounds.



Scheme 50: Iron(III) triflimide-catalysed thioarylation.

2.3 Optimisation Studies for the C–H Sulfenylation of Anisole and Subsequent Substrate Scope

Initial studies focused on the C–H sulfenylation of anisole (**62**) with *N*-(4-methoxyphenylthio)succinimide (**63a**), which was prepared by the reaction of NCS and 4-methoxybenzenethiol.[77] The first set of conditions adopted were based on the catalytic system of $FeCl_3$ (5 mol%) and [BMIM]NTf_2 (10 mol%) previously established within the group (Scheme 51). However, due to the poor solubility of the *N*-(4-methoxyphenylthio)succinimide in toluene, the reaction was carried out in chloroform. This showed full conversion by ^{1}H NMR spectroscopy in 2 h and gave the desired product (**64a**) in 90% yield.

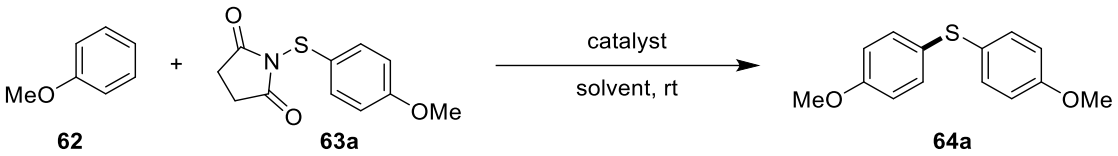


62 **63a** **64a**

Scheme 51: Iron(III) triflimide-catalysed thioetherification of anisole with *N*-(4-methoxyphenylthio)succinimide.

After confirming the viability of iron(III) triflimide as a catalyst for the transformation, optimal conditions were then investigated. Firstly, the catalyst loadings were successfully lowered from 5 and 15 mol% to 2.5 and 7.5 mol% without having a detrimental effect on the yield (Table 1, entry 2). Next, reactions were undertaken to establish the independent roles of iron(III) chloride and [BMIM]NTf_2 [which react in

situ to generate $Fe(NTf_2)_3$]. As expected, no reaction resulted in the absence of iron(III) chloride (entry 3) or with [BMIM]NTf_2 alone (entry 5). However, the reaction did proceed in the presence of iron(III) chloride (2.5 mol%), albeit at a slower rate relative to iron(III) triflimide (5 h) and with a lower yield (entry 4). After confirming the most efficient catalyst system, further studies were undertaken to identify the best solvent for the reaction. Whilst reactions conducted in acetonitrile and dichloromethane furnished the desired product **64a** in moderate or high yield, the reaction times were significantly longer (entries 6 and 7). No reaction was observed using tetrahydrofuran, dimethylcarbonate or *N,N*-dimethylformamide (entries 8, 9 and 10).



62 **63a** **64a**

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)
1	$FeCl_3$ (5)/[BMIM]NTf_2 (15)	$CHCl_3$	1.5	90
2	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	$CHCl_3$	2	90
3	–	$CHCl_3$	–	–
4	$FeCl_3$ (2.5)	$CHCl_3$	5	67
5	[BMIM]NTf_2 (7.5)	$CHCl_3$	–	–
6	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	MeCN	16	75
7	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	CH_2Cl_2	16	55
8	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	THF	–	–
9	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	DMC	–	–
10	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	DMF	–	–

Table 1: Optimisation of the C–H sulfenylation of anisole.

2.4 Kinetic Experiments and Proposed Reaction Mechanism

Interestingly, ^{1}H NMR experiments uncovered that, whilst the reaction employing the optimal conditions (Table 1, entry 2) reached full conversion after 2 h, only limited conversion (<10%) was observed after 0.5 h. As such, a kinetic study was undertaken to investigate the role of the product in the reaction. When *bis*(4-

methoxyphenyl)sulfane (**64a**) (10 mol%) was added at the beginning of the reaction alongside the catalyst, the reaction was notably faster than in its absence. This suggests that **64a** – which is Lewis basic – can also serve as a catalyst for the transformation, causing the reaction to proceed autocatalytically. Similar product autocatalytic effects were observed by Gustafson and co-workers in a TFA-promoted thioarylation reaction.[57]

To probe the potential for autocatalysis, kinetics experiments were performed in which the reactions were monitored at 0.5 h increments using ^{1}H NMR spectroscopy. The kinetics experiments were undertaken on the reactions using only $FeCl_3$, $FeCl_3$ and [BMIM]NTf_2 (forming $Fe(NTf_2)_3$ in situ) and $FeCl_3$, [BMIM]NTf_2 and **64a** (10 mol%) as the catalysts (Figure 7). Firstly, it should be noted that the conversion studies highlight the difference in relative rates between the $FeCl_3$ and $Fe(NTf_2)_3$ catalytic systems. Whilst the reaction with $Fe(NTf_2)_3$ had reached completion after 2 h, the reaction employing $FeCl_3$ had only reached 52% conversion in the same timeframe. Secondly, as suspected, both reactions catalysed by either $FeCl_3$ and $Fe(NTf_2)_3$ exhibit sigmoidal curves characteristic of autocatalytic processes. The graphs display lag periods at the beginning of the reactions – known as the induction period – before showing a sharp increase in rate as the amount of product (catalyst) increases. The rate eventually slows down towards the end of the reaction as the concentration of reactants decreases. Conversely, the reaction with product **64a** (10 mol%) in addition to $Fe(NTf_2)_3$ displayed no such lag, further confirming the process to be autocatalytic.

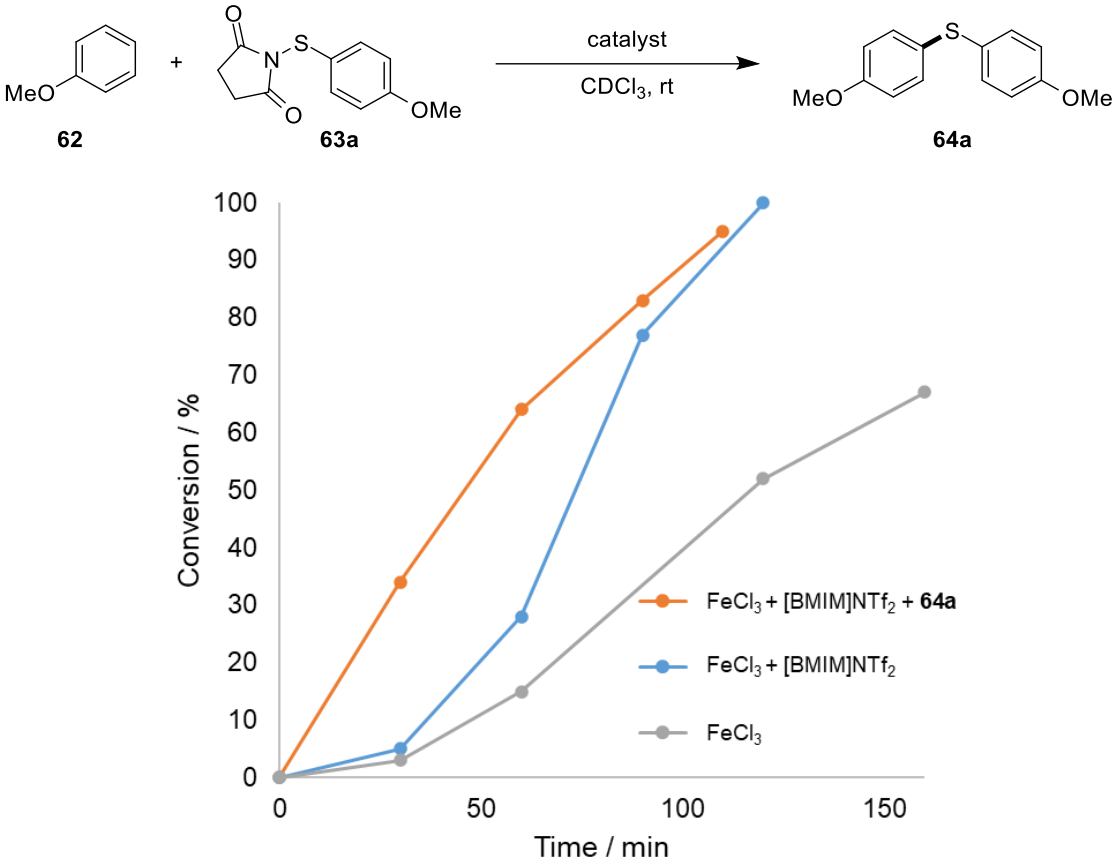
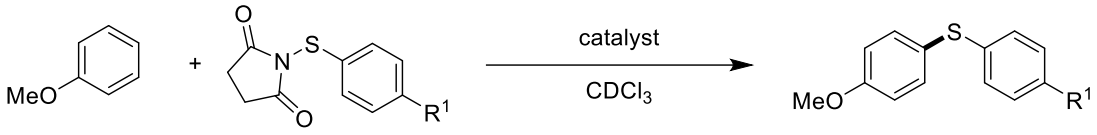


Figure 7: Conversion study of the thioetherification of anisole with *N*-(4-methoxyphenylthio)succinimide (measured using ^{1}H NMR spectroscopy in $CDCl_3$ and hexamethylcyclotrisiloxane as an internal standard).

To determine the extent of autocatalysis, the same kinetic experiments were carried out using *N*-(arylthio)succinimides with different electronic properties, namely *N*-(4-methylphenylthio)succinimide (**63b**) and *N*-(4-chlorophenylthio)succinimide (**63c**) (Scheme 52). Similar results were observed in the reaction between anisole and **63b** (Figure 8a). Despite (4-methoxyphenyl)(*p*-tolyl)sulfane (**64b**) being a weaker Lewis base than **64a** – due to the lesser electron donating ability of the methyl group versus the methoxy group – autocatalysis was still observed. However, when the more electron deficient **63c** was used in the reaction, the conversion graphs did not display sigmoidal curves and, in fact, an elevated temperature of 60 °C and a longer reaction time (68 h) was required to reach full conversion (Figure 8b). In this case, the product of the reaction – (4-methoxyphenyl)(4'-chlorophenyl)sulfane (**64c**) – contains an electron-withdrawing substituent which considerably lowers the Lewis basicity of **64c**, resulting in no autocatalysis.



62 **63b**, R^1 = Me **63c**, R^1 = Cl **64b**, R^1 = Me **64c**, R^1 = Cl

Scheme 52: Thioetherification reactions of anisole with *N*-(arylthio)succinimides **63b** and **63c**.

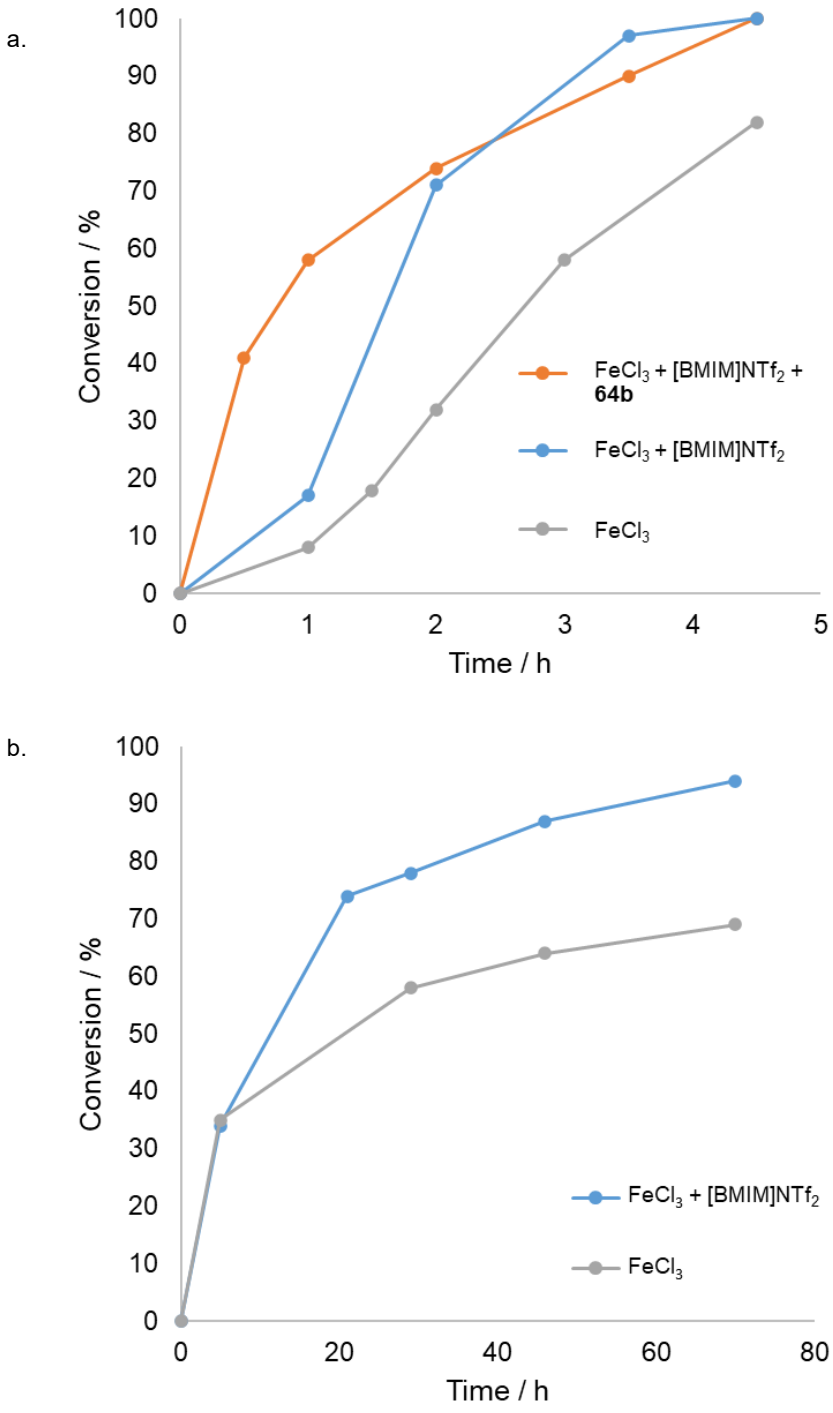
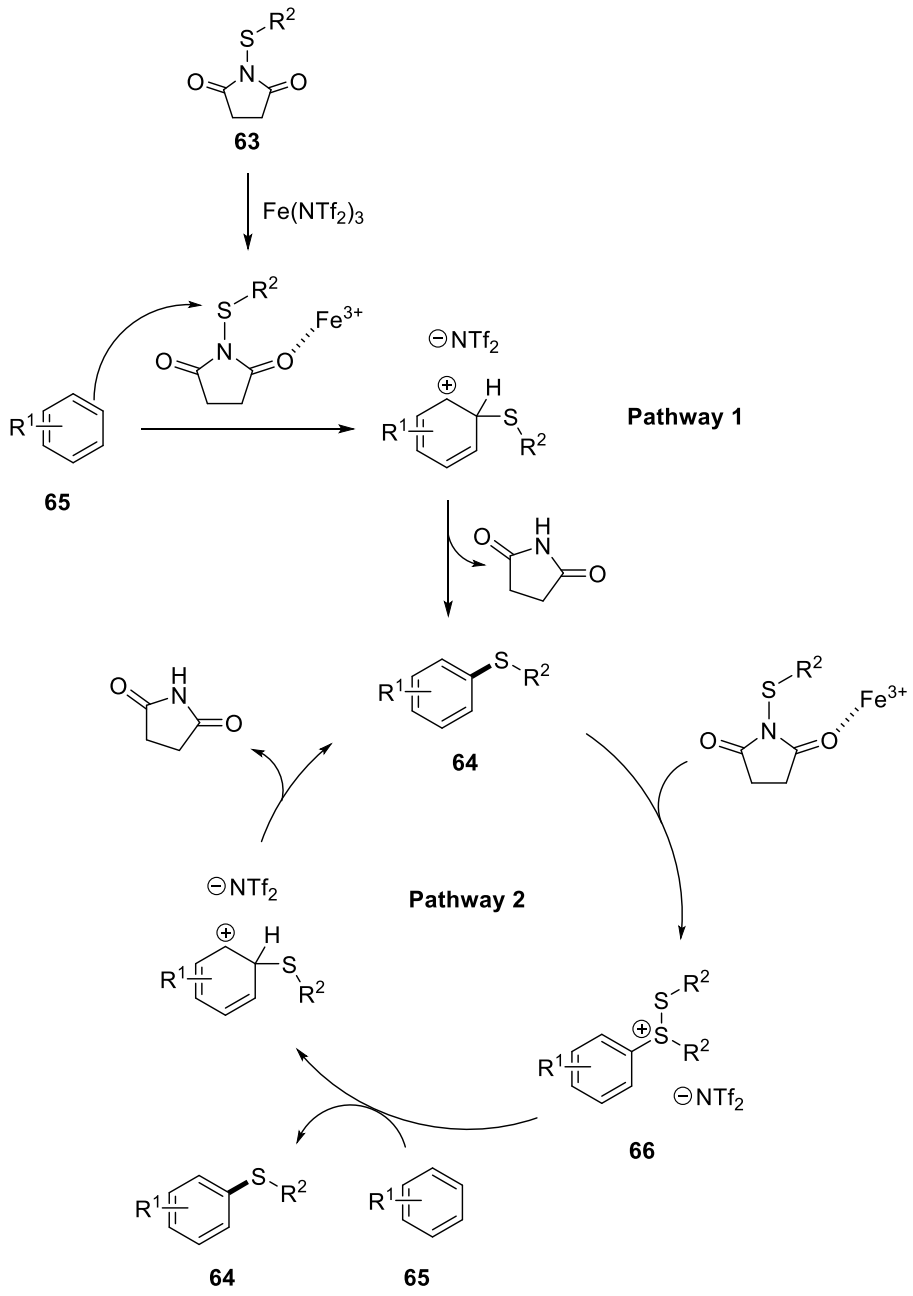


Figure 8: Conversion study of the thioetherification of anisole with: a. *N*-(4-methylphenylthio)succinimide; b. *N*-(4-chlorophenylthio)succinimide (measured using ^{1}H NMR spectroscopy in $CDCl_3$ and hexamethylcyclotrisiloxane as an internal standard). Reaction with **63b** performed at room temperature, while the reaction with **63c** was done at 60 °C.

Based on these results, mechanisms have been proposed for the iron(III) triflimide-catalysed C–H thioetherification of arenes (**65**) with *N*-(arylthio)succinimides (**63**) (Scheme 53). As previously discussed, the combination of iron(III) chloride and [BMIM]NTf_2 leads to the formation of the super Lewis acid $Fe(NTf_2)_3$. The highly delocalised nature of the triflimide counterion allows for the effective activation of the *N*-(arylthio)succinimide through coordination of Fe^{3+}, resulting in a regioselective electrophilic aromatic sulfenylation of the arene ring system (Pathway 1). Pathway 1 outlines the Lewis acid-mediated mechanism where product formation occurs slowly, representing either the lag period when the *N*-(arylthio)succinimide is electron rich, or the entire process when the *N*-(arylthio)succinimide is electron deficient. In the case where the *N*-(arylthio)succinimide is electron rich, once enough of the biaryl sulfide product has accumulated, a second pathway (Pathway 2) becomes viable. Pathway 2 represents a faster, Lewis base-mediated autocatalytic process. Here, the product reacts with the activated *N*-(arylthio)succinimide to form a cationic disulfide intermediate **66**. As a charged species, this reacts rapidly with a second arene, liberating two equivalents of product.

The iron(III) triflimide-catalysed thioarylation of arenes resulted in the formation of the *para*-substituted products exclusively. Previous work done within the group involved studying the *para*-selectivity of iron(III) triflimide-catalysed halogenation reactions. The group demonstrated that DFT calculations using Fukui functions provided a molecular orbital rationale for the high regioselectivity of the transformation.[78] The DFT calculations were performed by Hans Martin Senn at the University of Glasgow, and used the electrophilic Fukui functions to assess the reactivity of different sites of activated arenes towards electrophilic attack. The electrophilic Fukui functions describe the electron density distribution in a frontier molecular orbital and, thus, allows for the prediction of the most nucleophilic and electrophilic sites. If it is assumed that the reactivity towards electrophilic aromatic substitution is entirely controlled by the frontier orbitals, then the Fukui function can be well approximated by the density of the HOMO. From the results of the calculations, it was concluded that, the p_z atomic orbital of the *para*-carbon atom relative to the directing group makes the largest contribution to the HOMO orbital during halogenation and as such, this is why substitution is strongly favoured at this position. We propose that these results can also be used to rationalise the observed regioselectivity of the iron(III) triflimide-catalysed C–H sulfenylation of arenes.

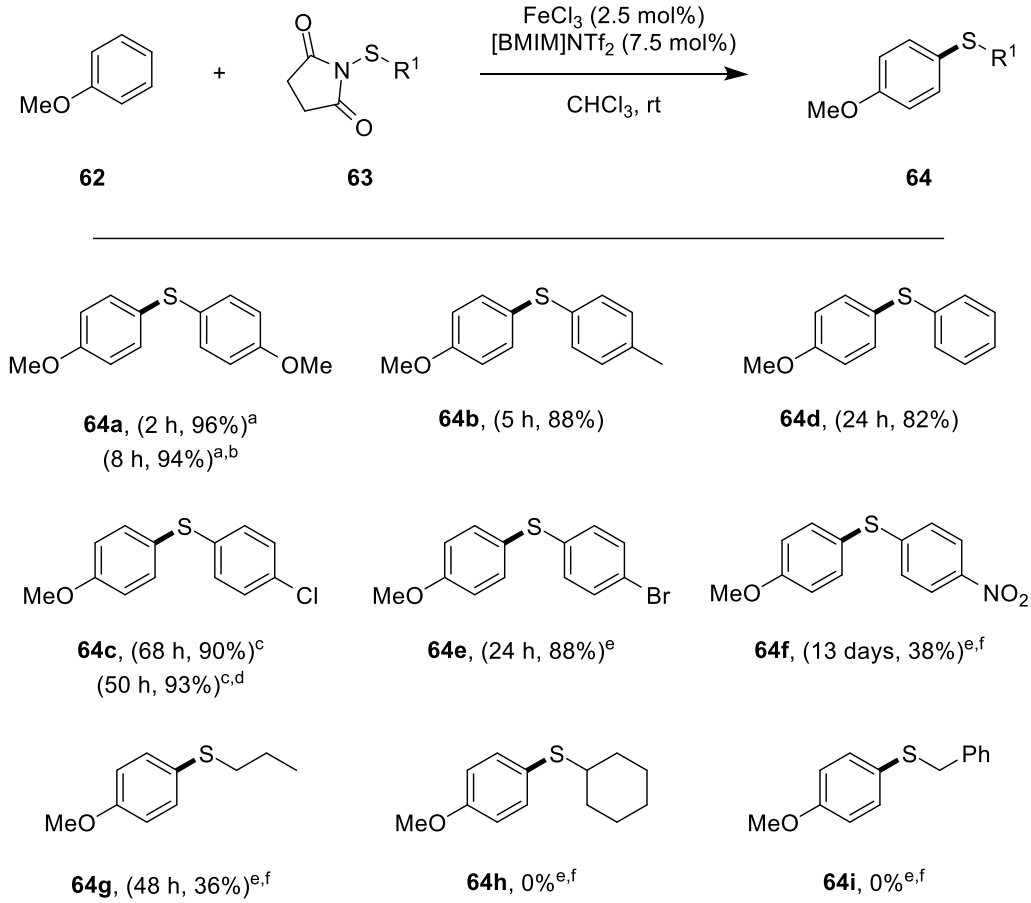


Scheme 53: Proposed mechanism of iron(III) triflimide-catalysed aryl C–H sulfenylation.

2.5 Substrate Scope

After establishing the optimal conditions and the mechanism for the reaction, the substrate scope was explored. Firstly, the scope of the transformation with a range of *N*-thiosuccinimides was examined (Scheme 54). As previously discussed, the reaction between anisole and *N*-(4-methoxyphenylthio)succinimide was the focus of the initial optimisation studies, and the desired product from this reaction, **64a**, was obtained in a 90% yield using the optimised conditions outlined in Table 1 (entry 2). Under the same conditions (2.5 + 7.5 mol% catalyst loading, rt, 2 h), a 96% yield

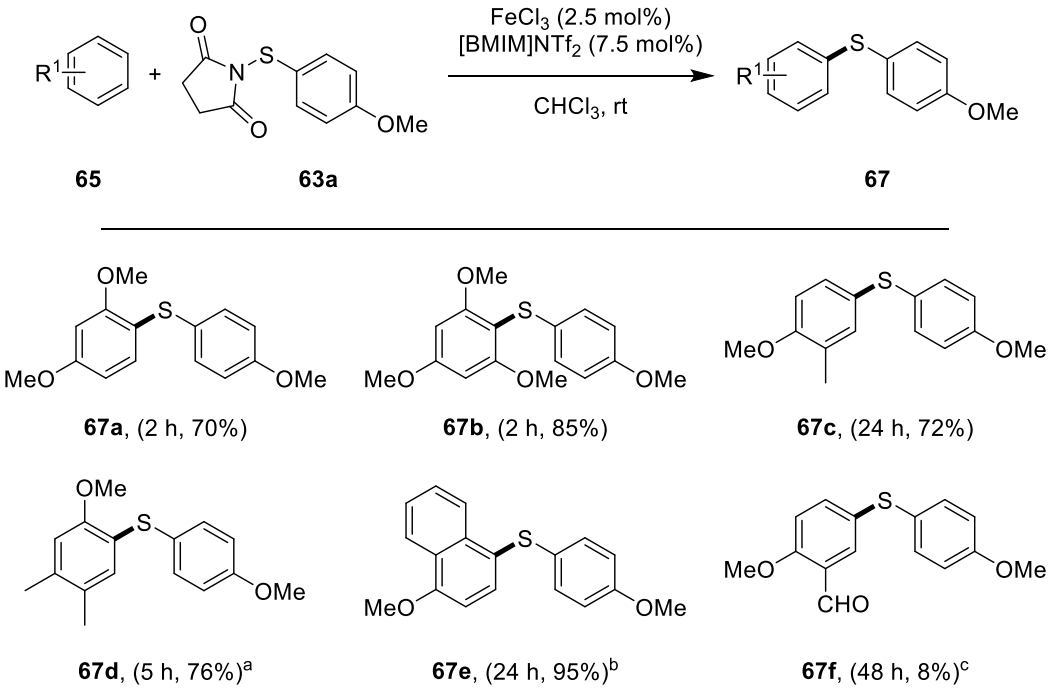
was achieved when the reaction was performed on a one-gram scale. Additionally, at this scale, lower catalyst loadings of 1 + 3 mol% were also successful giving **64a** in a 94% yield, albeit a longer reaction time of 8 h was required. In the cases where the *N*-thiosuccinimide was electron rich, most reactions proceeded at room temperature to give the desired products **64a**, **64b**, and **64d** in high yields (82–96%). High yields were also obtained for the electron deficient 4-chloro and 4-bromo analogues, albeit employing higher reaction temperatures (60–75 °C) and longer reaction times (24–68 h) were required. Kinetic studies discussed earlier highlighted that the reaction between anisole and electron deficient *N*-(arylthio)succinimides does not proceed *via* an autocatalytic mechanism, justifying the need for more forcing conditions in the reactions yielding **64c**, **64e** and **64f**. The reaction between anisole and *N*-(4-chlorophenylthio)succinimide was repeated using a catalyst loading of 1 + 3 mol% $FeCl_3$ and [BMIM]NTf_2 respectively, with the addition of 1 mol% **64a**. It was proposed that the Lewis basic *bis*(4-methoxyphenyl)sulfane could act as a catalyst alongside the $Fe(NTf_2)_3$, leading to an increase in the rate of reaction. Whilst a reaction temperature of 60 °C was still required for product formation, the reaction time was successfully reduced from 68 h to 50 h without impacting the yield. Even the extremely electron withdrawing *N*-(4-nitrophenylthio)succinimide (**63f**) reacted with anisole to give **64f** in 38% yield, although this required a higher catalyst loading of 10 + 30 mol% $FeCl_3$ and [BMIM]NTf_2, respectively, and a reaction time of 13 days. The main limitation of this methodology was found with *N*-(alkylthio)succinimides. Whilst *N*-(propanethio)succinimide (**63g**) gave the corresponding sulfide (**64h**) in 36% yield following 48 h at 75 °C with a catalyst loading of 10 + 30 mol% $FeCl_3$ and [BMIM]NTf_2, both *N*-(cyclohexylthio)succinimide and *N*-(benzylthio)succinimide failed to produce any desired product. Whilst it is unclear the reason for the poor reactivity of the *N*-(alkylthio)succinimides, it is proposed that steric hinderance could be a contributing factor. Additionally, a small proportion of **64a** was isolated from the reactions between anisole and *N*-(alkylthio)succinimides, suggesting side reactions such as homolytic C–S bond cleavage may be occurring.



Scheme 54: Reaction Scope of *N*-thiosuccinimides with anisole. [a]Gram scale reaction; [b]$FeCl_3$ (1 mol%) and [BMIM]NTf_2 (3 mol%) was used; [c]Reaction performed at 60 °C; [d]$FeCl_3$ (1 mol%), [BMIM]NTf_2 (3 mol%) and **64a** (1 mol%) was used; [e]Reaction performed at 75 °C; [f]$FeCl_3$ (10 mol%) and [BMIM]NTf_2 (30 mol%) was used.

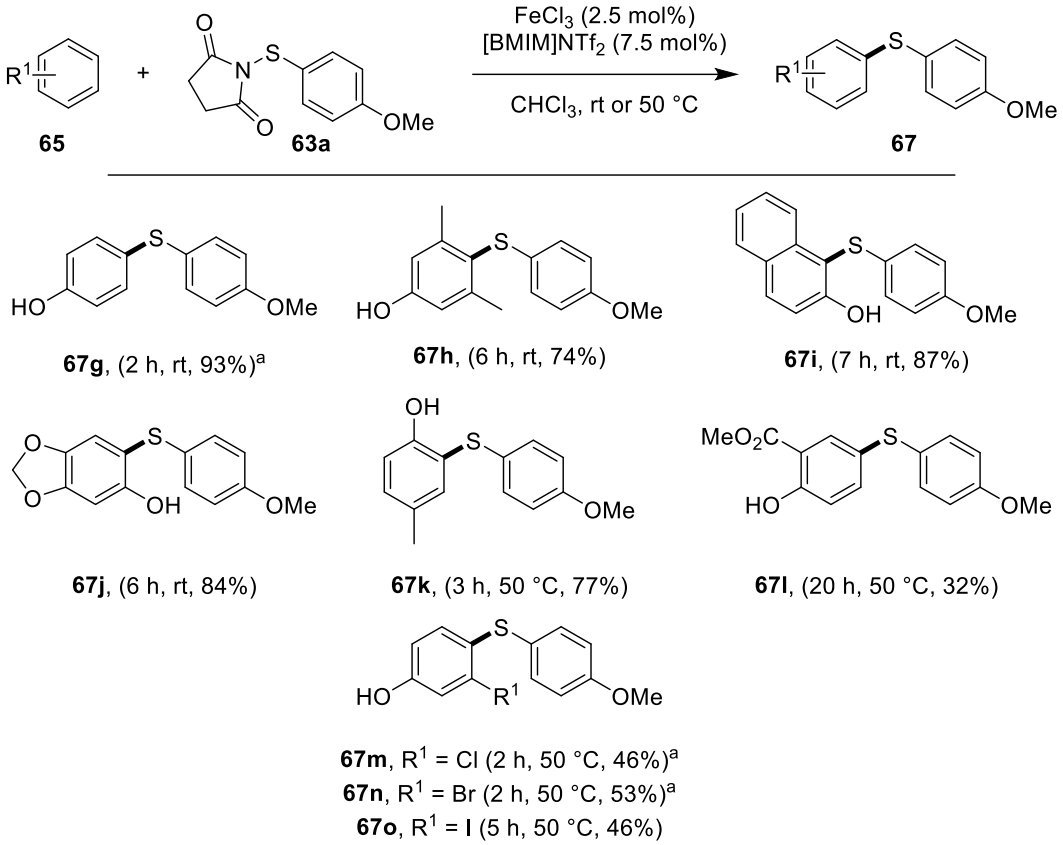
The project then focused on investigating the scope of the arene component. Anisole and anisole derivatives were generally coupled with ease, delivering the desired products in good to excellent yields (Scheme 55). In the cases where the reactants were electron rich, most reactions proceeded at room temperature with reaction times ranging between 2–24 h. When the coupling was attempted with *o*-anisaldehyde, the desired product (**67f**) was obtained in only 8% yield (alongside 40% arene starting material), despite complete consumption of the *N*-(4-methoxyphenylthio)succinimide, as measured by ^{1}H NMR spectroscopy and TLC analysis. Due to the electron deficient nature of *o*-anisaldehyde, it is unlikely that its reaction follows the autocatalytic mechanism, rationalising the need for an elevated temperature of 50 °C and a long reaction time. In the reaction of 3,4-dimethylanisole, the *para*-position relative to the methoxy group is blocked, forcing sulfenylation to occur in the *ortho*-position, furnishing **67d** in 76% yield. A slightly raised temperature

of 40 °C was required for this substrate, to overcome the steric barrier of sulfenylation at the *ortho*-position.



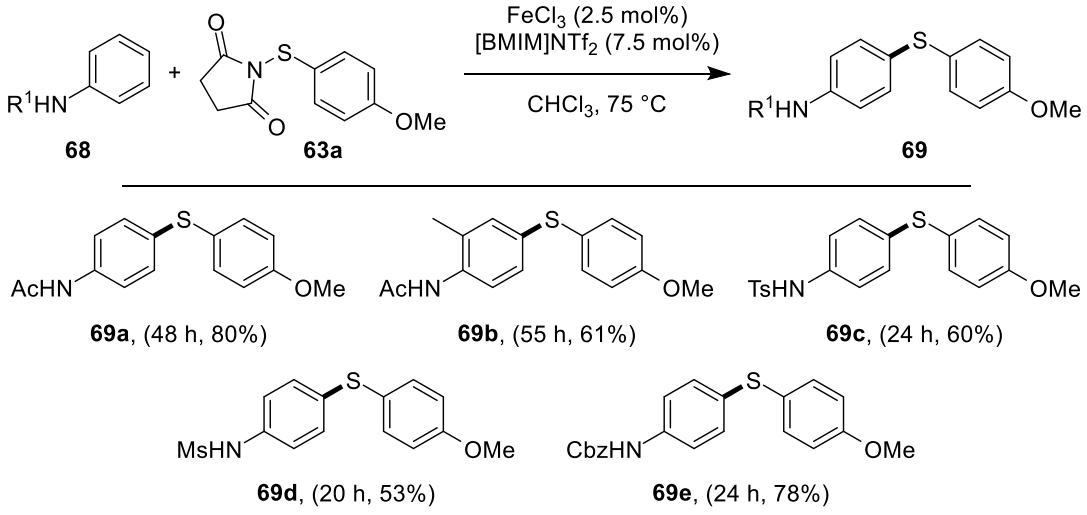
Scheme 55: $Fe(NTf_2)_3$-catalysed sulfenylation of anisole derivatives. [a]Reaction was performed at 40 °C; [b]Reaction was performed at 75 °C; [c]Reaction was performed at 50 °C.

The reaction was also compatible with phenols (Scheme 56). Like the anisole analogues, electron-rich phenols coupled at room temperature to deliver the desired products in moderate to good yields (**67g–67j**). In the reaction of *p*-cresol, a higher catalyst loading (5 + 15 mol% $FeCl_3$ and $[BMIM]NTf_2$) and a slightly higher temperature of 50 °C was required to achieve *ortho*-sulfenylation, providing **67k** in 77% yield. The ester functionality was tolerated (**67l**), however, the presence of the deactivating group was detrimental to the yield (32%). Additionally, the methodology was amenable to phenols bearing halogens (**67m–67o**), which proves promising for reactions requiring further functionalisation. The reactions of the 3-halophenols required a slightly elevated temperature of 50 °C, which can be rationalised due to the electron-withdrawing nature of the halogens decreasing the rate of electrophilic aromatic substitution. The moderate yields of the reaction is likely due to the large size of the halogen atoms causing steric hinderance at the *para*-position relative to the hydroxy group.



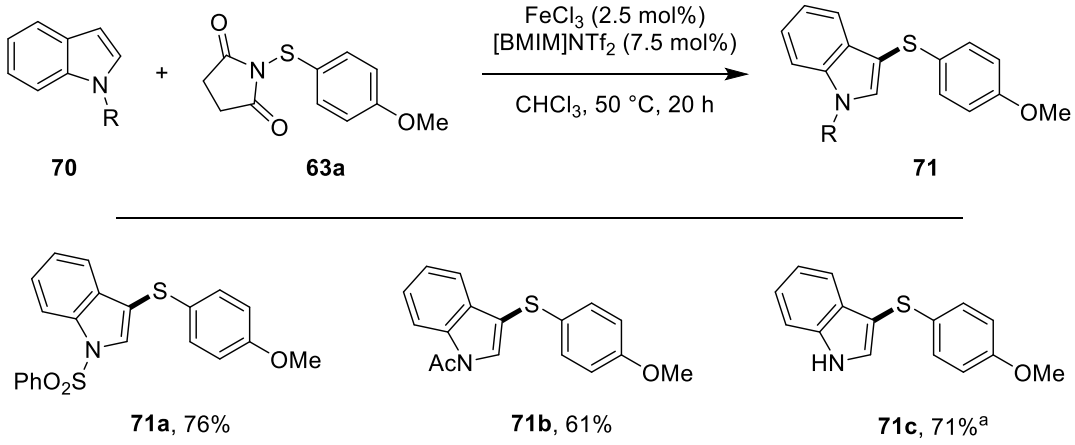
Scheme 56: $Fe(NTf_2)_3$-catalysed sulfenylation of phenol derivatives. [a]$FeCl_3$ (5 mol%) and $[BMIM]NTf_2$ (15 mol%) were used.

Unprotected anilines proved to be troublesome when subjected to the optimised reaction conditions, and it is likely that these reacted to form *N*-sulfenylated products instead of desired products. To overcome this issue, protecting groups were installed, and the resulting protected anilines were successfully coupled at 75 °C to give the desired products **69a–69e** in moderate to good yields (Scheme 57).



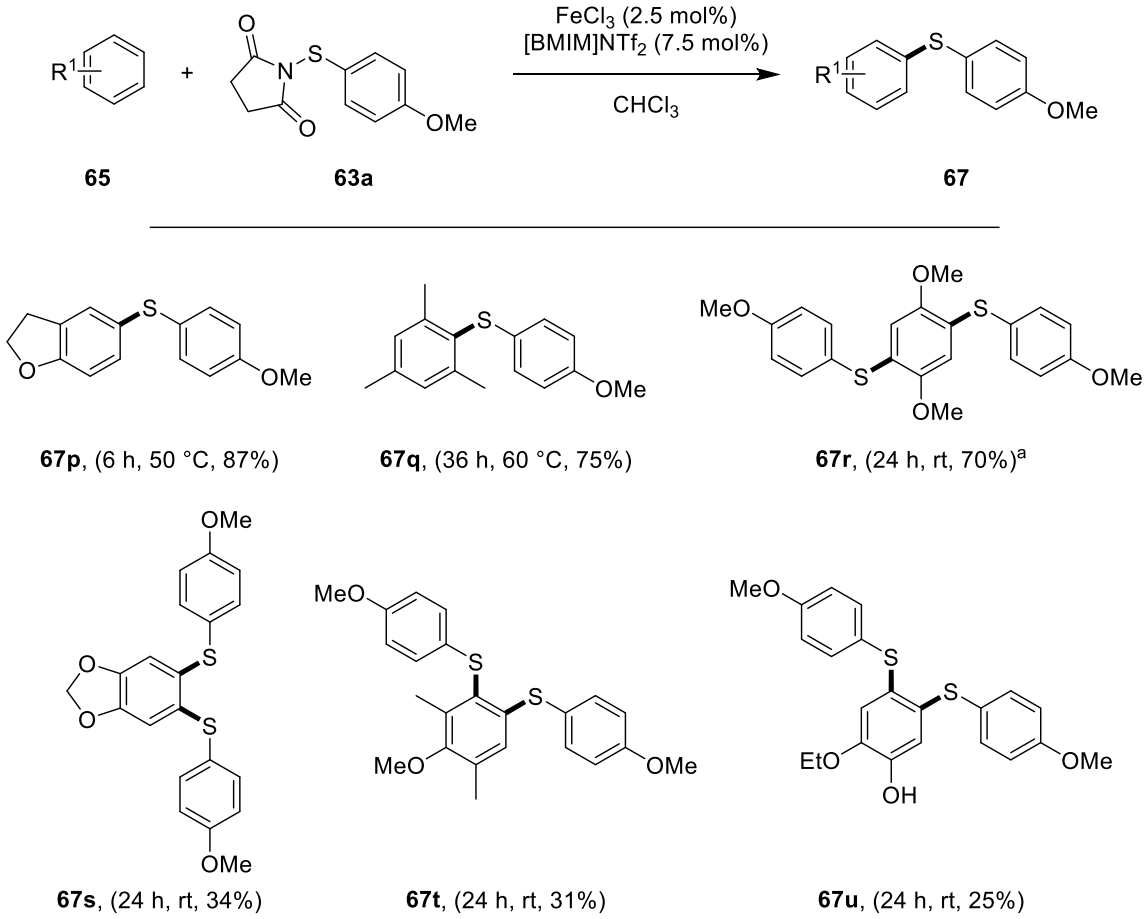
Scheme 57: $Fe(NTf_2)_3$-catalysed C–H sulfenylation of protected anilines.

In the case of indole, protecting groups were installed to combat solubility issues (Scheme 58). Mono C–H sulfenylation was then achieved selectively at the C-3 position, with the sulfonamide- and acetyl- protected derivatives reacting at 50 °C to give the desired products **71a** and **71b** in 76 and 61% yields, respectively. In attempt to overcome the solubility issues presented by free indole, it was proposed that the arene could be coupled with *N*-(4-methoxyphenylthio)succinimide using silver *bis*(trifluoromethanesulfonyl)imide ($AgNTf_2$) as a catalyst. It was thought that the use of silver(I), which is a much softer metal than iron(III), would minimise any coordination of the metal to the free NH and, thus, prevent the indole from forming a precipitate in the chloroform solvent. Pleasingly, the desired product, **71c**, was obtained in a 71% yield after 24 h at 60 °C using a catalyst loading of 7.5 mol%.



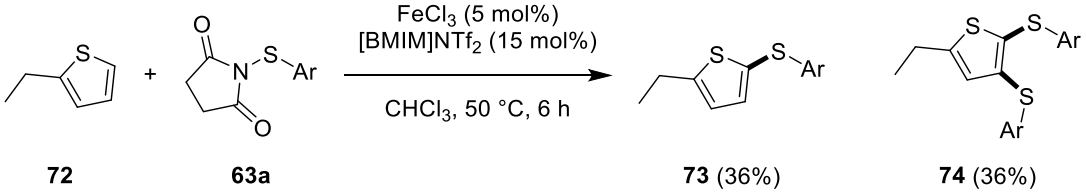
Scheme 58: $Fe(NTf_2)_3$-catalysed C–H sulfenylation of indoles. [a]$AgNTf_2$ (7.5 mol%) was used as the catalyst. Reaction was performed at 60 °C for 24 h.

Furthermore, other substrates such as 2,3-dihydrobenzofuran and mesitylene were also coupled successfully to give the desired products **67p** and **67q** in good yields. The effective coupling of mesitylene was a welcome result which demonstrated that the developed iron(III) triflimide-catalysed C–H sulfenylation reaction is amenable to weakly activated arenes (Scheme 59). In some cases, di-substitution was observed when the arene contained multiple activating groups. For example, when 1,4-dimethoxybenzene was subjected to the reaction conditions – to investigate the viability of *ortho*-sulfenylation – only the *bis*-substituted product was isolated from the reaction mixture. This is likely due to the mono-substituted products displaying higher reactivities than the original starting materials. In the case of the reaction of 1,4-dimethoxybenzene, the reaction was performed using 2 equivalents of *N*-(4-methoxyphenylthio)succinimide to give the di-substituted product **67r** in 70% yield.



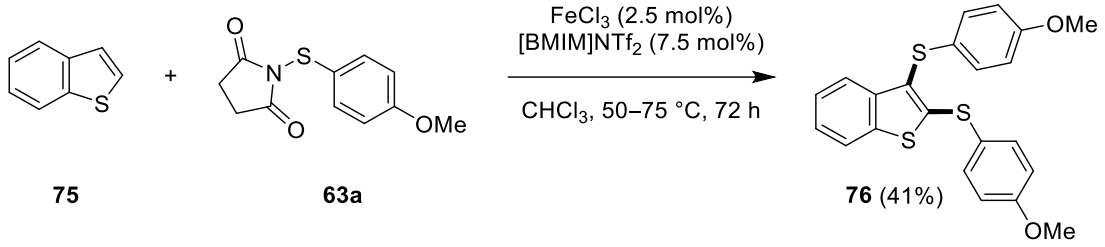
Scheme 59: $Fe(NTf_2)_3$-catalysed C–H sulfenylation of arenes. [a]Reaction was performed with 2 equiv. *N*-(4-methoxyphenylthio)succinimide.

Issues with this methodology were only found for highly activated heterocycles e.g. thiophenes and pyrroles. Despite being able to isolate mono-substituted products cleanly in some cases (e.g. **73** in the reaction of 2-ethylthiophene), the yields for these reactions were often hindered by overreaction of the arenes, leading to a mixture of polythioarylated products (Scheme 60).



Scheme 60: Thioetherification of 2-ethylthiophene. Ar = *p*-MeOPh.

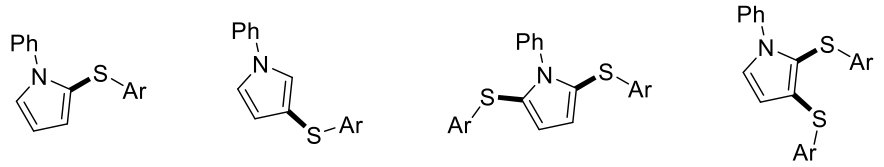
The only product which resulted from the reaction between benzo[*b*]thiophene (**75**) and *N*-(4-methoxyphenylthio)succinimide (**63a**) was 2,3-*bis*-[(4'-methoxyphenyl)sulfane]benzo[*b*]thiophene (**76**) (Scheme 61).



75 **63a** **76** (41%)

Scheme 61: Thioetherification of benzo[*b*]thiophene. Reaction was performed with 1.2 equiv. *N*-(4-methoxyphenylthio)succinimide.

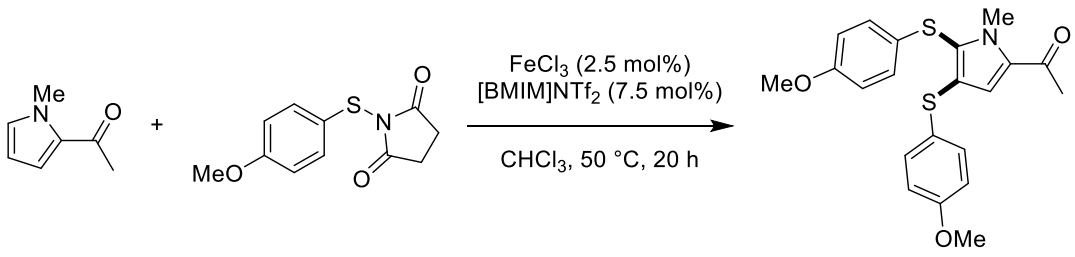
Pyrrole derivatives were undoubtedly the most problematic substrates, with the thioetherification of 1-phenylpyrrole furnishing a wide range of products (**77–80**) (Figure 9).



77 (16%) **78** (19%) **79** (17%) **80** (8%)

Figure 9: Products resulting from the thioetherification of 1-phenylpyrrole. Ar = *p*-MeOPh.

We hypothesised that the formation of polythioarylated products could be limited by using deactivated pyrroles. As such, the reaction was attempted with *N*-methyl-2-acetylpyrrole (**81**) but, unfortunately, di-substitution was observed once again (Scheme 62).



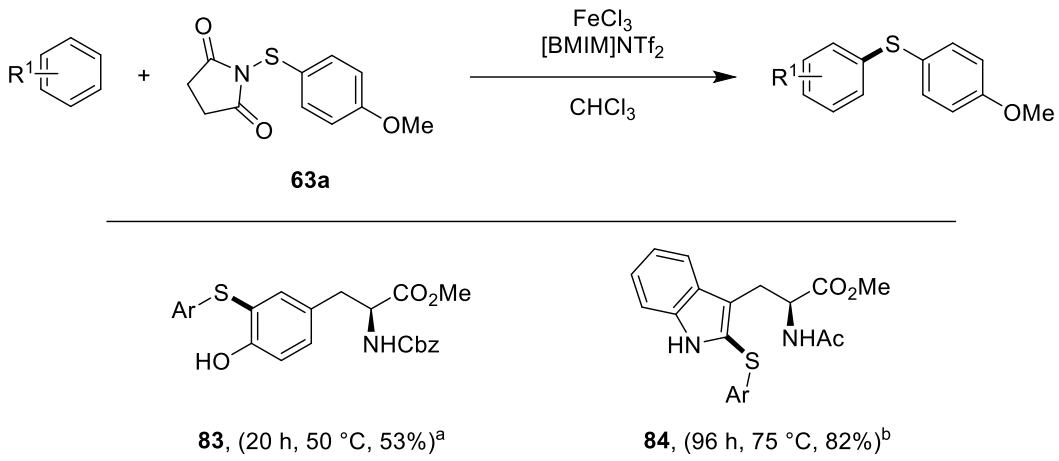
81 **63a** **82** (27%)

Scheme 62: Fe(NTf$_2$)$_3$-catalysed C–H sulfenylation of *N*-methyl-2-acetylpyrrole. Reaction was performed with 1.2 equiv. *N*-(4-methoxyphenylthio)succinimide.

2.6 Late-Stage Functionalisation of Protected Amino Acids

One of the main aims of this project was to develop a method for C–H sulfenylation which could be used for the late-stage functionalisation of amino acids and

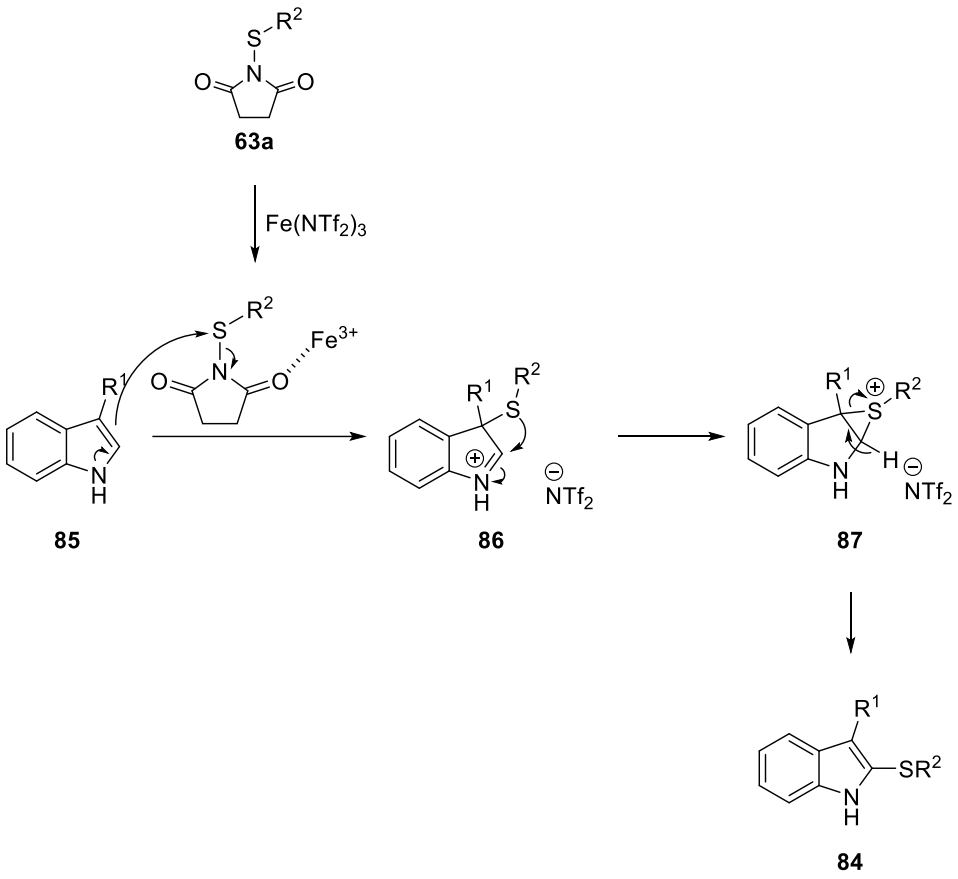
biologically active compounds. Encouragingly, iron(III) triflimide proved to be an effective catalyst for the thioarylation of tyrosine and tryptophan derivatives (Scheme 63). Higher catalyst loadings [5–10 mol% $Fe(NTf_2)_3$] and elevated temperatures were required for these analogues, but in both cases only mono-thioarylation was observed, giving the desired products, **83** and **84**, in 53% and 82% yield, respectively.



Scheme 63: $Fe(NTf_2)_3$-catalysed C–H sulfenylation of tyrosine and tryptophan derivatives. [a]$FeCl_3$ (5 mol%) and $[BMIM]NTf_2$ (15 mol%) were used. [b]$FeCl_3$ (10 mol%) and $[BMIM]NTf_2$ (30 mol%) were used. Ar = *p*-MeOPh.

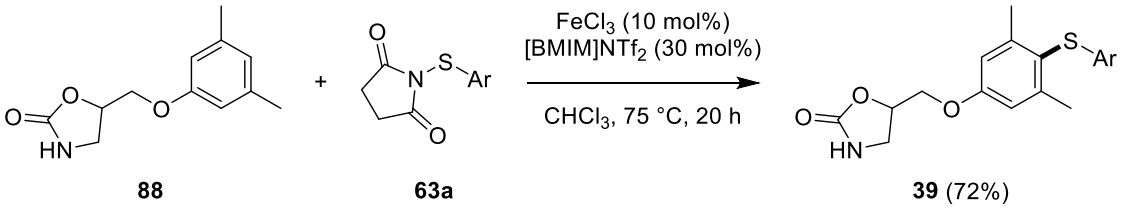
Due to the nucleophilic nature of an indole ring, these arenes can be easily functionalised at the C-3 position *via* reaction with the electrophilic *N*-(4-methoxyphenylthio)succinimide, which is activated by the coordination of the super Lewis acid $Fe(NTf_2)_3$ to the carbonyl oxygen. Conversely, functionalisation at the C-2 position is more challenging due to the weak reactivity of the C-2 C–H bond. This rationale can be used to justify the need for more forcing conditions in the thioarylation of *N*-acetyl-L-tryptophanate (where the C-3 position is blocked) versus the other indoles which have been functionalised (see Scheme 58). 2-Thioindoles are generally obtained by C-2-lithiation of an *N*-protected indole, followed by reaction with an electrophilic thiol source.[79] In this case, however, the formation of the desired 2-thioindole is likely a result from the rearrangement of the C-3-sulfenylated indole, rather than direct C-2 C–H sufenylation. A plausible mechanism for the reaction is outlined in Scheme 64. Nucleophilic attack of *N*-acetyl-L-tryptophanate (**85**) on the activated *N*-(arylthio)succinimide leads to the formation of an indolenium intermediate **86**. Migration of the sulfide group to the C2 position follows, *via* the formation of the episulfonium species **87**, leading to the formation of

the desired product **84**. Similar results were reported by Cossy and co-workers in their TFA-promoted C–H sulfenylation of indoles.[80]



Scheme 64: Proposed mechanism for the $Fe(NTf_2)_3$ catalysed C2-sulfenylation of *N*-acetyl-L-tryptophanate. R^1 = methyl (2*S*)-2-acetamido-3-propanoate, R^2 = *p*-MeOPh.

Additionally, the use of iron(III) triflimide allowed for the successful late-stage functionalisation of metaxalone (**88**),[81] an FDA approved drug molecule used for pain relief and as a muscle relaxant (Scheme 65). A catalyst loading of 10 + 30 mol% for $FeCl_3$ and $[BMIM]NTf_2$ delivered the best results for this reaction, with the desired product being obtained in 72% yield after 20 h at 75 °C. This result demonstrates the great potential of this strategy in the modification of pharmaceuticals.

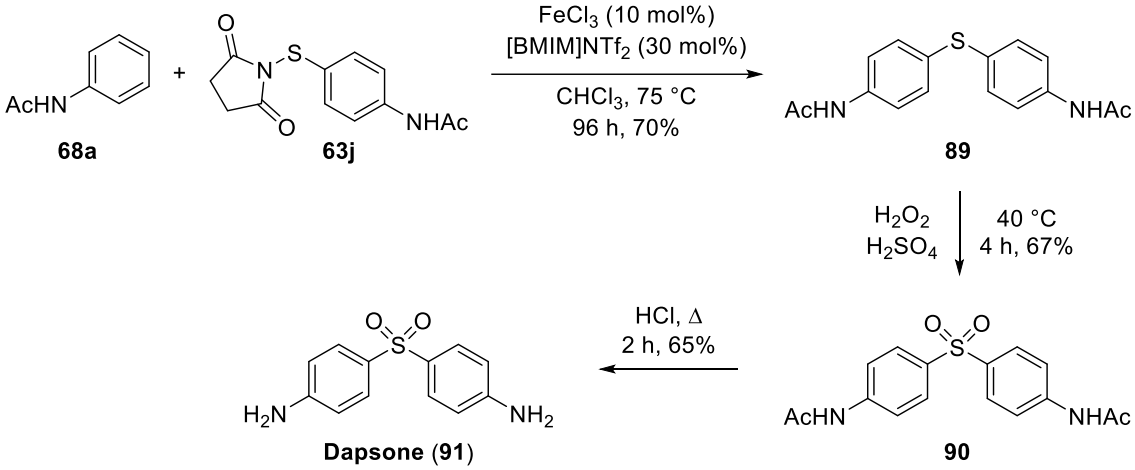


Scheme 65: $Fe(NTf_2)_3$-catalysed C–H sulfenylation of metaxalone. Ar = *p*-MeOPh.

2.7 Synthesis of Dapsone and Vortioxetine

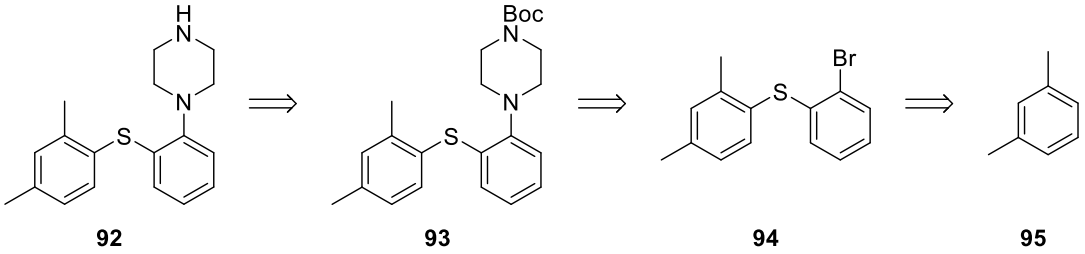
Dapsone is an antibiotic that is used to treat leprosy.[82] It is also an example of a pharmaceutically relevant aryl sulfide containing compound and, as such, it was proposed that the developed iron(III) triflimide-catalysed thioarylation reaction could be employed as a key step towards its synthesis (Scheme 66).

The iron(III) triflimide-catalysed thioarylation reaction between acetanilide (**68a**) and *N*-(4-acetamidophenylthio)succinimide (**63j**) resulted in the isolation of biaryl sulfide **89** in 70% yield after 96 h at 75 °C. A catalyst loading of 10 mol% $Fe(NTf_2)_3$ was optimal for this reaction, and more forcing conditions were required to counteract the presence of deactivating acetyl protecting groups on both the arene and *N*-(arylthio)succinimide, which slow the rate of electrophilic aromatic substitution. Hydrogen peroxide was used in combination with sulfuric acid to oxidise **89**, to give sulfone **90** (67% yield). Subsequent deprotection under acidic conditions (65% yield) completed the three-step synthesis of dapsone (**91**).



Scheme 66: Three-step synthesis of dapsone.

To further demonstrate the synthetic utility of the developed methodology, it was also applied to the synthesis of the antidepressant, vortioxetine (**92**).[83] The proposed retrosynthetic analysis towards this target molecule is detailed in Scheme 67.



92 **93** **94** **95**

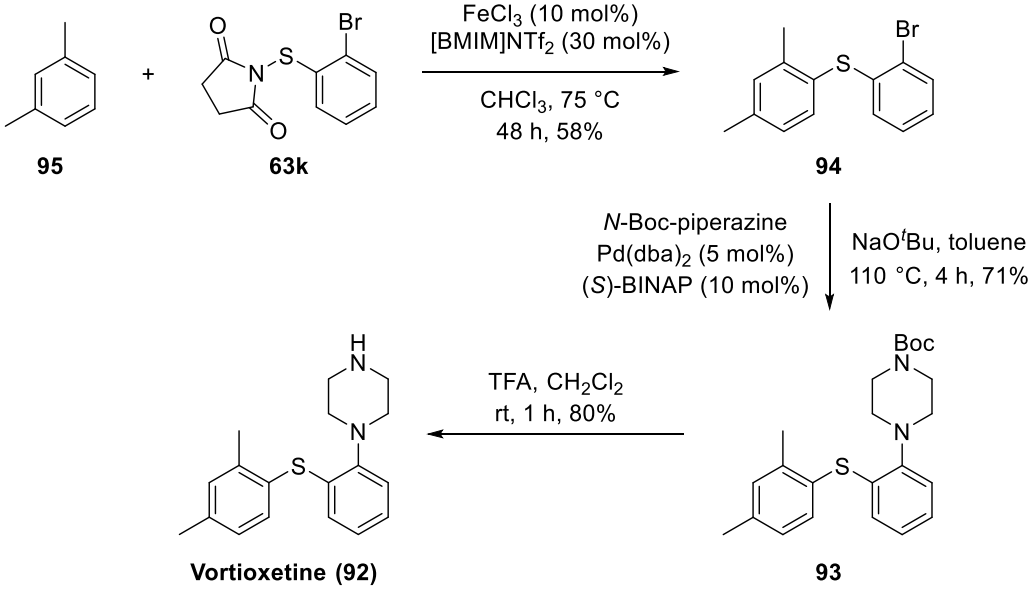
Scheme 67: Retrosynthesis of vortioxetine.

A key step in the synthesis of vortioxetine requires the thioetherification of *meta*-xylene with *N*-(2-bromophenylthio)succinimide **63k**. This transformation appears potentially challenging due to the electron-deficient nature of the *N*-(arylthio)succinimide, in combination with the arene component (*meta*-xylene) exhibiting minimal activation. With this in mind, an initial reaction was attempted employing electron rich *N*-(4-methoxyphenylthio)succinimide as the coupling partner, to explore the viability of *meta*-xylene as the arene component (Scheme 68). This reaction was successful in generating desired product **96**, albeit in a relatively low yield of 33% and with the reaction requiring a temperature of 60 °C.

95 **63a** **96**, 33%

Scheme 68: $Fe(NTf_2)_3$-catalysed C–H sulfenylation of *m*-xylene.

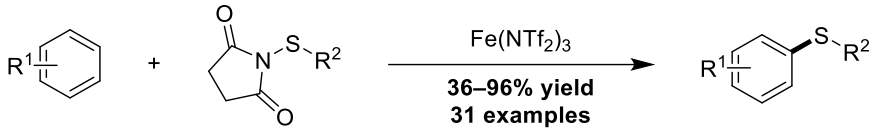
This confirms that even arenes with limited activation can undergo thioarylation using iron(III) triflimide catalysis and, so, the proposed route towards vortioxetine was attempted (Scheme 69). As suspected, since *N*-(2-bromophenylthio)succinimide is more electron-deficient than *N*-(4-methoxyphenylthio)succinimide, a higher catalyst loading of 10 mol% $FeCl_3$ and 30 mol% $[BMIM]NTf_2$ was required alongside a temperature of 75 °C. The reaction reached completion after 48 h and gave desired sulfide **94** in a good yield. Subsequent palladium-catalysed Buchwald-Hartwig cross-coupling with *N*-Boc-piperazine,[83,84] followed by TFA-mediated Boc-deprotection[85] completed the three-step synthesis of target compound **92**.



Scheme 69: Total synthesis of vortioxetine (**92**).

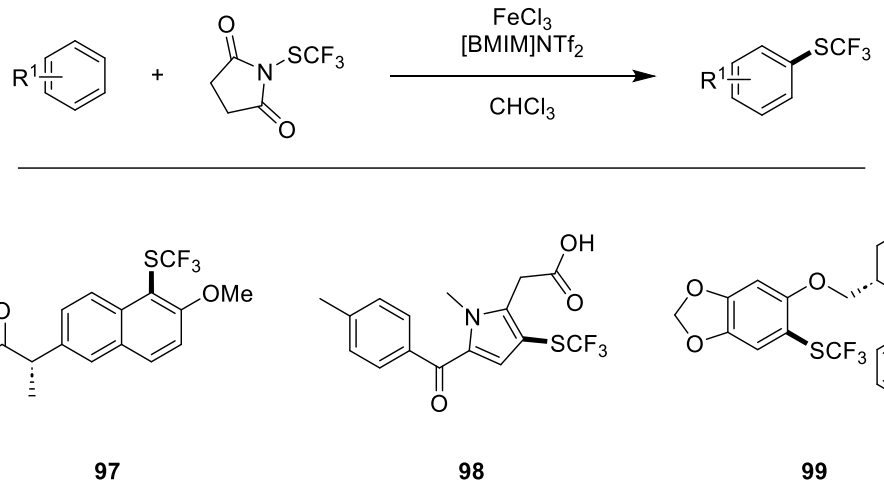
2.8 Conclusions and Outlook

In conclusion, an iron(III) triflimide-catalysed protocol was developed which allows the regioselective synthesis of aryl thioethers using a reaction of *N*-(arylthio)succinimides with activated arenes (Scheme 70). The methodology makes use of iron(III) chloride (an earth abundant, nonprecious transition metal) in combination with [BMIM]NTf_2 (a readily available and inexpensive ionic liquid), with the process generally using low catalyst loadings and allowing for the thioarylation of a wide range of arenes containing activating groups. Additionally, kinetic experiments were undertaken to gain a deeper understanding of the reaction mechanism, with results indicating that, when the *N*-(arylthio)succinimide is electron rich, the reaction proceeds *via* an autocatalytic mechanism. On the other hand, when the *N*-(arylthio)succinimide is electron deficient, the reaction is catalysed predominantly by the iron(III) triflimide. The protocol has been found to be amenable for the late-stage functionalisation of tyrosine and tryptophan derivatives, as well as the FDA approved drug molecule, metaxalone. The synthetic utility of the reaction was exemplified with the synthesis of the antibiotic, dapsone (**91**) and the antidepressant, vortioxetine (**92**), whereby the iron(III) triflimide-catalysed thioetherification of arenes played a key step in each synthetic route.



Scheme 70: General $Fe(NTf_2)_3$-catalysed thioetherification.

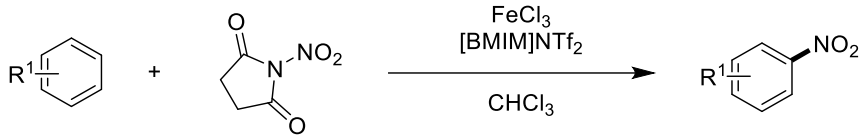
With the successful development of an efficient thioarylation procedure using *N*-(arylthio)succinimides, it is proposed that iron(III) triflimide catalysis could also be employed to facilitate trifluoromethylthiolation (Scheme 71). The SCF_3 group is of great interest and is becoming increasingly employed by medicinal chemists, since its introduction generally contributes to better physiochemical properties of drug molecules, by modulating their lipophilicity and bioavailability.[44] It follows that the development of methods which permit the late-stage introduction of the SCF_3 group is an attractive area in synthetic chemistry. The methodology could be used for the incorporation of the SCF_3 group within known FDA-approved drug molecules such as naproxen and tolmetin, which are both nonsteroidal anti-inflammatory drugs (NSAIDs), and paroxetine, which is an antidepressant, to furnish derivatives **97**, **98** and **99**, respectively. Gustafson and co-workers have previously performed similar work, reporting the successful trifluoromethylthiolation of FDA-approved drug molecules using triflic acid in combination with a selenide ether catalyst.[57]



Scheme 71: Proposed $Fe(NTf_2)_3$-catalysed trifluoromethylthiolation of activated arenes and application to FDA-approved drug molecules.

In 2020, Katayev and co-workers reported the use of *N*-nitrosuccinimide for the photochemical-mediated *ipso*-nitration of aryl and heteroarylboronic acids.[86] As such, it is proposed that these bench-stable nitrating reagents could be used in the

iron(III) triflimide-catalysed electrophilic aromatic substitution reactions for the regioselective nitration of activated arenes (Scheme 72). This would offer a promising alternative to the ‘mixed acid’ approach of aromatic nitration of activated arenes, which uses nitric and sulfuric acid, and exhibits poor functional group tolerance, often resulting in unfavourable by-products.[87]



Scheme 72: Proposed $Fe(NTf_2)_3$-catalysed nitration of activated arenes.

3.0 Development of a Two-Step Process for the Synthesis of Phenoxathiins

3.1 Introduction to Phenoxathiins

Phenoxathiins are interesting sulfur containing heterocycles with a wide range of uses in pharmaceutical science and materials chemistry (Figure 10).[88,89,90] In particular, due to their interesting optical properties, phenoxathiin derivatives have been used to develop high-efficiency, room-temperature phosphorescent materials such as **100**.[91] They have also seen use in drug candidate molecules such as thrombin inhibitor **101**,[92] and monoamine oxidase A inhibitor **102**.[93] Additionally, phenoxathiin-dioxide has been identified as an electron-acceptor unit for blue thermally activated delayed fluorescence (TADF) emitters such as **103**.[94] Owing to their unique chemical and physical properties, novel and efficient methods to prepare phenoxathiins are highly sought after.

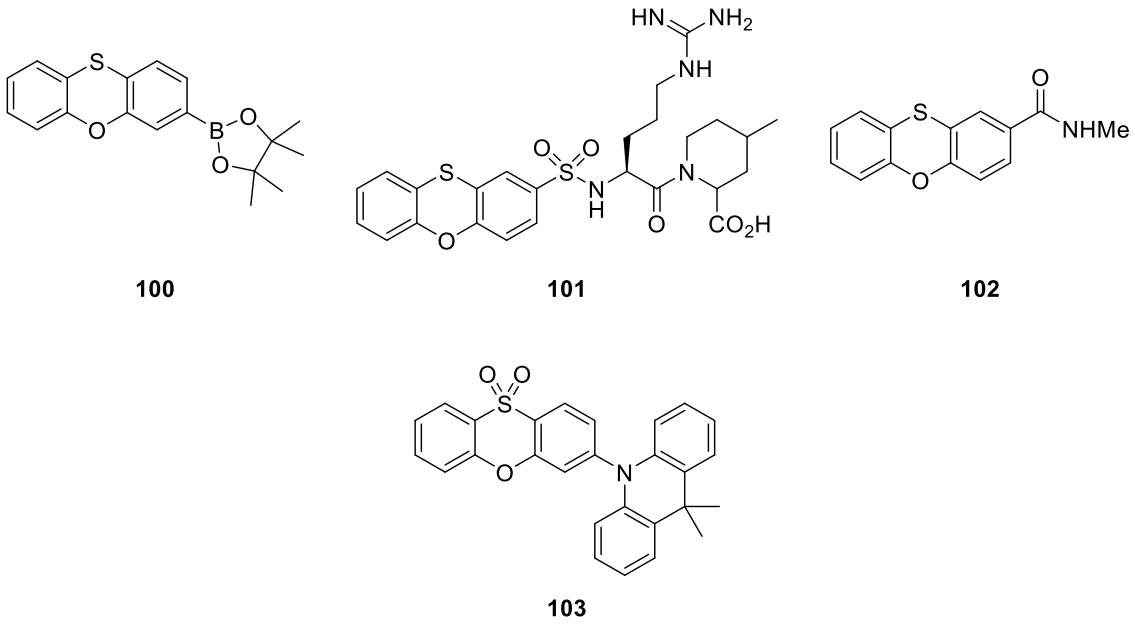


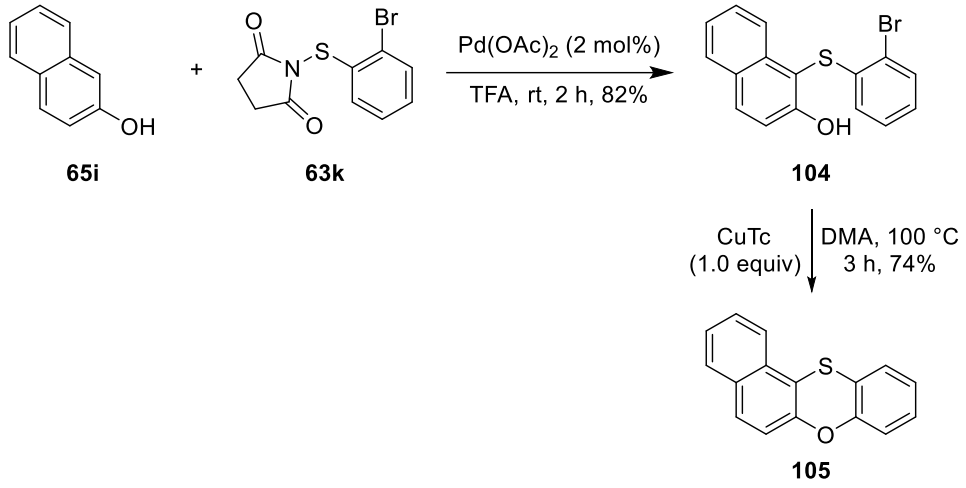
Figure 10: Examples of phosphorescent and biologically active molecules containing a phenoxathiin moiety.

Conventional methods for the synthesis of phenoxathiins involve the reaction of diaryl ethers with elemental sulfur, however, this transformation is limited by the harsh reaction conditions required as well as poor selectivity (Scheme 73).[95]

Scheme 73: Conventional method of phenoxathiin synthesis.

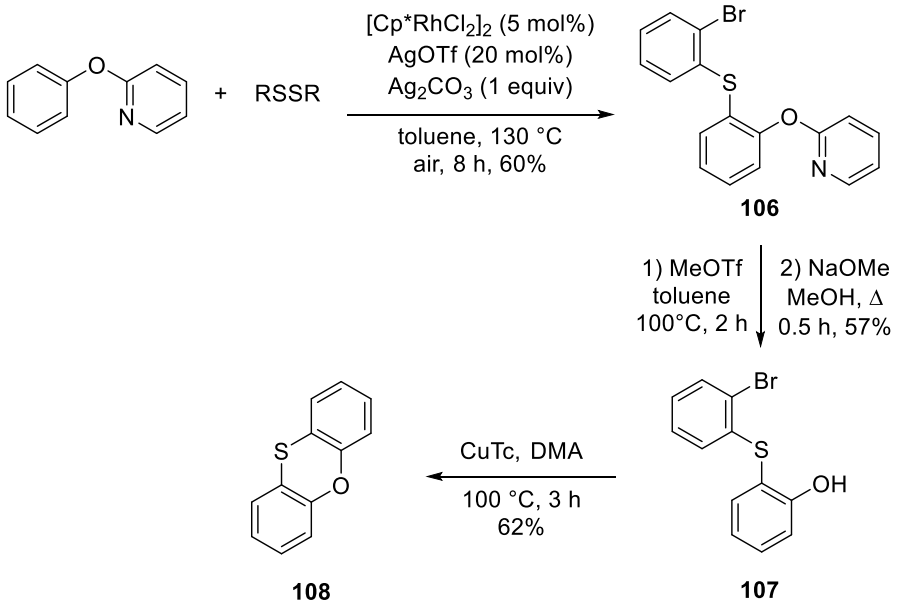
Recent developments for the construction of phenoxathiins have tended to focus on a two-step approach, involving initial thioarylation of phenols using transition-metal catalysis, and subsequent cyclisation.[96,97,98]

In 2014, Anbarasan and co-workers developed a palladium-catalysed thioarylation of electron rich arenes (discussed earlier) for the synthesis of aryl thioethers (Scheme 74).[99] When this methodology was used for the reaction between 2-naphthol and *N*-(2-bromophenylthio)succinimide, the resulting aryl thioether (**104**) was then cyclised with stoichiometric quantities of copper(I) thiophene-2-carboxylate (CuTc) to give the corresponding phenoxathiin **105**.



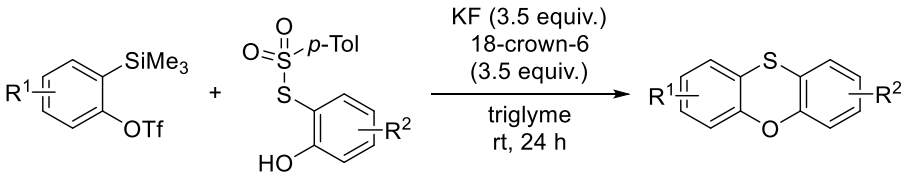
Scheme 74: Synthesis of benzo[*a*]phenoxathiin.

Additionally, Yang and co-workers reported a Rh(III)-catalysed *ortho*-thioarylation of phenols using a 2-pyridyl directing group (Scheme 75).[97] Following successful formation of aryl thioether (**106**), removal of the 2-pyridyl group ensued and subsequent intramolecular C–O cross-coupling (again mediated by CuTc) gave phenoxathiin **108**.



Scheme 75: Synthesis of phenoxathiin.

Another recent advance in the synthesis of phenoxathiins was disclosed by Yoshida and co-workers. Here, phenoxathiins were prepared from the reaction between *ortho*-silylaryl triflates and thiosulfonates, under mild conditions (Scheme 76).[100] It is proposed that the reaction proceeds *via* the formation of aryne intermediates.

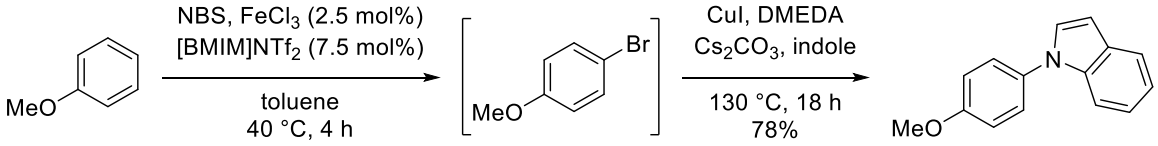


Scheme 76: One-step synthesis of phenoxathiins from *o*-silylaryl triflates and thiosulfonates.

Whilst some of these methods demonstrate general synthetic routes towards phenoxathiins, they often require harsh reaction conditions, the use of precious transition-metal catalysis, or highly functionalised starting materials. As such, the development of novel, robust techniques to construct these moieties, from easily accessible starting materials is of considerable interest.

3.2 Previous Work in the Sutherland Group

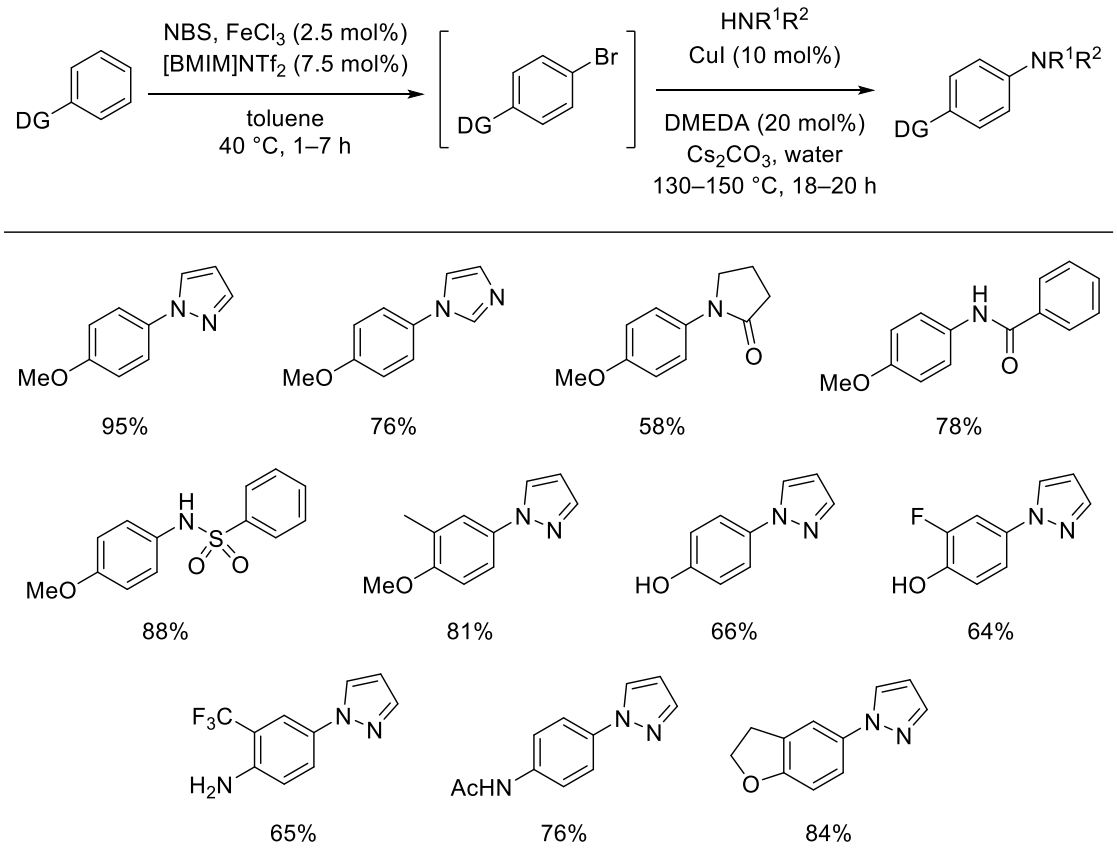
After developing a range of iron(III) triflimide-catalysed halogenation reactions, the group proposed that selective amination of *para*-C–H bonds of electron rich arenes could be achieved by combining the iron(III) triflimide-catalysed halogenation process with a copper(I)-catalysed Ullman-Goldberg reaction.[74] Having already shown the effectiveness of the iron(III) triflimide-catalysed bromination reaction, optimisation studies focused on identifying conditions for the one-pot, two-step amination process. Initially, the optimised conditions for the bromination reaction ($FeCl_3$ – 2.5 mol% in combination with [BMIM]NTf_2 as the solvent) were employed, followed by the addition of catalytic quantities of copper(I) iodide and DMEDA, indole and caesium carbonate (Scheme 77). Despite achieving full conversion to the brominated intermediate, no amination was observed in the second step. To overcome the incompatibility between the two steps the bromination conditions were altered, using catalytic quantities of both $FeCl_3$ and [BMIM]NTF_2 and toluene as the solvent. This allowed for complete bromination after 4 h at 40 °C and, when combined with the copper-catalysed amination reaction the desired coupled product was observed in 45% conversion (determined by ^{1}H NMR analysis of the crude reaction mixture). It was proposed that the low conversion observed in the second step was resultant of the poor solubility of the caesium carbonate base. The addition of water as a co-solvent in the second step greatly enhanced the reaction, leading to near quantitative conversion to the desired C–N coupled product and an isolated yield of 78%.



Scheme 77: One-pot, *para*-directed coupling of anisole and indole. Copper(I) iodide (10 mol%) and DMEDA (20 mol%) were used in the amination reaction and water (40% of reaction volume) was added to the second step.

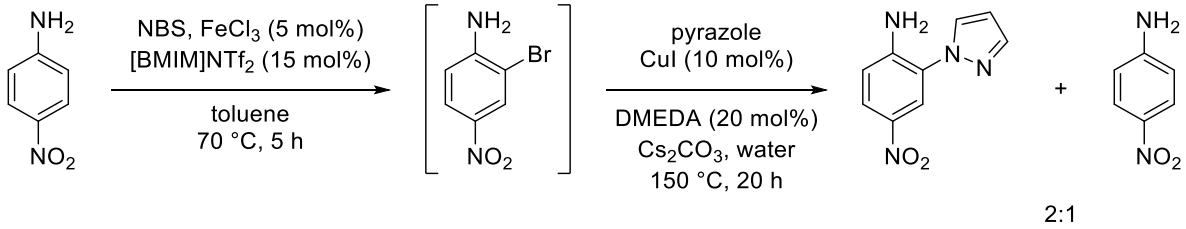
After successful optimisation of the one-pot, two-step process, the substrate scope of the reaction was explored. Firstly, the coupling of anisole to various *N*-nucleophiles was investigated, and subsequent inspection of the arene component was carried out using pyrazole and benzamide as the nucleophiles (Scheme 78). In all cases, *para*-substituted products were formed exclusively in moderate to high

yields, with the methodology proving to be amenable to a range of *N*-heterocycles such as indole, pyrazole, imidazole, pyrrole and pyrrolidin-2-one as well as amides and sulfonamides. In terms of the aryl coupling partner, the one-pot process gave desired products in good yields using various anisoles, phenols, anilines and acetanilides.



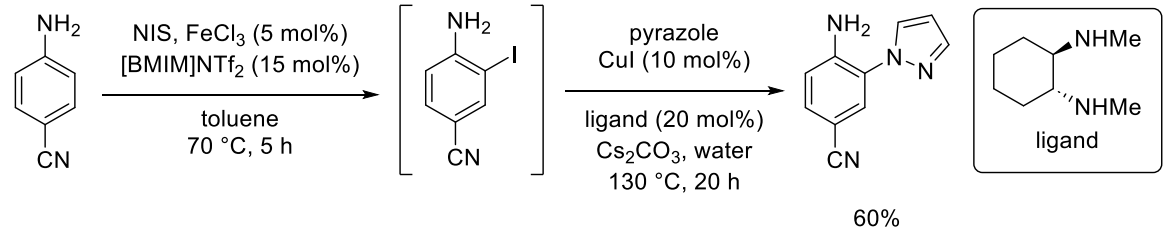
Scheme 78: One-pot, two-step, *para*-C–H amination of arenes. Water (40% of reaction volume) was added to the second step.

Despite proving highly successful for one-pot, two-step *para*-C–H amination reactions, a limitation of this methodology was identified during attempted *ortho*-couplings of *para*-substituted arenes.[74] When 4-nitroaniline was subjected to the optimised reaction conditions, the starting material was returned as a major by-product (Scheme 79). However, ^{1}H NMR analysis of the crude reaction mixture after 5 h at 70 °C confirmed that the bromination step had reached full conversion. As such, it was proposed that the slower Ullman-Goldberg coupling associated with *ortho*-amination had resulted in a competing reaction pathway involving reduction of the organocopper intermediate.



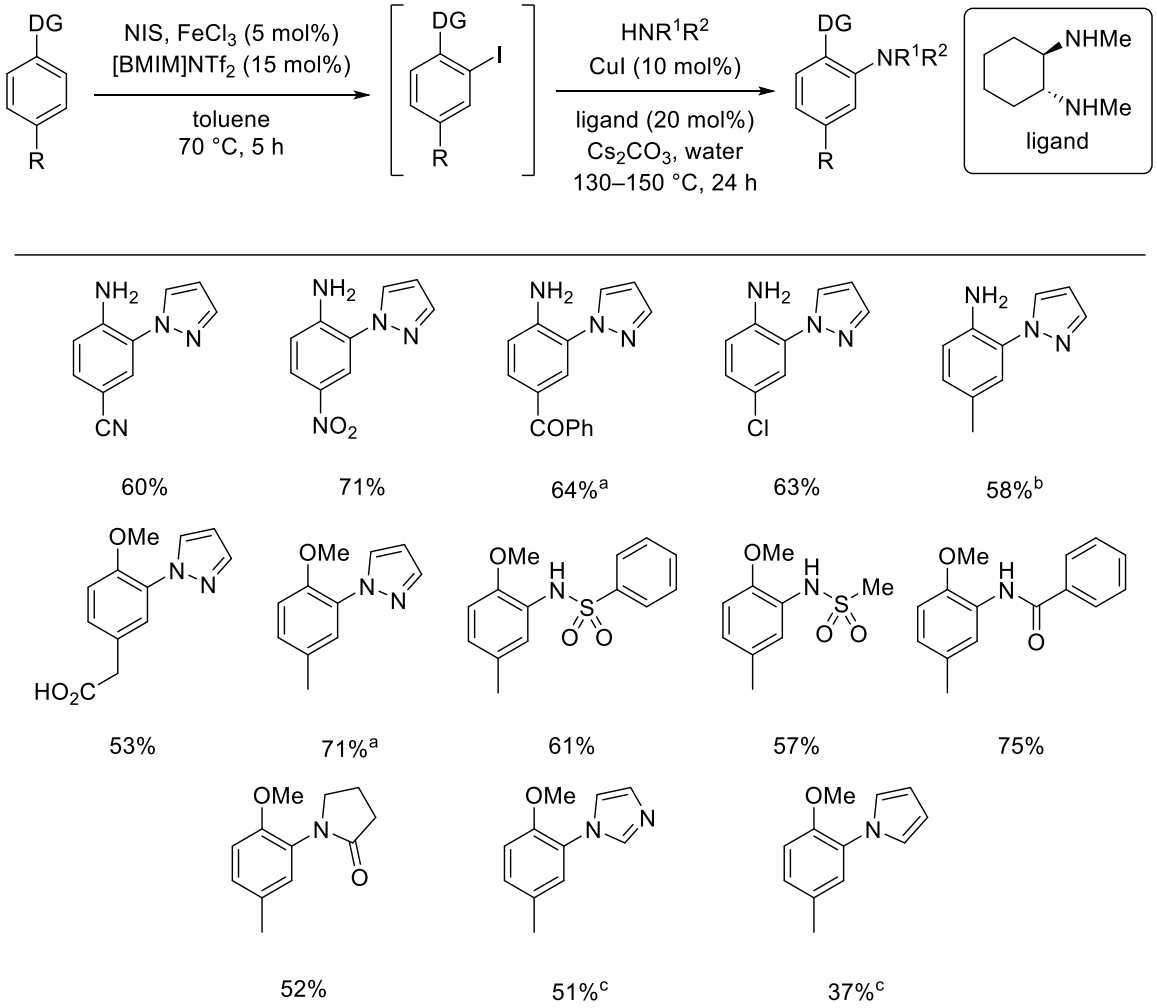
Scheme 79: Attempted *ortho*-amination of 4-nitroaniline.

The group then sought to optimise the one-pot protocol for *ortho*-functionalisation.[101] Firstly, it was proposed that using the more reactive aryl-iodide bond might promote the coupling reaction over the reduction pathway. Whilst this only resulted in a modest improvement under identical conditions, the use of the aryl iodide allowed for the second step to proceed at a lower temperature of 130 °C, giving a 6:1 ratio of the desired coupled product and starting material. Various ligands were then screened in the copper(I)-catalysed step, with hopes of completely suppressing the competing proto-decupration reaction. The studies highlighted that using racemic *trans-N,N*-dimethylcyclohexane-1,2-diamine (20 mol%) as the ligand gave the best results with the desired product being formed in a 12:1 ratio relative to the re-formed starting material. Further optimisation revealed that the generation of only desired product could be achieved by increasing the equivalents of the *N*-nucleophile to 3 versus 1.5 (Scheme 80).



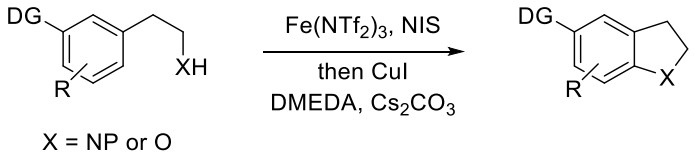
Scheme 80: Optimisation of the one-pot *ortho*-C–H amination process.

The scope of the methodology was then studied, with anisoles, phenols and anilines all proving to be effective arene components, as well as nucleophiles including *N*-heterocycles, amides and sulfonamides serving as effective coupling partners (Scheme 81). The *ortho*-coupled arenes were the sole products, being isolated in moderate to high yields.



Scheme 81: One-pot *ortho*-amination of arenes. [a]Iodination step was complete after 20 h. [b]Iodination step was done at 40 °C. [c]The second step required 36 h.

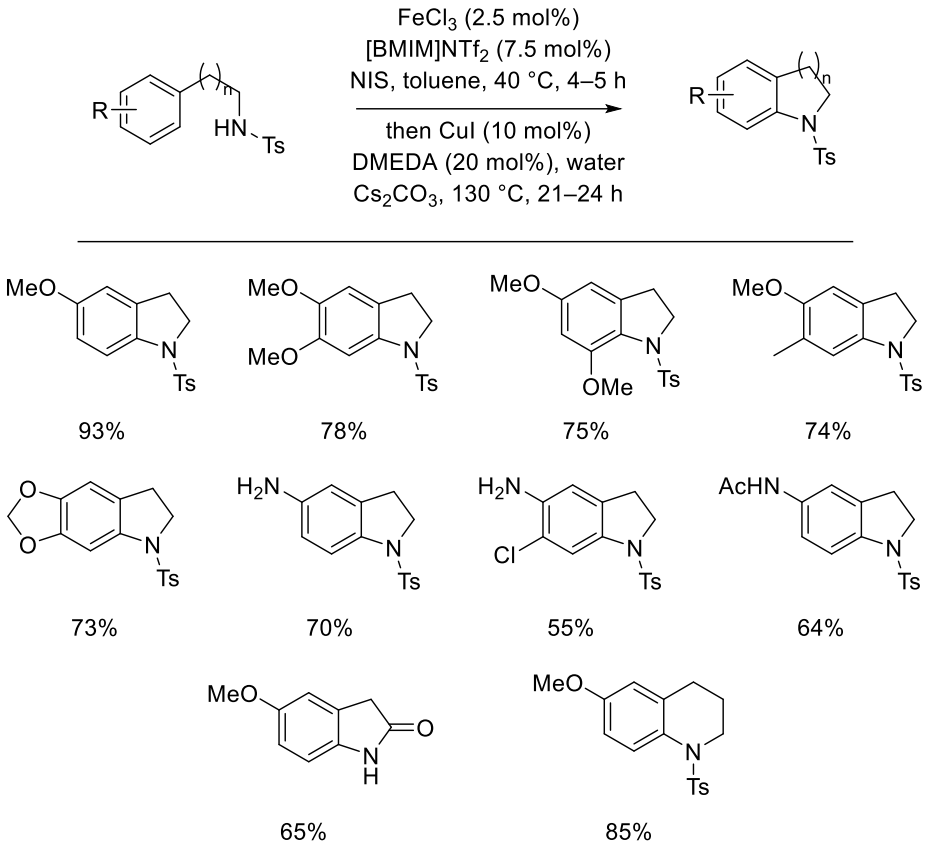
Next, the group looked to extend the methodology, focusing on the formation of intramolecular carbon-nitrogen bonds. It was proposed that indolines and 2,3-dihydrobenzofurans could be prepared from 2-phenylethylamines and 2-phenylethylalcohols, respectively, by a one-pot intramolecular iron(III) triflimide-catalysed iodination and subsequent copper(I)-catalysed cyclisation (Scheme 82).[78]



Scheme 82: Proposed one-pot synthesis of benzannulated heterocycles.

A range of *N*-protecting groups were screened, to identify the *N*-protected 2-phenylethylamine most compatible with the Cu(I)-catalysed *N*-arylation. The tosyl

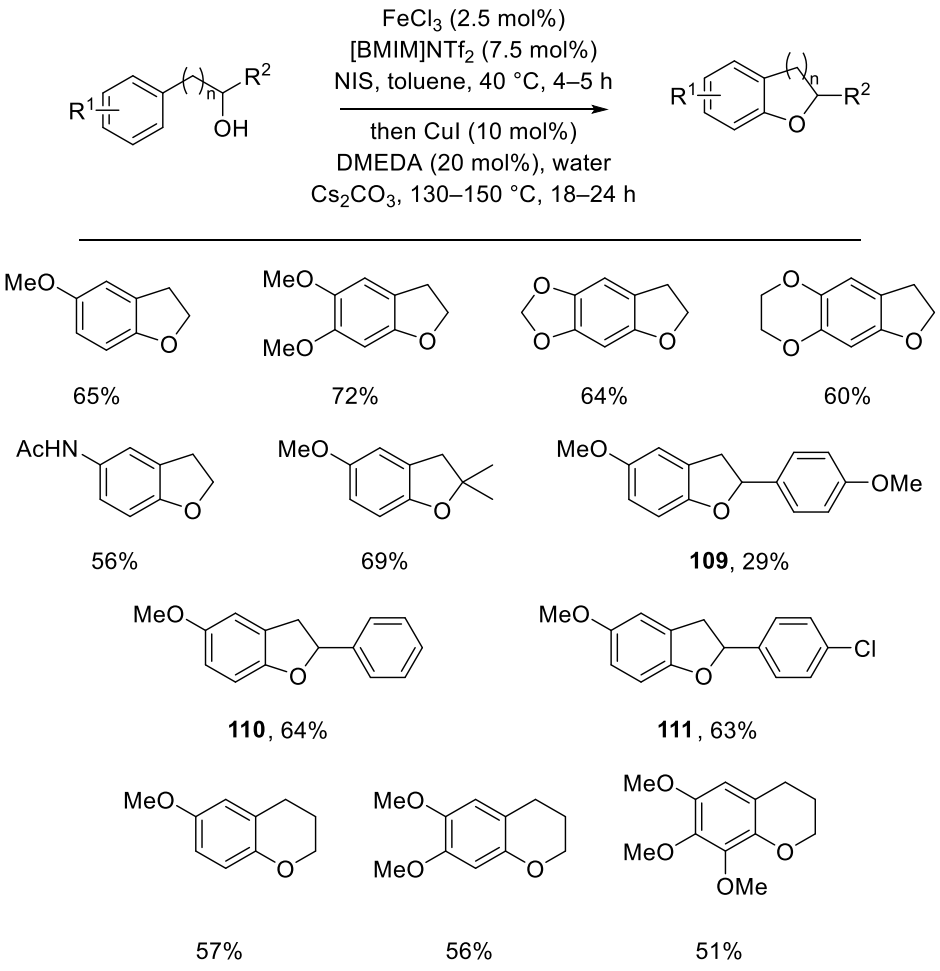
group was found to be the most efficient, with the one-pot activation and cyclisation of *N*-tosyl phenylethylamine furnishing the corresponding indoline in 93% yield. The scope of the one-pot process was explored by varying the aryl activating group, with a range of substituted anisoles, anilines and acetanilides all being converted into the desired indolines in moderate to high yields (Scheme 83). Access to other benzannulated heterocycles such as 2-oxindoles and tetrahydroquinolines were also achieved using this methodology.



Scheme 83: One-pot intramolecular amination.

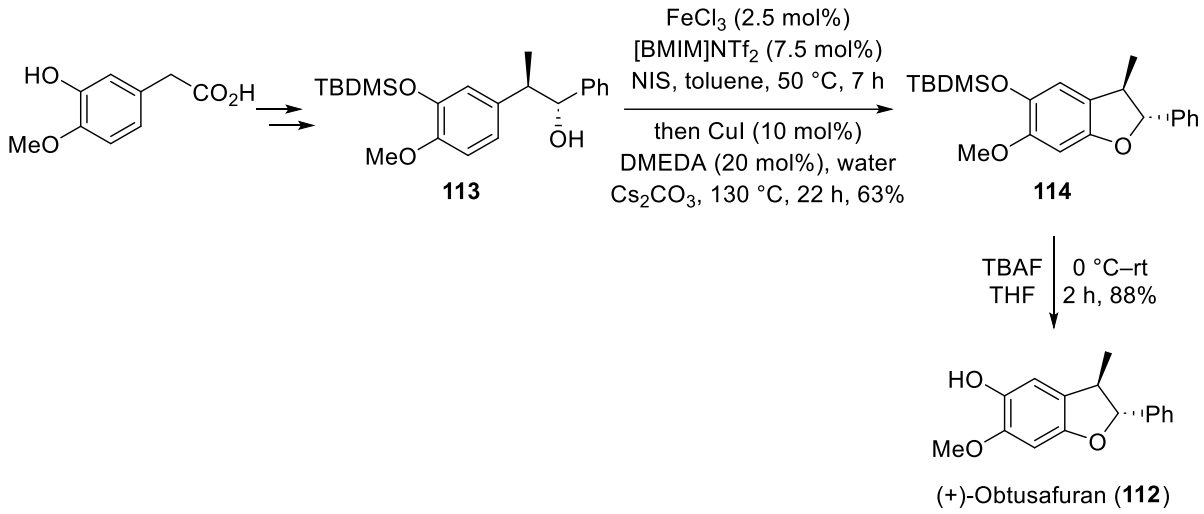
Following on from the successful synthesis of *N*-heterocycles, the group sought to discover whether the one-pot iron(III)-catalysed activation and copper(I)-catalysed cyclisation conditions could be applied for the preparation of dihydrobenzofurans from phenylethyl alcohols (Scheme 84). Whilst the standard iodination conditions worked well, in some cases, the copper(I)-catalysed cyclisation step required a slightly higher temperature of 150 °C to reach full conversion. The scope of the reaction was investigated using a range of substrates with various activating groups, as well as employing primary, secondary and tertiary alcohol nucleophiles. The only limitation was found with compounds containing two activated aryl rings e.g. in the

synthesis of natural product corsifuran A (**109**).[102] The presence of two activated aryl rings results in a mixture of products forming during the iodination step and, resultantly, a low yield of isolated desired product following copper(I)-catalysed cyclisation. However, the use of secondary benzylic alcohols with less activated rings allows for the selective iodination of the 3-methoxyphenyl moiety, giving desired products **110** and **111**, respectively.



Scheme 84: One-pot activation and cyclisation for the synthesis of *O*-heterocycles.

The synthetic utility of the methodology was demonstrated with the total synthesis of (+)-obtusafuran (**112**), a neolignan natural product possessing antiplasmoidal activity[103] and anti-carcinogenic activity (Scheme 85).[104] In the total synthesis, an enantioselective hydrogenation reaction using a base-mediated dynamic kinetic resolution was employed to synthesise a chiral phenethyl alcohol (**113**). The developed one-pot iron(III) triflimide-catalysed iodination and subsequent copper(I)-catalysed cyclisation reaction ensued, generating the desired dihydrobenzofuran (**114**) in 63% yield. Subsequent deprotection furnished (+)-obtusafuran in 88% yield.



Scheme 85: Total synthesis of (+)-obtusafuran (**112**) employing the one-pot, two-step synthesis of benzofurans.

The one-pot intramolecular process has also been extended to the synthesis of benzo[*b*]furans (**115**)[105] and 2-arylbenzoxazoles (**116**)[106] (Figure 11).

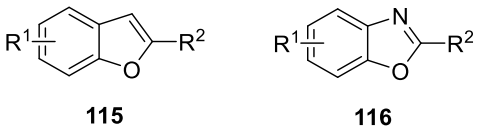
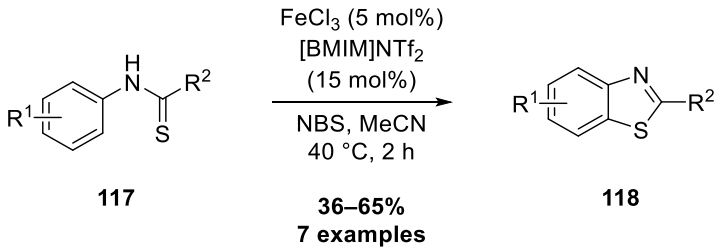


Figure 11: General structures of benzo[*b*]furans and 2-arylbenzoxazoles synthesised *via* iron(III) triflimide and copper(I)-catalysed one-pot, two step activation and cyclisation.

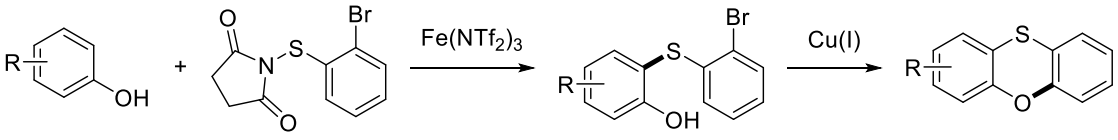
Interestingly, reaction of *N*-arylthiobenzamides **117** with *N*-bromosuccinimide catalysed by iron triflimide led directly to the isolation of the corresponding 2-arylbenzothiazoles (**118**) *via* an intramolecular C–S bond formation (Scheme 86).[106] The proposed mechanism involved bromination of the sulfur atom, followed by C-S bond formation *via* electrophilic aromatic substitution.



Scheme 86: Iron(III) triflimide-catalysed synthesis of 2-arylbenzothiazoles.

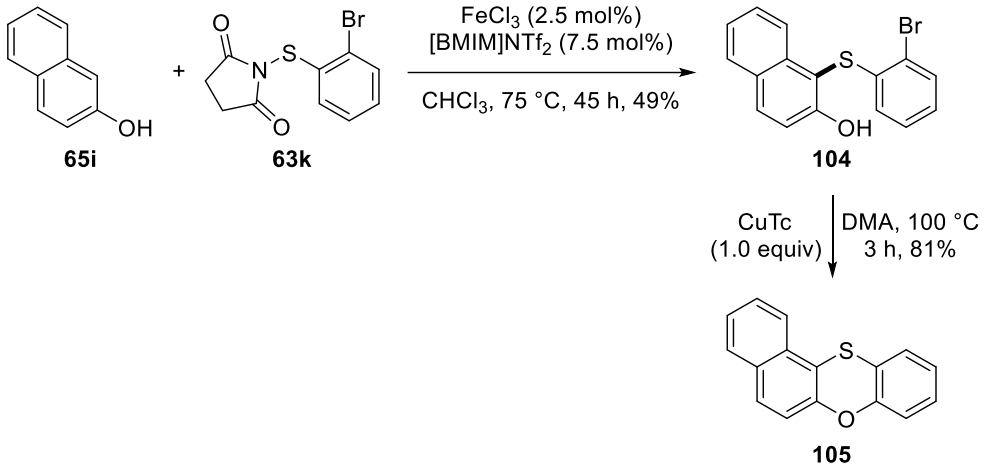
3.3 Project Aims and Proof of Concept

Following the success of previous research in the group, in combining iron-catalysed halogenations with other metal-catalysed transformations, particularly cyclisations, the aim of this project was to explore the use of the iron-catalysed thioarylation reaction and the latent utilities of aryl thioethers for the synthesis of more complex systems. During the synthesis of vortioxetine, the resulting thioether, (2'-bromophenyl)(2,4-dimethylphenyl)sulfane (**94**), contained a 2-bromo functionality which was exploited in a Buchwald-Hartwig cross-coupling. From this, we envisaged that synthesising aryl thioethers containing 2-halo functionalities would allow for their conversions into sulfur-based heterocycles, through intramolecular cyclisation. As such, the main objective of this project was to develop a two-step approach for the synthesis of phenoxathiins via the iron(III) triflimide-catalysed *ortho*-thioarylation of phenols, followed by a copper(I)-mediated Ullman-type cyclisation (Scheme 87). The first aim of the project was the optimisation of the two-step process, and subsequent investigation into the substrate scope. Finally, this methodology would be used for the preparation of biologically relevant phenoxathiins, as well as for the late-stage functionalisation of natural-product based phenols.



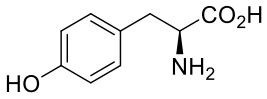
Scheme 87: Proposed synthesis of phenoxathiins.

As a proof of concept, 2-naphthol was subjected to an iron(III) triflimide-catalysed C–H sulfenylation reaction with *N*-(2-bromophenylthio)succinimide, followed by a cyclisation reaction mediated by stoichiometric quantities of copper(I) thiophene-2-carboxylate (Scheme 88). This reaction was chosen due to literature precedent for the cyclisation step,[18] as well as having had already synthesised the *N*-(arylthio)succinimide component for use in the synthesis of vortioxetine. The first step gave the desired aryl thioether in 49% yield after 45 h at 75 °C, and the subsequent copper(I)-mediated C–O cross-coupling reaction furnished benzo[*a*]phenoxathiin (**105**) in 81% yield.



Scheme 88: Synthesis of benzo[*a*]phenoxathiin.

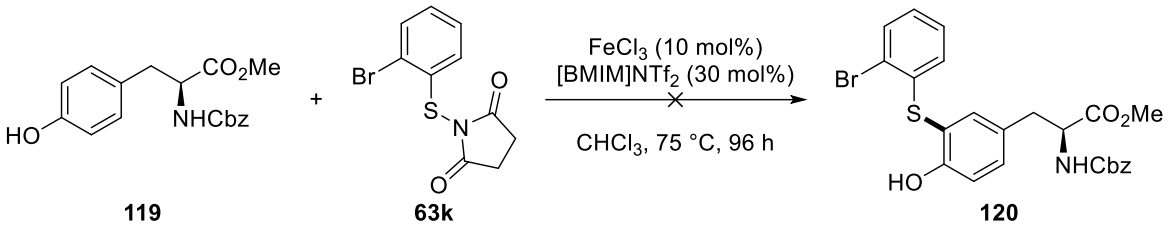
Fluorescent α-amino acids are widely used as probes in chemical biology and medicinal chemistry. Here, small molecule fluorophores feature as amino acid side-chains, allowing for the imaging of peptides and proteins.[107] It follows that, the synthesis of fluorescent amino acids which can be incorporated into proteins and peptides, with minimal disruption to the original structure and function, is an area of high demand. L-Tyrosine is a proteinogenic amino acid which displays fluorescent properties (Figure 12).[108] However, the photophysical properties of L-tyrosine are suboptimal for most biological imaging purposes. The amino acid absorbs and emits light in the UV range and has a low molar attenuation coefficient (ε). This means it is a poor fluorescent probe, particularly for *in vivo* applications where the use of UV light for excitation has the potential to damage the biological system. Despite this, the need for small molecule fluorescent probes similar in size to proteinogenic amino acids, makes L-tyrosine a good starting point for further functionalisation. With this in mind, it was proposed that iron(III) triflimide catalysed thioarylation reactions of L-tyrosine, and subsequent copper(I) mediated cyclisation could lead to the synthesis of a new class of fluorescent phenoxathiin derived α-amino acids.



L-Tyrosine
λ_{abs} = 275 nm
λ_{em} = 310 nm
ε = 1.41 × 10^3 $M^{-1}cm^{-1}$
Φ = 0.14

Figure 12: Naturally occurring fluorescent amino acid L-tryptophan.

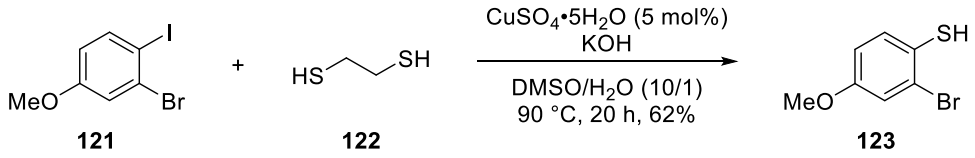
As such, it was decided to try this reaction sequence using *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester (**119**), with the idea of potentially synthesising fluorescent phenoxathiin-derived α-amino acids (Scheme 89). Unfortunately, this reaction was unsuccessful even at the highest catalyst loading of 10 mol% $FeCl_3$ and 30 mol% $[BMIM]NTf_2$ and with a reaction time of 96 h. Since desired product was formed in the reaction between *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester with *N*-(4-methoxyphenylthio)succinimide, it was suggested that the reaction failed due to the electron poor nature of *N*-(2-bromophenylthio)succinimide.



119 **63k** **120**

Scheme 89: Attempted thioetherification of *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester with *N*-(2-bromophenylthio)succinimide.

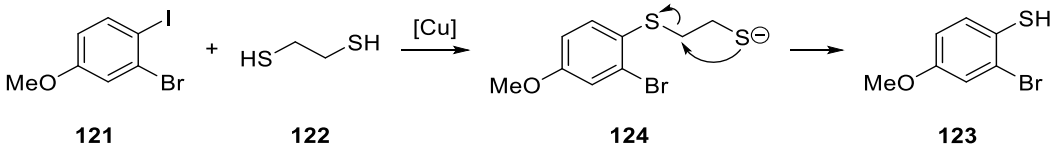
As such, the reaction was repeated with a more electron rich coupling partner, *N*-(2-bromo-4-methoxyphenylthio)succinimide (**63l**). However, the thiol required to make this coupling partner, 2-bromo-4-methoxythiophenol (**123**), was not commercially available. Instead, it was synthesised from 3-bromo-4-iodoanisole (**121**) using a copper(II)-catalysed thiolation, reported by Chae and co-workers (Scheme 90).[109]



121 **122** **123**

Scheme 90: Thiolation of 3-bromo-4-iodoanisole with 1,2-ethanedithiol.

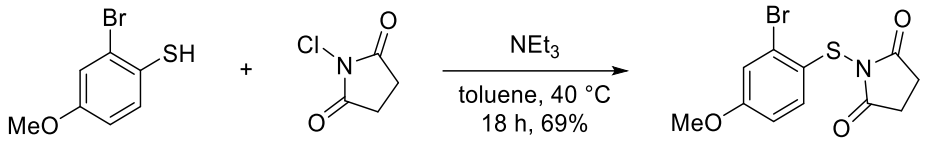
It is proposed that the C–S bond between the aryl halide (**121**) and aliphatic 1,2-ethanedithiol (**122**) is formed in the presence of the copper catalyst to give an aryl alkyl sulfide (Scheme 91). The alkyl chain is then cleaved from the intermediate *via* an 'intramolecular S_N2' reaction by the terminal alkyl thiolate (**124**) under basic conditions.[109]



121 **122** **124** **123**

Scheme 91: Proposed reaction mechanism for the formation of 2-bromo-4-methoxythiophenol from 3-bromo-4-iodoanisole.

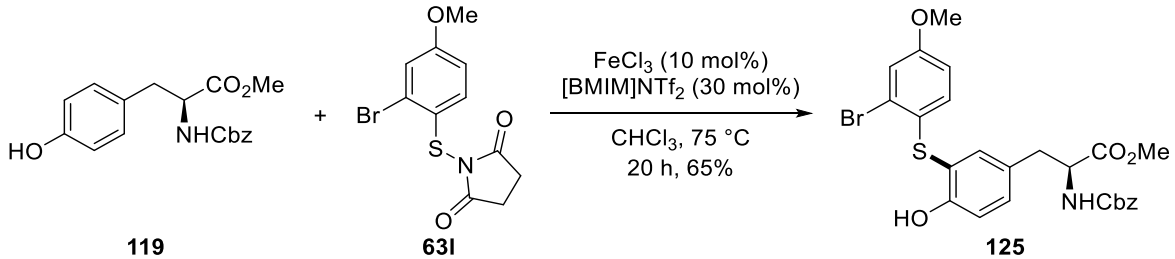
Following the successful synthesis of 2-bromo-4-methoxythiophenol (**123**), this was converted to the corresponding *N*-(arylthio)succinimide through reaction with *N*-chlorosuccinimide (Scheme 92).



123 **63l**

Scheme 92: Synthesis of *N*-(2-bromo-4-methoxyphenylthio)succinimide.

The iron(III) triflimide-catalysed thioetherification of tyrosine derivative **119** with *N*-(arylthio)succinimide **63l** was attempted. Fortunately, this reaction furnished the desired thioether (**125**) in 65% yield (Scheme 93). A catalyst loading of 10 mol% $FeCl_3$ and 30 mol% [BMIM]NTf_2, and a temperature of 75 °C was required for this reaction to overcome the steric barrier associated with *ortho*-sulfenylation of the arene, as well as to compensate for the presence of the electron withdrawing bromine substituent on the coupling partner.

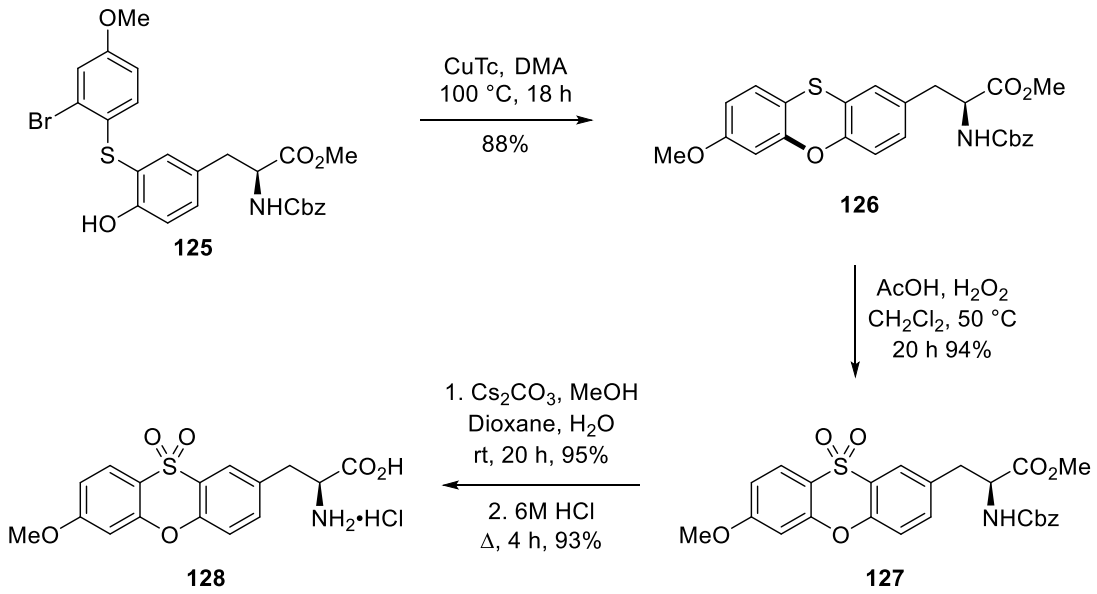


119 **63l** **125**

Scheme 93: Thioetherification of *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester with *N*-(2-bromo-4-methoxyphenylthio)succinimide.

From here, the aforementioned copper mediated C–O cross-coupling reaction was successfully employed to obtain the corresponding phenoxathiin **126** in 88% yield (Scheme 94). Next, oxidation of the heterocycle using hydrogen peroxide gave

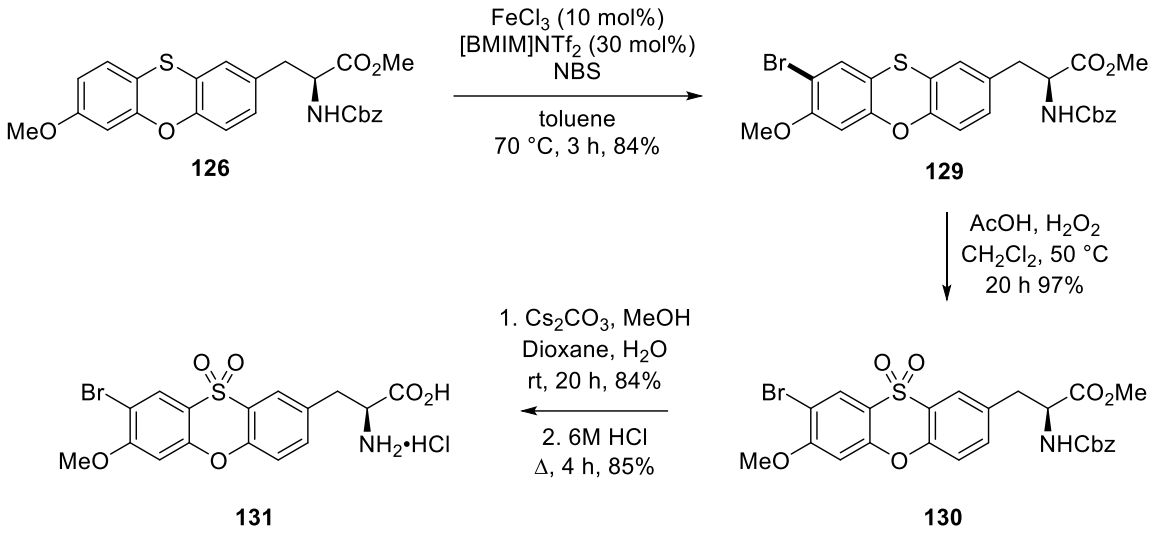
phenoxathiin-10,10-dioxide **127** in a 94% yield. It was proposed that introduction of the sulfone moiety would result in the establishment of a push-pull system within the molecule. It was envisaged that the combination of the electron donating 5'-oxygen atom alongside the electron withdrawing 10'-sulfone functionality would lead to a donor-π-acceptor system. This would allow for intramolecular charge transfer, and lead to favourable photophysical properties. Subsequent ester hydrolysis, followed by acid-mediated removal of the Cbz-group allowed for the isolation of the parent phenoxathiin derived α-amino acid (**128**) in 48% overall yield from tyrosine **119**. Establishment of a robust deprotection strategy was vital, with the deprotected amino acids being required for subsequent incorporation into peptides and proteins.



Scheme 94: Synthesis of phenoxathiin derived α-amino acids.

Additionally, the iron(III) triflimde-catalysed halogenation reaction previously developed within the Sutherland group was employed for the diversification of protected amino acid **126** (Scheme 95).[74] The installation of a bromine atom on the phenoxathiin core provides a functional handle, which can be exploited in cross-coupling reactions, for further functionalisation of the molecule. In terms of fluorescence, reactions such as Suzuki-Miyaura and Heck cross-couplings could be undertaken to extend the conjugation of the system, potentially leading to enhanced photophysical properties. Here, the 7'-methoxy substituent acted as a directing group alongside the 5'-oxygen atom, causing bromination to occur regioselectively at the 8'-position, furnishing **129** in 84% yield after 3 h at 70 °C. The heterocycle was oxidised, as before, and then the same deprotection strategy was employed to

deliver (2*S*)-2-amino-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (**131**).



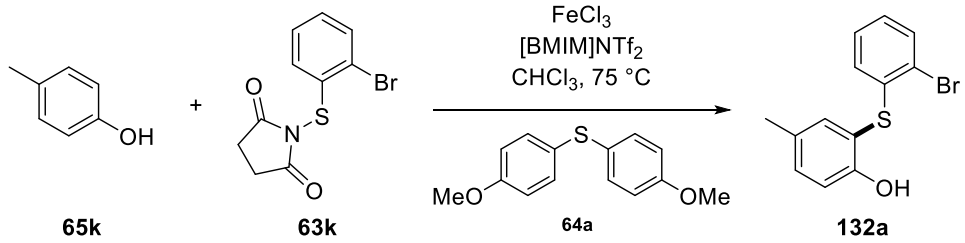
Scheme 95: Diversification of phenoxathiin **126**, resulting in the formation of (2*S*)-2-amino-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (**131**).

3.4 Optimisation Studies for the *ortho*-C–H Sulfenylation of *para*-Cresol and Subsequent C–O Bond Forming Cyclisation Reaction

Although the reaction between 2-naphthol and *N*-(2-bromophenylthio)succinimide gave the desired arylthioether in 49% yield after 45 h at 75 °C, using 2.5 and 7.5 mol% $FeCl_3$ and $[BMIM]NTf_2$, respectively (Scheme 88), it was proposed that optimisation studies should be undertaken to try and identify conditions which would allow complete *ortho*-sulfenylation of activated arenes in a reasonably short reaction time, whilst also delivering the desired products in good yields.[110]

Optimisation studies focused on the reaction of *p*-cresol (**65k**) with *N*-(2-bromophenylthio)succinimide (**63k**) (Table 2). Since the thioarylation of 2-naphthol took 45 h with a catalyst loading of 2.5 mol% $Fe(NTf_2)_3$, it was hypothesised that a higher catalyst loading would provide a more efficient reaction. As such, the first set of conditions used 10 and 30 mol% $FeCl_3$ and $[BMIM]NTf_2$, respectively, with chloroform as the solvent and a temperature of 75 °C. After 24 h, no further conversion was observed by ^{1}H NMR analysis of the crude reaction mixture, and the desired product **132a** was obtained in a 38% yield. This result highlighted the need for a more efficient catalyst system, to tackle the steric constraints associated with *ortho*-sulfenylation. The work done on the previous iron(III)-catalysed thioarylation reaction was revisited.[77] Here, kinetic experiments had revealed that

reactions involving electron rich arenes and *N*-arylthiosuccinimides proceed autocatalytically. In particular, the experiments uncovered that the resulting electron rich biaryl sulfide products acted as Lewis base catalysts, resulting in accelerated reactions. Based on this observation, it was proposed that the addition of an electron rich biaryl sulfane could result in an improved reaction. The reaction was repeated with the addition of commercially available *bis*(4-methoxyphenyl)sulfane (**64a**) as a Lewis base catalyst (10 mol%). After only 0.5 h, the reaction was complete, giving **132a** in 81% yield (entry 2). To confirm that the reaction was accelerated due to the presence of the dual Lewis-acid/Lewis-base catalytic system, a control experiment was performed using only the Lewis base (entry 3). After 24 h, no reaction was observed. As expected, no reaction resulted with [BMIM]NTf_2 alone (entry 4) or in the absence of any catalyst (entry 5).



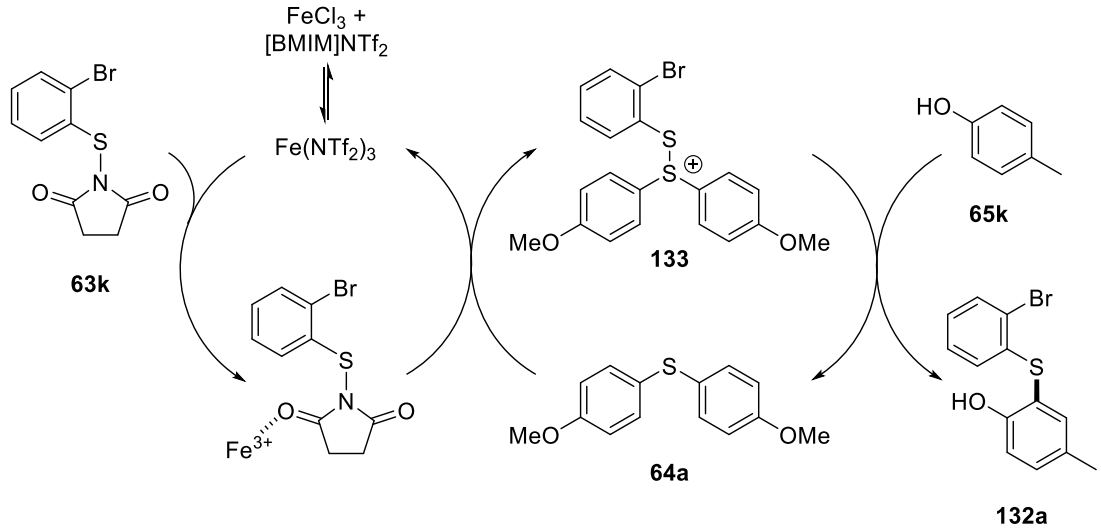
65k **63k** **64a** **132a**

Entry	$FeCl_3$ (mol%)	[BMIM]NTf_2 (mol%)	**64a** (mol%)	Time (h)	Yield (%)
1	10	30	–	24	38
2	10	30	10	0.5	81
3	–	–	10	24	–
4	–	30	–	24	–
5	–	–	–	24	–

Table 2: Optimisation studies for the *ortho*-thioarylation of *para*-cresol.

The proposed mechanism for this transformation is outlined in Scheme 96. The combination of iron(III) chloride and [BMIM]NTf_2 leads to the formation of the super Lewis acid, $Fe(NTf_2)_3$. The Fe^{3+} cation activates the *N*-(2-bromophenylthio)succinimide through coordination of the carbonyl oxygen. The activated *N*-(arylthio)succinimide can then react with the phenol *via* an electrophilic aromatic substitution reaction, however, this reaction proceeds slowly (Table 2, entry 1). Instead, reaction with the Lewis base, *bis*(4-methoxyphenyl)sulfane proceeds

much faster, forming a cationic di-sulfide intermediate (**133**). As a charged species, this is notably more reactive than the activated *N*-(arylthio)succinimide and reacts with the phenol to form the desired *ortho*-thioarylated product **132a**, and regenerate the Lewis base catalyst. Kinetic experiments undertaken in our previous work on iron(III) triflimide-catalysed thioarylation support the presence of a reactive intermediate.[77] Here, we observed conversion graphs with sigmoidal shapes for the reactions involving electron rich starting materials. This signifies an initial induction period whereby an activated intermediate is formed prior to rate acceleration. When the kinetic experiments were repeated with reactions which had a Lewis base biaryl sulfide (10 mol%) added from the beginning, the reaction displayed first-order kinetics, further confirming the presence of an activated sulfide intermediate in the reaction mechanism. Gustafson and co-workers have also suggested cationic disulfide intermediates are present during their thioarylation processes.[57,51]

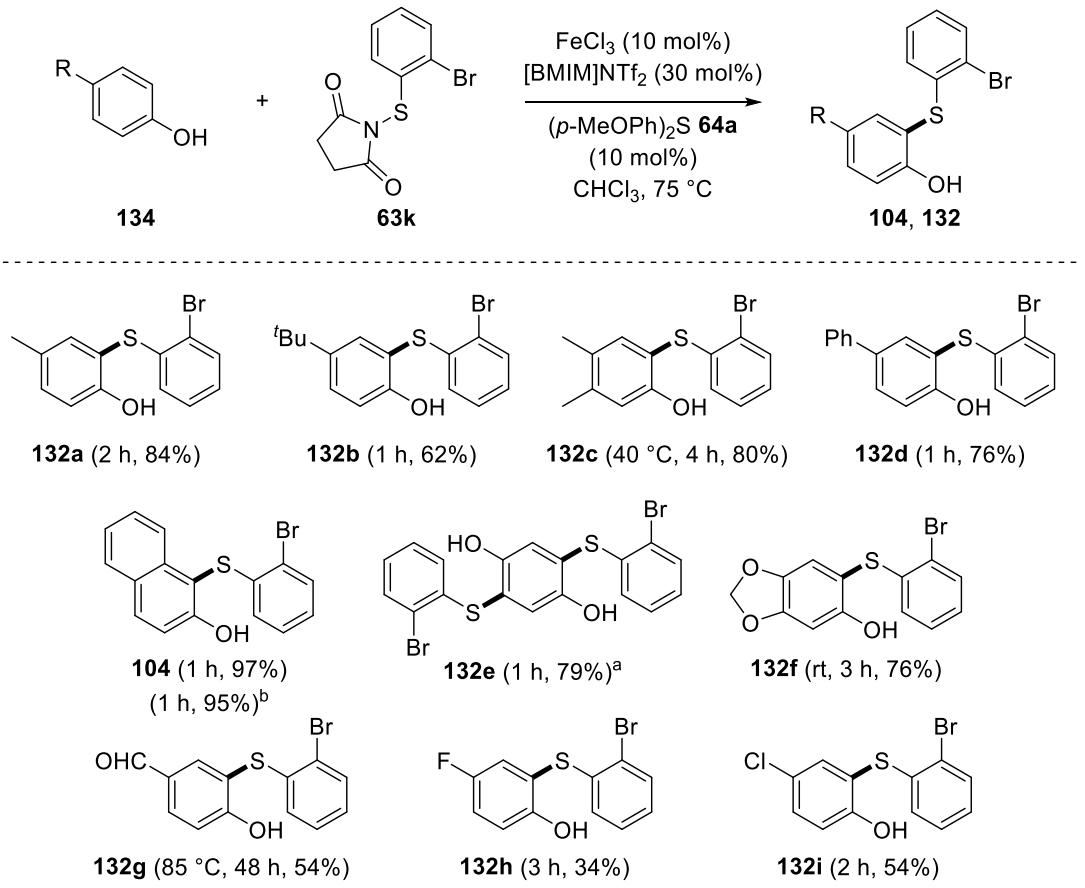


Scheme 96: Proposed mechanism for the dual Lewis acid/Lewis base catalysed thioarylation reaction.

3.5 Substrate Scope

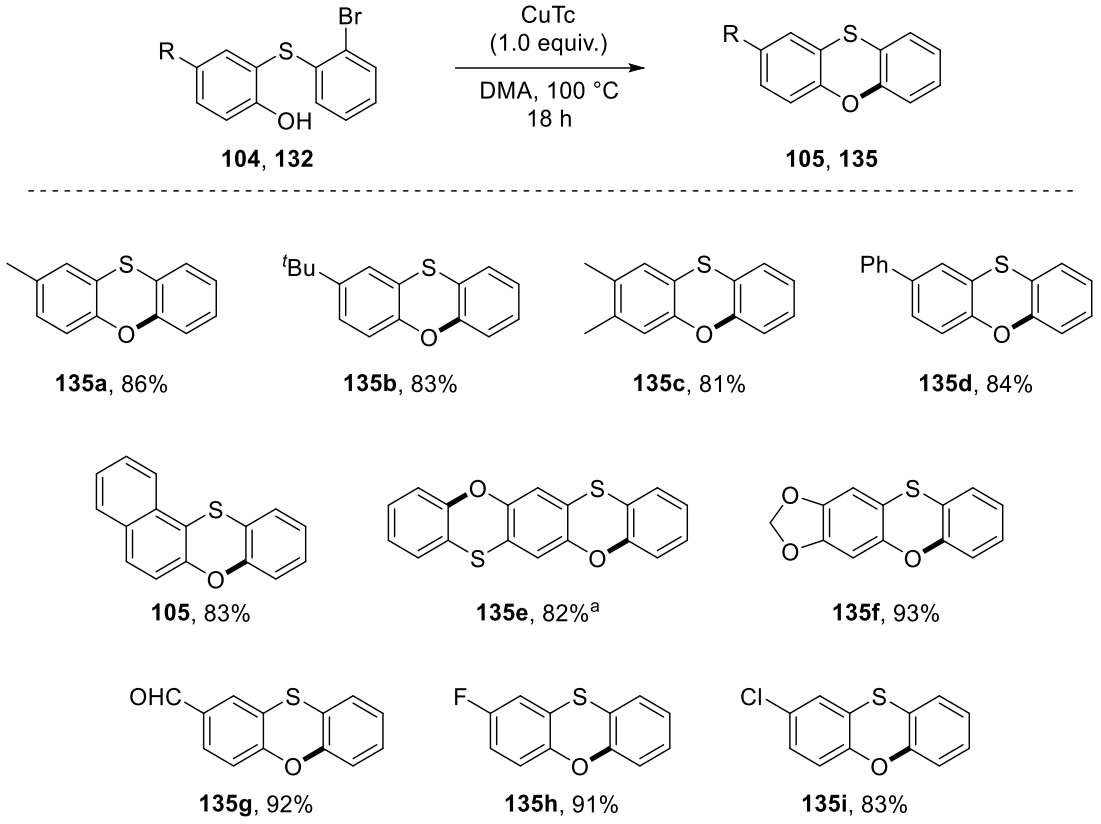
Following successful optimisation and establishment of a potential mechanism for the transformation, the scope of the Lewis acid/Lewis base catalysed *ortho*-thioarylation reaction was explored (Scheme 97). The methodology was found to be amenable for phenols bearing electron-rich and electron-deficient substituents. For most phenols containing alkyl or aryl substituents, the reactions were fast and efficient, yielding the desired aryl thioethers in moderate to good yields. For highly activated phenols such as 3,4-dimethylphenol and sesamol, reactions proceeded at

lower temperatures whilst maintaining short reaction times and high yields of desired products (**132c** and **132f** respectively). When hydroquinone was exposed to the optimised reaction conditions, di-substitution was observed. We chose to exploit this observation and optimised the reaction to investigate bi-directional thioarylation. When 2.2 equivalents of *N*-(2-bromophenylthio)succinimide was used in the reaction, the desired di-substituted product (**132e**) was isolated in 79% after 1 h at 75 °C. Conversely, the reaction required a higher temperature of 85 °C and a longer reaction time of 48 h for the effective C–H sulfenylation of 4-hydroxybenzaldehyde (54%). The methodology was also found to be amenable to phenols bearing halogens, with 4-fluoro and 4-chlorophenol both successfully being coupled to give desired aryl thioethers **132h** and **132i** in 34% and 54% yield, respectively. Additionally, when 2-naphthol was subjected to the optimised reaction conditions on a 5 mmol scale, a comparable yield of **104** was observed relative to the small-scale reaction (95% vs 97%).



Scheme 97: Substrate scope of phenols. [a]2.2 equivalents of *N*-(2-bromophenylthio)succinimide were used. [b]Reaction performed on a 5 mmol scale.

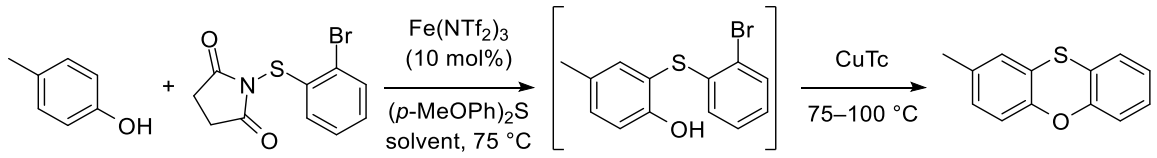
The resulting aryl thioethers were then converted to the corresponding phenoxathiins *via* a copper(I) thiophene-2-carboxylate (CuTc) mediated cyclisation reaction under standard conditions (Scheme 98). The cyclisation reaction was highly efficient, furnishing the desired products in high yields irrespective of the substituents and substitution pattern. The use of 2.0 equivalents of CuTc allowed for the effective bi-directional synthesis of 5,12-dioxa-7,14-dithiapentacene (**135e**) from **132e**.



Scheme 98: CuTc mediated cyclisation reaction to synthesise phenoxathiins. [a]2.0 equivalents of CuTc were used.

Efforts were made to try and combine the Lewis acid/Lewis base catalysed thioarylation with the copper(I)-mediated cyclisation reaction to develop a one-pot process (Table 3). Despite a range of different solvents being screened, none could be found to allow compatibility between the two steps. Unfortunately, the iron(III) triflimide-catalysed thioarylation reaction was unsuccessful using *N,N*-dimethylacetamide (DMA) (the optimal solvent for the cyclisation step). Likewise, the copper(I) thiophene-2-carboxylate reagent was insoluble in chloroform resulting in no reaction following thioarylation with this solvent. Optimisation studies performed on the iron(III) triflimide-catalysed thioarylation reaction of anisole with *N*-

(4-methoxyphenylthio)succinimide identified acetonitrile as an alternative solvent for the reaction. However, once again this solvent was unable to solubilise the CuTc reagent. The group had previously managed to combine an iron(III) triflimide-catalysed halogenation reaction with a copper(I)-catalysed amination reaction using toluene as a solvent, however, when this was employed for the attempted one-pot, two-step synthesis of phenoxathiins, no reaction resulted due to the insolubility of the *N*-(2-bromophenylthio)succinimide.



65k **63k** **132a** **135a**

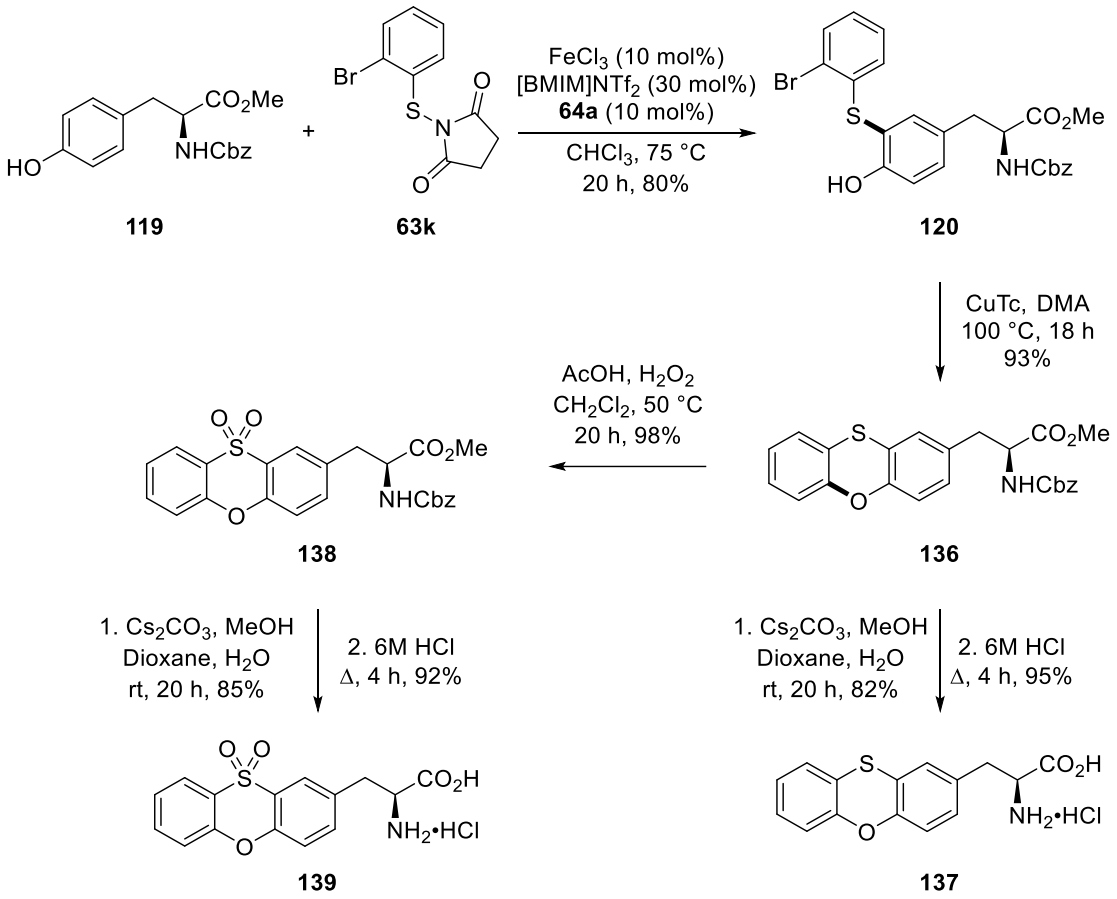
Entry	Solvent	Conversion to **132a** (%)	Conversion to **135a** (%)	Yield (%)
1	DMA	0	0	0
2	Chloroform	100	0	0
3	Acetonitrile	100	0	0
4	Toluene	0	0	0

Table 3: Solvent screen to investigate the one-pot synthesis of phenoxathiins.

3.6 Synthesis of Phenoxathiin Derived α-Amino Acids

After successfully establishing a two-step synthesis of phenoxathiins, the synthetic utility of the transformation was explored. Firstly, the reaction of *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester (**119**) with *N*-(2-bromophenylthio)succinimide was re-attempted (Scheme 99). As previously discussed, no reaction was observed between these compounds using only iron(III) triflimide with a catalyst loading of 10 + 30 mol% $FeCl_3$ and [BMIM]NTf_2, respectively. However, when iron(III) triflimide (10 mol%) was used in combination with *bis*(4-methoxyphenyl)sulfane (10 mol%), the desired aryl thioether (**120**) was obtained in 80% yield. Copper(I) thiophene-2-carboxylate was then used to construct the phenoxathiin core, giving **136** in 93% yield. Deprotection *via* ester hydrolysis and acid-mediated Cbz-removal ensued, furnishing the desired α-amino acid **137** in 58% yield from **119**. Diversification of **136** was achieved by oxidising the aryl sulfide to the corresponding sulfone (**138**) using hydrogen peroxide and glacial acetic acid.

The analogous phenoxathiin-dioxide derived α-amino acid (**139**) was then obtained in 57% overall yield by following the same deprotection method.



Scheme 99: Synthesis of phenoxathiin derived α-amino acids.

It was proposed that the phenoxathiin derived α-amino acids synthesised using the developed methodology could potentially function as fluorescent amino acids, allowing for use as fluorescent probes for chemical biology. The fluorescent properties of the phenoxathiin-dioxide analogue **139** were initially analysed. Here, it was proposed that the electron withdrawing sulfone functionality, in combination with the electron donating oxygen heteroatom, would result in an effective donor-π-acceptor moiety, allowing for intramolecular charge transfer, and resulting in favourable photophysical properties. Firstly, the absorbance and emission spectra of **139** were investigated (Figure 13). The absorbance maxima for **139** was 295 nm, with the emission maxima appearing at 320 nm.

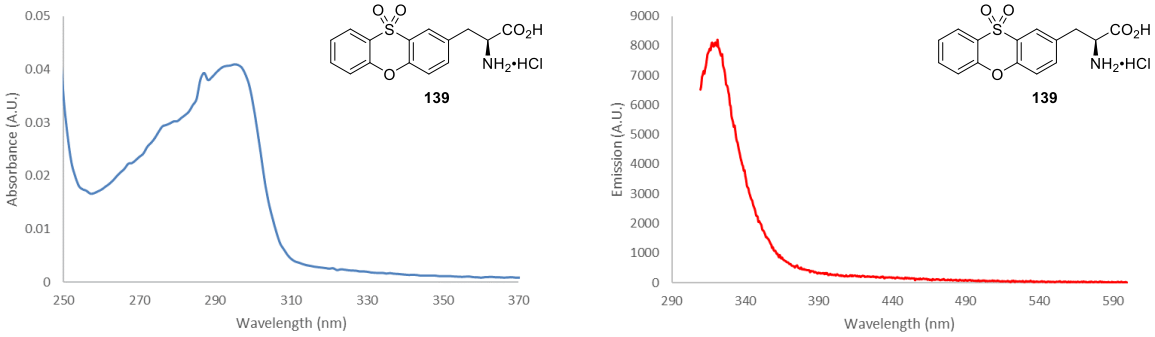


Figure 13: Absorbance and emission spectra for amino acid **139**. Measured in MeOH at 10 μM, excitation at 295 nm.

Following measurement of the absorption and emission spectra for **139**, further investigation of the photophysical properties were undertaken (Table 4). Molar attenuation coefficients (ε) and quantum yields (Φ) were measured to determine the brightness. The molar attenuation coefficient gives a measure of how strongly a molecule absorbs light at a given wavelength, and was calculated by plotting a graph of the absorbance values *vs* the concentration of the samples at which the measurements were taken. The quantum yield was calculated using tryptophan as a standard. This was achieved by measuring the absorbance and emission of tryptophan and **139** at five known concentrations, and then plotting a straight line of the integrated fluorescence intensity *vs* absorbance. The quantum yield could then be calculated by comparing the gradients of the two lines using Equation 1.

$$\phi_x = \phi_{ST}\left(\frac{Grad_{ST}}{Grad_X}\right)\left(\frac{\eta_x^2}{\eta_{ST}^2}\right)$$

Equation 1: Equation for the comparative determination of quantum yield. ST = standard. X = novel compound. Grad = gradient. η = refractive index of the solvent. η = 1.333 for water, 1.361 for ethanol and 1.331 for methanol.

Another important property to consider is the Stokes shift, which is a measure of the difference in wavelength between the absorption maximum and emission maximum. Here, the Stokes shift for the phenoxathiin-dioxide amino acid, **139**, was 25 nm. Ideally, a large Stokes shift is desirable to minimise the reabsorption of emitted light. Additionally, for use in biological imaging, chromophores which can be excited at long wavelengths are favoured, to minimise any damage caused to the biological

system. Here both the absorption and emission maxima wavelengths lie in the UV region. Furthermore, the quantum yield and brightness values for **139** are sub-optimal, confirming that **139** would be unlikely to operate efficiently as a fluorescent amino acid to visualise cells.

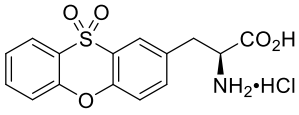
Compound	Absorption Maximum (nm)	Emission Maximum (nm)	Stokes Shift (nm)	Molar Attenuation Coefficient (cm^{-1} M^{-1})	Brightness (cm^{-1} M^{-1})	Quantum Yield
 **139**	295	320	25	12200	290	0.024

Table 4: Photophysical properties of **139** in methanol.

The absorption and emission spectrum of (2*S*)-2-amino-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (**128**) was next investigated. It was believed that the addition of an electron donating 7'-methoxy substituent would accentuate the push-pull system and lead to better photophysical properties. Unfortunately, upon inspection of the absorbance and emission spectra, it was clear that the introduction of the 7'-methoxy substituent had not led to any red-shift in absorption or emission wavelengths. Additionally, the emission maxima for this analogue appears substantially weaker than that of **139** (Figure 14). Despite not having made an analogue which enhanced the fluorescence properties of the parent phenoxathiin-dioxide, a robust synthesis towards these phenoxathiin-dioxide derived α-amino acids was developed with scope for further functionalisation, e.g. installation of halogen functional handles (**129**). This could be exploited to install functionalities capable of extending the conjugation of the system and potentially improve the photophysical properties.

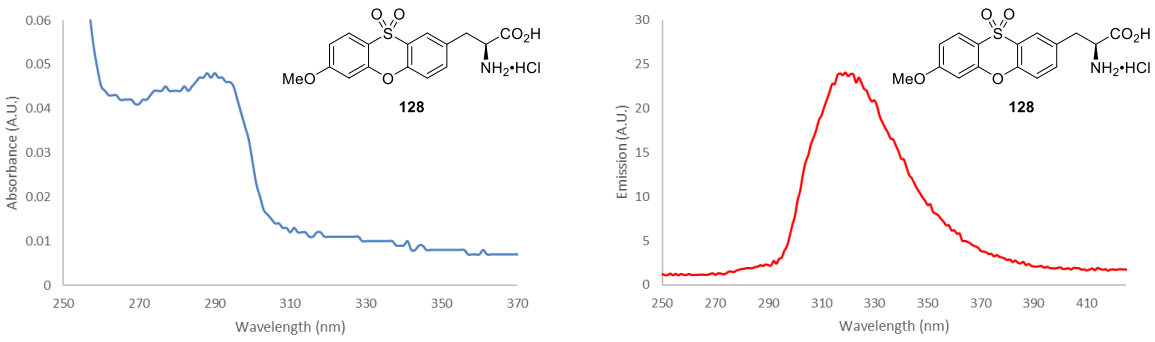
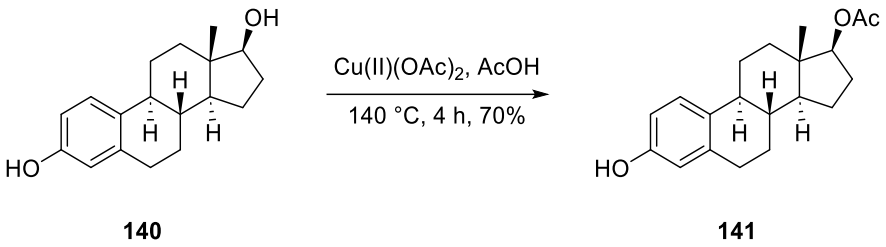


Figure 14: Absorbance and emission spectra for amino acid **128**. Measured in MeOH at 10 μM, excitation at 295 nm.

3.7 Synthesis of Phenoxathiin Derived Steroid

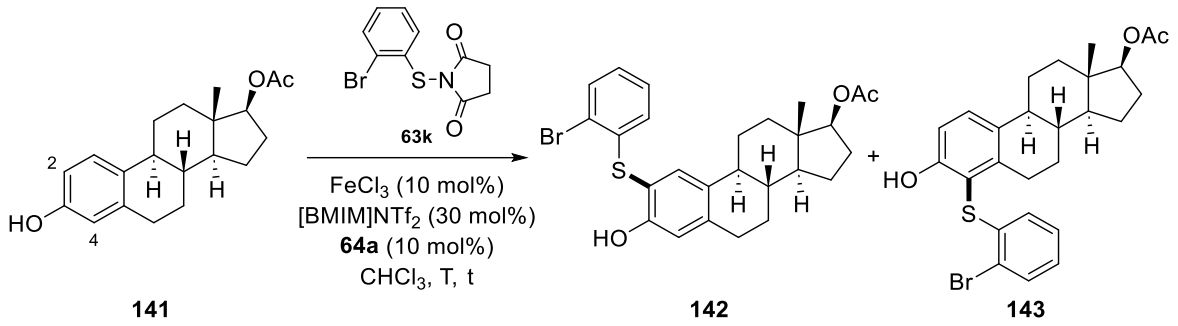
Next, the iron(III) triflimide/*bis*(4-methoxyphenyl)sulfane dual-catalytic system was investigated for the late stage functionalisation of biologically relevant molecules. Validating the methodology as an efficient approach for the thioarylation and cyclisation of highly functionalised, complex substrates would prove appealing in the field of drug discovery. This would allow for the late-stage modification of biologically active, phenolic compounds, synthesising analogues which may possess novel physiochemical and biological properties. As such, the two-step protocol was applied to β-estradiol (**140**), which is an estrogen steroid hormone. Firstly, the secondary alcohol functionality was acetyl protected using Cu(II)-catalysis to give β-estradiol-17-acetate (**141**) (Scheme 100).[111]



140 **141**

Scheme 100: Cu(II)-catalysed acetyl protection of β-estradiol (**140**).

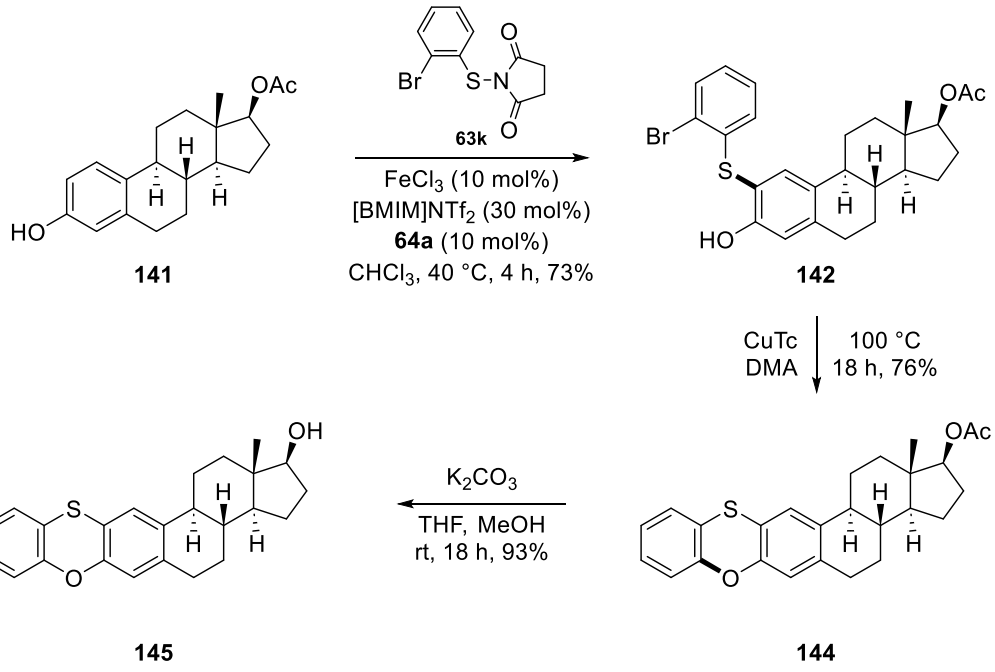
β-Estradiol derivative **141** was then subjected to the optimised thioarylation conditions. Despite all previous thioarylation reactions resulting in a single product, thioarylation of **141** gave a mixture of regioisomers via substitution at the 2- and 4-*ortho* positions (Table 5). Under the standard temperature of 75 °C, the 2- and 4-substituted products (**142** and **143**) were obtained in 62% and 19% yield, respectively, after 18 h. The reaction was then repeated at lower temperatures to try and maximise formation of the more sterically accessible 2-substituted regioisomer, whilst minimising formation of the undesired 4-substituted product. After 4 h at 40 °C the 2- and 4-substituted products were isolated in 73% and 13% yields, respectively. When the reaction was performed at room temperature, only 50% conversion was observed by ^{1}H NMR spectroscopy after 24 h. Additionally, even at this low temperature, the undesired product was still formed.



Entry	Temperature (°C)	Time (h)	Yield **142** (%)	Yield **143** (%)
1	75	18	62	19
2	40	4	73	13

Table 5: Optimisation of the *ortho*-thioarylation of β-estradiol-17-acetate.

From these results it was deemed that 40 °C was the optimal temperature for this reaction. Cyclisation of the resulting aryl thioether using copper(I) thiophene-2-carboxylate followed to give the desired product **144** in 76% yield (Scheme 101). Finally, potassium carbonate was employed for acetyl deprotection, giving the final steroid-containing phenoxathiin (**145**) in 93% yield.

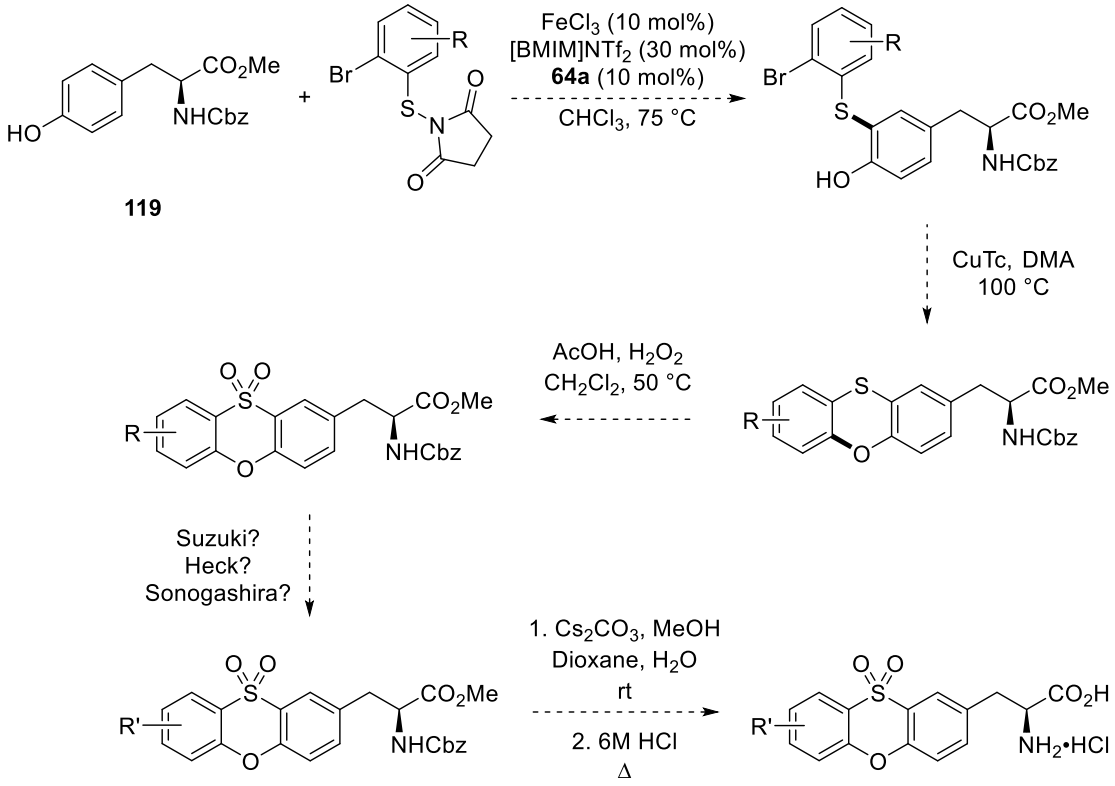


Scheme 101: Synthesis of phenoxathiin derived steroid **145** from β-estradiol-17-acetate (**141**) using iron(III) triflimide/*bis*(4-methoxyphenyl)sulfane-catalysis.

3.8 Conclusions and Outlook

In conclusion, a Lewis acidic/Lewis basic dual catalytic system has been developed, which allowed for the effective *ortho*-thioarylation of *para*-substituted phenols with *N*-(2-bromophenylthio)succinimide. The methodology made use of Lewis acid, iron(III) triflimide and Lewis base, *bis*(4-methoxyphenyl)sulfane, and resulted in the functionalisation of a range of phenols bearing both electron donating and electron withdrawing substituents. Additionally, the thioarylation reaction can be combined with a copper(I)-mediated cyclisation reaction to synthesise phenoxathiins. The synthetic utility of the two-step transformation was demonstrated with the late-stage functionalisation of β-estradiol and the subsequent conversion of the resulting aryl thioether into a phenoxathiin derived steroid. Furthermore, this new approach for the synthesis of phenoxathiins allowed for the synthesis of phenoxathiin derived α-amino acids from tyrosine.

Future work would involve further investigation into the fluorescence properties of phenoxathiin derived α-amino acids (Scheme 102). Synthesis of a library of these compounds containing substituents of different electronic nature, in a variety of positions, would allow insight of the positions/groups contributing to the push-pull system. This information could then be exploited to optimise the photophysical properties e.g. installing halogen substituents for use in Suzuki-Miyaura cross-coupling reactions to extend the conjugation of the system. Extended conjugation of the system could lead to red-shifts in the absorption and emission spectra, giving compounds which are more viable for use in biological systems.



Scheme 102: Potential route towards diversified phenoxathiin-dioxide derived α-amino acids.

4.0 Development of a Two-Step Process for the Synthesis of Phenothiazines

4.1 Introduction to Phenothiazines

Phenothiazines represent another important class of sulfur-based heterocycles, with their derivatives finding extensive use in pharmaceuticals,[112,90] insectisides, optoelectronic materials, antioxidants and photoredox catalysts.[113,114] In particular, the parent compound, phenothiazine (**146**) has been used as an anthelmintic agent for livestock and humans (Figure 15).[115] Additionally, methylene blue (**147**) is a water soluble dye which has been widely used as a treatment for malaria.[116] Furthermore, phenothiazines belong to a class of dopamine receptors antagonists which are used to treat severe mental illness.[90] As such, dimethylaminopropyl analogues of phenothiazines such as chlorpromazine (**148**) are used as anti-psychotic drugs for the treatment of conditions such as schizophrenia.[117] Literature also supports that these dopamine receptors are expressed in various cancer cells, rendering phenothiazines potential candidate molecules for anti-cancer therapy.[90,118] One example of this is thioridazine (**149**) which is used to treat glioblastoma.[119] Due to their versatile nature and widespread utility, the development of efficient and reliable methods for the synthesis of phenothiazines is of great importance.

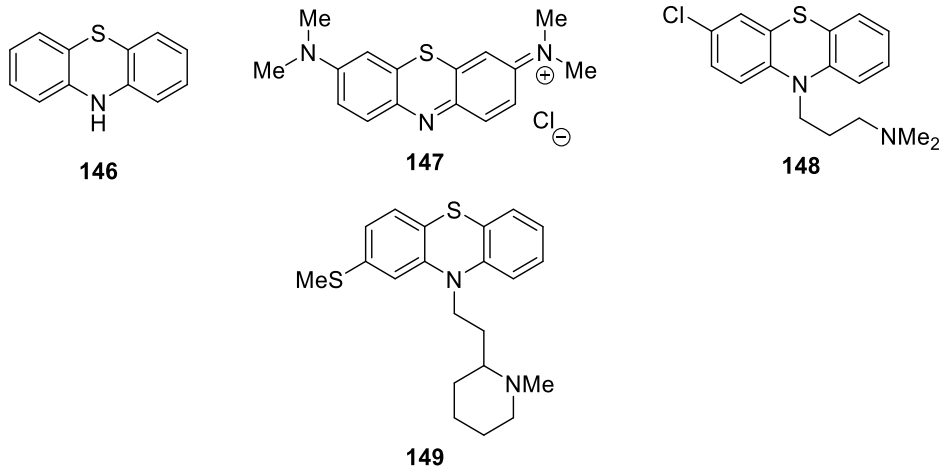
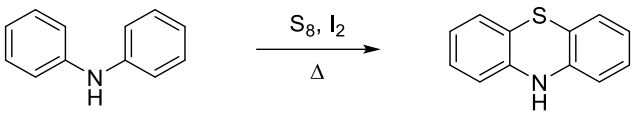


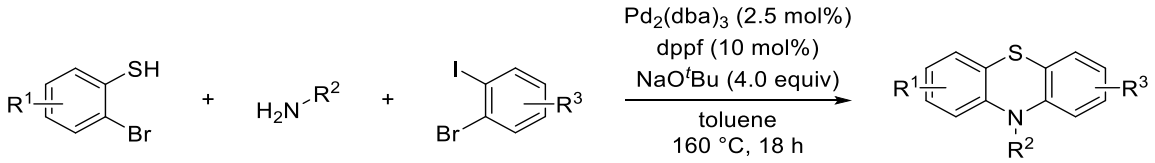
Figure 15: Structures of medicinally important phenothiazines.

Traditionally, phenothiazines were synthesised by treating diphenylamines with sulfur at high temperatures (250–260 °C) (Scheme 103). However, this protocol exhibits poor regioselectivity, meaning the synthesis of substituted phenothiazines is problematic.[120]



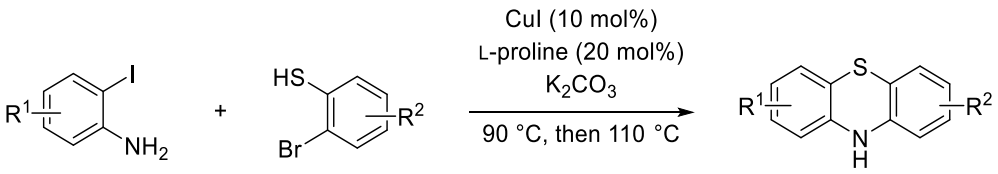
Scheme 103: Conventional method of phenothiazine synthesis.

Another method which has been utilised to construct phenothiazines was reported by Gupta and co-workers in 1999 and involves a base-mediated Smiles rearrangement.[121] However, this four-step approach is synthetically challenging and results in substituted phenothiazines with poor regioselectivity.[113] In 2008, Jørgensen and co-workers described an elegant protocol for the synthesis of phenothiazines *via* a palladium-catalysed three component cross-coupling reaction using 1-bromo-2-iodobenzenes, primary amines and 2-bromobenzenethiol (Scheme 104).[122]



Scheme 104: Palladium-catalysed three-component approach to phenothiazines.

Further to this, Ma and co-workers developed a novel approach for the synthesis of functionalised phenothiazines from 2-iodoanilines and 2-bromobenzenethiols (Scheme 105). This process was catalysed by CuI and L-proline.[123]

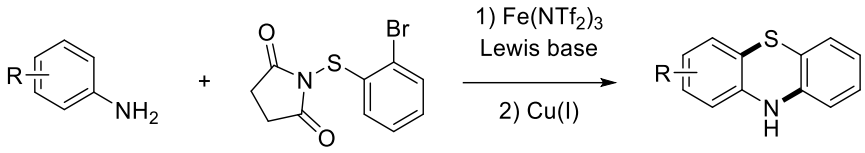


Scheme 105: CuI/L-proline-catalysed coupling of 2-iodoanilines and 2-bromobenzenethiols.

Whilst several of the reported methods towards phenothiazines are highly efficient, they often rely upon harsh reaction conditions, long reaction times, pre-functionalised starting materials or precious transition metal catalysis. It follows that, the development of milder techniques to synthesise these important scaffolds, from readily available starting materials, is highly desirable.

4.2 Project Aims

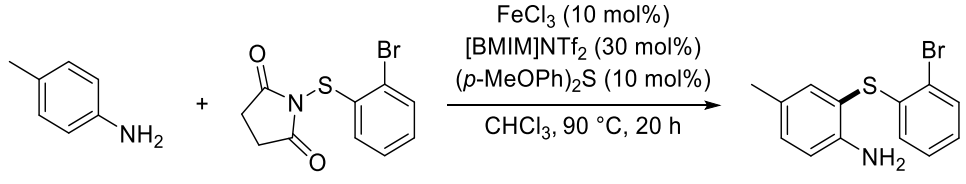
The main objective of this project was to develop a two-step synthesis towards phenothiazines (Scheme 106). This would build upon the previously developed methodology towards synthesis of phenoxathiins,[110] and would utilise the previously developed, regioselective, iron(III) triflimide/Lewis basic dual-catalysed thioarylation reaction for initial aniline functionalisation. This would be followed by a copper(I)-catalysed cyclisation reaction to give phenothiazines. The first aim was to carry out thorough optimisation studies on the reaction between *para*-toluidine and *N*-(2-bromophenylthio)succinimide, in order to develop a short, effective synthetic route towards phenothiazines. The scope of the reaction would then be investigated and, finally, the methodology would be applied to the synthesis of bioactive and pharmaceutically relevant target molecules.



Scheme 106: Proposed synthesis of phenothiazines.

4.3 Optimisation Studies for the *ortho*-C–H Sulfenylation of *para*-Toluidine and Subsequent C–N Bond Forming Cyclisation Reaction

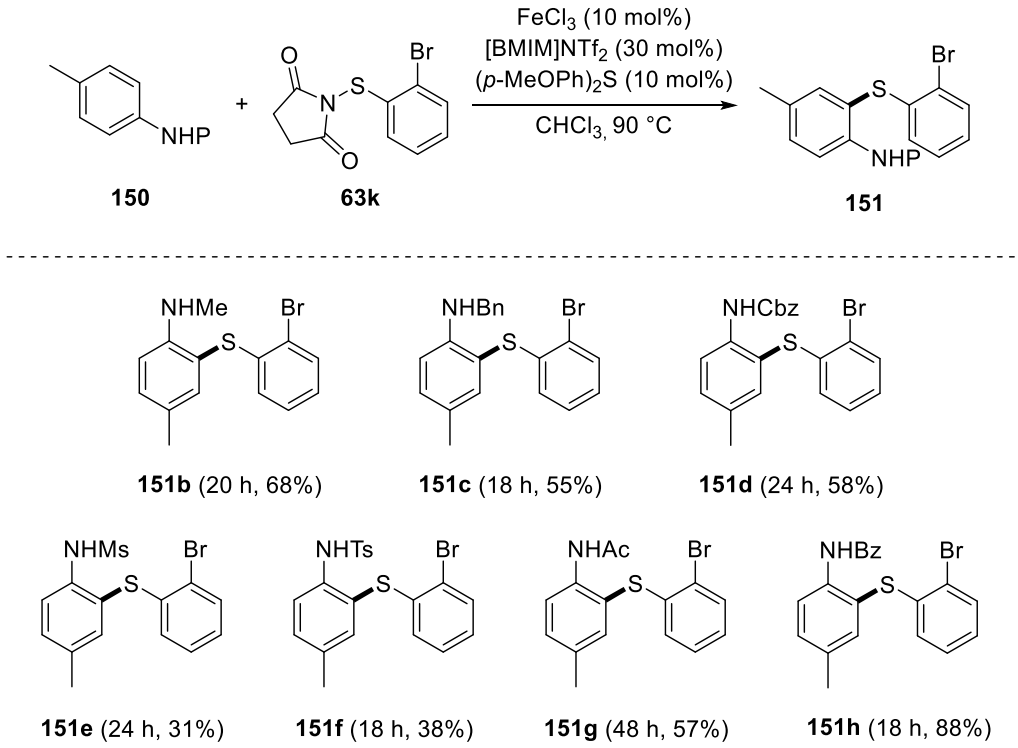
As stated above, optimisation studies focused on the reaction between *para*-toluidine (**150a**) and *N*-(2-bromophenylthio)succinimide (**63k**). When the reaction was performed using the conditions found to be optimal for the C–H sulfenlyation of *p*-cresol [$Fe(NTf_2)_3$ (10 mol%) in combination with *bis*(4-methoxyphenyl)sulfane (**64a**) (10 mol%)], the desired product (**151a**) was obtained in 42% yield after 20 h at 90 °C (Scheme 107).



150a **63k** **151a**, 42%

Scheme 107: Iron(III) triflimide and *bis*(4-methoxyphenyl)sulfane-catalysed C–H thioarylation of *p*-toluidine.

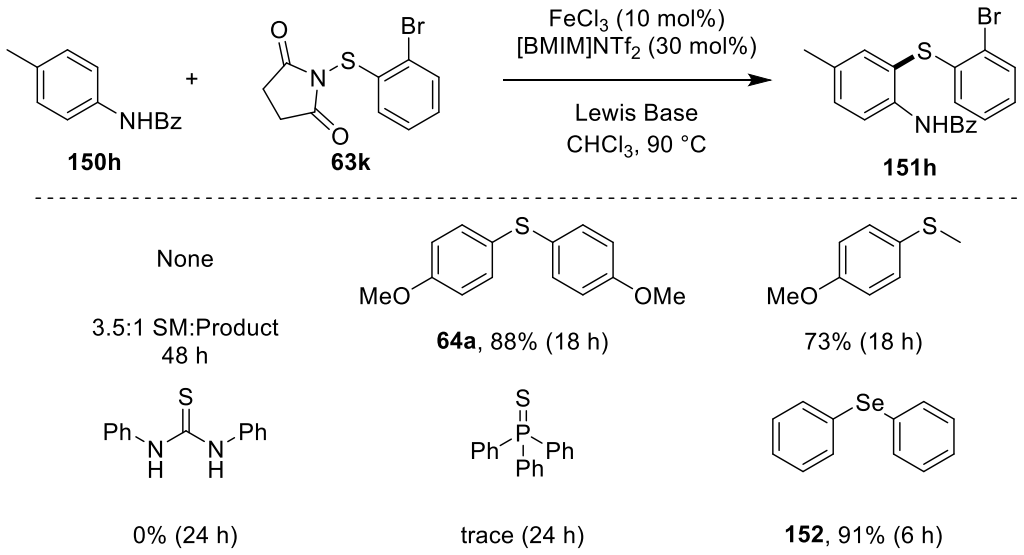
Whilst the reaction did produce the desired aryl thioether in moderate yield, it was hoped conditions could be identified which would improve on this. Whilst Fu and co-workers reported the effective thioarylation of anilines with *N*-(arylthio)succinimides in the absence of a catalyst,[124] the reported use of free anilines in catalytic reactions is scarce. In particular, whilst carrying out work on our previous iron(III) triflimide-catalysed thioarylation reaction,[77] it was found that free anilines were problematic, and it is likely that these arenes were reacting to form *N*-sulfenylated products instead of the desired products. To combat this issue and improve the efficiency of thioarylation, the use of protected anilines was investigated. As such, screening was carried out to identify the best protecting group for the transformation, with the benzoyl group giving the highest yield of desired product at 88% (Scheme 108). Whilst some of the other protecting groups (e.g. methyl, benzyl, Cbz- and acetyl) gave the desired products in moderate yields, the reactions were slower than with the benzoyl derivative.



Scheme 108: Screening of *p*-toluidine protecting groups for iron(III) triflimide and bis(4-methoxyphenyl)sulfane dual-catalytic C–H sulfenylation reaction.

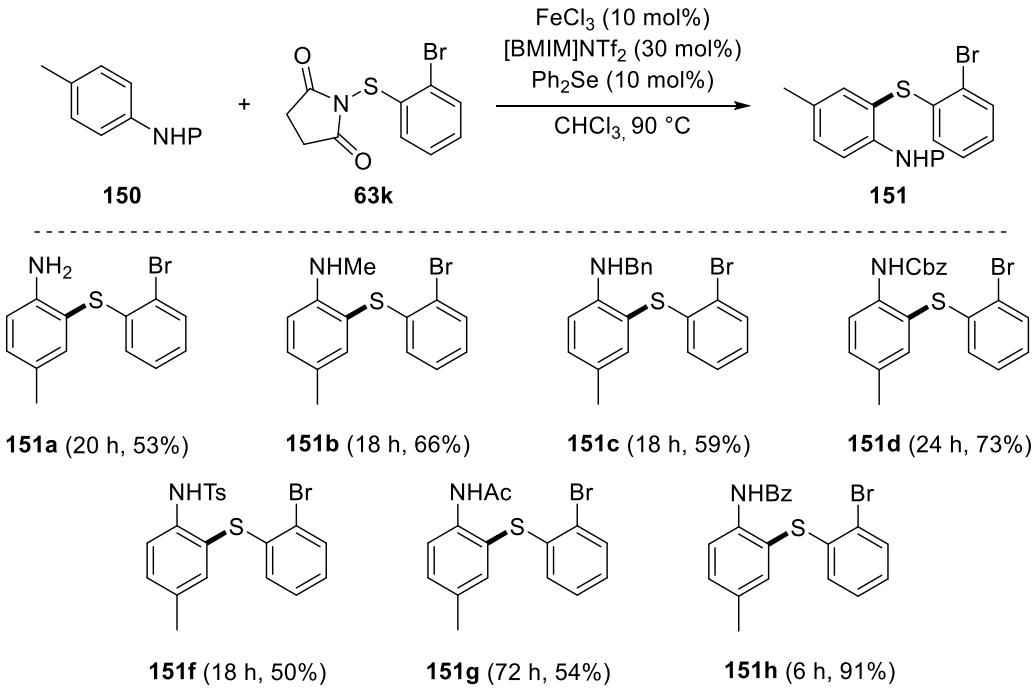
Next, the effect of different Lewis-bases on the reaction between *N*-benzoyl protected *p*-toluidine and *N*-(2-bromophenylthio)succinimide was examined (Scheme 109). Firstly, the reaction was attempted at 90 °C using iron(III) triflimide

(10 mol%) in the absence of a Lewis base. ^{1}H NMR analysis of the crude reaction mixture after 48 h revealed that, the reaction had not reached full conversion, with the starting material being present in a 3.5:1 ratio relative to the desired product. This result correlates well with the work done previously on the *ortho*-sulfenylation of *p*-cresol for the synthesis of phenoxathiins. When this reaction was performed with iron(III) triflimide alone, the reaction did not reach completion, with no further conversion being observed after 24 h. As previously discussed, when the reaction was performed employing *bis*(4-methoxyphenyl)sulfane as the Lewis base, the conversion was greatly enhanced, reaching completion in 18 h with the desired product isolated in 88% yield. Similar results were obtained with the use of methyl(4-methoxyphenyl)sulfane. The reaction was also attempted using *N,N*-diphenylthiourea and triphenylphosphine sulfide. Although used as Lewis bases for aryl chlorination,[49,50] their catalytic activity towards thioarylation was poor. Diphenyl selenide (**152**) proved to be the best Lewis base, allowing for a substantial reduction in the reaction time (6 h for complete conversion *vs* 18 h with *bis*(4-methoxyphenyl)sulfane) whilst maintaining a high yield of 91%. Control experiments were also carried out to ensure that the improvement in reaction was due to the presence of iron(III) triflimide in combination with diphenyl selenide, and not just due to diphenyl selenide alone. No reaction resulted when diphenyl selenide was employed as the sole catalyst confirming the role of both species in the dual-catalytic reaction.



Scheme 109: Iron(III) triflimide and Lewis base-catalysed C–H sulfenylation of benzoyl protected *p*-toluidines.

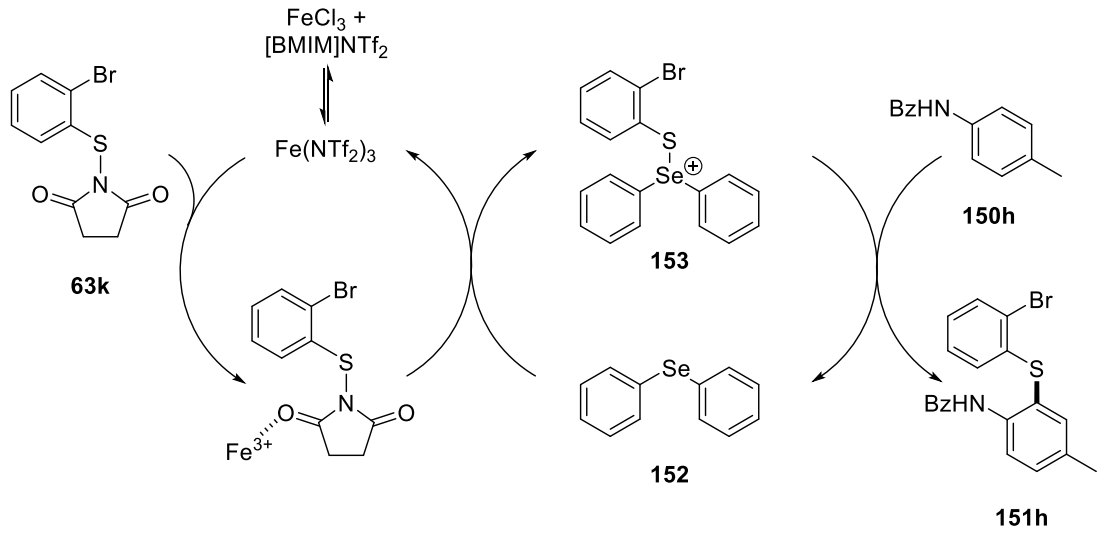
Since the Lewis base screening identified diphenyl selenide to be a superior catalyst relative to *bis*(4-methoxyphenyl)sulfane, the screening of *N*-protected *p*-toluidines was repeated to confirm benzoyl as the best protecting group for the transformation under the optimised conditions (Scheme 110). Similar results were observed to the previous study.



Scheme 110: Screening of protecting groups for iron(III) triflmide and diphenyl selenide dual-catalytic C–H sulfenylation.

When comparing the Lewis bases, to try and rationalise the enhancement in reaction using diphenyl selenide versus *bis*(4-methoxyphenyl)sulfane, both selenium and sulfur display similar reactivities, redox potentials and electronegativities.[125,126,127] They both belong to the chalcogen family, with selenium lying immediately below sulfur in the periodic table. However, due to the larger ionic radius, the outer valence electrons of selenium are less tightly bound, increasing its polarisability and, thus, its nucleophilicity. It is proposed that the iron(III) triflimide/diphenyl selenide dual-catalytic thioarylation reaction would follow the same mechanism outlined for the iron(III) triflimide/*bis*(4-methoxyphenyl)sulfane dual-catalysed protocol (Scheme 111). The higher nucleophilicity of the diphenyl selenide results in a faster reaction with the activated *N*-(2-bromophenylthio)succinimide to form the cationic intermediate **153**. Additionally, disulfide bonds have a higher bond dissociation energy than sulfur-selenium bonds,

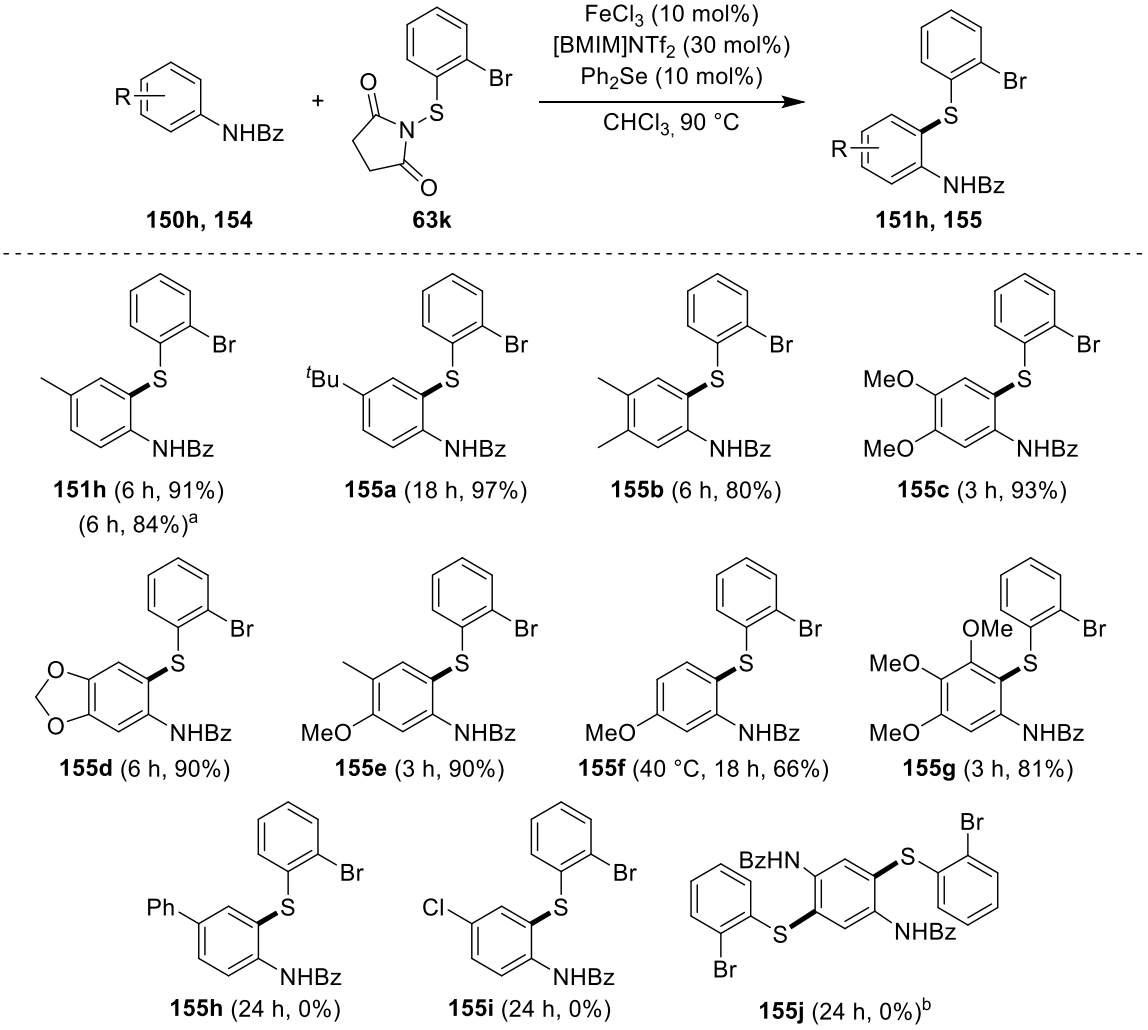
which results in an accelerated rate of electrophilic aromatic substitution since less energy is required to break the sulfur-selenium bond in **153**.



Scheme 111: Proposed mechanism for the iron(III) triflimide/diphenyl selenide dual-catalysed thioarylation reaction.

After establishing optimal reaction conditions for the transformation, the scope of the iron(III) triflimide/diphenyl selenide dual-catalytic thioarylation reaction was explored using a range of *N*-benzoyl protected anilines (Scheme 112). The developed methodology allowed for the efficient *ortho*-thioarylation of electron-rich arenes, providing the desired products in good to excellent yields in short reaction times. *N*-Benzoyl protected 3-methoxyaniline underwent successful *ortho*-thioarylation at 40 °C to give aryl thioether **155f**, in 66% yield. It was proposed that in this case where there are two directing groups in the starting material, the more electron-donating 3-methoxy substituent would direct reaction to the C-6 position. This allowed for the reaction to take place without having to block the *para*-position relative to the *N*-benzoyl group. Another promising result was the effective thioarylation of *N*-benzoyl protected 3,4,5-trimethoxyaniline, furnishing **155g** in 81% yield after 3 h. Here, C–H sulfenylation occurred at the extremely hindered *ortho*, *ortho*-substituted position. The reaction was also found to be scalable, and when the reaction between *N*-benzoyl protected *para*-toluidine and *N*-(2-bromophenylthio)succinimide was performed on a 1.5 mmol scale, an 84% yield of **151h** was obtained, comparable to that of the small-scale reaction (91%). Despite having success with electron rich arenes, when less reactive *N*-benzoyl protected anilines bearing aryl or electron withdrawing groups were subjected to the optimised

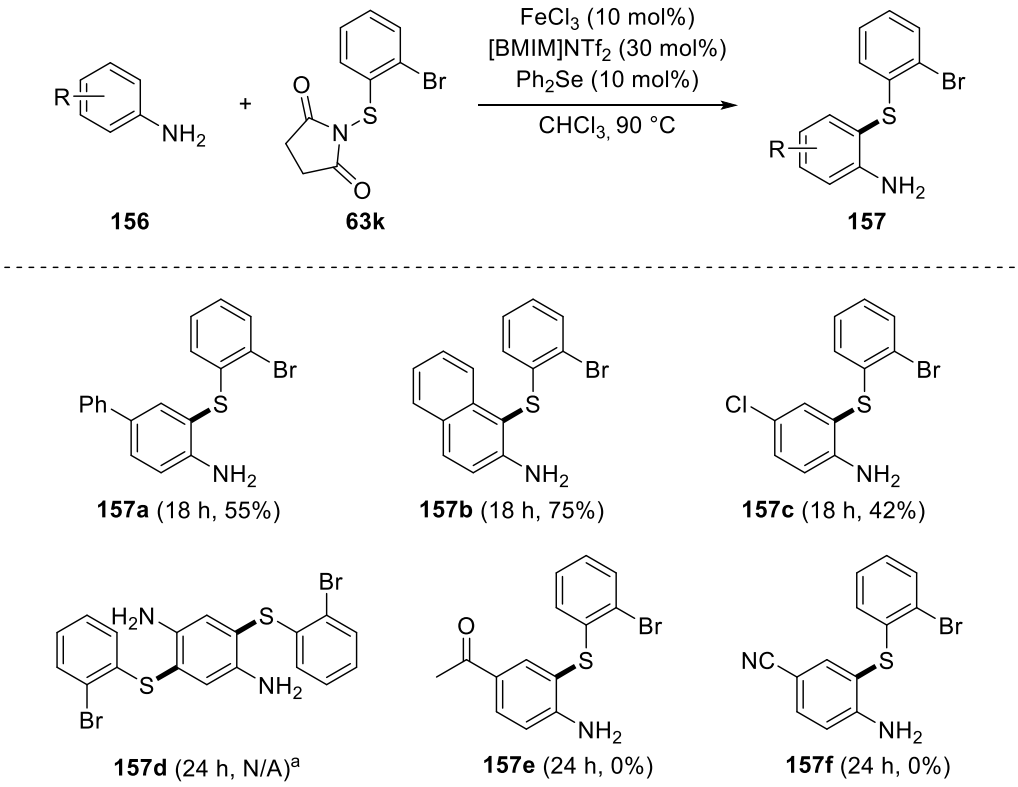
conditions, no reaction was observed after 24 h. These results were rationalised by noting the high insolubility of the arene starting materials in chloroform.



Scheme 112: Substrate scope of *N*-benzoyl protected anilines. [a]Reaction performed on a 1.5 mmol scale. [b]2.2 equivalents of *N*-(2-bromophenylthio)succinimide were used.

To combat the solubility issues associated with these substrates, it was proposed that the reaction would be more effective by employing the unprotected anilines as starting materials, since these are readily soluble in chloroform (Scheme 113). Despite previously outlining the problems associated with the iron(III) triflimde-catalysed thioarylation reactions of unprotected anilines, it was thought that the conjugated or deactivated nature of the substituents on these arenes would reduce the nucleophilicity of the amine moiety. This would in turn suppress the competing *N*-sulfenylation reaction, allowing for a cleaner, regioselective C–H thioarylation reaction. Fortunately, treatment of *N*-(2-bromophenylthio)succinimide with 4-aminobiphenyl (**156a**), 2-aminonaphthalene (**156b**) and 4-chloroaniline (**156c**) gave

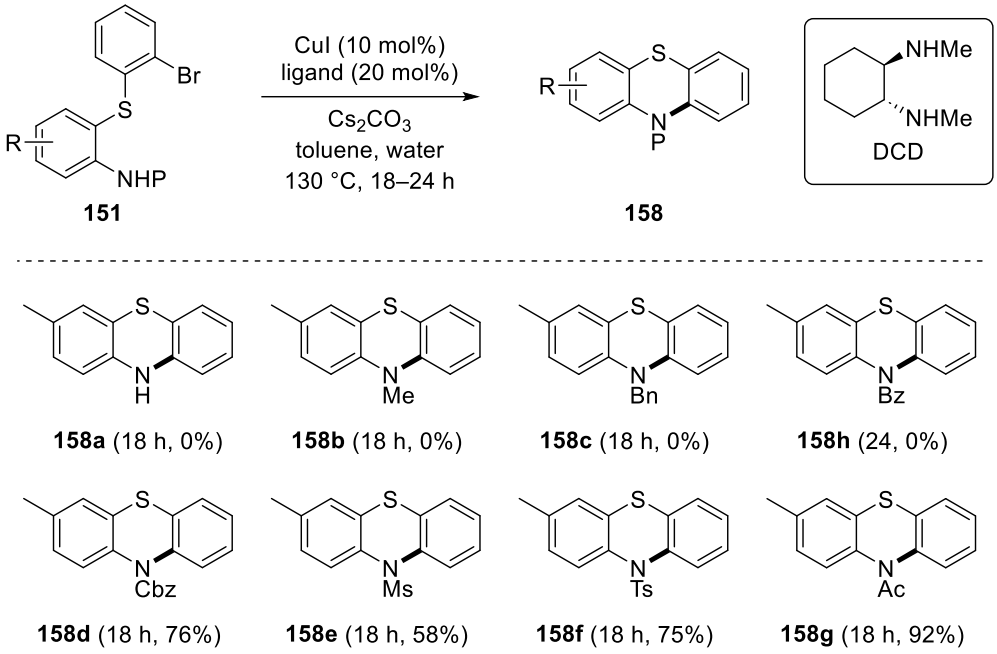
the desired products, **157a**–**157c**, in moderate to high yields (42–75%). In the case of 1,4-diaminobenzene, ^{1}H NMR analysis of the crude reaction mixture revealed a complex mixture of products. It was likely that, due to the highly electron-rich nature of the arene, reaction resulted in an array of poly-thioarylated products, as well as *N*-sulfenylated products. The main limitation of the methodology was found using anilines with strong electron withdrawing substituents. When 4-aminoacetophenone and 4-aminobenzonitrile were subjected to the optimised reaction conditions, no reaction was observed after 24 h.



Scheme 113: Substrate scope of anilines. [a]2.2 equivalents of *N*-(2-bromophenylthio)succinimide were used.

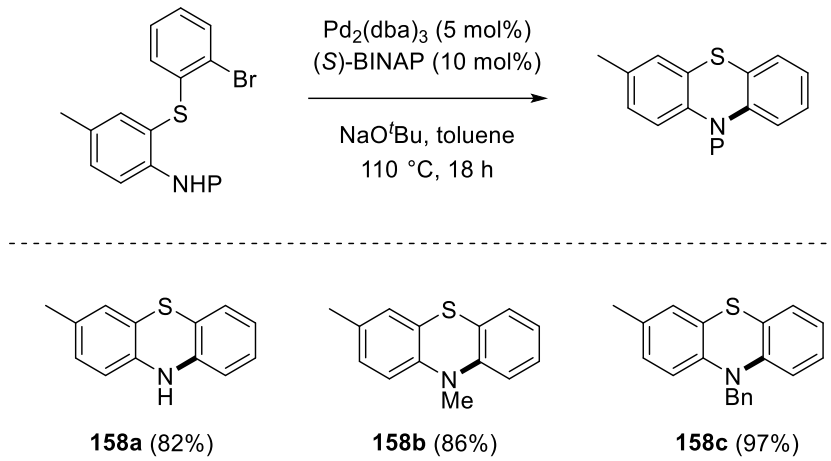
Following successful synthesis of a range of aryl thioethers using the optimised iron(III) triflimide/diphenyl selenide dual-catalytic C–H sulfenylation protocol, conditions for the subsequent cyclisation reaction were investigated. The first set of conditions investigated were those used previously within the group to achieve effective *ortho*-amination of arenes (Scheme 114).[101] Here, copper(I) iodide was employed as the a catalyst, and racemic *trans-N,N'*-dimethylcyclohexane-1,2-diamine (DCD) was added as a ligand. Cesium carbonate was used as the base and the solvent system comprised of toluene and water. Unfortunately, the copper(I)-catalysed cyclisation reaction was unsuccessful for *N*-alkyl and

unprotected *ortho*-thioarylated anilines. It was proposed that strong coordination of the nucleophilic amine moieties prevented cyclisation of these substrates. In the case of the *N*-benzoyl protected *ortho*-thioarylated aniline **151h**, ^{1}H NMR analysis of the crude reaction mixture did not reveal the presence of any desired product. Instead, trace amounts of the deprotected phenothiazine **158a** were observed, alongside a significant amount of decomposed substrate. However, these conditions were found to be compatible with Cbz-, mesyl, tosyl and acetyl-protected derivatives, giving the desired protected phenothiazines **158d**–**158g** in moderate to excellent yields (58–92%).



Scheme 114: Attempted cyclisation reactions of aryl thioethers using CuI (10 mol%) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (20 mol%) as a ligand.

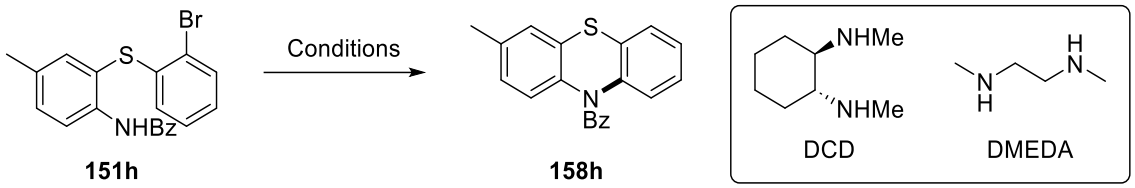
In order to achieve successful intramolecular cyclisation of the nucleophilic *N*-alkyl and unprotected *ortho*-thioarylated anilines (**151a**–**151c**), a palladium(0)-catalysed Buchwald-Hartwig reaction was undertaken (Scheme 115).[128,129] Using $Pd_2(dba)_3$ as a catalyst and (*S*)-BINAP as a ligand, under standard conditions, the desired phenothiazines **158a**–**158c** were obtained in good to excellent yields (82–97%).[130]



Scheme 115: Synthesis of phenothiazines via Pd(0)-catalysed intramolecular cyclisation.

Since the iron(III) triflimide/diphenyl selenide dual-catalytic thioarylation reaction worked best with *N*-benzoyl protected anilines, efforts were focused on optimising the cyclisation reaction. Since the conditions outlined in Scheme 114 resulted in the formation of small amounts of deprotected phenothiazine **158a**, it was proposed that cyclisation of **151h** into **158h** had actually occurred, followed by hydrolysis of the compound. Since cesium carbonate is a nucleophilic base, it was assumed that the base may have led to hydrolysis of the benzoyl group from **151h** (SM) or **158h** (product). As such, a screening of non-nucleophilic bases compatible with the CuI-system was performed (Table 6). No product resulted from the reaction employing sodium *tert*-butoxide (entry 2), however, a small amount of desired product was obtained from the reaction employing potassium phosphate (25% yield) (entry 3). Since no significant improvement was achieved by using alternative bases, next the metal/ligand system was investigated. Since palladium-catalysed reactions were shown to be successful for the synthesis of phenothiazines using nucleophilic anilines, the copper-mediated system was replaced with standard Buchwald-Hartwig cross-coupling conditions (entry 4). Despite complete consumption of the starting material, ^{1}H NMR analysis of the crude reaction mixture showed a complex mixture of products, with no formation of **158h**. Based on these results, it was suggested that the bulkiness of the *trans-N,N'*-dimethylcyclohexane-1,2-diamine ligand could be preventing the *N*-benzoyl protected amino group from coordinating to the metal complex. As such, the cyclisation reaction was re-attempted using the original conditions of CuI, cesium carbonate, toluene and water, but using *N,N'*-dimethylethylenediame (DMEDA) as a ligand instead of *trans-N,N'*-dimethylcyclohexane-1,2-diamine (entry 5). From these results, it was evident that

the choice of ligand played a key role in the promotion of intramolecular cyclisation. The use of the less bulky DMEDA ligand led to a vast improvement in reaction, with the desired *N*-benzoyl protected phenothiazine (**158h**) being isolated in 86% yield after 48 h at 130 °C.

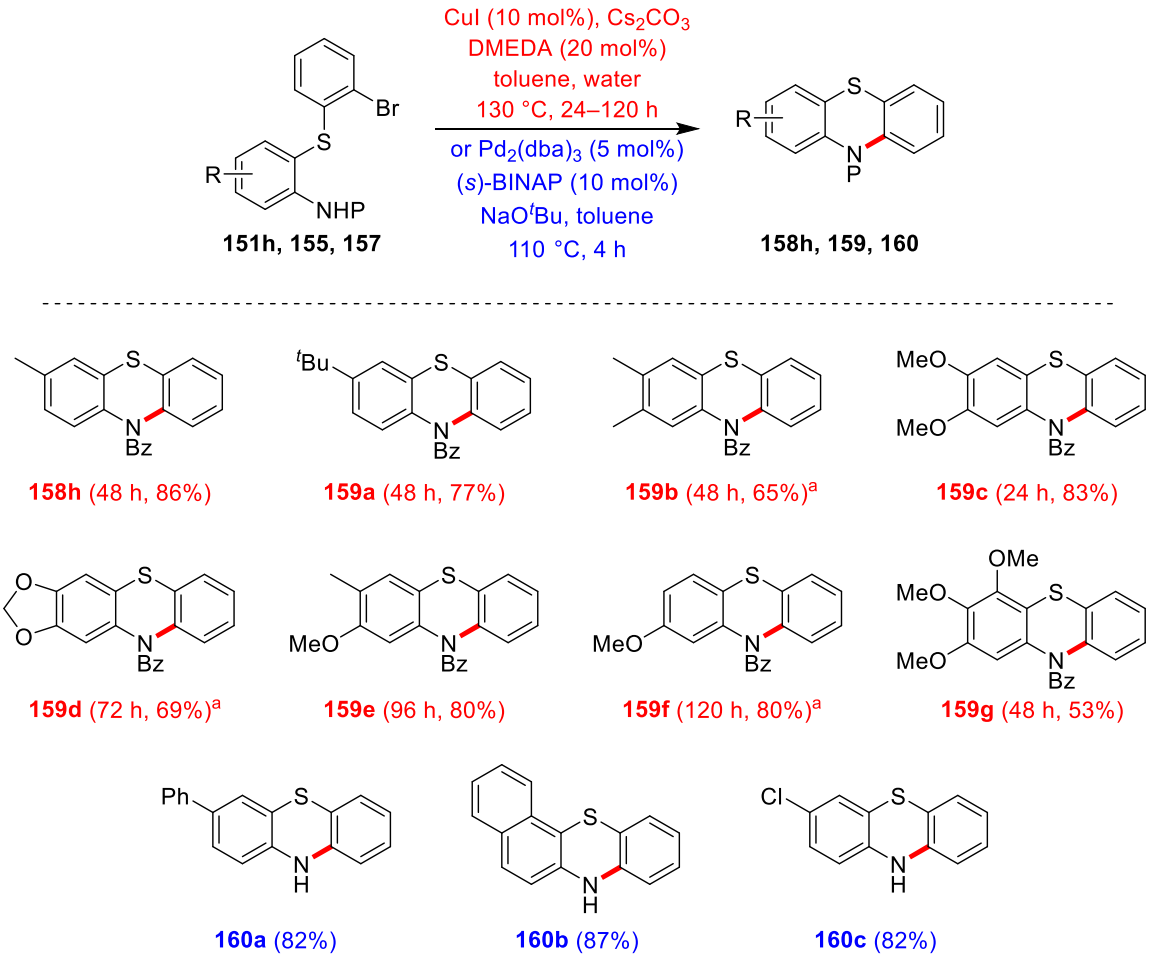


151h **158h**

Entry	Conditions	Temperature (°C)	Time (h)	Yield (%)
1	CuI (10 mol%), Cs_2CO_3 (2.0 equiv), DCD (20 mol%), toluene, water	130	24	–
2	CuI (10 mol%), NaO^{t}Bu (2.0 equiv), DCD (20 mol%), toluene, water	130	24	–
3	CuI (10 mol%), K_3PO_4 (2.0 equiv), DCD (20 mol%), toluene, water	130	24	25
4	$Pd_2(dba)_3$ (5 mol%), (*s*)-BINAP (10 mol%), NaO^{t}Bu (2.0 equiv), toluene	110	24	–
5	CuI (10 mol%), Cs_2CO_3 (2.0 equiv), DMEDA (20 mol%), toluene, water	130	48	86

Table 6: Optimisation of the intramolecular cyclisation of *N*-benzoyl protected *ortho*-thioarylated aniline **151h**.

Having identified optimised conditions for the cyclisation of *N*-benzoyl protected and unprotected *ortho*-thioarylated anilines, these were then applied to convert the aryl thioethers outlined in Schemes 112 and 113, into the corresponding phenothiazines (Scheme 116). For the *N*-benzoyl-protected derivatives, the Ullman-Goldberg copper(I)-catalysed cyclisation conditions were used, and for the unprotected derivatives, the standard Buchwald-Hartwig cross-coupling conditions were employed. Whilst the copper(I)-catalysed cyclisation reactions generally required long reaction times, the desired phenothiazine products were obtained in moderate to good yields (**159a**–**159g**). Alternatively, the unprotected *ortho*-thioarylated anilines were cyclised using the Buchwald-Hartwig coupling in short reaction times (4 h) to give the desired phenothiazines in good yield (**160a**–**160c**).

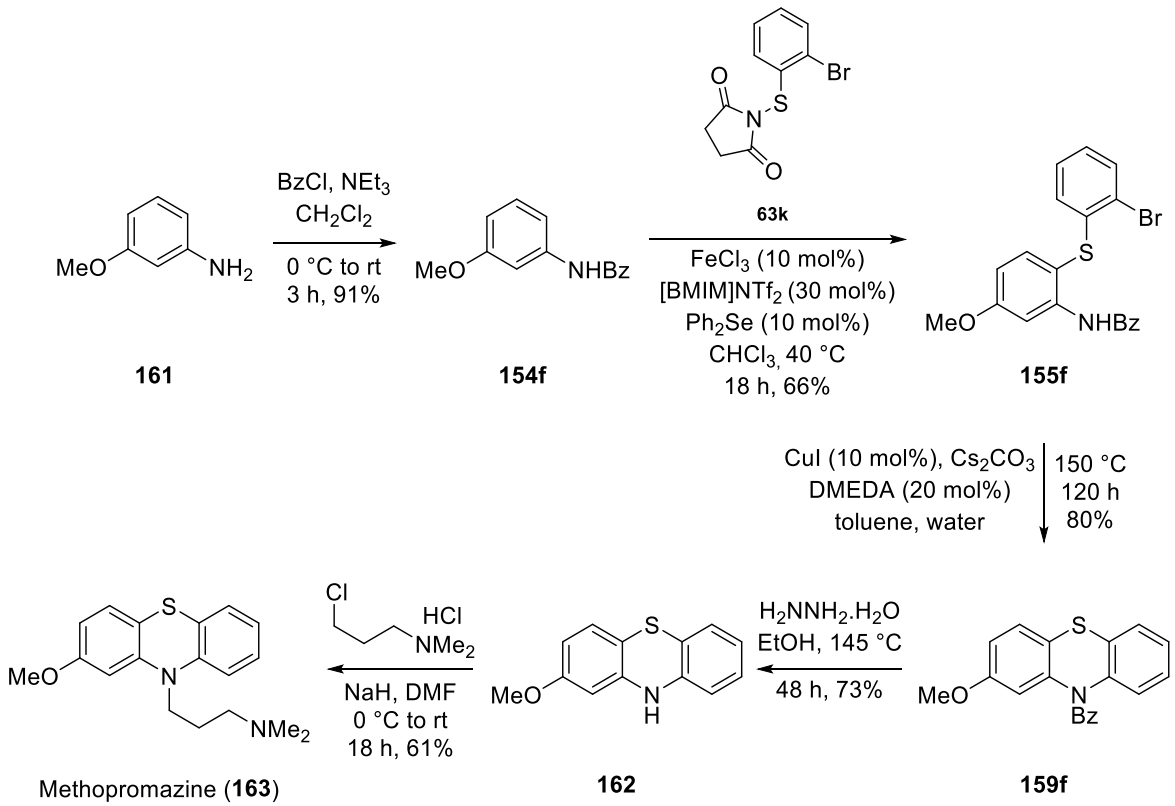


Scheme 116: Cyclisation of *N*-benzoyl-protected and unprotected *ortho*-thioarylated anilines. [a]Reaction was performed at 150 °C.

4.4 Synthesis of Methopromazine

The main aim of this project was to develop a two-step methodology for the synthesis of phenothiazines, which could subsequently be used for the preparation of medicinally important *N*-heterocycles. As such, the synthetic utility of the iron(III) triflimide/diphenyl selenide dual-catalysed thioarylation and subsequent cyclisation protocol was demonstrated with the synthesis of neuroleptic agent, methopromazine (Scheme 117).[131,132] Benzoyl protection of *m*-anisidine (**161**) gave arene **154f**, which was used as the starting material in the iron(III) triflimide/diphenyl selenide dual-catalysed thioarylation reaction. A limitation of this general approach for *ortho*-thioarylation of monosubstituted arenes is that the *para*-position is required to be blocked. In this case, the *para*-position relative to the *N*-benzoyl protected amino group in **154f** is not blocked, meaning that this site is available for substitution. However, **154f** also contains a 3-methoxy group, which should act as the dominant directing group, promoting reaction at the C6-position.[78] When the reaction was

performed under the optimised conditions (90 °C), the reaction was complete in 3 h. Whilst **155f** was the major product, as expected (54% yield), a significant amount of 4,6-dithioarylated product was also isolated (30%). From these results, it was proposed that the reaction should be repeated at lower temperatures in an attempt to minimise side-product formation. When the reaction was undertaken at 75 °C, the reaction reached completion in 4 h and gave the desired product **155f** in an improved yield of 64%. However, the disubstituted product was still observed, albeit in a lower yield of 15%. One final attempt was carried out at 40 °C, with the desired product being obtained in 66% yield. Although this reaction took a longer time of 18 h, the amount of di-substituted product was further reduced to 8% (See also Scheme 112). The resulting aryl thioether **155f** was cyclised using a copper(I) iodide-catalysed intramolecular Ullman-Goldberg reaction. While this required a reaction time of 120 h, *N*-benzoyl protected phenothiazine **159f** was still isolated in a high 80% yield. Hydrazine monohydrate was employed to remove the benzoyl group[133] and subsequent *N*-alkylation with 3-dimethylaminopropyl chloride, in the presence of sodium hydride allowed for the successful synthesis of methopromazine **163**.[134]



Scheme 117: Synthesis of methopromazine (**163**).

4.5 Synthesis of Phenothiazine Derived α-Amino Acids

As previously outlined in the synthesis of phenoxathiin derived α-amino acids, fluorescent amino acids are powerful tools in chemical biology. They can be used to monitor a variety of biological processes, such as the localisation, function and structure of proteins,[135,136] without significantly perturbing their native structure or function.[137] The Petersson group have reported an efficient synthesis of amino acid acridon-2-ylalanine (Acd) (Figure 16), which is a genetically incorporable, blue-wavelength fluorescent amino acid.[138,139,140] The utility of Acd as a fluorophore is demonstrated by its small size (222 $Å^3$), high quantum yield in water ($\Phi = 0.95$), long fluorescence lifetime ($\tau \sim 15$ ns) and high photostability.[139,141,142] However, the absorbance maxima of the amino acid lies within the UV region (389 nm), and with the emission maxima occurring at 411 nm, this can lead to photodamage. Although the molar attenuation coefficient is high ($2.43 \times 10^4\ M^{-1}cm^{-1}$), the Stokes shift is small (22 nm), which can lead to self-quenching.[135,141]

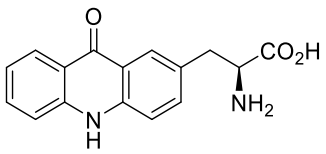
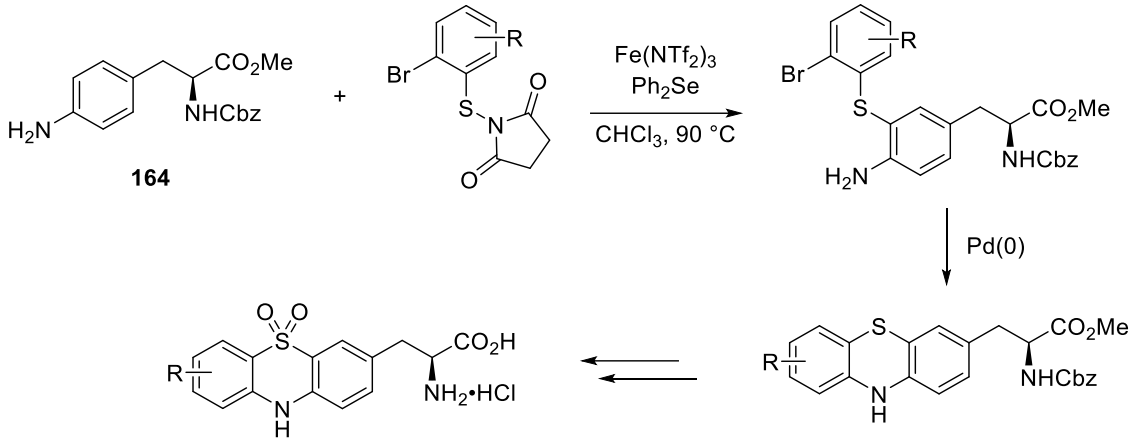


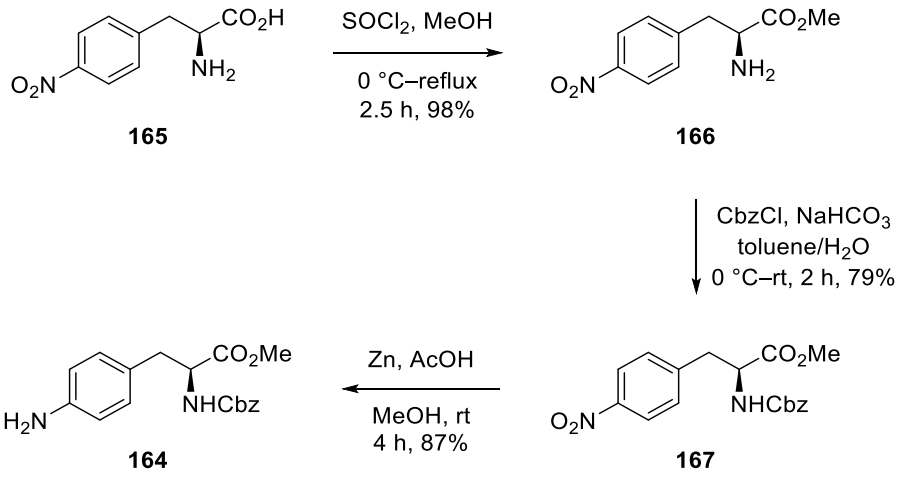
Figure 16: Amino acid acridon-2-ylalanine (Acd).

Based on the promising photophysical properties of Acd, it was proposed that a sulfone analogue could be prepared by the iron(III) triflimide/diphenyl selenide dual-catalytic C–H sulfenylation of protected L-*p*-aminophenylalanine (**164**) (Scheme 118). This would be followed by a Buchwald-Hartwig cross-coupling reaction and subsequent oxidation of the sulfide to the sulfone to generate a new class of potentially fluorescent phenothiazine-dioxide derived α-amino acids.



Scheme 118: Proposed synthesis towards phenothiazine-dioxide derived α-amino acids.

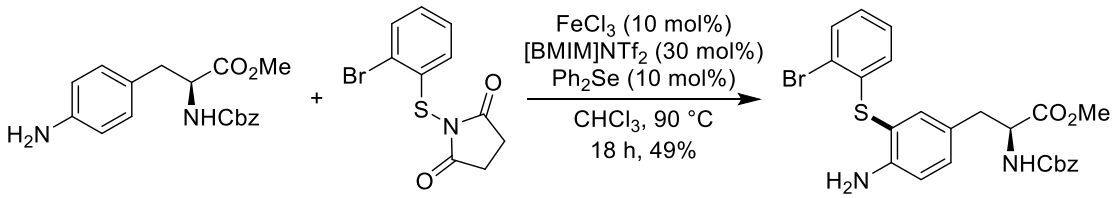
Firstly, a three-step synthesis was undertaken to provide methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate (**164**) from commercially available L-*p*-nitrophenylalanine (**165**) (Scheme 119). Initial protection of the carboxylic acid moiety as a methyl ester was achieved using thionyl chloride and methanol in quantitative yield. This was followed by amine protection with benzyl chloroformate under basic conditions and gave **167** in 79% yield. Subsequent chemoselective reduction of the nitro group using zinc and acetic acid gave **164** in 87% yield.



Scheme 119: Three-step synthesis of methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate (**164**).

Next, methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate (**164**) was subjected to the optimised conditions for the iron(III) triflimide/diphenyl selenide dual-catalysed C–H sulfenylation with *N*-(2-bromophenylthio)succinimide,

delivering the desired aryl thioether (**168**) in 49% yield (Scheme 120). This reaction was also performed with *N*-benzoyl and *N*-Cbz protected derivatives of **164**, although the yields for these reactions were lower than using the unprotected aniline (28% and 23%, respectively). It was proposed that, in this case, the decrease in yield can be attributed to increase in steric hinderance around the position of substitution. Additionally, the benefit of using the unprotected aniline **164** was the avoidance of performing a later deprotection step.

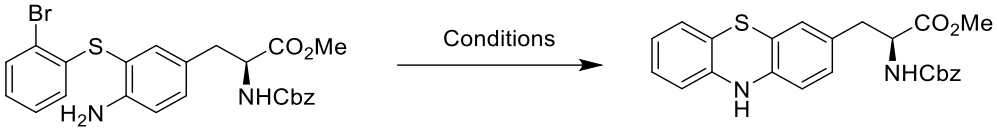


164 **63k** **168**

Scheme 120: Iron(III) triflimide/diphenyl selenide dual-catalysed C-H thioarylation of methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate (**164**).

Following successful synthesis of **168**, the Buchwald-Hartwig cross-coupling conditions identified for effective cyclisation of unprotected *ortho*-thioarylated anilines[130] were employed to construct the phenothiazine core. Unfortunately, no desired product was observed under these conditions after 4 h. Instead, the starting material (**168**) appeared to have decomposed. As such, optimisation studies were undertaken to identify optimal conditions for the cyclisation reaction. When the reaction was attempted using stoichiometric amounts of copper(I) thiophene-2-carboxylate (Table 7, entry 2) (the same conditions used to construct phenoxthiins), no reaction was observed. Next, the reaction was carried out using CuI/L-proline as the catalytic system (entry 3), since these conditions have been employed by Jiang and co-workers for the synthesis of phenothiazines from 2-iodoanilines and 2-bromobenzenethiols.[123] Once again, no desired product was formed and instead decomposition of the starting material was observed. This suggests that the difficulty of the cyclisation reaction can be attributed to the presence of the amino acid side chain. It was hypothesised that changing the identity of the ligand could result in an improvement in reaction. The first ligand to be investigated was (2-biphenyl)dicyclohexylphosphine (CyJohnphos – Figure 17), since this has been reported as an excellent ligand for C–N bond forming reactions, especially for hindered substrates (entry 4).[143] The effectiveness of CyJohnphos is thought to be due to a combination of steric and electronic properties which promote oxidative

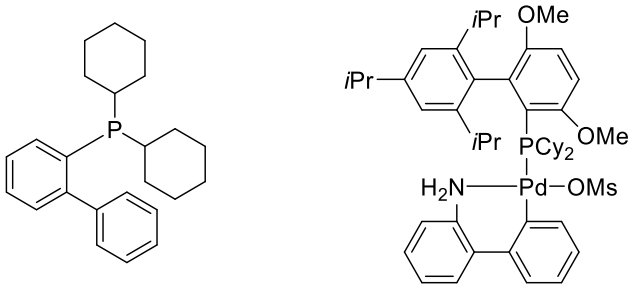
addition, Pd–N bond formation and reductive elimination.[143] Fortunately, the combination of $Pd_2(dba)_3$ and CyJohnphos with a catalyst loading of 5 mol% and potassium phosphate as a base resulted in the isolation of desired product **169** in 21% yield. An increase in catalyst loading did not result in an improved reaction (entry 5). The final ligand examined was Brettphos, which has been shown to be highly effective for the arylation of primary amines.[144] Here, third generation Buchwald precatalyst BrettPhos Pd G3 (Figure 17) was employed (entry 6). This is known to be an excellent reagent for Buchwald-Hartwig cross coupling reactions due to its air, moisture and thermal-stability, in combination with facile and efficient formation of the active catalytic species. Fortunately, these conditions improved the yield to 51%.



168 **169**

Entry	Conditions	Temperature (°C)	Time (h)	Yield (%)
1	$Pd_2(dba)_3$ (5 mol%), (*s*)-BINAP (10 mol%), NaO^{t}Bu (2.0 equiv), toluene	110	24	–
2	CuTc (1.0 equiv), DMA	100	18	–
3	CuI (20 mol%), L-proline (40 mol%), K_2CO_3, 2-methoxyethanol	110	18	–
4	$Pd_2(dba)_3$ (5 mol%), CyJohnphos (5 mol%), K_3PO_4, DME	100	40	21
5	$Pd_2(dba)_3$ (10 mol%), CyJohnphos (10 mol%), K_3PO_4, DME	100	40	23
6	BrettPhos Pd G3 (5 mol%), K_3PO_4, DME	120	20	51

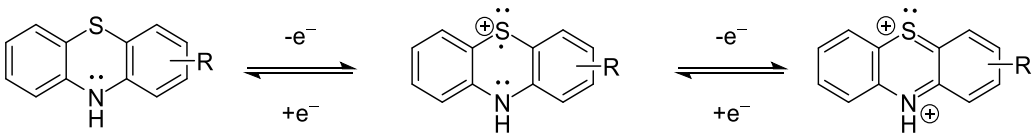
Table 7: Optimisation of the intramolecular cyclisation of amino acid **168**.



CyJohnphos **BrettPhos Pd G3**

Figure 17: Structures of the Buchwald ligand, CyJohnphos, and the Buchwald precatalyst, BrettPhos Pd G3.

Interestingly, when phenothiazine **169** was dissolved in $CDCl_3$ and analysed by ^1H NMR spectroscopy, rapid decomposition of the product was observed. This suggests that phenothiazines are unstable in chlorinated solvents. It is hypothesised that free radicals present in chlorinated solvents can act as initiators for their degradation (Figure 18). Firstly, a single-electron transfer reaction occurs to form the semiquinone radical cation, which is then converted into the phenothiazine ion via another single-electron transfer.[145] From here, it is proposed that this reacts with another phenothiazine molecule, leading to polymerisation.

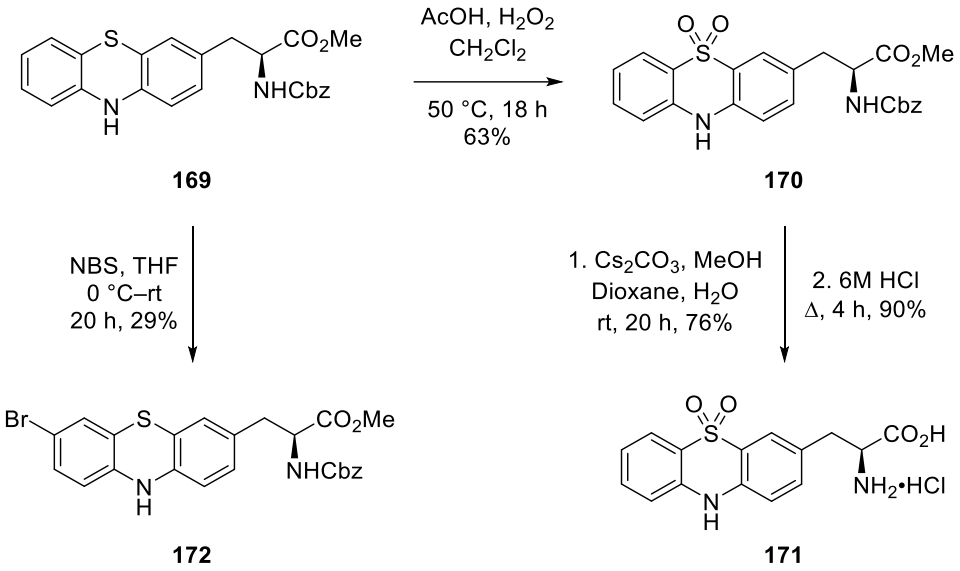


Semiquinone radical ion Phenothiazine ion

Figure 18: Phenothiazine radical oxidation.

After successfully optimising the intramolecular cyclisation of **168** to give phenothiazine derived α-amino acid **169**, the biaryl sulfide moiety was oxidised to give the corresponding sulfone (**170**) using hydrogen peroxide and glacial acetic acid (Scheme 121). The use of chlorinated solvent dichloromethane can be used to rationalise the moderate yield of 63%. Subsequent ester hydrolysis and acid-mediated Cbz removal allowed for the isolation of phenothiazine-dioxide derived α-amino acid **171**. Additionally, diversification of phenothiazine **169** was achieved through reaction with NBS to give **172**. As previously discussed as part of the synthesis of phenoxathiin-derived α-amino acids, the installation of a bromine functional handle will allow for further functionalisation of the molecule. In terms of

fluorescence, reaction of the halogen functionality will allow for the introduction of groups capable of extending the conjugation of the system and, thus, potentially improve the photophysical properties.



Scheme 121: Synthesis and diversification of phenothiazine derived α-amino acids.

Due to the structural similarities between Acd and the phenothiazine-dioxide α-amino acid **171**, it was proposed that phenothiazine-dioxide derived α-amino acids synthesised using the developed methodology could also function as fluorescent amino acids. As such, the absorbance and emission spectra of **171** were investigated (Figure 19). The main absorbance maxima appeared at 272 nm, with the emission maxima appearing at 372 nm. Additionally, the absorbance spectra displays two other absorbance bands at ~305 and 340 nm. This was a welcome result, confirming that amino acid **171** can be excited in the presence of natural fluorescent amino acids such as L-tryptophan, L-tyrosine and L-phenylalanine, since their absorption maxima occur at much shorter wavelengths of 279 nm, 275 nm and 258 nm, respectively.[108] Whilst **171** displays a larger Stokes shift than that of Acd, even with excitation at 340 nm, both the absorption and emission maxima are blue-shifted in **171** relative to that of Acd. This renders **171** a poor fluorescent probe, with limited use for *in vivo* applications since, the use of UV light for excitation can damage the biological system. However, these results provide a good starting point to synthesise more red-shifted analogues.

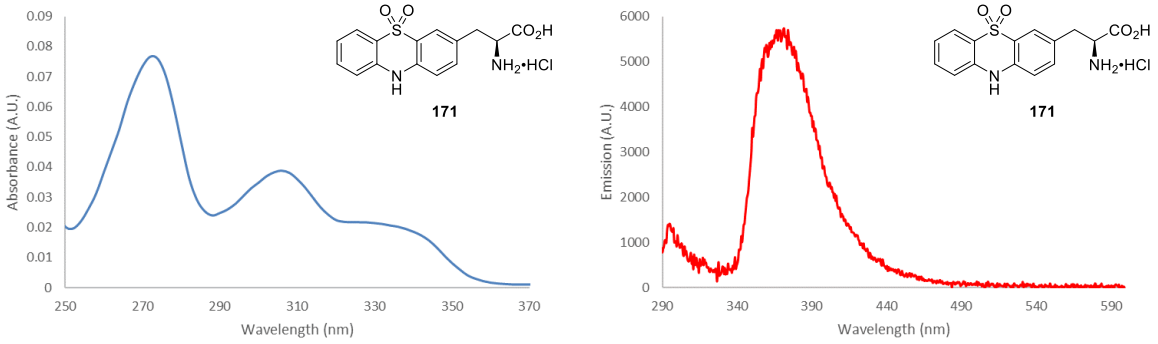
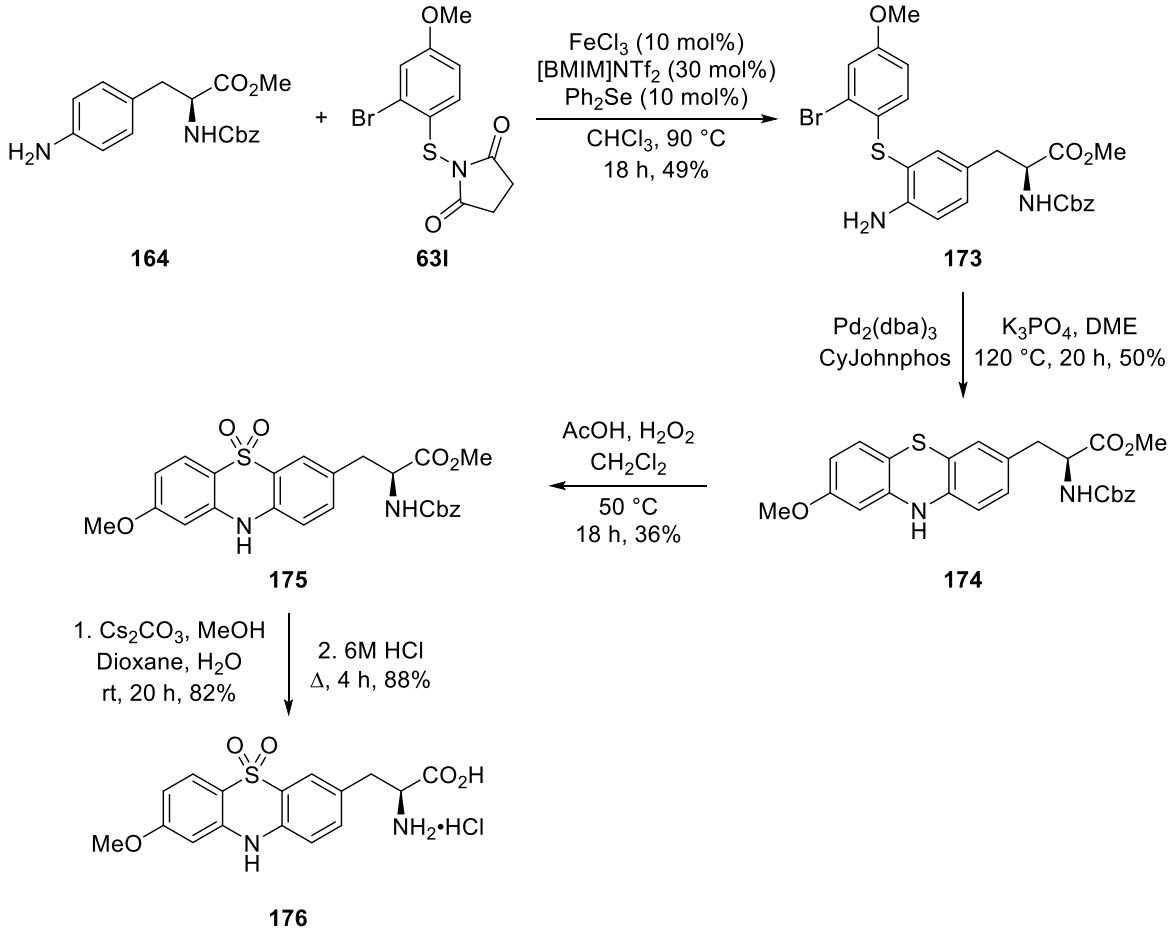


Figure 19: Absorbance and emission spectra for amino acid **171**. Measured in MeOH at 5 μM, excitation at 272 nm.

Another phenothiazine-dioxide derived α-amino acid (**176**) was synthesised through reaction of 4-aminophenylalanine derivative (**164**) with *N*-(2-bromo-4-methoxyphenylthio)succinimide (**63l**) (Scheme 122). The iron(III) triflimide/diphenylselenide dual-catalytic system was employed to give the desired aryl thioether (**173**) in 49% yield. The formation of the phenothiazine scaffold in (**174**) was achieved via cyclisation of **173** using $Pd_2(dba)_3$ (10 mol%) and CyJohnphos (10 mol%). It should be noted that optimisation of the cyclisation reaction (Table 7) was performed on both analogues in tandem and, since *N*-(2-bromo-4-methoxyphenylthio)succinimide (**63l**) is not commercially available, material was limited. As such, when the reaction employing CyJohnphos furnished desired product, it was decided to bring through the remaining material using these conditions. Later work with **168** identified BrettPhos Pd G3 as a better catalyst. Oxidation of the aryl sulfide to the sulfone ensued, furnishing **175** in 36% yield. The established deprotection strategy of ester hydrolysis and acid-mediated Cbz-group removal followed, to give the desired parent amino acid **176**.



Scheme 122: Synthesis of phenothiazine-dioxide derived α-amino acid **176**.

The absorption and emission spectrum of (2*S*)-2-amino-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (**176**) was next investigated. As previously discussed in the synthesis of phenoxathiin-dioxide derived α-amino acids, it was hypothesised that the addition of an electron donating 7'-methoxy substituent would ehnance the push-pull system and lead to better photophysical properties. Unfortunately, the absorbance and emission spectra highlight that the electron donating substituent does not lead to a red-shift in absorption or emission wavelengths (Figure 20). Although the synthesis of amino acids **171** and **176** did not result in an improvement in photophysical properties relative to the 'gold standard' Acd, a synthetic route towards phenothiazine derived α-amino acids has been established with points for diversification which can be utilised to synthesise analogues with better fluorescent properties.

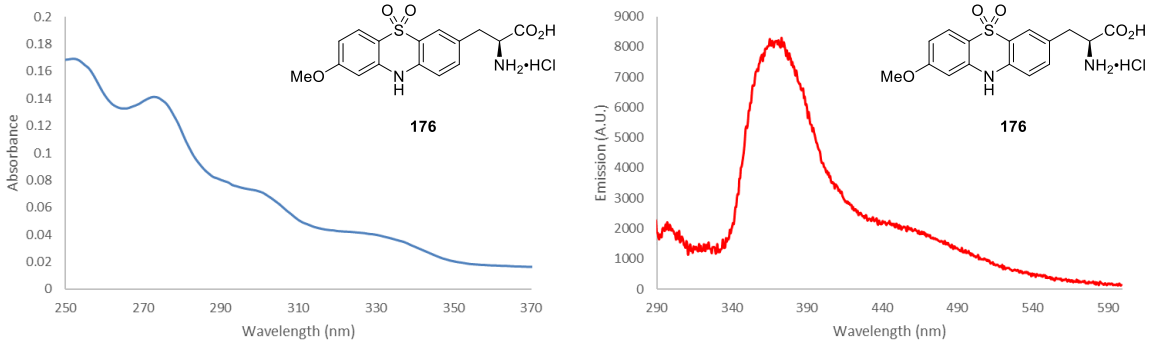
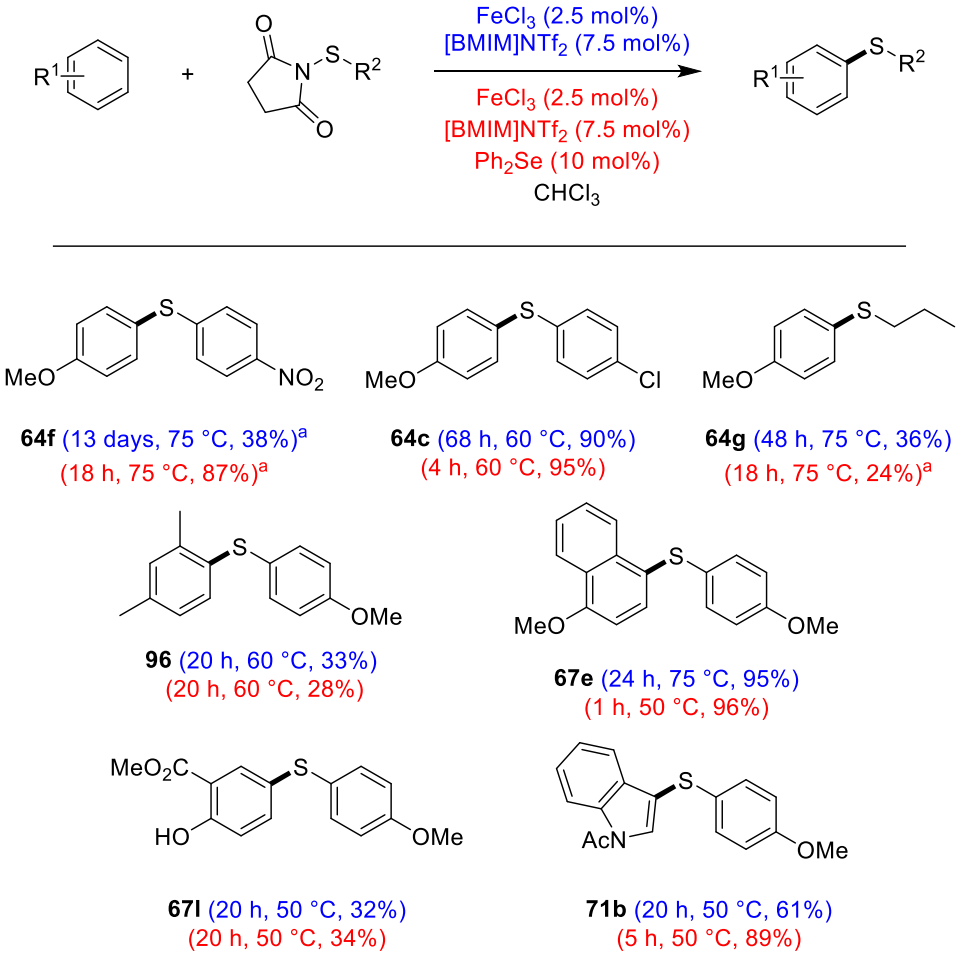


Figure 20: Absorbance and emission spectra for amino acid **176**. Measured in MeOH at 5 μM, excitation at 274 nm.

4.6 Re-visiting the Iron(III) Triflimide-Catalysed Thioarylation

The first aim of this PhD was to investigate the viability of the super Lewis acid, iron(III) triflimide, as a catalyst for the C–H sulfenylation of activated arenes.[77] Whilst iron(III) triflimide can operate independently as an effective catalyst for the transformation, it has since been confirmed that reactivity can be greatly enhanced when the Lewis acid is used in combination with a Lewis base.[110,146] As such, it was proposed that some of the reactions, which proved slow or low yielding using iron(III) triflimide alone, should be re-attempted with the new iron(III) triflimide/diphenyl selenide dual-catalytic system (Scheme 123). A promising result was observed when the C–H thioarylation of anisole using *N*-(4-nitrophenylthio)succinimide was undertaken using iron(III) triflimide in combination with diphenyl selenide. When the reaction was undertaken with iron(III) triflimide alone, desired product **64f** was isolated in 38% yield after 13 days at 75 °C. Under the new conditions, the reaction time was greatly reduced, with full conversion being observed after 18 h and product **64f** obtained in 87% yield. Similarly, aryl thioethers **64c** and **67e** were synthesised in high yield in much shorter reaction times than those observed when the reactions were performed with iron(III) triflmide alone. Unfortunately, the reactions of *m*-xylene and methyl salicylate did not show any improvement under the dual Lewis acid/Lewis base catalytic system, with desired aryl thioethers **96** and **67l** being produced in low yields of 28% and 34%, respectively. Repetition of the thioarylation of anisole with *N*-(propylthio)succinimide using iron(III) triflimide and diphenyl selenide resulted in a comparable yield of product **64g**. This confirms that the use of *N*-(alkylthio)succinimides is a limitation of the methodology.



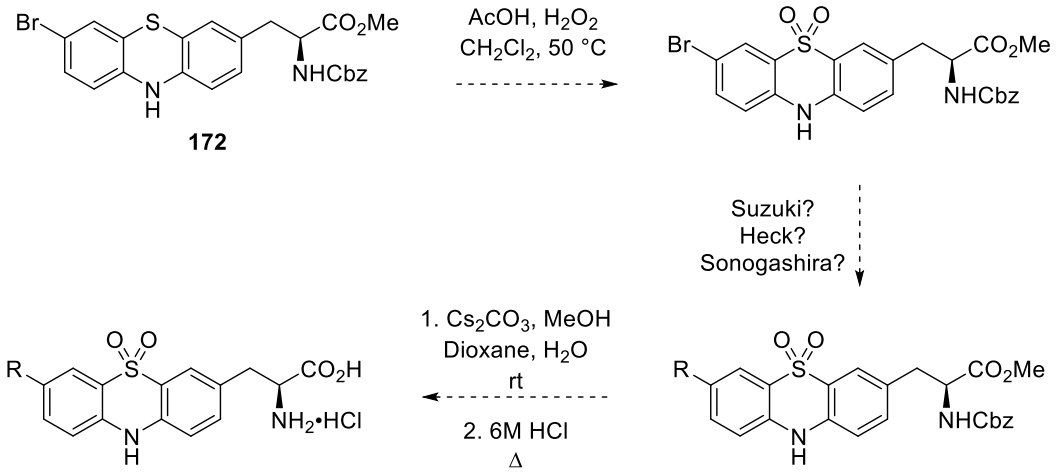
Scheme 123: Iron(III) triflimide/diphenyl selenide dual-catalysed C–H sulfenylation of activated arenes with *N*-arylthiosuccinimides. [a]$FeCl_3$ (10 mol%) and [BMIM]NTf_2 (30 mol%) was used.

4.7 Conclusions and Outlook

In conclusion, a new methodology for the synthesis of phenothiazines using a Lewis acid/Lewis base dual-catalytic system has been developed. Here, a combination of iron(III) triflimide and diphenyl selenide allowed for the efficient *ortho*-thioarylation of unprotected and *N*-benzoyl protected anilines. Optimisation studies identified a copper(I) iodide catalysed Ullman-Goldberg reaction as the best method to cyclise the resulting *N*-benzoyl protected aryl thioethers, giving a small library of *N*-benzoyl protected phenothiazines. Standard Buchwald-Hartwig conditions were undertaken to cyclise the unprotected *ortho*-thioarylated anilines, providing the corresponding phenothiazines. The synthetic utility of the transformation was demonstrated with the synthesis of neuroleptic agent, methopromazine. Furthermore, this new approach for the synthesis of phenothiazines was used to synthesise phenothiazine-dioxide derived α-amino acids. Due to the structural similarity of these compounds to known fluorescent amino acid, acridon-2-ylalanine (Acd), it was hypothesised that

the phenothiazine-dioxide derived α-amino acids may also display promising photophysical properties. Although the two analogues synthesised (**171** and **176**) do not show any red-shift in the absorption and emission relative to Acd, they provide a good starting point for the synthesis of other analogues.

Future work would involve further investigation into the fluorescence properties of phenothiazine-dioxide derived α-amino acids (Scheme 124). It was demonstrated that a bromine functional handle can be installed on the phenothiazine ring, which provides a point for further functionalisation. Transformations such as Suzuki-Miyaura, Heck or Sonogashira cross-coupling reactions could be undertaken to introduce moieties capable of extending the conjugation of the system, and consequentially improve the photophysical properties of the amino acids.



Scheme 124: Potential route towards diversified phenothiazine-dioxide derived α-amino acids.

Phenothiazines are structural motifs with substantial electron density which is generally concentrated around the sulfur atom. The electron rich sulfur atom renders the phenothiazine molecule a strong electron donor. On the other hand, when the sulfide moiety is oxidised to the sulfone, this substantially changes the electronic properties of the heterocycle. Here, the S-atom is electron deficient and so phenothiazine-dioxides are electron acceptors.[147] It follows that future work would also involve investigation of phenothiazine derived α-amino acids as potentially fluorescent amino acids. Due to the observed instability of unprotected phenothiazines in solution and the susceptibility of these structures to oxidising agents, it was proposed that amino acids bearing phenothiazine side-chains would not function as efficient probes in biological systems. However, interestingly, the

majority of fluorescent probes based upon phenothiazine all contain one structural similarity: a simple alkyl *N*-substituent (Figure 21).[148,149,150]

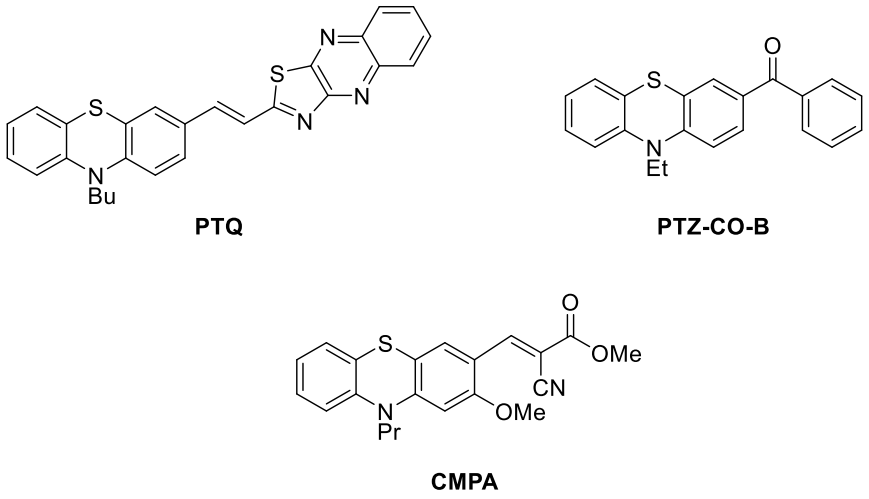
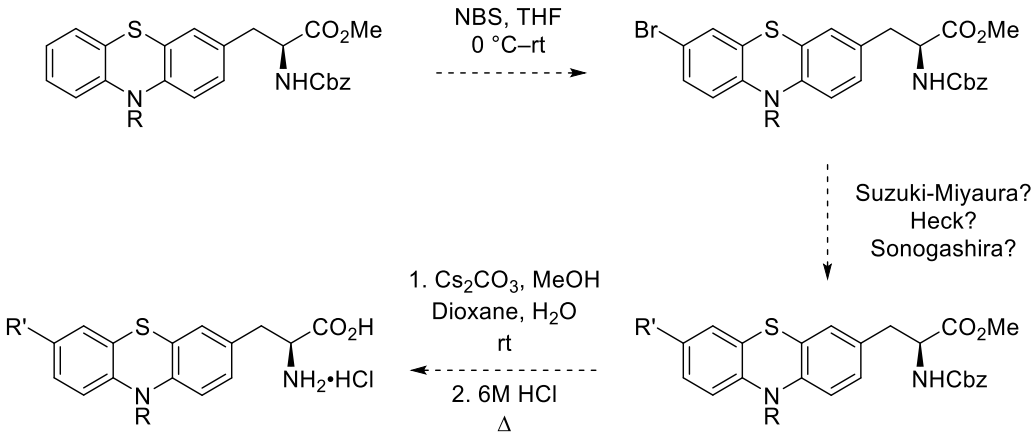


Figure 21: A selection of fluorescent probes based upon phenothiazine.

As such, it is hypothesised that, following cyclisation of *N*-(benzyloxycarbonyl)-[3'-(2''-bromophenylthio)]-L-4'-aminophenylalanine methyl ester (**168**), a simple alkylation could be performed to furnish a more stable phenothiazine scaffold (Scheme 125). From here, bromination with NBS could be used to install a bromine functional handle which is subsequently exploited in cross-coupling reactions to install electron deficient systems. It is proposed that this would allow for the establishment of a push-pull system and result in α-amino acids with good photophysical properties.



Scheme 125: Potential route towards phenothiazine derived α-amino acids.

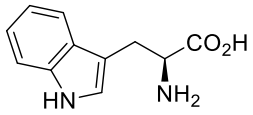
5.0 Tryptophan Derived Fluorescent Amino Acids

5.1 Introduction

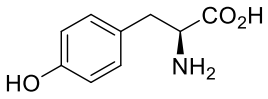
Fluorescence spectroscopy is a powerful technique for the visualisation of biological events.[135] As such, small molecule fluorescent probes are indispensable tools widely used in cell imaging, drug discovery and medical applications such as diagnostic imaging.[151,152] Small molecule fluorophores have the ability to undergo simple structural modifications, which allows for the fine-tuning of excitation and emission properties, as well as control over target binding affinity and chemical reactivity.[151] Whilst there are many examples of other fluorescent probes such as fluorescent proteins[153] and quantum dots,[154] the use of small molecule fluorophores presents several advantages over these techniques such as their small sizes, inexpensive nature, ease of use and their potential for structural modification.[135]

Whilst proteins and peptides play a crucial role in most cellular functions, the lack of intrinsic fluorescence means that fluorescence spectroscopy generally cannot be used to visualise them.[155] Protein labelling is a technique employed to overcome these limitations, which allows for the visualisation of proteins, and subsequent study of biological processes including enzyme activity and protein-protein interactions.[156] One example of protein labelling involves the expression of a protein of interest with a naturally occurring fluorescent protein such as green fluorescent protein (GFP).[157] Whilst the incorporation of GFP has allowed for successful visualisation of proteins and peptides, there are limitations to this approach. Fusion of GFP (or other fluorescent proteins) can result in perturbation of the structure and function of the protein of interest, which can lead to altered biomolecular properties, mislocalisation and misexpression.[107] Another example of protein labelling is to visualise peptides/proteins by using naturally occurring α-amino acids such as tyrosine, tryptophan or phenylalanine.[156,158] However, the poor photophysical properties of proteinogenic α-amino acids (Figure 22) limits their use in imaging, with the intrinsic fluorescence of a protein being dependent on the relative abundance of these amino acids. Additionally, the presence of multiple fluorescent residues in different environments leads to complicated spectroscopy. An alternative method to achieve the effective visualisation of proteins and peptides is to synthesise unnatural fluorescent amino acids where fluorescent scaffolds are affixed to amino acid side-chains.[159,107] Due to their small size, these provide relatively nondisruptive replacements for native residues, allowing the structural

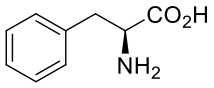
integrity of the target protein or peptide to remain intact.[160] Unnatural fluorescent α-amino acids can be selectively incorporated into peptides through solid phase peptide synthesis (SPPS) or proteins through genetic encoding.[156,160] Furthermore, establishing synthetic routes towards fluorescent unnatural α-amino acids makes them amenable to modification, allowing for the synthesis of analogues with specific photophysical properties for particular applications.



L-Tryptophan
λ_{abs} = 279 nm
λ_{em} = 365 nm
$\varepsilon = 5.58 \times 10^3\ M^{-1}cm^{-1}$
Φ = 0.01–0.4



L-Tyrosine
λ_{abs} = 275 nm
λ_{em} = 310 nm
$\varepsilon = 1.41 \times 10^3\ M^{-1}cm^{-1}$
Φ = 0.14



L-Phenylalanine
λ_{abs} = 258 nm
λ_{em} = 282 nm
$\varepsilon = 0.20 \times 10^3\ M^{-1}cm^{-1}$
Φ = 0.024

Figure 22: Naturally occurring fluorescent amino acids, L-tryptophan, L-tyrosine and L-phenylalanine.

Fluorescence of organic molecules arises when conjugated π systems absorb UV or visible light, and convert the absorbed energy into re-emitted light.[151] In particular, absorption of a photon of light with energy identical to that of the π/ π* energy gap, allows for excitation of a π (HOMO) electron into a π* (LUMO) orbital.[161] This results in the molecule becoming excited into either the first or second excited state energy levels (S_1 or S_2). These levels comprise a number of vibrational and rotational states and are well described by a Jablonski diagram (Figure 23). The excited states are of higher energy than the ground state, which provides a thermodynamic driving force for return to the lower energy level. Firstly, the molecule rapidly dissipates energy and undergoes relaxation to the lowest vibrational state of the S_1 energy level. This occurs through three primary mechanisms including internal conversion (IC), mechanical dissipation and intersystem crossing (ISC). Next, the molecule reverts back to the ground state (S_0), with the emission of a photon of lower energy than initially absorbed, in a process known as fluorescence emission.[135] Due to the difference in wavelengths between the absorbed and emitted light, emission can be efficiently measured with minimal interference from the light source used for excitation.

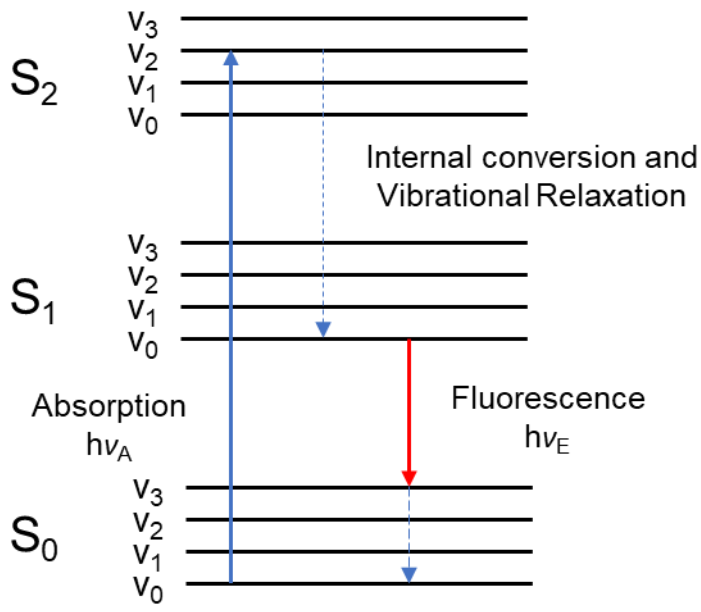


Figure 23: Jablonski diagram showing absorption of a photon of light and subsequent internal conversion and emission.

There are several parameters used to analyse the photophysical properties of a fluorophore.[135] These include the Stokes shift, molar attenuation coefficient (ε), quantum yield (Φ) and brightness. The Stokes shift is measured as the difference in wavelength between the absorption maximum (λ_{abs}) and emission maximum (λ_{em}). It is desirable for a fluorophore to possess as large a Stokes shift as possible, to minimise the reabsorption of emitted light. The molar attenuation coefficient (ε) gives a measure of the efficiency of a fluorophore to absorb light at a given wavelength (usually λ_{abs}). The quantum yield (Φ) is a measurement of the efficiency of a fluorophore to convert excitation energy into emitted energy. It is given as a ratio of the number of photons emitted relative to the number absorbed and it follows that values of quantum yield vary between 0–1, with 1 representing a 'perfect fluorophore'.[151] The brightness of a fluorophore is calculated by multiplication of the molar attenuation coefficient with the quantum yield ($\varepsilon \times \Phi$).

Organic synthesis can be employed to make structural changes to core scaffolds and improve the fluorescence properties. To help design fluorophores with good photophysical properties, three parameters are studied.[135] These include the absorption and emission maxima of a fluorophore, the brightness, and the adjustment of fluorescence properties using interchromophore Förster resonance energy transfer (FRET)[162] or photoinduced electron transfer (PeT).

To design efficient fluorophores, careful consideration should be given to the substituents installed on the core scaffold. In particular, when a core scaffold contains an electron withdrawing group, incorporation of electron donating groups can result in establishment of a donor-π-acceptor moiety.[163] This results in intramolecular charge transfer (ICT) which is understood to enhance photophysical properties and cause red-shifts in absorption and emission spectra. This can partly be rationalised since the excited state of fluorophores exhibiting ICT has a larger dipole moment than the ground state (Figure 24).[151,164]

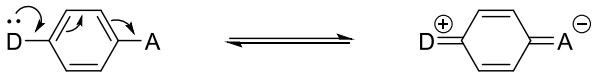


Figure 24: Intramolecular charge transfer resulting from a donor-π-acceptor framework in organic fluorophores.

Due to the change in dipole moment upon excitation, the optimal solvation shell in the ground state rearranges to accommodate this polarisation change. This results in a lower energy of the excited state. However, due to the rapid nature of fluorescence emission, return to the ground state occurs before the solvent shell can rearrange again. As such, the ground state has sub-optimal solvation. This raises the energy of the initial ground state, reducing the π/π* energy gap and leading to a red shift in emission wavelength (Figure 25).[151]

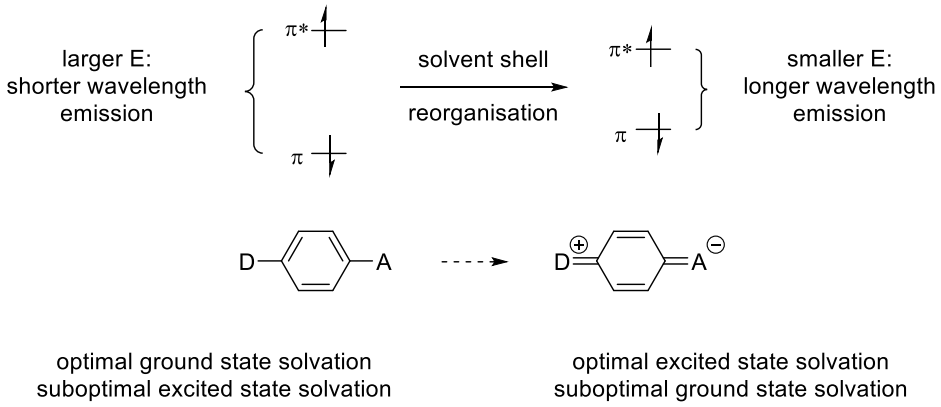


Figure 25: Energy diagram correlating ICT with solvation, in polar solvents.

Increasing the π-conjugation of a fluorophore through installation of aromatic rings and alkenyl groups can result in red-shifted absorption and emission maxima, as well as lead to improved molar attenuation coefficients (ε). The majority of fluorophores developed to date are modifications of known ‘core’ scaffolds such as

naphthalimide, fluorescein, xanthone, BODIPY and rhodamine (Figure 26). Each of these fluorescent scaffolds contain highly conjugated π-systems, with absorption maximum values ranging between 450–550 nm.[135,136,165,166]

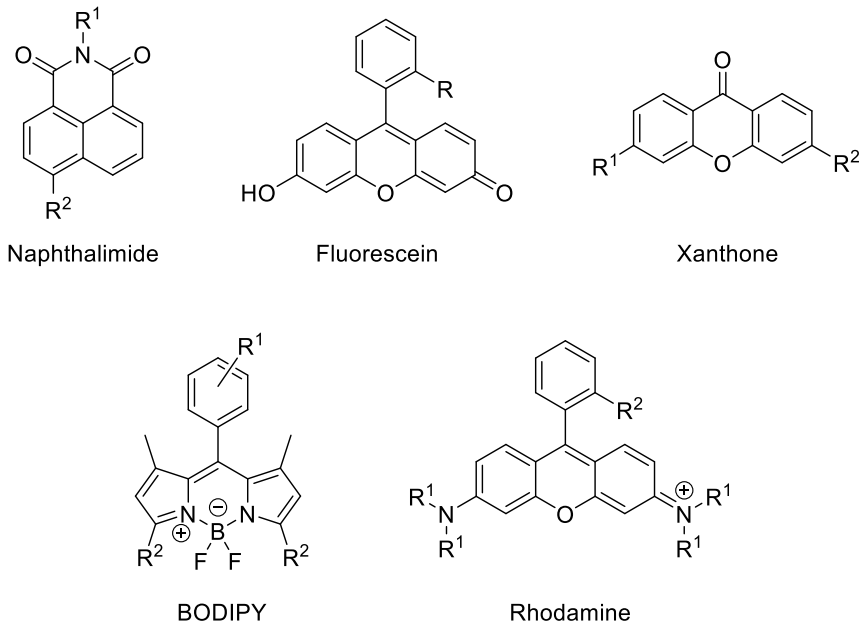
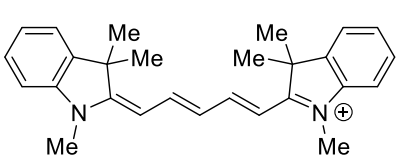
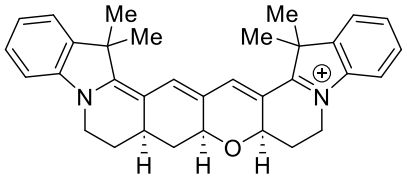


Figure 26: Structures of common core fluorescent scaffolds. R groups represent sites for functionalisation.

Another method widely used to improve the brightness and quantum yield of a fluorophore involves restricting bond rotation.[135,167,168] Conformationally rigid structures display more efficient π-overlap, and present fewer pathways for rotational de-excitation, leading to brighter chromophores.[169] This was demonstrated by Schnermann and co-workers with the structural modification of cyanine **177** to give **178** (Figure 27).[170] The group incorporated a tetracyclic ring system to the pentamethine cyanine polymethine bridge to prevent the main deactivation pathway of the fluorophore, excited-state *trans*-to-*cis* isomerisation. The structural change resulted in a slight red-shift of both the absorption and emission maxima, but the most interesting improvement was the large increase in quantum yield from 0.15 to 0.69.



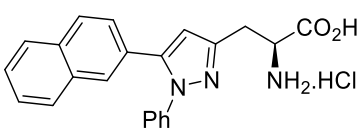
177
λ_{abs} = 638 nm
λ_{em} = 657 nm
ϕ = 0.15



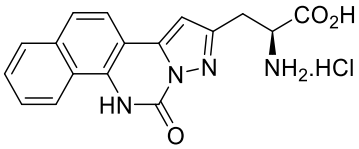
178
λ_{abs} = 662 nm
λ_{em} = 677 nm
ϕ = 0.69

Figure 27: Restriction of bond rotation in **177** resulting in enhanced photophysical properties of **178**.

Another example of restricted bond rotation leading to better fluorescence properties was demonstrated in the Sutherland group with the synthesis of conformationally rigid pyrazoloquinazoline α-amino acids.[169] The group had previously reported the synthesis of 5-arylpyrazole-derived α-amino acids such as **179** (Figure 28).[171] Whilst this class of compounds displayed some promising photophysical properties, the quantum yields and brightness values were sub-optimal. It was proposed that this was due to rotational flexibility between the arene components, and that conformational restriction of the motifs would result in enhanced properties. As such, the group developed a synthetic route towards pyrazoloquinazoline α-amino acids such as **180**. By comparing the photophysical data of **179** and **180**, it is evident that the restriction of bond rotation gave enhanced values of brightness and quantum yield.



179
λ_{abs} = 249 nm
λ_{em} = 356 nm
ϕ = 0.04
brightness = 950 $cm^{-1}M^{-1}$



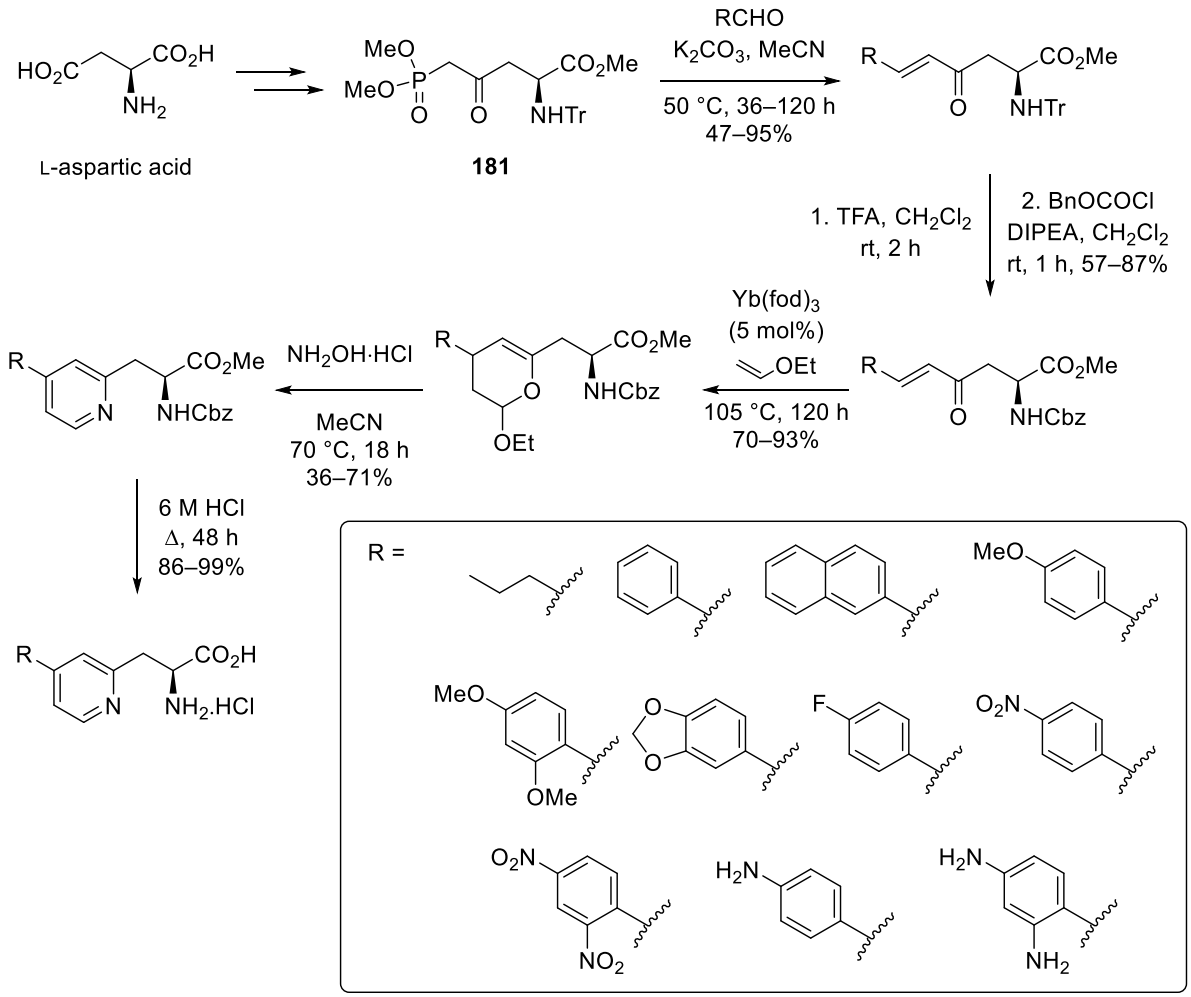
180
λ_{abs} = 350 nm
λ_{em} = 372 nm
ϕ = 0.47
brightness = 3600 $cm^{-1}M^{-1}$

Figure 28: Photophysical data for **179** and **180**.

5.2 Previous work in the Sutherland Group

Previous work in the Sutherland group described the synthesis and fluorescent properties of novel β-pyridyl α-amino acids (Scheme 126).[172] The synthetic route began with commercially available L-aspartic acid, which underwent a short three-

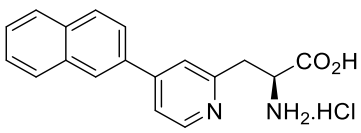
step synthesis to give *N*-trityl protected phosphonate ester **181** (92% overall yield). Subsequent Horner-Wadsworth-Emmons reaction of **181**, with a variety of aldehydes, gave a small library of enones. Following replacement of the *N*-trityl protecting group with the smaller *N*-Cbz protecting group, the enone derived α-amino acids served as substrates for the two-step construction of the pyridine ring. The first step involved a highly regioselective hetero-Diels-Alder cyclisation with ethyl vinyl ether. Next, a modified Knoevenagel-Stobbe reaction gave the desired pyridine ring. Finally, acid-mediated removal of both protecting groups allowed for the isolation of the parent amino acids.



Scheme 126: Synthesis of β-pyridyl α-amino acids.

The library of synthesised analogues contained substituents with various electronic properties. Due to the presence of the π-deficient pyridine moiety, it was hypothesised that the best photophysical properties would result from the compounds containing electron donating functionalities, since this would result in a

'push-pull' system. As expected, weak fluorescence resulted from the α-amino acids containing alkyl and electron-deficient systems, whilst the electron-rich analogues displayed good fluorescence. Two compounds from the substrate scope were found to possess interesting photophysical properties (Figure 29). One was the naphthalene analogue **182**, which displayed the most red-shifted emission spectrum and possessed a MegaStokes shift of 193 nm. However, the best compound was deemed to be the 4-methoxy analogue **183**, which had the largest quantum yield and brightness value. This amino acid was subsequently incorporated into a cell-penetrating hexapeptide using Fmoc-based SPPS methodology.



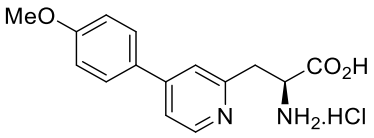
182

λ_{abs} = 259 nm

λ_{em} = 380, 452 nm[a]

ϕ = 0.18

brightness = 6185 $cm^{-1}M^{-1}$



183

λ_{abs} = 286 nm

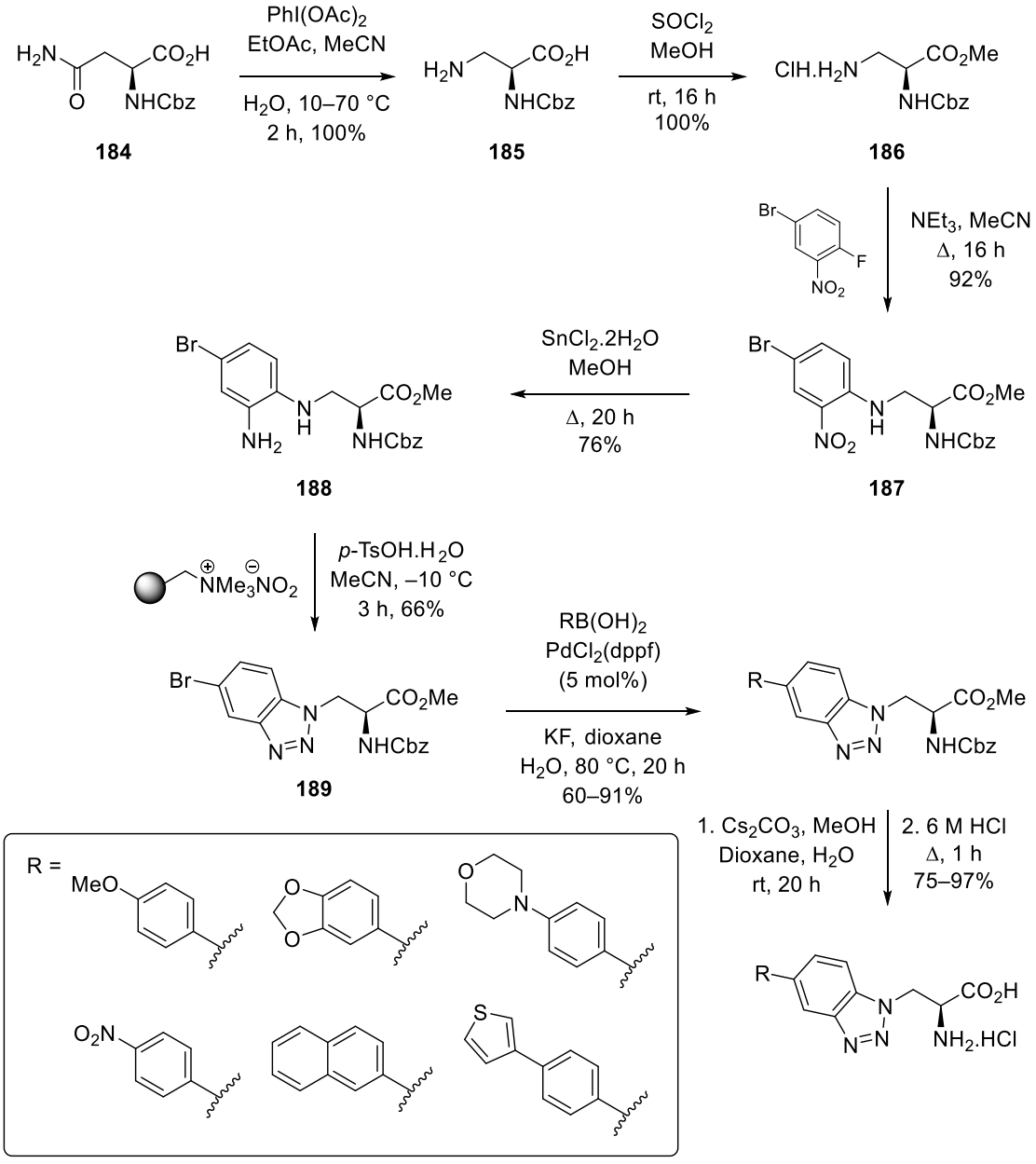
λ_{em} = 366 nm[b]

ϕ = 0.46

brightness = 11,923 $cm^{-1}M^{-1}$

Figure 29: Photophysical data of β-pyridyl α-amino acids containing electron rich substituents. Measured in MeOH at [a]0.5×10^{-5} M, [b]1×10^{-7} M.

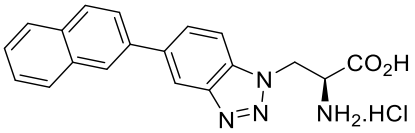
The group have also reported the synthesis of a series of novel fluorescent benzotriazole-derived α-amino acids.[173] Commercially available *N*-Cbz-L-asparagine (**184**) served as the starting material for the synthetic route (Scheme 127). This was converted into L-3-aminoalanine derivative (**186**) *via* a Hofmann rearrangement and subsequent esterification with thionyl chloride and methanol. **186** was then reacted with 5-bromo-2-fluoro-1-nitrobenzene in a nucleophilic aromatic substitution reaction to give **187**. Tin dichloride mediated reduction of the nitro group ensued, and then cyclisation of intermediate **188** was performed using a polymer-supported nitrite reagent and *p*-tosic acid to give benzotriazole **189**. Next, the conjugation of the system was extended by using Suzuki-Miyaura cross-coupling reactions with a range of aryl boronic acids. Deprotection *via* base mediated ester hydrolysis followed by acid-mediated Cbz removal allowed access to the final α-amino acids.



Scheme 127: Synthesis of 5-aryl benzotriazole-derived α-amino acids.

It was proposed that the benzotriazole-derived α-amino acids bearing electron-rich 5-aryl substituents would display the best photophysical properties due to the electron-deficient nature of the benzotriazole ring, and this was confirmed when the 4-nitro analogue did not display any fluorescence in methanol. As expected, the electron rich analogues exhibited strong fluorescence, with emission maxima values ranging between 384–454 nm, and MegaStokes shifts of between 99 and 196 nm. Similar to the results obtained from the synthesis of β-pyridyl α-amino acids, the two best compounds were the 5-naphthalene and 5-*p*-methoxyphenyl substituted analogues (**190** and **191**), which had the highest quantum yields and brightness

values (Figure 30). However, the main limitation associated with the benzotriazole-derived α-amino acids is the similarities of their absorption maxima to that of proteinogenic α-amino acids such as L-phenylalanine, L-tyrosine and L-tryptophan (258 nm, 275 nm and 279 nm, respectively). This prevents their use as fluorescent probes in proteins where, ideally, the absorption maxima of fluorescent amino acids should be above 320 nm, to avoid interference from the aforementioned residues.[107]



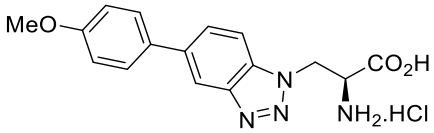
190

λ_{abs} = 286 nm

λ_{em} = 417 nm[a]

ϕ = 0.18

brightness = 1866 $cm^{-1}M^{-1}$



191

λ_{abs} = 256 nm

λ_{em} = 418 nm

ϕ = 0.17

brightness = 3857 $cm^{-1}M^{-1}$

Figure 30: Photophysical data of benzotriazole-derived α-amino acids **190** and **191**, recorded at 1 × 10^{-5} M in MeOH.

To overcome this limitation, the group developed a new class of analogues with extended conjugation in attempt to achieve red-shifted absorption maxima.[174] Here, alkynyl or alkenyl units were installed between the benzotriazole and aryl groups to give alkynyl- and alkenyl-fused benzotriazole-derived α-amino acids, respectively. As hypothesised, the new analogues with extended conjugation all displayed red-shifted absorption maxima (Figure 31). Comparison of the *p*-methoxy analogues shows superior absorption values of 321 nm for alkyne **192** and 320 nm for alkene **193**, relative to **191**. In addition, incorporation of the alkyne unit in **192** led to a compound with improved brightness and quantum yield. An improvement in quantum yield and brightness was also observed in naphthyl-substituted alkyne **194**. As such, these compounds can now be excited in the presence of fluorescent proteinogenic α-amino acids and, alongside their enhanced quantum yields and brightness values, this makes them good candidates for use as fluorescent probes in chemical biology applications.

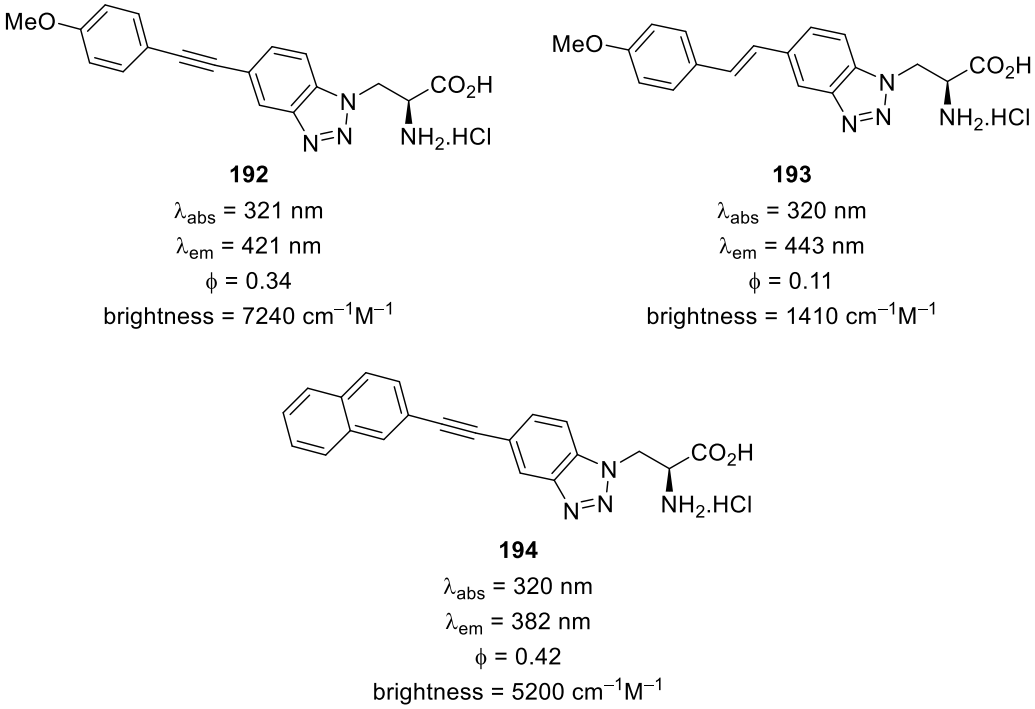
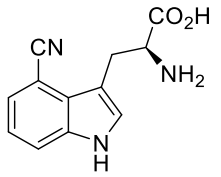


Figure 31: Photophysical data of benzotriazole-derived α-amino acids **192**, **193** and **194** recorded at 1 × 10^{-5} M in MeOH.

5.3 Tryptophan as a Fluorescent Amino Acid

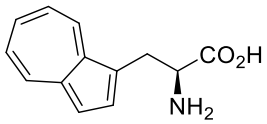
As previously discussed, native protein structures can be easily disrupted by the incorporation of fluorescent labels. As such, there has been great interest in the development of small molecule fluorescent probes derived from fluorescent proteinogenic α-amino acids, such as L-tryptophan, so as to minimise any undesired structural perturbations.[175] Since the absorption and emission maxima for L-tryptophan resides in the ultraviolet region, and its fluorescence quantum yield is relatively low (<0.2 in water), this limits its use as a fluorescent probe. To improve the photophysical properties of the fluorescent amino acid, as well as red-shift the absorption maximum to prevent spectroscopic overlap, efforts have focused on synthesising analogues with extended conjugation.[174] One example of this is 4-cyanotryptophan (Figure 32) which was reported by Hilaire and co-workers.[176] The probe displayed a red-shifted absorption maximum of 325 nm, emission maximum of 405 nm in methanol and a large quantum yield of >0.8 in water.[175] The photophysical properties of 4-cyanotryptophan make it a suitable fluorescent probe for imaging applications, and it has been used to image peptide-cell membrane interactions.[174,176,177]



4-Cyanotryptophan
λ_{abs} = 325 nm
λ_{em} = 405 nm

Figure 32: Structure and absorption and emission maxima for 4-cyanotryptophan.

Additionally, other unnatural α-amino acid fluorescent probes have been developed to act as L-tryptophan mimics, such as β-(1-azulenyl)-L-alanine (AzAla) (Figure 33).[178] The excitation spectrum of this compound shows two absorption maxima at 276 nm and 339 nm, respectively. This allows for selective excitation of AzAla at 339 nm and results in a slight red-shift in emission maximum to 381 nm.[179] AzAla has successfully been incorporated into proteins in place of tryptophan, without any structural or functional disruption.[178] Additionally, the emission profile of AzAla is easy to analyse since it does not possess any functional groups which are environmentally sensitive.



AzAla
λ_{abs} = 276, 339 nm
λ_{em} = 381 nm

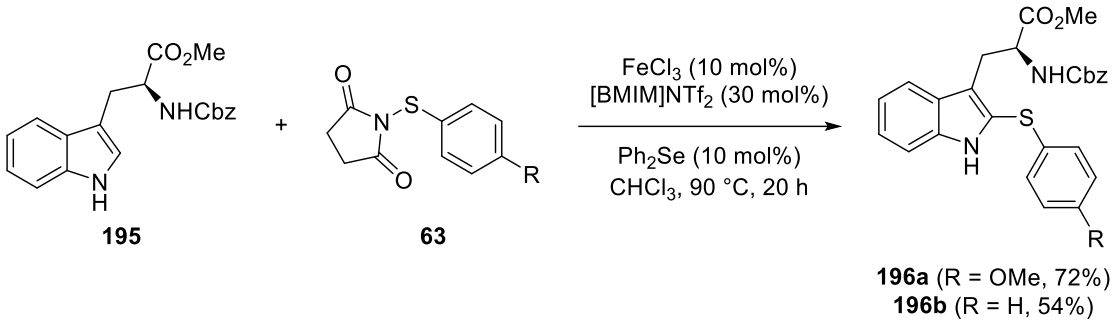
Figure 33: Structure and absorption and emission maxima for AzAla.

5.4 Project Aims

Following the success of previous research in the group, in synthesising fluorescent unnatural α-amino acids, the aim of this project was to explore the use of the iron(III) triflimide/diphenyl selenide dual-catalysed thioarylation reaction for the synthesis of fluorescent α-amino acids. In particular, due to the successful iron(III) triflimide catalysed C-2 thioarylation of *N*-acetyl-L-tryptophanate, discussed in Chapter 2.0, it was proposed that a small library of tryptophan analogues, with extended conjugation, could be synthesised which might possess interesting photophysical properties.

5.5 Synthesis of Tryptophan Derived α-Amino Acids

Firstly, the developed iron(III) triflimide/diphenyl selenide dual-catalytic system was employed for the C–H thioarylation of *N*-[(benzyloxycarbonyl)amino]-L-tryptophan methyl ester (**195**) with *N*-(4-methoxyphenylthio)succinimide (**63a**) and *N*-(phenylthio)succinimide (**63d**), furnishing desired products **196a** and **196b**, in yields of 72% and 54%, respectively (Scheme 128).



Scheme 128: Iron(III) triflimide/diphenyl selenide dual-catalysed C-H thioarylation of **195**.

Next, the absorption and emission spectra of the C-2 functionalised tryptophans, **196a** and **196b**, were investigated (Figures 34 and 35). The graphs for both analogues are very similar, with both **196a** and **196b** exhibiting absorbance maxima at 294 nm – a slight red-shift relative to L-tryptophan. The emission maxima for these compounds both appear around 350 nm although, unfortunately, both analogues are too weakly emissive for quantum yields and brightness to be measured. It follows that neither **196a** or **196b** are likely to function as good fluorescent probes.

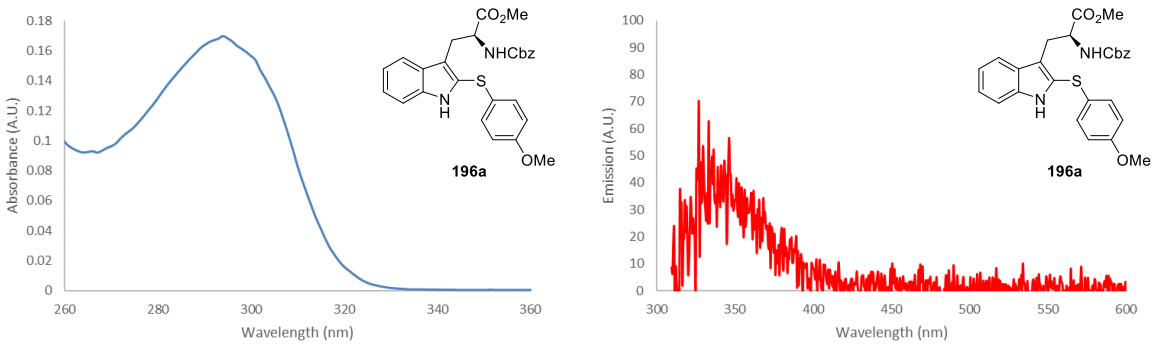


Figure 34: Absorbance and emission spectra for amino acid **196a**. Measured in MeOH at 10 μM, excitation at 294 nm.

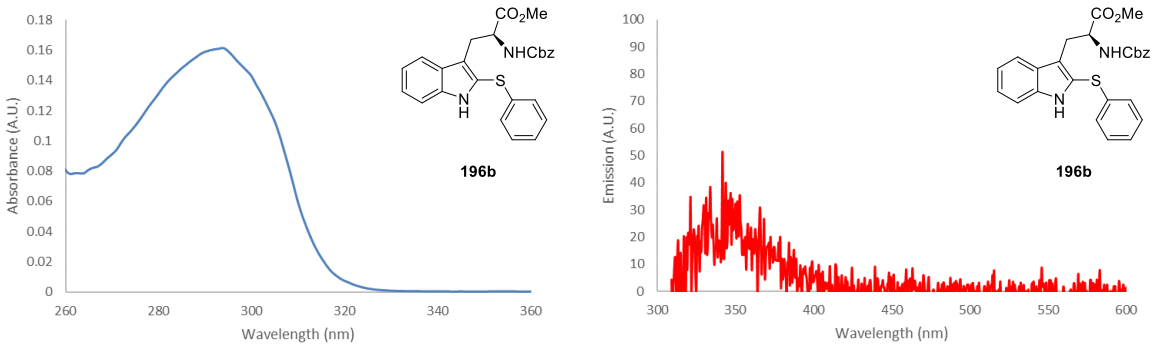
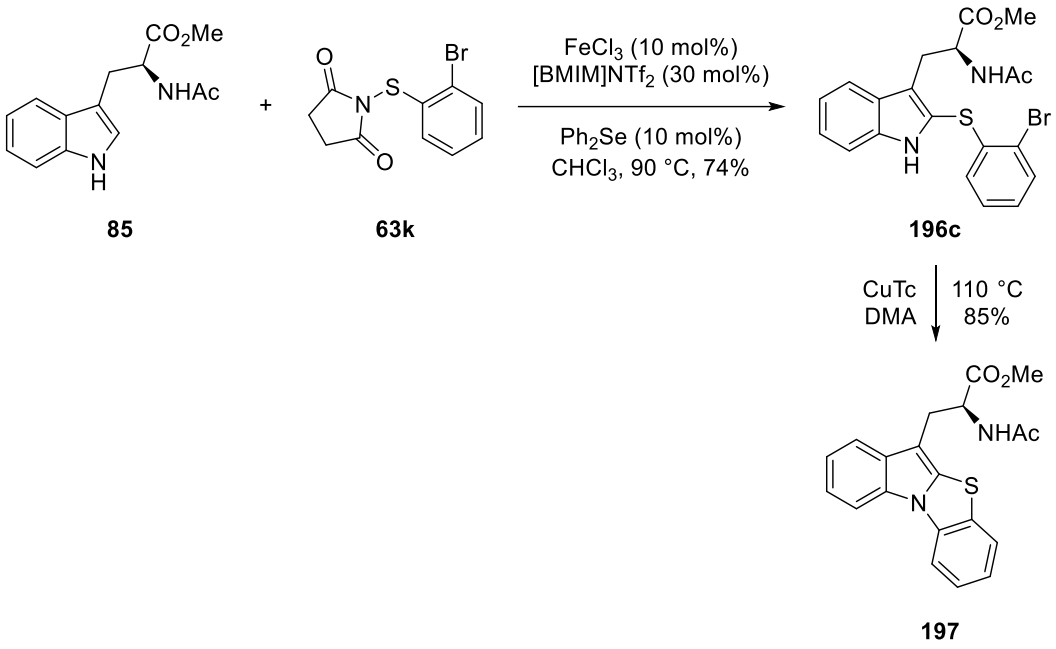


Figure 35: Absorbance and emission spectra for amino acid **196b**. Measured in MeOH at 10 μM, excitation at 294 nm.

It was proposed that the weak emission of these two analogues could be a result of rotational de-excitation. As such, efforts were focused on synthesising a more rigid structure with restricted bond rotation. As well as reducing the number of potential rotational decay pathways, this would deliver a compound with more efficient π-overlap and hopefully result in improved photophysical properties. As the iron(III) triflimide/diphenyl selenide dual-catalysed thioarylation reaction for C-2 functionalisation of protected tryptophan **195** was successful, it was hypothesised that this could be combined with a copper(I)-mediated cyclisation reaction to prepare α-amino acids with benzo[4,5]thiazolo[3,2-*a*]indole side chains. As such, *N*-acetyl-L-tryptophan methyl ester (**85**) was reacted with *N*-(2-bromophenylthio)succinimide under the optimised conditions to give the desired aryl thioether (**196c**) in 74% yield (Scheme 129). This was then cyclised using stoichiometric quantities of copper(I) thiophene-2-carboxylate to give the desired tryptophan-derived α-amino acid **197** in 85% yield.



Scheme 129: Synthesis of tryptophan-derived α-amino acid **197**.

Following the synthesis of tryptophan-derived α-amino acid **197**, the photophysical properties were examined and the absorption and emission spectra were compared to the uncyclized analogues **196a** and **196b** (Figure 36). Inspection of the absorption spectrum shows two absorption maxima, one at 255 nm and a second at 331 nm. As expected, the synthesis of the more rigid compound **197**, resulted in a red-shifted absorption band, allowing for **197** to be selectively excited at 331 nm in the presence of fluorescent proteinogenic α-amino acids. The emission spectrum also highlights a red-shift in emission maximum to 364 nm, with a slight improvement in emission intensity relative to **196a** and **196b**.

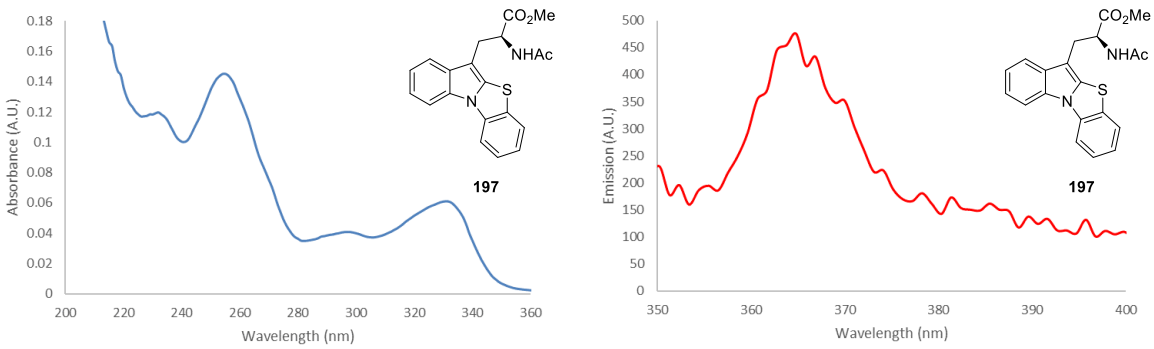


Figure 36: Absorbance and emission spectra for amino acid **197**. Measured in MeOH at 5 μM, excitation at 330 nm.

Despite the implementation of restricted bond rotation resulting in improved photophysical properties, the fluorescence intensity of **197** was still not strong enough for practical applications as a fluorescent probe in chemical biology. As such, it was proposed that analogues of **197** should be synthesised with extended conjugation (Scheme 130). In particular, substituents should be incorporated which result in the establishment of a donor-π-acceptor moiety, allowing for intramolecular charge transfer and enhanced fluorescence. It should be noted that, for further studies, the *N*-acetyl protecting group of the tryptophan starting material was replaced with an *N*-Cbz protecting group. Since work done on the synthesis of phenothiazines (Chapter 4.0) had identified the *N*-Cbz protecting group to be better than the *N*-acetyl protecting group for the iron(III) triflimide/diphenyl selenide dual-catalysed C–H thioarylation reaction, it was decided to use *N*-Cbz protected analogue **195**, as the new starting material. Thioarylation under the optimised conditions gave the desired aryl thioether **196d** in an enhanced yield of 88% relative to the *N*-acetyl protected tryptophan. Next, cyclisation of the aryl thioether using stoichiometric quantities of copper thiophene-2-carboxylate gave **198**, upon which a bromine functional handle was installed using NBS and catalytic hydrogen bromide, furnishing **199** in 79% yield. Suzuki-Miyaura cross-coupling reactions were then undertaken with a range of boronic acids, delivering a small library of protected tryptophan-derived α-amino acids in good yields (74–88%). Here, XPhos Pd G2 (5 mol%) was employed as the catalyst (Figure 37). XPhos Pd G2 is a Buchwald second-generation pre-catalyst which can undergo rapid reductive elimination to form a reactive, monoligated Pd(0) species.[180] The high acidity of the palladium bound aromatic amine allows deprotonation to be achieved in the presence of weak bases. Next, C–N reductive elimination occurs to form indoline and the catalytically active XPhos Pd(0).[181] Additionally, the electron rich nature of the monodentate biaryl ligand promotes oxidative addition, and its steric bulk drives reductive elimination, which results in rapid Suzuki-Miyaura cross-coupling reactions under mild conditions.

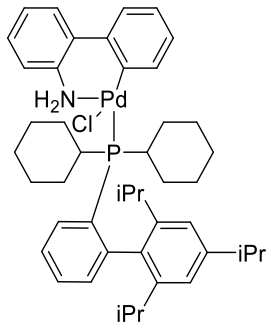
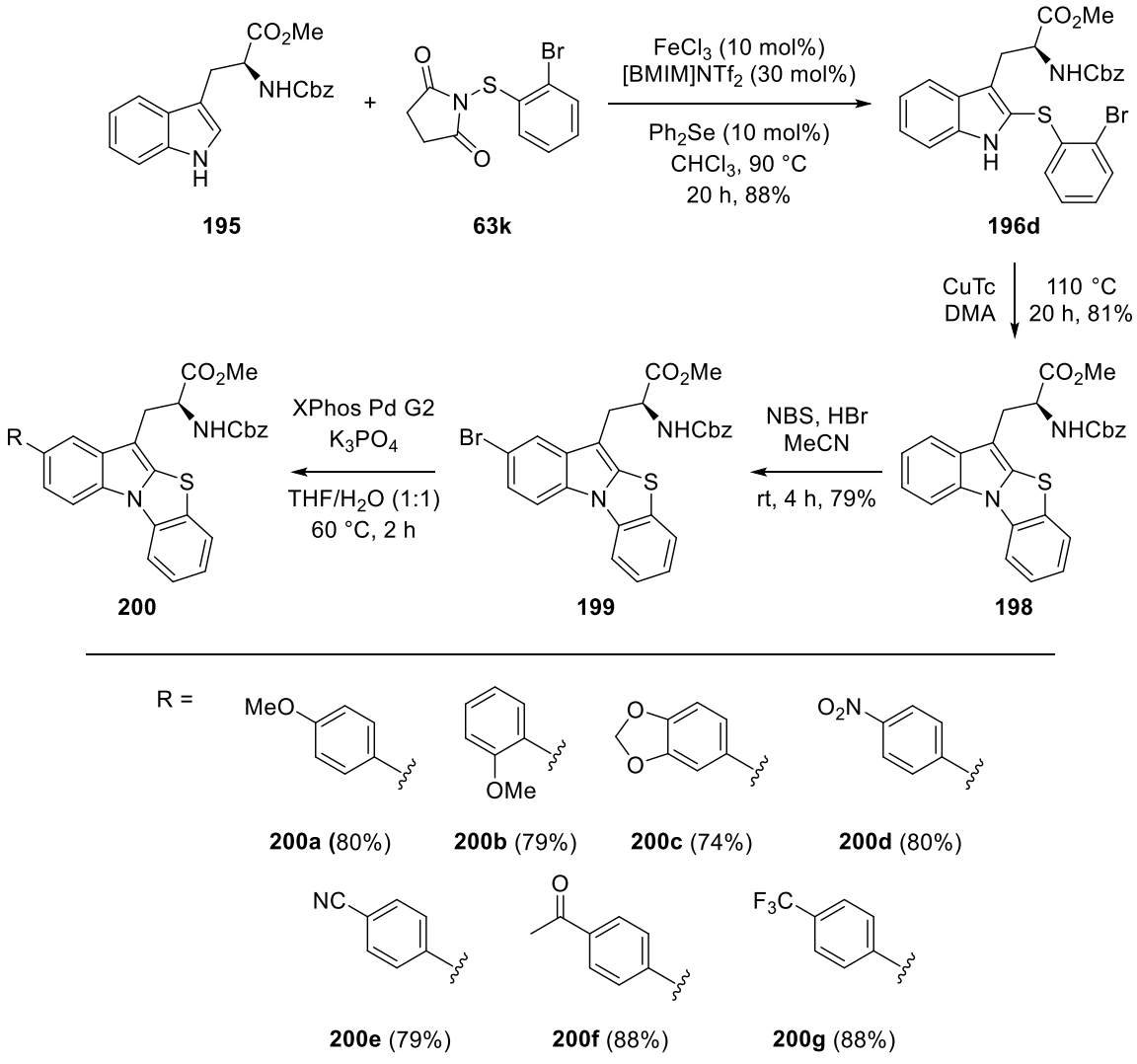


Figure 37: Structure of second-generation Buchwald catalyst, XPhos Pd G2.



Scheme 130: Synthetic route towards tryptophan-derived α-amino acids with extended conjugation.

The absorbance and emission spectra for amino acids **200a**–**200g** were then recorded, to observe how variation of the substituents affected these properties. Although these compounds still contained protecting groups, it was proposed that these would not have a large impact on the photophysical properties, since the

absorption and emission of the Cbz protecting group is outwith the spectroscopic range of interest. Compared to unsubstituted analogue **197**, electron rich 4-methoxy analogue **200a** showed a slight red-shifted absorption band to 348 nm and emission maximum of 392 nm (Figure 38). Data for the 2-methoxy analogue **200b** was similar to that of the 4-methoxy analogue, exhibiting an absorption band at 343 nm, and an emission maximum at 405 nm (Figure 39). The electron donating benzodioxazole analogue **200c** displayed an absorption band at 350 nm, and an emission maximum of 408 nm, slightly red-shifted relative to the two methoxy analogues (Figure 40). The electron withdrawing 4-cyano analogue **200e** showed a substantial bathochromic shift for both spectra with an absorption band at 373 nm and an emission maxima at 497 nm (Figure 41). It should also be noted that the introduction of the 4-cyanophenyl substituent resulted in a much stronger emission peak. The spectra for the 4-acetyl analogue **200f** presented the most red-shifted absorption band of all the compounds, with a value of 376 nm (Figure 42). Additionally, a huge bathochromic shift in emission maximum was observed (541 nm), with **200f** possessing a MegaStokes shift of 165 nm. Finally, promising results were also obtained from the study of the 4-trifluoromethyl analogue **200g**, with this compound showing a strong absorption band at 359 nm, and a strong emission peak with a maximum value at 453 nm (figure 43). It follows that all these compounds possess interesting photophysical properties. They all exhibit strong absorption bands above the threshold of 320 nm, which allows excitation in the presence of fluorescent proteinogenic α-amino acids. It should also be noted that the emission maxima for these compounds lie in the visible region, which is favourable for a wide range of biological applications.

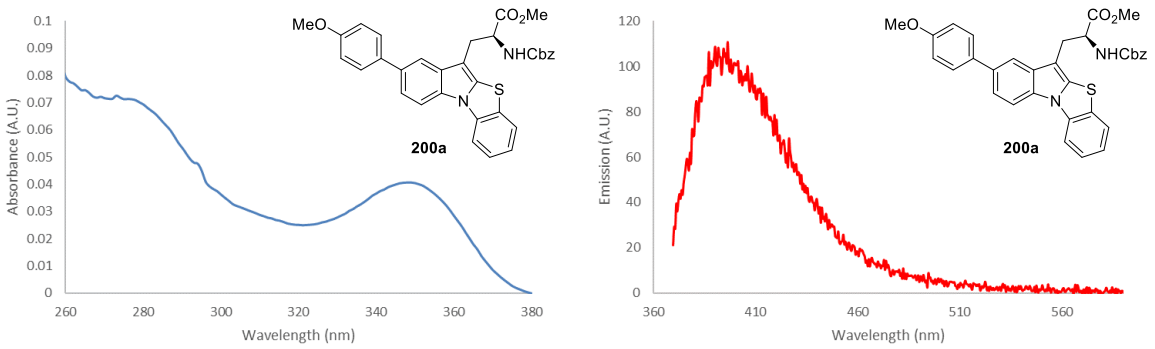


Figure 38: Absorbance and emission spectra of amino acid **200a**. Measured in DMSO at 2 μM, excitation at 348 nm.

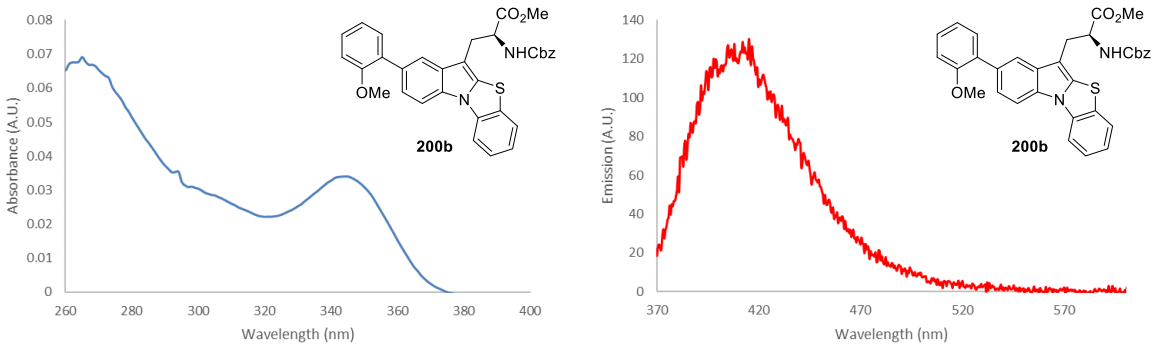


Figure 39: Absorbance and emission spectra of amino acid **200b**. Measured in DMSO at 2 μM, excitation at 343 nm.

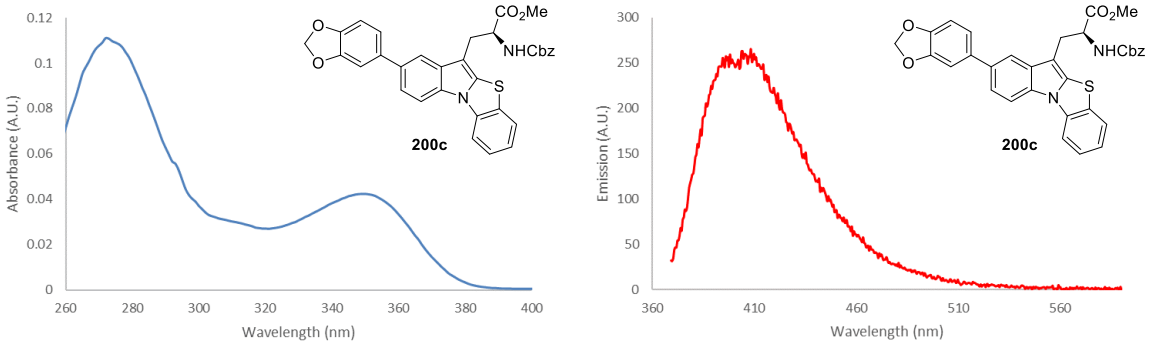


Figure 40: Absorbance and emission spectra of amino acid **200c**. Measured in DMSO at 2 μM, excitation at 350 nm.

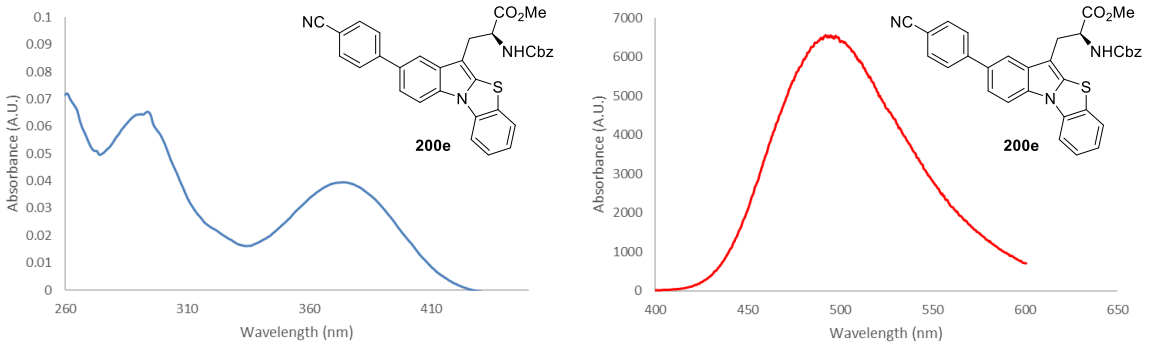


Figure 41: Absorbance and emission spectra of amino acid **200e**. Measured in DMSO at 2 μM, excitation at 373 nm.

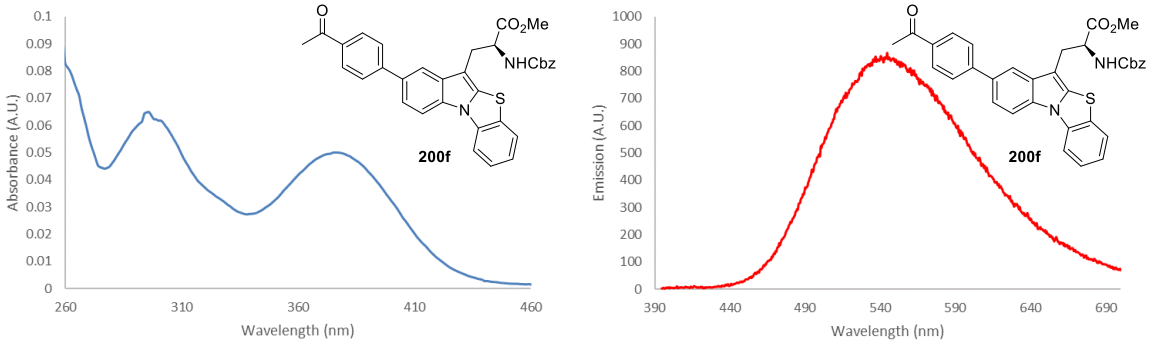


Figure 42: Absorbance and emission spectra of amino acid **200f**. Measured in DMSO at 2 μM, excitation at 376 nm.

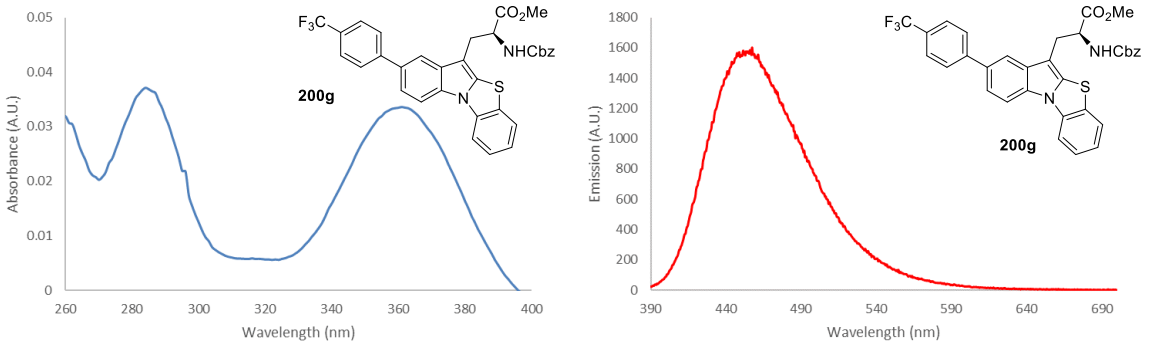


Figure 43: Absorbance and emission spectra of amino acid **200g**. Measured in DMSO at 2 μM, excitation at 359 nm.

Following the measurement of absorbance and emission for the amino acids, further investigation of their photophysical properties was undertaken (Table 8). Molar attenuation coefficients (ε) and quantum yields (Φ) were measured and subsequently used to calculate the brightness of the compounds. The quantum yields were calculated using anthracene as a standard, since all analogues displayed strong absorption peaks around 350 nm. Of all the Suzuki-Miyaura cross-coupling products, the compounds bearing electron withdrawing substituents showed the best fluorescence properties. Despite showing a high molar attenuation coefficient of 19100 cm^{-1} M^{-1}, the 4-methoxy analogue **200a** exhibited the smallest Stokes shift, brightness and quantum yield. Although being slightly red-shifted and having a better brightness and quantum yield than the 4-methoxy analogue, the 2-methoxy analogue **200b** did not display fluorescent properties which could compete with the electron withdrawing analogues. Of all the electron rich analogues, benzodioxazole analogue **200c** demonstrated the most promising photophysical properties, with a molar extinction coefficient of 21100 cm^{-1} M^{-1} and a quantum yield

of 0.136. However, this did not result in a strong brightness value. The 4-cyano analogue **200e** remained a compound of interest with a MegaStokes shift of 124 nm. Alongside the large molar attenuation coefficient of 20400 cm^{-1} M^{-1} and good quantum yield (0.777), **200e** possessed a strong brightness of 15860 cm^{-1} M^{-1}. The 4-acetyl analogue **200f** possessed both the most red-shifted absorption and emission wavelengths at 376 nm and 541 nm respectively, resulting in a MegaStokes shift of 165 nm. The large molar attenuation coefficient of 20800 cm^{-1} M^{-1}, and quantum yield of 0.643 resulted in a brightness value of 13380 cm^{-1} M^{-1}. Finally, the 4-trifluoromethyl analogue **200g** showed the strongest brightness (17450 cm^{-1} M^{-1}) as a result of the extremely high quantum yield (0.920) and large molar attenuation coefficient (18900 cm^{-1} M^{-1})

Studies have shown that in indoles, excitation from the ground state to the first excited state coincide with a partial charge transfer from the pyrrole ring to the benzene ring.[175,182,183] Therefore, it was proposed that installation of electron withdrawing substituents would invoke red-shifts in the absorption and emission data. This was demonstrated by Hilaire and co-workers in their analysis of the photophysical properties of 4-cyanotryptophan.[176] It follows that, the benzo[4,5]thiazolo[3,2-*a*]indole core in compounds **200a**–**200g**, which is electron rich, was operating as the 'electron donor' component of a donor-π-acceptor moiety. Incorporation of the electron withdrawing groups likely led to the efficient establishment of a 'push-pull' system, allowing for intramolecular charge transfer and rationalising the best photophysical properties being observed in compounds **200e**, **200f** and **200g**. From these results, it was decided to carry forward these three analogues as lead compounds for further investigation.

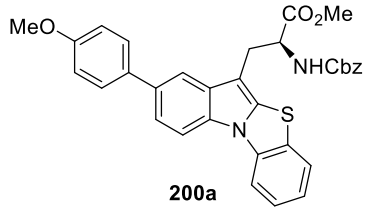
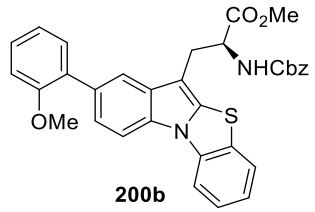
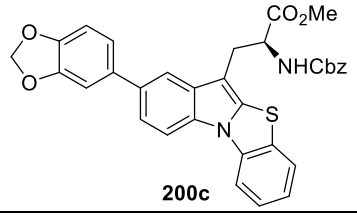
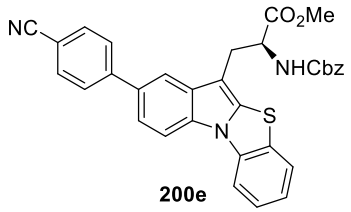
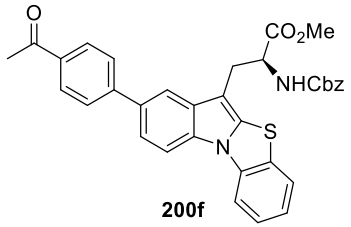
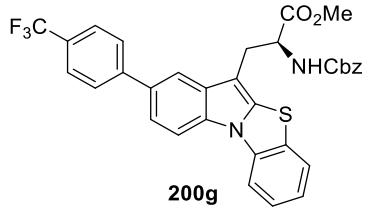
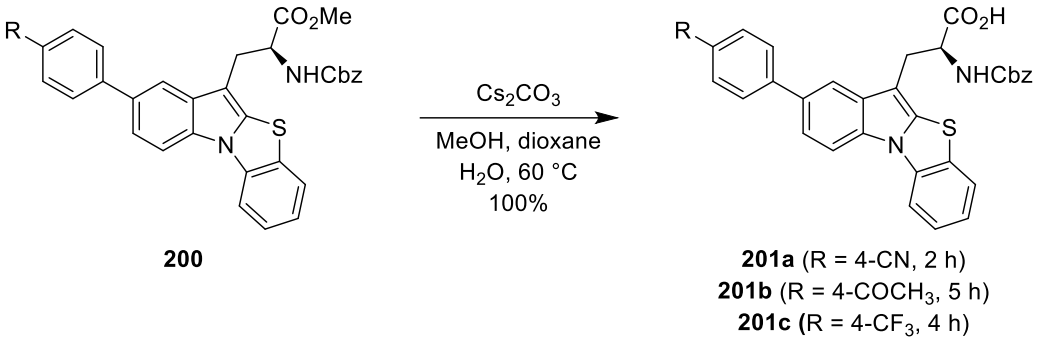
Compound	λ_{abs} (nm)	λ_{em} (nm)	ε ($cm^{-1}\,M^{-1}$)	Stokes Shift (nm)	Quantum Yield (Φ)	Brightness ($cm^{-1}\,M^{-1}$)
 **200a**	348	392	19100	44	0.049	932
 **200b**	343	405	18500	62	0.084	1560
 **200c**	350	408	21100	58	0.136	2870
 **200e**	**373**	**497**	**20400**	**124**	**0.777**	**15860**
 **200f**	**376**	**541**	**20800**	**165**	**0.643**	**13380**
 **200g**	**359**	**453**	**18900**	**94**	**0.920**	**17450**

Table 8: Photophysical properties of protected amino acids **200a**–**200f**.

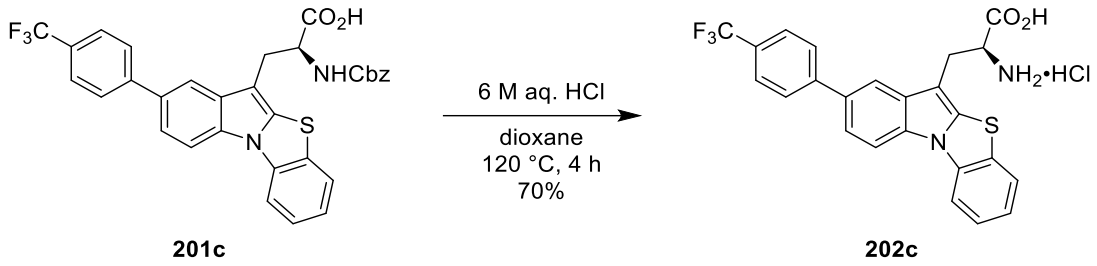
Next, a robust deprotection strategy was proposed to allow access to the final α-amino acids. Firstly, the conditions which allowed for successful deprotection of the phenoxathiin and phenothiazine-dioxide-derived α-amino acids were attempted. This involved initial ester hydrolysis at room temperature using cesium carbonate in a mixture of methanol, water and 1,4-dioxane (Scheme 131). Compounds **200e**–**200g** were found to be insoluble in this solvent system at room temperature and, as such, the temperature was raised to 60 °C to aid dissolution. This resulted in the

isolation of the desired carboxylic acids **201a**–**201c** in quantitative yields after 2–5 h.



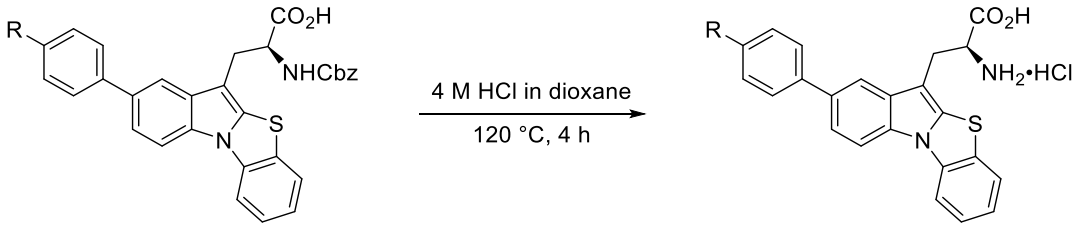
Scheme 131: Ester deprotection of fluorescent α-amino acids **200** using cesium carbonate.

Next, acid mediated removal of the Cbz-protecting group using 6 M aqueous hydrochloric acid was attempted. Whilst this resulted in isolation of the desired product in 70% yield for the 4-trifluoromethyl analogue (**201c**) (Scheme 132), Cbz-deprotection of the 4-acetyl and 4-cyano analogues under these conditions did not give clean reactions. For the 4-cyano analogue, hydrolysis of the nitrile group to the corresponding carboxylic acid was the main side reaction. It was proposed that the harsh acidic conditions resulted in decomposition of the 4-acetyl analogue **201b**.



Scheme 132: Acid mediated Cbz-deprotection of α-amino acid **201c**.

To prevent undesired hydrolysis occurring, it was proposed that the reactions should be performed using anhydrous 4 M hydrochloric acid in 1,4-dioxane (Scheme 133). Fortunately, this minimised the formation of side products and allowed for the isolation of desired products of **202a** and **202b** in 23% and 49% yield, respectively, following recrystallisation. The low yields of these reactions can be rationalised by the small scale of reaction.



201a (R = 4-CN)
201b (R = 4-$COCH_3$)

202a (R = 4-CN, 23%)
202b (R = 4-$COCH_3$, 49%)

Scheme 133: Acid mediated Cbz-deprotection of α-amino acids **201a** and **201b**.

Following successful deprotection, the photophysical properties of the free amino acids (**202a**, **202b** and **202c**) were investigated. It was observed that removal of the methyl and Cbz- protecting groups did not result in any sizable alteration to the absorption and emission maxima values (Figures 44–46). Compounds **202a**, **202b** and **202c** display strong absorption bands at 375 nm, 378 nm and 362 nm, respectively, which is almost identical to the absorption bands of the protected analogues. The emission maxima wavelengths also remained very similar, appearing at 499 nm, 545 nm and 461 nm for compounds **202a**, **202b** and **202c**, respectively.

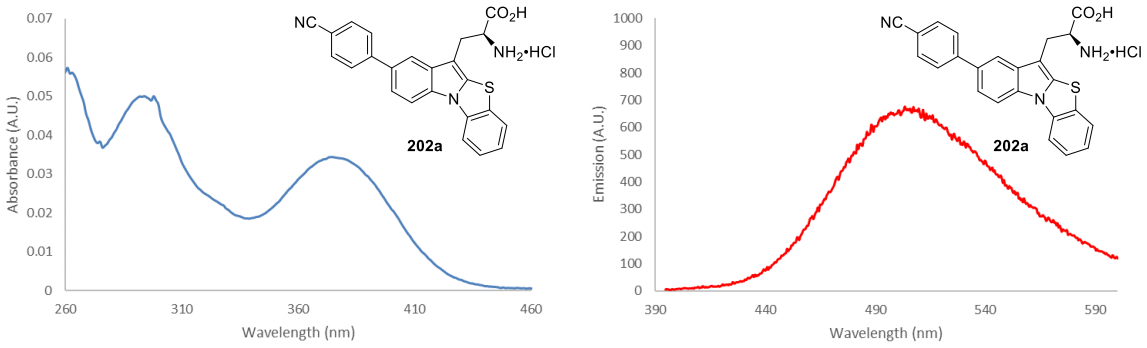


Figure 44: Absorbance and emission spectra of amino acid **202a**. Measured in DMSO at 2 μM, excitation at 375 nm.

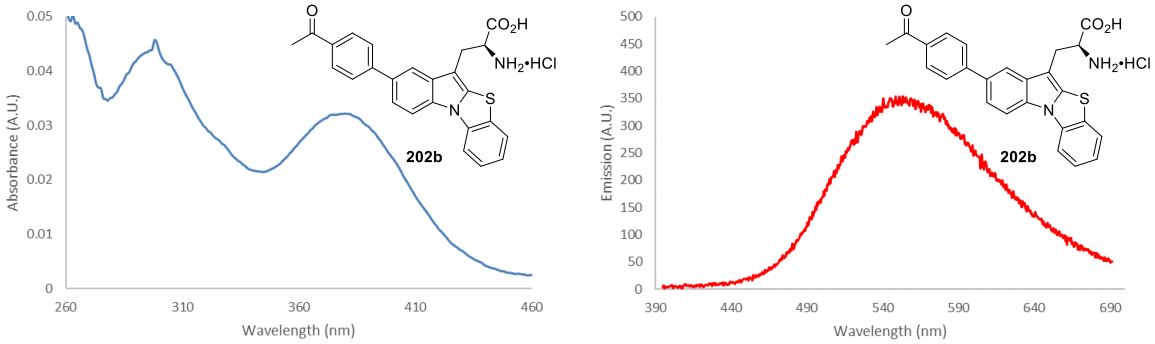


Figure 45: Absorbance and emission spectra of amino acid **202b**. Measured in DMSO at 2 μM, excitation at 378 nm.

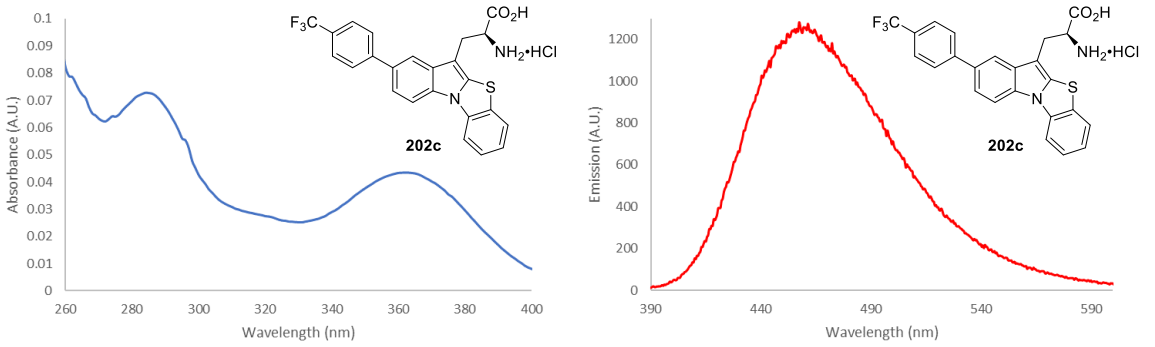


Figure 46: Absorbance and emission spectra of amino acid **202c**. Measured in DMSO at 2 μM, excitation at 362 nm.

Further photophysical properties of the three lead compounds were next determined (Table 9). These highlighted that, whilst deprotection of the α-amino acids resulted in a decrease in quantum yield and therefore brightness values for all analogues, the fluorescence data remained positive. The 4-cyano analogue **202a** displayed the highest molar attenuation coefficient (16200 $^{-1}$ M^{-1}) and maintained a MegaStokes shift of 124 nm upon deprotection. The high value of quantum yield also gave rise to a large brightness value (11370 $^{-1}$ M^{-1}). The 4-acetyl analogue **202b** displayed the largest Stokes shift (167 nm), and possessed the most red-shifted absorption and emission maxima of the three compounds. Whilst the quantum yield for this analogue was the lowest of the three (0.46), it remains very high, emphasizing the highly attractive fluorescence properties of all the lead compounds. Finally, the 4-trifluoromethyl analogue **202c** possessed a large molar attenuation coefficient (16100 cm^{-1} M^{-1}) which, in combination with the highest value of quantum yield (0.73), resulted in the brightest fluorophore. Based on this data, 4-trifluoromethyl analogue **202c** was selected for further analysis, since this had the highest values of brightness and quantum yield.

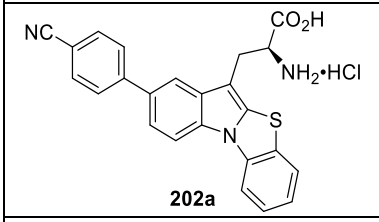
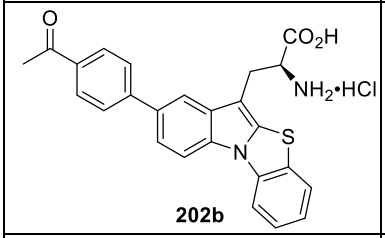
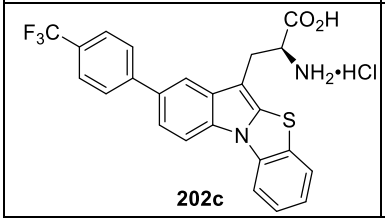
Compound	λ_{abs} (nm)	λ_{em} (nm)	ε (cm^{-1} M^{-1})	Stokes Shift (nm)	Quantum Yield (Φ)	Brightness (cm^{-1} M^{-1})
 **202a**	375	499	16200	124	0.70	11370
 **202b**	378	545	14800	167	0.46	6743
 **202c**	362	461	16100	99	0.73	11677

Table 9: Photophysical properties of amino acids **202a**–**202c**.

A solvatochromic study was undertaken with this analogue (**202c**), which showed that the emission wavelength was not solvent dependent (Figure 47). This is a positive result, since a lack of environmental sensitivity allows easy analysis of the fluorophore's emission profile.[178] It was proposed that the weak emission of **202c** in buffer solution was due to the lack of solubility of the compound in aqueous media, as opposed to fluorescence quenching.

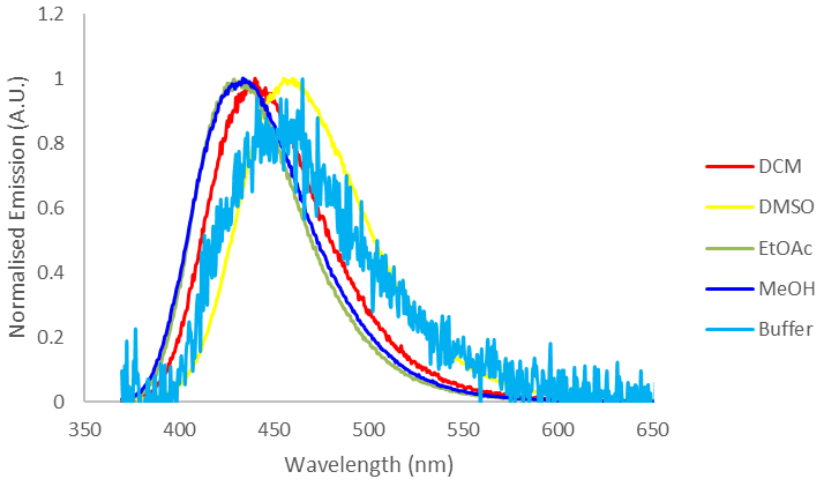
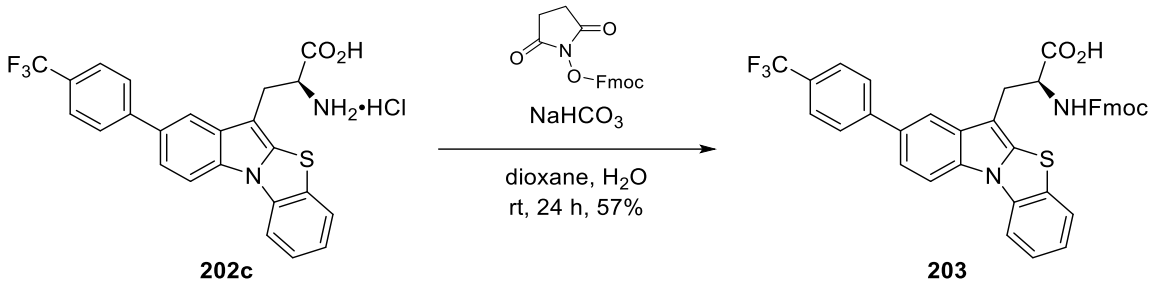


Figure 47: Solvatochromic study undertaken with 4-trifluoromethyl analogue **202c**.

The main aim of this project was to investigate the use of the developed iron(III) triflimide/diphenyl selenide dual-catalysed C–H thioarylation reaction as a key step in the synthesis of fluorescent amino acids derived from L-tryptophan, which was achieved. The next stage of this project would be the incorporation of **202c** into a peptide for chemical biology imaging applications. To allow for incorporation of **202c** into a peptide using SPPS, this required the synthesis of Fmoc protected analogue (**203**). *N*-Fmoc-protection of **202c** was achieved using *N*-(9-fluorenylmethoxycarbonyloxy)succinimide and sodium hydrogencarbonate as the base (Scheme 134). Desired product (**203**) was obtained in 57% yield after 24 h at room temperature.

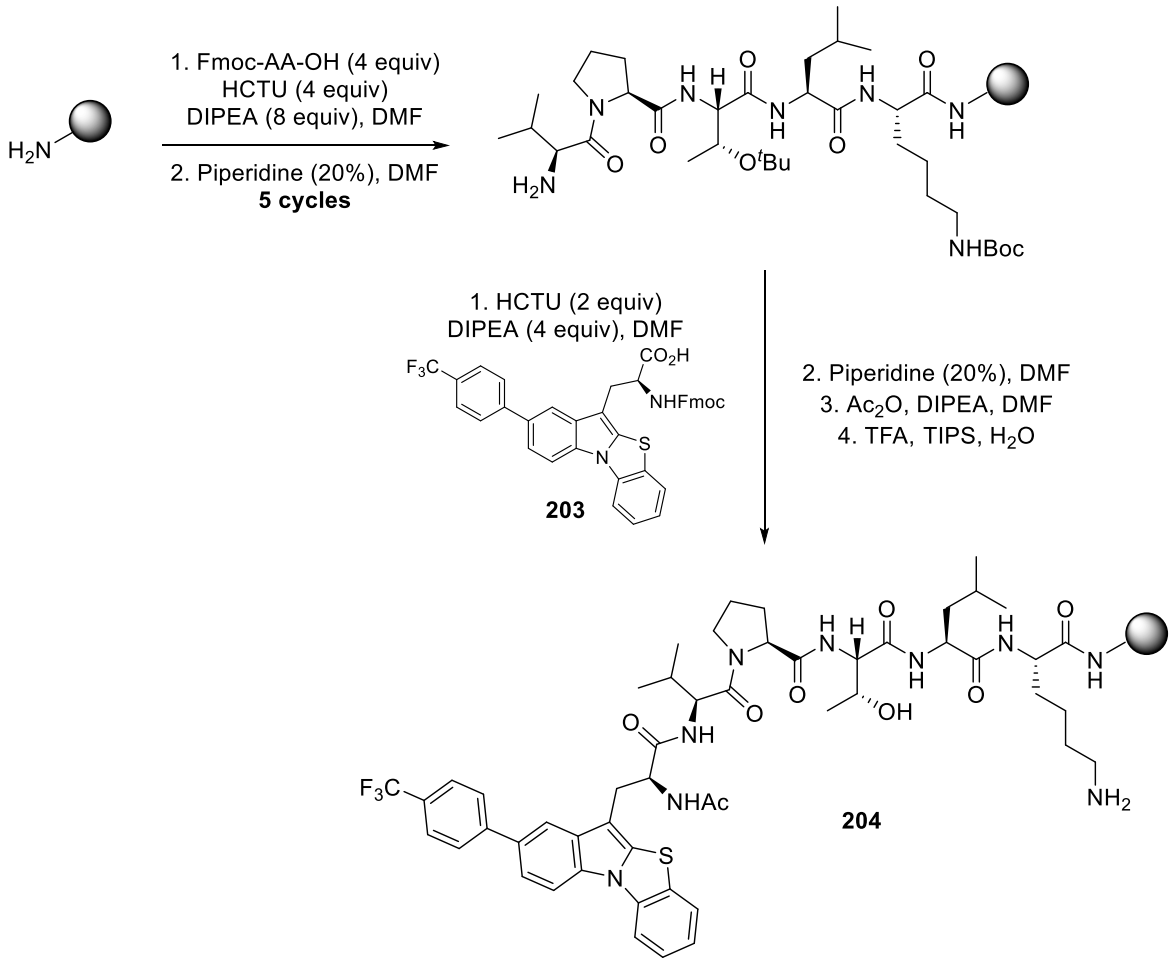


Scheme 134: Fmoc protection of α-amino acid **202c**.

5.6 Conclusions and Outlook

In conclusion, a route to a new class of fluorescent α-amino acids derived from tryptophan has been developed, which used the iron(III) triflimide/diphenyl selenide dual-catalytic C–H thioarylation reaction as the key step. Subsequent cyclisation, bromination and Suzuki-Miyaura cross-coupling reactions allowed for the synthesis of a small library of compounds, which all displayed red-shifted absorption and emission maxima relative to L-tryptophan. This allows for their selective excitation in the presence of fluorescent proteinogenic α-amino acids. Further analysis of the photophysical properties revealed that the most fluorescent compounds contained electron withdrawing functionalities. As such, three compounds were identified as lead compounds and deprotection strategies for these analogues were developed to give the final α-amino acids. A solvent study was then carried out on the 4-trifluoromethyl analogue (**202c**), demonstrating that emission wavelengths were not solvent dependent. Fmoc protection of **202c** was also performed to give **203**, which could be used in SPPS for incorporation into a peptide.

Future work would involve investigating the suitability of Fmoc protected amino acid **203** for use in SPPS. This would also be used to confirm if the key photophysical properties of **202c** are retained upon incorporation into a peptide. One example of a peptide which could be used includes the pentapeptide (Val-Pro-Thr-Leu-Lys), which has been previously employed within the group for the incorporation of a fluorescent pyrazoloquinazoline α-amino acid.[169] This peptide is based on the Bax-binding domain of Ku70,[184] and was chosen due to its low cytotoxicity and cell penetrating abilities.[185] It is hypothesised that this peptide could be prepared using standard SPPS procedures, followed by incorporation of **203** to achieve a hexapeptide (**204**) (Scheme 135). Upon synthesis of **204**, the photophysical properties would be studied.



Scheme 135: Proposed synthesis of a hexapeptide containing α-amino acid **202c**.

Additionally, future work would investigate the viability of two-photon excitation for amino acids **202a**, **202b** and **202c**. Two-photon excitation involves the use of light of near-IR wavelength for fluorophore excitation.[186] The use of UV light for excitation

has the potential to cause cellular and tissue damage due to photobleaching. As such, the use of longer wavelengths of light for excitation would allow for cellular imaging with less risk of biological damage. Two-photon excitation involving light of wavelength 700 nm, requires the fluorophore to exhibit an absorption maximum at half this wavelength (350 nm).[187] Since the absorption maxima of **202a**, **202b** and **202c** appear at wavelengths of 375 nm, 378 nm and 362 nm, respectively, these compounds have the potential to act as good candidates for two-photon excitation.

6.0 Experimental

6.1 General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. *N*-Bromosuccinimide was recrystallised from water and dried under high vacuum before use. Dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed open to air unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Merck Millipore matrix silicagel 60 (40–63 μM). Merck aluminium-backed plates pre-coated with silica gel 60 (UV254) were used for thin-layer chromatography and visualised with a UV lamp. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 or 500 MHz spectrometer, with chemical shift values reported in ppm relative to tetramethylsilane (δ_H 0.00 and δ_c 0.00), or residual chloroform (δ_H 7.26), dimethylsulfoxide (δ_H 2.50) or methanol (δ_H 3.31) as standard. For ^{13}C NMR the chemical shifts are reported relative to the central resonance of $CDCl_3$ (δ_c 77.2), DMSO-*d*$_6$ (δ_c 39.5) or CD_3OD (δ_c 49.0) as standard. Proton and carbon assignments are based on two-dimensional COSY, HSQC, HMBC and DEPT experiments. Mass spectra were obtained either using a JEOL JMS-700 spectrometer for EI and CI, and Bruker Microtof-q or Agilent 6125B for ESI. Infrared spectra were obtained neat using a Shimadzu IR Prestige-21 spectrometer or Shimadzu 8400S spectrometer; wavenumbers are indicated in cm^{-1}. Melting points were determined on either a Reichert platform melting point apparatus or Stuart Scientific melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Both UV-Vis spectra and fluorescence spectra were recorded on a Horiba Duetta Fluorescence and Absorbance spectrometer. Absorbance spectra were recorded with an integration time of 0.05 s, and a band pass of 5 nm. Fluorescence spectra for phenoxathiin and phenothiazine derived α-amino acids were recorded with an excitation and emission band pass of 5 nm, an integration time of 2 s, and with detector accumulations set to 1. Fluorescence spectra for L-tryptophan derived α-amino acids were recorded with excitation and emission band pass of 5 nm, an integration time of 0.05 s, and with detector accumulations set to 1. Respective standard samples were recorded with the same parameters.

Quantum yields were determined using a comparative method against two standards. Anthracene (Φ = 0.27, in ethanol) and L-tryptophan (Φ = 0.14 in water) were used as standard references. The integrated fluorescence intensity of each compound was determined from the emission spectra given. Measurements were performed at five different concentrations. Concentrations were chosen to ensure the absorption value was below 0.1 to avoid re-absorption effects. Integrated fluorescence intensity was plotted as a function of the measured absorbance and a linear fit was calculated. The resultant gradient was then used to calculate the quantum yield, using the equation below:

$$\phi_x = \phi_{ST}\left(\frac{Grad_{ST}}{Grad_X}\right)\left(\frac{\eta_x^2}{\eta_{ST}^2}\right)$$

Subscript ST signifies the quantities associated with the quantum yield standard. Subscript X signifies the quantities associated with the novel compound. $Grad_X$ is the determined gradient associated with the novel compound. $Grad_{ST}$ is the determined gradient associated with quantum yield standard. η is the refractive index of the solvent used in the fluorescence measurements. η = 1.333 for water, 1.361 for ethanol, 1.331 for methanol and 1.4772 for DMSO.

6.2 Regioselective C–H Thioarylation of Electron Rich Arenes Experimental

General Procedure A: Preparation of *N*-thiosuccinimides

N-Chlorosuccinimide (1.0 equiv.) was added to a stirred solution of thiol (1.0 equiv.) in toluene (4 mL toluene/1.0 mmol thiol) at room temperature under argon. After 1 h, the solution had changed colour from colourless to yellow-orange. A solution of triethylamine (1.0 equiv.) in toluene (1.6 mL toluene/1.0 mmol triethylamine) was then added dropwise over a period of 0.5 h. The resulting reaction mixture was stirred at 40 °C for 16 h before being diluted with diethyl ether (12 mL ether/1.0 mmol thiol). The resulting white precipitate was filtered and the filtrate concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography.

General Procedure B: Preparation of sulfenylated products

Iron(III) trichloride (2.5 mol%) was dissolved in [BMIM]NTf_2 (7.5 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-

thiosuccinimide (1.2 equiv.) in chloroform (1.0 M in arene). The arene (1.0 equiv.) was then added and the reaction mixture was left to stir at the required temperature for 2 – 68 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

General Procedure C: Preparation of sulfenylated products

Iron(III) trichloride (5 mol%) was dissolved in [BMIM]NTf_2 (15 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-thiosuccinimide (1.2 equiv.) in chloroform (1.0 M in arene). The arene (1.0 equiv.) was then added and the reaction mixture was left to stir at the required temperature for 2 – 20 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

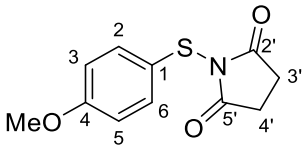
General Procedure D: Preparation of sulfenylated products

Iron(III) trichloride (10 mol%) was dissolved in [BMIM]NTf_2 (30 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-thiosuccinimide (1.2 equiv.) in chloroform (1.0 M in arene). The arene (1.0 equiv.) was then added and the reaction mixture was left to stir at the required temperature for 20 – 96 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

Time Dependent NMR Studies

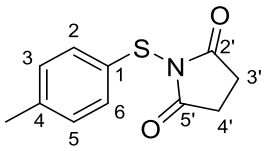
To a solution of $CDCl_3$ (0.5 mL), was added anisole (50 µL, 0.46 mmol), 1.2 equivalents of *N*-thiosuccinimide and 2 mg of hexamethylcyclotrisiloxane (as an internal standard). An NMR spectrum was recorded prior to the addition of catalyst for internal standard calibration. The catalyst was added and the reaction mixture divided into 5 vials corresponding to each time point. Spectra were recorded at the relevant time points and conversion was determined by internal standard with integration of the *N*-thiosuccinimide peak.

N-(4-Methoxyphenylthio)succinimide (63a)[48]



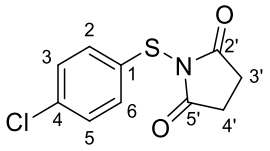
The reaction was performed as described in general procedure A using 4-methoxythiophenol (614 µL, 4.99 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(4-methoxyphenylthio)succinimide (878 mg, 74%) as a pale pink solid. Mp 102−103 °C (lit.[48] 106−110 °C); δ_H (400 MHz, $CDCl_3$) 2.75 (4H, s, 3'-H_2 and 4'-H_2), 3.80 (3H, s, OCH_3), 6.82–6.87 (2H, m, 3-H and 5-H), 7.72–7.76 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 28.7 (2 × CH_2), 55.6 (CH_3), 114.8 (2 × CH), 124.7 (C), 137.5 (2 × CH), 161.9 (C), 176.6 (2 × C); *m/z* (ESI) 260 (MNa^+. 100%).

N-(4-Methylphenylthio)succinimide (63b)[48]



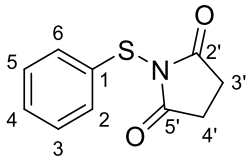
The reaction was performed as described in general procedure A using 4-methylthiophenol (500 mg, 4.03 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(4-methylphenylthio)succinimide (798 mg, 90%) as a white solid. Mp 113−114 °C (lit.[48] 113−115 °C); δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, 4-CH_3), 2.77 (4H, s, 3'-H_2 and 4'-H_2), 7.13 (2H, d, *J* 8.0 Hz, 2-H and 6-H), 7.57 (2H, d, *J* 8.0 Hz, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 21.4 (CH_3), 28.7 (2 × CH_2), 130.2 (2 × CH), 130.5 (C), 133.8 (2 × CH), 141.0 (C), 176.6 (2 × C); *m/z* (ESI) 244 (MNa^+. 100%).

***N*-(4-Chlorophenylthio)succinimide (63c)**[188]



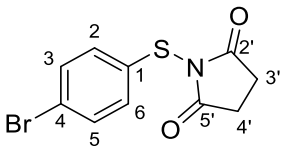
The reaction was performed as described in general procedure A using 4-chlorothiophenol (500 mg, 3.46 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(4-chlorophenylthio)succinimide (453 mg, 54%) as a white solid. Mp 141−143 °C (lit.[188] 142−144 °C); δ_H (400 MHz, $CDCl_3$) 2.82 (4H, s, 3'-H_2 and 4'-H_2), 7.29–7.34 (2H, m, 2-H and 6-H), 7.57–7.63 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 28.7 (2 × CH_2), 129.7 (2 × CH), 132.3 (C), 134.5 (2 × CH), 136.8 (C), 176.3 (2 × C); *m/z* (ESI) 264 (MNa^+. 100%).

***N*-(Phenylthio)succinimide (63d)**[48]



The reaction was performed as described in general procedure A using thiophenol (466 µL, 4.54 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(phenylthio)succinimide (447 mg, 47%) as a white solid. Mp 112–113 °C (lit.[48] 115–116 °C); δ_H (400 MHz, $CDCl_3$) 2.81 (4H, s, 3'-H_2 and 4'-H_2), 7.30–7.37 (3H, m, 3-H, 4-H and 5-H), 7.59–7.64 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 28.7 (2 × CH_2), 129.5 (2 × CH), 130.1 (CH), 132.5 (2 × CH), 134.1 (C), 176.5 (2 × C); *m/z* (ESI) 230 (MNa^+. 100%).

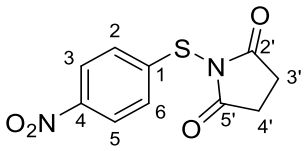
***N*-(4-Bromophenylthio)succinimide (63e)**[48]



The reaction was performed as described in general procedure A using 4-bromothiophenol (500 mg, 2.64 mmol). Purification by flash column chromatography

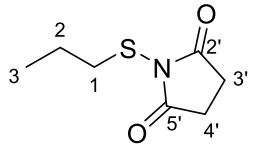
(hexane/ethyl acetate, 3:2) gave *N*-(4-bromophenylthio)succinimide (321 mg, 43%) as a white solid. Mp 141−143 °C (lit.[48] 143−146 °C); δ_H (400 MHz, $CDCl_3$) 2.81 (4H, s, 3'-H_2 and 4'-H_2), 7.45–7.52 (4H, m, 2-H, 3-H, 5-H and 6-H); δ_C (101 MHz, $CDCl_3$) 28.7 (2 × CH_2), 124.9 (C), 132.7 (2 × CH), 133.0 (C), 134.4 (2 × CH), 176.3 (2 × C); *m/z* (ESI) 310 (MNa^+. 100%).

N-(4-Nitrophenylthio)succinimide (63f)[48]



The reaction was performed as described in general procedure A using 4-nitrothiophenol (500 mg, 3.22 mmol). Purification by flash column chromatography (dichloromethane) gave *N*-(4-nitrophenylthio)succinimide (256 mg, 32%) as a white solid. Mp 169−173 °C (lit.[48] 172−175 °C); δ_H (400 MHz, $CDCl_3$) 2.96 (4H, s, 3'-H_2 and 4'-H_2), 7.43–7.46 (2H, m, 2-H and 6-H), 8.15–8.19 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 28.9 (2 × CH_2), 124.6 (2 × CH), 127.8 (2 × CH), 143.1 (C), 147.5 (C), 175.7 (2 × C); *m/z* (ESI) 275 (MNa^+. 100%).

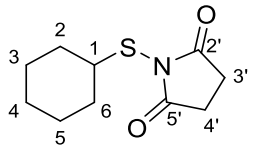
N-(Propanethio)succinimide (63g)[189]



A round bottomed flask was charged with a solution of *N*-chlorosuccinimide (877 mg, 6.57 mmol) in toluene (25 mL) under an atmosphere of argon. To the flask was added a solution of 1-propanethiol (610 µL, 6.57 mmol) in toluene (7 mL) dropwise and the resulting suspension was left to stir at 40 °C for 1 h. A solution of triethylamine (916 µL, 6.57 mmol) in toluene (5 mL) was added dropwise and the resulting reaction mixture was left to stir at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product. Purification by flash

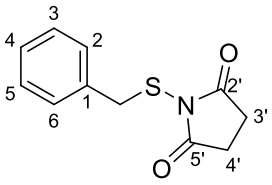
column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(propanethio)succinimide (927 mg, 82%) as a colourless oil. Spectroscopic data were consistent with the literature.[189] δ_H (400 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7.3 Hz, 3-H_3), 1.55 (2H, sext., *J* 7.3 Hz, 2-H_2), 2.81 (2H, t, *J* 7.3 Hz, 1-H_2), 2.83 (4H, s, 3'-H_2 and 4'-H_2); δ_C (101 MHz, $CDCl_3$) 13.1 (CH_3), 21.6 (CH_2), 28.7 (2 × CH_2), 39.7 (CH_2), 177.3 (2 × C); *m/z* (ESI) 196 (MNa^+. 100%).

N-(Cyclohexylthio)succinimide (63h)[190]



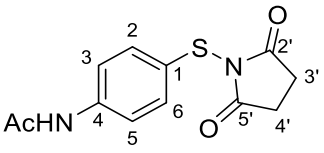
A round bottomed flask was charged with a solution of *N*-chlorosuccinimide (1.15 g, 8.60 mmol) in toluene (20 mL) under an atmosphere of argon. To the flask was added a solution of cyclohexanethiol (1.05 mL, 8.60 mmol) in toluene (15 mL) dropwise and the resulting suspension was left to stir at 40 °C for 1 h. A solution of triethylamine (1.20 mL, 8.60 mmol) in toluene (13 mL) was added dropwise and the resulting reaction mixture was left to stir at 40 °C for 16 h. The toluene was removed under reduced pressure and the resulting residue was dissolved in water (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(cyclohexylthio)succinimide (1.45 g, 79%) as a white solid. Mp 100−103 °C (lit.[190] 102−104 °C); δ_H (400 MHz, $CDCl_3$) 1.21−1.37 (5H, m, 3-H_2, 4-H, 5-H_2), 1.58−1.65 (1H, m, 4-H), 1.76−1.86 (4H, m, 2-H_2, 6-H_2), 2.84 (4H, s, 3'-H_2 and 4'-H_2), 3.13−3.25 (1H, m, 1-H); δ_C (101 MHz, $CDCl_3$) 25.5 (2 × CH_2), 25.6 (CH_2), 28.7 (2 × CH_2), 31.1 (2 × CH_2), 48.6 (CH), 177.6 (2 × C); *m/z* (ESI) 236 (MNa^+. 100%).

***N*-(Benzylthio)succinimide (63i)**[190]



A round bottomed flask was charged with a solution of *N*-chlorosuccinimide (537 mg, 4.03 mmol) in toluene (15 mL) under an atmosphere of argon. To the flask was added a solution of benzyl mercaptan (475 μL, 4.03 mmol) in toluene (6 mL) dropwise and the resulting suspension was left to stir at 40 °C for 1 h. A solution of triethylamine (561 μL, 4.03 mmol) in toluene (5 mL) was added dropwise and the resulting reaction mixture was left to stir at 40 °C for 16 h. The toluene was removed under reduced pressure and the resulting residue was dissolved in water (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(benzylthio)succinimide (526 mg, 59%) as a white solid. Mp 158−160 °C (lit.[190] 159−161 °C); δ_H (400 MHz, $CDCl_3$) 2.62 (4H, s, 3'-H_2 and 4'-H_2), 4.09 (2H, s, SCH_2), 7.23−7.33 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 28.5 (2 × CH_2), 41.1 (CH_2), 128.2 (CH), 128.7 (2 × CH), 129.8 (2 × CH), 134.0 (C), 176.6 (2 × C); ***m/z*** (ESI) 244 (MNa^+. 100%).

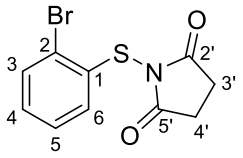
***N*-(4-Acetamidophenylthio)succinimide (63j)**



A round bottomed flask was charged with a solution of *N*-chlorosuccinimide (399 mg, 2.99 mmol) in chloroform (5 mL) under an atmosphere of argon. To the flask was added a suspension of 4-acetamidothiophenol (500 mg, 2.99 mmol) in chloroform (10 mL) dropwise and the resulting suspension was left to stir at 50 °C for 1 h. A solution of triethylamine (417 μL, 2.99 mmol) in chloroform (5 mL) was added dropwise and the resulting reaction mixture was left to stir at 50 °C for 20 h. The reaction mixture was allowed to cool to room temperature prior to the addition of saturated aqueous ammonium chloride (30 mL). The organic layer was separated

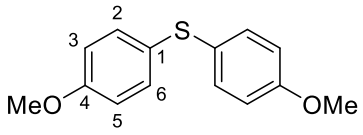
and the aqueous layer was further extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (hexane/ethyl acetate, 1:9) gave *N*-(4-acetamidophenylthio)succinimide (320 mg, 41%) as a yellow solid. Mp 145–147 °C; ν_{max}/cm^{-1} (neat) 3348 (NH), 2984 (CH), 1713 (CO), 1684 (CO), 1591 (C=C), 1520, 1288, 1142, 1007, 816; δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, CH_3), 2.79 (4H, s, 3'-H_2 and 4'-H_2), 7.47 (2H, d, *J* 8.5 Hz, 2-H and 6-H), 7.58–7.70 (3H, m, 3-H, 5-H and NH); δ_C (101 MHz, $CDCl_3$) 24.8 (CH_3), 28.7 (2 × CH_2), 120.3 (2 × CH), 128.5 (C), 135.3 (2 × CH), 140.2 (C), 168.7 (C), 176.6 (2 × C); *m/z* (ESI) 287.0466 (MNa^+. $C_{12}H_{12}N_2NaO_3S$ requires 287.0461).

N-(2-Bromophenylthio)succinimide (63k)[188]



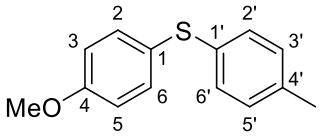
A round bottomed flask was charged with a solution of *N*-chlorosuccinimide (1.42 g, 10.6 mmol) in toluene (28 mL) under an atmosphere of argon. To the flask was added a solution of 2-bromothiophenol (1.27 mL, 10.6 mmol) in toluene (20 mL) dropwise and the resulting suspension was left to stir at 40 °C for 1 h. A solution of triethylamine (1.48 mL, 10.6 mmol) in toluene (20 mL) was added dropwise and the resulting reaction mixture was left to stir at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product. Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(2-bromophenylthio)succinimide (2.05 g, 68%) as a white solid. Mp 126−129 °C (lit.[188] 128−130 °C); δ_H (400 MHz, $CDCl_3$) 2.97 (4H, s, 3'-H_2 and 4'-H_2), 6.80 (1H, dd, *J* 8.0, 1.5 Hz, 6-H), 7.06−7.11 (1H, m, 4-H), 7.22−7.27 (1H, m, 5-H), 7.52 (1H, dd, *J* 8.0, 1.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 29.0 (2 × CH_2), 119.2 (C), 125.2 (CH), 128.2 (CH), 128.4 (CH), 133.3 (CH), 135.5 (C), 175.9 (2 × C); *m/z* (ESI) 310 (MNa^+. 100%).

Bis(4-methoxyphenyl)sulfane (64a)[191]



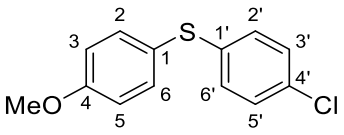
The reaction was performed as described in general procedure B using anisole (50.0 µL, 0.460 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave *bis*(4-methoxyphenyl)sulfane (102 mg, 90%) as a white solid. Mp 43−44 °C (lit.[191] 44−45 °C); δ_H (400 MHz, $CDCl_3$) 3.79 (6H, s, 2 × OCH_3), 6.80–6.88 (4H, m, 2 × 3-H and 2 × 5-H), 7.24–7.34 (4H, m, 2 × 2-H and 2 × 6-H); δ_C (101 MHz, $CDCl_3$) 55.5 (2 × CH_3), 114.9 (4 × CH), 127.6 (2 × C), 132.9 (4 × CH), 159.1 (2 × C); *m/z* (ESI) 269 (MNa^+. 100%).

(4-Methoxyphenyl)(*p*-tolyl)sulfane (64b)[191]



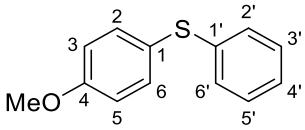
The reaction was performed as described in general procedure B using anisole (50 µL, 0.46 mmol). The reaction mixture was stirred at room temperature for 5 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (4-methoxyphenyl)(*p*-tolyl)sulfane (93 mg, 88%) as a white solid. Mp 42−43 °C (lit.[191] 43−44 °C); δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, 4'-CH_3), 3.81 (3H, s, 4-OCH_3), 6.85–6.89 (2H, m, 3-H and 5-H), 7.04–7.09 (2H, m, 2'-H and 6'-H), 7.11–7.16 (2H, m, 3'-H and 5'-H), 7.34–7.39 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 21.1 (CH_3), 55.5 (CH_3), 115.0 (2 × CH), 125.8 (C), 129.6 (2 × CH), 129.9 (2 × CH), 134.5 (2 × CH), 134.5 (C), 136.3 (C), 159.6 (C); *m/z* (EI) 230 (M^+. 100%), 215 (35).

(4'-Chlorophenyl)(4-methoxyphenyl)sulfane (64c)[26]



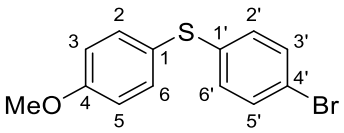
The reaction was performed as described in general procedure B using anisole (50.0 µL, 0.460 mmol). The reaction mixture was stirred at 60 °C for 68 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (4'-chlorophenyl)(4-methoxyphenyl)sulfane (103 mg, 90%) as a white solid. Mp 59−61 °C (lit.[26] 59.2−60.5 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.88–6.93 (2H, m, 3-H and 5-H), 7.05–7.10 (2H, m, 2'-H and 6'-H), 7.16–7.21 (2H, m, 3'-H and 5'-H), 7.38–7.43 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 115.3 (2 × CH), 124.0 (C), 129.2 (2 × CH), 129.5 (2 × CH), 131.8 (C) 135.6 (2 × CH), 137.5 (C), 160.2 (C); *m/z* (EI) 250 (M^+. 100%), 235 (39), 172 (24), 83 (22).

(4-Methoxyphenyl)(phenyl)sulfane (64d)[26]



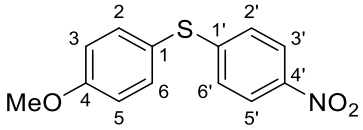
The reaction was performed as described in general procedure B using anisole (50 µL, 0.46 mmol). The reaction mixture was stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (4-methoxyphenyl)(phenyl)sulfane (82 mg, 82%) as a colourless oil. Spectroscopic data was consistent with the literature.[26] δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 6.88–6.93 (2H, m, 3-H and 5-H), 7.12–7.27 (5H, m, Ph), 7.40–7.45 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 115.1 (2 × CH), 124.5 (C), 125.9 (CH), 128.4 (2 × CH), 129.0 (2 × CH), 135.5 (2 × CH), 138.7 (C), 160.0 (C); *m/z* (EI) 216 (M^+. 100%), 201 (84), 129 (30), 83 (28).

(4'-Bromophenyl)(4-methoxyphenyl)sulfane (64e)[192]



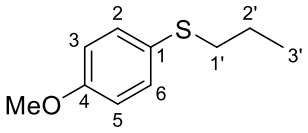
The reaction was performed as described in general procedure B using anisole (50.0 µL, 0.460 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 7:1) gave (4'-bromophenyl)(4-methoxyphenyl)sulfane (119 mg, 88%) as a white solid. Mp 59−61 °C (lit.[192] 60 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.89–6.93 (2H, m, 3-H and 5-H), 6.99–7.02 (2H, m, 2'-H and 6'-H), 7.32–7.35 (2H, m, 3'-H and 5'-H), 7.39–7.43 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 115.3 (2 × CH), 119.5 (C), 123.7 (C), 129.6 (2 × CH), 132.1 (2 × CH), 135.8 (2 × CH), 138.3 (C), 160.3 (C); *m/z* (EI) 296 (M^+. 100%), 294 (98), 281 (30), 172 (33).

(4-Methoxyphenyl)(4'-nitrophenyl)sulfane (64f)[37]



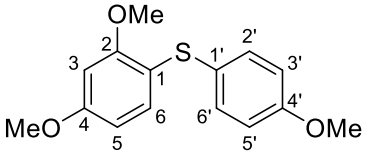
The reaction was performed as described in general procedure D using anisole (50 µL, 0.46 mmol). The reaction mixture was stirred at 75 °C for 13 days. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave (4-methoxyphenyl)(4'-nitrophenyl)sulfane (46 mg, 38%) as a yellow solid. Mp 63–65 °C (lit.[193] 63–65 °C); δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, 4-OCH_3), 6.95–7.02 (2H, m, 3-H and 5-H), 7.05–7.12 (2H, m, 2'-H and 6'-H), 7.44–7.52 (2H, m, 2-H and 6-H), 8.01–8.07 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 55.6 (CH_3), 115.8 (2 × CH), 120.3 (C), 124.1 (2 × CH), 125.7 (2 × CH), 137.3 (2 × CH), 145.2 (C), 150.2 (C), 161.3 (C); *m/z* (ESI) 284 (MNa^+. 100%).

4-Methoxyphenyl propylsulfane (64g)[194]



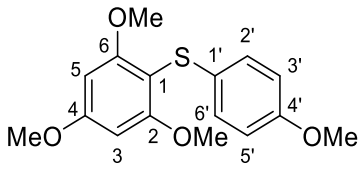
The reaction was performed as described in general procedure D using anisole (50 µL, 0.46 mmol). The reaction mixture was stirred at 75 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave 4-methoxyphenyl propylsulfane (30 mg, 36%) as a colourless oil. Spectroscopic data was consistent with the literature.[194] δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.3 Hz, 3'-H_3), 1.60 (2H, sext., *J* 7.3 Hz, 2'-H_2), 2.79 (2H, t, *J* 7.3 Hz, 1'-H_2), 3.79 (3H, s, 4-OCH_3), 6.81−6.87 (2H, m, 3-H and 5-H), 7.32−7.37 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 13.5 (CH_3), 22.8 (CH_2), 38.0 (CH_2), 55.5 (CH_3), 114.6 (2 × CH), 127.0 (C), 133.2 (2 × CH), 158.9 (C); *m/z* (EI) 182 (M^+. 100%), 153 (52), 140 (98), 125 (55), 84 (42).

(2,4-Dimethoxyphenyl)(4'-methoxyphenyl)sulfane (67a)[195]



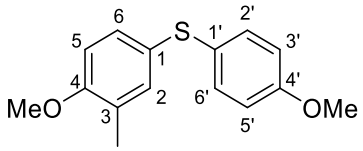
The reaction was performed as described in general procedure B using 1,3-dimethoxybenzene (47 µL, 0.36 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (hexane/diethyl ether, 3:1) gave (2,4-dimethoxyphenyl)(4'-methoxyphenyl)sulfane (70 mg, 70%) as a colourless oil. Spectroscopic data was consistent with the literature.[195] δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, 4-OCH_3), 3.79 (3H, s, 4'-OCH_3), 3.83 (3H, s, 2-OCH_3), 6.43 (1H, dd, *J* 8.5, 2.5 Hz, 5-H), 6.49 (1H, d, *J* 2.5, Hz, 3-H), 6.81–6.86 (2H, m, 3'-H and 5'-H), 7.08 (1H, d, *J* 8.5 Hz, 6-H), 7.24–7.29 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 55.6 (CH_3), 56.0, (CH_3), 99.2 (CH), 105.3 (CH), 114.8 (2 × CH), 115.9 (C), 126.4 (C), 132.8 (2 × CH), 133.5 (CH), 158.9 (C), 159.0 (C), 160.8 (C); *m/z* (ESI) 299 (MNa^+. 100%).

(4'-Methoxyphenyl)(2,4,6-trimethoxyphenyl)sulfane (67b)[48]



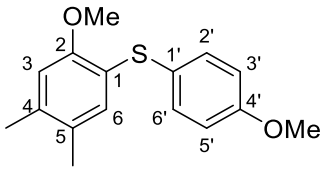
The reaction was performed as described in general procedure B using 1,3,5-trimethoxybenzene (50 mg, 0.30 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (hexane/diethyl ether, 1:1) gave (4'-methoxyphenyl)(2,4,6-trimethoxyphenyl)sulfane (77 mg, 85%). Mp 83–85 °C (lit.[48] 86–89 °C); δ_H (400 MHz, $CDCl_3$) 3.74 (3H, s, 4'-OCH_3), 3.81 (6H, s, 2-OCH_3 and 6-OCH_3), 3.85 (3H, s, 4-OCH_3), 6.19 (2H, s, 3-H and 5-H), 6.70–6.77 (2H, m, 3'-H and 5'-H), 7.01–7.12 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 55.5 (CH_3), 56.4 (2 × CH_3), 91.4 (2 × CH), 100.9 (C), 114.4 (2 × CH), 128.8 (2 × CH), 129.4 (C), 157.7 (C), 162.5 (2 × C), 162.7 (C); *m/z* (ESI) 329 (MNa^+. 100%).

(4'-Methoxyphenyl)(3-methyl-4-methoxyphenyl)sulfane (67c)



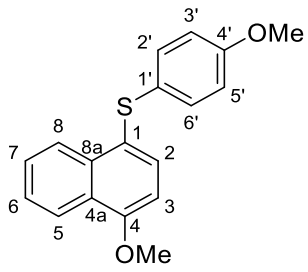
The reaction was performed as described in general procedure B using 2-methylanisole (51 μL, 0.41 mmol). The reaction mixture was stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 2:1) gave (4'-methoxyphenyl)(3-methyl-4-methoxyphenyl)sulfane (75 mg, 72%) as a white solid. Mp 38–39 °C; ν_{max}/cm^{-1} (neat) 2955 (CH), 1587 (C=C), 1489, 1437, 1238, 1030, 810; δ_H (500 MHz, $CDCl_3$) 2.16 (3H, s, 3-CH_3), 3.78 (3H, s, 4'-OCH_3), 3.80 (3H, s, 4-OCH_3), 6.74 (1H, d, *J* 8.3 Hz, 5-H), 6.80–6.84 (2H, m, 3'-H and 5'-H), 7.14–7.18 (2H, m, 2-H and 6-H), 7.24–7.28 (2H, m, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 16.3 (CH_3), 55.5 (CH_3), 55.5 (CH_3), 110.7 (CH), 114.8 (2 × CH), 126.6 (C), 127.9 (C), 128.0 (C), 130.5 (CH), 132.6 (2 × CH), 134.1 (CH), 157.5 (C), 159.0 (C); *m/z* (ESI) 283.0765 (MNa^+. $C_{15}H_{16}NaO_2S$ requires 283.0763).

(2-Methoxy-4,5-dimethylphenyl)(4'-methoxyphenyl)sulfane (67d)



The reaction was performed as described in general procedure B using 3,4-dimethylanisole (51 μL, 0.37 mmol). The reaction mixture was stirred at 40 °C for 5 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave (2-methoxy-4,5-dimethylphenyl)(4'-methoxyphenyl)sulfane (76 mg, 76%) as a white solid. Mp 61–62 °C; ν_{max}/cm^{-1} (neat) 2963 (CH), 1591 (C=C), 1491, 1244, 1057, 1030, 825; δ_H (400 MHz, $CDCl_3$) 2.09 (3H, s, 5-CH_3), 2.23 (3H, s, 4-CH_3), 3.81 (3H, s, 4'-OCH_3), 3.85 (3H, s, 2-OCH_3), 6.68 (1H, s, 3-H), 6.75 (1H, s, 6-H), 6.84–6.90 (2H, m, 3'-H and 5'-H), 7.32–7.38 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 18.9 (CH_3), 20.0 (CH_3), 55.5 (CH_3), 56.2 (CH_3), 112.8 (CH), 114.9 (2 × CH), 122.3 (C), 125.0 (C), 129.3 (C), 131.7 (CH), 134.3 (2 × CH), 136.3 (C), 155.1 (C) 159.4 (C); *m/z* (ESI) 297.0915 (MNa^+. $C_{16}H_{18}NaO_2S$ requires 297.0920).

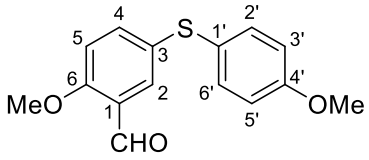
(4-Methoxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (67e)[196]



The reaction was performed as described in general procedure B using 1-methoxynaphthalene (46 μL, 0.32 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 2:1) gave (4-methoxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (89 mg, 95%) as a white solid. Mp 87–88 °C (lit.[197] 83–85 °C); δ_H (500 MHz, $CDCl_3$) 3.74 (3H, s, 4'-OCH_3), 4.02 (3H, s, 4-OCH_3), 6.74–6.78 (2H, m, 3'-H and 5'-H), 6.79 (1H, d, *J* 8.0 Hz, 3-H), 7.10–7.16 (2H, m, 2'-H and 6'-H), 7.48–7.56 (2H, m, 6-H and 7-H), 7.66 (1H, d, *J* 8.0 Hz, 2-H), 8.30 (1H, dd, *J* 7.9, 1.4 Hz, 8-H), 8.37 (1H, dd, *J* 7.9, 1.0 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 55.8 (CH_3), 104.1 (CH), 114.8 (2 × CH), 122.6 (CH), 122.7 (C), 125.8 (CH), 125.9 (CH), 126.6 (C), 127.5 (CH), 128.7 (C),

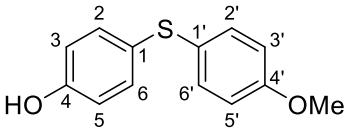
130.4 (2 × CH), 133.9 (CH), 134.7 (C), 156.6 (C), 158.4 (C); *m/z* (ESI) 319 (MNa^+. 100%).

3-(4'-Methoxyphenylthio)-6-methoxybenzaldehyde (67f)



The reaction was performed as described in general procedure B using 2-methoxybenzaldehyde (50 mg, 0.39 mmol). The reaction mixture was stirred at 50 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 3-(4'-methoxyphenylthio)-6-methoxybenzaldehyde (8.0 mg, 8.0%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2938 (CH), 1676 (CO), 1589 (C=C), 1481, 1244, 1024, 827; δ_H (500 MHz, $CDCl_3$) 3.80 (3H, s, 4'-OCH_3), 3.91 (3H, s, 6-OCH_3), 6.84–6.88 (2H, m, 3'-H and 5'-H), 6.92 (1H, d, *J* 8.7 Hz, 5-H), 7.31–7.36 (2H, m, 2'-H and 6'-H), 7.46 (1H, dd, *J* 8.7, 2.5 Hz, 4-H), 7.76 (1H, d, *J* 2.5 Hz, 2-H), 10.39 (1H, s, CHO); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 56.0 (CH_3), 112.8 (CH), 115.2 (2 × CH), 125.4 (C), 125.7 (C), 129.7 (C), 130.4 (CH), 134.2 (2 × CH), 137.8 (CH), 159.7 (C), 160.9 (C), 189.2 (CH); *m/z* (ESI) 297.0548 (MNa^+. $C_{15}H_{14}NaO_3S$ requires 297.0556).

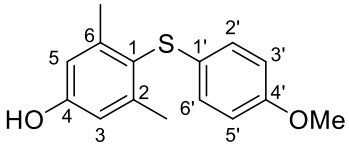
(4-Hydroxyphenyl)(4'-methoxyphenyl)sulfane (67g)[198]



The reaction was performed as described in general procedure C using phenol (50.0 mg, 0.530 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (dichloromethane) gave (4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (114 mg, 93%) as a pale orange solid. Mp 61–62 °C (lit.[198] 60 °C); δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 4.98 (1H, s, OH), 6.73–6.79 (2H, m, 3-H and 5-H), 6.81–6.87 (2H, m, 3'-H and 5'-H), 7.19–7.25 (2H, m, 2-H and 6-H), 7.26–7.31 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.5

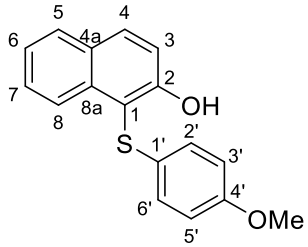
(CH_3), 114.9 (2 × CH), 116.4 (2 × CH), 127.4 (C), 127.9 (C), 133.0 (4 × CH), 155.0 (C), 159.1 (C); *m/z* (EI) 232 (M^+. 100%), 217 (33), 84 (53).

(2,6-Dimethyl-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (67h)



The reaction was performed as described in general procedure B using 3,5-dimethylphenol (50 mg, 0.41 mmol). The reaction mixture was stirred at room temperature for 6 h. Purification by flash column chromatography (dichloromethane) gave (2,6-dimethyl-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (78 mg, 74%) as a white solid. Mp 150–152 °C; ν_{max}/cm^{-1} (neat) 3345 (OH), 2947 (CH), 1587 (C=C), 1489, 1227, 1163, 1013, 812; δ_H (400 MHz, $CDCl_3$) 2.38 (6H, s, 2-CH_3 and 6-CH_3), 3.75 (3H, s, OCH_3), 4.75 (1H, s, OH), 6.66 (2H, s, 3-H and 5-H), 6.73–6.78 (2H, m, 3'-H and 5'-H), 6.86–6.91 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 22.1 (2 × CH_3), 55.5 (CH_3), 114.8 (2 × CH), 115.4 (2 × CH), 123.1 (C), 127.5 (2 × CH), 129.5 (C), 145.8 (2 × C), 156.0 (C), 157.5 (C); *m/z* (ESI) 283.0760 (MNa^+. $C_{15}H_{16}NaO_2S$ requires 283.0763).

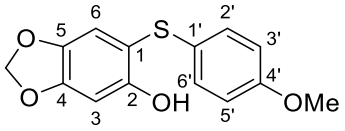
(2-Hydroxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (67i)[199]



The reaction was performed as described in general procedure B using 2-naphthol (50 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 7 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave (2-hydroxynaphthalen-1-yl)(4'-methoxyphenyl)sulfane (85 mg, 87%). Mp 73–75 °C (lit.[199] 71–73 °C); δ_H (400 MHz, $CDCl_3$) 3.70 (3H, s, OCH_3), 6.71–6.77 (2H, m, 3'-H and 5'-H), 7.01–7.09 (2H, m, 2'-H and 6'-H), 7.30 (1H, s, OH), 7.33 (1H, d, *J* 8.9 Hz, 3-H), 7.35–7.39 (1H, m, 6-H), 7.47–7.53 (1H, m, 7-H), 7.79 (1H, d, *J* 8.1 Hz, 5-H),

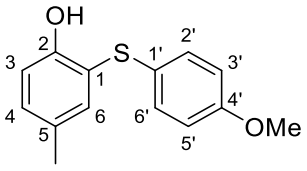
7.86 (1H, d, *J* 8.9 Hz, 4-H), 8.26 (1H, d, *J* 8.5 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 109.9 (C), 115.1 (2 × CH), 117.0 (CH), 123.9 (CH), 124.9 (CH), 126.1 (C), 128.0 (CH), 128.7 (CH), 128.9 (2 × CH), 129.6 (C), 132.7 (CH), 135.5 (C), 156.8 (C), 158.6 (C); *m/z* (ESI) 305 (MNa^+. 100%).

[2-Hydroxy-4,5-(methylenedioxy)phenyl](4'-methoxyphenyl)sulfane (67j)



The reaction was performed as described in general procedure B using 2*H*-1,3-benzodioxol-5-ol (50 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave [2-hydroxy-4,5-(methylenedioxy)phenyl](4'-methoxyphenyl)sulfane (84 mg, 84%) as a white solid. Mp 113–115 °C; ν_{max}/cm^{-1} (neat) 3385 (OH), 2899 (CH), 1472, 1242, 1173, 1032, 820; δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, 4'-OCH_3), 5.94 (2H, s, CH_2), 6.51 (1H, s, OH), 6.59 (1H, s, 3-H), 6.78–6.82 (2H, m, 3'-H and 5'-H), 6.93 (1H, s, 6-H), 7.08–7.13 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 97.4 (CH), 101.7 (CH_2), 107.9 (C), 114.3 (CH), 115.1 (2 × CH), 127.0 (C), 129.6 (2 × CH), 141.7 (C), 150.7 (C), 153.3 (C), 158.9 (C); *m/z* (ESI) 299.0345 (MNa^+. $C_{14}H_{12}NaO_4S$ requires 299.0349).

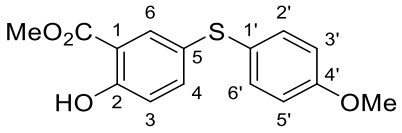
(2-Hydroxy-5-methylphenyl)(4'-methoxyphenyl)sulfane (67k)[200]



The reaction was performed as described in general procedure B using *p*-cresol (50 mg, 0.46 mmol). The reaction mixture was stirred at 50 °C for 3 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave (2-hydroxy-5-methylphenyl)(4'-methoxyphenyl)sulfane (88 mg, 77%) as a colourless oil. Spectroscopic data was consistent with the literature.[200] δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, 5-CH_3), 3.76 (3H, s, 4'-OCH_3), 6.40 (1H, s, OH), 6.78−6.83 (2H, m, 3'-H and 5'-H), 6.93 (1H, d, *J* 8.3 Hz, 3-H), 7.10−7.17 (3H, m, 4-H, 2'-H and 6'-H), 7.31 (1H,

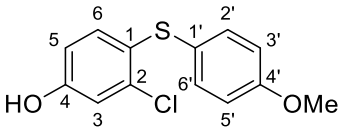
d, *J* 1.9 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_3), 55.5 (CH_3), 115.1 (2 × CH), 115.2 (CH), 118.0 (C), 126.5 (C), 130.1 (2 × CH), 130.6 (C), 132.5 (CH), 136.3 (CH), 154.7 (C), 158.9 (C); *m/z* (ESI) 269 (MNa^+. 100%).

Methyl 2-hydroxy-5-(4'-methoxyphenylsulfanyl)benzoate (67l)



The reaction was performed as described in general procedure B using methyl salicylate (43 μL, 0.33 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave methyl 2-hydroxy-5-(4'-methoxyphenylsulfanyl)benzoate (30 mg, 32%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3175 (OH), 2951 (CH), 1674 (CO), 1589 (C=C), 1491, 1439, 1285, 1030, 827; δ_H (400 MHz, $CDCl_3$) 3.79 (3H, s, 4'-OCH_3), 3.93 (3H, s, CO_2CH_3), 6.84 (2H, d, *J* 8.6 Hz, 3'-H and 5'-H), 6.92 (1H, d, *J* 8.6 Hz, 3-H), 7.28 (2H, d, *J* 8.6 Hz, 2'-H and 6'-H), 7.41 (1H, dd, *J* 8.6, 1.8 Hz, 4-H), 7.89 (1H, d, *J* 1.8 Hz, 6-H), 10.76 (1H, s, OH); δ_C (101 MHz, $CDCl_3$) 52.6 (CH_3), 55.5 (CH_3), 113.1 (C), 115.0 (2 × CH), 118.9 (CH), 126.5 (C), 126.9 (C), 133.0 (CH), 133.0 (2 × CH), 139.2 (CH), 159.3 (C), 161.1 (C), 170.2 (C); *m/z* (ESI) 313.0497 (MNa^+. $C_{15}H_{14}NaO_4S$ requires 313.0505).

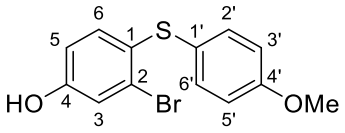
(2-Chloro-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (67m)



The reaction was performed as described in general procedure C using 3-chlorophenol (50 mg, 0.39 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification by flash column chromatography (dichloromethane) gave (2-chloro-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (48 mg, 46%) as a white solid. Mp 79–82 °C; ν_{max}/cm^{-1} (neat) 3418 (OH), 2959 (CH), 1589 (C=C), 1468, 1221, 1180, 1016, 816; δ_H (500 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 4.77 (1H, s, OH), 6.63 (1H, dd, *J* 8.6, 2.7 Hz, 5-H), 6.87–6.96 (4H, m, 3-H, 6-H, 3'-H and 5'-H), 7.32–7.37 (2H, m, 2'-H

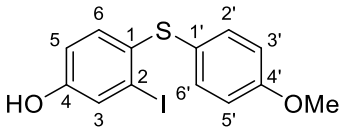
and 6'-H); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 115.0 (CH), 115.2 (2 × CH), 117.2 (CH), 124.5 (C), 128.2 (C), 132.3 (CH), 134.7 (2 × CH), 134.8 (C) 155.0 (C), 159.9 (C); *m/z* (ESI) 289.0051 (MNa^+. $C_{13}H_{11}{}^{35}ClNaO_2S$ requires 289.0060).

(2-Bromo-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (67n)



The reaction was performed as described in general procedure C using 3-bromophenol (50 mg, 0.39 mmol). The reaction mixture was stirred at 50 °C for 2 h. Purification by flash column chromatography (dichloromethane) gave (2-bromo-4-hydroxyphenyl)(4'-methoxyphenyl)sulfane (47 mg, 53%) as a brown solid. Mp 74–77 °C; ν_{max}/cm^{-1} (neat) 3387 (OH), 2938 (CH), 1589 (C=C), 1491, 1464, 1244, 1018, 826; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 5.07 (1H, s, OH), 6.67 (1H, dd, *J* 8.6, 2.7 Hz, 5-H), 6.87–6.92 (3H, m, 6-H, 3'-H and 5'-H), 7.10 (1H, d, *J* 2.7 Hz, 3-H), 7.33–7.38 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.6 (CH_3), 115.3 (2 × CH), 115.7 (CH), 120.3 (CH), 124.5 (C), 124.8 (C), 130.2 (C), 131.9 (CH), 134.8 (2 × CH), 154.8 (C), 159.8 (C); *m/z* (ESI) 332.9559 (MNa^+. $C_{13}H_{11}{}^{79}BrNaO_2S$ requires 332.9555).

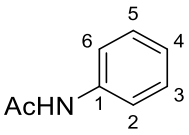
(4-Hydroxy-2-iodophenyl)(4'-methoxyphenyl)sulfane (67o)



The reaction was performed as described in general procedure B using 3-iodophenol (50 mg, 0.23 mmol). The reaction mixture was stirred at 50 °C for 5 h. Purification by flash column chromatography (dichloromethane) gave (4-hydroxy-2-iodophenyl)(4'-methoxyphenyl)sulfane (37 mg, 46%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3379 (OH), 2924 (CH), 1582 (C=C) 1458, 1242, 1018, 826; δ_H (500 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 4.94 (1H, s, OH), 6.72 (1H, dd, *J* 8.6, 2.6 Hz, 5-H), 6.87–6.94 (3H, m, 6-H, 3'-H and 5'-H), 7.31–7.35 (2H, m, 2'-H and 6'-H), 7.36 (1H, d, *J* 2.6 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 100.9 (C), 115.3 (2 × CH), 116.6

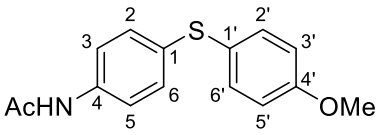
(CH), 125.8 (C), 126.6 (CH), 131.3 (CH), 133.9 (C), 134.4 (2 × CH), 154.5 (C), 159.8 (C); *m/z* (ESI) 380.9414 (MNa^+. $C_{13}H_{11}INaO_2S$ requires 380.9417).

Acetanilide (68a)[201]



To a stirred solution of aniline (489 µL, 5.37 mmol) in dichloromethane (15 mL) was added acetic anhydride (762 µL, 8.06 mmol). The resulting reaction mixture was left to stir at room temperature for 3 h. The reaction mixture was washed with saturated aqueous sodium bicarbonate (30 mL) and the organic layer separated. The aqueous layer was further extracted with dichloromethane (2 × 30 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 1:1) gave acetanilide (646 mg, 89%) as a white solid. Mp 112−114 °C (lit.[201] 111−113 °C); δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 7.10 (1H, t, *J* 7.4 Hz, 4-H), 7.31 (2H, t, *J* 7.9 Hz, 2-H and 6-H), 7.41 (1H, br s, NH), 7.50 (2H, d, *J* 7.8 Hz, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 24.7 (CH_3), 120.0 (CH), 124.4 (2 × CH), 129.1 (2 × CH), 138.0 (C), 168.5 (C); *m/z* (EI) 135 (M^+. 100%).

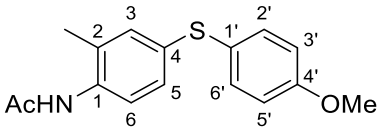
***N*-{4-[(4'-Methoxyphenyl)thio]phenyl}acetamide (69a)**



The reaction was performed as described in general procedure B using acetanilide (50 mg, 0.37 mmol). The reaction mixture was stirred at 75 °C for 48 h. Purification by flash column chromatography (30–60% ethyl acetate in hexane) gave *N*-{4-[(4'-methoxyphenyl)thio]phenyl}acetamide (80 mg, 80%) as an off-white solid. Mp 94–96 °C; ν_{max}/cm^{-1} (neat) 3296 (NH), 2837 (CH), 1661 (CO), 1587 (C=C), 1244, 1171, 1028, 814; δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, $COCH_3$), 3.81 (3H, s, 4'-OCH_3), 6.84–6.89 (2H, m, 3'-H and 5'-H), 7.14–7.20 (2H, m, 2-H and 6-H), 7.28 (1H, br s, NH), 7.32–7.42 (4H, m, 3-H, 5-H, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 24.7 (CH_3), 55.5

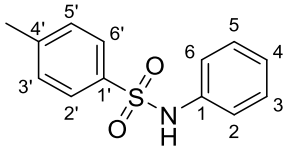
(CH_3), 115.1 (2 × CH), 120.7 (2 × CH), 125.5 (C), 130.2 (2 × CH), 133.3 (C), 134.5 (2 × CH), 136.4 (C), 159.7 (C), 168.4 (C); *m/z* (ESI) 296.0713 (MNa^+. $C_{15}H_{15}NNaO_2S$ requires 296.0716).

N-[4-(4'-Methoxyphenylthio)-2-(methyl)phenyl]acetamide (69b)



The reaction was performed as described in general procedure B using *N*-(2-methylphenyl)acetamide (50 mg, 0.34 mmol). The reaction mixture was stirred at 75 °C for 55 h. Purification by flash column chromatography (diethyl ether) gave *N*-[4-(4'-methoxyphenylthio)-2-(methyl)phenyl]acetamide (59 mg, 61%) as a white solid. Mp 124–126 °C; ν_{max}/cm^{-1} (neat) 3260 (NH), 2963 (CH), 1639 (CO), 1589 (C=C), 1524, 1302, 1242, 1030, 835; δ_H (400 MHz, $CDCl_3$) 2.15 (6H, br s, $COCH_3$ and 2-CH_3), 3.80 (3H, s, 4'-OCH_3), 6.87 (2H, d, *J* 8.6 Hz, 3'-H and 5'-H), 6.98−7.05 (2H, m, 3-H and 5-H), 7.11 (1H, br s, NH), 7.36 (2H, d, *J* 8.6 Hz, 2'-H and 6'-H), 7.58 (1H, d, *J* 8.3 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 17.9 (CH_3), 24.2 (CH_3), 55.5 (CH_3), 115.0 (2 × CH), 124.3 (CH), 125.1 (C), 127.5 (CH), 130.6 (C), 131.0 (CH), 134.1 (C), 134.6 (C), 134.8 (2 × CH), 159.7 (C), 168.6 (C); *m/z* (ESI) 310.0864 (MNa^+. $C_{16}H_{17}NNaO_2S$ requires 310.0872).

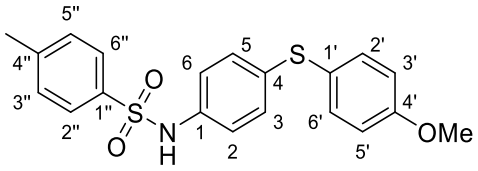
N-Tosylaniline (68c)[202]



To a mixture of aniline (245 μL, 2.69 mmol) and pyridine (2.6 mL, 32.2 mmol) in dichloromethane (10 mL) was added a solution of *p*-toluenesulfonyl chloride (615 mg, 3.22 mmol) in dichloromethane (5 mL) dropwise. The resulting reaction mixture was left to stir at room temperature for 16 h. The reaction mixture was then washed with 5% aqueous HCl (15 mL). The organic layer was further washed with saturated aqueous sodium bicarbonate (15 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate

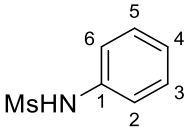
7:3) gave *N*-tosylaniline (584 mg, 88%) as a pale yellow solid. Mp 100−102 °C (lit.[202] 97−99 °C); δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, CH_3), 6.82 (1H, br s, NH), 7.05−7.13 (3H, m, 2-H, 4-H and 6-H), 7.20−7.26 (4H, m, 3'-H, 5'-H, 3-H and 5-H), 7.64−7.69 (2H, m, 2'-H and 6'-H); (101 MHz, $CDCl_3$) 21.7 (CH_3), 121.8 (2 × CH), 125.5 (CH), 127.4 (2 × CH), 129.5 (2 × CH), 129.8 (2 × CH), 136.3 (C), 136.7 (C), 144.0 (C); *m/z* (ESI) 270 (MNa^+. 100%).

N-[4-(4'-Methoxyphenylthio)phenyl]toluenesulfonamide (69c)



The reaction was performed as described in general procedure B using phenyl toluenesulfonamide (100 mg, 0.400 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave *N*-[4-(4'-methoxyphenylthio)phenyl]toluenesulfonamide (94.0 mg, 60%) as a white solid. Mp 127−129 °C; ν_{max}/cm^{-1} (neat) 3242 (NH), 2922 (CH), 1593 (C=C), 1489, 1333, 1146, 922, 812; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, 4''-CH_3), 3.81 (3H, s, 4'-OCH_3), 6.81−6.89 (3H, m, NH, 3'-H and 5'-H), 6.91−6.97 (2H, m, 3-H and 5-H), 7.00−7.06 (2H, m, 2-H and 6-H), 7.22 (2H, d, *J* 8.0 Hz, 3''-H and 5''-H), 7.31−7.37 (2H, m, 2'-H and 6'-H), 7.62−7.67 (2H, m, 2''-H and 6''-H); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 55.5 (CH_3), 115.2 (2 × CH), 122.5 (2 × CH), 124.4 (C), 127.4 (2 × CH), 129.5 (2 × CH), 129.8 (2 × CH), 134.7 (C), 135.2 (2 × CH), 135.4 (C), 136.2 (C), 144.1 (C), 160.0 (C); *m/z* (ESI) 408.0696 (MNa^+. $C_{20}H_{19}NNaO_3S_2$ requires 408.0699).

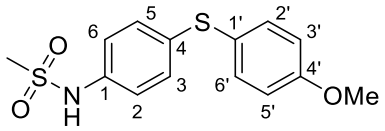
N-Phenylmethanesulfonamide (68d)[203]



To a solution of aniline (245 μL, 2.69 mmol) in pyridine (13.5 mL) was added methanesulfonyl chloride (229 μL, 2.96 mmol) at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and left to stir for 3 h. The pyridine was removed *in vacuo* and water (30 mL) was added to the resulting residue. The

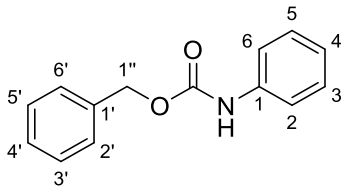
aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 3:1) gave *N*-phenylmethanesulfonamide (424 mg, 92%) as a white solid. Mp 93−95 °C (lit.[203] 96−98 °C); δ_H (400 MHz, $CDCl_3$) 3.02 (3H, s, CH_3), 7.02 (1H, br s, NH), 7.17−7.22 (1H, m, 4-H), 7.23−7.27 (2H, m, 2-H and 6-H), 7.33−7.39 (2H, m, 3-H and 5-H); (101 MHz, $CDCl_3$) 39.4 (CH_3), 120.9 (2 × CH), 125.6 (CH), 129.8 (2 × CH), 136.9 (C); *m/z* (EI) 171 (M^+. 44%), 92 (100).

N-[4-(4'-Methoxyphenylthio)phenyl]methanesulfonamide (69d)



The reaction was performed as described in general procedure B using *N*-phenylmethanesulfonamide (100 mg, 0.580 mmol). The reaction mixture was stirred at 75 °C for 20 h. Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave *N*-[4-(4'-methoxyphenylthio)phenyl]methanesulfonamide (95.0 mg, 53%) as a white solid. Mp 128−130 °C; ν_{max}/cm^{-1} (neat) 3246 (NH), 2938 (CH), 1589 (C=C), 1491, 1140, 1028, 833; δ_H (400 MHz, $CDCl_3$) 2.99 (3H, s, SCH_3), 3.82 (3H, s, 4'-OCH_3), 6.51 (1H, br s, NH), 6.86−6.95 (2H, m, 3'-H and 5'-H), 7.08−7.13 (2H, m, 3-H and 5-H), 7.13−7.18 (2H, m, 2-H and 6-H), 7.36−7.43 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 39.5 (CH_3), 55.5 (CH_3), 115.3 (2 × CH), 121.9 (2 × CH), 124.1 (C), 129.7 (2 × CH), 134.6 (C), 135.5 (2 × CH), 136.1 (C), 160.1 (C); *m/z* (ESI) 332.0386 (MNa^+. $C_{14}H_{15}NNaO_3S_2$ requires 332.0386).

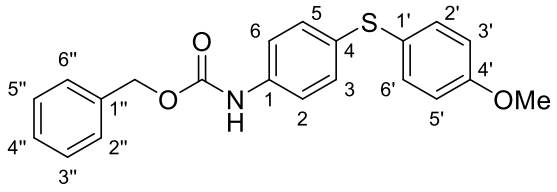
N-(Benzyloxycarbonyl)aniline (68e)[204]



To a solution of aniline (245 μL, 2.69 mmol) in tetrahydrofuran (6 mL) at 0 °C was added sodium bicarbonate (249 mg, 2.96 mmol) followed by benzyl chloroformate

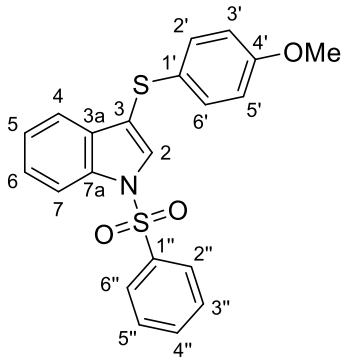
(415 μL 2.96 mmol). After 16 h the reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 9:1) gave *N*-(benzyloxycarbonyl)aniline (340 mg, 56%) as a pale yellow solid. Mp 70−72 °C (lit.[204] 70−72 °C); δ_H (400 MHz, $CDCl_3$) 5.21 (2H, s, 1''-H_2), 6.68 (1H, br s, NH), 7.04−7.10 (1H, m, 4-H), 7.28−7.43 (9H, m, 2-H, 3-H, 5-H, 6-H and Ph); (101 MHz, $CDCl_3$) 67.2 (CH_2), 118.9 (CH), 123.7 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 128.8 (2 × CH), 129.2 (2 × CH), 136.2 (C), 137.9 (C), 153.5 (C); *m/z* (ESI) 250 (MNa^+. 100%).

Benzyl [4-(4'-methoxyphenylthio)phenyl]carbamate (69e)



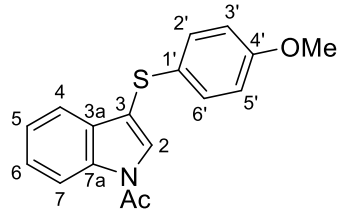
The reaction was performed as described in general procedure B using *N*-(benzyloxycarbonyl)aniline (100 mg, 0.440 mmol). The reaction mixture was stirred at 75 °C for 24 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave benzyl [4-(4'-methoxyphenylthio)phenyl]carbamate (125 mg, 78%) as a white solid. Mp 108−109 °C; ν_{max}/cm^{-1} (neat) 3296 (NH), 2943 (CH), 1697 (CO), 1589 (C=C), 1512, 1491, 1242, 1026, 829; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, 4'-OCH_3), 5.19 (2H, s, PhCH_2), 6.66 (1H, br s, NH), 6.84−6.89 (2H, m, 3'-H and 5'-H), 7.17−7.22 (2H, m, 3-H and 5-H), 7.27−7.41 (9H, m, 2-H, 6-H, 2'-H, 6'-H and Ph); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 67.3 (CH_2), 115.0 (2 × CH), 119.5 (C), 125.9 (C), 128.5 (2 × CH), 128.5 (2 × CH) 128.8 (2 × CH), 130.8 (2 × CH), 132.1 (C), 134.2 (2 × CH), 136.1 (CH), 136.5 (C), 153.3 (C), 159.6 (C); *m/z* (ESI) 388.0974 (MNa^+. $C_{21}H_{19}NNaO_3S$ requires 388.0978).

[1-(Phenylsulfonyl)indol-3-yl](4'-methoxyphenyl)sulfane (71a)[205]



The reaction was performed as described in general procedure B using 1-(phenylsulfonyl)indole (100 mg, 0.390 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave [1-(phenylsulfonyl)indol-3-yl](4'-methoxyphenyl)sulfane (117 mg, 76%) as a white solid. Mp 85−88 °C (lit.[205] 86−88 °C); δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, OCH_3), 6.75–6.79 (2H, m, 3'-H and 5'-H), 7.18–7.23 (3H, m, 7-H, 2'-H and 6'-H), 7.32–7.36 (1H, m, 5-H), 7.44–7.48 (3H, m, 3''-H, 4''-H and 5''-H), 7.53–7.59 (1H, m, 6-H), 7.70 (1H, s, 2-H), 7.87–7.92 (2H, m, 2''-H and 6''-H), 8.00 (1H, d, *J* 8.3 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 113.9 (CH), 114.9 (2 × CH), 120.5 (CH), 123.9 (CH), 125.5 (CH), 125.8 (C), 127.0 (2 × CH), 129.2 (CH), 129.5 (2 × CH and C), 131.0 (2 × CH), 134.2 (CH and C), 135.6 (C), 138.1 (C), 158.9 (C); *m/z* (ESI) 418 (MNa^+. 100%).

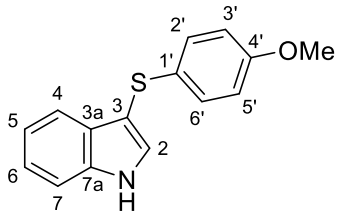
[1-(Acetyl)indol-3-yl](4'-methoxyphenyl)sulfane (71b)



The reaction was performed as described in general procedure B using *N*-acetylindole (100 mg, 0.620 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (hexane/diethyl ether, 4:1) gave [1-(acetyl)indol-3-yl](4'-methoxyphenyl)sulfane (114 mg, 61%) as a white solid. Mp 91−93 °C; ν_{max}/cm^{-1} (neat) 2999 (CH), 1709 (CO), 1526 (C=C), 1491, 1308, 1211, 814; δ_H (400 MHz, $CDCl_3$) 2.63 (3H, s, $COCH_3$), 3.76 (3H, s, 4'-OCH_3), 6.77−6.83

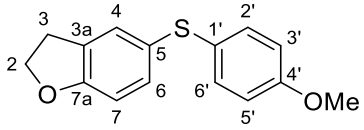
(2H, m, 3'-H and 5'-H), 7.23−7.30 (3H, m, 6-H, 2'-H and 6'-H), 7.34−7.40 (1H, m, 5-H), 7.47−7.52 (1H, m, 7-H), 7.58 (1H, s, 2-H), 8.44 (1H, d, *J* 8.3 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 24.0 (CH_3), 55.4 (CH_3), 114.3 (C), 114.9 (2 × CH), 116.8 (CH), 120.0 (CH), 124.2 (CH), 126.0 (CH), 126.1 (C), 128.6 (CH), 130.7 (C), 130.8 (2 × CH), 136.3 (C), 158.8 (C), 168.2 (C); *m/z* (ESI) 320.0713 (MNa^+. $C_{17}H_{15}NNaO_2S$ requires 320.0716).

1*H*-Indol-3-yl(4'-methoxyphenyl)sulfane (71c)[206]



To a solution of *N*-(4-methoxyphenylthio)succinimide (102 mg, 0.430 mmol) in chloroform (0.7 mL) was added silver *bis*(trifluoromethanesulfonyl)imide (12.5 mg, 32.3 μmol) and indole (50.0 mg, 0.430 mmol) and the reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (hexane/diethyl ether 7:3) to give 1*H*-indol-3-yl(4'-methoxyphenyl)sulfane (77.0 mg, 71%) as a white solid. Mp 109−111 °C (lit.[206] 111−113 °C); δ_H (400 MHz, $CDCl_3$) 3.73 (3H, s, 4'-OCH_3), 6.72–6.77 (2H, m, 3'-H and 5'-H), 7.12–7.18 (3H, m, 5-H, 2'-H and 6'-H), 7.22–7.28 (1H, m, 6-H), 7.41 (1H, d, *J* 8.1 Hz, 7-H), 7.46 (1H, d, *J* 2.6 Hz, 2-H), 7.64 (1H, d, *J* 7.9 Hz, 4-H), 8.32 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 104.9 (C), 111.6 (CH), 114.6 (2 × CH), 119.8 (CH), 120.9 (CH), 123.1 (CH), 128.7 (2 × CH), 129.2 (C), 129.7 (C), 130.1 (CH), 136.6 (C), 158.0 (C); *m/z* (ESI) 278 (MNa^+. 100%).

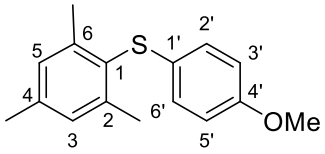
(2,3-Dihydro-1-benzofuran-5-yl)(4'-methoxyphenyl)sulfane (67p)



The reaction was performed as described in general procedure B using 2,3-dihydrobenzofuran (47 μL, 0.42 mmol). The reaction mixture was stirred at 50 °C for

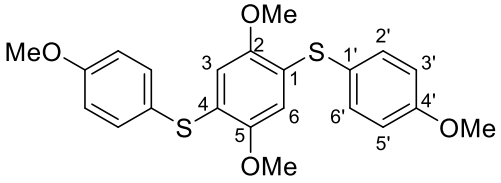
6 h. Purification by flash column chromatography (hexane/dichloromethane, 4:3) gave (2,3-dihydro-1-benzofuran-5-yl)(4'-methoxyphenyl)sulfane (93 mg, 87%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2895 (CH), 1589 (C=C), 1481, 1466, 1231, 818; δ_H (500 MHz, $CDCl_3$) 3.22 (2H, t, *J* 8.7 Hz, 3-H_2), 3.84 (3H, s, 4'-OCH_3), 4.62 (2H, t, *J* 8.7 Hz, 2-H_2), 6.78 (1H, d, *J* 8.3 Hz, 7-H), 6.86–6.91 (2H, m, 3'-H and 5'-H), 7.22 (1H, dd, *J* 8.3, 1.9 Hz, 6-H), 7.26 (1H, d, *J* 1.9 Hz, 4-H), 7.29–7.35 (2H, m, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 29.7 (CH_2), 55.5 (CH_3), 71.6 (CH_2), 110.0 (CH), 114.8 (2 × CH), 126.7 (C), 128.3 (C), 128.5 (C), 128.9 (CH), 132.3 (CH), 132.4 (2 × CH), 158.9 (C), 160.0 (C); *m/z* (ESI) 281.0600 (MNa^+. $C_{15}H_{14}NaO_2S$ requires 281.0607).

Mesityl-(4'-methoxyphenyl)sulfane (67q)[48]



The reaction was performed as described in general procedure B using mesitylene (58 µL, 0.42 mmol). The reaction mixture was stirred at 60 °C for 36 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave mesityl-(4'-methoxyphenyl)sulfane (80 mg, 75%) as a white solid. Mp 66−67 °C (lit.[48] 69−71 °C); δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, 4-CH_3), 2.40 (6H, s, 2-CH_3 and 6-CH_3), 3.75 (3H, s, 4'-OCH_3), 6.72–6.77 (2H, m, 3'-H and 5'-H), 6.87–6.93 (2H, m, 2'-H and 6'-H), 6.99 (2H, s, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 21.2 (CH_3), 21.9 (2 × CH_3), 55.5 (CH_3), 114.8 (2 × CH), 127.8 (2 × CH), 128.5 (C), 129.2 (C), 129.4 (2 × CH), 139.0 (C), 143.5 (2 × C), 157.6 (C); *m/z* (ESI) 258 (M^+. 100%).

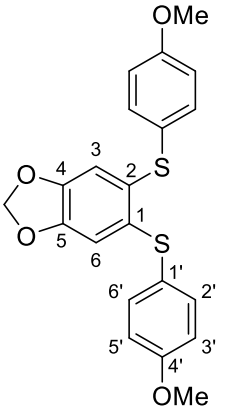
1,2-*Bis*-[(4'-methoxyphenyl)sulfane]-2,5-dimethoxybenzene (67r)



The reaction was performed as described in general procedure B using 1,4-dimethoxybenzene (50.0 mg, 0.360 mmol) and *N*-(4-methoxyphenylthio)succinimide (189 mg, 0.800 mmol). The reaction mixture was

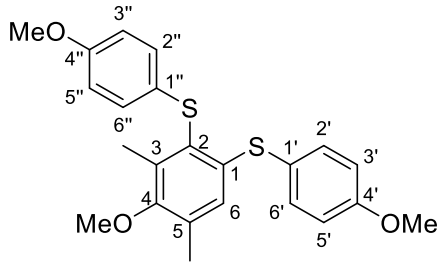
stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave 1,2-*bis*-[(4'-methoxyphenyl)sulfane]-2,5-dimethoxybenzene (105 mg, 70%) as an orange solid. Mp 156–158 °C; ν_{max}/cm^{-1} (neat) 2941 (CH), 1589 (C=C), 1489, 1447, 1246, 1024, 829; δ_H (400 MHz, $CDCl_3$) 3.63 (6H, s, 2-OCH_3 and 5-OCH_3), 3.82 (6H, s, 2 × 4'-OCH_3), 6.43 (2H, s, 3-H and 6-H), 6.87–6.93 (4H, m, 2 × 3'-H and 2 × 5'-H), 7.35–7.42 (4H, m, 2 × 2'-H and 2 × 6'-H); δ_C (126 MHz, $CDCl_3$) 55.5 (2 × CH_3), 56.6 (2 × CH_3), 112.6 (2 × CH), 115.1 (4 × CH), 123.6 (2 × C), 125.2 (2 × C), 135.3 (4 × CH), 151.0 (2 × C), 159.9 (2 × C); *m/z* (ESI) 437.0847 (MNa^+. $C_{22}H_{22}NaO_4S_2$ requires 437.0852).

1,2-*Bis*-[(4'-methoxyphenyl)sulfane]-4,5-methylenedioxybenzene (67s)



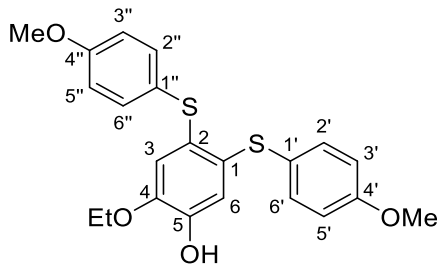
The reaction was performed as described in general procedure B using 1,3-benzodioxole (47 μL, 0.41 mmol). The reaction mixture was stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 1,2-*bis*-[(4'-methoxyphenyl)sulfane]-4,5-methylenedioxybenzene (56 mg, 34%) as a white solid. Mp 65–67 °C; ν_{max}/cm^{-1} (neat) 2897 (CH), 1589 (C=C), 1491, 1460, 1229, 1028, 826; δ_H (400 MHz, $CDCl_3$) 3.81 (6H, s, 2 × 4'-OCH_3), 5.87 (2H, s, CH_2), 6.56 (2H, s, 3-H and 6-H), 6.84–6.93 (4H, m, 2 × 3'-H and 2 × 5'-H), 7.29–7.40 (4H, m, 2 × 2'-H and 2 × 6'-H); δ_C (101 MHz, $CDCl_3$) 55.5 (2 × CH_3), 101.6 (CH_2), 111.1 (2 × CH), 115.2 (4 × CH), 125.5 (2 × C), 130.8 (2 × C), 134.3 (4 × CH), 147.4 (2 × C), 159.7 (2 × C); *m/z* (ESI) 421.0536 (MNa^+. $C_{21}H_{18}NaO_4S_2$ requires 421.0539).

1,2-*Bis*-[(4'-methoxyphenyl)sulfane]-3,5-dimethyl-4-methoxybenzene (67t)



The reaction was performed as described in general procedure B using 2,6-dimethylanisole (52 μL, 0.37 mmol). The reaction mixture was stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave 1,2-*bis*-[(4'-methoxyphenyl)sulfane]-3,5-dimethyl-4-methoxybenzene (47 mg, 31%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2936 (CH), 1591 (C=C), 1491, 1242, 1024, 822; δ_H (400 MHz, $CDCl_3$) 2.14 (3H, s, CH_3), 2.37 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.44 (1H, s, 6-H), 6.76–6.83 (2H, m, 2 × ArH), 6.90–6.96 (2H, m, 2 × ArH), 7.04–7.12 (2H, m, 2 × ArH), 7.39–7.46 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 14.7 (CH_3), 16.6 (CH_3), 55.4 (CH_3), 55.5 (CH_3), 60.1 (CH_3), 114.8 (2 × CH), 115.3 (2 × CH), 124.1 (C), 126.6 (CH), 127.7 (C), 127.9 (C), 128.7 (2 × CH), 133.4 (C), 137.0 (2 × CH), 137.2 (C), 142.5 (C), 155.2 (C), 158.0 (C), 160.3 (C); *m/z* (ESI) 435.1052 (MNa^+. $C_{23}H_{24}NaO_3S_2$ requires 435.1059).

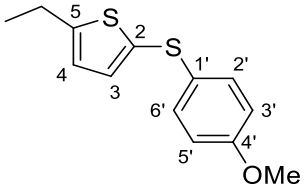
1,2-*Bis*-[(4'-methoxyphenyl)sulfane]-4-ethoxy-5-hydroxybenzene (67u)



The reaction was performed as described in general procedure B using 2-ethoxyphenol (51 μL, 0.37 mmol). The reaction mixture was stirred at room temperature for 24 h. Purification by flash column chromatography (hexane/diethyl ether, 1:1) 1,2-*bis*-[(4'-methoxyphenyl)sulfane]-4-ethoxy-5-hydroxybenzene (38 mg, 25%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3428 (OH), 2938 (CH), 1589 (C=C), 1489, 1242, 1028, 826; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.0 Hz, $OCH_2C\mathit{H}_3$), 3.80 (3H,

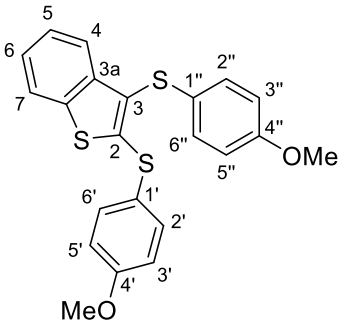
s, OCH_3), 3.82 (3H, s, OCH_3), 3.95 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 5.61 (1H, s, OH), 6.57 (1H, s, 6-H), 6.76 (1H, s, 3-H), 6.83–6.92 (4H, m, 4 × ArH), 7.24–7.30 (2H, m, 2 × ArH), 7.33–7.39 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 14.8 (CH_3), 55.5 (2 × CH_3), 64.9 (CH_2), 115.0 (2 × CH), 115.2 (2 × CH), 115.9 (CH), 116.5 (CH), 124.9 (C), 125.5 (C), 127.1 (C), 132.3 (2 × CH), 133.8 (C), 135.3 (2 × CH), 144.9 (C), 146.2 (C), 159.1 (C), 159.9 (C); *m/z* (ESI) 437.0850 (MNa^+. $C_{22}H_{22}NaO_4S_2$ requires 437.0852).

(5-Ethylthiophen-2-yl)(4'-methoxyphenyl)sulfane (73)



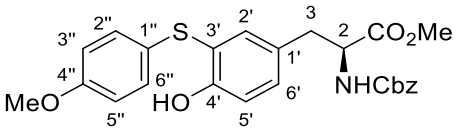
The reaction was performed as described in general procedure C using 2-ethylthiophene (50 μL, 0.45 mmol). The reaction mixture was stirred at 50 °C for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (5-ethylthiophen-2-yl)(4'-methoxyphenyl)sulfane (43 mg, 36%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2965 (CH), 1591 (C=C), 1491, 1244, 1032, 824; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.5 Hz, CH_2CH_3), 2.81 (2H, qd, *J* 7.5, 1.0 Hz, CH_2CH_3), 3.78 (3H, s, 4'-OCH_3), 6.70 (1H, dt, *J* 3.5, 1.0 Hz, 4-H), 6.81–6.85 (2H, m, 3'-H and 5'-H), 7.07 (1H, d, *J* 3.5 Hz, 3-H), 7.25–7.29 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 15.7 (CH_3), 24.0 (CH_2), 55.5 (CH_3), 114.8 (2 × CH), 124.1 (CH), 129.2 (C), 130.5 (C), 130.7 (2 × CH), 134.7 (CH), 153.0 (C), 158.9 (C); *m/z* (ESI) 273.0385 (MNa^+. $C_{13}H_{14}NaOS_2$ requires 273.0378).

2,3-*Bis*-[(4'-methoxyphenyl)sulfane]benzo[*b*]thiophene (76)[207]



The reaction was performed as described in general procedure B using benzo[*b*]thiophene (50 mg, 0.37 mmol). The reaction mixture was stirred at 50 °C for 24 h and then 75 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave 2,3-*bis*-[(4'-methoxyphenyl)sulfane]benzo[*b*]thiophene (62 mg, 41%) as a white solid. Mp 125−128 °C (lit.[207] 127.2−127.9 °C); δ_H (400 MHz, $CDCl_3$) 3.75 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.75−6.81 (2H, m, 2 × ArH), 6.89−6.95 (2H, m, 2 × ArH), 7.19−7.23 (2H, m, 2 × ArH), 7.24−7.28 (1H, m, 6-H), 7.29−7.34 (1H, m, 5-H), 7.51−7.58 (2H, m, 2 × ArH), 7.59−7.65 (1H, m, 7-H), 7.70−7.76 (1H, m, 4-H); δ_C (101 MHz, $CDCl_3$) 55.4 (CH_3), 55.5 (CH_3), 114.8 (2 × CH), 115.2 (2 × CH), 121.9 (CH), 122.3 (C), 122.7 (CH), 123.5 (C), 124.5 (CH), 125.1 (CH), 126.8 (C), 130.2 (2 × CH), 136.0 (2 × CH), 139.1 (C), 140.8 (C), 148.4 (C), 158.5 (C), 160.8 (C); *m/z* (ESI) 433 (MNa^+. 100%).

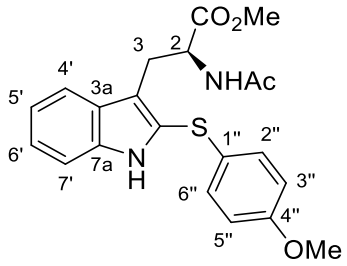
_N_-(Benzyloxycarbonyl)-[3'-(4''-methoxyphenylthio)]-L-tyrosine methyl ester (83)



The reaction was performed as described in general procedure C using *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester (100 mg, 0.30 mmol). The reaction mixture was stirred at 50 °C for 20 h. Purification by flash column chromatography (dichloromethane/diethyl ether, 100:2) gave *N*-(benzyloxycarbonyl)-[3'-(4''-methoxyphenylthio)]-L-tyrosine methyl ester (75.0 mg, 53%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3408 (OH), 2949 (CH), 1713 (CO), 1591 (C=C), 1491, 1244, 1026, 826, 754; δ_H (400 MHz, $CDCl_3$) 2.99 (1H, dd, *J* 14.0, 5.8 Hz, 3-*H*H), 3.06 (1H, dd, *J* 14.0, 5.6 Hz 3-H*H*), 3.64 (3H, s, CO_2CH_3), 3.73 (3H, s, 4''-OCH_3), 4.61 (1H, ddd, *J*

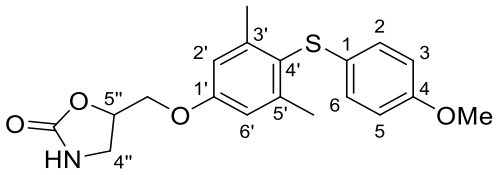
7.9, 5.8, 5.6 Hz, 2-H), 5.09 (2H, s, PhC*H*$_2$), 5.27 (1H, d, *J* 7.9 Hz, NH), 6.53 (1H, s, OH), 6.78 (2H, d, *J* 8.8 Hz, 3''-H and 5''-H), 6.92 (1H, d, *J* 8.3 Hz, 5'-H), 7.03 (1H, dd, *J* 8.3, 2.0 Hz, 6'-H), 7.07–7.15 (2H, m, 2''-H and 6''-H), 7.23 (1H, d, *J* 2.0 Hz, 2'-H), 7.27–7.40 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 37.4 (CH_2), 52.4 (CH_3), 55.0 (CH), 55.5 (CH_3), 67.1 (CH_2), 115.1 (2 × CH), 115.7 (CH), 118.9 (C), 126.0 (C), 128.2 (2 × CH), 128.3 (CH), 128.5 (C), 128.7 (2 × CH), 130.3 (2 × CH), 132.6 (CH), 136.3 (C), 136.7 (CH), 155.7 (C), 155.9 (C), 159.0 (C), 171.9 (C); *m/z* (ESI) 490.1293 (MNa^+. $C_{25}H_{25}NNaO_6S$ requires 490.1295).

N-Acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (84)



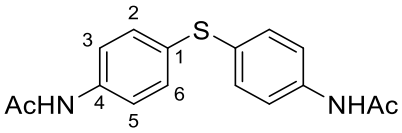
The reaction was performed as described in general procedure D using methyl *N*-acetyl-L-tryptophanate (50 mg, 0.19 mmol). The reaction mixture was stirred at 75 °C for 96 h. Purification by flash column chromatography (dichloromethane/methanol, 99:1) gave *N*-acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (125 mg, 82%) as a pale pink solid. Mp 139−142 °C; ν_{max}/cm^{-1} (neat) 3368 (NH), 3281 (NH), 2949 (CH), 1736 (CO), 1655 (CO), 1491, 1242, 1173, 1028, 824, 743; δ_H (400 MHz, $CDCl_3$) 1.86 (3H, s, $NHCOCH_3$), 3.37 (1H, dd, *J* 14.5, 5.9 Hz, 3-*H*H), 3.44 (1H, dd, *J* 14.5, 5.9 Hz, 3-H*H*), 3.70 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.92 (1H, dt, *J* 7.7, 5.9 Hz, 2-H), 6.04 (1H, d, *J* 7.7 Hz, N*H*$COCH_3$), 6.78−6.83 (2H, m, 3''-H and 5''-H), 7.09−7.16 (3H, m, 5'-H, 2''-H and 6''-H), 7.17−7.22 (1H, m, 6'-H), 7.26 (2H, d, *J* 8.0 Hz, 7'-H), 7.55 (1H, d, *J* 7.9 Hz, 4'-H), 8.11 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 23.3 (CH_3), 27.5 (CH_2), 52.6 (CH_3), 53.0 (CH), 55.5 (CH_3), 111.1 (CH), 115.2 (2 × CH), 115.8 (C), 119.1 (CH), 120.3 (CH), 123.5 (CH), 125.8 (C), 125.9 (C), 128.2 (C), 130.5 (2 × CH), 136.9 (C), 159.1 (C), 169.9 (C), 172.4 (C); *m/z* (ESI) 421.1194 (MNa^+. $C_{21}H_{22}N_2NaO_4S$ requires 421.1192).

5-{[4'-(4-Methoxyphenylthio)-3',5'-dimethylphenoxy]methyl}oxazolidin-2''-one (39)[36]



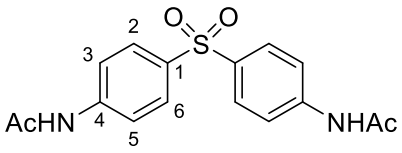
The reaction was performed as described in general procedure D using anisole (50 µL, 0.46 mmol). The reaction mixture was stirred at 75 °C for 20 h. Purification by flash chromatography (dichloromethane/methanol, 49:1) gave 5-{[4'-(4-methoxyphenylthio)-3',5'-dimethylphenoxy]methyl}oxazolidin-2''-one (58 mg, 72%) as a white solid. Mp 38−41 °C (lit.[36] 40.3−42.5 °C); δ_H (400 MHz, $CDCl_3$) 2.39 (6H, s, 3'-CH_3 and 5'-CH_3), 3.54−3.61 (1H, m, 4''-*H*H), 3.71−3.78 (4H, m, 4-OCH_3, 4''-H*H*), 4.12 (2H, d, *J* 4.9 Hz, OCH_2), 4.92−5.00 (1H, m, 5''-H), 6.26 (1H, s, NH), 6.69−6.78 (4H, m, 3-H, 5-H, 2'-H and 6'-H), 6.83−6.89 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 22.3 (2 × CH_3), 42.8 (CH_2), 55.4 (CH_3), 67.9 (CH_2), 74.6 (CH), 114.5 (2 × CH), 114.8 (2 × CH), 124.1 (C), 127.5 (2 × CH), 129.0 (C), 145.6 (2 × C), 157.5 (C), 158.3 (C), 160.3 (C); *m/z* (ESI) 382 (MNa^+. 100%).

***Bis*(4-acetylaminophenyl)sulfane (89)**[208]



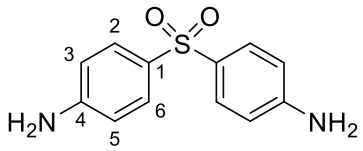
The reaction was performed as described in general procedure D using acetanilide (50 mg, 0.37 mmol). The reaction mixture was stirred at 75 °C for 96 h. Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave *bis*(4-acetylaminophenyl)sulfane (78 mg, 70%) as a white solid. Mp 209−213 °C (lit.[208] 212−214 °C); δ_H (400 MHz, DMSO-d_6) 2.03 (6H, s, 2 × 4-CH_3), 7.21−7.26 (4H, m, 2 × 2-H and 2 × 6-H), 7.54−7.59 (4H, m, 2 × 3-H and 2 × 5-H), 10.02 (2H, br s, 2 × NH); δ_C (101 MHz, DMSO-d_6) 24.0 (2 × CH_3), 119.9 (4 × CH), 128.6 (2 × C), 131.4 (4 × CH), 138.7 (2 × C), 168.4 (2 × C); *m/z* (ESI) 323 (MNa^+. 100%).

Acedapsone (90)[209]



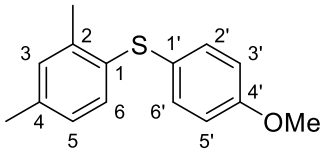
A flask was charged with *bis*(4-acetylaminophenyl)sulfane (150 mg, 0.500 mmol) and sulfuric acid (750 µL, 3.75 mmol) was added. The reaction mixture was cooled to 10 °C before 30% aqueous hydrogen peroxide (150 µL) was added dropwise, maintaining the temperature between 25−30 °C. The mixture was then left to stir at 40 °C for 4 h before being poured into a beaker containing crushed ice. The resulting white precipitate was filtered and washed with water. The solid was then dried to give acedapsone (111 mg, 67%) as an off-white solid. Mp 284−287 °C (lit.[209] 287−288 °C); δ_H (400 MHz, DMSO-d_6) 2.06 (6H, s, 2 × $COCH_3$), 7.73−7.79 (4H, m, 2 × 3-H and 2 × 5-H), 7.81−7.86 (4H, m, 2 × 2-H and 2 × 6-H), 10.35 (2H, br s, 2 × NH); δ_C (101 MHz, DMSO-d_6) 24.1 (2 × CH_3), 118.9 (4 × CH), 128.4 (4 × CH), 135.1 (2 × C), 143.6 (2 × C), 169.1 (2 × C); *m/z* (ESI) 335 (MNa^+. 100%).

Dapsone (91)[210]



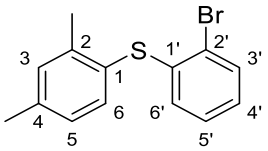
A suspension of acedapsone (80 mg, 0.24 mmol) in 10% aqueous hydrochloric acid (1 mL) was heated under reflux for 1 h. To the reaction mixture was added activated carbon before being heated under reflux for a further 1 h. The mixture was then filtered hot and then cooled to room temperature. Sodium hydroxide (2 M) was added dropwise to adjust the pH to 14 and the resulting precipitate was isolated by filtration and dried to give dapsone (39 mg, 65%) as a white solid. Mp 169−172 °C (lit.[210] 172.2−172.8 °C); δ_H (400 MHz, DMSO-d_6) 5.98 (4H, br s, 2 × NH_2), 6.57 (4H, d, *J* 8.5 Hz, 2 × 3-H and 2 × 5-H), 7.43 (4H, d, *J* 8.5 Hz, 2 × 2-H and 2 × 6-H); δ_C (101 MHz, DMSO-d_6) 112.8 (4 × CH), 128.1 (2 × C), 128.6 (4 × CH), 152.8 (2 × C); *m/z* (ESI) 271 (MNa^+. 100%).

(2,4-Dimethylphenyl)(4'-methoxyphenyl)sulfane (96)



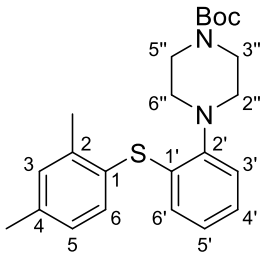
The reaction was performed as described in general procedure C using *m*-xylene (58 μL, 0.47 mmol). The reaction mixture was stirred at 60 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 4:2) gave (2,4-dimethylphenyl)(4'-methoxyphenyl)sulfane (38 mg, 33%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2940 (CH), 2833 (CH), 1591 (C=C), 1491, 1242, 1171, 1030, 822; δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 2.36 (3H, s, CH_3), 3.81 (3H, s, 4'-OCH_3), 6.83−6.89 (2H, m, 3'-H and 5'-H), 6.92 (1H, dd, *J* 7.9, 0.7 Hz, 5-H), 7.00−7.05 (2H, m, 3-H and 6-H), 7.23−7.29 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_3), 21.1 (CH_3), 55.5 (CH_3), 115.0 (2 × CH), 126.1 (C), 127.4 (CH), 131.1 (CH), 131.4 (CH), 132.7 (C), 133.2 (2 × CH), 136.9 (C), 138.3 (C), 159.2 (C); *m/z* (ESI) 267.0814 (MNa^+. $C_{15}H_{16}NaOS$ requires 267.0814).

(2'-Bromophenyl)(2,4-dimethylphenyl)sulfane (94)[211]



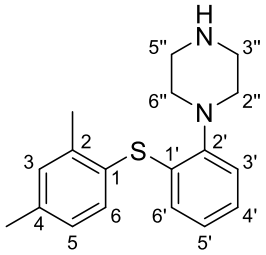
The reaction was performed as described in general procedure D using *m*-xylene (29 μL, 0.24 mmol). The reaction mixture was stirred at 75 °C for 48 h. Purification by flash column chromatography (hexane) gave (2'-bromophenyl)(2,4-dimethylphenyl)sulfane (40 mg, 58%) as a colourless oil. Spectroscopic data were consistent with the literature.[211] δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, CH_3), 2.37 (3H, s, CH_3), 6.58 (1H, dd, *J* 7.9, 1.6 Hz, 3'-H), 6.93–6.99 (1H, m, 5'-H), 7.03–7.11 (2H, m, 5-H and 4'-H), 7.18 (1H, d, *J* 1.1 Hz, 3-H), 7.40 (1H, d, *J* 7.8 Hz, 6-H), 7.53 (1H, dd, *J* 7.9, 1.3 Hz, 6'-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 21.4 (CH_3), 121.3 (C), 126.2 (CH), 127.3 (CH), 127.5 (C), 127.8 (CH), 128.2 (CH), 132.1 (CH), 132.9 (CH), 136.3 (CH), 139.6 (C), 140.1 (C), 142.5 (C); *m/z* (ESI) 317 (MNa^+. 100%).

***N*-(*tert*-Butoxycarbonyl)vortioxetine (93)**[212]



(2'-Bromophenyl)(2,4-dimethylphenyl)sulfane (50.0 mg, 0.170 mmol), *N*-(*tert*-butoxycarbonyl)piperazine (63 mg, 0.34 mmol), $Pd(dba)_2$ (4.89 mg, 8.50 μmol) and (*S*)-BINAP (10.6 mg, 17.0 μmol) were added in toluene (0.3 mL). The reaction mixture was purged with nitrogen and sodium *tert*-butoxide (32.7 mg, 0.34 mmol) was added. The reaction mixture was then heated at 110 °C for 4 h. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added before being filtered through celite and washed with dichloromethane (10 mL). The layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford an orange residue. Purification by flash chromatography (hexane/ethyl acetate, 9:1) gave *N*-(*tert*-butoxycarbonyl)vortioxetine (48.0 mg, 71%) as a pale yellow oil. Spectroscopic data were consistent with the literature.[212] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, 3 × CH_3), 2.32 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.92−3.08 (4H, m, 2''-H_2 and 6''-H_2), 3.55−3.68 (4H, m, 3''-H_2 and 5''-H_2), 6.49−6.55 (1H, m, 3'-H), 6.85−6.90 (1H, m, 4'-H), 7.01−7.10 (3H, m, 5-H, 5'-H and 6'-H), 7.15 (1H, s, 3-H), 7.37 (1H, d *J* 7.8 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 21.3 (CH_3), 28.6 (3 × CH_3), 43.8 (2 × CH_2), 51.8 (2 × CH_2), 79.8 (C), 120.1 (CH), 124.8 (CH), 125.7 (CH), 126.5 (CH), 128.0 (CH and C), 131.9 (CH), 134.8 (C), 136.3 (CH), 139.4 (C), 142.5 (C), 149.1 (C), 155.1 (C); *m/z* (ESI) 421 (MNa^+. 100%).

Vortioxetine (92)[212]



To a round bottomed flask containing *N*-(*tert*-butoxycarbonyl)vortioxetine (40 mg, 0.10 mmol) was added anhydrous dichloromethane (0.3 mL) and trifluoroacetic acid (0.3 mL). The resulting reaction mixture was left to stir at room temperature for 1 h. The solvent was removed *in vacuo* and the resulting residue was dissolved in dichloromethane (10 mL) and extracted with saturated aqueous sodium bicarbonate (10 mL). The aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give vortioxetine (24 mg, 80%) as a pale-yellow solid. Mp 98−100 °C (lit.[212] 99−101 °C); δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.46 (1H, br s, NH), 2.98−3.16 (8H, m, 2''-H_2, 3''-H_2, 5''-H_2 and 6''-H_2), 6.51 (1H, d, *J* 7.8 Hz, 3'-H), 6.81−6.89 (1H, m, 4'-H), 7.00−7.10 (3H, m, 5-H, 5'-H and 6'-H), 7.15 (1H, br s, 3-H), 7.38 (1H, d, *J* 7.8 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 21.3 (CH_3), 46.5 (2 × CH_2), 52.9 (2 × CH_2), 120.0 (CH), 124.5 (CH), 125.6 (CH), 126.3 (CH), 127.9 (CH), 128.1 (C), 131.8 (CH), 134.8 (C), 136.3 (CH), 139.3 (C), 142.6 (C), 149.6 (C); *m/z* (ESI) 299 (MH^+. 100%).

6.3 Synthesis of Phenoxathiins Experimental

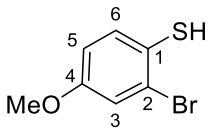
General Procedure E: Preparation of Sulfenylated Products

Iron(III) trichloride (10 mol%) was dissolved in [BMIM]NTf_2 (30 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (1.2 equiv.) in chloroform (0.6 M in arene). The arene (1.0 equiv.) and *bis*(4-methoxyphenyl)sulfane (10 mol%) was then added and the reaction mixture was left to stir at the required temperature for 1 – 48 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

General Procedure F: Preparation of Phenoxathiins

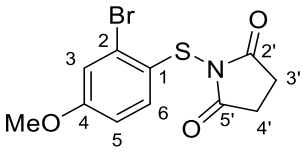
To a solution of biaryl sulfide (1.0 equiv.) in *N,N*-dimethylacetamide (0.03 M in arene) was added copper(I) thiophene-2-carboxylate (1.0 equiv.). The reaction mixture was stirred at 100 °C for 18 h. The reaction mixture was extracted with ethyl acetate (30 mL) and washed with 5% aqueous lithium chloride (2 × 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting material was purified by flash column chromatography.

2-Bromo-4-methoxythiophenol (123)



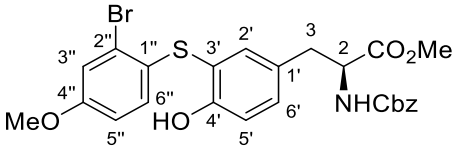
To a microwave vial was added 3-bromo-4-iodoanisole (750 mg, 2.40 mmol), $CuSO_4$•$5H_2O$ (30.0 mg, 0.120 mmol), potassium hydroxide (672 mg, 12.0 mmol), DMSO (4.8 mL) and water (0.48 mL) and the vial was sealed and flushed with argon. To the vial was added 1,2-ethanedithiol (402 µL, 4.80 mmol) and the resulting reaction mixture was stirred at 90 °C for 20 h. The reaction mixture was cooled to room temperature before being added to 5% aqueous hydrochloric acid (50 mL) and ethyl acetate (50 mL). The layers were separated and the aqueous layer was further extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/dichloromethane, 9:1) gave 2-bromo-4-methoxythiophenol (324 mg, 62%) as a pale-yellow oil. ν_{max}/cm^{-1} (neat) 2833 (CH), 2561 (SH) 1592 (C=C), 1470, 1283, 1032, 847; δ_H (400 MHz, $CDCl_3$) 3.77 (3H, s, OCH_3), 3.78 (1H, s, SH), 6.77 (1H, dd, *J* 8.7, 2.7 Hz, 5-H), 7.12 (1H, d, *J* 2.7 Hz, 3-H), 7.29 (1H, d, *J* 8.7 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 55.8 (CH_3), 114.8 (CH), 118.5 (CH), 123.8 (C), 123.9 (C), 131.1 (CH), 158.5 (C); *m/z* (EI) 217.9408 (M^+. $C_7H_7{}^{79}BrOS$ requires 217.9401).

N-(2-Bromo-4-methoxyphenylthio)succinimide (63l)



A round bottomed flask was charged with a solution of *N*-chlorosuccinimide (171 mg, 1.28 mmol) in toluene (4 mL) under an atmosphere of argon. To the flask was added a solution of 2-bromo-4-methoxythiophenol (280 mg, 1.28 mmol) in toluene (2 mL) dropwise and the resulting suspension was left to stir at 40 °C for 1 h. A solution of triethylamine (178 µL, 1.28 mmol) in toluene (2 mL) was added dropwise and the resulting reaction mixture was left to stir at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in water (20 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 3:2) gave *N*-(2-bromo-4-methoxyphenylthio)succinimide (278 mg, 69%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2939 (CH), 1716 (CO), 1584 (C=C), 1470, 1286, 1240, 1131, 874; δ_H (400 MHz, $CDCl_3$) 2.84 (4H, s, 3'-H_2 and 4'-H_2), 3.79 (3H, s, OCH_3), 6.82 (1H, dd, *J* 8.7, 2.7 Hz, 5-H), 7.13 (1H, d, *J* 2.7 Hz, 3-H), 7.46 (1H, d, *J* 8.7 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 28.8 (2 × CH_2), 55.9 (CH_3), 114.5 (CH), 118.9 (CH), 125.4 (C), 126.2 (C), 134.5 (CH), 161.1 (C), 176.2 (2 × C); *m/z* (ESI) 337.9458 (MNa^+. $C_{11}H_{10}{}^{79}BrNNaO_3S$ requires 337.9457).

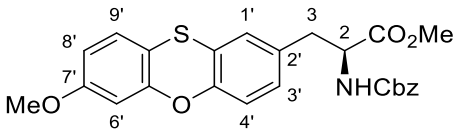
N-(Benzyloxycarbonyl)-[3'-(2''-bromo-4''-methoxyphenylthio)]-L-tyrosine methyl ester (125)



Iron(III) trichloride (11.0 mg, 0.0680 mmol) was dissolved in [BMIM]NTf_2 (59.4 µL, 0.204 mmol) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(2-bromo-4-methoxyphenylthio)succinimide (260 mg, 0.820 mmol) in chloroform (0.7 mL). *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester (224 mg, 0.680

mmol) was then added and the reaction mixture was left to stir 75 °C for 20 h. Purification by flash column chromatography (dichloromethane/diethyl ether, 99:1) gave *N*-(benzyloxycarbonyl)-[3'-(2''-bromo-4''-methoxyphenylthio)]-L-tyrosine methyl ester (240 mg, 65%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3336 (OH), 2952 (CH), 1699 (CO), 1587 (C=C), 1469, 1221, 1028, 908; $[\alpha]_D^{24}$ +35.4 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 14.0, 5.8 Hz, 3-*H*H), 3.09 (1H, dd, *J* 14.0, 5.5 Hz, 3-H*H*), 3.67 (3H, s, CO_2CH_3), 3.72 (3H, s, 4''-OCH_3), 4.62 (1H, ddd, *J* 8.1, 5.8, 5.5 Hz, 2-H), 5.07 (1H, d, *J* 14.7 Hz, PhC*H*H), 5.10 (1H, d, *J* 14.7 Hz, PhCH*H*), 5.26 (1H, d, *J* 8.1 Hz, NH), 6.41 (1H, s, OH), 6.64 (1H, d, *J* 8.8 Hz, 6''-H), 6.69 (1H, dd, *J* 8.8, 2.6 Hz, 5''-H), 6.96 (1H, d, *J* 8.3 Hz, 5'-H), 7.05–7.12 (2H, m, 3''-H and 6'-H), 7.24 (1H, d, *J* 2.1 Hz, 2'-H), 7.27–7.40 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 37.4 (CH_2), 52.6 (CH_3), 55.0 (CH), 55.8 (CH_3), 67.2 (CH_2), 114.9 (CH), 116.0 (CH), 117.1 (C), 118.6 (CH), 123.0 (C), 127.4 (C), 128.2 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 128.9 (C), 129.5 (CH), 133.4 (CH), 136.3 (C), 137.4 (CH), 155.6 (C), 156.4 (C), 158.9 (C), 171.9 (C); *m/z* (ESI) 568.0393 (MNa^+. $C_{25}H_{24}{}^{79}BrNNaO_6S$ requires 568.0400).

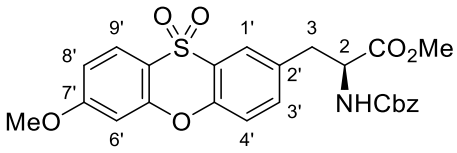
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiin-2'-yl)propanoate (126)



To a solution of *N*-(benzyloxycarbonyl)-[3'-(2''-bromo-4''-methoxyphenylthio)]-L-tyrosine methyl ester (260 mg, 0.476 mmol) in *N,N*-dimethylacetamide (15 mL) was added copper(I) thiophene-2-carboxylate (91.0 mg, 0.486 mmol). The reaction mixture was stirred at 100 °C for 18 h. The reaction mixture was extracted with ethyl acetate (30 mL) and washed with saturated aqueous lithium chloride (2 × 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiin-2'-yl)propanoate (195 mg, 88%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3358 (NH), 2948 (CH), 1715 (CO), 1480 (C=C), 1229, 1157, 1026, 755; $[\alpha]_D^{24}$ +40.5 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.98 (1H, dd, *J* 14.0, 5.9 Hz, 3-*H*H), 3.05 (1H, dd, *J* 14.0, 5.6 Hz, 3-H*H*), 3.73 (3H, s, CO_2CH_3), 3.78 (3H, s, 7'-OCH_3), 4.61 (1H, ddd, *J* 8.2, 5.9, 5.6 Hz, 2-H), 5.09 (1H, d, *J* 17.2 Hz, PhC*H*H), 5.12 (1H, d, *J* 17.2 Hz, PhCH*H*), 5.22 (1H, d, *J* 8.2 Hz, NH),

6.57–6.63 (2H, m, 6'-H and 8'-H), 6.79–6.85 (2H, m, 1'-H and 3'-H), 6.86–6.90 (1H, m, 4'-H), 6.94–6.99 (1H, m, 9'-H), 7.26–7.41 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 37.5 (CH_2), 52.6 (CH_3), 54.9 (CH), 55.7 (CH_3), 67.2 (CH_2), 104.2 (CH), 110.4 (C), 110.9 (CH), 117.9 (CH), 121.1 (C), 127.2 (CH), 127.5 (CH), 128.2 (2 × CH), 128.4 (CH), 128.5 (CH), 128.7 (2 × CH), 132.3 (C), 136.3 (C), 151.3 (C), 153.2 (C), 155.7 (C), 160.0 (C), 171.9 (C); *m/z* (ESI) 488.1141 (MNa^+. $C_{25}H_{23}NNaO_6S$ requires 488.1138).

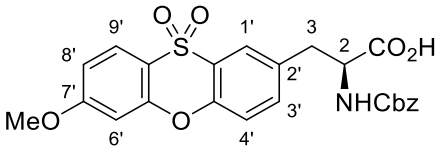
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoate (127)



Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiin-2'-yl)propanoate (100 mg, 0.215 mmol) was dissolved in dichloromethane (1.5 mL) with stirring under argon. Glacial acetic acid (338 µL, 5.91 mmol) was then added to the solution, followed by 30% H_2O_2 (120 µL). The reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (20 mL). The organic layer was washed with water (20 mL) and the aqueous layer was further extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane/methanol 99:1) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoate (116 mg, 94%) as a white solid. Mp 161−163 °C; ν_{max}/cm^{-1} (neat) 3345 (NH), 2946 (CH), 1710 (CO), 1603 (C=C), 1483, 1279, 1133, 965, 750; $[\alpha]_D^{24}$ +59.6 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.16 (1H, dd, *J* 14.0, 6.2 Hz, 3-*H*H), 3.26 (1H, dd, *J* 14.0, 5.1 Hz, 3-H*H*), 3.76 (3H, s, CO_2CH_3), 3.90 (3H, s, 7'-OCH_3), 4.68 (1H, ddd, *J* 7.5, 6.2, 5.1 Hz, 2-H), 5.11 (2H, s, PhCH_2), 5.33 (1H, d, *J* 7.5 Hz, NH), 6.81 (1H, d, *J* 2.4 Hz, 6'-H), 6.94 (1H, dd, *J* 8.9, 2.4 Hz, 8'-H), 7.24 (1H, d, *J* 8.0 Hz, 4'-H), 7.27–7.41 (6H, m, Ph and 3'-H), 7.77 (1H, d, *J* 2.1 Hz, 1'-H), 7.93 (1H, d, *J* 8.9 Hz, 9'-H); δ_C (101 MHz, $CDCl_3$) 37.8 (CH_2), 52.9 (CH_3), 54.9 (CH), 56.1 (CH_3), 67.3 (CH_2), 102.5 (CH), 113.1 (CH), 117.4 (C), 119.1 (CH), 123.7 (CH), 125.0 (CH), 125.4 (C), 128.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 133.3 (C), 135.0 (CH), 136.3 (C), 150.8 (C), 153.4 (C), 155.7

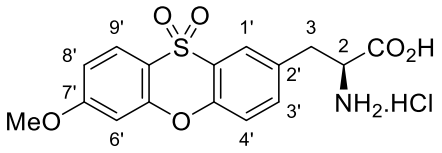
(C), 164.2 (C), 171.4 (C); *m/z* (ESI) 520.1033 (MNa^+. $C_{25}H_{23}NNaO_8S$ requires 520.1037).

(2*S*)-2-[(Benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoic acid



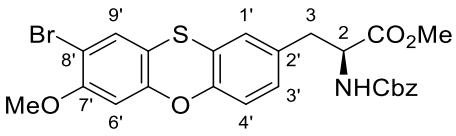
To a stirred solution of methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoate (20 mg, 0.040 mmol) in methanol (1.0 mL), 1,4-dioxane (0.5 mL) and water (0.5 mL) was added cesium carbonate (17 mg, 0.052 mmol). The resulting reaction mixture was left to stir at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoic acid as a white solid (18 mg, 95%). Mp 201−204 °C; ν_{max}/cm^{-1} (neat) 2940 (CH), 1712 (CO), 1603 (C=C), 1483, 1243, 1132, 1086, 834; $[\alpha]_D^{22}$ +19.0 (*c* 0.1, MeOH); δ_H (400 MHz, CD_3OD) 3.04 (1H, dd, *J* 14.0, 9.6 Hz, 3-*H*H), 3.29–3.36 (2H, m, 3-H*H* and NH), 3.89 (3H, s, 7'-OCH_3), 4.47 (1H, dd, *J* 9.6, 4.7 Hz, 2-H), 4.97 (1H, d, *J* 12.5 Hz, PhC*H*H), 5.02 (1H, d, *J* 12.5 Hz, PhCH*H*), 6.94 (1H, d, *J* 2.3 Hz, 6'-H), 7.00 (1H, dd, *J* 8.9, 2.3 Hz, 8'-H), 7.17–7.27 (5H, m, Ph), 7.30 (1H, d, *J* 8.6 Hz, 4'-H) 7.56 (1H, dd, *J* 8.6, 1.8 Hz, 3'-H), 7.86 (1H, d, *J* 1.8 Hz, 1'-H), 7.87 (1H, d, *J* 8.9 Hz, 9'-H); δ_C (101 MHz, CD_3OD) 37.8 (CH_2), 56.5 (CH), 56.7 (CH_3), 67.6 (CH_2), 103.5 (CH), 114.2 (CH), 118.3 (C), 120.0 (CH), 124.3 (CH), 125.5 (CH), 126.2 (C), 128.7 (2 × CH), 128.9 (CH), 129.4 (2 × CH), 136.4 (C), 136.5 (CH), 138.1 (C), 151.9 (C), 154.8 (C), 158.4 (C), 165.9 (C), 174.7 (C); *m/z* (ESI) 506.0873 (MNa^+. $C_{24}H_{21}NNaO_8S$ requires 506.0880).

(2*S*)-2-Amino-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (128)



A solution of (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoic acid (55 mg, 0.11 mmol) in 6 M aqueous hydrochloric acid (5.5 mL) and 1,4-dioxane (0.5 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue recrystallised from methanol and diethyl ether to afford (2*S*)-2-amino-3-(7'-methoxyphenoxathiine-10',10'-dioxide-2'-yl)propanoic acid hydrochloride as a white solid (41 mg, 93%). Mp 243−245 °C; ν_{max}/cm^{-1} (neat) 3201 (NH), 2883 (CH), 1732 (CO), 1606 (C=C), 1486, 1281, 1247, 1160, 840; $[\alpha]_D^{23}$ +40.0 (*c* 0.1, MeOH); δ_H (500 MHz, CD_3OD) 3.32 (1H, dd, *J* 14.7, 7.5 Hz, 3-*H*H), 3.44 (1H, dd, *J* 14.7, 5.9 Hz, 3-H*H*), 3.93 (3H, s, 7'-OCH_3), 4.36 (1H, dd, *J* 7.5, 5.9 Hz, 2-H), 7.03 (1H, d, *J* 2.4 Hz, 6'-H), 7.07 (1H, dd, *J* 8.9, 2.4 Hz, 8'-H), 7.51 (1H, d, *J* 8.7 Hz, 4'-H), 7.70 (1H, dd, *J* 8.7, 2.1 Hz, 3'-H), 7.91 (1H, d, *J* 8.9 Hz, 9'-H), 7.96 (1H, d, *J* 2.1 Hz, 1'-H); δ_C (126 MHz, CD_3OD) 36.4 (CH_2), 54.7 (CH), 56.8 (CH_3), 103.6 (CH), 114.4 (CH), 118.3 (C), 120.8 (CH), 124.8 (CH), 125.6 (CH), 126.8 (C), 133.3 (C), 136.6 (CH), 152.7 (C), 154.7 (C), 166.0 (C), 170.9 (C); *m/z* (ESI) 350.0688 (MH^+. $C_{16}H_{16}NO_6S$ requires 350.0693).

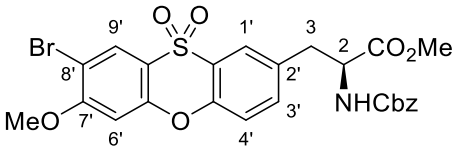
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiin-2'-yl)propanoate (129)



Iron(III) trichloride (1.91 mg, 0.0118 mmol) was dissolved in [BMIM]NTf_2 (10.3 µL, 35.4 µmol) and left to stir for 0.5 h at room temperature before being added to a suspension of *N*-bromosuccinimide (46.3 mg, 0.260 mmol) in toluene (0.6 mL). To the suspension was added methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenoxathiin-2'-yl)propanoate (110 mg, 0.236 mmol) and the resulting reaction material was left to stir at 70 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was diluted with

ethyl acetate (20 mL) and washed with 1 M aqueous sodium thiosulfate (20 mL). The aqueous layer was further extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/dichloromethane 1:4) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiin-2'-yl)propanoate as a white solid (109 mg, 84%). Mp 134−136 °C; ν_{max}/cm^{-1} (neat) 3345 (NH), 2948 (CH), 1709 (CO), 1471 (C=C), 1439, 1229, 1047, 873, 753; $[\alpha]_D^{26}$ +43.3 (*c* 0.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 2.97 (1H, dd, *J* 14.0, 6.0 Hz, 3-*H*H), 3.06 (1H, dd, *J* 14.0, 5.5 Hz, 3-H*H*), 3.73 (3H, s, CO_2CH_3), 3.86 (3H, s, 7'-OCH_3), 4.61 (1H, ddd, *J* 8.0, 6.0, 5.5 Hz, 2-H) 5.09 (1H, d, *J* 12.6 Hz, PhC*H*H), 5.11 (1H, d, *J* 12.6 Hz, PhCH*H*), 5.25 (1H, d, *J* 8.0 Hz, NH), 6.60 (1H, s, 6'-H), 6.81–6.90 (3H, m, 1'-H, 3'-H and 4'-H), 7.22 (1H, s, 9'-H), 7.29–7.38 (5H, m, Ph); δ_C (126 MHz, $CDCl_3$) 37.5 (CH_2), 52.6 (CH_3), 54.8 (CH), 56.6 (CH_3), 67.2 (CH_2), 102.7 (CH), 106.3 (C), 111.7 (C), 117.9 (CH), 120.2 (C), 127.6 (CH), 128.2 (CH), 128.4 (CH), 128.7 (2 × CH), 128.7 (2 × CH), 130.0 (CH), 132.6 (C), 136.3 (C), 150.9 (C), 152.4 (C), 155.7 (C), 155.7 (C), 171.8 (C); *m/z* (ESI) 566.0243 (MNa^+. $C_{25}H_{22}{}^{79}BrNNaO_6S$ requires 566.0243).

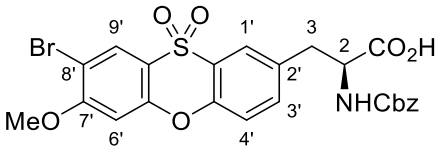
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoate (130)



Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiin-2'-yl)propanoate (60.0 mg, 0.110 mmol) was dissolved in dichloromethane (1 mL) with stirring under argon. Glacial acetic acid (173 µL, 3.03 mmol) was then added to the solution followed by 30% H_2O_2 (62.0 µL). The reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (20 mL). The organic layer was washed with water (20 mL) and the aqueous layer was further extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane/methanol 199:1) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-

3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoate (62.0 mg, 97%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3356 (NH), 3021 (CH), 1713 (CO), 1478 (C=C), 1440, 1218, 1150, 756; $[\alpha]_D^{25}$ +52.1 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.15 (1H, dd, *J* 14.0, 6.0 Hz, 3-*H*H), 3.26 (1H, dd, *J* 14.0, 5.5 Hz, 3-H*H*), 3.76 (3H, s, CO_2CH_3), 3.98 (3H, s, 7'-OCH_3), 4.67 (1 H, ddd, *J* 7.6, 6.0, 5.5 Hz, 2-H), 5.10 (2H, s, PhCH_2), 5.37 (1H, d, *J* 7.6 Hz, NH), 6.81 (1H, s, 6'-H), 7.26–7.43 (7H, m, 3'-H, 4'-H and Ph), 7.76 (1H, d, *J* 2.1 Hz, 1'-H), 8.16 (1H, s, 9'-H); δ_C (101 MHz, $CDCl_3$) 37.8 (CH_2), 52.9 (CH_3), 54.8 (CH), 57.1 (CH_3), 67.3 (CH_2), 101.5 (CH), 108.3 (C), 118.1 (C), 119.1 (CH), 123.7 (CH), 125.1 (C), 127.5 (CH), 128.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 133.7 (C), 135.2 (CH), 136.2 (C), 150.5 (C), 152.4 (C), 155.7 (C), 160.2 (C), 171.4 (C); *m/z* (ESI) 598.0143 (MNa^+. $C_{25}H_{22}{}^{79}BrNNaO_8S$ requires 598.0142).

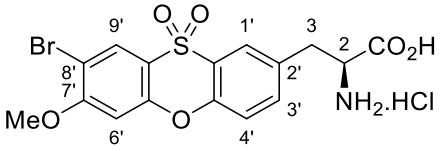
(2*S*)-2-[(Benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoic acid



To a stirred solution of methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoate (32.0 mg, 0.0555 mmol) in methanol (1 mL), 1,4-dioxane (0.5 mL) and water (0.5 mL) was added cesium carbonate (23.5 mg, 0.0722 mmol). The resulting reaction mixture was left to stir at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoic acid as a white solid (26.0 mg, 84%). Mp 231−234 °C; ν_{max}/cm^{-1} (neat) 3091 (CH), 1694 (CO), 1597 (C=C), 1438, 1264, 1147, 1099, 830; $[\alpha]_D^{26}$ +22.6 (*c* 0.1, MeOH); δ_H (500 MHz, CD_3OD) 3.04 (1H, dd, *J* 14.0, 9.6 Hz, 3-*H*H), 3.34 (1H, dd, *J* 14.0, 4.5 Hz, 3-H*H*), 3.99 (3 H, s, 7'-OCH_3), 4.47 (1H, dd, *J* 9.6, 4.5 Hz, 2-H), 4.98 (1H, d, *J* 12.5 Hz, PhC*H*H), 5.02 (1H, d, *J* 12.5 Hz, PhCH*H*), 7.08 (1H, s, 6'-H), 7.18–7.26 (5H, m, Ph), 7.32 (1H, d, *J* 8.6 Hz,

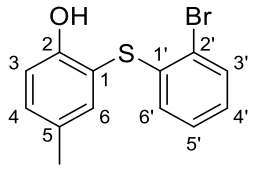
4'-H), 7.58 (1H, dd, *J* 8.6, 1.3 Hz, 3'-H), 7.87 (1H, d, *J* 1.3 Hz, 1'-H), 8.07 (1H, s, 9'-H); δ_C (126 MHz, CD_3OD) 37.8 (CH_2), 57.7 (CH), 57.7 (CH_3), 67.6 (CH_2), 103.1 (CH), 108.9 (C), 119.1 (C), 120.1 (CH), 124.3 (CH), 124.3 (C), 125.9 (C), 127.8 (CH), 128.7 (2 × CH), 128.9 (CH), 129.4 (2 × CH), 136.6 (CH), 136.8 (C), 138.1 (C), 151.6 (C), 153.9 (C), 158.4 (C), 161.7 (C); *m/z* (ESI) 583.9987 (MNa^+. $C_{24}H_{20}{}^{79}BrNNaO_8S$ requires 583.9985).

(2*S*)-2-Amino-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (131)



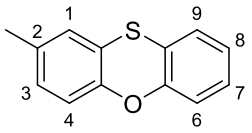
A solution of (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoic acid (20.0 mg, 0.0356 mmol) in 6 M aqueous hydrochloric acid (2 mL) and 1,4-dioxane (0.2 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue recrystallised from methanol and diethyl ether to afford (2*S*)-2-amino-3-(7'-methoxy-8'-bromophenoxathiine-10',10'-dioxide-2'-yl)propanoic acid hydrochloride as a white solid (14.0 mg, 85%). Mp 283−286 °C; ν_{max}/cm^{-1} (neat) 3003 (NH), 2845 (CH), 1725 (CO), 1597 (C=C), 1476, 1281, 1246, 1148, 827; $[\alpha]_D^{26}$ +18.4 (*c* 0.1, MeOH); δ_H (500 MHz, CD_3OD) 3.31 (1H, dd, *J* 14.7, 6.9 Hz, 3-*H*H), 3.44 (1H, dd, *J* 14.7, 5.8 Hz, 3-H*H*), 4.02 (3H, s, 7'-OCH_3), 4.34 (1H, dd, *J* 6.9, 5.8 Hz, 2-H), 7.18 (1H, s, 6'-H), 7.52 (1H, d, *J* 8.6 Hz, 4'-H), 7.71 (1H, dd, *J* 8.6, 1.1 Hz, 3'-H), 7.97 (1H, d, *J* 1.1 Hz, 1'-H), 8.12 (1H, s, 9'-H); δ_C (126 MHz, CD_3OD) 36.4 (CH_2), 57.8 (CH), 57.8 (CH_3), 103.2 (CH), 109.1 (C), 119.1 (C), 120.9 (CH), 124.8 (CH), 126.5 (C), 127.8 (CH), 133.7 (C), 136.8 (CH), 152.5 (C), 154.0 (C), 161.9 (C), 170.9 (C); *m/z* (ESI) 449.9617 (MNa^+. $C_{16}H_{14}{}^{79}BrNNaO_6S$ requires 449.9617).

(2-Hydroxy-5-methylphenyl)(2'-bromophenyl)sulfane (132a)[96]



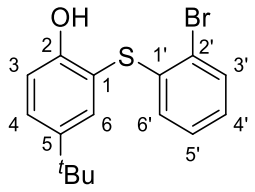
The reaction was performed as described in general procedure E using *p*-cresol (31 mg, 0.29 mmol). The reaction mixture was stirred at 75 °C for 0.5 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (2-hydroxy-5-methylphenyl)(2'-bromophenyl)sulfane (69 mg, 81%) as a white solid. Mp 67−69 °C; Spectroscopic data was consistent with the literature.[96] δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, CH_3), 6.21 (1H, s, OH), 6.60 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 6.96−7.04 (2H, m, 3-H and 4'-H), 7.09−7.15 (1H, m, 5'-H), 7.23 (1H, dd, *J* 8.3, 2.0 Hz, 4-H), 7.33 (1H, d, *J* 2.0 Hz, 6-H), 7.53 (1H, dd, *J* 7.9, 1.3 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_3), 114.8 (C), 115.7 (CH), 121.1 (C), 126.8 (CH), 127.0 (CH), 128.2 (CH), 131.2 (C), 133.1 (CH), 133.8 (CH), 137.3 (CH), 137.6 (C), 155.5 (C); *m/z* (ESI) 319 (MNa^+. 100%).

2-Methylphenoxathiin (135a)[96]



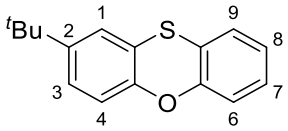
The reaction was performed as described in general procedure F using (2-hydroxy-5-methylphenyl)(2'-bromophenyl)sulfane (60 mg, 0.46 mmol). Purification by flash column chromatography (hexane) gave 2-methylphenoxathiin (38 mg, 86%) as a colourless oil. Spectroscopic data was consistent with the literature.[96] δ_H (500 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 6.87−6.93 (3H, m, 1-H, 3-H and 4-H), 6.97−7.02 (2H, m, 6-H and 8-H), 7.07−7.14 (2H, m, 7-H and 9-H); δ_C (126 MHz, $CDCl_3$) 20.7 (CH_3), 117.5 (CH), 117.9 (CH), 119.7 (C), 120.3 (C), 124.4 (CH), 126.9 (CH), 127.2 (CH), 127.7 (CH), 128.4 (CH), 134.3 (C), 150.0 (C), 152.5 (C); *m/z* (ESI) 214 (M^+. 100%).

(2-Hydroxy-5-*t*-butylphenyl)(2'-bromophenyl)sulfane (132b)



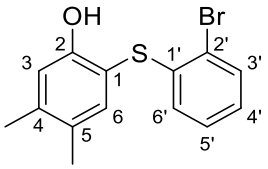
The reaction was performed as described in general procedure E using *p*-*t*-butylphenol (44 mg, 0.29 mmol). The reaction mixture was stirred at 75 °C for 1 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (2-hydroxy-5-*t*-butylphenyl)(2'-bromophenyl)sulfane (61 mg, 62%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3455 (OH), 2959 (CH), 1486 (C=C), 1446, 1181, 1018, 822, 744; δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, 3 × CH_3), 6.22 (1H, s, OH), 6.57 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 7.01 (1H, td, *J* 8.0, 1.5 Hz, 4'-H), 7.05 (1H, d, *J* 8.6 Hz, 3-H), 7.12 (1H, td, *J* 8.0, 1.5 Hz, 5'-H), 7.47 (1H, dd, *J* 8.6, 2.5 Hz, 4-H), 7.53 (1H, d, *J* 2.5 Hz, 6-H), 7.54 (1H, dd, *J* 8.0, 1.5 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 31.6 (3 × CH_3), 34.4 (C), 114.3 (C), 115.5 (CH), 120.9 (C), 126.5 (CH), 126.9 (CH), 128.2 (CH), 130.2 (CH), 133.1 (CH), 134.0 (CH), 137.7 (C), 144.8 (C), 155.4 (C); *m/z* (ESI) 359.0072 (MNa^+. $C_{16}H_{17}{}^{79}BrNaOS$ requires 359.0076).

2-*t*-Butylphenoxathiin (135b)



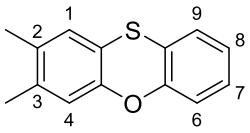
The reaction was performed as described in general procedure F using (2-hydroxy-5-*t*-butylphenyl)(2'-bromophenyl)sulfane (55 mg, 0.16 mmol). Purification by flash column chromatography (hexane) gave 2-*t*-butylphenoxathiin (35 mg, 83%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2960 (CH), 1462 (C=C), 1442, 1262, 1227, 853, 750; δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, 3 × CH_3), 6.95 (1H, d, *J* 8.4 Hz, 4-H), 6.97−7.02 (2H, m, 6-H and 8-H), 7.09−7.16 (4H, m, 1-H, 3-H, 7-H and 9-H); δ_C (101 MHz, $CDCl_3$) 31.5 (3 × CH_3), 34.5 (C), 117.3 (CH), 117.9 (CH), 119.4 (C), 120.4 (C), 123.8 (CH), 124.5 (CH), 124.9 (CH), 126.9 (CH), 127.7 (CH), 147.8 (C), 150.0 (C), 152.5 (C); *m/z* (ESI) 279.0815 (MNa^+. $C_{16}H_{16}NaOS$ requires 279.0814).

(2-Hydroxy-4,5-dimethylphenyl)(2'-bromophenyl)sulfane (132c)



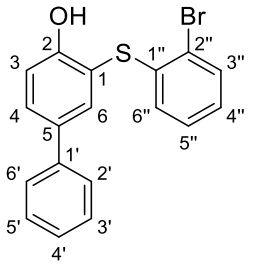
The reaction was performed as described in general procedure E using 3,4-dimethylphenol (36 mg, 0.29 mmol). The reaction mixture was stirred at 40 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 17:3) gave (2-hydroxy-4,5-dimethylphenyl)(2'-bromophenyl)sulfane (72 mg, 80%) as a white solid. Mp 86−88 °C; ν_{max}/cm^{-1} (neat) 3446 (OH), 3012 (CH), 1479 (C=C), 1446, 1311, 1204, 1019, 747; δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, CH_3), 2.29 (3H, s, CH_3), 6.13 (1H, s, OH), 6.58 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.91 (1H, s, 3-H), 6.96−7.01 (1H, m, 4'-H), 7.07−7.13 (1H, m, 5'-H), 7.26 (1H, s, 6-H), 7.52 (1H, dd, *J* 7.9, 1.3 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 18.9 (CH_3), 20.2 (CH_3), 111.4 (C), 116.9 (CH), 120.8 (C), 126.6 (CH), 126.8 (CH), 128.1 (CH), 130.1 (C), 133.0 (CH), 137.5 (CH), 137.9 (C), 142.4 (C), 155.6 (C); *m/z* (ESI) 330.9763 (MNa^+. $C_{14}H_{13}{}^{79}BrNaOS$ requires 330.9763).

2,3-Dimethylphenoxathiin (135c)



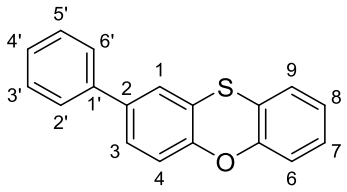
The reaction was performed as described in general procedure F using (2-hydroxy-4,5-dimethylphenyl)(2'-bromophenyl)sulfane (50 mg, 0.16 mmol). Purification by flash column chromatography (hexane) gave 2,3-dimethylphenoxathiin (30 mg, 81%) as a white solid. Mp 117−119 °C; ν_{max}/cm^{-1} (neat) 2984 (CH), 1449 (C=C), 1441, 1218, 1023, 874, 756; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 2.20 (3H, s, CH_3), 6.81 (1H, s, 4-H), 6.85 (1H, s, 1-H), 6.95−7.01 (2H, m, 6-H and 8-H), 7.06−7.13 (2H, m, 7-H and 9-H); δ_C (101 MHz, $CDCl_3$) 19.0 (CH_3), 19.6 (CH_3), 116.2 (C), 117.8 (CH), 118.9 (CH), 120.6 (C), 124.3 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 132.9 (C), 136.4 (C), 150.1 (C), 152.5 (C); *m/z* (ESI) 251.0502 (MNa^+. $C_{14}H_{12}NaOS$ requires 251.0501).

(2-Hydroxy-5-biphenyl)(2'-bromophenyl)sulfane (132d)



The reaction was performed as described in general procedure E using 4-phenylphenol (50 mg, 0.29 mmol). The reaction mixture was stirred at 75 °C for 1 h. Purification by flash column chromatography (hexane/ethyl acetate, 49:1) gave (2-hydroxy-5-biphenyl)(2'-bromophenyl)sulfane (79 mg, 76%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3440 (OH), 3028 (CH), 1504 (C=C), 1472 (C=C), 1285, 1174, 1018, 830, 742; δ_H (400 MHz, $CDCl_3$) 6.40 (1H, s, OH), 6.68 (1H, dd, *J* 8.0, 1.6 Hz, 6''-H), 6.99−7.05 (1H, m, 4''-H), 7.10−7.16 (1H, m, 5''-H), 7.19 (1H, d, *J* 8.5 Hz, 3-H), 7.31−7.36 (1H, m, 4'-H), 7.40−7.46 (2H, m, 3'-H and 5'-H), 7.53−7.60 (3H, m, 2'-H, 6'-H and 3''-H), 7.68 (1H, dd, *J* 8.5, 2.3 Hz, 4-H), 7.79 (1H, d, *J* 2.3 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 115.9 (C), 116.4 (CH), 121.3 (C), 126.8 (2 × CH), 127.0 (CH), 127.2 (CH), 127.3 (CH), 128.3 (CH), 129.0 (2 × CH), 131.7 (CH), 133.2 (CH), 135.1 (C), 135.7 (CH), 137.2 (C), 139.7 (C), 157.1 (C); *m/z* (ESI) 378.9761 (MNa^+. $C_{18}H_{13}{}^{79}BrNaOS$ requires 378.9763).

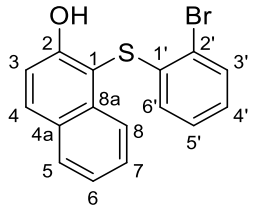
2-Phenylphenoxathiin (135d)



The reaction was performed as described in general procedure F using (2-hydroxy-5-biphenyl)(2'-bromophenyl)sulfane (65 mg, 0.18 mmol). Purification by flash column chromatography (hexane) gave 2-phenylphenoxathiin (42 mg, 84%) as a white solid. Mp 85−86 °C; ν_{max}/cm^{-1} (neat) 3056 (CH), 1456 (C=C), 1439 (C=C), 1262, 1210, 1077, 938, 745; δ_H (400 MHz, $CDCl_3$) 6.98−7.05 (2H, m, 6-H and 8-H), 7.07 (1H, d, *J* 8.3 Hz, 4-H), 7.10−7.18 (2H, m, 7-H and 9-H), 7.29−7.39 (3H, m, 1-H, 3-H and 4'-H), 7.40−7.47 (2H, m, 3'-H and 5'-H), 7.50−7.56 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 117.9 (CH), 118.1 (CH), 119.9 (C), 120.5 (C), 124.7 (CH), 125.4 (CH), 126.6 (CH), 126.9 (2 × CH), 127.0 (CH), 127.5 (CH), 127.9 (CH), 129.0

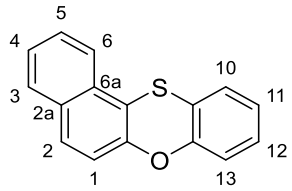
(2 × CH), 138.0 (C), 139.9 (C), 151.6 (C), 152.2 (C); *m/z* (ESI) 299.0501 (MNa^+. $C_{18}H_{12}NaOS$ requires 299.0501).

(2-Hydroxynaphthalen-1-yl)(2'-bromophenyl)sulfane (104)[18]



The reaction was performed as described in general procedure E using 2-naphthol (42 mg, 0.29 mmol). The reaction mixture was stirred at 75 °C for 1 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (2-hydroxynaphthalen-1-yl)(2'-bromophenyl)sulfane (93 mg, 97%) as a colourless oil. Spectroscopic data was consistent with the literature.[18] δ_H (400 MHz, $CDCl_3$) 6.32–6.37 (1H, m, 6'-H), 6.92–7.00 (2H, m, 4'-H and 5'-H), 7.02 (1H, s, OH), 7.36 (1H, d, *J* 8.9 Hz, 3-H), 7.40 (1H, ddd, *J* 8.1, 6.9, 1.2 Hz, 6-H), 7.51 (1H, ddd, *J* 8.4, 6.9, 1.3 Hz, 7-H), 7.54–7.59 (1H, m, 3'-H), 7.84 (1H, dd, *J* 8.1, 1.3 Hz, 5-H), 7.96 (1H, d, *J* 8.9 Hz, 4-H), 8.15 (1H, dd, *J* 8.4, 1.2 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 107.3 (C), 117.2 (CH), 121.2 (C), 124.2 (CH), 124.7 (CH), 126.5 (CH), 127.0 (CH), 128.1 (CH), 128.4 (CH), 128.8 (CH), 129.7 (C), 133.1 (CH), 133.5 (CH), 135.4 (C), 136.6 (C), 157.4 (C); *m/z* (ESI) 355 (MNa^+. 100%).

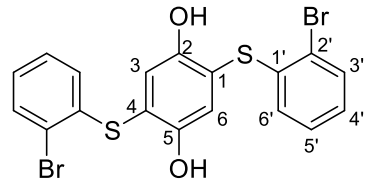
Benzo[*a*]phenoxathiin (105)[18]



The reaction was performed as described in general procedure F using (2-hydroxynaphthalen-1-yl)(2'-bromophenyl)sulfane (80 mg, 0.24 mmol). Purification by flash column chromatography (hexane) gave benzo[*a*]phenoxathiin (50 mg, 83%) as a white solid. Mp 63−64 °C (lit.[4] 63 °C); δ_H (400 MHz, $CDCl_3$) 7.02–7.08 (2H, m, 11-H and 13-H), 7.13–7.24 (3H, m, 1-H, 10-H and 12-H), 7.44 (1H, ddd, *J* 8.1, 6.9, 1.0 Hz, 4-H), 7.55 (1H, ddd, *J* 8.4, 6.9, 1.3 Hz, 5-H), 7.65 (1H, d, *J* 8.8 Hz, 2-H), 7.79 (1H, dd, *J* 8.1, 1.3 Hz, 3-H), 7.92 (1H, dd, *J* 8.4, 1.0 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 113.6 (C), 117.8 (CH), 118.5 (CH), 119.7 (C), 123.1 (CH), 124.8 (CH), 125.1 (CH),

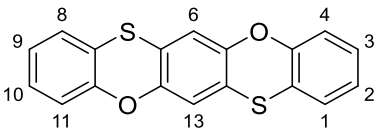
127.0 (CH), 127.2 (CH), 127.8 (CH), 128.1 (CH), 128.5 (CH), 130.3 (C), 131.1 (C), 149.8 (C), 152.5 (C); *m/z* (ESI) 273 (MNa^+. 100%).

1,4-*Bis*-[(2'-bromophenyl)sulfane]-2,5-dihydroxybenzene (132e)



Iron(III) trichloride (5.2 mg, 0.032 mmol) was dissolved in $[BMIM]NTf_2$ (28 μL, 0.095 mmol) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (200 mg, 0.70 mmol) in chloroform (0.6 mL). Hydroquinone (35 mg, 0.32 mmol) and *bis*(4-methoxyphenyl)sulfane (7.8 mg, 0.032 mmol) was then added and the reaction mixture was left to stir at 75 °C for 1 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography (hexane/dichloromethane 3:2) to give 1,4-*bis*-[(2'-bromophenyl)sulfane]-2,5-dihydroxybenzene (121 mg, 79%) as a white solid. Mp 189−190 °C; ν_{max}/cm^{-1} (neat) 3414 (OH), 3056 (CH), 1458 (C=C), 1443, 1302, 1189, 1018, 798, 739; δ_H (400 MHz, $CDCl_3$) 5.98 (2H, s, 2 × OH), 6.81 (2H, dd, *J* 7.8, 1.5 Hz, 2 × 6'-H), 7.07 (2H, td, *J* 7.8, 1.5 Hz, 2 × 4'-H), 7.19 (2H, td, *J* 7.8, 1.5 Hz, 2 × 5'-H), 7.24 (2H, s, 3-H and 6-H), 7.57 (2H, dd, *J* 7.8, 1.5 Hz, 2 × 3'-H); δ_C (101 MHz, $CDCl_3$) 120.6 (2 × C), 122.3 (2 × C), 122.5 (2 × CH), 127.9 (2 × CH), 128.1 (2 × CH), 128.4 (2 × CH), 133.4 (2 × CH), 136.1 (2 × C), 151.1 (2 × C); *m/z* (ESI) 482.8698 (MH^+. $C_{18}H_{13}{}^{79}Br_2O_2S_2$ requires 482.8718).

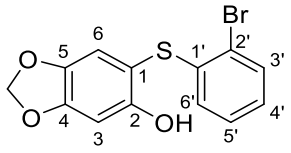
5,12-Dioxa-7,14-dithiapentacene (135e)



To a solution of 1,4-*bis*-[(2'-bromophenyl)sulfane]-2,5-dihydroxybenzene (90 mg, 0.19 mmol) in *N,N*-dimethylacetamide (6.4 mL) was added copper(I) thiophene-2-carboxylate (71 mg, 0.37 mmol). The reaction mixture was stirred at 100 °C for 18 h. The reaction mixture was extracted with ethyl acetate (30 mL) and washed with 5% aqueous lithium chloride (2 × 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography

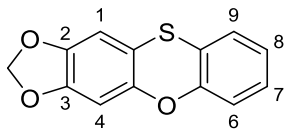
(hexane/dichloromethane 9:1) gave 5,12-dioxa-7,14-dithiapentacene (49 mg, 82%) as a white solid. Mp 216−218 °C; ν_{max}/cm^{-1} (neat) 3070 (CH), 1450 (C=C), 1439, 1370, 1261, 1205, 1169, 874, 747; δ_H (400 MHz, $CDCl_3$) 6.77 (2H, s, 6-H and 13-H), 6.95–7.03 (4H, m, 2 × 2-H and 2 × 4-H), 7.07–7.15 (4H, m, 2 × 1-H and 2 × 3-H); δ_C (101 MHz, $CDCl_3$) 115.5 (2 × CH), 118.0 (2 × CH), 119.3 (2 × C), 119.5 (2 × C), 124.8 (2 × CH), 126.9 (2 × CH), 128.1 (2 × CH), 148.7 (2 × C), 152.1 (2 × C); *m/z* (ESI) 340.0465 ([MNH_4]$^+$. $C_{18}H_{14}NO_2S_2$ requires 340.0460).

[2-Hydroxy-4,5-(methylenedioxy)phenyl](2'-bromophenyl)sulfane (132f)



The reaction was performed as described in general procedure E using sesamol (40 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (hexane/dichloromethane, 7:3) gave [2-hydroxy-4,5-(methylenedioxy)phenyl](2'-bromophenyl)sulfane (72 mg, 76%) as a white solid. Mp 95−97 °C; ν_{max}/cm^{-1} (neat) 3397 (OH), 2899 (CH), 1617 (C=C), 1468, 1272, 1181, 1113, 1034, 1016, 935, 856, 760; δ_H (400 MHz, $CDCl_3$) 5.99 (2H, s, CH_2), 6.27 (1H, s, OH), 6.60–6.68 (2H, m, 3-H and 6'-H), 6.92 (1H, s, 6-H), 7.01 (1H, td, *J* 7.8, 1.6 Hz, 4'-H), 7.11–7.16 (1H, m, 5'-H), 7.52 (1H, dd, *J* 7.8, 1.3 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 97.9 (CH_2), 101.9 (CH), 104.5 (C), 114.7 (CH), 120.8 (C), 126.5 (CH), 127.1 (CH), 128.2 (CH), 133.1 (CH), 137.9 (C), 142.2 (C), 151.6 (C), 154.1 (C); *m/z* (ESI) 346.9348 (MNa$^+$. $C_{13}H_9{}^{79}BrNaO_3S$ requires 346.9348).

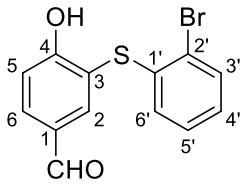
2,3-(Methylenedioxy)phenoxathiin (135f)



The reaction was performed as described in general procedure F using [2-hydroxy-4,5-(methylenedioxy)phenyl](2'-bromophenyl)sulfane (54 mg, 0.17 mmol). Purification by flash column chromatography (hexane/dichloromethane 4:1) gave 2,3-(methylenedioxy)phenoxathiin (38 mg, 93%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2888 (CH), 1459 (C=C), 1219, 1118, 1032, 933, 850, 746; δ_H (400 MHz, $CDCl_3$) 5.94 (2H, s, CH_2), 6.57 (1H, s, 4-H), 6.62 (1H, s, 1-H), 6.98–7.04 (2H, m, 6-H and 8-H),

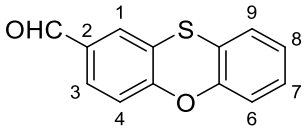
7.10–7.16 (2H, m, 7-H and 9-H); δ_C (101 MHz, $CDCl_3$) 100.6 (CH), 101.8 (CH_2), 106.2 (CH), 111.4 (C), 117.8 (CH), 121.0 (C), 124.7 (CH), 126.9 (CH), 127.9 (CH), 144.6 (C), 147.4 (C), 147.5 (C), 152.9 (C); *m/z* (ESI) 267.0087 (MNa^+. $C_{13}H_8NaO_3S$ requires 267.0086).

3-(2'-Bromophenylthio)-4-hydroxybenzaldehyde (132g)



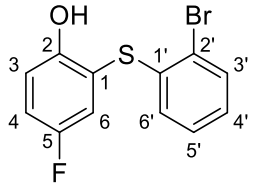
Iron(III) trichloride (4.7 mg, 0.029 mmol) was dissolved in [BMIM]NTf_2 (25 μL, 0.087 mmol) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (100 mg, 0.35 mmol) in chloroform (0.5 mL). 4-Hydroxybenzaldehyde (36 mg, 0.29 mmol) and *bis*(4-methoxyphenyl)sulfane (7.2 mg, 0.029 mmol) was then added and the reaction mixture was left to stir at 85 °C for 24 h. Further *N*-(2-bromophenylthio)succinimide (100 mg, 0.35 mmol) was added and the reaction mixture was left to stir at 85 °C for a further 24 h. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography (hexane/dichloromethane 1:1) to give 3-(2'-bromophenylthio)-4-hydroxybenzaldehyde (49 mg, 54%) as an off-white solid. Mp 136−138 °C; ν_{max}/cm^{-1} (neat) 3207 (OH), 1663 (C=O), 1593 (C=C), 1558, 1488, 1263, 1147, 1018, 745, 719; δ_H (400 MHz, $CDCl_3$) 6.64 (1H, dd, *J* 7.9, 1.6 Hz, 6'-H), 7.03–7.08 (2H, m, 4-OH and 4'-H), 7.12–7.16 (1H, m, 5'-H), 7.22 (1H, d, *J* 8.5 Hz, 5-H), 7.56 (1H, dd, *J* 7.9, 1.4 Hz, 3'-H), 7.97 (1H, dd, *J* 8.5, 2.0 Hz, 6-H), 8.08 (1H, d, *J* 2.0 Hz, 2-H), 9.87 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 116.8 (CH), 117.3 (C), 121.9 (C), 127.5 (CH), 127.9 (CH), 128.4 (CH), 131.0 (C), 133.4 (CH), 134.1 (CH), 136.0 (C), 140.0 (CH), 162.6 (C), 189.9 (CH); *m/z* (ESI) 330.9397 (MNa^+. $C_{13}H_9{}^{79}BrNaO_2S$ requires 330.9399).

2-Formylphenoxathiin (135g)



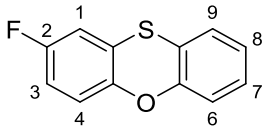
The reaction was performed as described in general procedure F using 3-(2'-bromophenylthio)-4-hydroxybenzaldehyde (53 mg, 0.17 mmol). Purification by flash column chromatography (hexane/dichloromethane 7:3) gave 2-formylphenoxathiin (36 mg, 92%) as a yellow solid. Mp 82−83 °C; ν_{max}/cm^{-1} (neat) 2727 (CH), 1683 (C=O), 1592 (C=C), 1466, 1238, 1198, 1080, 810, 752; δ_H (400 MHz, $CDCl_3$) 6.97–7.08 (4H, m, 4-H, 6-H, 8-H and 9-H), 7.14 (1H, ddd, *J* 8.0, 6.9, 2.1 Hz, 7-H), 7.59 (1H, d, *J* 2.0 Hz, 1-H), 7.62 (1H, dd, *J* 8.3, 2.0 Hz, 3-H), 9.84 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 118.0 (CH), 118.3 (CH), 118.6 (C), 121.4 (C), 125.4 (CH), 126.9 (CH), 128.1 (CH), 128.2 (CH), 130.2 (CH), 133.3 (C), 150.9 (C), 156.6 (C), 190.1 (CH); *m/z* (ESI) 251.0136 (MNa^+. $C_{13}H_8NaO_2S$ requires 251.0137).

(2-Hydroxy-5-fluorophenyl)(2'-bromophenyl)sulfane (132h)



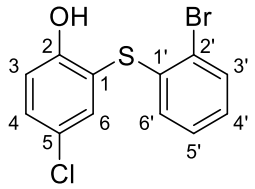
The reaction was performed as described in general procedure E using 4-fluorophenol (33 mg, 0.29 mmol). The reaction mixture was stirred at 75 °C for 3 h. Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave (2-hydroxy-5-fluorophenyl)(2'-bromophenyl)sulfane (30 mg, 34%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3437 (OH), 3061 (CH), 1478 (C=C), 1445, 1194, 1017, 818, 770, 743; δ_H (400 MHz, $CDCl_3$) 6.20 (1H, s, OH), 6.66 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 7.01–7.08 (2H, m, 3-H and 4'-H), 7.11–7.17 (2H, m, 6-H and 5'-H), 7.22–7.27 (1H, m, 4-H), 7.55 (1H, dd, *J* 7.9, 1.4 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 116.3 (d, $^3J_{CF}$ 8.3 Hz, C), 116.8 (d, $^3J_{CF}$ 7.9 Hz, CH), 119.9 (d, $^2J_{CF}$ 23.0 Hz, CH), 121.7 (C), 122.7 (d, $^2J_{CF}$ 23.1 Hz, CH), 127.3 (CH), 127.6 (CH), 128.3 (CH), 133.3 (CH), 136.5 (C), 154.0 (d, $^4J_{CF}$ 2.4 Hz, C), 156.7 (d, $^1J_{CF}$ 242.1 Hz, C); *m/z* (ESI) 296.9392 ($[M–H]^–$. $C_{12}H_7{}^{79}BrFOS$ requires 296.9391).

2-Fluorophenoxathiin (135h)



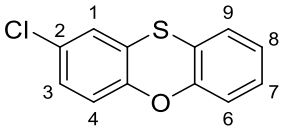
The reaction was performed as described in general procedure F using (2-hydroxy-5-fluorophenyl)(2'-bromophenyl)sulfane (45 mg, 0.15 mmol). Purification by flash column chromatography (hexane) gave 2-fluorophenoxathiin (30 mg, 91%) as a white solid. Mp 58–60 °C; ν_{max}/cm^{-1} (neat) 3062 (CH), 1458 (C=C), 1442, 1245, 1183, 853, 753; δ_H (400 MHz, $CDCl_3$) 6.78–6.85 (2H, m, 1-H and 3-H), 6.95 (1H, ddd, *J* 8.5, 4.8, 0.7 Hz, 4-H), 6.99–7.04 (2H, m, 6-H and 8-H), 7.09 (1H, dd, *J* 7.7, 1.7 Hz, 9-H), 7.12–7.17 (1H, m, 7-H); δ_C (101 MHz, $CDCl_3$) 113.5 (d, $^2J_{CF}$ 26.0 Hz, CH), 114.3 (d, $^2J_{CF}$ 23.3 Hz, CH), 118.0 (CH), 118.7 (d, $^3J_{CF}$ 8.6 Hz, CH), 119.3 (C), 122.1 (d, $^3J_{CF}$ 8.9 Hz, C), 124.8 (CH), 126.9 (CH), 128.1 (CH), 148.4 (d, $^4J_{CF}$ 2.7 Hz, C), 152.3 (C), 159.3 (d, $^1J_{CF}$ 243.9 Hz, C); *m/z* (ESI) 218.0198 (M^+. $C_{12}H_7FOS$ requires 218.0196).

(2-Hydroxy-5-chlorophenyl)(2'-bromophenyl)sulfane (132i)



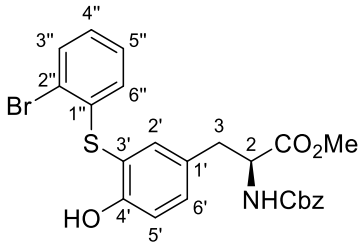
The reaction was performed as described in general procedure E using 4-chlorophenol (37 mg, 0.29 mmol). The reaction mixture was stirred at 75 °C for 2 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (2-hydroxy-5-chlorophenyl)(2'-bromophenyl)sulfane (50 mg, 54%) as a white solid. Mp 77–79 °C; ν_{max}/cm^{-1} (neat) 3391 (OH), 3050 (CH), 1464 (C=C), 1447, 1188, 1017, 817, 740; δ_H (400 MHz, $CDCl_3$) 6.36 (1H, s, OH), 6.64 (1H, dd, *J* 7.9, 1.5 Hz, 6'-H), 7.00–7.08 (2H, m, 3-H and 4'-H), 7.15 (1H, td, *J* 7.9, 1.4 Hz, 5'-H), 7.38 (1H, dd, *J* 8.8, 2.6 Hz, 4-H), 7.52 (1H, d, *J* 2.6 Hz, 6-H), 7.55 (1H, dd, *J* 7.9, 1.4 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 117.1 (C), 117.2 (CH), 121.6 (C), 125.9 (C), 127.2 (CH), 127.6 (CH), 128.4 (CH), 132.9 (CH), 133.3 (CH), 136.2 (CH), 136.4 (C), 156.3 (C); *m/z* (ESI) 336.9059 (MNa^+. $C_{12}H_8{}^{79}Br^{35}ClNaOS$ requires 336.9060).

2-Chlorophenoxathiin (135i)



The reaction was performed as described in general procedure F using (2-hydroxy-5-chlorophenyl)(2'-bromophenyl)sulfane (40 mg, 0.13 mmol). Purification by flash column chromatography (hexane) gave 2-chlorophenoxathiin (25 mg, 83%) as a white solid. Mp 88–90 °C; ν_{max}/cm^{-1} (neat) 3059 (CH), 1462 (C=C), 1439, 1377, 1285, 1261, 1099, 799, 737; δ_H (400 MHz, $CDCl_3$) 6.89–6.94 (1H, m, 6-H), 6.96–7.10 (5H, m, 1-H, 3-H, 4-H, 8-H and 9-H), 7.14 (1H, ddd, *J* 7.9, 7.4, 1.8 Hz, 7-H); δ_C (101 MHz, $CDCl_3$) 118.0 (CH), 118.8 (CH), 119.2 (C), 122.2 (C), 124.9 (CH), 126.4 (CH), 126.9 (CH), 127.7 (CH), 128.1 (CH), 129.5 (C), 150.9 (C), 152.0 (C); *m/z* (ESI) 233.9901 (M^+. $C_{12}H_7ClOS$ requires 233.9901).

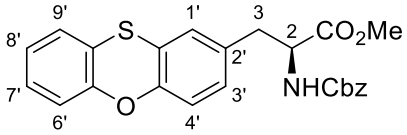
***N*-(Benzyloxycarbonyl)-[3'-(2''-bromophenylthio)]-L-tyrosine methyl ester (120)**



The reaction was performed as described in general procedure E using *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester (192 mg, 0.582 mmol). The reaction mixture was stirred at 75 °C for 20 h. Purification by flash column chromatography (dichloromethane) gave *N*-(benzyloxycarbonyl)-[3'-(2''-bromophenylthio)]-L-tyrosine methyl ester (240 mg, 80%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3379 (OH), 3318 (NH), 2948 (CH), 1705 (CO), 1507 (C=C), 1446, 1216, 1019, 757; $[\alpha]_D^{25}$ +42.7 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 14.0, 5.8 Hz, 3-*H*H), 3.11 (1H, dd, *J* 14.0, 5.5 Hz, 3-H*H*), 3.67 (3H, s, CO_2CH_3), 4.63 (1H, ddd, *J* 8.0, 5.8, 5.5 Hz, 2-H), 5.07 (1H, d, *J* 12.2 Hz, PhC*H*H), 5.10 (1H, d, *J* 12.2 Hz, PhCH*H*), 5.29 (1H, d, *J* 8.0 Hz, NH), 6.36 (1H, s, OH), 6.53 (1H, dd, *J* 8.0, 1.5 Hz, 6''-H), 6.95–7.03 (2H, m, 5'-H and 4''-H), 7.05–7.12 (1H, m, 5''-H), 7.15 (1H, dd, *J* 8.4, 2.2 Hz, 6'-H), 7.28–7.39 (6H, m, 2'-H and Ph), 7.52 (1H, dd, *J* 7.9, 1.3 Hz, 3''-H); δ_C (101 MHz, $CDCl_3$) 37.4 (CH_2), 52.6 (CH_3), 55.0 (CH), 67.2 (CH_2), 115.4 (C), 116.2 (CH), 121.1 (C), 126.8

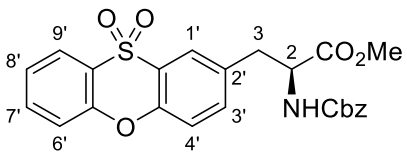
(CH), 127.1 (CH), 128.2 (2 × CH), 128.3 (CH), 128.4 (CH), 128.7 (2 × CH), 129.2 (C), 133.1 (CH), 133.9 (CH), 136.3 (C), 137.3 (C), 137.9 (CH) 155.6 (C), 156.8 (C), 171.8 (C); *m/z* (ESI) 538.0288 (MNa^+. $C_{24}H_{22}{}^{79}BrNNaO_5S$ requires 538.0294).

Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-2'-yl)propanoate (136)



The reaction was performed as described in general procedure F using *N*-(benzyloxycarbonyl)-[3'-(2''-bromophenylthio)]-L-tyrosine methyl ester (100 mg, 0.194 mmol). Purification by flash column chromatography (dichloromethane) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-2'-yl)propanoate (78.0 mg, 93%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3342 (NH), 2950 (CH), 1699 (CO), 1511 (C=C), 1464, 1442, 1230, 1206, 1056, 747; $[\alpha]_D^{25}$ +48.7 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.98 (1H, dd, *J* 14.0, 6.0 Hz, 3-*H*H), 3.06 (1H, dd, *J* 14.0, 5.6 Hz, 3-H*H*), 3.73 (3H, s, CO_2CH_3), 4.62 (1H, ddd, *J* 8.0, 6.0, 5.6 Hz, 2-H), 5.08 (1H, d, *J* 12.2 Hz, PhC*H*H), 5.13 (1H, d, *J* 12.2 Hz, PhCH*H*), 5.23 (1H, d, *J* 8.0 Hz, NH), 6.81–6.85 (2H, m, 1'-H and 4'-H), 6.87–6.91 (1H, m, 3'-H), 6.97–7.02 (2H, m, 6'-H and 8'-H), 7.08 (1H, dd, *J* 7.7, 1.5 Hz, 9'-H), 7.10–7.14 (1H, m, 7'-H), 7.29–7.38 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 37.5 (CH_2), 52.6 (CH_3), 54.9 (CH), 67.2 (CH_2), 117.9 (CH), 118.0 (CH), 119.9 (C), 120.5 (C), 124.7 (CH), 126.9 (CH), 127.5 (CH), 127.9 (CH), 128.2 (2 × CH), 128.4 (CH), 128.7 (CH), 128.7 (2 × CH), 132.3 (C), 136.3 (C), 151.4 (C), 152.2 (C), 155.7 (C) 171.9 (C); *m/z* (ESI) 458.1031 (MNa^+. $C_{24}H_{21}NNaO_5S$ requires 458.1033).

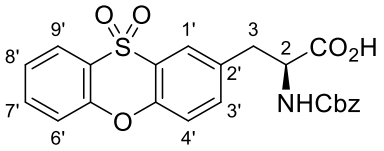
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoate (138)



Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-2'-yl)propanoate (135 mg, 0.310 mmol) was dissolved in dichloromethane (2.50 mL) with stirring under

argon. Glacial acetic acid (487 μL, 8.52 mmol) was then added to the solution followed by 30% H_2O_2 (176 μL). The reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (20 mL). The organic layer was washed with water (20 mL) and the aqueous layer was further extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (dichloromethane/methanol 199:1) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoate (143 mg, 98%) as a white solid. Mp 122−124 °C; ν_{max}/cm^{-1} (neat) 3348 (NH), 2954 (CH), 1714 (CO), 1520 (C=C), 1469, 1273, 1152, 1063, 757; $[\alpha]_D^{25}$ +65.9 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.15 (1H, dd, *J* 14.0, 6.2 Hz, 3-*H*H), 3.26 (1H, dd, *J* 14.0, 5.4 Hz, 3-H*H*), 3.75 (3H, s, CO_2CH_3), 4.67 (1H, ddd, *J* 7.6, 6.2, 5.4 Hz, 2-H), 5.10 (2H, s, PhCH_2), 5.42 (1H, d, *J* 7.6 Hz, NH), 7.26−7.43 (9H, m, 3'-H, 4'-H, 6'-H, 8'-H and Ph), 7.61−7.67 (1H, m, 7'-H), 7.79 (1H, d, *J* 1.9 Hz, 1'-H), 8.04 (1H, dd, *J* 7.9, 1.2 Hz, 9'-H); δ_C (101 MHz, $CDCl_3$) 37.7 (CH_2), 52.8 (CH_3), 54.8 (CH), 67.2 (CH_2), 119.0 (CH), 119.2 (CH), 123.5 (CH), 123.8 (CH), 124.9 (C), 124.9 (C), 125.0 (CH), 128.2 (2 × CH), 128.3 (CH), 128.6 (2 × CH), 133.4 (C), 134.3 (CH), 135.2 (CH), 136.2 (C), 150.6 (C), 151.6 (C), 155.7 (C), 171.4 (C); *m/z* (ESI) 490.0931 (MNa^+. $C_{24}H_{21}NNaO_7S$ requires 490.0931).

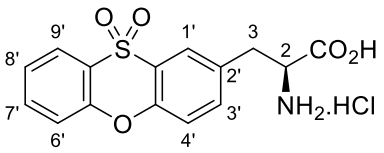
(2*S*)-2-[(Benzyloxycarbonyl)amino]-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoic acid



To a stirred solution of methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoate (45.0 mg, 0.0963 mmol) in methanol (2 mL), 1,4-dioxane (1 mL) and water (1 mL) was added cesium carbonate (40.7 mg, 0.125 mmol). The resulting reaction mixture was left to stir at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoic acid

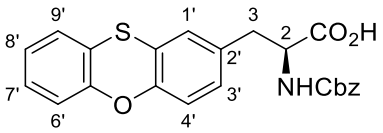
as a white solid (37.0 mg, 85%). Mp 231−234 °C; ν_{max}/cm^{-1} (neat) 3013 (CH), 2672 (OH), 1698 (CO), 1469 (C=C), 1273, 1150, 1062, 750; $[\alpha]_D^{24}$ +13.8 (*c* 0.1, MeOH); δ_H (500 MHz, CD_3OD) 3.05 (1H, dd, *J* 14.0, 9.6 Hz, 3-*H*H), 3.34 (1H, dd, *J* 14.0, 4.4 Hz, 3-H*H*), 4.48 (1H, dd, *J* 9.6, 4.4 Hz, 2-H), 4.97 (1H, d, *J* 12.5 Hz, PhC*H*H), 5.02 (1H, d, *J* 12.5 Hz, PhCH*H*), 7.13−7.29 (5H, m, Ph), 7.34 (1H, d, *J* 8.5 Hz, 4'-H), 7.43−7.48 (2H, m, 6'-H and 8'-H), 7.59 (1H, dd, *J* 8.5, 1.9 Hz, 3'-H), 7.72 (1H, t, *J* 7.8 Hz, 7'-H), 7.89 (1H, d, *J* 1.9 Hz, 1'-H), 8.00 (1H, d, *J* 8.1 Hz, 9'-H); δ_C (126 MHz, CD_3OD) 37.8 (CH_2), 56.5 (CH), 67.6 (CH_2), 120.1 (CH), 120.2 (CH), 124.1 (CH), 124.4 (CH), 125.9 (C), 126.2 (CH), 126.3 (C), 128.7 (2 × CH), 128.8 (CH), 129.4 (2 × CH), 135.7 (CH), 136.5 (C), 136.7 (CH), 138.1 (C), 151.8 (C), 153.0 (C), 158.4 (C) 174.6 (C); *m/z* (ESI) 476.0776 (MNa^+. $C_{23}H_{19}NNaO_7S$ requires 476.0774).

(2*S*)-2-Amino-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (139)



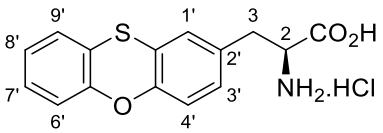
A solution of (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoic acid (25 mg, 0.055 mmol) in 6 M aqueous hydrochloric acid (2.5 mL) and 1,4-dioxane (0.5 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue recrystallised from methanol and diethyl ether to afford (2*S*)-2-amino-3-(phenoxathiin-10',10'-dioxide-2'-yl)propanoic acid hydrochloride as a white solid (18 mg, 92%). Mp 235−236 °C; ν_{max}/cm^{-1} (neat) 3075 (NH), 2948 (CH), 2831 (OH), 1732 (CO), 1592 (C=C), 1471, 1272, 1199, 1148, 758; $[\alpha]_D^{24}$ +30.3 (*c* 0.1, MeOH); δ_H (500 MHz, CD_3OD) 3.34 (1H, dd, *J* 14.7, 7.4 Hz, 3-*H*H), 3.45 (1H, dd, *J* 14.7, 5.9 Hz, 3-H*H*), 4.37 (1H, dd, *J* 7.4, 5.9 Hz, 2-H), 7.49−7.55 (3H, m, 4'-H, 6'-H and 8'-H), 7.72 (1H, dd, *J* 8.6, 1.5 Hz, 3'-H), 7.78 (1H, t, *J* 7.9 Hz, 7'-H), 7.99 (1H, d, *J* 1.5 Hz, 1'-H), 8.03 (1H, d, *J* 7.9 Hz, 9'-H); δ_C (126 MHz, CD_3OD) 36.4 (CH_2), 54.7 (CH), 120.2 (CH), 120.9 (CH), 124.1 (CH), 125.0 (CH), 126.3 (C), 126.4 (CH), 126.5 (C) 133.4 (C), 135.9 (CH), 136.9 (CH), 152.6 (C), 152.9 (C), 170.9 (C); *m/z* (ESI) 342.0405 (MNa^+. $C_{15}H_{13}NNaO_5S$ requires 342.0407).

(2*S*)-2-[(Benzyloxycarbonyl)amino]-3-(phenoxathiin-2'-yl)propanoic acid



To a stirred solution of methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-2'-yl)propanoate (130 mg, 0.299 mmol) in methanol (6 mL), 1,4-dioxane (3 mL) and water (3 mL) was added cesium carbonate (126 mg, 0.388 mmol). The resulting reaction mixture was left to stir at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with water (20 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-2'-yl)propanoic acid as a colourless oil (103 mg, 82%). ν_{max}/cm^{-1} (neat) 3306 (OH), 2920 (CH), 1697 (CO), 1462 (C=C), 1265, 1231, 1053, 748; $[\alpha]_D^{20}$ +7.1 (*c* 0.1, MeOH); δ_H (400 MHz, CD_3OD) 2.84 (1H, dd, *J* 14.0, 9.4 Hz, 3-*H*H), 3.13 (1H, dd, *J* 14.0, 4.8 Hz, 3-H*H*), 4.39 (1H, dd, *J* 9.4, 4.8 Hz, 2-H), 4.98 (1H, d, *J* 12.5 Hz, PhC*H*H), 5.06 (1H, d, *J* 12.5 Hz, PhCH*H*), 6.88 (1H, d, *J* 8.2 Hz, 6'-H), 6.96−7.06 (4H, m, 1'-H, 4'-H, 8'-H and 9'-H), 7.10 (1H, dd, *J* 7.7, 1.5 Hz, 3'-H), 7.12−7.31 (5H, m, 7'-H and Ph); δ_C (101 MHz, CD_3OD) 37.8 (CH_2), 56.7 (CH), 67.5 (CH_2), 118.5 (CH), 118.7 (CH), 121.1 (C), 121.3 (C), 125.7 (CH), 127.8 (CH), 128.5 (CH), 128.6 (2 × CH), 128.9 (CH), 129.0 (CH), 129.4 (2 × CH), 129.9 (CH), 135.4 (C), 138.2 (C), 152.3 (C), 153.5 (C), 158.4 (C), 175.0 (C); *m/z* (ESI) 422.1060 (MH^+. $C_{23}H_{20}NO_5S$ requires 422.1057).

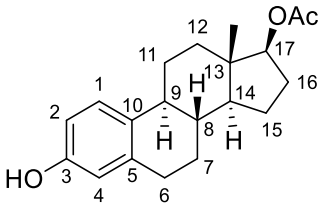
(2*S*)-2-Amino-3-(phenoxathiin-2'-yl)propanoic acid hydrochloride (137)



A solution of (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenoxathiin-2'-yl)propanoic acid (75 mg, 0.16 mmol) in 6 M aqueous hydrochloric acid (7.5 mL) and 1,4-dioxane (1.5 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue recrystallised from methanol and diethyl ether to afford (2*S*)-2-amino-3-(phenoxathiin-2'-yl)propanoic acid hydrochloride as a white solid (49 mg, 95%). Mp 234−236 °C; ν_{max}/cm^{-1} (neat) 3387 (NH), 2889 (OH), 1728 (CO), 1470 (C=C), 1439, 1265, 1200,

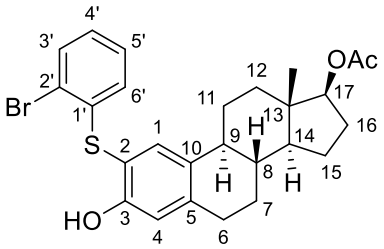
1123, 741; $[\alpha]_D^{21}$ −3.1 (*c* 0.1, MeOH); δ_H (400 MHz, CD_3OD) 3.09 (1H, dd, *J* 14.6, 7.7 Hz, 3-*H*H), 3.25 (1H, dd, *J* 14.6, 5.5 Hz, 3-H*H*), 4.22 (1H, dd, *J* 7.7, 5.5 Hz, 2-H), 6.99−7.20 (7H, m, 1'-H, 3'-H, 4'-H, 6'-H, 7'-H, 8'-H and 9'-H); δ_C (101 MHz, CD_3OD) 36.4 (CH_2), 55.0 (CH), 118.7 (CH), 119.2 (CH), 120.9 (C), 122.2 (C), 126.0 (CH), 127.9 (CH), 128.8 (CH), 129.2 (CH), 130.1 (CH), 132.3 (C), 153.2 (C), 153.4 (C), 171.2 (C); *m/z* (ESI) 288.0690 (MH^+. $C_{15}H_{14}NO_3S$ requires 288.0689).

17-β-Estradiol-17-acetate (141)[213]



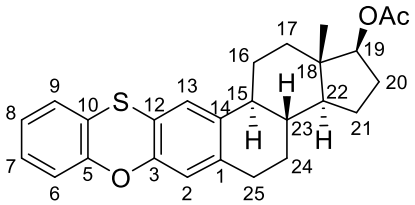
A mixture of β-estradiol (300 mg, 1.10 mmol) and copper(II) acetate (40.0 mg, 0.220 mmol) in acetic acid (8 mL) was stirred at 140 °C for 4 h. The solvent was removed *in vacuo* and the resulting residue was dissolved in water (20.0 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 4:1) gave 17-β-estradiol-17-acetate as a white solid (243 mg, 70%). Mp 209−211 °C; $[\alpha]_D^{20}$ +43.6 (*c* 0.1, $CHCl_3$) (lit.[213] $[\alpha]_D^{26}$ +44.3 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, s, 13-CH_3), 1.24−1.56 (7H, m, 7-H_2, 8-H, 11-*H*H, 15-H_2 and 16-*H*H), 1.69−1.78 (1H, m, 9-H), 1.83−1.90 (2H, m, 11-H*H* and 14-H), 2.06 (3H, s, $COCH_3$), 2.15−2.32 (3H, m, 12-H_2 and 16-H*H*), 2.76−2.89 (2H, m, 6-H_2), 4.66 (1H, s, OH), 4.69 (1H, dd, *J* 9.1, 7.9 Hz, 17-H), 6.56 (1H, d, *J* 2.8 Hz, 4-H), 6.63 (1H, dd, *J* 8.4, 2.8 Hz, 2-H), 7.15 (1H, d, *J* 8.4 Hz, 1-H); δ_C (101 MHz, $CDCl_3$) 12.2 (CH_3), 21.4 (CH_3), 23.4 (CH_2), 26.4 (CH_2), 27.3 (CH_2), 27.7 (CH_2), 29.7 (CH_2), 37.0 (CH_2), 38.7 (CH), 43.1 (C), 43.9 (CH), 49.9 (CH), 82.9 (CH), 112.8 (CH), 115.4 (CH), 126.7 (CH), 132.7 (C), 138.4 (C), 153.5 (C), 171.5 (C); *m/z* (ESI) 337 (MNa^+. 100%).

2-(2'-Bromophenylthio)-17-β-Estradiol-17-acetate (142)



The reaction was performed as described in general procedure E using β-estradiol (91.5 mg, 0.291 mmol). The reaction mixture was stirred at 40 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave 2-(2'-bromophenylthio)-17-β-estradiol-17-acetate (107 mg, 73%) as a white solid. Mp 172−175 °C; ν_{max}/cm^{-1} (neat) 3406 (OH), 2924 (CH), 1724 (CO), 1481 (C=C), 1427, 1346, 1015, 891, 745; $[\alpha]_D^{20}$ +48.7 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, s, 13-CH_3), 1.21−1.61 (7H, m, 7-H_2, 8-H, 11-*H*H, 15-H_2 and 16-*H*H), 1.70−1.81 (1H, m, 9-H), 1.84−1.94 (2H, m, 11-H*H* and 14-H), 2.05 (3H, s, $COCH_3$), 2.16−2.28 (3H, m, 12-H_2 and 16-H*H*), 2.86−2.92 (2H, m, 6-H_2), 4.68 (1H, dd, *J* 9.0, 8.0 Hz, 17-H), 6.13 (1H, s, OH), 6.59 (1H, dd, *J* 7.8, 1.5 Hz, 6'-H), 6.82 (1H, s, 4-H), 6.99 (1H, td, *J* 7.8, 1.5 Hz, 4'-H), 7.11 (1H, td, *J* 7.8, 1.3 Hz, 5'-H), 7.41 (1H, s, 1-H), 7.52 (1H, dd, *J* 7.8, 1.3 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 12.2 (CH_3), 21.3 (CH_3), 23.4 (CH_2), 26.3 (CH_2), 27.1 (CH_2), 27.7 (CH_2), 29.8 (CH_2), 36.9 (CH_2), 38.4 (CH), 43.0 (C), 43.8 (CH), 49.9 (CH), 82.8 (CH), 112.0 (C), 115.7 (CH), 120.8 (C), 126.6 (CH), 126.8 (CH), 128.1 (CH), 133.0 (CH), 134.2 (CH), 134.3 (C), 138.0 (C), 142.6 (C), 155.3 (C), 171.4 (C); *m/z* (ESI) 501.1091 (MH^+. $C_{26}H_{30}{}^{79}BrO_3S$ requires 501.1090).

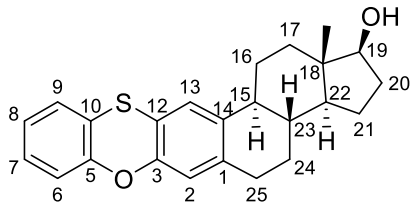
(15*S*,18*S*,19*S*,22*S*,23*R*)-18-methyl-4-oxa-11-thiahexacyclo[12.11.0.0^{3,12}.0^{5,10}.0^{15,23}.0^{18,22}]pentacosa-1(14),2,5(10),6,8,12-hexaen-19-yl acetate (144)



The reaction was performed as described in general procedure F using 2-(2'-bromophenylthio)-17-β-estradiol-17-acetate (50 mg, 0.17 mmol). Purification by flash column chromatography (hexane/dichloromethane 7:3) gave (15*S*,18*S*,19*S*,22*S*,23*R*)-18-methyl-4-oxa-11-thiahexacyclo[12.11.0.0^{3,12}.0^{5,10}.0^{15,23}.0^{18,22}]pentacosa-1(14),2,5(10),6,8,12-

hexaen-19-yl acetate (32 mg, 76%) as a white solid. Mp 185−187 °C; ν_{max}/cm^{-1} (neat) 2928 (CH), 1724 (C=O), 1462 (C=C), 1288, 1037, 879, 752; $[\alpha]_D^{21}$ +44.9 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, s, 18-CH_3), 1.21−1.56 (7H, m, 16-*H*H, 20-*H*H, 21-H_2, 23-H and 24-H_2), 1.69−1.77 (1H, m, 15-H), 1.82−1.91 (2H, m, 16-H*H* and 22-H), 2.06 (3H, s, $COCH_3$), 2.09−2.28 (3H, m, 17-H_2 and 20-H*H*), 2.76−2.82 (2H, m, 25-H_2), 4.68 (1H, dd, *J* 9.1, 7.9 Hz, 19-H), 6.73 (1H, s, 2-H), 6.87−7.00 (3H, m, 6-H, 8-H and 13-H), 7.05−7.13 (2H, m, 7-H and 9-H); δ_C (101 MHz, $CDCl_3$) 12.2 (CH_3), 21.3 (CH_3), 23.4 (CH_2), 26.3 (CH_2) 27.1 (CH_2), 27.7 (CH_2), 29.3 (CH_2), 36.9 (CH_2), 38.4 (CH), 43.0 (C), 43.9 (CH), 49.9 (CH), 82.8 (CH), 116.6 (C), 117.7 (CH), 117.8 (CH), 120.6 (C), 123.7 (CH), 124.4 (CH), 126.9 (CH), 127.6 (CH), 136.8 (C), 136.9 (C), 150.0 (C), 152.4 (C), 171.3 (C); *m/z* (ESI) 443.1651 (MNa^+. $C_{26}H_{28}NaO_3S$ requires 443.1651).

(15*S*,18*S*,19*S*,22*S*,23*R*)-18-methyl-4-oxa-11-thiahexacyclo[12.11.0.0^{3,12}.0^{5,10}.0^{15,23}.0^{18,22}]pentacosa-1(14),2,5(10),6,8,12-hexaen-19-ol (145)



A solution of (15*S*,18*S*,19*S*,22*S*,23*R*)-18-methyl-4-oxa-11-thiahexacyclo[12.11.0.0^{3,12}.0^{5,10}.0^{15,23}.0^{18,22}]pentacosa-1(14),2,5(10),6,8,12-hexaen-19-yl acetate (17 mg, 40 μmol) in tetrahydrofuran (0.5 mL) and methanol (0.5 mL) was treated with potassium carbonate (7.0 mg, 49 μmol). The resulting reaction mixture was left to stir at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between a saturated aqueous solution of ammonium chloride (10 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexane/ethyl acetate 7:3) gave (15*S*,18*S*,19*S*,22*S*,23*R*)-18-methyl-4-oxa-11-thiahexacyclo[12.11.0.0^{3,12}.0^{5,10}.0^{15,23}.0^{18,22}]pentacosa-1(14),2,5(10),6,8,12-hexaen-19-ol (14 mg, 93%) as a white solid. Mp 197−199 °C; ν_{max}/cm^{-1} (neat), 3565 (OH), 2905 (CH), 1466 (C=C), 1443, 1215, 1065, 860, 745;

$[\alpha]_D^{21}$ +89.1 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.77 (3H, s, 18-CH_3), 1.10−1.55 (8H, m, OH, 16-*H*H, 20-*H*H, 21-H_2, 23-H and 24-H_2), 1.65 (1H, m, 15-H), 1.83−1.90 (1H, m, 16-H*H*), 1.92−1.97 (1H, m, 22-H), 2.06−2.17 (2H, m, 17-H_2), 2.22−2.29 (1H, m, 20-H*H*), 2.76−2.82 (2H, m, 25-H_2), 3.72 (1H, t, *J* 8.4 Hz, 19-H), 6.74 (1H, s, 2-H), 6.93−7.01 (3H, m, 6-H, 8-H and 13-H), 7.07−7.12 (2H, m, 7-H and 9-H); δ_C (101 MHz, $CDCl_3$) 11.2 (CH_3), 23.3 (CH_2), 26.4 (CH_2), 27.2 (CH_2), 29.3 (CH_2), 30.7 (CH_2), 36.7 (CH_2), 38.7 (CH), 43.3 (C), 44.0 (CH), 50.1 (CH), 82.0 (CH), 116.6 (C), 117.7 (CH), 117.8 (CH), 120.6 (C), 123.7 (CH), 124.4 (CH), 126.9 (CH), 127.6 (CH), 136.9 (C), 137.1 (C), 150.0 (C), 152.4 (C); *m/z* (ESI) 401.1532 (MNa^+. $C_{24}H_{26}NaO_2S$ requires 401.1546).

6.4 Synthesis of Phenothiazines Experimental

General Procedure G: Preparation of Sulfenylated Products

Iron(III) trichloride (10 mol%) was dissolved in [BMIM]NTf_2 (30 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (1.2 equiv.) in chloroform (0.6 M in arene). The arene (1.0 equiv.) and diphenyl selenide (10 mol%) was then added and the mixture was left to stir at 90 °C, until the reaction was deemed complete. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

General Procedure H: Palladium Catalysed Synthesis of Phenothiazines

To a solution of biaryl sulfide (1.0 equiv.) in toluene (0.33 M in arene) was added $Pd_2(dba)_3$ (5 mol%) and (*S*)-BINAP (10 mol%). The mixture was purged with nitrogen and sodium *tert*-butoxide (2.0 equiv.) was added. The mixture was then heated at 110 °C until the reaction was deemed complete. The reaction mixture was allowed to cool to room temperature and water (10 mL) was added before being filtered through celite and washed with dichloromethane (10 mL). The layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting material was purified by flash column chromatography.

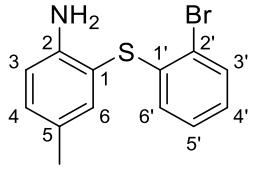
General Procedure I: Copper Catalysed Synthesis of Phenothiazines

To a solution of biaryl sulfide (1.0 equiv.) in toluene (0.4 M in arene) was added copper(I) iodide (10 mol%), cesium carbonate (2.0 equiv.), *N,N'*-dimethylethylenediamine (20 mol%) and water (1 M in arene). The mixture was purged with nitrogen and then heated to 130 °C or 150 °C, until the reaction was deemed complete. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting material was purified by flash column chromatography.

General Procedure J: Benzoyl Protection[106]

To a stirred solution of arene (1.0 equiv) in dichloromethane (1 M in arene) was added triethylamine (1.2 equiv). The resulting solution was cooled to 0 °C and benzoyl chloride (1.2 equiv) was slowly added. The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water (40 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 40 mL). The combined organic layers were washed with 1 M aqueous hydrochloric acid (80 mL), dried over $MgSO_4$ and filtered. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

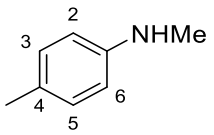
(2-Amino-5-methylphenyl)(2'-bromophenyl)sulfane (151a)[34]



The reaction was performed as described in general procedure G using *p*-toluidine (31 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 20 h. Purification by flash column chromatography (hexane/dichloromethane, 7:3) gave (2-amino-5-methylphenyl)(2'-bromophenyl)sulfane (46 mg, 53%) as a white solid. Mp 83−86 °C (lit.[34] 82−84 °C); δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 4.16 (2H, br s, NH_2), 6.63 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.75 (1H, d, *J* 8.2 Hz, 3-H), 6.97 (1H, ddd, *J* 7.9, 7.4,

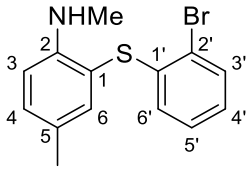
1.6 Hz, 4'-H), 7.08–7.12 (2H, m, 4-H and 5'-H), 7.29 (1H, d, *J* 2.0 Hz, 6-H), 7.52 (1H, dd, *J* 7.9, 1.4 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 20.3 (CH_3), 113.2 (C), 115.7 (CH), 120.8 (C), 126.3 (CH), 126.4 (CH), 127.9 (CH), 128.5 (C), 132.7 (CH), 132.9 (CH), 138.0 (CH), 138.3 (C), 146.9 (C); *m/z* (ESI) 294 (MH^+. 100%).

_N_-Methyl-_p_-toluidine (150a)[214]



To a stirred solution of *p*-toluidine (0.50 g, 4.7 mmol) and paraformaldehyde (0.42 g, 14 mmol) in methanol (23 mL), was added sodium methoxide (0.76 g, 14 mmol) and the suspension was stirred at 50 °C for 5 h. Sodium borohydride (0.53 g, 14 mmol) was added under argon and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was washed with a saturated solution of ammonium chloride (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate 9:1) gave *N*-methyl-*p*-toluidine (0.42 g, 74%) as a yellow oil. Spectroscopic data were consistent with the literature.[214] δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, 4-CH_3), 2.83 (3H, s, NHC*H*$_3$), 3.56 (1H, br s, NH), 6.54–6.59 (2H, m, 2-H and 6-H), 6.99–7.05 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_3), 31.2 (CH_3), 112.7 (2 × CH), 126.6 (C), 129.8 (2 × CH), 147.3 (C); m/z (ESI) 122 (MH^+. 100%).

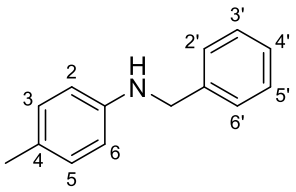
(2-Methylamino-5-methylphenyl)(2'-bromophenyl)sulfane (151b)



The reaction was performed as described in general procedure G using *N*-methyl-*p*-toluidine (35 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave (2-methylamino-5-methylphenyl)(2'-bromophenyl)sulfane (59 mg, 66%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3395 (NH), 2909 (CH), 1605 (C=C), 1512, 1443, 1312, 1169, 1018, 745; δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 2.81 (3H, d, *J* 4.9 Hz, NHC*H*$_3$),

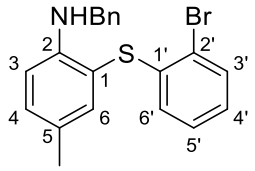
4.73 (1H, q, *J* 4.9 Hz, N*H*CH_3), 6.56 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.63 (1H, d, *J* 8.3 Hz, 3-H), 6.95 (1H, ddd, 7.9, 7.4, 1.6 Hz, 4'-H), 7.08 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5'-H), 7.21 (1H, dd, *J* 8.3, 2.1 Hz, 4-H), 7.30 (1H, d, *J* 2.1 Hz, 6-H), 7.51 (1H, dd, *J* 7.9, 1.4 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 20.2 (CH_3), 30.8 (CH_3), 110.5 (CH), 112.4 (C), 120.7 (C), 126.2 (CH), 126.2 (CH), 126.4 (C), 127.9 (CH), 132.8 (CH), 132.9 (CH), 138.3 (CH), 138.5 (C), 148.9 (C); *m/z* (ESI) 329.9929 (MNa^+. $C_{14}H_{14}{}^{79}BrNNaS$ requires 329.9923).

N-Benzyl-*p*-toluidine (150c)[215]



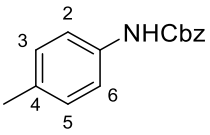
To a stirred solution of *p*-toluidine (0.50 g, 4.7 mmol) and benzaldehyde (1.42 mL, 14 mmol) in methanol (23 mL), was added sodium methoxide (0.76 g, 14 mmol) and the suspension was stirred at 50 °C for 4 h. Sodium borohydride (0.53 g, 14 mmol) was added under argon and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was washed with a saturated solution of ammonium chloride (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate 49:1) gave *N*-benzyl-*p*-toluidine (0.89 g, 97%) as a yellow oil. Spectroscopic data were consistent with the literature.[215] δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, 4-CH_3), 3.92 (1H, br s, NH), 4.32 (2H, s, NHCH_2), 6.58 (2H, d, *J* 8.0 Hz, 2-H and 6-H), 7.00 (2H, d, *J* 8.0 Hz, 3-H and 5-H), 7.25–7.31 (1H, m, 4'-H), 7.32–7.40 (4H, m, 2'-H, 3'-H, 5'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 20.5 (CH_3), 48.8 (CH_2), 113.2 (2 × CH), 127.0 (C), 127.3 (CH), 127.7 (2 × CH), 128.7 (2 × CH), 129.9 (2 × CH), 139.7 (C), 146.0 (C); m/z (EI) 197 (M^+. 100%).

(2-Benzylamino-5-methylphenyl)(2'-bromophenyl)sulfane (151c)



The reaction was performed as described in general procedure G using *N*-benzyl-*p*-toluidine (57 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave (2-benzylamino-5-methylphenyl)(2'-bromophenyl)sulfane (66 mg, 59%) as a yellow solid. Mp 72−75 °C; ν_{max}/cm^{-1} (neat) 3403 (NH), 2897 (CH), 1605 (C=C), 1508, 1443, 1316, 1015, 806, 748; δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, CH_3), 4.34 (2H, d, *J* 5.8 Hz, PhC*H*$_2$), 5.24 (1H, t, *J* 5.8 Hz, NH), 6.56 (1H, d, *J* 8.3 Hz, 3-H), 6.64 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.98 (1H, ddd, *J* 7.8, 7.4, 1.6 Hz, 4'-H), 7.07–7.29 (7H, m, 4-H, 5'-H and Ph), 7.32 (1H, d, *J* 1.8 Hz, 6-H), 7.51 (1H, dd, *J* 7.8, 1.3 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 20.2 (CH_3), 47.8 (CH_2), 111.4 (CH), 112.9 (C), 121.0 (C), 126.4 (CH), 126.7 (CH), 126.8 (C), 127.0 (2 × CH), 127.2 (CH), 127.8 (CH), 128.7 (2 × CH), 132.8 (CH), 132.9 (CH), 138.3 (CH), 138.4 (C), 139.3 (C), 147.4 (C); *m/z* (ESI) 406.0239 (MNa^+. $C_{20}H_{18}{}^{79}BrNNaS$ requires 406.0236).

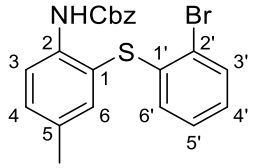
Benzyl-*p*-tolylcarbamate (150d)[216]



To a stirred solution of *p*-toluidine (0.50 g, 4.7 mmol) in tetrahydrofuran (11 mL) at 0 °C, was added sodium hydrogen carbonate (0.43 g, 5.1 mmol) followed by benzyl chloroformate (0.72 mL, 5.13 mmol). The reaction mixture was stirred at 0 °C for 0.5 h, warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate 9:1) gave benzyl-*p*-tolyl carbamate as a white solid. Mp 80–82 °C (lit.[216] 82–84 °C); δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, 4-CH_3), 5.20 (2H, s, PhC*H*$_2$), 6.60 (1H, br s, NH), 7.11 (2H, d, *J* 8.2 Hz, 3-H and 5-H), 7.27 (2H, d, *J* 8.0 Hz, 2-H and 6-H), 7.31–7.43 (5 H, m, Ph); δ_C (101 MHz, $CDCl_3$) 20.9 (CH_3), 67.1 (CH_2), 119.0 (C), 128.5 (2 × CH),

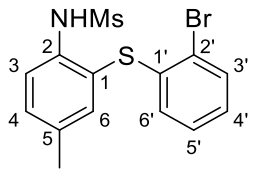
128.5 (2 × CH), 128.8 (2 × CH), 129.7 (2 × CH), 133.3 (C), 135.3 (C), 136.3 (CH), 153.6 (C); m/z (ESI) 242 (MH^+. 100%).

(2-[Benzyloxycarbonyl]amino-5-methylphenyl)(2'-bromophenyl)sulfane (151d)



The reaction was performed as described in general procedure G using benzyl-*p*-tolylcarbamate (70 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 24 h. Purification by flash column chromatography (hexane/dichloromethane, 7:3) gave (2-[benzyloxycarbonyl]amino-5-methylphenyl)(2'-bromophenyl)sulfane (91 mg, 73%) as a yellow solid. Mp 84−86 °C; ν_{max}/cm^{-1} (neat) 3381 (NH), 2945 (CH), 1732 (CO), 1519 (C=C), 1443, 1219, 1049, 824, 740; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, CH_3), 5.14 (2H, s, PhCH_2), 6.52 (1H, dd, *J* 7.7, 1.5 Hz, 6'-H), 6.98 (1H, td, *J* 7.7, 1.5 Hz, 4'-H), 7.08 (1H, td, *J* 7.7, 1.4 Hz, 5'-H), 7.28–7.36 (6H, m, 4-H and Ph), 7.38 (1H, d, *J* 1.6 Hz, 6-H), 7.52 (1H, dd, *J* 7.7, 1.4 Hz, 3'-H), 7.64 (1H, br s, NH), 8.18 (1H, d, *J* 8.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.6 (CH_3), 67.1 (CH_2), 118.1 (C), 119.6 (CH), 121.2 (C), 126.9 (CH), 127.0 (CH), 128.2 (CH), 128.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 132.6 (CH), 133.1 (CH), 133.9 (C), 136.1 (C), 137.6 (CH), 137.8 (C), 138.3 (C), 153.4 (C); *m/z* (ESI) 428.0312 (MH^+. $C_{21}H_{19}{}^{79}BrNO_2S$ requires 428.0314).

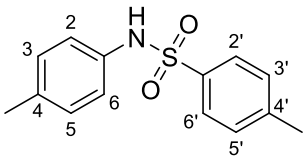
[2-(Methanesulfonyl)amino-5-methylphenyl](2'-bromophenyl)sulfane (151e)



Iron(III) trichloride (4.7 mg, 10 mol%) was dissolved in [BMIM]NTf_2 (25 μL, 30 mol%) and stirred for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (100 mg, 0.35 mmol) in chloroform (0.5 mL). *N*-(4-methylphenyl)methanesulfonamide (54 mg, 0.29 mmol) and *bis*(4-methoxyphenyl)sulfane (7.2 mg, 10 mol%) were added and the reaction mixture was left to stir at 90 °C for 48 h. Purification by flash column chromatography

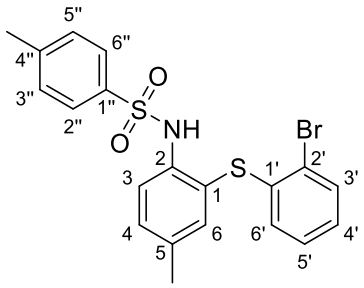
(hexane/dichloromethane, 2:3) gave [2-(methanesulfonyl)amino-5-methylphenyl](2'-bromophenyl)sulfane (33 mg, 31%) as a white solid. Mp 76−78 °C; ν_{max}/cm^{-1} (neat) 3287 (NH), 2924 (CH), 1489 (C=C), 1377, 1327, 1150, 964, 745; δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, CH_3), 2.84 (3H, s, SO_2CH_3), 6.60 (1H, dd, *J* 7.8, 1.6 Hz, 6'-H), 7.04 (1H, td, *J* 7.8, 1.6 Hz, 4'-H), 7.13 (1H, td, *J* 7.8, 1.4 Hz, 5'-H), 7.20 (1H, br s, NH), 7.31 (1H, dd, *J* 8.4, 1.9 Hz, 4-H), 7.44 (1H, d, *J* 1.9 Hz, 6-H), 7.57 (1H, dd, *J* 7.8, 1.4 Hz, 3'-H), 7.67 (1H, d, *J* 8.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 39.5 (CH_3), 120.4 (CH), 120.8 (C), 121.9 (C), 127.6 (CH), 127.6 (CH), 128.3 (CH), 132.9 (CH), 133.4 (CH), 135.9 (C), 137.1 (C), 137.2 (C), 138.0 (CH); *m/z* (ESI) 371.9718 (MH^+. $C_{14}H_{15}{}^{79}BrNO_2S_2$ requires 371.9722).

N-(4-Methylphenyl)-*p*-toluenesulfonamide (150f)[217]



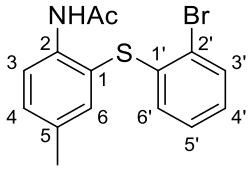
To a stirred solution of *p*-toluidine (0.50 g, 4.7 mmol) and pyridine (4.5 mL, 56 mmol) in dichloromethane (26 mL), was added a solution of *p*-toluenesulfonyl chloride (1.1 g, 5.6 mmol) in dichloromethane (10 mL), dropwise. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was washed with 5% aqueous hydrochloric acid (30 mL). The organic layer was washed with a saturated solution of sodium hydrogen carbonate (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography gave *N*-(4-methylphenyl)-*p*-toluenesulfonamide (1.1 g, 90%) as a white solid. Mp 118–121 °C (lit.[217] 117–118 °C); δ_H (500 MHz, $CDCl_3$) 2.26 (3H, s, 4-CH_3), 2.37 (3H, s, 4'-CH_3), 6.79 (1H, br s, NH), 6.96 (2H, d, *J* 8.2 Hz, 3-H and 5-H), 7.02 (2H, d, *J* 8.2 Hz, 2-H and 6-H), 7.21 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.64 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 21.0 (CH_3), 21.6 (CH_3), 122.4 (2 × CH), 127.4 (2 × CH), 129.7 (2 × CH), 130.0 (2 × CH), 133.9 (C), 135.5 (C), 136.2 (C), 143.9 (C); m/z (ESI) 262 (MH^+. 100%).

[2-(4''-Methylphenylsulfonyl)amino-5-methylphenyl](2'-bromophenyl)sulfane (151f)



The reaction was performed as described in general procedure G using *N*-(4-methylphenyl)-*p*-toluenesulfonamide (76 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave [2-(4-methylphenylsulfonyl)amino-5-methylphenyl](2'-bromophenyl)sulfane (65 mg, 50%) as a white solid. Mp 108−110 °C; ν_{max}/cm^{-1} (neat) 3212 (NH), 2918 (CH), 1486, 1340, 1185, 1019, 806, 677; δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, 5-CH_3), 2.35 (3H, s, 4''-CH_3), 6.23 (1H, dd, *J* 7.8, 1.6 Hz, 6'-H), 6.92 (1H, ddd, *J* 7.8, 7.4, 1.5 Hz, 5'-H), 6.98 (1H, dd, *J* 7.8, 7.4, 1.6 Hz, 4'-H), 7.09–7.13 (2H, m, 3''-H and 5''-H), 7.20–7.26 (2H, m, 4-H and 6-H), 7.49 (1H, br s, NH), 7.51 (1H, dd, *J* 7.8, 1.5 Hz, 3'-H), 7.55–7.60 (2H, m, 2''-H and 6''-H), 7.70 (1H, d, *J* 8.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.7 (CH_3), 21.7 (CH_3), 120.4 (CH), 121.4 (C), 127.0 (CH), 127.2 (CH), 127.2 (C), 127.4 (2 × CH), 128.1 (CH), 129.7 (2 × CH), 132.6 (CH), 133.1 (CH), 135.4 (C), 136.0 (C), 137.3 (C), 137.4 (C), 137.9 (CH), 144.0 (C); *m/z* (ESI) 469.9852 (MNa^+. $C_{20}H_{18}{}^{79}BrNNaO_2S_2$ requires 469.9855).

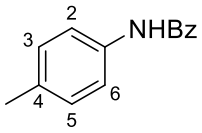
(2-Acetylamino-5-methylphenyl)(2'-bromophenyl)sulfane (151g)



Iron(III) trichloride (4.7 mg, 10 mol%) was dissolved in [BMIM]NTf_2 (25 μL, 30 mol%) and stirred for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (100 mg, 0.35 mmol) in chloroform (0.5 mL). 4-Methylacetanilide (43 mg, 0.29 mmol) and *bis*(4-methoxyphenyl)sulfane (7.2 mg, 10 mol%) was then added and the reaction mixture was left to stir at 90 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave

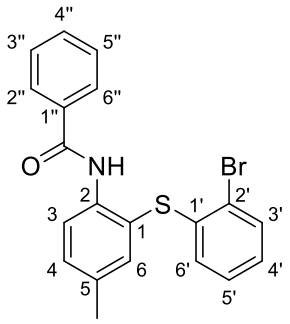
(2-acetylamino-5-methylphenyl)(2'-bromophenyl)sulfane (56 mg, 57%) as a white solid. Mp 55−57 °C; ν_{max}/cm^{-1} (neat) 3256 (NH), 2919 (CH), 1656 (CO), 1511, 1445, 1645, 1295, 1017, 825, 747; δ_H (400 MHz, $CDCl_3$) 2.04 (3H, s, $COCH_3$), 2.33 (3H, s, 5-CH_3), 6.61 (1H, dd, *J* 7.7, 1.3 Hz, 6'-H), 7.01 (1H, td, *J* 7.7, 1.3 Hz, 4'-H), 7.10 (1H, td, *J* 7.7, 1.4 Hz, 5'-H), 7.29 (1H, dd, *J* 8.3, 1.9 Hz, 4-H), 7.41 (1H, d, *J* 1.9 Hz, 6-H), 7.54 (1H, dd, *J* 7.7, 1.4 Hz, 3'-H), 8.04 (1H, br s, NH), 8.34 (1H, d, *J* 8.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.8 (CH_3), 24.9 (CH_3), 119.0 (C), 121.2 (CH), 121.4 (C), 127.3 (CH), 127.7 (CH), 128.3 (CH), 132.4 (CH), 133.1 (CH), 134.6 (C), 137.3 (CH), 137.4 (C), 138.0 (C), 168.4 (C); *m/z* (ESI) 336.0051 (MH^+. $C_{15}H_{15}{}^{79}BrNOS$ requires 336.0052).

N-(*p*-Tolyl)benzamide (150h)[218]



The reaction was performed as described in general procedure D using *p*-toluidine (0.40 mg, 3.7 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 9:1) gave *N*-(*p*-tolylbenzamide) (0.78 g, 99%) as a white solid. Mp 154–156 °C (lit.[218] 155–156 °C). δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, 4-CH_3), 7.17 (2H, d, *J* 8.0 Hz, 3-H and 5-H), 7.44–7.60 (5H, m, Ph), 7.80 (1H, br s, NH), 7.86 (2H, d, *J* 8.0 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 20.9 (CH_3), 120.5 (2 × CH), 127.1 (2 × CH), 128.6 (2 × CH), 129.5 (2 × CH), 131.6 (CH), 134.1 (C), 135.0 (C), 135.4 (C), 165.9 (C); m/z (ESI) 234 (MNa^+. 100%).

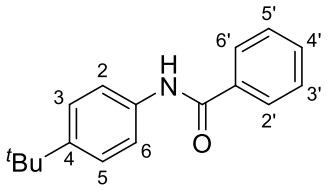
(2-Benzoylamino-5-methylphenyl)(2'-bromophenyl)sulfane (151h)



The reaction was performed as described in general procedure G using *N*-(*p*-tolyll)benzamide (61 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for

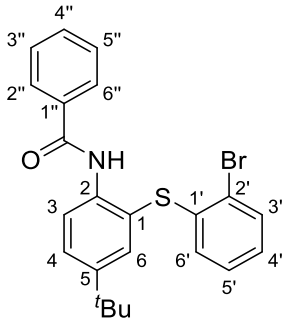
6 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave (2-benzoylamino-5-methylphenyl)(2'-bromophenyl)sulfane (105 mg, 91%) as a white solid. Mp 105−107 °C; ν_{max}/cm^{-1} (neat) 3379 (NH), 2920 (CH), 1678 (CO), 1516, 1443, 1304, 1246, 1018, 822; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 6.65 (1H, dd, *J* 7.9, 1.6 Hz, 6'-H), 6.98 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4'-H), 7.10 (1H, ddd, *J* 7.9, 7.4, 1.4 Hz, 5'-H), 7.36–7.44 (3H, m, 4-H, 3''-H and 5''-H), 7.47–7.52 (2H, m, 6-H and 4''-H), 7.54 (1H, dd, *J* 7.9, 1.4 Hz, 3'-H), 7.65–7.69 (2H, m, 2''-H and 6''-H), 8.61 (1H, d, *J* 8.4 Hz, 3-H), 8.95 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 20.8 (CH_3), 119.1 (C), 120.9 (CH), 121.2 (C), 127.1 (2 × CH), 127.3 (CH), 127.4 (CH), 128.4 (CH), 128.9 (2 × CH), 132.0 (CH), 132.6 (CH), 133.1 (CH), 134.7 (C), 134.7 (C), 137.3 (C), 137.5 (CH), 138.0 (C), 165.2 (C); *m/z* (ESI) 398.0218 (MH^+. $C_{20}H_{17}{}^{79}BrNOS$ requires 398.0209).

N-(4-*tert*-Butylphenyl)benzamide (154a)[219]



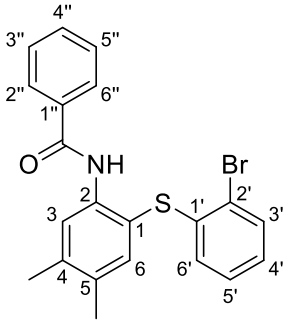
The reaction was performed as described in general procedure J using 4-*tert*-butylaniline (0.40 g, 2.7 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 9:1) gave *N*-(4-*tert*-butylphenyl)benzamide (0.60 g, 89%) as a white solid. Mp 144–146 °C (lit.[219] 144–146 °C); δ_H (400 MHz, $CDCl_3$) 1.33 (9H, s, 3 × CH_3), 7.36–7.41 (2H, m, 3-H and 5-H), 7.44–7.50 (2H, m, 3'-H and 5'-H), 7.51–7.60 (3H, m, 2-H, 6-H and 4'-H), 7.77–7.94 (3H, m, NH, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 31.5 (3 × CH_3), 34.6 (C), 120.2 (2 × CH), 126.1 (2 × CH), 127.1 (2 × CH), 128.9 (2 × CH), 131.9 (CH), 135.3 (C), 135.4 (C), 147.7 (C), 165.8 (C); *m/z* (ESI) 254 (MH^+. 100%).

(2-Benzoylamino-5-*tert*-butylphenyl)(2'-bromophenyl)sulfane (155a)



The reaction was performed as described in general procedure G using *N*-(4-*tert*-butylphenyl)benzamide (74 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave (2-benzoylamino-5-*tert*-butylphenyl)(2'-bromophenyl)sulfane (124 mg, 97%) as a white solid. Mp 109−111 °C; ν_{max}/cm^{-1} (neat) 3352 (NH), 2955 (CH), 1678 (CO), 1505, 1427, 1308, 1022, 841, 752; δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, 3 × CH_3), 6.62 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 6.98 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, 4'-H), 7.10 (1H, ddd, *J* 8.0, 7.5, 1.4 Hz, 5'-H), 7.38–7.44 (2H, m, 3''-H and 5''-H), 7.47–7.52 (1H, m, 4''-H), 7.54 (1H, dd, *J* 7.9, 1.4 Hz, 3'-H), 7.60 (1H, dd, *J* 8.7, 2.3 Hz, 4-H), 7.63–7.70 (3H, m, 6-H, 2''-H and 6''-H), 8.63 (1H, d, *J* 8.7 Hz, 3-H), 8.92 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 31.4 (3 × CH_3), 34.7 (C), 118.8 (C), 120.7 (CH), 121.1 (C), 127.1 (2 × CH), 127.1 (CH), 127.2 (CH), 128.4 (CH), 128.9 (2 × CH), 129.1 (CH), 132.0 (CH), 133.1 (CH), 134.1 (CH), 134.8 (C), 137.4 (C), 137.9 (C), 148.2 (C), 165.2 (C); *m/z* (ESI) 440.0686 (MH^+. $C_{23}H_{23}{}^{79}BrNOS$ requires 440.0678).

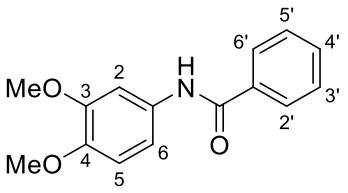
(2-Benzoylamino-4,5-dimethylphenyl)(2'-bromophenyl)sulfane (155b)



The reaction was performed as described in general procedure G using *N*-(3,4-dimethylphenyl)benzamide (66 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave (2-benzoylamino-4,5-dimethylphenyl)(2'-

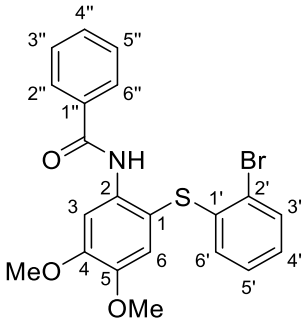
bromophenyl)sulfane (96 mg, 80%) as a white solid. Mp 135−140 °C; ν_{max}/cm^{-1} (neat) 3375 (NH), 2916 (CH), 1678 (C=O), 1519, 1442, 1249, 1199, 1018, 752; δ_H (400 MHz, $CDCl_3$) 2.28 (3H, s, CH_3), 2.38 (3H, s, CH_3), 6.64 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.97–7.00 (1H, m, 4'-H), 7.08 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5'-H), 7.38–7.43 (3H, m, 6-H, 3''-H and 5''-H), 7.46–7.54 (2H, m, 3'-H and 4''-H), 7.64–7.69 (2H, m, 2''-H and 6''-H), 8.54 (1H, s, 3-H), 8.92 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 19.3 (CH_3), 20.4 (CH_3), 115.8 (C), 121.0 (C), 122.1 (CH), 127.1 (2 × CH), 127.1 (CH), 127.1 (CH), 128.3 (CH), 128.9 (2 × CH), 132.0 (CH), 133.0 (CH), 133.6 (C), 134.8 (C), 137.7 (C), 137.9 (CH), 138.2 (C), 141.3 (C), 165.1 (C); *m/z* (ESI) 412.0366 (MH^+. $C_{21}H_{19}{}^{79}BrNOS$ requires 412.0365).

N-(3,4-Dimethoxyphenyl)benzamide (154c)[220]



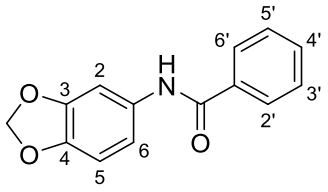
The reaction was performed as described in general procedure J using 3,4-dimethoxyaniline (0.30 g, 2.0 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave *N*-(3,4-dimethoxyphenyl)benzamide (0.38 g, 75%) as a brown solid. Mp 180–181 °C (lit.[220] 179–181 °C); δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.82 (1H, d, *J* 8.8 Hz, 5-H), 7.01 (1H, dd, *J* 8.4, 2.4 Hz, 6-H), 7.41–7.49 (3H, m, 2-H, 3'-H and 5'-H), 7.52 (1H, t, *J* 7.2 Hz, 4'-H), 7.86 (2H, d, *J* 7.2 Hz, 2'-H and 6'-H), 7.97 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 55.9 (CH_3), 56.1 (CH_3), 105.3 (CH), 111.4 (CH), 112.3 (CH), 127.0 (2 × CH), 128.7 (2 × CH), 131.6 (C), 131.7 (CH), 135.0 (C), 146.1 (C), 149.1 (C), 165.7 (C); m/z (ESI) 280 (MNa^+. 100%).

(2-Benzoylamino-4,5-dimethoxyphenyl)(2'-bromophenyl)sulfane (155c)



The reaction was performed as described in general procedure G using *N*-(3,4-dimethoxyphenyl)benzamide (75 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 3 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave (2-benzoylamino-4,5-dimethoxyphenyl)(2'-bromophenyl)sulfane (120 mg, 93%) as a pale-yellow solid. Mp 119−120 °C; ν_{max}/cm^{-1} (neat) 3329 (NH), 2943 (CH), 1659 (CO), 1586, 1516, 1439, 1250, 1204, 1045, 868; δ_H (400 MHz, $CDCl_3$) 3.89 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.61 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 6.98 (1H, td, *J* 7.7, 1.5 Hz, 4'-H), 7.08–7.13 (2H, m, 6-H and 5'-H), 7.40–7.45 (2H, m, 3''-H and 5''-H), 7.48–7.52 (1H, m, 4''-H), 7.54 (1H, dd, *J* 7.7, 1.3 Hz, 3'-H), 7.66–7.70 (2H, m, 2''-H and 6''-H), 8.52 (1H, s, 3-H), 8.97 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 56.3 (CH_3), 56.4 (CH_3), 104.7 (CH), 108.6 (C), 118.9 (CH), 120.7 (C), 126.8 (CH), 127.0 (2 × CH), 127.2 (CH), 128.4 (CH), 129.0 (2 × CH), 132.1 (CH), 133.1 (CH), 134.7 (C), 135.6 (C), 137.8 (C) 145.8 (C), 151.7 (C), 165.2 (C); *m/z* (ESI) 444.0273 (MH^+. $C_{21}H_{19}{}^{79}BrNO_3S$ requires 444.0264).

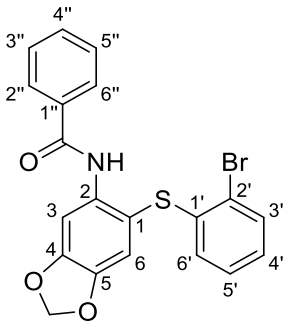
***N*-(3,4-Methylenedioxyphenyl)benzamide (154d)**[221]



The reaction was performed as described in general procedure J using 3,4-methylenedioxyaniline (0.20 g, 1.5 mmol). Purification by flash column chromatography (petroleum ether/dichloromethane, 9:1) gave *N*-(3,4-methylenedioxyphenyl)benzamide (0.21 g, 61%) as a white solid. Mp 133–135 °C (lit.[221] 137–140 °C); δ_H (500 MHz, $CDCl_3$) 5.97 (2H, s, OCH_2O), 6.77 (1H, d, *J* 8.3 Hz, 5-H), 6.90 (1H, dd, *J* 8.3, 2.1 Hz, 6-H), 7.35 (1H, br s, 2-H), 7.44–7.49 (2H, m, 3′-H and 5′-H), 7.51–7.56 (1H, m, 4′-H), 7.80 (1H, br s, NH), 7.84 (2H, d, *J* 7.5 Hz,

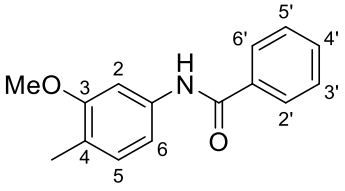
2′-H and 6′-H); δ_C (126 MHz, $CDCl_3$) 101.3 (CH_2), 103.2 (CH), 108.1 (CH), 113.6 (CH), 127.0 (2 × CH), 128.8 (2 × CH), 131.8 (CH), 132.1 (C), 134.9 (C), 144.5 (C), 147.9 (C), 165.7 (C); m/z (ESI) 264 (MNa^+. 100%).

(2-Benzoylamino-4,5-methylenedioxyphenyl)(2'-bromophenyl)sulfane (155d)



The reaction was performed as described in general procedure G using *N*-(3,4-methylenedioxyphenyl)benzamide (70 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 6 h. Purification by flash column chromatography (hexane/dichloromethane, 3:7) gave (2-benzoylamino-4,5-methylenedioxyphenyl)(2'-bromophenyl)sulfane (113 mg, 90%) as a white solid. Mp 160–161 °C; ν_{max}/cm^{-1} (neat) 3375 (NH), 1670 (C=O), 1516 (C=C), 1465 (C=C), 1238, 1176, 1030, 933, 879; δ_H (400 MHz, $CDCl_3$) 6.07 (2H, s, OCH_2O), 6.69 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.99 (1H, ddd, *J* 8.0, 7.5, 1.6 Hz, 4'-H), 7.09 (1H, s, 6-H), 7.12 (1H, ddd, *J* 8.0, 7.5, 1.4 Hz, 5'-H), 7.39–7.44 (2H, m, 3''-H and 5''-H), 7.48–7.55 (2H, m, 3'-H and 4''-H), 7.65–7.70 (2H, m, 2''-H and 6''-H), 8.36 (1H, s, 3-H), 9.00 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 102.2 (CH_2), 102.9 (CH), 110.2 (C), 115.8 (CH), 121.0 (C), 127.0 (CH), 127.1 (2 × CH), 127.3 (CH), 128.4 (CH), 128.9 (2 × CH), 132.1 (CH), 133.1 (CH), 134.6 (C), 136.3 (C), 137.5 (C), 144.3 (C), 150.6 (C), 165.0 (C); *m/z* (ESI) 427.9950 (MH^+. $C_{20}H_{15}{}^{79}BrNO_3S$ requires 427.9951).

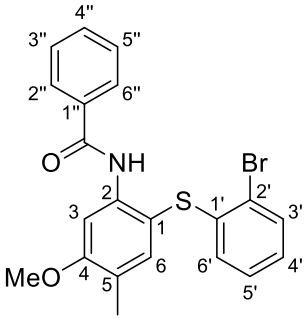
***N*-(3-Methoxy-4-methylphenyl)benzamide (154e)**[222]



The reaction was performed as described in general procedure J using 3-methoxy-4-methylaniline (0.40 g, 2.9 mmol). Purification by flash column chromatography

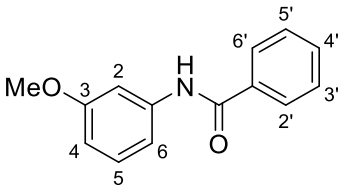
(hexane/ethyl acetate, 4:1) gave *N*-(3-methoxy-4-methylphenyl)benzamide (0.67 g, 95%) as a white solid. Mp 126–128 °C (lit.[222] 130–131 °C); δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, 4-CH3), 3.84 (3H, s, OCH_3), 6.89 (1H, dd, *J* 8.0, 2.0 Hz, 6-H), 7.07 (1H, d, *J* 8.0 Hz, 5-H), 7.42–7.57 (4H, m, 2-H, 3′-H, 4'-H and 5′-H), 7.83–7.88 (2H, m, 2′-H and 6′-H), 7.90 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 15.8 (CH_3), 55.4 (CH_3), 103.1 (CH), 111.6 (CH), 122.9 (C), 127.0 (2 × CH), 128.8 (2 × CH), 130.5 (CH), 131.8 (CH), 135.1 (C), 136.9 (C), 158.0 (C), 165.7 (C); m/z (ESI) 264 (MNa^+. 100%).

(2-Benzoylamino-4-methoxy-5-methylphenyl)(2'-bromophenyl)sulfane (155e)



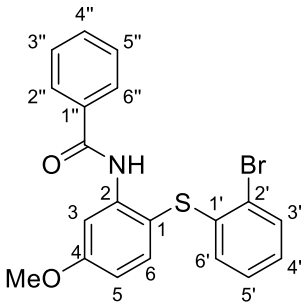
The reaction was performed as described in general procedure G using *N*-(3-methoxy-4-methylphenyl)benzamide (70 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 3 h. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave (2-benzoylamino-4-methoxy-5-methylphenyl)(2'-bromophenyl)sulfane (112 mg, 90%) as a white solid. Mp 142–144 °C; ν_{max}/cm^{-1} (neat) 3379 (NH), 2916 (CH), 1678 (C=O), 1581 (C=C), 1392, 1249, 1168, 1053, 887, 882, 790; δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, 5-CH_3), 3.97 (3H, s, OCH_3), 6.61 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.97 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4'-H), 7.09 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5'-H), 7.39–7.45 (3H, m, 3-H, 3''-H and 5''-H), 7.48–7.54 (2H, m, 3'-H and 4''-H), 7.67–7.71 (2H, m, 2''-H and 6''-H), 8.44 (1H, s, 6-H), 9.09 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 15.9 (CH_3), 55.8 (CH_3), 103.0 (CH), 108.3 (C), 120.7 (C), 123.5 (C), 126.9 (CH), 127.0 (CH), 127.1 (2 × CH), 128.3 (CH), 129.0 (2 × CH), 132.1 (CH), 133.0 (CH), 134.7 (C), 138.1 (C), 138.6 (CH), 140.0 (C), 160.5 (C), 165.3 (C); *m/z* (ESI) 428.0317 (MH^+. $C_{21}H_{19}{}^{79}BrNO_2S$ requires 428.0314).

***N*-(3-methoxyphenyl)benzamide (154f)**[223]



The reaction was performed as described in general procedure J using 3-methoxyaniline (0.30 g, 2.4 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 3:1) gave *N*-(3-methoxyphenyl)benzamide (0.52 g, 94%) as a white solid. Mp 113–116 °C (lit.[223] 112–114 °C); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.71 (1H, ddd, *J* 8.2, 2.4, 1.0 Hz, 6-H), 7.10 (1H, ddd, *J* 8.2, 1.9, 0.8 Hz, 4-H), 7.24 (1H, t, *J* 8.2 Hz, 5-H), 7.43–7.51 (3H, m, 2-H, 3'-H and 5'-H), 7.52–7.58 (1H, m, 4'-H), 7.80–7.90 (3H, m, NH, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 105.9 (CH), 110.7 (CH), 112.4 (CH), 127.1 (2 × CH), 129.0 (2 × CH), 129.9 (CH), 132.0 (CH), 135.1 (C), 139.3 (C), 160.4 (C), 165.9 (C); m/z (ESI) 228 (MH^+. 100%).

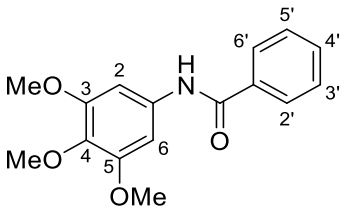
(2-Benzoylamino-4-methoxyphenyl)(2'-bromophenyl)sulfane (155f)



The reaction was performed as described in general procedure G using *N*-(3-methoxyphenyl)benzamide (66 mg, 0.29 mmol). The reaction mixture was stirred at 40 °C for 18 h. Purification by flash column chromatography (hexane/ethyl acetate, 9:1) gave (2-benzoylamino-4-methoxyphenyl)(2'-bromophenyl)sulfane (80 mg, 66%) as a white solid. Mp 78−81 °C; ν_{max}/cm^{-1} (neat) 3360 (NH), 2936 (CH), 1678 (CO), 1574 (C=C), 1443, 1250, 1169, 1018, 748; δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 6.61 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 6.77 (1H, dd, *J* 8.6, 2.8 Hz, 5-H), 6.98 (1H, td, *J* 7.7, 1.5 Hz, 4'-H), 7.10 (1H, ddd, *J* 8.0, 7.7, 1.4 Hz, 5'-H), 7.40–7.45 (2H, m, 3''-H and 5''-H), 7.48–7.55 (2H, m, 3'-H and 4''-H), 7.56 (1H, d, *J* 8.6 Hz, 6-H), 7.67–7.71 (2H, m, 2''-H and 6''-H), 8.47 (1H, d, *J* 2.8 Hz, 3-H), 9.13 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 55.8 (CH_3), 105.6 (CH), 109.4 (C), 111.7 (CH), 120.8 (C), 126.8

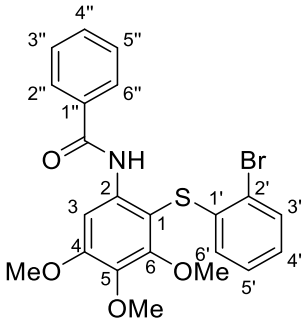
(CH), 127.1 (2 × CH), 127.1 (CH), 128.3 (CH), 129.0 (2 × CH), 132.2 (CH), 133.1 (CH), 134.6 (C), 137.9 (C), 138.4 (CH), 141.9 (C), 162.7 (C), 165.4 (C); *m/z* (ESI) 414.0160 (MH^+. $C_{20}H_{17}{}^{79}BrNO_2S$ requires 414.0158).

N-(3,4,5-Trimethoxyphenyl)benzamide (154g)[224]



The reaction was performed as described in general procedure J using 3,4,5-trimethoxyaniline (1.0 g, 5.5 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave *N*-(3,4,5-trimethoxyphenyl)benzamide (1.5 g, 93%) as a white solid. Mp 140–141 °C. Spectroscopic data were consistent with the literature.[224] δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 3.87 (6H, s, 2 × OCH_3), 6.96 (2H, s, 2-H, and 6-H), 7.45–7.52 (2H, m, 3'-H and 5'-H), 7.53–7.59 (1H, m, 4'-H), 7.81 (1H, s, NH), 7.85–7.91 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 56.3 (2 × CH_3), 61.1 (CH_3), 98.1 (2 × CH), 127.1 (2 × CH), 129.0 (2 × CH), 132.1 (CH), 134.2 (C), 135.1 (2 × C), 153.6 (2 × C), 165.8 (C); m/z (ESI) 310 (MNa^+. 100%).

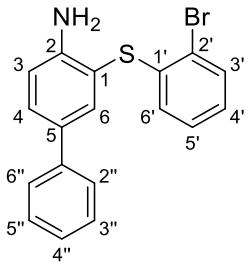
(2-Benzoylamino-4,5,6-trimethoxyphenyl)(2'-bromophenyl)sulfane (155g)



The reaction was performed as described in general procedure G using *N*-(3,4,5-trimethoxyphenyl)benzamide (84 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 3 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave (2-benzoylamino-4,5,6-trimethoxyphenyl)(2'-bromophenyl)sulfane (112 mg, 81%) as a white solid. Mp 134−137 °C; ν_{max}/cm^{-1} (neat) 3352 (NH), 2936 (CH), 1663 (CO), 1582 (C=C), 1512, 1442, 1288, 1111, 1015, 930; δ_H (400 MHz, $CDCl_3$)

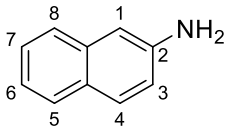
3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 6.65 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 6.98 (1H, ddd, *J* 7.9, 7.4, 1.5 Hz, 4'-H), 7.10 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5'-H), 7.40–7.46 (2H, m, 3''-H and 5''-H), 7.49–7.55 (2H, m, 3'-H and 4''-H), 7.70–7.75 (2H, m, 2''-H and 6''-H), 8.36 (1H, s, 3-H), 9.28 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 56.3 (CH_3), 61.3 (CH_3), 62.0 (CH_3), 100.3 (CH), 104.5 (C), 121.1 (C), 126.8 (CH), 127.1 (2 × CH), 127.1 (CH), 128.3 (CH), 129.0 (2 × CH), 132.2 (CH), 133.1 (CH), 134.6 (C), 137.6 (C), 137.6 (C), 139.1 (C), 155.8 (C), 156.4 (C), 165.4 (C); *m/z* (ESI) 474.0377 (MH^+. $C_{22}H_{20}{}^{79}BrNO_4S$ requires 474.0369).

(2-Amino-5-biphenyl)(2'-bromophenyl)sulfane (157e)



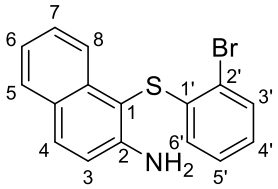
The reaction was performed as described in general procedure G using 4-aminobiphenyl (99 mg, 0.58 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave (2-amino-5-biphenyl)(2'-bromophenyl)sulfane (113 mg, 55%) as a yellow oil. ν_{max}/cm^{-1} (neat) 3371 (NH), 3024 (CH), 1613 (C=C), 1477, 1393, 1157, 1018, 745; δ_H (400 MHz, $CDCl_3$) 4.37 (2H, br s, NH_2), 6.72 (1H, dd, *J* 8.0, 1.6 Hz, 6'-H), 6.91 (1H, d, *J* 8.4 Hz, 3-H), 6.99 (1H, ddd, *J* 7.9, 7.4, 1.6 Hz, 4'-H), 7.12 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, 5'-H), 7.27–7.32 (1H, m, 4''-H), 7.39–7.44 (2H, m, 3''-H and 5''-H), 7.53–7.59 (4H, m, 4-H, 3'-H, 2''-H and 6''-H), 7.77 (1H, d, *J* 2.2 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 113.7 (C), 115.9 (CH), 120.9 (C), 126.4 (2 × CH), 126.4 (CH), 126.5 (CH), 126.8 (CH), 128.0 (CH), 128.9 (2 × CH), 130.5 (CH), 132.2 (C), 133.0 (CH), 136.3 (CH), 138.0 (C), 140.1 (C), 148.6 (C); *m/z* (ESI) 356.0109 (MH^+. $C_{18}H_{15}{}^{79}BrNS$ requires 356.0103).

2-Aminonaphthalene (156b)[225]



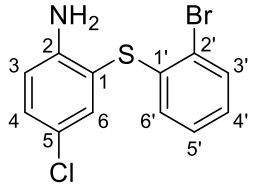
To a solution of 2-naphthalene boronic acid (0.50 g, 2.9 mmol) in acetonitrile (15 mL), was added hydroxylamine-O-sulfonic acid (0.49 g, 4.4 mL), followed by a solution of 1 M aqueous sodium hydroxide (15 mL). The resulting mixture was left to stir at room temperature for 18 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 4:1) gave 2-aminonaphthalene (0.17 g, 40%) as a brown solid. Mp 110–112 °C (lit.[225] 111–113 °C); δ_H (400 MHz, $CDCl_3$) 3.84 (2H, s, NH_2), 6.95 (1H, dd, *J* 8.6, 2.2 Hz, 3-H), 6.99 (1H, d, *J* 2.2 Hz, 1-H), 7.23 (1H, ddd, *J* 8.1, 6.8, 1.2 Hz, 6-H), 7.37 (1H, ddd, *J* 8.2, 6.8, 1.3 Hz, 7-H), 7.57–7.61 (1H, m, 8-H), 7.66 (1H, d, *J* 8.6 Hz, 4-H), 7.68 – 7.71 (2 H, m, 5-H); δ_C (101 MHz, $CDCl_3$) 108.7 (CH), 118.4 (CH), 122.6 (CH), 125.9 (CH), 126.5 (CH), 127.9 (CH), 128.1 (C), 129.4 (CH), 135.1 (C), 144.2 (C); m/z (ESI) 144 (MH^+. 100%).

1-(2'-Bromophenylthio)-2-aminonaphthalene (157b)[199]



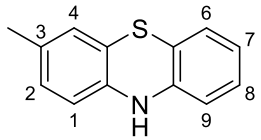
The reaction was performed as described in general procedure G using 2-aminonaphthalene (83 mg, 0.58 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 7:3) gave 1-(2'-bromophenylthio)-2-aminonaphthalene (142 mg, 75%) as an orange solid. Mp 125−127 °C; Spectroscopic data were consistent with the literature.[199] δ_H (400 MHz, $CDCl_3$) 4.72 (2H, br s, NH_2), 6.37–6.46 (1H, m, 8-H), 6.90–6.98 (2H, m, 6-H and 7-H), 7.07 (1H, d, *J* 8.7 Hz, 3-H), 7.29 (1H, ddd, *J* 8.0, 6.9, 1.2 Hz, 5'-H), 7.45 (1H, ddd, *J* 8.4, 6.9, 1.3 Hz, 4'-H), 7.50–7.57 (1H, m, 5-H), 7.74 (1H, dd, *J* 8.0, 1.3 Hz, 6'-H), 7.80 (1H, d, *J* 8.7 Hz, 4-H), 8.19 (1H, dd, *J* 8.4, 1.2 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 103.7 (C), 117.8 (CH), 121.1 (C), 122.9 (CH), 124.1 (CH), 126.1 (CH), 126.2 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 128.6 (C), 132.4 (CH), 132.9 (CH), 136.6 (C), 137.7 (C), 148.8 (C); *m/z* (ESI) 330 (MH^+. 100%).

(2-Amino-5-chloro)(2'-bromophenyl)sulfane (157c)



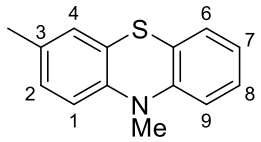
The reaction was performed as described in general procedure G using 4-chloroaniline (37 mg, 0.29 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/dichloromethane, 7:3) gave (2-amino-5-chloro)(2'-bromophenyl)sulfane (38 mg, 42%) as a colourless oil. ν_{max}/cm^{-1} (neat) 3372 (NH), 3055 (CH), 1609 (C=C), 1474, 1442, 1296, 1103, 1018, 745; δ_H (400 MHz, $CDCl_3$) 4.30 (2H, br s, NH_2), 6.65 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 6.75 (1H, d, *J* 8.6 Hz, 3-H), 7.00 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, 4'-H), 7.13 (1H, ddd, *J* 8.0, 7.5, 1.3 Hz, 5'-H), 7.23 (1H, dd, *J* 8.6, 2.5 Hz, 4-H), 7.45 (1H, d, *J* 2.5 Hz, 6-H), 7.53 (1H, dd, *J* 7.9, 1.3 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 114.7 (C), 116.5 (CH), 121.1 (C), 122.8 (C), 126.6 (CH), 126.8 (CH), 128.0 (CH), 131.8 (CH), 133.1 (CH), 136.8 (CH), 137.2 (C), 147.9 (C); *m/z* (ESI) 313.9401 (MH^+. $C_{12}H_{10}{}^{79}BrClNS$ requires 313.9400).

3-Methyl-10*H*-phenothiazine (158a)[226]



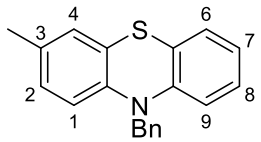
The reaction was performed as described in general procedure H using (2-amino-5-methylphenyl)(2'-bromophenyl)sulfane (30 mg, 0.10 mmol). Purification by flash column chromatography (hexane/ethyl acetate, 9:1) gave 3-methyl-10*H*-phenothiazine (18 mg, 82%) as a white solid. Mp 166−169 °C (lit.[226] 169−170 °C); δ_H (400 MHz, DMSO-d_6) 2.12 (3H, s, 3-CH_3), 6.58 (1H, d, *J* 8.0 Hz, 1-H), 6.66 (1H, dd, *J* 7.9, 1.1 Hz, 9-H), 6.68–6.75 (2H, m, 4-H and 7-H), 6.79 (1H, dd, *J* 8.0, 1.8 Hz, 2-H), 6.89 (1H, dd, *J* 7.7, 1.3 Hz, 6-H), 6.97 (1H, td, *J* 7.9, 1.3 Hz 8-H), 8.45 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 19.9 (CH_3), 114.3 (CH), 114.3 (CH), 116.18 (C), 116.24 (C), 121.4 (CH), 126.2 (CH), 126.5 (CH), 127.5 (CH), 128.0 (CH), 130.7 (C), 139.5 (C), 142.4 (C); *m/z* (ESI) 214 (MH^+. 100%).

3,10-Dimethylphenothiazine (158b)[227]



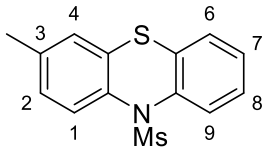
The reaction was performed as described in general procedure H using (2-methylamino-5-methylphenyl)(2'-bromophenyl) (48 mg, 0.16 mmol). Purification by flash column chromatography (hexane/dichloromethane, 9:1) gave 3,10-dimethylphenothiazine (30 mg, 86%) as a white solid. Mp 143−145 °C (lit.[227] 145−146 °C); δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, 3-CH_3), 3.35 (3H, s, NCH_3), 6.71 (1H, d, *J* 8.1 Hz, 1-H), 6.80 (1H, dd, *J* 8.0, 1.2 Hz, 9-H), 6.92 (1H, td, *J* 7.6, 1.2 Hz, 7-H), 6.95–7.01 (2H, m, 2-H and 4-H), 7.11–7.21 (2H, m, 6-H and 8-H); δ_C (101 MHz, $CDCl_3$) 20.4 (CH_3), 35.4 (CH_3), 113.97 (CH), 113.98 (CH) 122.3 (CH), 123.3 (C) 123.4 (C), 127.3 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 132.1 (C), 143.5 (C), 146.2 (C); *m/z* (ESI) 228 (MNa^+. 100%).

***N*-Benzyl-3-methylphenothiazine (158c)**



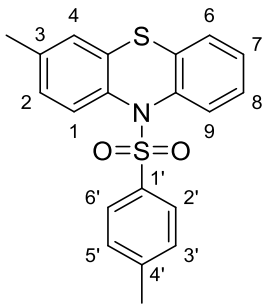
The reaction was performed as described in general procedure H using (2-benzylamino-5-methylphenyl)(2'-bromophenyl)sulfane (46 mg, 0.12 mmol). Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave *N*-benzyl-3-methylphenothiazine (35 mg, 97%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2916 (CH), 1578 (C=C), 1466, 1358, 1254, 1111, 871, 729; δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, 3-CH_3), 5.07 (2H, s, PhCH_2), 6.53 (1H, d, *J* 8.3 Hz, 1-H), 6.62 (1H, dd, *J* 8.2, 1.1 Hz, 9-H), 6.77 (1H, dd, *J* 8.3, 1.6 Hz, 2-H), 6.85 (1H, td, *J* 7.5, 1.1 Hz, 7-H), 6.92 (1H, d, *J* 1.6 Hz, 4-H), 6.97 (1H, ddd, *J* 8.2, 7.5, 1.6 Hz, 8-H), 7.09 (1H, dd, *J* 7.5, 1.6 Hz, 6-H), 7.22–7.38 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 20.4 (CH_3), 52.7 (CH_2), 115.3 (CH), 115.4 (CH), 122.3 (CH), 123.0 (C), 123.1 (C), 126.7 (2 × CH), 126.9 (CH), 127.1 (CH), 127.3 (CH), 127.4 (CH), 127.8 (CH), 128.8 (2 × CH), 132.2 (C), 137.0 (C), 142.1 (C), 144.8 (C); *m/z* (ESI) 326.0982 (MNa^+. $C_{20}H_{17}NNaS$ requires 326.0974).

***N*-Methanesulfonyl-3-methylphenothiazine (158e)**



To a solution of [2-(methanesulfonyl)amino-5-methylphenyl](2'-bromophenyl)sulfane (55 mg, 0.15 mmol) in toluene (0.5 mL) was added copper(I) iodide (2.8 mg, 10 mol%), cesium carbonate (96 mg, 0.30 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (4.7 μL, 20 mol%) and water (0.2 mL). The reaction mixture was purged with nitrogen and then heated to 130 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organics were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave *N*-methanesulfonyl-3-methylphenothiazine (25 mg, 58%) as a yellow solid. Mp 181−183 °C; ν_{max}/cm^{-1} (neat) 2928 (CH), 1462, 1358, 1157, 964, 826, 760; δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, 3-CH_3), 2.89 (3H, s, SO_2CH_3), 7.13 (1H, dd, *J* 8.2, 1.9 Hz, 2-H), 7.17 (1H, d, *J* 1.9 Hz, 4-H), 7.27 (1H, td, *J* 7.5, 1.5 Hz, 7-H), 7.30–7.37 (2H, m, 6-H and 8-H), 7.51 (1H, d, *J* 8.2 Hz, 1-H), 7.63 (1H, dd, *J* 7.7, 1.5 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 21.1 (CH_3), 39.3 (CH_3), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.7 (CH), 129.5 (CH), 129.8 (CH), 131.9 (C), 132.3 (C), 133.9 (C), 136.7 (C), 138.4 (C); *m/z* (ESI) 314.0279 (MNa^+. $C_{14}H_{13}NNaO_2S_2$ requires 314.0280).

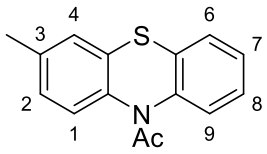
***N*-(4'-Methylphenylsulfonyl)-3-methylphenothiazine (158f)**



To a solution of [2-(4-methylphenylsulfonyl)amino-5-methylphenyl](2'-bromophenyl)sulfane (39 mg, 0.087 mmol) in toluene (0.5 mL) was added copper(I)

iodide (1.7 mg, 10 mol%), cesium carbonate (57 mg, 0.17 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (2.7 μL, 20 mol%) and water (0.2 mL). The reaction mixture was purged with nitrogen and then heated to 130 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave *N*-(4'-methylphenylsulfonyl)-3-methylphenothiazine (24 mg, 75%) as a yellow solid. Mp 146−148 °C; ν_{max}/cm^{-1} (neat) 2920 (CH), 1597 (C=C), 1447, 1354, 1165, 922, 760; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, 3-CH_3), 2.37 (3H, s, 4'-CH_3), 6.92 (1H, d, *J* 1.1 Hz, 4-H), 7.05 (2H, d, *J* 8.1 Hz, 3'-H and 5'-H), 7.08–7.16 (4H, m, 2-H, 6-H, 2'-H and 6'-H), 7.20 (1H, td, *J* 7.5, 1.3 Hz, 7-H), 7.32 (1H, ddd, *J* 7.9, 7.5, 1.5 Hz, 8-H), 7.61 (1H, d, *J* 8.2 Hz, 1-H), 7.73 (1H, dd, *J* 7.9, 1.3 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 21.1 (CH_3), 21.8 (CH_3), 127.0 (CH), 127.2 (CH), 127.3 (CH), 127.7 (CH), 127.8 (2 × CH), 128.2 (CH), 129.4 (2 × CH), 129.8 (CH), 130.1 (CH), 132.8 (C), 133.3 (C), 133.5 (C), 136.2 (C), 136.3 (C), 138.0 (C), 144.1 (C); *m/z* (ESI) 402.0395 (MCl^-. $C_{20}H_{17}{}^{35}ClNO_2S_2$ requires 402.0395).

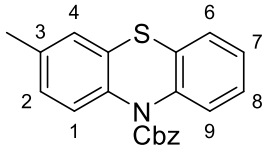
_N_-Acetyl-3-methylphenothiazine (158g)



To a solution of (2-acetylamino-5-methylphenyl)(2'-bromophenyl)sulfane (50 mg, 0.15 mmol) in toluene (0.5 mL) was added copper(I) iodide (2.8 mg, 10 mol%), cesium carbonate (97 mg, 0.30 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (4.7 μL, 20 mol%) and water (0.2 mL). The reaction mixture was purged with nitrogen and then heated to 130 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography

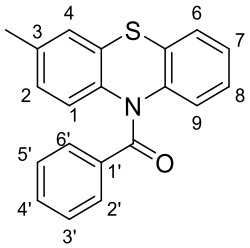
(hexane/dichloromethane, 1:4) gave *N*-acetyl-3-methylphenothiazine (35 mg, 92%) as a yellow oil. ν_{max}/cm^{-1} (neat) 2924 (CH), 1674 (CO), 1466, 1308, 1258, 1011, 818, 752; δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, $COCH_3$), 2.34 (3H, s, 3-CH_3), 7.12 (1H, dd, *J* 8.0, 1.8 Hz, 2-H), 7.21 (1H, td, *J* 7.7, 1.3 Hz, 7-H), 7.25 (1H, d, *J* 1.8 Hz, 4-H), 7.31 (1H, td, *J* 7.7, 1.4 Hz, 8-H), 7.37 (1H, br d, *J* 8.0 Hz, 1-H), 7.42 (1H, dd, *J* 7.7, 1.4 Hz, 6-H), 7.50 (1H, br d, *J* 7.7 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 21.0 (CH_3), 23.1 (CH_3), 126.8 (CH), 126.9 (CH), 127.0 (CH), 127.3 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 132.9 (C), 133.2 (C), 136.5 (C), 137.0 (C), 139.3 (C), 169.5 (C); *m/z* (ESI) 278.0612 (MNa^+. $C_{15}H_{13}NNaOS$ requires 278.0610).

_N_-Benzyloxycarbonyl-3-methylphenothiazine (158d)



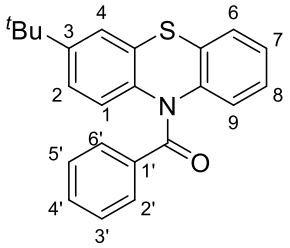
To a solution of [2-(benzyloxycarbonyl)amino-5-methylphenyl](2'-bromophenyl)sulfane (50 mg, 0.12 mmol) in toluene (0.5 mL) was added copper(I) iodide (2.2 mg, 10 mol%), cesium carbonate (76 mg, 0.23 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (3.7 µL, 23 mol%) and water (0.2 mL). The reaction mixture was purged with nitrogen and then heated to 130 °C for 18 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (20 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL) and the combined organic layers were washed with brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave *N*-benzyloxycarbonyl-3-methylphenothiazine (31 mg, 76%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2952 (CH), 1711 (CO), 1469, 1318, 1216, 1093, 748; δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, 3-CH_3), 5.26 (2H, s, PhCH_2), 7.08 (1H, dd, *J* 8.2, 1.3 Hz, 2-H), 7.14–7.20 (2H, m, 4-H and 7-H), 7.27 (1H, ddd, *J* 8.0, 7.5, 1.5 Hz, 8-H), 7.30–7.39 (6H, m, 6-H and Ph), 7.42 (1H, d, *J* 8.2 Hz, 1-H) 7.54 (1H, dd, *J* 8.0, 1.0 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 21.0 (CH_3), 68.1 (CH_2), 126.5 (CH), 126.8 (CH), 126.9 (CH), 127.1 (CH), 127.7 (CH), 127.8 (CH), 127.9 (2 × CH), 128.0 (CH), 128.2 (CH), 128.6 (2 × CH), 132.0 (C), 132.4 (C), 135.8 (C), 136.1 (C), 136.6 (C), 138.6 (C), 153.8 (C); *m/z* (ESI) 348.1052 (MH^+. $C_{21}H_{18}NO_2S$ requires 348.1053).

_N_-Benzoyl-3-methylphenothiazine (158h)



The reaction was performed as described in general procedure I using (2-benzoylamino-5-methylphenyl)(2'-bromophenyl)sulfane (32 mg, 0.080 mmol). The reaction mixture was stirred at 130 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave *N*-benzoyl-3-methylphenothiazine (22 mg, 86%) as a white solid. Mp 123−125 °C; ν_{max}/cm^{-1} (neat) 2916 (CH), 1667 (CO), 1462, 1319, 1258, 1111, 810, 760; δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, 3-CH_3), 6.95 (1H, dd, *J* 8.2, 1.9 Hz, 2-H), 7.11–7.17 (2H, m, 6-H and 8-H), 7.19–7.33 (5H, m, 1-H, 4-H, 3'-H, 4'-H and 5'-H), 7.35–7.46 (4H, m, 7-H, 9-H, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 21.0 (CH_3), 126.5 (CH), 126.8 (CH), 126.9 (CH), 127.2 (CH), 127.8 (CH), 127.8 (CH), 128.1 (2 × CH), 128.2 (CH), 129.0 (2 × CH), 130.4 (CH), 132.0 (C), 132.4 (C), 135.5 (C), 136.6 (C), 137.1 (C), 139.8 (C), 169.0 (C); *m/z* (ESI) 318.0954 (MH^+. $C_{20}H_{16}NOS$ requires 318.0947).

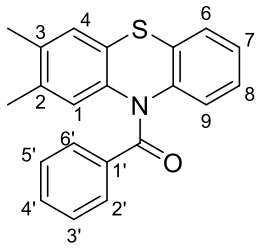
_N_-Benzoyl-3-*tert*-butylphenothiazine (159a)



The reaction was performed as described in general procedure I using (2-benzoylamino-5-*tert*-butylphenyl)(2'-bromophenyl)sulfane (80 mg, 0.18 mmol). The reaction mixture was stirred at 130 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 1:1) gave *N*-benzoyl-3-*tert*-butylmethylphenothiazine (50 mg, 77%) as a white solid. Mp 123−124 °C; ν_{max}/cm^{-1} (neat) 2963 (CH), 1651 (CO) 1462, 1323, 1258, 1115, 880, 756; δ_H (400 MHz, $CDCl_3$) 1.30 (9H, s, 3 × CH_3), 7.07–7.16 (2H, m, 7-H and 8-H), 7.18–7.24 (3H, m, 2-H, 3'-H and 5'-H), 7.26–7.33 (2H, m, 6-H and 4'-H), 7.36–7.40 (2H, m, 2'-H and 6'-H), 7.42–7.47 (3H, m, 1-H, 4-H and 9-H); δ_C (101 MHz, $CDCl_3$) 31.4 (3 × CH_3), 34.8

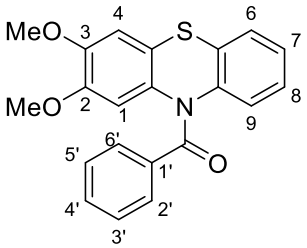
(C), 124.3 (CH), 124.6 (CH), 126.4 (CH), 126.6 (CH), 126.9 (CH), 127.2 (CH), 127.8 (CH), 128.0 (2 × CH), 129.0 (2 × CH), 130.4 (CH), 131.6 (C), 132.6 (C), 135.5 (C), 136.8 (C), 139.9 (C), 150.0 (C), 169.0 (C); *m/z* (ESI) 360.1425 (MH^+. $C_{23}H_{22}NOS$ requires 360.1417).

_N_-Benzoyl-2,3-dimethylphenothiazine (159b)



The reaction was performed as described in general procedure I using (2-benzoylamino-4,5-dimethylphenyl)(2'-bromophenyl)sulfane (30 mg, 0.072 mmol). The reaction mixture was stirred at 150 °C for 48 h. Purification by flash column chromatography (hexane/dichloromethane, 3:2) gave *N*-benzoyl-2,3-dimethylphenothiazine (15 mg, 65%) as a white solid. Mp 170–171 °C; ν_{max}/cm^{-1} (neat) 2916 (CH), 1678 (C=O), 1492, 1392, 1246, 1014, 883, 794; δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, CH_3), 2.21 (3H, s, CH_3), 7.05–7.13 (2H, m, 6-H and 8-H), 7.19–7.22 (3H, m, 4-H, 3'-H and 5'-H), 7.26–7.31 (3H, m, 4'-H, 1-H, 7-H), 7.35–7.37 (2H, m, 2'-H and 6'-H), 7.42 (1H, dd, *J* 7.6, 1.8 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 19.5 (CH_3), 19.6 (CH_3), 126.4 (CH), 126.8 (CH), 127.2 (CH), 127.8 (CH), 128.0 (2 × CH),128.1 (CH), 128.4 (CH), 128.8 (C), 128.9 (2 × CH), 130.3 (CH), 132.9 (C), 135.3 (C), 135.6 (C), 135.8 (C), 137.1 (C), 140.0 (C), 169.0 (C); *m/z* (ESI) 332.1111 (MH^+. $C_{21}H_{18}NOS$ requires 332.1104).

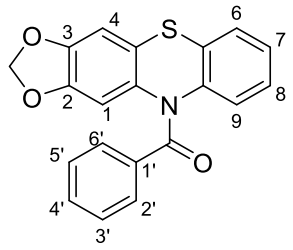
_N_-Benzoyl-2,3-dimethoxyphenothiazine (159c)



The reaction was performed as described in general procedure I using (2-benzoylamino-4,5-dimethoxyphenyl)(2'-bromophenyl)sulfane (50 mg, 0.11 mmol). The reaction mixture was stirred at 130 °C for 24 h. Purification by flash column

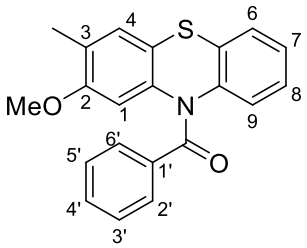
chromatography (hexane/diethyl ether, 3:2) gave *N*-benzoyl-2,3-dimethoxyphenothiazine (34 mg, 83%) as a white solid. Mp 112−114 °C; ν_{max}/cm^{-1} (neat) 2936 (CH), 1663 (CO), 1501, 1443, 1308, 1261, 1026, 849; δ_H (400 MHz, $CDCl_3$) 3.66 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.89 (1H, s, 4-H), 6.92 (1H, s, 1-H), 7.12–7.18 (2H, m, 6-H and 8-H), 7.20–7.25 (2H, m, 3'-H and 5'-H), 7.29–7.33 (1H, m, 4'-H), 7.35–7.46 (4H, m, 7-H, 9-H, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 56.2 (CH_3), 56.3 (CH_3), 109.9 (CH), 111.1 (CH), 123.0 (C), 126.4 (CH), 126.9 (CH), 127.1 (CH), 127.7 (CH), 128.2 (2 × CH), 128.8 (2 × CH), 130.4 (CH), 132.7 (C), 132.8 (C), 135.6 (C), 139.8 (C), 147.6 (C), 148.1 (C), 169.1 (C); *m/z* (ESI) 364.1011 (MH^+. $C_{21}H_{18}NO_3S$ requires 364.1002).

N-Benzoyl-2,3-methylenedioxyphenothiazine (159d)



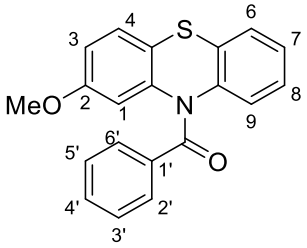
The reaction was performed as described in general procedure I using (2-benzoylamino-4,5-methylenedioxyphenyl)(2'-bromophenyl)sulfane (79 mg, 0.18 mmol). The reaction mixture was stirred at 150 °C for 72 h. Purification by flash column chromatography (hexane/dichloromethane, 3:7) gave *N*-benzoyl-2,3-methylenedioxyphenothiazine (44 mg, 69%) as a white solid. Mp 185–187 °C; ν_{max}/cm^{-1} (neat) 3055 (CH), 1647 (C=O), 1462, 1327, 1238, 1030, 922, 860, 806; δ_H (400 MHz, $CDCl_3$) 5.95 (2H, s, OCH_2O), 6.87 (1H, s, 4-H), 7.03 (1H, s, 1-H), 7.09 (1H, td, *J* 7.6, 1.4 Hz, 8-H), 7.14 (1H, td, *J* 7.6, 1.4 Hz, 7-H), 7.21–7.25 (3H, m, 6-H, 3'-H and 5'-H), 7.32 (1H, tt, *J* 7.4, 1.2 Hz, 4'-H), 7.35–7.38 (2H, m, 2'-H and 6'-H), 7.43 (1H, dd, *J* 7.6, 1.4 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 102.1 (CH_2), 107.4 (CH), 108.6 (CH), 124.8 (C), 126.5 (CH), 127.0 (CH), 127.2 (CH), 127.7 (CH), 128.2 (2 × CH), 128.9 (2 × CH), 130.5 (CH), 133.2 (C), 133.6 (C), 135.3 (C), 140.1 (C), 146.3 (C), 147.3 (C), 169.0 (C); *m/z* (ESI) 348.0691 (MH^+. $C_{20}H_{14}NO_3S$ requires 348.0689).

***N*-Benzoyl-2-methoxy-3-methylphenothiazine (159e)**



The reaction was performed as described in general procedure I using (2-benzoylamino-4-methoxy-5-methylphenyl)(2'-bromophenyl)sulfane (60 mg, 0.14 mmol). The reaction mixture was stirred at 130 °C for 96 h. Purification by flash column chromatography (hexane/dichloromethane, 3:7) gave *N*-benzoyl-2-methoxy-3-methylphenothiazine (52 mg, 80%) as a white solid. Mp 180–181 °C; ν_{max}/cm^{-1} (neat) 3050 (CH), 1654 (C=O), 1462, 1338, 1249, 1057, 756, 706; δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, 3-CH_3), 3.62 (3H, s, 2-OCH_3), 6.91 (1H, s, 4-H), 7.10–7.17 (3H, m, 1-H, 7-H and 8-H), 7.21–7.25 (2H, m, 3'-H and 5'-H), 7.29–7.34 (1H, m, 4'-H), 7.37–7.44 (4H, m, 6-H, 9-H, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 16.0 (CH_3), 55.7 (CH_3), 109.9 (CH), 122.1 (C), 125.7 (C), 126.4 (CH), 126.7 (CH), 127.1 (CH), 127.7 (CH), 128.1 (2 × CH), 128.8 (CH) 128.8 (2 × CH), 130.4 (CH), 133.2 (C), 135.6 (C), 138.3 (C), 139.7 (C), 156.9 (C), 169.1 (C); *m/z* (ESI) 348.1060 (MH^+. $C_{21}H_{18}NO_2S$ requires 348.1053).

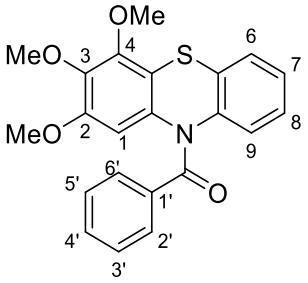
***N*-Benzoyl-2-methoxyphenothiazine (159f)**



The reaction was performed as described in general procedure I using (2-benzoylamino-4-methoxyphenyl)(2'-bromophenyl)sulfane (250 mg, 0.60 mmol). The reaction mixture was stirred at 150 °C for 120 h. Purification by flash column chromatography (hexane/ethyl acetate, 9:1) gave *N*-benzoyl-2-methoxyphenothiazine (160 mg, 80%) as a white solid. Mp 156−157 °C; ν_{max}/cm^{-1} (neat) 2920 (CH), 1655 (CO), 1578 (C=C), 1442, 1335, 1246, 1022, 756; δ_H (400 MHz, $CDCl_3$) 3.65 (3H, s, OCH_3), 6.74 (1H, dd, *J* 8.6, 2.7 Hz, 3-H), 7.01 (1H, d, *J* 2.7 Hz, 1-H), 7.10–7.17 (2H, m, 7-H and 8-H), 7.21–7.25 (2H, m, 3'-H and 5'-H),

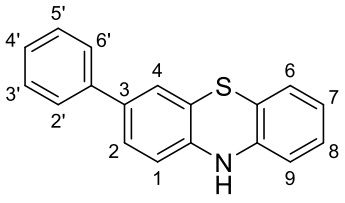
7.29–7.44 (6H, m, 4-H, 6-H, 9-H, 2'-H, 4'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.7 (CH_3), 112.8 (CH), 113.6 (CH), 123.0 (C), 126.5 (CH), 126.9 (CH), 127.2 (CH), 127.8 (CH), 128.2 (CH), 128.2 (2 × CH), 128.9 (2 × CH), 130.5 (CH), 133.0 (C), 135.4 (C), 139.7 (C), 140.8 (C), 159.1 (C), 169.1 (C); *m/z* (ESI) 334.0902 (MH^+. $C_{20}H_{16}NO_2S$ requires 334.0896).

_N_-Benzoyl-2,3,4-trimethoxyphenothiazine (159g)



The reaction was performed as described in general procedure I using (2-benzoylamino-4,5,6-trimethoxyphenyl)(2'-bromophenyl)sulfane (50 mg, 0.11 mmol). The reaction mixture was stirred at 130 °C for 48 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave *N*-benzoyl-2,3,4-trimethoxyphenothiazine (22 mg, 53%) as a white solid. Mp 111−113 °C; ν_{max}/cm^{-1} (neat) 2936 (CH), 1659 (CO), 1447, 1308, 1242, 1107, 926, 745; δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.86 (1H, s, 1-H), 7.08–7.16 (2H, m, 7-H and 8-H), 7.20–7.39 (6H, m, 6-H and Ph), 7.46 (1H, dd, *J* 7.5, 1.6 Hz, 9-H); δ_C (101 MHz, $CDCl_3$) 56.4 (CH_3), 61.3 (CH_3), 61.4 (CH_3), 107.5 (CH), 118.0 (C), 126.5 (CH), 126.9 (CH), 127.1 (CH), 128.0 (CH), 128.1 (2 × CH), 128.8 (2 × CH), 130.5 (CH), 132.5 (C), 134.7 (C) 135.5 (C), 139.7 (C), 140.8 (C), 149.6 (C), 152.5 (C), 169.2 (C); *m/z* (ESI) 394.1117 (MH^+. $C_{22}H_{20}NO_4S$ requires 394.1108).

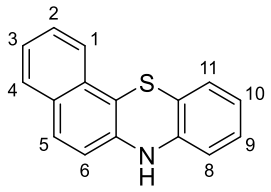
3-Phenyl-10*H*-phenothiazine (160a)[228]



The reaction was performed as described in general procedure H using (2-amino-5-biphenyl)(2'-bromophenyl)sulfane (100 mg, 0.28 mmol). The reaction mixture was

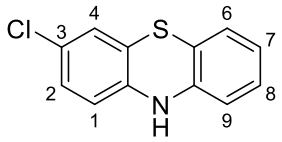
stirred at 110 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 5:1) gave 3-phenyl-10*H*-phenothiazine (63 mg, 82%) as a yellow solid. Mp 220−222 °C (lit.[228] 216−218 °C); δ_H (400 MHz, DMSO-d_6) 6.69 (1H, dd, *J* 7.9, 1.1 Hz, 9-H), 6.73–6.79 (2H, m, 1-H and 7-H), 6.93 (1H, dd, *J* 7.7, 1.4 Hz, 6-H), 7.00 (1H, td, *J* 7.9, 1.4 Hz, 8-H), 7.22 (1H, d, *J* 2.1 Hz, 4-H), 7.25–7.32 (2H, m, 2-H and 4'-H), 7.37–7.43 (2H, m, 3'-H and 5'-H), 7.54–7.59 (2H, m, 2'-H and 6'-H), 8.70 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 114.4 (CH), 114.7 (CH), 116.1 (C), 117.0 (C), 121.8 (CH), 124.1 (CH), 125.7 (2 × CH), 125.8 (CH), 126.2 (CH), 126.8 (CH), 127.6 (CH), 128.8 (2 × CH), 133.7 (C), 139.1 (C), 141.3 (C), 141.7 (C); *m/z* (ESI) 299 (MNa^+. 100%).

7*H*-Benzo[c]phenothiazine (160b)[229]



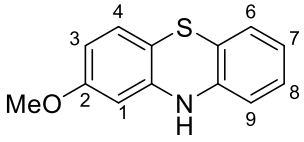
The reaction was performed as described in general procedure H using 1-(2'-bromophenylthio)-2-aminonaphthalene (100 mg, 0.39 mmol). The reaction mixture was stirred at 110 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 5:1) gave benzo[a]phenothiazine (85 mg, 87%) as a yellow solid. Mp 184−186 °C (lit.[229] 185 °C); δ_H (400 MHz, DMSO-d_6) 6.74 (1H, dd, *J* 8.3, 1.3 Hz, 8-H), 6.80 (1H, td, *J* 7.5, 1.3 Hz, 10-H), 7.00–7.05 (3H, m, 6-H, 9-H and 11-H), 7.31 (1H, ddd, *J* 8.0, 6.9, 1.1 Hz, 3-H), 7.49 (1H, ddd, *J* 8.3, 6.9, 1.3 Hz, 2-H), 7.63 (1H, d, *J* 8.6 Hz, 5-H), 7.70 (1H, dd, *J* 8.3, 1.1 Hz, 1-H), 7.76 (1H, dd, *J* 8.0, 1.3 Hz, 4-H), 8.80 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 107.0 (C), 114.5 (CH), 116.0 (C), 116.8 (CH), 121.4 (CH), 122.3 (CH), 123.3 (CH), 126.6 (CH), 127.0 (CH), 127.4 (CH), 127.8 (CH), 128.4 (CH), 129.6 (C), 129.9 (C), 139.8 (C), 142.4 (C); *m/z* (ESI) 288 (MK^+. 100%).

3-Chloro-10*H*-phenothiazine (160c)[230]



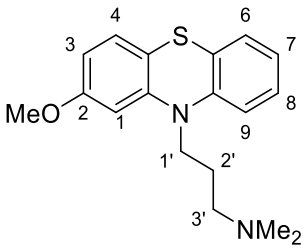
The reaction was performed as described in general procedure H using (2-amino-5-chloro)(2'-bromophenyl)sulfane (60 mg, 0.19 mmol). The reaction mixture was stirred at 110 °C for 4 h. Purification by flash column chromatography (hexane/dichloromethane, 5:1) gave 3-chloro-10*H*-phenothiazine (37 mg, 82%) as a white solid. Mp 201−203 °C (lit.[230] 200−201 °C); δ_H (400 MHz, DMSO-*d*$_6$) 6.63–6.68 (2H, m, 1-H and 9-H), 6.77 (1H, td, *J* 7.7, 1.3 Hz, 7-H), 6.91 (1H, dd, *J* 7.7, 1.4 Hz, 6-H), 6.97–7.05 (3H, m, 2-H, 4-H and 8-H), 8.71 (1H, br s, NH); δ_C (101 MHz, DMSO-*d*$_6$) 114.6 (CH), 115.4 (CH), 115.5 (C), 118.6 (C), 122.1 (CH), 124.9 (C), 125.4 (CH), 126.3 (CH), 127.2 (CH), 127.8 (CH), 141.1 (C), 141.6 (C); *m/z* (EI) 233 (M^+. 100%).

2-Methoxyphenothiazine (162)[123]



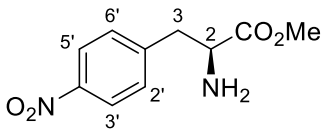
To a solution of *N*-benzoyl-2-methoxyphenothiazine (100 mg, 0.30 mmol) in ethanol (5.3 mL) was added hydrazine monohydrate (11 mL) under an atmosphere of argon. The reaction mixture was stirred at 145 °C for 48 h. The resulting residue was cooled and poured onto ice-water (30 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave 2-methoxyphenothiazine (50 mg, 73%) as a white solid. Mp 183–185 °C (lit.[123] 184–185 °C); δ_H (400 MHz, DMSO-*d*$_6$) 3.68 (3H, s, OCH_3), 6.32 (1H, d, *J* 2.7 Hz, 1-H), 6.38 (1H, dd, *J* 8.4, 2.7 Hz, 3-H), 6.67 (1H, dd, *J* 8.0, 1.3 Hz, 6-H), 6.75 (1H, ddd, *J* 7.7, 7.4, 1.3 Hz, 8-H), 6.82 (1H, d, *J* 8.4 Hz, 4-H), 6.91 (1H, dd, *J* 7.7, 1.5 Hz, 9-H), 6.98 (1H, ddd, *J* 8.0, 7.4, 1.5 Hz, 7-H), 8.59 (1H, s, NH); δ_C (101 MHz, DMSO-*d*$_6$) 55.0 (CH_3), 100.7 (CH), 107.1 (C), 107.2 (CH), 114.4 (CH), 117.0 (C), 121.8 (CH), 126.2 (CH), 126.8 (CH), 127.4 (CH), 141.8 (C), 143.3 (C), 159.3 (C); *m/z* (EI) 229 (M^+. 100%).

Methopromazine (163)[134]



Sodium hydride (7.5 mg, 0.43 mmol) was slowly added to DMF (0.4 mL) under an atmosphere of argon and the resulting suspension was cooled to 0 °C. 3-Dimethylamino-1-propyl chloride hydrochloride (41 mg, 0.26 mmol) and 2-methoxyphenothiazine (30 mg, 0.13 mmol) were subsequently added. The reaction mixture was stirred at room temperature for 18 h. The resulting residue was diluted with dichloromethane (20 mL) and washed with 5% aqueous lithium chloride (30 mL). The aqueous layer was further extracted with dichloromethane (2 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane/methanol, 19:1) gave methopromazine (25 mg, 61%) as a brown oil. Spectroscopic data were consistent with the literature.[134] δ_H (400 MHz, $CDCl_3$) 1.98 (2H, p, *J* 7.1 Hz, 2'-H_2), 2.23 (6H, s, 2 × CH_3), 2.44 (2H, t, *J* 7.1 Hz, 3'-H_2), 3.78 (3H, s, OCH_3), 3.90 (2H, t, *J* 7.1 Hz, 1'-H_2), 6.43–6.52 (2H, m, 1-H and 3-H), 6.86–6.94 (2H, m, 6-H and 8-H), 6.99–7.06 (1H, m, 4-H), 7.09–7.17 (2H, m, 7-H and 9-H); δ_C (101 MHz, $CDCl_3$) 24.6 (CH_2), 45.1 (2 × CH_3), 45.3 (CH_2), 55.7 (CH_3), 57.0 (CH_2), 103.6 (CH), 107.3 (CH), 115.9 (CH), 116.5 (C), 122.8 (CH), 126.1 (C), 127.3 (CH), 127.6 (CH), 127.9 (CH), 145.0 (C), 146.7 (C), 160.0 (C); *m/z* (ESI) 315 (MH^+. 100%).

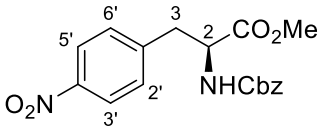
L-*p*-Nitrophenylalanine methyl ester (166)[231]



To a round bottomed flask containing L-*p*-nitrophenylalanine (1.00 g, 4.76 mmol) in methanol (20.0 mL) was added thionyl chloride (0.490 mL, 6.67 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and heated under reflux for 2.5 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, dissolved in water and basified to pH 7–8 with saturdated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane (3 × 30 mL).

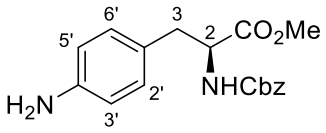
The combined organic layers were washed with water (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give L-*p*-nitrophenylalanine methyl ester as a yellow oil (1.05 g, 98%). Spectroscopic data were consistent with the literature. $[\alpha]_D^{20}$ +26.7 (*c* 0.1, EtOH), lit.[231] $[\alpha]_D^{24}$ +34.2 (*c* 0.1, EtOH); δ_H (400 MHz, $CDCl_3$) 2.96 (1H, dd, *J* 13.6, 7.9 Hz, 3-*H*H), 3.16 (1H, dd, *J* 13.6, 5.4 Hz, 3-H*H*), 3.72 (3H, s, OCH_3), 3.76 (1H, dd, *J* 7.9, 5.4 Hz, 2-H), 7.36–7.40 (2H, m, 2'-H and 6'-H), 8.13–8.18 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 40.7 (CH_2), 52.2 (CH), 55.5 (CH_3), 123.7 (2 × CH), 130.2 (2 × CH), 145.3 (C), 147.0 (C), 175.0 (C); *m/z* (ESI) 225 (MH^+. 100%).

Methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-nitrophenyl)propanoate (167)[231]



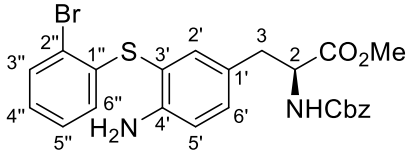
To a round bottomed flask containing L-*p*-nitrophenylalanine methyl ester (1.00 g, 4.46 mmol) and water at 0 °C was added sodium bicarbonate (941 mg, 11.2 mmol). A solution of benzyl chloroformate (750 µL, 5.35 mmol) in toluene (3 mL) was added to the reaction mixture dropwise. The reaction mixture was warmed to room temperature and left to stir for 2 h. The reaction mixture was diluted with water (30 mL) and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 7:3) gave methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-nitrophenyl)propanoate as a yellow oil (1.27 g, 79%). Spectroscopic data were consistent with the literature.[231] $[\alpha]_D^{21}$ +29.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.13 (1H, dd, *J* 13.8, 6.5 Hz, 3-*H*H), 3.29 (1H, dd, *J* 13.8, 5.6 Hz, 3-H*H*), 3.74 (3H, s, OCH_3), 4.70 (1H, ddd, *J* 7.8, 6.5, 5.6 Hz, 2-H), 5.05 (1H, d, *J* 12.2 Hz, PhC*H*H), 5.11 (1H, d, *J* 12.2 Hz, PhCH*H*), 5.37 (1H, d, *J* 7.8 Hz, NH), 7.26 (2H, d, *J* 8.5 Hz, 2'-H and 6'-H), 7.28–7.40 (5H, m, Ph), 8.10 (2H, d, *J* 8.5 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 38.3 (CH_2), 52.7 (CH_3), 54.6 (CH), 67.2 (CH_2), 123.8 (2 × CH), 128.3 (2 × CH), 128.5 (CH), 128.6 (2 × CH), 130.3 (2 × CH), 136.1 (C), 143.8 (C), 147.2 (C), 155.6 (C), 171.4 (C); *m/z* (ESI) 381 (MNa^+. 100%).

Methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate (164)[231]



To a round bottomed flask containing methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-nitrophenyl)propanoate (1.18 g, 3.29 mmol) in methanol (28 mL) was added zinc (2.15 g, 32.9 mmol) and glacial acetic acid (1.88 mL, 32.9 mmol) dropwise at 0 °C. The reaction mixture was left to stir at room temperature for 4 h. The reaction mixture was filtered through celite and washed with methanol. The filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and extracted with water (5 × 40 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate as a yellow oil (939 mg, 87%). Spectroscopic data were consistent with the literature.[231] $[\alpha]_D^{21}$ +29.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.98 (2H, dd, *J* 12.8, 5.8 Hz, 3-*H*H), 3.04 (2H, dd, *J* 12.8, 5.9 Hz, 3-H*H*), 3.61 (2H, br s, 4'-NH_2), 3.71 (3H, s, OCH_3), 4.59 (1H, ddd, *J* 8.0, 5.9, 5.8 Hz, 2-H), 5.08 (2H, d, *J* 12.5 Hz, PhC*H*H), 5.13 (2H, d, *J* 12.5 Hz, PhCH*H*), 5.19 (1H, d, *J* 8.0 Hz, 2-NH), 6.55–6.62 (2H, m, 3'-H and 5'-H), 6.83–6.90 (2H, m, 2'-H and 6'-H), 7.27–7.39 (5H, m, Ph); δ_C (101 MHz, $CDCl_3$) 37.5 (CH_2), 52.4 (CH_3), 55.1 (CH), 67.0 (CH_2), 115.5 (2 × CH), 125.4 (C), 128.2 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 130.3 (2 × CH), 136.5 (C), 145.6 (C), 155.8 (C), 172.3 (C); *m/z* (ESI) 329 (MH^+. 100%).

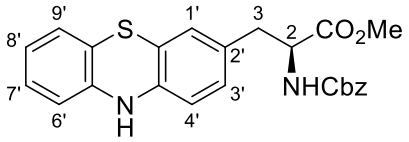
_N_-(Benzyloxycarbonyl)-[3'-(2''-bromophenylthio)]-L-4'-aminophenylalanine methyl ester (168)



The reaction was performed as described in general procedure G using methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate (381 mg, 1.16 mmol). The reaction mixture was stirred at 90 °C for 20 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave *N*-(benzyloxycarbonyl)-[3'-(2''-bromophenylthio)]-L-4'-aminophenylalanine methyl ester (292 mg, 49%) as a white

solid. Mp 85−87 °C; ν_{max}/cm^{-1} (neat) 3356 (NH), 2951 (CH), 1709 (CO), 1616 (C=C), 1497, 1211, 1018, 732; $[\alpha]_D^{23}$ +53.0 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.98 (2H, dd, *J* 14.0, 5.7 Hz, 3-*H*H), 3.05 (1H, dd, *J* 14.0, 5.5 Hz, 3-H*H*), 3.67 (3H, s, OCH_3), 4.26 (2H, br s, 4'-NH_2), 4.60 (1H, ddd, *J* 8.0, 5.7, 5.5 Hz, 2-H), 5.09 (2H, s, PhC*H*$_2$), 5.26 (1H, d, *J* 8.0 Hz, 2-NH), 6.56 (1H, dd, *J* 8.0, 1.4 Hz, 6''-H), 6.73 (1H, d, *J* 8.2 Hz, 5'-H), 6.94 (1H, ddd, *J* 7.9, 7.8, 1.4 Hz, 4''-H), 7.02 (1H, dd, *J* 8.2, 2.0 Hz, 6'-H), 7.08 (1H, ddd, *J* 8.0, 7.8, 1.3 Hz, 5''-H), 7.19 (1H, d, *J* 2.0 Hz, 2'-H), 7.27–7.39 (5H, m, Ph), 7.50 (1H, dd, *J* 7.9, 1.3 Hz, 3''-H); δ_C (101 MHz, $CDCl_3$) 37.4 (CH_2), 52.5 (CH_3), 55.1 (CH), 67.1 (CH_2), 113.4 (C), 115.8 (CH), 120.9 (C), 126.2 (C), 126.4 (CH), 126.4 (2 × CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.7 (2 × CH), 132.8 (CH), 132.9 (CH), 136.4 (C), 138.0 (C), 138.6 (CH), 148.4 (C), 155.7 (C), 172.0 (C); *m/z* (ESI) 515.0632 (MH^+. $C_{24}H_{24}{}^{79}BrN_2O_4S$ requires 515.0635).

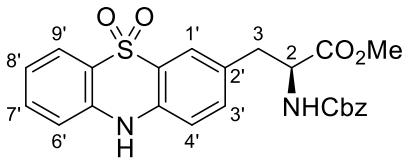
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-2'-yl)propanoate (169)



To an oven dried sealed tube was added *N*-(benzyloxycarbonyl)-[3'-(2''-bromophenylthio)]-L-4'-aminophenylalanine methyl ester (220 mg, 0.427 mmol), Brettphos Pd G3 (19.3 mg, 21.3 μmol), potassium phosphate tribasic (127 mg, 0.598 mmol) and dimethoxyethane (6 mL). The resulting reaction mixture was degassed under argon and stirred at 120 °C for 20 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in ethyl acetate then partitioned against 1 M aqueous sodium thiosulfate. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether 3:2) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-2'-yl)propanoate as a white solid (95.0 mg, 51%). ν_{max}/cm^{-1} (neat) 3337 (NH), 2955 (CH), 1709 (CO), 1528, 1478, 1292, 1037, 756; $[\alpha]_D^{22}$ −6.3 (*c* 0.1, DMSO); δ_H (400 MHz, DMSO-d_6) 2.68 (1H, dd, *J* 13.8, 10.3 Hz, 3-*H*H), 2.87 (1H, dd, *J* 13.8, 5.3 Hz, 3-H*H*), 3.63 (3H, s, OCH_3), 4.17 (1H, ddd, *J* 10.3, 8.3, 5.3 Hz, 2-H), 4.99 (2H, s, PhC*H*$_2$), 6.59 (1H, d, *J* 8.0 Hz, 4'-H), 6.68 (1H, dd, *J* 8.0, 1.3 Hz, 6'-H), 6.74 (1H, ddd, *J* 7.7, 7.4, 1.3 Hz, 8'-H), 6.80–6.86 (2H, m, 1'-H and 3'-H), 6.90 (1H, dd, *J* 7.7,

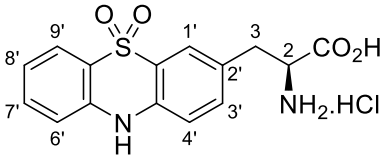
1.5 Hz, 9'-H), 6.98 (1H, ddd, *J* 8.0, 7.4, 1.5 Hz, 7'-H), 7.25–7.36 (5H, m, Ph), 7.76 (1H, d, *J* 8.3 Hz, 2-NH), 8.53 (1H, br s, 5'-H); δ_C (101 MHz, DMSO-*d*$_6$) 35.5 (CH_2), 51.9 (CH_3), 55.5 (CH), 65.3 (CH_2), 114.2 (CH), 114.4 (CH), 116.1 (C), 116.2 (C), 121.6 (CH), 126.2 (CH), 126.8 (CH), 127.4 (2 × CH), 127.5 (CH), 127.7 (CH), 128.2 (CH), 128.3 (2 × CH), 130.8 (C), 136.9 (C), 140.6 (C), 142.2 (C), 155.9 (C), 172.3 (C); *m/z* (ESI) 457.1196 (MNa^+. $C_{24}H_{22}N_2NaO_4S$ requires 457.1192).

Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-10',10'-dioxide-2'-yl)propanoate (170)



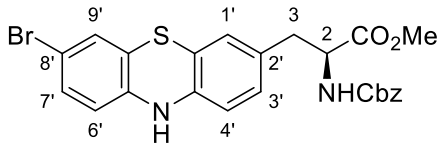
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-2'-yl)propanoate (30.0 mg, 69.0 μmol) was dissolved in dichloromethane (0.5 mL) with stirring under argon. Glacial acetic acid (109 μL, 1.90 mmol) was then added to the solution followed by 30% H_2O_2 (40.0 μL). The reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (20 mL). The organic layer was washed with water (20 mL) and the aqueous layer was further extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 1:1) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-10',10'-dioxide-2'-yl)propanoate as a red oil (20.0 mg, 63%). ν_{max}/cm^{-1} (neat) 3318 (NH), 2955 (CH), 1701 (CO), 1516, 1481, 1269, 1134, 729; $[\alpha]_D^{22}$ +53.6 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.01 (1H, dd, *J* 14.4, 6.5 Hz, 3-*H*H), 3.13 (1H, dd, *J* 14.4, 5.3 Hz, 3-H*H*), 3.76 (3H, s, OCH_3), 4.62 (1H, ddd, *J* 7.7, 6.5, 5.3 Hz, 2-H), 5.09 (2H, s, PhCH_2), 5.41 (1H, d, *J* 7.7 Hz, 2-NH), 6.73 (1H, d, *J* 8.3 Hz, 4'-H), 6.86 (1H, br d, *J* 8.4 Hz, 6'-H), 7.05–7.16 (2H, m, 3'-H and 8'-H), 7.27–7.41 (6H, m, 7'-H and Ph), 7.73 (1H, d, *J* 2.1 Hz, 1'-H), 7.89 (1H, br s, 5'-H), 7.97 (1H, dd, *J* 8.1, 1.6 Hz, 9'-H); δ_C (101 MHz, $CDCl_3$) 37.9 (CH_2), 52.9 (CH_3), 55.1 (CH), 67.4 (CH_2), 116.6 (CH), 117.0 (CH), 121.2 (C), 121.9 (CH), 123.3 (CH), 123.5 (CH), 128.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 128.7 (C), 129.9 (C), 133.1 (CH), 134.0 (CH), 136.1 (C), 136.8 (C), 137.6 (C), 155.9 (C), 171.7 (C); *m/z* (ESI) 467.1272 (MH^+. $C_{24}H_{23}N_2O_6S$ requires 467.1271).

(2*S*)-2-Amino-3-(phenothiazin-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (171)



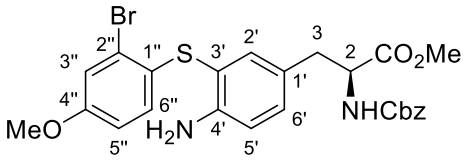
To a stirred solution of methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-10',10'-dioxide-2'-yl)propanoate (15 mg, 0.032 mmol) in methanol (1.0 mL), 1,4-dioxane (0.5 mL) and water (0.5 mL) was added cesium carbonate (14 mg, 0.042 mmol). The resulting reaction mixture was left to stir at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-10',10'-dioxide-2'-yl)propanoic acid as a white solid (11 mg, 76%). This was used for the next reaction without any further purification. A solution of (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-10',10'-dioxide-2'-yl)propanoic acid (10 mg, 22 μmol) in 6 M aqueous hydrochloric acid (2.5 mL) and 1,4-dioxane (0.5 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue recrystallised from methanol and diethyl ether to afford (2*S*)-2-amino-3-(phenothiazin-10',10'-dioxide-2'-yl)propanoic acid hydrochloride as an orange oil (7.0 mg, 90%). ν_{max}/cm^{-1} (neat) 3295 (NH), 2859 (CH), 1728 (CO), 1604 (C=C), 1481, 1253, 1122, 752; $[\alpha]_D^{21}$ −131.1 (*c* 0.1, MeOH); δ_H (400 MHz, CD_3OD) 3.25 (1H, dd, *J* 14.8, 7.6 Hz, 3-*H*H), 3.39 (1H, dd, *J* 14.8, 5.7 Hz, 3-H*H*), 4.28 (1H, dd, *J* 7.6, 5.7 Hz, 2-H), 7.25 (1H, ddd, *J* 8.2, 7.2, 1.0 Hz, 8'-H), 7.28–7.35 (2H, m, 4'-H and 6'-H), 7.57 (1H, dd, *J* 8.6, 2.1 Hz, 3'-H), 7.62 (1H, ddd, *J* 8.6, 7.2, 1.5 Hz, 7'-H), 7.90 (1H, d, *J* 2.1 Hz, 1'-H), 7.95 (1H, dd, *J* 8.2, 1.5 Hz, 9'-H); δ_C (101 MHz, CD_3OD) 36.6 (CH_2), 55.1 (CH), 118.0 (CH), 118.9 (CH), 122.1 (C), 122.2 (C), 122.8 (CH), 123.7 (CH), 124.5 (CH), 129.1 (C), 134.5 (CH), 135.5 (CH), 139.5 (C), 139.9 (C), 168.6 (C); *m/z* (ESI) 319.0747 (MH^+. $C_{15}H_{15}N_2O_4S$ requires 319.0747).

Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(8'-bromophenothiazin-2'-yl)propanoate (172)



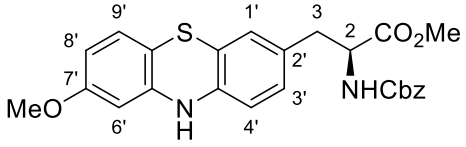
A solution of methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(phenothiazin-2'-yl)propanoate (35 mg, 0.081 mmol) in tetrahydrofuran (1 mL) was degassed under argon before being cooled to 0 °C. A solution of *N*-bromosuccinimide (16 mg, 0.089 mmol) was added dropwise and the resulting reaction mixture was warmed to room temperature and stirred for 20 h. The reaction mixture was diluted with ethyl acetate (20 mL) and extracted with 1 M aqueous sodium thiosulfate (20 mL). The aqueous layer was further extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/diethyl ether, 2:3) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(8'-bromophenothiazin-2'-yl)propanoate as a yellow oil (12 mg, 29%).ν_{max}/cm^{-1} (neat) 3324 (NH), 2949 (CH), 1696 (CO), 1498, 1462, 1291, 1056, 807; $[\alpha]_D^{18}$ −4.9 (*c* 0.1, DMSO); δ_H (400 MHz, DMSO-*d*$_6$) 2.67 (1H, dd, *J* 13.8, 10.2 Hz, 3-*H*H), 2.87 (1H, dd, *J* 13.8, 4.8 Hz, 3-H*H*), 3.62 (3H, s, CO_2CH_3), 4.17 (1H, ddd, *J* 10.2, 8.3, 4.8 Hz, 2-H), 4.98 (2H, s, PhCH_2), 6.55–6.62 (2H, m, 4'-H and 6'-H), 6.79–6.90 (2H, m, 1'-H and 3'-H), 7.08–7.15 (2H, m, 7'-H and 9'-H), 7.24–7.36 (5H, m, Ph), 7.76 (1H, d, *J* 8.3 Hz, 2-NH), 8.67 (1H, s, 5'-H); δ_C (101 MHz, DMSO-*d*$_6$) 35.5 (CH_2), 51.9 (CH_3), 55.4 (CH), 65.3 (CH_2), 112.2 (C), 114.4 (CH), 115.3 (C), 115.8 (CH), 118.9 (C), 126.9 (CH), 127.4 (2 × CH), 127.7 (CH), 128.1 (CH), 128.3 (2 × CH), 128.5 (CH), 130.1 (CH), 131.2 (C), 136.9 (C), 140.0 (C), 141.6 (C), 155.9 (C), 172.3 (C); *m/z* (ESI) 535.0294 (MNa^+. $C_{24}H_{21}{}^{79}BrN_2NaO_4S$ requires 535.0298).

_N_-(Benzyloxycarbonyl)-[3'-(2''-bromo-4''-methoxyphenylthio)]-L-4'-aminophenylalanine methyl ester (173)



The reaction was performed as described in general procedure G using methyl (2*S*)-2-(benzyloxycarbonylamino)-3-(*p*-aminophenyl)propanoate (208 mg, 0.633 mmol). The reaction mixture was stirred at 90 °C for 20 h. Purification by flash column chromatography (hexane/ethyl acetate, 7:3) gave *N*-(benzyloxycarbonyl)-[3'-(2''-bromo-4''-methoxyphenylthio)]-L-4'-aminophenylalanine methyl ester as a colourless oil (292 mg, 49%). ν_{max}/cm^{-1} (neat) 3356 (NH), 2951 (CH), 1709 (CO), 1616 (C=C), 1497, 1219, 1011, 752; $[\alpha]_D^{24}$ +33.1 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.97 (1H, dd, *J* 14.0, 5.6 Hz, 3-*H*H), 3.03 (1H, dd, *J* 14.0, 5.7 Hz, 3-H*H*), 3.68 (3H, s, CO_2CH_3), 3.72 (3H, s, 4''-OCH_3), 4.25 (2H, br s, 4'-NH_2), 4.60 (1H, ddd, *J* 8.2, 5.7, 5.6 Hz, 2-H), 5.09 (2H, s, PhCH_2), 5.23 (1H, d, *J* 8.2 Hz, 2-NH), 6.61 (1H, d, *J* 8.8 Hz, 6''-H), 6.66–6.71 (2H, m, 5'-H and 5''-H), 6.97 (1H, dd, *J* 8.2, 2.1 Hz, 6'-H), 7.10 (1H, d, *J* 2.6 Hz, 3''-H), 7.16 (1H, d, *J* 2.1 Hz, 2'-H), 7.28–7.38 (5H, m, Ph); δ_C (101 MHz, $CHCl_3$) 37.4 (CH_2), 52.5 (CH_3), 55.1 (CH), 55.7 (CH_3), 67.1 (CH_2), 114.7 (CH), 115.0 (C), 115.8 (CH), 118.5 (CH), 122.3 (C), 126.0 (C), 128.2 (CH), 128.3 (2 × CH), 128.6 (CH), 128.7 (2 × CH), 128.7 (C), 132.3 (CH), 136.4 (C), 138.0 (CH), 147.9 (C), 155.7 (C), 158.4 (C), 172.0 (C); *m/z* (ESI) 545.0747 (MH^+. $C_{25}H_{26}{}^{79}BrN_2O_5S$ requires 545.0740).

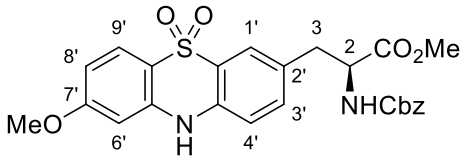
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-2'-yl)propanoate (174)



To an oven dried sealed tube was added *N*-(benzyloxycarbonyl)-[3'-(2''-bromo-4''-methoxyphenylthio)]-L-4'-aminophenylalanine methyl ester (160 mg, 0.293 mmol), $Pd_2(dba)_3$ (30.3 mg, 0.0293 mmol), CyJohnPhos (10.3 mg, 0.0293 mmol),

potassium phosphate tribasic (87.0 mg, 0.410 mmol) and 1,2-dimethoxyethane (2 mL). The resulting reaction mixture was degassed under argon before being left to stir at 120 °C for 20 h. The reaction mixture was filtered through celite and the filtrate concentrated *in vacuo*. The resulting residue was diluted with ethyl acetate (20 mL) and washed with 1 M aqueous sodium thiosulfate (20 mL). The aqueous layer was further extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate, 1:1) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-2'-yl)propanoate as a white solid (68 mg, 50%). Product was found to be unstable and therefore used directly in the next step without characterisation.

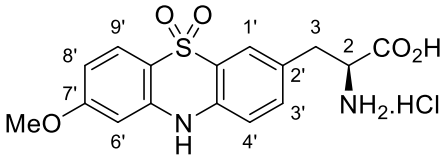
Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoate (175)



Methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-2'-yl)propanoate (60.0 mg, 0.129 mmol) was dissolved in dichloromethane (1 mL) with stirring under argon. Glacial acetic acid (0.203 mL, 3.55 mmol) was then added to the solution followed by 30% H_2O_2 (0.073 mL). The reaction mixture was stirred at 50 °C for 18 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (20 mL). The organic layer was washed with water (20 mL) and the aqueous layer was further extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexane/ethyl acetate 1:1) gave methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoate as a red oil (23.0 mg, 36%). ν_{max}/cm^{-1} (neat) 3314 (NH), 2951 (CH), 1701 (CO), 1613, 1485, 1269, 1130, 756; $[\alpha]_D^{22}$ +67.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.99 (1H, dd, *J* 14.2, 7.0 Hz, 3-*H*H), 3.12 (1H, dd, *J* 14.2, 5.1 Hz, 3-H*H*), 3.72 (3H, s, CO_2CH_3), 3.76 (3H, s, 7'-OCH_3), 4.61 (1H, ddd, *J* 7.9, 7.0, 5.1 Hz, 2-H), 5.09 (2H, s, PhCH_2), 5.47 (1H, d, *J* 7.9 Hz, 2-NH), 6.19 (1H, d, *J* 2.4 Hz, 6'-H), 6.55–6.69 (2H, m, 3'-H and 4'-H), 7.06

(1H, dd, *J* 9.0, 2.4 Hz, 8'-H), 7.27–7.35 (5H, m, Ph), 7.71 (1H, d, *J* 2.1 Hz, 1'-H), 7.84 (1H, d, *J* 9.0 Hz, 9'-H), 7.95 (1H, br s, 5'-H); δ_C (101 MHz, $CHCl_3$) 37.8 (CH_2), 52.8 (CH_3), 55.1 (CH), 55.7 (CH_3), 67.4 (CH_2), 99.3 (CH), 110.6 (CH), 113.8 (CH), 117.0 (C), 121.5 (C), 123.2 (C), 124.8 (CH), 128.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 129.8 (C), 133.8 (C), 136.1 (C), 136.8 (CH), 139.5 (CH), 155.9 (C), 163.2 (C), 171.8 (C); *m/z* (ESI) 519.1201 (MNa^+. $C_{25}H_{24}N_2NaO_7S$ requires 519.1196).

(2*S*)-2-Amino-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoic acid hydrochloride (176)



To a stirred solution of methyl (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoate (15 mg, 0.030 mmol) in methanol (1.0 mL), 1,4-dioxane (0.5 mL) and water (0.5 mL) was added cesium carbonate (13 mg, 0.039 mmol). The resulting reaction mixture was left to stir at room temperature for 20 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoic acid as a white solid (12 mg, 82%). This was used for the next reaction without any further purification. A solution of (2*S*)-2-[(benzyloxycarbonyl)amino]-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoic acid (10 mg, 22 μmol) in 6 M aqueous hydrochloric acid (2.5 mL) and 1,4-dioxane (0.5 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue recrystallised from methanol and diethyl ether to afford (2*S*)-2-amino-3-(7'-methoxyphenothiazin-10',10'-dioxide-2'-yl)propanoic acid hydrochloride as an orange oil (7.0 mg, 88%). ν_{max}/cm^{-1} (neat) 3318 (NH), 2858 (CH), 1612 (CO), 1589 (C=C), 1489, 1258, 1123, 829; $[\alpha]_D^{22}$ −15.2 (*c* 0.1, MeOH); δ_H (400 MHz, CD_3OD) 3.24 (1H, dd, *J* 14.7, 7.6 Hz, 3-*H*H), 3.38 (1H, dd, *J* 14.7, 5.5 Hz, 3-H*H*), 3.90 (3H, s, 7'-OCH_3), 4.28 (1H, dd, *J* 7.6, 5.5 Hz, 2-H), 6.75 (1H, d, *J* 2.3 Hz, 6'-H), 6.84 (1H, dd, *J* 9.0, 2.3 Hz, 8'-H), 7.29 (1H, d, *J* 8.6 Hz, 4'-H), 7.54 (1H, dd, *J* 8.6, 2.1 Hz, 3'-

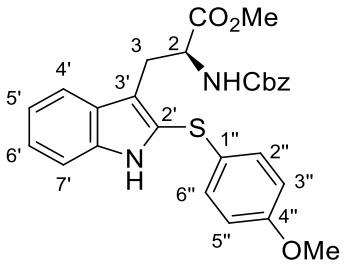
H), 7.85 (1H, d, *J* 9.0 Hz, 9'-H), 7.87 (1H, d, *J* 2.1 Hz, 1'-H); δ_C (101 MHz, $CHCl_3$) 36.5 (CH_2), 55.0 (CH), 56.2 (CH_3), 100.4 (CH), 111.6 (CH), 114.9 (C), 118.8 (CH), 122.7 (C), 124.4 (CH), 125.6 (CH), 129.0 (C), 135.3 (CH), 139.6 (C), 141.8 (C), 165.1 (C), 171.1 (C); *m/z* (ESI) 349.0853 (MH^+. $C_{16}H_{17}N_2O_5S$ requires 349.0853).

6.5 Tryptophan Derived Fluorescent Amino Acids Experimental

General Procedure K: Preparation of Sulfenylated Products

Iron(III) trichloride (10 mol%) was dissolved in $[BMIM]NTf_2$ (30 mol%) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(2-bromophenylthio)succinimide (1.2 equiv.) in chloroform (0.6 M in arene). The arene (1.0 equiv.) and diphenyl selenide (10 mol%) was then added and the mixture was left to stir at 90 °C, until the reaction was deemed complete. The reaction mixture was concentrated *in vacuo* and purified using flash column chromatography.

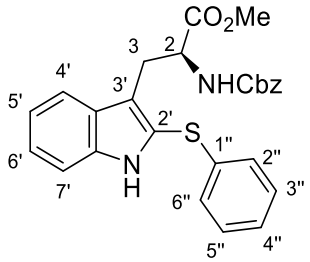
N-[(Benzyloxycarbonyl)amino]-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (196a)



Iron(III) trichloride (9.21 mg, 0.0568 mmol) was dissolved in $[BMIM]NTf_2$ (0.0495 mL, 0.170 mmol) and stirred for 0.5 h at room temperature before being added to a solution of *N*-(4-methoxyphenylthio)succinimide (161 mg, 0.681 mmol) in chloroform (2 mL). *N*-[(Benzyloxycarbonyl)amino]-L-tryptophan methyl ester (200 mg, 0.568 mmol) and diphenyl selenide (0.00980 mL, 0.0568 mmol) were then added and the mixture was left to stir at 90 °C for 20 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave *N*-[(benzyloxycarbonyl)amino]-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (200 mg, 72%) as a white solid. Mp 210−212 °C; ν_{max}/cm^{-1} (neat) 3331 (NH), 2954 (CH), 1698 (CO), 1491, 1242, 1025, 741; $[\alpha]_D^{23}$ +26.8 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.36 (1H, dd, *J* 14.3, 6.0 Hz, 3-*H*H), 3.44 (1H, dd, *J* 14.3, 5.7 Hz, 3-H*H*), 3.69 (3H, s, CO_2CH_3), 3.73 (3H, s, 4''-OCH_3), 4.72 (1H, ddd, *J* 8.1, 6.0, 5.7 Hz, 2-H), 5.05 (1H, d, *J* 15.9 Hz, PhC*H*H), 5.09

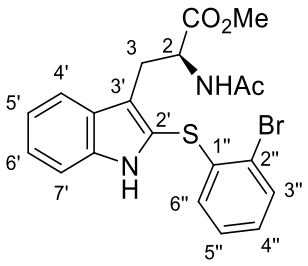
(1H, d, *J* 15.9 Hz, PhCH*H*), 5.37 (1H, d, *J* 8.1 Hz, 2-NH), 6.76 (2H, d, *J* 8.9 Hz, 3''-H and 5''-H), 7.06–7.38 (10H, m, 5'-H, 6'-H, 7'-H, 2''-H, 6''-H and Ph), 7.55 (1H, br d, *J* 8.2 Hz, 4'-H), 7.99 (1H, s, 1'-H); δ_C (101 MHz, $CDCl_3$) 27.9 (CH_2), 52.6 (CH_3), 54.6 (CH), 55.5 (CH_3), 67.0 (CH_2), 111.0 (CH), 115.1 (2 × CH), 115.6 (C), 119.1 (CH), 120.3 (CH), 123.4 (CH), 125.7 (C), 126.2 (C), 128.1 (C), 128.2 (2 × CH), 128.2 (CH), 128.6 (2 × CH), 130.8 (2 × CH), 136.5 (C), 136.9 (C), 155.8 (C), 159.1 (C), 172.4 (C); *m/z* (ESI) 489.1490 ($M-H^-$. $C_{27}H_{25}N_2O_5S$ requires 489.1490).

N-[(Benzyloxycarbonyl)amino]-[2'-(phenylthio)]-L-tryptophan methyl ester (196b)



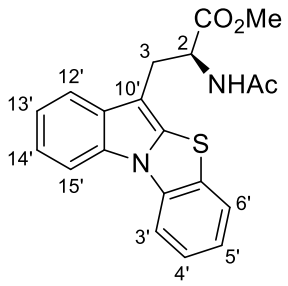
Iron(III) trichloride (9.21 mg, 0.0568 mmol) was dissolved in [BMIM]NTf_2 (0.0495 mL, 0.170 mmol) and left to stir for 0.5 h at room temperature before being added to a solution of *N*-(phenylthio)succinimide (141 mg, 0.681 mmol) in chloroform (2 mL). *N*-[(Benzyloxycarbonyl)amino]-L-tryptophan methyl ester (200 mg, 0.568 mmol) and diphenyl selenide (0.00980 mL, 0.0568 mmol) were then added and the mixture was left to stir at 90 °C for 20 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave *N*-[(benzyloxycarbonyl)amino]-[2'-(phenylthio)]-L-tryptophan methyl ester (141 mg, 54%) as a white solid. Mp 216−218 °C; ν_{max}/cm^{-1} (neat) 3320 (NH), 3061 (CH), 1696 (CO), 1505, 1438, 1338, 1023, 736; $[\alpha]_D^{24}$ +25.5 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.35 (1H, dd, *J* 14.4, 6.5 Hz, 3-*H*H), 3.44 (1H, dd, *J* 14.4, 5.8 Hz, 3-H*H*), 3.67 (3H, s, CO_2CH_3), 4.72 (1H, ddd, *J* 8.1, 6.5, 5.8 Hz, 2-H), 5.02 (1H, d, *J* 15.0 Hz, PhC*H*H), 5.07 (1H, d, *J* 15.0 Hz, PhCH*H*), 5.33 (1H, d, *J* 8.1 Hz, 2-NH), 7.01–7.07 (2H, m, 2''-H and 6''-H), 7.08–7.38 (11H, m, 5'-H, 6'-H, 7'-H, 3''-H, 4''-H, 5''-H and Ph), 7.60 (1H, br d, *J* 8.0 Hz, 4'-H), 8.12 (1H, s, 1'-H); δ_C (101 MHz, $CDCl_3$) 28.0 (CH_2), 52.6 (CH_3), 54.6 (CH), 67.0 (CH_2), 111.2 (CH), 117.5 (C), 119.4 (CH), 120.4 (CH), 123.9 (CH), 124.0 (C), 126.4 (CH), 127.2 (2 × CH), 128.0 (C), 128.2 (2 × CH), 128.3 (CH), 128.6 (2 × CH), 129.4 (2 × CH), 136.3 (C), 136.5 (C), 137.1 (C), 155.8 (C), 172.4 (C); *m/z* (ESI) 461.1531 (MH^+. $C_{26}H_{25}N_2O_4S$ requires 461.1530).

***N*-Acetyl-[2'-(2''-bromophenylthio)]-L-tryptophan methyl ester (196c)**



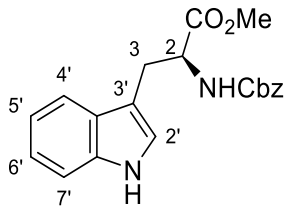
The reaction was performed as described in general procedure K using *N*-acetyl-L-tryptophan methyl ester (200 mg, 0.768 mmol). The reaction mixture was stirred at 90 °C for 24 h. Purification by flash column chromatography (dichloromethane/methanol, 99:1) gave *N*-acetyl-[2'-(2''-bromophenylthio)]-L-tryptophan methyl ester (253 mg, 74%) as a white solid. Mp 158−160 °C; ν_{max}/cm^{-1} (neat) 3237 (NH), 2951 (CH), 1732 (CO), 1651 (CO), 1520, 1427, 1215, 1018, 740; $[\alpha]_D^{24}$ +46.6 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.82 (3H, s, NHCOC*H*$_3$), 3.33 (1H, dd, *J* 14.5, 5.5 Hz, 3-*H*H), 3.44 (1H, dd, *J* 14.5, 5.5 Hz, 3-H*H*), 3.70 (3H, s, CO_2CH_3), 4.92 (1H, dt, *J* 7.9, 5.5 Hz, 2-H), 6.00 (1H, d, *J* 7.9 Hz, 2-NH), 6.53 (1H, dd, *J* 8.0, 1.6 Hz, 6''-H), 7.00 (1H, ddd, *J* 7.9, 7.3, 1.6 Hz, 4''-H), 7.09 (1H, ddd, *J* 8.0, 7.3, 1.4 Hz, 5''-H), 7.18 (1H, ddd, *J* 8.2, 7.0, 1.1 Hz, 5'-H), 7.29 (1H, ddd, *J* 8.2, 7.0, 1.1 Hz, 6'-H), 7.34 (1H, dt, *J* 8.2, 1.1 Hz, 7'-H), 7.52 (1H, dd, *J* 7.9, 1.4 Hz, 3''-H), 7.63 (1H, dd, *J* 8.2, 1.1 Hz, 4'-H), 8.25 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 23.2 (CH_3), 27.5 (CH_2), 52.7 (CH_3), 52.9 (CH), 111.4 (CH), 119.2 (C), 119.6 (CH), 120.2 (C), 120.6 (CH), 122.0 (C), 124.3 (CH), 127.0 (CH), 127.1 (CH), 128.2 (C), 128.3 (CH), 133.1 (CH), 137.4 (C), 138.4 (C), 169.9 (C), 172.3 (C); *m/z* (ESI) 447.0378 (MH^+. $C_{20}H_{20}{}^{79}BrN_2O_3S$ requires 447.0373).

Methyl (2*S*)-2-acetamido-3-{8-thia-1-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (197)



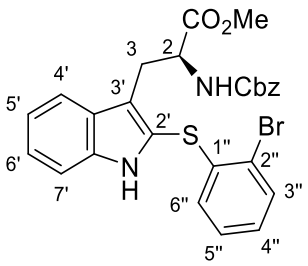
To a solution of *N*-acetyl-[2'-(2''-bromophenylthio)]-L-tryptophan methyl ester (230 mg, 0.514 mmol) in dimethylacetamide (15 mL) was added copper(I) thiophene-2-carboxylate (98 mg, 0.514 mmol). The reaction mixture was degassed under argon then stirred at 110 °C for 20 h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate and washed with 5% aqueous lithium chloride (50 mL). The aqueous layer was further extracted with ethyl acetate (2 × 30 mL) and the combined organic layers were washed with 5% aqueous lithium chloride (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate 3:2) gave methyl (2*S*)-2-acetamido-3-{8-thia-1-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2(7),3,5,9,11,13,15-heptaen-10-yl}propanoate as an orange solid (160 mg, 85%). Mp 211−213 °C; ν_{max}/cm^{-1} (neat) 3295 (NH), 2924 (CH), 1732 (CO), 1643 (CO), 1535, 1478, 1373, 1215, 733; $[\alpha]_D^{20}$ +72.0 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.02 (3H, s, NHCOC*H*$_3$), 3.42 (1H, dd, *J* 14.9, 4.4 Hz, 3-*H*H), 3.47 (1H, dd, *J* 14.9, 4.9 Hz, 3-H*H*), 3.72 (3H, s CO_2CH_3), 5.04 (1H, ddd, *J* 7.7, 4.9, 4.4 Hz, 2-H), 6.16 (1H, d, *J* 7.7 Hz, NH), 7.23 (1H, ddd, *J* 8.1, 7.4, 1.1 Hz, 5'-H), 7.26–7.32 (2H, m, 13'-H and 14'-H), 7.44 (1H, ddd, *J* 8.1, 7.4, 1.3 Hz, 4'-H), 7.55 (1H, ddd, *J* 6.0, 3.2, 0.8 Hz, 12'-H), 7.59 (1H, dd, *J* 8.1, 1.3 Hz, 6'-H), 7.90 (1H, dd, *J* 8.1, 1.1 Hz, 3'-H), 7.92–7.99 (1H, m, 15'-H); δ_C (101 MHz, $CDCl_3$) 23.5 (CH_2), 27.9 (CH), 52.9 (CH_3), 52.9 (CH_3), 100.3 (C), 111.2 (CH), 112.2 (CH), 118.0 (CH), 120.9 (CH), 121.6 (CH), 123.2 (CH), 123.9 (CH), 126.4 (CH), 130.1 (C), 131.3 (C), 133.1 (C), 135.2 (C), 136.1 (C), 169.9 (C), 172.2 (C); *m/z* (ESI) 367.1110 (MH^+. $C_{20}H_{19}N_2O_3S$ requires 367.1111).

(2*S*)-*N*-Benzyloxycarbonyl-L-tryptophan methyl ester (195)[232]



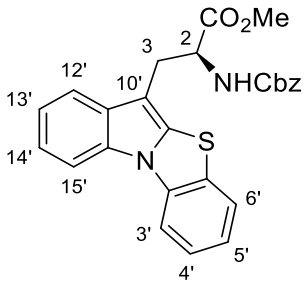
To a solution of L-tryptophan methyl ester hydrochloride (2.00 g, 7.85 mmol) and sodium hydrogen carbonate (3.30 g, 39.3 mmol) in water (20 mL) and dichloromethane (60 mL) at 0 °C, was added benzyl chloroformate (1.23 mL, 8.64 mmol) dropwise. The reaction mixture was warmed to room temperature and left to stir for 2 h. The two layers were separated and the aqueous layer was further extracted with dichloromethane (2 × 30 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 2:3) gave (2*S*)-*N*-benzyloxycarbonyl-L-tryptophan methyl ester as a colourless oil (2.77 g, 100%). Spectroscopic data were consistent with the literature.[232] $[\alpha]_D^{23}$ +49.0 (*c* 0.1, $CHCl_3$), lit.[232] $[\alpha]_D^{20}$ +47.6 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.32 (2H, d, *J* 5.5 Hz, 3-H_2), 3.68 (3H, s, CO_2CH_3), 4.73 (1H, dt, *J* 8.3, 5.5 Hz, 2-H), 5.09 (1H, d, *J* 12.3 Hz, PhC*H*H), 5.14 (1H, d, *J* 12.3 Hz, PhCH*H*), 5.34 (1H, d, *J* 8.3 Hz, 2-NH), 6.94 (1H, d, *J* 2.5 Hz, 2'-H), 7.10 (1H, ddd, *J* 8.1, 7.2, 1.1 Hz, 5'-H), 7.19 (1H, ddd, *J* 8.1, 7.0, 1.3 Hz, 6'-H), 7.26–7.42 (6H, m, 7'-H and Ph), 7.53 (1H, dd, *J* 7.2, 1.3 Hz, 4'-H), 8.13 (1H, br s, 1'-H); δ_C (101 MHz, $CDCl_3$) 28.1 (CH_2), 52.5 (CH_3), 54.6 (CH), 67.0 (CH_2), 110.0 (C), 111.4 (CH), 118.7 (CH), 119.8 (CH), 122.4 (CH), 122.9 (CH), 127.7 (C), 128.2 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 136.2 (C), 136.4 (C), 155.9 (C), 172.5 (C); *m/z* (ESI) 375 (MNa^+. 100%).

_N_-[(Benzyloxycarbonyl)amino]-[2'-(2''-bromophenylthio)]-L-tryptophan methyl ester (196d)



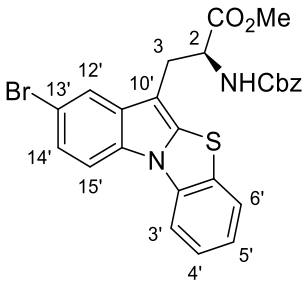
The reaction was performed as described in general procedure K using *N*-[(benzyloxycarbonyl)amino]-L-tryptophan methyl ester (1.15 g, 3.26 mmol). The reaction mixture was stirred at 90 °C for 18 h. Purification by flash column chromatography (hexane/ethyl acetate, 4:1) gave *N*-[(benzyloxycarbonyl)amino]-[2'-(2''-bromophenylthio)]-L-tryptophan methyl ester (1.54 g, 88%) as a white solid. Mp 82−84 °C; ν_{max}/cm^{-1} (neat) 3295 (NH), 2951 (CH), 1698 (CO), 1506, 1444, 1343, 1209, 741; $[\alpha]_D^{24}$ +33.5 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.33 (1H, dd, *J* 14.4, 6.4 Hz, 3-*H*H), 3.45 (1H, dd, *J* 14.4, 5.7 Hz, 3-H*H*), 3.69 (3H, s, CO_2CH_3), 4.72 (1H, ddd, *J* 8.7, 6.4, 5.7 Hz, 2-H), 5.05 (2H, s, PhCH_2), 5.30 (1H, d, *J* 8.7 Hz, 2-NH), 6.50 (1H, dd, *J* 7.8, 1.7 Hz, 7'-H), 6.93 (1H, ddd, *J* 7.8, 7.5, 1.7 Hz, 5'-H), 7.01 (1H, ddd, *J* 7.8, 7.5, 1.5 Hz, 6'-H), 7.15 (1H, ddd, *J* 8.2, 6.9, 1.2 Hz, 4''-H), 7.27–7.38 (7H, m, 5''-H, 6''-H and Ph), 7.48 (1H, dd, *J* 7.8, 1.5 Hz, 4'-H), 7.63 (1H, br d, *J* 8.2 Hz, 3''-H), 8.17 (1H, br s, 1'-H); δ_C (101 MHz, $CDCl_3$) 27.9 (CH_2), 52.7 (CH_3), 54.5 (CH), 67.0 (CH_2), 111.4 (CH), 119.0 (C), 119.6 (CH), 120.2 (C), 120.6 (CH), 122.4 (C), 124.3 (CH), 127.0 (CH), 127.1 (CH), 128.0 (C), 128.2 (CH), 128.2 (2 × CH), 128.2 (CH), 128.6 (2 × CH), 133.0 (CH), 136.4 (C), 137.4 (C), 138.3 (C), 155.8 (C), 172.2 (C); *m/z* (ESI) 561.0460 (MNa^+. $C_{26}H_{23}{}^{79}BrN_2NaO_4S$ requires 561.0454).

Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (198)



To a solution of *N*-[(benzyloxycarbonyl)amino]-[2'-(2''-bromophenylthio)]-L-tryptophan methyl ester (845 mg, 1.57 mmol) in dimethylacetamide (45 mL) was added copper(I) thiophene-2-carboxylate (299 mg, 1.57 mmol). The reaction mixture was degassed under argon then stirred at 110 °C for 6 h. The reaction mixture was cooled to room temperature, extracted with ethyl acetate (50 mL) and washed with 5% aqueous lithium chloride (50 mL). The aqueous layer was further extracted with ethyl acetate (2 × 30 mL) and the combined organic layers were washed with 5% aqueous lithium chloride (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane 2:3) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as a white solid (581 mg, 81%). Mp 211−213 °C; ν_{max}/cm^{-1} (neat) 3315 (NH), 2950 (CH), 1699 (CO), 1505, 1473, 1208, 1054, 732; $[\alpha]_D^{24}$ +73.1 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.44 (2H, d, *J* 5.0 Hz, 3-H_2), 3.70 (3H, s, CO_2CH_3), 4.82 (1H, dt, *J* 8.1, 5.0 Hz, 2-H), 5.11 (1H, d, *J* 12.4 Hz, PhC*H*H), 5.22 (1H, d, *J* 12.4 Hz, PhCH*H*), 5.46 (1H, d, *J* 8.1 Hz, NH), 7.20–7.30 (3H, m, 4'-H, 13'-H and 14'-H), 7.30–7.40 (5H, m, Ph), 7.44 (1H, ddd, *J* 8.1, 7.4, 1.2 Hz, 5'-H), 7.50–7.62 (2H, m, and 3'-H and 15'-H), 7.91 (1H, ddd, *J* 8.1, 1.1, 0.6 Hz, 6'-H), 7.93–7.97 (1H, m, 12'-H); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 52.9 (CH_3), 54.6 (CH), 67.1 (CH_2), 100.1 (C), 111.1 (CH), 112.2 (CH), 118.0 (CH), 120.8 (CH), 121.6 (CH), 123.1 (CH), 123.9 (CH), 126.3 (CH), 128.3 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 130.2 (C), 131.3 (C), 133.0 (C), 135.5 (C), 136.1 (C), 136.5 (C), 155.8 (C), 172.1 (C); *m/z* (ESI) 459.1369 (MH^+. $C_{26}H_{23}N_2O_4S$ requires 459.1373).

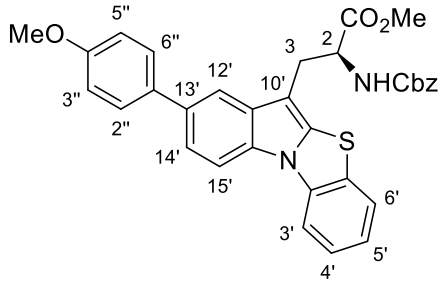
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (199)



To a solution of methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{8-thia-1-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2(7),3,5,9,11,13,15-heptaen-10-yl}propanoate (585 mg, 1.28 mmol) in anhydrous acetonitrile (100 mL) was added 11 drops of hydrobromic acid (48% in acetic acid) and the resulting reaction mixture was stirred at room temperature for 10 minutes. To the reaction mixture was added a solution of *N*-bromosuccinimide (238 mg, 1.34 mmol) in acetonitrile (20 mL) dropwise over 10 minutes. The resulting reaction mixture was left to stir at room temperature in the dark for 4 h. The reaction mixture was concentrated *in vacuo*, diluted with dichloromethane (30 mL) and washed with saturated aqueous ammonium chloride (30 mL). The aqueous layer was further extracted with dichloromethane (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 2:3) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as an off-white solid (541 mg, 79%). Mp 177−179 °C; ν_{max}/cm^{-1} (neat) 3307 (NH), 2947 (CH), 1736 (CO), 1687 (CO), 1527, 1479, 1292, 735; $[\alpha]_D^{23}$ +66.9 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.35 (1H, dd, *J* 14.9, 4.6 Hz, 3-*H*H), 3.40 (1H, dd, *J* 14.9, 5.6 Hz, 3-H*H*), 3.70 (3H, s, CO_2CH_3), 4.79 (1H, ddd, *J* 7.9, 5.6, 4.6 Hz, 2-H), 5.09 (1H, d, *J* 12.2 Hz, PhC*H*H), 5.22 (1H, d, *J* 12.2 Hz, PhCH*H*), 5.44 (1H, d, *J* 7.9 Hz, NH), 7.22–7.40 (8H, m, 4'-H, 14'-H, 15'-H and Ph), 7.45 (1H, td, *J* 7.9, 1.2 Hz, 5'-H), 7.55 (1H, dd, *J* 7.9, 1.2 Hz, 3'-H), 7.83 (1H, br d, *J* 7.9 Hz, 6'-H), 8.06 (1H, d, *J* 1.5 Hz, 12'-H); δ_C (101 MHz, $CDCl_3$) 28.2 (CH_2), 53.0 (CH_3), 54.6 (CH), 67.1 (CH_2), 100.4 (C), 112.3 (CH), 114.1 (CH), 114.1 (C), 119.1 (CH), 123.6 (CH), 124.0 (CH), 124.7 (CH), 126.5 (CH), 128.4 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 130.2 (C), 131.7 (C), 131.7 (C), 135.6 (C),

136.2 (C), 136.5 (C), 155.7 (C), 171.9 (C); *m/z* (ESI) 559.0295 (MNa^+. $C_{26}H_{21}{}^{79}BrN_2NaO_4S$ requires 559.0298).

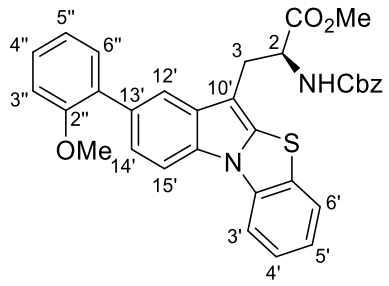
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-methoxyphenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200a)



To a microwave vial containing methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (100 mg, 0.225 mmol) and water (2 mL) was added 4-methoxyphenylboronic acid (51.2 mg, 0.337 mmol) and potassium phosphate tribasic (95.5 mg, 0.450 mmol). The reaction mixture was degassed under argon prior to the addition of Xphos Pd G2 (8.85 mg, 0.0113 mmol) and tetrahydrofuran (2 mL). The reaction mixture was heated to 60 °C and left to stir for 1 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 2:3 + 0.5% ethyl acetate) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-methoxyphenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as an off-white solid (84.0 mg, 80%). Mp 143−145 °C; ν_{max}/cm^{-1} (neat) 3304 (NH), 2954 (CH), 1688 (CO), 1516, 1474, 1245, 735; $[\alpha]_D^{22}$ +58.8 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.42 (1H, dd, *J* 15.1, 5.0 Hz, 3-*H*H), 3.47 (1H, dd, *J* 15.1, 4.6 Hz, 3-H*H*), 3.73 (3H, s, CO_2CH_3), 3.89 (3H, s, 4''-OCH_3), 4.83 (1H, ddd, *J* 8.1, 5.0, 4.6 Hz, 2-H), 5.11 (1H, d, *J* 12.2 Hz, PhC*H*H), 5.24 (1H, d, *J* 12.2 Hz, PhCH*H*), 5.49 (1H, d, *J* 8.1 Hz, NH), 7.02–7.07 (2H, m, 3''-H and 5''-H), 7.23 (1H, td, *J* 7.6, 1.0 Hz, 4'-H), 7.31–7.40 (5H, m, Ph), 7.42–7.47 (2H, m, 5'-H and 14'-H), 7.51–7.59 (2H, m, 3'-H and 15'-H), 7.61–7.65 (2H, m, 2''-H and 6''-H), 7.95 (1H, dd, *J* 8.3, 1.0 Hz, 6'-H), 8.06 (1H, d, *J* 1.6 Hz, 12'-

H); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 52.9 (CH_3), 54.6 (CH), 55.5 (CH_3), 67.1 (CH_2), 100.1 (C), 109.4 (CH), 112.2 (CH), 114.4 (2 × CH), 118.2 (CH), 121.1 (CH), 123.2 (CH), 123.9 (CH), 126.3 (CH), 128.3 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 128.6 (2 × CH), 130.3 (C), 131.8 (C), 132.0 (C), 134.2 (C), 134.8 (C), 135.7 (C), 136.1 (C), 136.5 (C), 155.8 (C), 159.0 (C), 172.1 (C); *m/z* (ESI) 587.1622 (MNa^+. $C_{33}H_{28}N_2NaO_5S$ requires 587.1611).

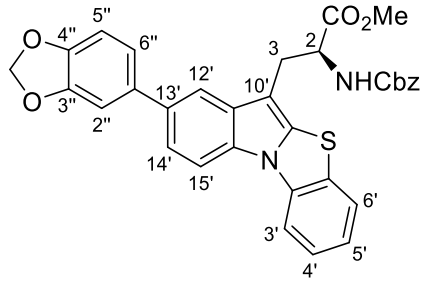
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(2''-methoxyphenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200b)



To a microwave vial containing methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (60.0 mg, 0.112 mmol) and water (1 mL) was added 2-methoxyphenylboronic acid (25.0 mg, 0.167 mmol) and potassium phosphate tribasic (48.0 mg, 0.224 mmol). The reaction mixture was degassed under argon prior to the addition of Xphos Pd G2 (4.50 mg, 0.00575 mmol) and tetrahydrofuran (1 mL). The reaction mixture was heated to 60 °C and left to stir for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 2:3 + 0.5% ethyl acetate) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(2''-methoxyphenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as a yellow solid (51.0 mg, 79%). Mp 129−131 °C; ν_{max}/cm^{-1} (neat) 3435 (NH), 3065 (CH), 2359, 1707 (CO), 1504, 1350, 1180, 1027, 699; $[\alpha]_D^{24}$ +60.1 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.46 (1H, dd, *J* 15.0, 5.1 Hz, 3-*H*H), 3.49 (2 H, dd, *J* 15.0, 5.3 Hz, 3-H*H*), 3.74 (3H, s, CO_2CH_3), 3.86 (3H, s, 2''-OCH_3), 4.85 (1H, ddd, *J* 8.1, 5.3, 5.1 Hz, 2-H), 5.13 (1H,

d, *J* 12.3 Hz, PhC*H*H), 5.24 (1H, d, *J* 12.3 Hz, PhCH*H*), 5.51 (1H, d, *J* 8.1 Hz, NH), 7.06 (1H, dd, *J* 8.0, 1.5 Hz, 14'-H), 7.11 (1H, td, *J* 7.4, 1.1 Hz, 5''-H), 7.22 (1H, td, *J* 8.0, 0.9 Hz, 5'-H), 7.31–7.47 (9H, m, 4'-H, 3''-H, 4''-H, 6''-H and Ph), 7.52–7.61 (2H, m, 3'-H and 15'-H), 7.91 (1H, br d, *J* 8.0 Hz, 6'-H), 8.14 (1H, d, *J* 1.5 Hz, 12'-H); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 52.9 (CH_3), 54.6 (CH), 55.8 (CH_3), 67.0 (CH_2), 100.2 (C), 111.6 (CH), 112.2 (CH), 112.3 (CH), 117.4 (CH), 121.1 (CH), 123.1 (CH), 123.6 (CH), 123.8 (CH), 126.3 (CH), 128.2 (CH), 128.3 (2 × CH), 128.5 (CH), 128.6 (2 × CH), 130.2 (C), 131.3 (C), 131.4 (C), 131.5 (CH), 131.5 (C), 131.9 (C), 135.7 (C), 136.2 (C), 136.6 (C), 155.8 (C), 156.8 (C), 172.1 (C); *m/z* (ESI) 587.1627 (MNa^+. $C_{33}H_{28}N_2NaO_5S$ requires 587.1611).

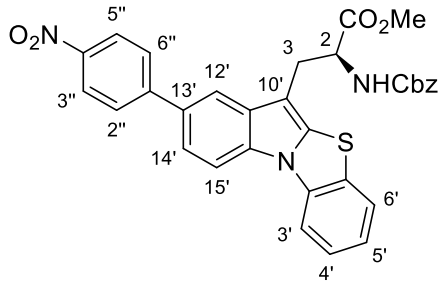
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[(3'',4''-methylenedioxy)phenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200c)



To a microwave vial containing methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (60.0 mg, 0.112 mmol) and water (1 mL) was added 3,4-(methylenedioxy)phenylboronic acid (28.0 mg, 0.167 mmol) and potassium phosphate tribasic (48.0 mg, 0.224 mmol). The reaction mixture was degassed under argon prior to the addition of Xphos Pd G2 (4.50 mg, 0.00575 mmol) and tetrahydrofuran (1 mL). The reaction mixture was heated to 60 °C and left to stir for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 2:3 + 0.5% ethyl acetate) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[(3'',4''-methylenedioxy)phenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-

yl}propanoate as a white solid (48.0 mg, 74%). Mp 129−131 °C; ν_{max}/cm^{-1} (neat) 3316 (NH), 2898 (CH), 2360, 1738 (CO), 1689 (CO), 1471, 1222, 1032, 734; $[\alpha]_D^{24}$ +52.9 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.40 (1H, dd, *J* 14.1, 4.9 Hz, 3-*H*H), 3.45 (1H, dd, *J* 14.1, 5.0 Hz, 3-H*H*), 3.73 (3H, s, CO_2CH_3), 4.83 (1H, ddd, *J* 7.9, 5.0, 4.9 Hz, 2-H), 5.11 (1H, d, *J* 12.3 Hz, PhC*H*H), 5.24 (1H, d, *J* 12.3 Hz, PhCH*H*), 5.50 (1H, d, *J* 7.9 Hz, NH), 6.03 (2H, s, OCH_2), 6.94 (1H, d, *J* 8.0 Hz, 5''-H), 7.13–7.19 (2H, m, 2''-H and 6''-H), 7.23 (1H, t, *J* 7.7 Hz, 5'-H), 7.29–7.47 (7H, m, 4'-H, 6'-H and Ph), 7.50–7.61 (2H, m, 3'-H and 15'-H), 7.93 (1H, dd, *J* 8.0, 1.5 Hz, 14'-H), 8.02 (1H, d, *J* 1.5 Hz, 12'-H); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 52.9 (CH_3), 54.6 (CH), 67.1 (CH_2), 100.1 (C), 101.3 (CH_2), 108.2 (CH), 108.8 (CH), 109.5 (CH), 112.3 (CH), 118.2 (CH), 121.0 (CH), 121.2 (CH), 123.2 (CH), 123.9 (CH), 126.4 (CH), 128.3 (CH), 128.4 (2 × CH), 128.6 (2 × CH), 130.3 (C), 131.9 (C), 132.0 (C), 134.2 (C), 135.9 (C), 136.1 (C), 136.5 (C), 136.6 (C), 146.9 (C), 148.3 (C), 155.8 (C), 172.1 (C); *m/z* (ESI) 601.1419 (MNa^+. $C_{33}H_{26}N_2NaO_6S$ requires 601.1404).

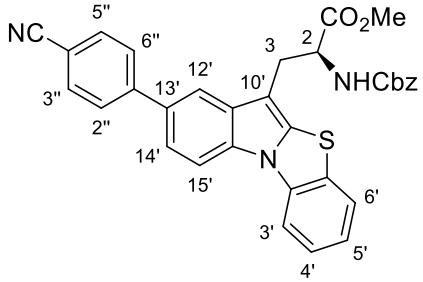
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-nitrophenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200d)



To a microwave vial containing methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (100 mg, 0.225 mmol) and water (3 mL) was added 4-nitrophenylboronic acid (56.3 mg, 0.337 mmol) and potassium phosphate tribasic (95.5 mg, 0.450 mmol). The reaction mixture was degassed under argon prior to the addition of Xphos Pd G2 (8.85 mg, 0.0113 mmol) and tetrahydrofuran (1.5 mL). The reaction mixture was heated to 60 °C and left to stir for 1 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

Purification by flash column chromatography (dichloromethane/ethyl acetate, 199:1) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-nitrophenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as an orange solid (86.0 mg, 80%). Mp 224−226 °C; ν_{max}/cm^{-1} (neat) 3295 (NH), 2947 (CH), 1688 (CO), 1587, 1475, 1337, 739; $[\alpha]_D^{20}$ −10.1 (*c* 0.1, DMSO); δ_H (400 MHz, DMSO-*d*$_6$) 3.26 (1H, dd, *J* 14.7, 8.5 Hz, 3-*H*H), 3.30 (1H, dd, *J* 14.7, 6.2 Hz, 3-H*H*), 3.64 (3H, s, CO_2CH_3), 4.43 (1H, td, *J* 8.5, 6.2 Hz, 2-H), 4.99 (2H, s, PhC*H*$_2$), 7.18–7.28 (5H, m, Ph), 7.36 (1H, td, *J* 7.6, 1.0 Hz, 5'-H), 7.56 (1H, ddd, *J* 8.3, 7.6, 1.3 Hz, 4'-H), 7.70 (1H, dd, *J* 8.5, 1.3 Hz, 14'-H), 7.79 (1H, d, *J* 8.5 Hz, 15'-H), 7.84–7.99 (2H, m, 6'-H and NH), 8.10–8.22 (2H, m, 2''-H and 6''-H), 8.29–8.34 (2H, m, 3''-H and 5''-H), 8.49 (1H, dd, *J* 8.3, 1.0 Hz, 3'-H), 8.56 (1H, d, *J* 1.3 Hz, 12'-H); δ_C (101 MHz, DMSO-*d*$_6$) 26.6 (CH_2), 52.2 (CH_3), 54.0 (CH), 65.4 (CH_2), 101.7 (C), 110.0 (CH), 113.1 (CH), 118.5 (CH), 120.7 (CH), 123.7 (CH), 123.9 (2 × CH), 124.3 (CH), 126.7 (CH), 127.5 (2 × CH), 127.7 (CH), 128.0 (2 × CH), 128.2 (2 × CH), 129.4 (C), 130.3 (C), 131.0 (C), 132.6 (C), 134.9 (C), 136.4 (C), 136.9 (C), 146.0 (C), 147.5 (C), 155.9 (C), 172.0 (C); *m/z* (ESI) 580.1537 (MH^+. $C_{32}H_{26}N_3O_6S$ requires 580.1537).

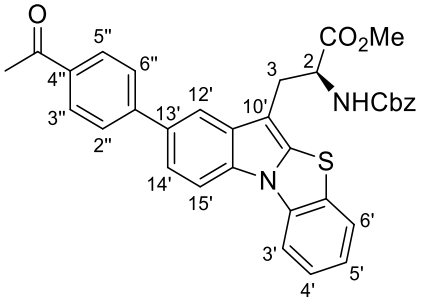
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-cyanophenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200e)



To a microwave vial containing methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200 mg, 0.372 mmol) and water (3 mL) was added 4-cyanophenylboronic acid (82.0 mg, 0.558 mmol) and potassium phosphate tribasic (158 mg, 0.744 mmol). The reaction mixture was degassed under argon prior to the addition of Xphos Pd G2 (14.6 mg, 0.0186 mmol) and tetrahydrofuran (3 mL). The reaction mixture was heated to 60 °C and left to stir for 1 h. The reaction mixture

was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 2:3 + 0.5% ethyl acetate) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-cyanophenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as a yellow solid (165 mg, 79%). Mp 218−219 °C; ν_{max}/cm^{-1} (neat) 3316 (NH), 2898 (CH), 2222 (CN), 1689 (CO), 1474, 1250, 736; $[\alpha]_D^{22}$ +55.9 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.45 (1H, dd, *J* 15.1, 4.4 Hz, 3-*H*H), 3.49 (1H, dd, *J* 15.1, 5.4 Hz, 3-H*H*), 3.73 (3H, s, CO_2CH_3), 4.83 (1H, ddd, *J* 7.9, 5.4, 4.4 Hz, 2-H), 5.10 (1H, d, *J* 12.3 Hz, PhC*H*H), 5.24 (1H, d, *J* 12.3 Hz, PhCH*H*), 5.48 (1H, d, *J* 7.9 Hz, NH), 7.21–7.41 (6H, m, 4'-H and Ph), 7.42–7.51 (2H, m, and 5'-H and 14'-H), 7.58–7.64 (2H, m, 3'-H and 15'-H), 7.73–7.82 (4H, m, 2''-H, 3''-H, 5''-H and 6''-H), 7.95 (1H, br d, *J* 8.1 Hz, 6'-H), 8.11 (1H, d, *J* 1.5 Hz, 12'-H); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 53.0 (CH_3), 54.6 (CH), 67.1 (CH_2), 100.5 (C), 109.9 (CH), 110.4 (C), 112.3 (CH), 118.6 (CH), 119.3 (C), 121.1 (CH), 123.6 (CH), 124.1 (CH), 126.5 (CH), 128.0 (2 × CH), 128.3 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 130.3 (C), 131.8 (C), 132.0 (C), 132.8 (2 × CH), 133.2 (C), 135.9 (C), 136.5 (C), 137.3 (C), 146.6 (C), 155.8 (C), 172.0 (C); *m/z* (ESI) 560.1642 (MH^+. $C_{33}H_{26}N_3O_4S$ requires 560.1639).

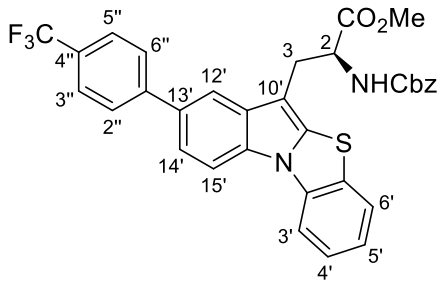
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-acetylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200f)



To a microwave vial containing methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3'-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200 mg, 0.372 mmol) and water (3 mL) was added 4-

acetylphenylboronic acid (92.0 mg, 0.558 mmol) and potassium phosphate tribasic (158 mg, 0.744 mmol). The reaction mixture was degassed under argon prior to the addition of Xphos Pd G2 (15.0 mg, 0.0186 mmol) and tetrahydrofuran (3 mL). The reaction mixture was heated to 60 °C and left to stir for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 1:9 + 0.5% ethyl acetate) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-acetylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as a yellow solid (189 mg, 88%). Mp 201−203 °C; ν_{max}/cm^{-1} (neat) 3314 (NH), 2908 (CH), 2356, 1695 (CO), 1673 (CO), 1533, 1254, 1024, 733; $[\alpha]_D^{26}$ +56.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.67 (3H, s, 4''-$COCH_3$), 3.43 (1H, dd, *J* 15.0, 4.7 Hz, 3-*H*H), 3.47 (1H, dd, *J* 15.0, 5.5 Hz, 3-H*H*), 3.73 (3H, s CO_2CH_3), 4.83 (1H, ddd, *J* 8.0, 5.5, 4.7 Hz, 2-H), 5.11 (1H, d, *J* 12.3 Hz, PhC*H*H), 5.24 (1H, d, *J* 12.3 Hz, PhCH*H*), 5.48 (1H, d, *J* 8.0 Hz, NH), 7.24–7.40 (6H, m, 5'-H and Ph), 7.44–7.52 (2H, m, 4'-H and 14'-H), 7.54–7.63 (2H, m, 3'-H and 6'-H), 7.74–7.82 (2H, m, 2''-H and 6''-H), 7.97 (1H, d, *J* 7.3 Hz, 15'-H), 8.03–8.12 (2H, m, 3''-H and 5''-H), 8.15 (1H, d, *J* 2.0 Hz, 12'-H); δ_C (101 MHz, $CDCl_3$) 26.8 (CH_3), 28.3 (CH_2), 53.0 (CH_3), 54.6 (CH), 67.1 (CH_2), 100.4 (C), 109.9 (CH), 112.4 (CH), 118.5 (CH), 121.3 (CH), 123.5 (CH), 124.0 (CH), 126.5 (CH), 127.6 (2 × CH), 128.3 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH), 130.3 (C), 131.9 (C), 132.8 (C), 133.0 (C), 135.6 (C), 136.0 (C), 136.5 (C), 136.9 (C), 146.8 (C), 155.8 (C), 172.0 (C), 197.9 (C); *m/z* (ESI) 599.1623 (MNa^+. $C_{34}H_{28}N_2NaO_5S$ requires 599.1611).

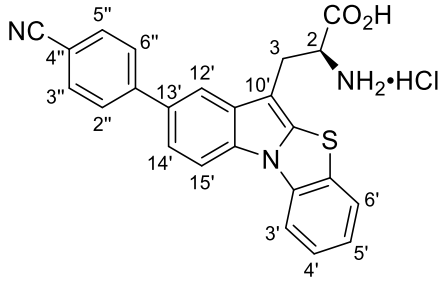
Methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200g)



To a microwave vial containing methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-bromo-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (200 mg, 0.372 mmol) and water (3. mL) was added 4-trifluoromethylphenylboronic acid (106 mg, 0.558 mmol) and potassium phosphate tribasic (158 mg, 0.744 mmol). The reaction mixture was degassed under argon prior to the addition of Xphos Pd G2 (15.0 mg, 0.0186 mmol) and tetrahydrofuran (3 mL). The reaction mixture was heated to 60 °C and left to stir for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/dichloromethane, 1:1 + 0.5% ethyl acetate) gave methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate as an off-white solid (198 mg, 88%). Mp 221−223 °C; ν_{max}/cm^{-1} (neat) 3310 (NH), 3037 (CH), 1738 (CO), 1691 (CO), 1476, 1329, 1106, 737; $[\alpha]_D^{26}$ +49.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.43 (1H, dd, *J* 15.0, 4.4 Hz, 3-*H*H), 3.48 (1H, dd, *J* 15.0, 5.4 Hz, 3-H*H*), 3.73 (3H, s, CO_2CH_3), 4.84 (1H, ddd, *J* 7.9, 5.4, 4.4 Hz, 2-H), 5.11 (1H, d, *J* 12.3 Hz, PhC*H*H), 5.25 (1H, d, *J* 12.3 Hz, PhCH*H*), 5.49 (1H, d, *J* 7.9 Hz, NH), 7.22–7.27 (1H, m, 5'-H), 7.30–7.41 (5H, m, Ph), 7.43–7.50 (2H, m, 4'-H and 14'-H), 7.54–7.63 (2H, m, 3'-H and 6'-H), 7.74 (2H, d, *J* 8.5 Hz, 2''-H and 6''-H), 7.80 (2H, d, *J* 8.5 Hz, 3''-H and 5''-H), 7.95 (1H, d, *J* 7.9 Hz, 15'-H), 8.11 (1H, d, *J* 1.6 Hz, 12'-H); δ_C (101 MHz, $CDCl_3$) 28.3 (CH_2), 53.0 (CH_3), 54.6 (CH), 67.1 (CH_3), 100.3 (C), 109.9 (CH), 112.3 (CH), 118.5 (CH), 121.2 (CH), 123.5 (CH), 124.0 (CH), 124.9 (q, $^1J_{CF}$ 273.3 Hz, C), 125.9 (q, $^3J_{CF}$ 3.6 Hz, 2 × CH), 126.5 (CH), 127.8 (2 × CH), 128.3 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 129.1 (q, $^2J_{CF}$ 32.4 Hz, C), 130.3 (C), 131.9 (C), 132.7 (C),

132.9 (C), 136.0 (C), 136.5 (C), 136.8 (C), 145.7 (C), 155.8 (C), 172.0 (C); *m/z* (ESI) 603.1557 (MH^+. $C_{33}H_{26}F_3N_2O_4S$ requires 603.1560).

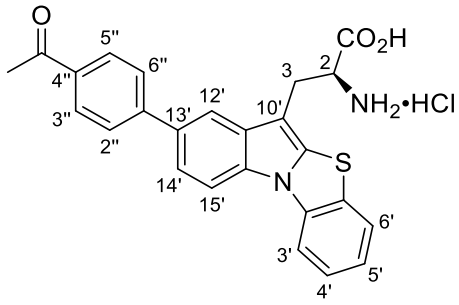
(2*S*)-2-Amino-3-{13'-[4''-cyanophenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid hydrochloride (202a)



To a stirred solution of methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-cyanophenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (164 mg, 0.293 mmol) in methanol (9.0 mL), 1,4-dioxane (4.5 mL) and water (4.5 mL) was added cesium carbonate (124 mg, 0.381 mmol). The resulting reaction mixture was left to stir at 60 °C for 2 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-(4''-cyanophenyl)-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid as a yellow solid (156 mg, 100%). This was used for the next reaction without any further purification. A suspension of (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-cyanophenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid (47.0 mg, 0.0861 mmol) in 4 M hydrochloric acid in dioxane (8 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue was recrystallised from ethanol and diethyl ether to give (2*S*)-2-amino-3-{13'-[4''-cyanophenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid hydrochloride as a black solid (9.00 mg, 23%). Mp 307−309 °C (decomposition); ν_{max}/cm^{-1} (neat) 2856 (CH), 2217 (CN), 1600 (CO), 1583, 1472,

1181, 1003, 810; $[\alpha]_D^{24}$ −47.8 (*c* 0.05, DMSO); δ_H (400 MHz, DMSO-*d*$_6$) 3.40–3.55 (2H, m, 3-H_2), 4.20 (1H, t, *J* 6.8 Hz, 2-H), 7.37 (1H, td, *J* 7.7, 0.8 Hz, 5'-H), 7.57 (1H, td, *J* 7.7, 1.2 Hz, 4'-H), 7.73 (1H, dd, *J* 8.5, 1.5 Hz, 14'-H), 7.88 (1H, d, *J* 8.5 Hz, 15'-H), 7.94–7.99 (3H, m, 6'-H, 2''-H and 6''-H), 8.13 (2H, d, *J* 8.5 Hz, 3''-H and 5''-H), 8.43 (2H, s, NH_2), 8.53 (1H, d, *J* 7.7, 0.8 Hz, 3'-H), 8.56 (1H, d, *J* 1.5 Hz, 12'-H); δ_C (101 MHz, DMSO-*d*$_6$) 25.9 (CH_2), 52.1 (CH), 99.0 (C), 109.2 (CH), 109.8 (C), 113.2 (CH), 118.6 (CH), 119.1 (CH), 120.7 (CH), 123.8 (CH), 124.3 (CH), 126.8 (C), 127.9 (2 × CH), 129.4 (C), 131.1 (C), 131.3 (C), 132.3 (C), 132.7 (2 × CH), 134.9 (C), 137.4 (C), 145.3 (C), 170.5 (C); *m/z* (ESI) 412.1116 (MH^+. $C_{24}H_{18}N_3O_2S$ requires 412.1114).

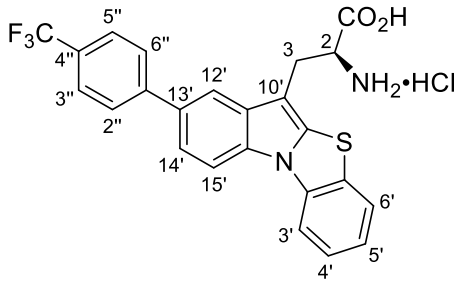
(2*S*)-2-Amino-3-{13'-[4''-acetylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid hydrochloride (202b)



To a stirred solution of methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-acetylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (175 mg, 0.303 mmol) in methanol (10.0 mL), 1,4-dioxane (5.0 mL) and water (5.0 mL) was added cesium carbonate (129 mg, 0.395 mmol). The resulting reaction mixture was left to stir at 60 °C for 5 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-acetylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid as a yellow solid (171 mg, 100%). This was used for the next reaction without any further purification. A suspension of (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-acetylphenyl]-8'-thia-1'-

azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid (50.0 mg, 0.0889 mmol) in 4 M hydrochloric acid in dioxane (8 mL) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue was recrystallised from ethanol and diethyl ether to give (2*S*)-2-amino-3-{13'-[4''-acetylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid hydrochloride as a black solid (20.0 mg, 49%). Mp 312−314 °C (decomposition); ν_{max}/cm^{-1} (neat) 2901 (CH), 1760 (CO), 1676 (CO), 1600, 1474, 1266, 1197, 735; $[\alpha]_D^{24}$ −40.0 (*c* 0.0125, DMSO); δ_H (400 MHz, DMSO-*d*$_6$) 2.64 (3H, s, 4''-COCH$_3$), 3.40–3.55 (2H, m, 3-H$_2$), 4.20 (1H, t, *J* 6.2 Hz, 2-H), 7.37 (1H, td, *J* 7.9, 1.0 Hz, 5'-H), 7.57 (1H, td, *J* 7.9, 1.2 Hz, 4'-H), 7.73 (1H, dd, *J* 8.5, 1.6 Hz, 14'-H), 7.88 (1H, d, *J* 8.5 Hz, 15'-H), 7.96 (1H, br d, *J* 7.9, 1.2 Hz, 6'-H), 8.01–8.13 (4H, m, 2''-H, 3''-H, 5''-H and 6''-H), 8.44 (2H, s, NH$_2$), 8.51 (1H, d, *J* 7.9, 1.0 Hz, 3'-H), 8.55 (1H, d, *J* 1.6 Hz, 12'-H); δ_C (101 MHz, DMSO-*d*$_6$) 26.0 (CH$_2$), 26.8 (CH$_3$), 52.1 (CH), 99.0 (C), 109.6 (CH), 113.1 (CH), 118.6 (CH), 120.8 (CH), 123.8 (CH), 124.3 (CH), 126.8 (CH), 127.3 (2 × CH), 128.8 (2 × CH), 129.5 (C), 131.3 (C), 131.8 (C), 132.1 (C), 135.0 (C), 135.1 (C), 137.1 (C), 145.3 (C), 170.5 (C), 197.5 (C); *m/z* (ESI) 429.1264 (MH$^+$. $C_{25}H_{21}N_2O_3S$ requires 429.1267).

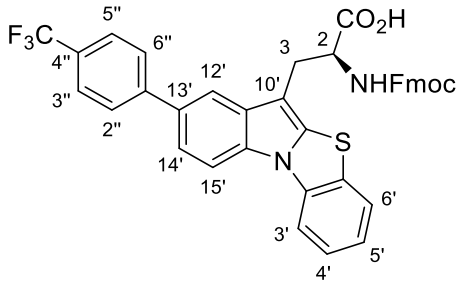
(2*S*)-2-Amino-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid hydrochloride (202c)



To a stirred solution of methyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoate (260 mg, 0.431 mmol) in methanol (14.0 mL), 1,4-dioxane (7.0 mL) and water (7.0 mL) was added cesium carbonate (183 mg, 0.561 mmol). The resulting reaction mixture was left to stir at 60 °C for 4 h. The reaction mixture was concentrated *in vacuo*, diluted with water

(10 mL) and acidified to pH 1 with 1 M aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid as a white solid (254 mg, 100%). This was used for the next reaction without any further purification. A suspension of (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid (75.0 mg, 0.127 mmol) in 6 M aqueous hydrochloric acid (9 mL) and 1,4-dioxane (4.5 mL) was heated under reflux in a sealed tube for 4 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue was recrystallised from ethanol and diethyl ether to give (2*S*)-2-amino-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid hydrochloride as an off-white solid (44.0 mg, 70%). Mp 315−317 °C (decomposition); ν_{max}/cm^{-1} (neat) 3104 (NH), 2890 (CH), 1762 (CO), 1587, 1477, 1330, 1108, 736; $[\alpha]_D^{18}$ −44.0 (*c* 0.1, DMSO); δ_H (400 MHz, DMSO-*d*$_6$) 3.42 (1H, dd, *J* 15.0, 7.0 Hz, 3-*H*H), 3.48 (1H, dd, *J* 15.0, 6.1 Hz, 3-H*H*), 4.18 (1H, dd, *J* 7.0, 6.1 Hz, 2-H), 7.37 (1H, td, *J* 7.7, 1.1 Hz, 5'-H), 7.56 (1H, td, *J* 7.7, 1.3 Hz, 4'-H), 7.70 (1H, dd, *J* 8.4, 1.6 Hz, 14'-H), 7.84 (2H, d, *J* 8.4 Hz, 2''-H and 6''-H), 7.91 (1H, d, *J* 8.4 Hz, 15'-H), 7.96 (1H, dd, *J* 7.7, 1.3 Hz, 6'-H), 8.12 (2H, d, *J* 8.4 Hz, 3''-H and 5''-H), 8.44–8.61 (5H, m, 3'-H, 12'-H and NH_3); δ_C (101 MHz, DMSO-*d*$_6$) 26.0 (CH_2), 52.1 (CH), 99.0 (C), 109.8 (CH), 113.1 (CH), 118.7 (CH), 120.8 (CH), 123.8 (CH), 124.3 (CH), 124.5 (q, $^1J_{CF}$ 272.1 Hz, C), 125.6 (q, $^3J_{CF}$ 3.7 Hz, 2 × CH), 126.8 (CH), 127.2 (q, $^2J_{CF}$ 33.0 Hz, C), 127.9 (2 × CH), 129.5 (C), 131.3 (C), 131.5 (C), 132.1 (C), 135.0 (C), 137.0 (C), 144.9 (C), 170.5 (C); *m/z* (ESI) 455.1037 (MH^+. $C_{24}H_{18}F_3N_2O_2S$ requires 455.1036).

(2*S*)-2-[(9*H*-Fluoren-9-ylmethoxycarbonyl)amino-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid (203)



A suspension of (2*S*)-2-amino-3-{13'-[4''-trifluoromethylphenyl]-8'-thia-1'-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2'(7'),3',5',9',11',13',15'-heptaen-10'-yl}propanoic acid hydrochloride (17.0 mg, 0.0346 mmol) in 1,4-dioxane (0.5 mL) and water (0.5 mL) was added sodium hydrogen carbonate (11.6 mg, 0.138 mmol) followed by *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (11.4 mg, 0.0339 mmol). The reaction mixture was stirred at room temperature for 24 h, acidified to pH 2 with 1 M aqueous hydrochloric acid and concentrated *in vacuo*. The resulting residue was recrystallised from chloroform and diethyl ether to give (2*S*)-2-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino-3-{13-[4''-trifluoromethylphenyl]-8-thia-1-azatetracyclo[7.7.0.0^{2,7}.0^{11,16}]hexadeca-2(7),3,5,9,11,13,15-heptaen-10-yl}propanoic acid as an off-white solid (13.0 mg, 57%). Mp 215−217 °C (decomposition); ν_{max}/cm^{-1} (neat) 3302 (NH), 3043 (OH), 2917 (CH), 1690 (CO), 1540, 1476, 1328, 1165, 735; $[\alpha]_D^{22}$ +26.7 (*c* 0.1, DMSO); δ_H (400 MHz, DMSO-*d*$_6$) 3.26 (1H, dd, *J* 14.7, 8.8 Hz, 3-*H*H), 3.39 (1H, dd, *J* 14.7, 5.2 Hz, 3-H*H*), 4.10–4.27 (3H, m, OCH$_2$CH), 4.36 (1H, td, *J* 8.8, 5.2 Hz, 2-H), 7.16 (1H, t, *J* 7.5 Hz, ArH), 7.24 (1H, t, *J* 7.5 Hz, ArH), 7.32–7.38 (3H, m, 5'-H and 2 × ArH), 7.54 (1H, t, *J* 8.0 Hz, 4'-H), 7.59–7.68 (3H, m, 14'-H and 2 × ArH), 7.80–7.89 (7H, m, NH, 6'-H, 15'-H, 2''-H, 6''-H and 2 × ArH), 8.06 (2H, d, *J* 8.1 Hz, 3''-H and 5''-H), 8.45 (1H, br d, *J* 8.0 Hz, 3'-H), 8.49 (1H, br s, 12'-H), 12.86 (1H, br s, OH); ^{13}C data unavailable due to compound decomposition in DMSO; *m/z* (ESI) 677.1718 (M+H$^+$. $C_{39}H_{28}F_3N_2O_4S$ requires 677.1716).

7.0 References

1 C. F. Lee, Y. C. Liu and S. S. Badsara, *Chem. Asian J.*, 2014, **9**, 706–722.

2 M. Feng, B. Tang, S. H. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200–1216.

3 C. Mitsui, T. Okamoto, M. Yamagishi, J. Tsurumi, K. Yoshimoto, K. Nakahara, J. Soeda, Y. Hirose, H. Sato, A. Yamano, T. Uemura and J. Takeya, *Adv. Mater.*, 2014, **26**, 4546–4551.

4 K. Takimiya, S. Shinamura, I. Osaka and E. Miyazaki, *Adv. Mater.*, 2011, **23**, 4347–4370.

5 J. L. Farmer, M. Pompeo, A. J. Lough and M. G. Organ, *Chem. Eur. J.*, 2014, **20**, 15790–15798.

6 J. Li, S. Yang, W. Wu and H. Jiang, *Org. Chem. Front.*, 2020, **7**, 1395–1417.

7 T. Kondo and T. Mitsudo, *Chem. Rev.*, 2000, **100**, 3205–3220.

8 A. Bhowmik, M. Yadav and R. A. Fernandes, *Org. Biomol. Chem.*, 2020, **18**, 2447–2458.

9 M. Murata and S. L. Buchwald, *Tetrahedron*, 2004, **60**, 7397–7403.

10 I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596–1636.

11 Z. Qiao, J. Wei and X. Jiang, *Org. Lett.*, 2014, **16**, 1212–1215.

12 M. Kosugi, T. Shimizu and T. Migita, *Chem. Lett.*, 1978, **7**, 13–14.

13 T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato and M. Kosugi, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1385–1389.

14 M. A. Fernández-Rodríguez, Q. Shen and J. F. Hartwig, *Chem. Eur. J.*, 2006, **12**, 7782–7796.

15 M. A. Fernández-Rodríguez, Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 2180–2181.

16 J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609–3612.

17 Q. Shen, S. Shekhar, J. P. Stambuli and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2005, **44**, 1371–1375.

18 P. Saravanan and P. Anbarasan, *Org. Lett.*, 2014, **16**, 848–851.

19 N. Ichiishi, C. A. Malapit, Ł. Woźniak and M. S. Sanford, *Org. Lett.*, 2018, **20**, 44–47.

20 N. Robbins, S. E. Koch, M. Tranter and J. Rubinstein, *Cardiovasc. Toxicol.*, 2012, **12**, 1–9.

21 S. P. Bakare and M. Patil, *New J. Chem.*, 2022, **46**, 6283–6295.

22 F. Yee Kwong and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3517–3520.

23 H.-J. Xu, Y.-Q. Zhao, T. Feng and Y.-S. Feng, *J. Org. Chem.*, 2012, **77**, 2878–2884.

24 Y. Liu, L. Y. Lam, J. Ye, N. Blanchard and C. Ma, *Adv. Synth. Catal.*, 2020, **362**, 2326–2331.

25 L. Y. Lam and C. Ma, *Org. Lett.*, 2021, **23**, 6164–6168.

26 X.-B. Xu, J. Liu, J.-J. Zhang, Y.-W. Wang and Y. Peng, *Org. Lett.*, 2013, **15**, 550–553.

27 C.-S. Yan, Y. Peng, X.-B. Xu and Y.-W. Wang, *Chem. Eur. J.*, 2012, **18**, 6039–6048.

28 X. T. Liang, X. D. Xu, Z. P. Zhang, H. E. Gu and W. X. Wang, *Sci. Sin.*, 1977, **20**, 106.

29 X. Liu, Q. Cao, W. Xu, M. T. Zeng and Z. B. Dong, *Eur. J. Org. Chem.*, 2017, 5795–5799.

30 E. Grignard, S. Lapenna and S. Bremer, *Toxicol. Vitr.*, 2012, **26**, 727–731.

31 A. Basta-Kaim, B. Budziszewska, L. Jaworska-Feil, M. Tetich, M. Leśkiewicz, M. Kubera and W. Lasoń, *Neuropharmacology*, 2002, **43**, 1035–1043.

32 M. Zhang, S. Zhang, C. Pan and F. Chen, *Synth. Commun.*, 2012, **42**, 2844–2853.

33 D. Seckler, Q. Eduardo, G. L. Silvério, G. Badshah, D. B. Lima, E. A. Abreu, B. Albach, R. R. Ribeiro and D. S. Rampon, *Synlett*, 2021, **32**, 940–946.

34 W. Zhao, F. Zhang and G.-J. Deng, *J. Org. Chem.*, 2021, **86**, 291–301.

35 S. Sarkar, N. Wojciechowska, A. A. Rajkiewicz and M. Kalek, *Eur. J. Org. Chem.*, 2022, **2022**, e202101408.

36 J.-H. Wang, T. Lei, H.-L. Wu, X.-L. Nan, X.-B. Li, B. Chen, C.-H. Tung and L.-Z. Wu, *Org. Lett.*, 2020, **22**, 3804–3809.

37 M. Jiang, H. Li, H. Yang and H. Fu, *Angew. Chem. Int. Ed.*, 2017, **56**, 874–879.

38 M. S. Oderinde, M. Frenette, D. W. Robbins, B. Aquila and J. W. Johannes, *J. Am. Chem. Soc.*, 2016, **138**, 1760–1763.

39 L. Pan, M. V. Cooke, A. Spencer and S. Laulhé, *Adv. Synth. Catal.*, 2022, **364**, 420–425.

40 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 2002, **91**, 165–195.

41 D. E. Clark, *Drug Discov. Today*, 2003, **8**, 927–933.

42 X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2014, **115**, 731–764.

43 A. Ferry, T. Billard, E. Bacqué and B. R. Langlois, *J. Fluor. Chem.*, 2012, **134**, 160–163.

44 S. Alazet and T. Billard, *Synlett*, 2015, **26**, 76–78.

45 R. Kurose, Y. Nishii and M. Miura, *Org. Lett.*, 2021, **23**, 2380–2385.

46 M. Diaferia, F. Veronesi, G. Morganti, L. Nisoli and D. P. Fioretti, *Parasitol. Res.*, 2013, **112**, 163–168.

47 H. Tian, C. Zhu, H. Yang and H. Fu, *Chem. Commun.*, 2014, **50**, 8875–8877.

48 T. Hostier, V. Ferey, G. Ricci, D. Gomez Pardo and J. Cossy, *Org. Lett.*, 2015, **17**, 3898–3901.

49 S. M. Maddox, C. J. Nalbandian, D. E. Smith and J. L. Gustafson, *Org. Lett.*, 2015, **17**, 1042–1045.

50 S. M. Maddox, A. N. Dinh, F. Armenta, J. Um and J. L. Gustafson, *Org. Lett.*, 2016, **18**, 5476–5479.

51 C. J. Nalbandian, E. M. Miller, S. T. Toenjes and J. L. Gustafson, *Chem. Commun.*, 2017, **53**, 1494–1497.

52 S. E. Denmark and H. M. Chi, *J. Am. Chem. Soc.*, 2014, **136**, 8915–8918.

53 S. E. Denmark, S. Rossi, M. P. Webster and H. Wang, *J. Am. Chem. Soc.*, 2014, **136**, 13016–13028.

54 M. Toure and C. M. Crews, *Angew. Chem. Int. Ed.*, 2016, **55**, 1966–1973.

55 B. Lomenick, R. W. Olsen and J. Huang, *ACS Chem. Biol.*, 2011, **6**, 34–46.

56 Z. Zhu, J. Luo and X. Zhao, *Org. Lett.*, 2017, **19**, 4940–4943.

57 C. J. Nalbandian, Z. E. Brown, E. Alvarez and J. L. Gustafson, *Org. Lett.*, 2018, **20**, 3211–3214.

58 C. S. McKay and M. G. Finn, *Chem. Biol.*, 2014, **21**, 1075–1101.

59 D. S. Rampon, D. Seckler, E. Q. Luz, D. B. Paixão, A. Larroza, P. H. Schneider and D. Alves, *Org. Biomol. Chem.*, 2022, **20**, 6072–6177.

60 N. Kambe, T. Iwasaki and J. Terao, *Chem. Soc. Rev.*, 2011, **40**, 4937–4947.

61 S. L. Pimlott and A. Sutherland, *Chem. Soc. Rev.*, 2011, **40**, 149–162.

62 A. A. Cant, R. Bhalla, S. L. Pimlott and A. Sutherland, *Chem. Commun.*, 2012, **48**, 3993–3995.

63 A. A. Cant, S. Champion, R. Bhalla, S. L. Pimlott and A. Sutherland, *Angew. Chem. Int. Ed.*, 2013, **52**, 7829–7832.

64 N. L. Sloan, S. K. Luthra, G. McRobbie, S. L. Pimlott and A. Sutherland, *RSC Adv.*, 2017, **7**, 54881–54891.

65 N. L. Sloan, S. K. Luthra, G. McRobbie, S. L. Pimlott and A. Sutherland, *Chem. Commun.*, 2017, **53**, 11008–11011.

66 S. Webster, K. M. O'Rourke, C. Fletcher, S. L. Pimlott, A. Sutherland and A.-L. Lee, *Chem. Eur. J.*, 2018, **24**, 937–943.

67 J. J. Molloy, K. M. O'Rourke, C. P. Frias, N. L. Sloan, M. J. West, S. L. Pimlott, A. Sutherland and A. J. B. Watson, *Org. Lett.*, 2019, **21**, 2488–2492.

68 D. T. Racys, C. E. Warrilow, S. L. Pimlott and A. Sutherland, *Org. Lett.*, 2015, **17**, 4782–4785.

69 S. Antoniotti, V. Dalla and E. Duñach, *Angew. Chem. Int. Ed.*, 2010, **49**,

7860–7888.

70 M. J. Earle, U. Hakala, B. J. McAuley, M. Nieuwenhuyzen, A. Ramani and K. R. Seddon, *Chem. Commun.*, 2004, 1368–1369.

71 V. Caveliers, H. Everaert, C. S. John, T. Lahoutte and A. Bossuyt, *J. Nucl. Med.*, 2002, **43**, 1647–1649.

72 H. F. Kung, R. Kasliwal, S. G. Pan, M. P. Kung, R. H. Mach and Y. Z. Guo, *J. Med. Chem.*, 1988, **31**, 1039–1043.

73 J. A. Sintas and A. A. Vitale, *J. Label. Compd. Radiopharm.*, 1999, **42**, 409–413.

74 M. A. B. Mostafa, E. D. D. Calder, D. T. Racys and A. Sutherland, *Chem. Eur. J.*, 2017, **23**, 1044–1047.

75 M. A. Cutulle, G. R. Armel, J. T. Brosnan, M. D. Best, D. A. Kopsell, B. D. Bruce, H. E. Bostic and D. S. Layton, *J. Agric. Food Chem.*, 2014, **62**, 329–336.

76 M. A. B. Mostafa, R. M. Bowley, D. T. Racys, M. C. Henry and A. Sutherland, *J. Org. Chem.*, 2017, **82**, 7529–7537.

77 A. C. Dodds and A. Sutherland, *J. Org. Chem.*, 2021, **86**, 5922–5932.

78 M. C. Henry, H. M. Senn and A. Sutherland, *J. Org. Chem.*, 2019, **84**, 346–364.

79 D. C. Qian, P. E. Alford, T. L. S. Kishbaugh, S. T. Jones and G. W. Gribble, *ARKIVOC*, 2010, **4**, 66–73.

80 T. Hostier, V. Ferey, G. Ricci, D. G. Pardo and J. Cossy, *Chem. Commun.*, 2015, **51**, 13898–13901.

81 R. B. Bruce, L. Turnbull, J. Newman and J. Pitts, *J. Med. Chem.*, 1966, **9**, 286–288.

82 R. Wolf and R. Orni-Wasserlauf, *Int. J. Dermatol.*, 2000, **39**, 779–783.

83 B. Bang-Andersen, T. Ruhland, M. Jørgensen, G. Smith, K. Frederiksen, K. G. Jensen, H. Zhong, S. M. Nielsen, S. Hogg and A. Mørk, *J. Med. Chem.*, 2011, **54**, 3206–3221.

84 Y. Wang, J. Deng, J. Chen, F. Cao, Y. Hou, Y. Yang, X. Deng, J. Yang, L. Wu, X. Shao, T. Shi and Z. Wang, *ACS Catal.*, 2020, **10**, 2707–2712.

85 J.-A. García-López, M. Çetin and M. F. Greaney, *Angew. Chem. Int. Ed.*, 2015, **54**, 2156–2159.

86 K. Zhang, A. Budinská, A. Passera and D. Katayev, *Org. Lett.*, 2020, **22**, 2714–2719.

87 G. Koleva, B. Galabov, B. Hadjieva, H. F. Schaefer III and P. von R. Schleyer, *Angew. Chem. Int. Ed.*, 2015, **54**, 14123–14127.

88 N. Svenstrup and J. Becher, *Synthesis (Stuttg).*, 1995, 215–235.

89 S. Pathania, R. K. Narang and R. K. Rawal, *Eur. J. Med. Chem.*, 2019, **180**, 486–508.

90 K. Laxmikeshav, P. Kumari and N. Shankaraiah, *Med. Res. Rev.*, 2022, **42**, 513–575.

91 M. Li, X. Cai, Z. Qiao, K. Liu, W. Xie, L. Wang, N. Zheng and S.-J. Su, *Chem. Commun.*, 2019, **55**, 7215–7218.

92 R. Kikumoto, Y. Tamao, K. Ohkubo, T. Tezuka, S. Tonomura, S. Okamoto, Y. Funahara and A. Hijikata, *J. Med. Chem.*, 1980, **23**, 830–836.

93 M. Harfenist, D. M. Joseph, S. C. Spence, D. P. C. Mcgee, M. D. Reeves and H. L. White, *J. Med. Chem.*, 1997, **40**, 2466–2473.

94 S. Y. Lee, T. Yasuda, H. Komiyama, J. Lee and C. Adachi, *Adv. Mater.*, 2016, **28**, 4019–4024.

95 G. M. Bennett, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.*, 1937, 444–446.

96 K. Komeyama, K. Aihara, T. Kashihara and K. Takaki, *Chem. Lett.*, 2011, **40**, 1254–1256.

97 S. Yang, B. Feng and Y. Yang, *J. Org. Chem.*, 2017, **82**, 12430–12438.

98 N. Liu, F. Chao, Y. Huang, Y. Wang, X. Meng, L. Wang and X. Liu, *Tetrahedron Lett.*, 2019, **60**, 151259.

99 P. Saravanan and P. Anbarasan, *Org. Lett.*, 2014, **16**, 848–851.

100 K. Kanemoto, Y. Sakata, T. Hosoya and S. Yoshida, *Chem. Lett.*, 2020, **49**, 593–596.

101 M. C. Henry, R. McGrory, R. J. Faggyas, M. A. B. Mostafa and A. Sutherland, *Org. Biomol. Chem.*, 2019, **17**, 4629–4639.

102 S. H. von Reuss and W. A. König, *Phytochemistry*, 2004, **65**, 3113–3118.

103 N. Beldjoudi, L. Mambu, M. Labaïed, P. Grellier, D. Ramanitrahasimbola, P. Rasoanaivo, M. T. Martin and F. Frappier, *J. Nat. Prod.*, 2003, **66**, 1447–1450.

104 H.-Q. Yin, B.-W. Lee, Y.-C. Kim, D.-H. Sohn and B.-H. Lee, *Arch. Pharm. Res.*, 2004, **27**, 919–922.

105 M. C. Henry and A. Sutherland, *Org. Lett.*, 2020, **22**, 2766–2770.

106 M. C. Henry, V. M. Abbinante and A. Sutherland, *Eur. J. Org. Chem.*, 2020, 2819–2826.

107 A. R. Katritzky and T. Narindoshvili, *Org. Biomol. Chem.*, 2009, **7**, 627–634.

108 Y. Xiong, C. Shi, L. Li, Y. Tang, X. Zhang, S. Liao, B. Zhang, C. Sun and C. Ren, *New J. Chem.*, 2021, **45**, 15180–15194.

109 Y. Liu, J. Kim, H. Seo, S. Park and J. Chae, *Adv. Synth. Catal.*, 2015, **357**, 2205–2212.

110 A. C. Dodds and A. Sutherland, *Org. Biomol. Chem.*, 2022, **20**, 1738–1748.

111 C. A. Horiuchi, A. Haga and J. Y. Satoh, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2459–2462.

112 M. J. Ohlow and B. Moosmann, *Drug Discov. Today*, 2011, **16**, 119–131.

113 C. Dai, X. Sun, X. Tu, L. Wu, D. Zhan and Q. Zeng, *Chem. Commun.*, 2012, **48**, 5367–5369.

114 E. H. Discekici, N. J. Treat, S. O. Poelma, K. M. Mattson, Z. M. Hudson, Y. Luo, C. J. Hawker and J. R. de Alaniz, *Chem. Commun.*, 2015, **51**, 11705–11708.

115 S. C. Mitchell, *Curr. Drug Targets*, 2006, **7**, 1181–1189.

116 G. Lu, M. Nagbanshi, N. Goldau, M. Mendes Jorge, P. Meissner, A. Jahn, F.

P. Mockenhaupt and O. Müller, *BMC Med.*, 2018, **16**, 59.

117 D. Boyd-Kimball, K. Gonczy, B. Lewis, T. Mason, N. Siliko and J. Wolfe, *ACS Chem. Neurosci.*, 2019, **10**, 79–88.

118 C. L. B. Kline, M. D. Ralff, A. R. Lulla, J. M. Wagner, P. H. Abbosh, D. T. Dicker, J. E. Allen and W. S. El-Deiry, *Neoplasia*, 2018, **20**, 80–91.

119 H.-W. Cheng, Y.-H. Liang, Y.-L. Kuo, C.-P. Chuu, C.-Y. Lin, M.-H. Lee, A. T. H. Wu, C.-T. Yeh, E. I.-T. Chen, J. Whang-Peng, C.-L. Su and C.-Y. F. Huang, *Cell Death Dis.*, 2015, **6**, e1753.

120 N. L. SMITH, *J. Org. Chem.*, 1950, **15**, 1125–1130.

121 N. Sharma, R. Gupta, M. Kumar and R. R. Gupta, *J. Fluor. Chem.*, 1999, **98**, 153–157.

122 T. Dahl, C. W. Tornøe, B. Bang-Andersen, P. Nielsen and M. Jørgensen, *Angew. Chem. Int. Ed.*, 2008, **47**, 1726–1728.

123 D. Ma, Q. Geng, H. Zhang and Y. Jiang, *Angew. Chem. Int. Ed.*, 2010, **49**, 1291–1294.

124 H. Tian, H. Yang, C. Zhu and H. Fu, *Adv. Synth. Catal.*, 2015, **357**, 481–488.

125 R. E. Huber and R. S. Criddle, *Arch. Biochem. Biophys.*, 1967, **122**, 164–173.

126 L. A. Wessjohann, A. Schneider, M. Abbas and W. Brandt, *Biol. Chem.*, 2007, **388**, 997–1006.

127 H. J. Reich and R. J. Hondal, *ACS Chem. Biol.*, 2016, **11**, 821–841.

128 J. F. Hartwig, *Angew. Chem. Int. Ed.*, 1998, **37**, 2046–2067.

129 B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125–146.

130 J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215–7216.

131 S. Courvoisier, R. Ducrot, J. Fournel and L. Julou, *C. R. Seances Soc. Biol. Fil.*, 1957, **151**, 1144–1148.

132 F. Jourdan, P. Duchene-Marullaz, G. Faucon and P. Bouverot, *C. R. Seances Soc. Biol. Fil.*, 1958, **152**, 91–93.

133 D. L. Boger, K. Machiya, D. L. Hertzog, P. A. Kitos and D. Holmes, *J. Am. Chem. Soc.*, 1993, **115**, 9025–9036.

134 V. Quesneau, K. Renault, M. Laly, S. Jenni, F. Ponsot and A. Romieu, *Tetrahedron Lett.*, 2020, **61**, 152582.

135 J. V Jun, D. M. Chenoweth and E. J. Petersson, *Org. Biomol. Chem.*, 2020, **18**, 5747–5763.

136 L. D. Lavis and R. T. Raines, *ACS Chem. Biol.*, 2014, **9**, 855–866.

137 C. M. Jones, G. A. Petersson and E. J. Petersson, *ARKIVOC*, 2021, **5**, 97–109.

138 L. C. Speight, A. K. Muthusamy, J. M. Goldberg, J. B. Warner, R. F. Wissner, T. S. Willi, B. F. Woodman, R. A. Mehl and E. J. Petersson, *J. Am. Chem. Soc.*, 2013, **135**, 18806–18814.

139 I. Sungwienwong, Z. M. Hostetler, R. J. Blizzard, J. J. Porter, C. M. Driggers, L. Z. Mbengi, J. A. Villegas, L. C. Speight, J. G. Saven, J. J. Perona, R. M. Kohli, R. A. Mehl and E. J. Petersson, *Org. Biomol. Chem.*, 2017, **15**, 3603–3610.

140 C. M. Jones, D. M. Robkis, R. J. Blizzard, M. Munari, Y. Venkatesh, T. S. Mihaila, A. J. Eddins, R. A. Mehl, W. N. Zagotta, S. E. Gordon and E. J. Petersson, *Chem. Sci.*, 2021, **12**, 11955–11964.

141 I. Sungwienwong, J. J. Ferrie, J. V Jun, C. Liu, T. M. Barrett, Z. M. Hostetler, N. Ieda, A. Hendricks, A. K. Muthusamy, R. M. Kohli, D. M. Chenoweth, G. A. Petersson and E. J. Petersson, *J. Phys. Org. Chem.*, 2018, **31**, e3813.

142 M. Taki, Y. Yamazaki, Y. Suzuki and M. Sisido, *Chem. Lett.*, 2010, **39**, 818–819.

143 J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158–1174.

144 D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 57–68.

145 A. T. Florence and D. Attwood, eds. A. T. Florence and D. Attwood, Macmillan Education UK, London, 1998, pp. 101–151.

146 A. C. Dodds, S. Puddu and A. Sutherland, *Org. Biomol. Chem.*, 2022, **20**, 5602–5614.

147 F. Khan, M. Mahmoudi, D. Volyniuk, J. V. Grazulevicius and R. Misra, *J. Phys. Chem. C*, 2022, **126**, 15573–15586.

148 S. S. Deshpande, H. S. Kumbhar and G. S. Shankarling, *Spectrochim. Acta. A. Mol. Biomol. Spectrosc.*, 2017, **174**, 154–163.

149 F. Zhao, J. Du, Z. Li and T. Sun, *J. Lumin.*, 2023, **254**, 119529.

150 L. Li, R. Wang, L. Wang and L. Huang, *J. Mol. Struct.*, 2022, **1249**, 131596.

151 Y. Fu and N. S. Finney, *RSC Adv.*, 2018, **8**, 29051–29061.

152 D. Wu, A. C. Sedgwick, T. Gunnlaugsson, E. U. Akkaya, J. Yoon and T. D. James, *Chem. Soc. Rev.*, 2017, **46**, 7105–7123.

153 N. C. Shaner, P. A. Steinbach and R. Y. Tsien, *Nat. Methods*, 2005, **2**, 905–909.

154 D. Svechkarev and A. M. Mohs, *Curr. Med. Chem.*, 2019, **26**, 4042–4064.

155 Z. Cheng, E. Kuru, A. Sachdeva and M. Vendrell, *Nat. Rev. Chem.*, 2020, **4**, 275–290.

156 A. H. Harkiss and A. Sutherland, *Org. Biomol. Chem.*, 2016, **14**, 8911–8921.

157 R. Y. Tsien, *Annu. Rev. Biochem.*, 1998, **67**, 509–544.

158 R. W. Sinkeldam, N. J. Greco and Y. Tor, *Chem. Rev.*, 2010, **110**, 2579–2619.

159 M. S. T. Gonçalves, *Chem. Rev.*, 2009, **109**, 190–212.

160 A. T. Krueger and B. Imperiali, *Chembiochem*, 2013, **14**, 788–799.

161 J. R. Lakowicz, Ed., *Introduction to Fluorescence BT - Principles of Fluorescence Spectroscopy*, Springer US, Boston, MA, 2006.

162 L. Stryer and R. P. Haugland, *Proc. Natl. Acad. Sci. U. S. A.*, 1967, **58**, 719–726.

163 J. Shaya, F. Fontaine-Vive, B. Y. Michel and A. Burger, *Chem. Eur. J.*, 2016, **22**, 10627–10637.

164 C. Zhang, Z. Han, M. Wang, Z. Yang, X. Ran and W. He, *Dalt. Trans.*, 2018, **47**, 2285–2291.

165 L. D. Lavis and R. T. Raines, *ACS Chem. Biol.*, 2008, **3**, 142–155.

166 T. Terai and T. Nagano, *Pflügers Arch. - Eur. J. Physiol.*, 2013, **465**, 347–359.

167 J. B. Grimm, B. P. English, H. Choi, A. K. Muthusamy, B. P. Mehl, P. Dong, T. A. Brown, J. Lippincott-Schwartz, Z. Liu, T. Lionnet and L. D. Lavis, *Nat. Methods*, 2016, **13**, 985–988.

168 J. B. Grimm, A. K. Muthusamy, Y. Liang, T. A. Brown, W. C. Lemon, R. Patel, R. Lu, J. J. Macklin, P. J. Keller, N. Ji and L. D. Lavis, *Nat. Methods*, 2017, **14**, 987–994.

169 J. D. Bell, A. H. Harkiss, D. Nobis, E. Malcolm, A. Knuhtsen, C. R. Wellaway, A. G. Jamieson, S. W. Magennis and A. Sutherland, *Chem. Commun.*, 2020, **56**, 1887–1890.

170 M. S. Michie, R. Götz, C. Franke, M. Bowler, N. Kumari, V. Magidson, M. Levitus, J. Loncarek, M. Sauer and M. J. Schnermann, *J. Am. Chem. Soc.*, 2017, **139**, 12406–12409.

171 L. Gilfillan, R. Artschwager, A. H. Harkiss, R. M. J. Liskamp and A. Sutherland, *Org. Biomol. Chem.*, 2015, **13**, 4514–4523.

172 A. H. Harkiss, J. D. Bell, A. Knuhtsen, A. G. Jamieson and A. Sutherland, *J. Org. Chem.*, 2019, **84**, 2879–2890.

173 J. D. Bell, T. E. F. Morgan, N. Buijs, A. H. Harkiss, C. R. Wellaway and A. Sutherland, *J. Org. Chem.*, 2019, **84**, 10436–10448.

174 L. M. Riley, T. N. Mclay and A. Sutherland, *J. Org. Chem.*, 2023, **88**, 2453–2463.

175 A. Acharyya, W. Zhang and F. Gai, *J. Phys. Chem. B*, 2021, **125**, 5458–5465.

176 M. R. Hilaire, I. A. Ahmed, C.-W. Lin, H. Jo, W. F. DeGrado and F. Gai, *Proc. Natl. Acad. Sci.*, 2017, **114**, 6005–6009.

177 K. Zhang, I. A. Ahmed, H. T. Kratochvil, W. F. DeGrado, F. Gai and H. Jo,

Chem. Commun., 2019, **55**, 5095–5098.

178 Y. S. Moroz, W. Binder, P. Nygren, G. A. Caputo and I. V Korendovych, *Chem. Commun.*, 2013, **49**, 490–492.

179 G. Loidl, H. J. Musiol, N. Budisa, R. Huber, S. Poirot, D. Fourmy and L. Moroder, *J. Pept. Sci.*, 2000, **6**, 139–144.

180 G. A. Molander, K. M. Traister and T. Barcellos, *J. Org. Chem.*, 2013, **78**, 4123–4131.

181 T. Kinzel, Y. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 14073–14075.

182 D. W. Pierce and S. G. Boxer, *Biophys. J.*, 1995, **68**, 1583–1591.

183 R. J. Micikas, I. A. Ahmed, A. Acharyya, A. B. Smith and F. Gai, *Phys. Chem. Chem. Phys.*, 2021, **23**, 6433–6437.

184 J. A. Downs and S. P. Jackson, *Nat. Rev. Mol. Cell Biol.*, 2004, **5**, 367–378.

185 J. A. Gomez, J. Chen, J. Ngo, D. Hajkova, I.-J. Yeh, V. Gama, M. Miyagi and S. Matsuyama, *Pharmaceuticals*, 2010, 3, 3594–3613.

186 A. Diaspro, G. Chirico and M. Collini, *Q. Rev. Biophys.*, 2005, **38**, 97–166.

187 D. B. Nowak, A. J. Lawrence and E. J. Sánchez, *Appl. Opt.*, 2010, **49**, 6766–6771.

188 W.-C. Gao, T. Liu, B. Zhang, X. Li, W.-L. Wei, Q. Liu, J. Tian and H.-H. Chang, *J. Org. Chem.*, 2016, **81**, 11297–11304.

189 D. Huang, H. Wang, H. Guan, H. Huang and Y. Shi, *Org. Lett.*, 2011, **13**, 1548–1551.

190 S. J. Singha Roy and S. Mukherjee, *Org. Biomol. Chem.*, 2017, **15**, 6921–6925.

191 C. W. Chen, Y. L. Chen, D. M. Reddy, K. Du, C. E. Li, B. H. Shih, Y. J. Xue and C. F. Lee, *Chem. Eur. J.*, 2017, **23**, 10087–10091.

192 J. Vicente, J. A. Abad and R. M. López-Nicolás, *Tetrahedron Lett.*, 2005, **46**, 5839–5840.

193 L. Li, H. Miao and Y. Ding, *Tetrahedron Lett.*, 2015, **56**, 6405–6408.

194 N. Sakai, H. Maeda and Y. Ogiwara, *Synthesis (Stuttg).*, 2019, **51**, 2323–2330.

195 Q. Feng, D. Chen, M. Hong, F. Wang and S. Huang, *J. Org. Chem.*, 2018, **83**, 7553–7558.

196 J. A. Fernández-Salas, A. P. Pulis and D. J. Procter, *Chem. Commun.*, 2016, **52**, 12364–12367.

197 R. Di Santo, R. Costi, G. Cuzzucoli Crucitti, L. Pescatori, F. Rosi, L. Scipione, D. Celona, M. Vertechy, O. Ghirardi, P. Piovesan, M. Marzi, S. Caccia, G. Guiso, F. Giorgi and P. Minetti, *J. Med. Chem.*, 2012, **55**, 8538–8548.

198 M. C. Bagley, V. Fusillo, E. G. B. Hills, A. T. Mulholland, J. Newcombe, L. J. Pentecost, E. L. Radley, B. R. Stephens and C. C. Turrell, *Arkivoc*, 2012, **7**, 294–313.

199 X. Huang, Y. Chen, S. Zhen, L. Song, M. Gao, P. Zhang, H. Li, B. Yuan and G. Yang, *J. Org. Chem.*, 2018, **83**, 7331–7340.

200 L. Bering, L. D'Ottavio, G. Sirvinskaite and A. P. Antonchick, *Chem. Commun.*, 2018, **54**, 13022–13025.

201 U. P. Saikia, F. L. Hussain, M. Suri and P. Pahari, *Tetrahedron Lett.*, 2016, **57**, 1158–1160.

202 C. Alp, Ş. Özsoy, N. A. Alp, D. Erdem, M. S. Gültekin, Ö. İ. Küfrevioğlu, M. Şentürk and C. T. Supuran, *J. Enzyme Inhib. Med. Chem.*, 2012, **27**, 818–824.

203 D. Qiu, J. He, X. Yue, J. Shi and Y. Li, *Org. Lett.*, 2016, **18**, 3130–3133.

204 S. Li, R. Khan, X. Zhang, Y. Yang, Z. Wang, Y. Zhan, Y. Dai, Y. Liu and B. Fan, *Org. Biomol. Chem.*, 2019, **17**, 5891–5896.

205 H. Shirani and T. Janosik, *Synthesis (Stuttg).*, 2007, 2690–2698.

206 D. Equbal, R. Singh, Saima, A. G. Lavekar and A. K. Sinha, *J. Org. Chem.*, 2019, **84**, 2660–2675.

207 L. Chen, J. Pu, P. Liu and B. Dai, *J. Chem. Res.*, 2018, **42**, 456–462.

208 R. Chandrasekaran, S. Perumal and D. A. Wilson, *Magn. Reson. Chem.*,

1987, **25**, 1001–1006.

209 E. F. Elslager, Z. B. Gavrilis, A. A. Phillips and D. F. Worth, *J. Med. Chem.*, 1969, **12**, 357–363.

210 H. Tanaka, H. Konishi and K. Manabe, *Chem. Lett.*, 2019, **48**, 760–763.

211 Q. Cao, W. I. Nicholson, A. C. Jones and D. L. Browne, *Org. Biomol. Chem.*, 2019, **17**, 1722–1726.

212 R. N. Gaykar, S. Bhattacharjee and A. T. Biju, *Org. Lett.*, 2019, **21**, 737–740.

213 K. Oyama and T. Kondo, *Org. Lett.*, 2003, **5**, 209–212.

214 S. Choi, J. Park, E. Yu, J. Sim and C. Park, *Angew. Chem. Int. Ed.*, 2020, **59**, 11886–11891.

215 R. Wang, X. Han, J. Xu, P. Liu and F. Li, *J. Org. Chem.*, 2020, **85**, 2242–2249.

216 P. Wipf and J. P. Maciejewski, *Org. Lett.*, 2008, **10**, 4383–4386.

217 J. Jiang, S. Zeng, D. Chen, C. Cheng, W. Deng and J. Xiang, *Org. Biomol. Chem.*, 2018, **16**, 5016–5020.

218 Y. Qiao, G. Li, S. Liu, Y. Yangkai, J. Tu and F. Xu, *Synthesis (Stuttg).*, 2017, **49**, 1834–1838.

219 C.-C. Chien, S.-C. Kao, C.-J. Chen and Y.-K. Wu, *Chem. Commun.*, 2020, **56**, 15470–15472.

220 S. Fujimoto, K. Matsumoto, T. Iwata and M. Shindo, *Tetrahedron Lett.*, 2017, **58**, 973–976.

221 C. L. Magyar, T. J. Wall, S. B. Davies, M. V Campbell, H. A. Barna, S. R. Smith, C. J. Savich and R. A. Mosey, *Org. Biomol. Chem.*, 2019, **17**, 7995–8000.

222 L. Schulz, M. Enders, B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke and S. R. Waldvogel, *Angew. Chem. Int. Ed.*, 2017, **56**, 4877–4881.

223 K. Dooleweerdt, B. P. Fors and S. L. Buchwald, *Org. Lett.*, 2010, **12**, 2350–2353.

224 H. Dai, C. Yu, C. Lu and H. Yan, *Eur. J. Org. Chem.*, 2016, 1255–1259.

225 T. Maejima, Y. Shimoda, K. Nozaki, S. Mori, Y. Sawama, Y. Monguchi and H. Sajiki, *Tetrahedron*, 2012, **68**, 1712–1722.

226 M. Huang, D. Huang, X. Zhu and Y. Wan, *Eur. J. Org. Chem.*, 2015, 4835–4839.

227 Q. Chen, R. Xie, H. Jia, J. Sun, G. Lu, H. Jiang and M. Zhang, *J. Org. Chem.*, 2020, **85**, 5629–5637.

228 Y. Lin, G. Lu, R. Wang and W. Yi, *Org. Lett.*, 2016, **18**, 6424–6427.

229 T. Matsumoto and Y. Matsunaga, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 648–653.

230 W. Hu and S. Zhang, *J. Org. Chem.*, 2015, **80**, 6128–6132.

231 B. Zhu, J. Ge and S. Q. Yao, *Bioorg. Med. Chem.*, 2015, **23**, 2917–2927.

232 S. R. Kandukuri, J. A. Schiffner and M. Oestreich, *Angew. Chem. Int. Ed.*, 2012, **51**, 1265–1269.