Iron-Catalysed Regioselective Functionalisation of Activated Arenes

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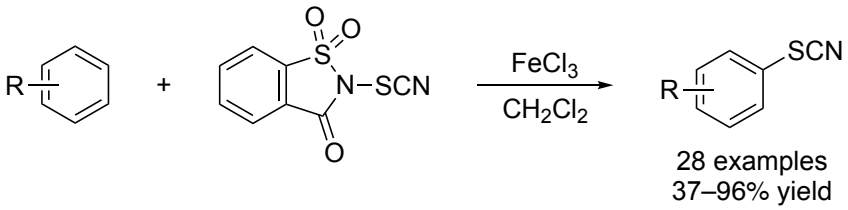
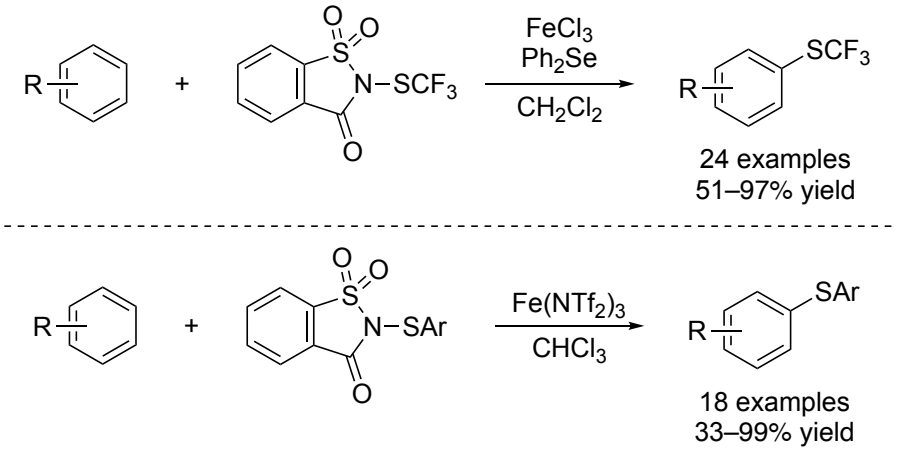
Abstract

The primary aim of this PhD was the development of new iron(III)-catalysed methodology for the regioselective functionalisation of activated arenes. The first section describes the optimisation and application of an iron(III) chloride-catalysed thiocyanation protocol using a saccharin-based electrophilic reagent. This was shown to be an efficient and rapid procedure with a wide substrate scope. The utility of the methodology was demonstrated with the synthesis and functionalisation of various biologically active compounds. The *para*-thiocyanation process was also combined with a subsequent tandem *ortho*-bromination for the one-pot dual functionalisation of anisole. This dual functionalised arene was then used as a key building block for the bi-directional, late-stage synthesis of a diverse library of arenes.

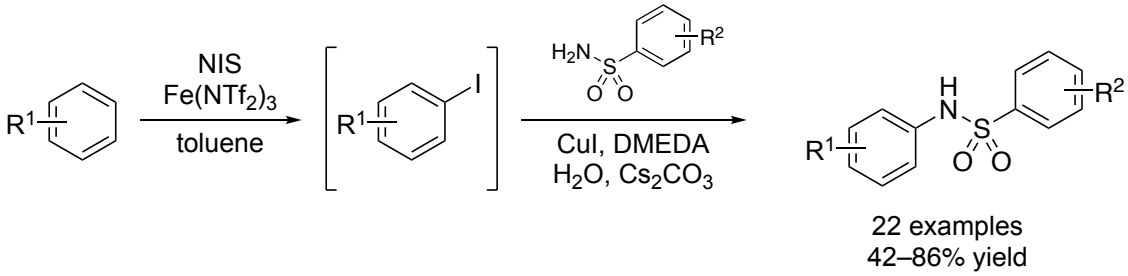


Analogous saccharin-based reagents were then used to develop procedures for the trifluoromethylthiolation and thioarylation of activated arenes. For the trifluoromethylthiolation process, diphenyl selenide was utilised as Lewis base in a dual catalytic Lewis acid/Lewis base process. The iron(III) triflimide-catalysed thioarylation process was faster and was performed under milder conditions than the previously developed methodology in the group, which used succinimide-based reagents.

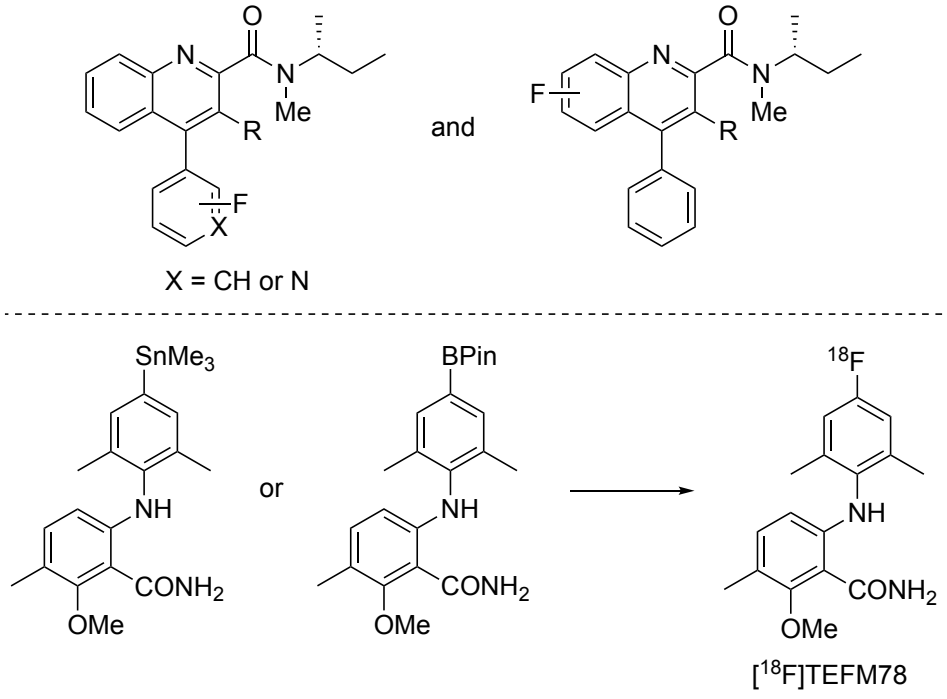


The final methodology project focused on the extension of a previously developed one-pot, two-step amidation process for the rapid synthesis of diaryl sulfonamides. This consisted of an iron(III) triflimide-catalysed iodination of activated arenes using NIS, followed by a

copper-catalysed Ullmann-type coupling with primary sulfonamides. This was found to give good to excellent yields and allowed the preparation of a wide range of diaryl sulfonamides. The utility of the one-pot process was demonstrated by the synthesis of three BET bromodomain inhibitors.



The second aim of this PhD was the development of novel PET imaging agents for two biological targets, the translocator protein (TSPO) and the sphingosine-1-phosphate-5 receptor ($S1P_5$). Ten potential TSPO ligands were synthesised based on the structure of the quinoline-2-carboxamide, [^{18}F]LW223, a promising TSPO radiotracer previously developed in the group. The physicochemical properties of these compounds were evaluated and future work will determine their binding affinities with TSPO in human tissue. In the $S1P_5$ project, synthetic routes to organotin and organoboron precursors of lead candidate TEFM78 were developed for radiofluorination and preparation of PET imaging agent [^{18}F]TEFM78. Both precursors are currently being assessed for automated radiofluorination and the preparation of high activity [^{18}F]TEFM78 for subsequent animal studies.



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Acknowledgements

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Thank you to all my friends outside of the lab, especially at triathlon club, for making it easier to switch off and remember that life isn't all about chemistry.

Most importantly, thanks to my mum, dad, brothers and wider family (and pets!) for all the support and encouragement during my PhD, undergraduate degree and everything else up to this point, even if you don't fully understand what I'm talking about most of the time. Finally, a massive thank you to Eilidh for being amazing throughout. You've kept me sane for the past three years and I'm not sure what I'd have done without you!

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis represents the original work of Lachlan J. N. Waddell 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 2020 and February 2024. Aspects of the work described herein have been published elsewhere as listed below.

L. J. N. Waddell, M. C. Henry, M. A. B. Mostafa and A. Sutherland, One-Pot Synthesis of Diaryl Sulfonamides using an Iron- and Copper-Catalyzed Aryl C–H Amidation Process, *Synthesis*, 2022, **54**, 4551–4560.

A. C. Dodds, L. J. N. Waddell and A. Sutherland, Regioselective Functionalization of Arenes Using Iron Triflimide Catalysis, *Synlett*, 2023, **34**, 1852–1865.

L. J. N. Waddell, M. R. Senkans and A. Sutherland, Regioselective C–H Thiocyanation of Arenes by Iron(III) Chloride, *J. Org. Chem.*, 2023, **88**, 7208–7218.

L. J. N. Waddell, C. Wilson and A. Sutherland, Trifluoromethylthiolation of Arenes Using Lewis Acid and Lewis Base Dual Catalysis, *J. Org. Chem.*, 2024, **89**, 1275–1284.

Abbreviations

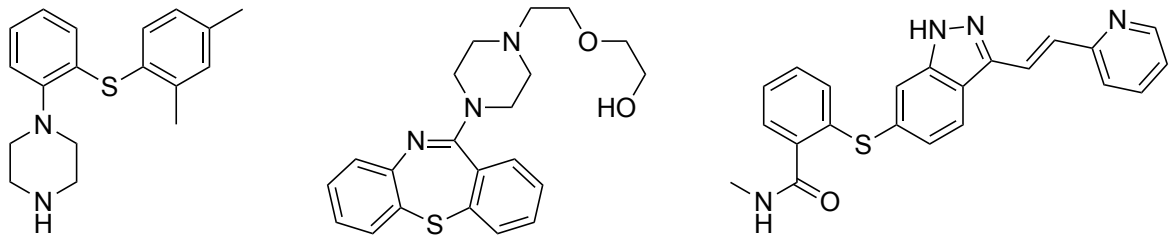
Ac	Acetyl
Ar	Aromatic
APCI	Atmospheric pressure chemical ionisation
[BMIM]NTf_2	1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide
BBB	Blood brain barrier
Bn	Benzyl
br	Broad
bpy	2,2'-Bipyridine
Cbz	Carboxybenzyl
CBX	1-Cyano-1,2-benziodoxol-3-(1*H*)-one
CBDX	1-Cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxol
CI	Chemical ionisation
CNS	Central nervous system
COD	1,5-Cyclooactadiene
COSY	Correlated spectroscopy
Cy	Cyclohexyl
d	Doublet
Da	Dalton
DCE	1,2-Dichloroethane
DEPT	Distortionless enhancement of polarisation transfer
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMEDA	1,2-Dimethylethylenediamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dtbbpy	4,4'-Bis-(*tert*-butyl)-2-2'-dipyridine
EDG	Electron donating group
EI	Electron impact
equiv.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
EDA	Electron-Donor-Acceptor

FDA	Food and Drug Administration
FTIR	Fourier-transform infrared spectroscopy
g	Gram(s)
GPCR	G-protein coupled receptor
h	Hour(s)
HAB	High affinity binder
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HMBC	Heteronuclear multiple bond correlation
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HSA	Human serum albumin
HSQC	Heteronuclear single quantum coherence
HRMS	High Resolution Mass Spectrometry
IAM	Immobilised artificial membrane
^{i}Pr	Isopropyl
IR	Infrared spectroscopy
J	Coupling constant
K_{222}	Kryptofix® 222
K_D	Dissociation constant
K_m	Membrane partition coefficient
LAB	Low affinity binder
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilamide
lit.	Literature
m	Multiplet
m	*meta*
MAB	Medium affinity binder
Me	Methyl
MeSal	Methyl salicylate
Mp	Melting point
Ms	Mesyl
MS	Multiple Sclerosis
m/z	Mass to charge ratio
n-Bu	*n*-Butyl
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide

NIS	*N*-Iodosuccinimide
nm	Nanometer
o	*ortho*
p	*para*
PET	Positron emission tomography
Ph	Phenyl
phen	1,10-Phenanthroline
P_m	Permeability
PPA	Polyphosphoric acid
PPB	Plasma protein binding
ppm	Parts per million
ppy	2-Phenylpyridine
q	Quartet
RCY	Radiochemical yield
rt	Room temperature
s	Singlet
S1P	Sphingosine-1-phosphate
SAR	Structure activity relationship
S_NAr	Nucleophilic aromatic substitution
SPECT	Single photon emission computed tomography
t	triplet
t-Bu	*tert*-Butyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
TSPO	Translocator protein
UV	Ultraviolet
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

1.0 Introduction

Sulfur is the 10th most abundant element in the periodic table and exists in oxidation states from −2 to +6.[1] Due to this versatility, it plays crucial roles in a variety of chemical and biochemical processes.[2] Thus, it is not a surprise that aryl sulfides are common motifs in many pharmaceuticals, agrochemicals and natural products.[3] In 2014, a survey revealed that 25% of the top 200 most prescribed drugs in the U.S. contain sulfur.[4] Examples include vortioxetine (**1**)**,** used for the treatment of major depressive disorder;[5] quetiapine (**2**), an antipsychotic drug;[6] and axitinib (**3**), which is used for the treatment of renal cell carcinoma (Figure 1).[7]



Vortioxetine (**1**) Quetiapine (**2**) Axitinib (**3**)

Figure 1: Vortioxetine (**1**), quetiapine (**2**) and axitinib (**3**).

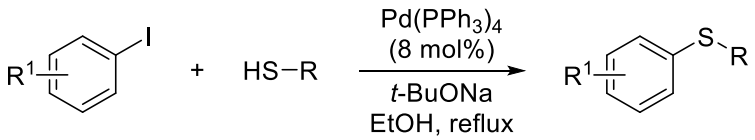
Given the widespread prevalence of aryl sulfides, the synthesis of aryl C–S bonds has attracted significant attention from organic chemists. Traditionally, aryl C–S disconnections were achieved by alkylation of aryl thiols however, this approach can be complicated by the use of thiols as precursors, which can be toxic, pungent and unstable. In addition, the use of this approach for introduction of moieties such as thiocyanates, trifluoromethyl thioethers and diaryl sulfides is rendered undesirable due to hard to handle gaseous reagents and poor reactivity, respectively.

Transition-metal-catalysis offers an attractive alternative and metals such as palladium, copper and nickel have found widespread use in the construction of C–S bonds.[3,8–10] Brønsted and Lewis acid-catalysis has also been found to be effective in the synthesis of aryl sulfides.[11–13]

1.1 Transition-Metal-Catalysed C–S Bond Formation

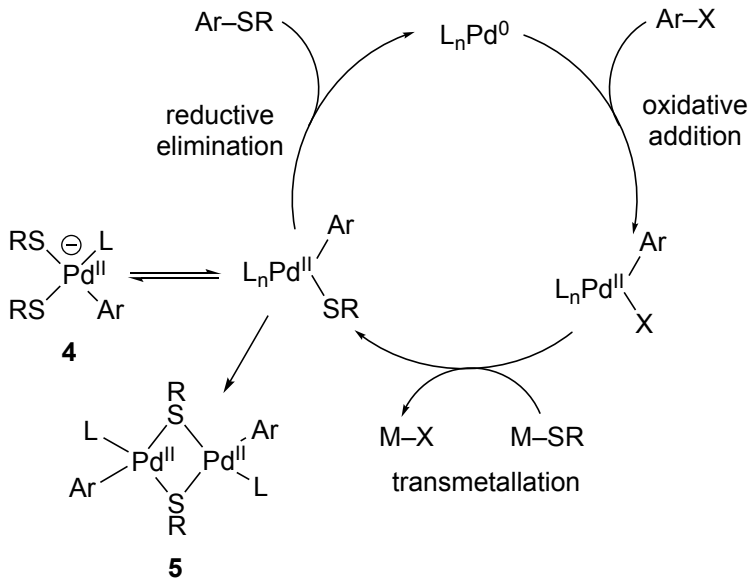
Migita and co-workers reported the first example of palladium-catalysed synthesis of aryl sulfides (Scheme 1).[14,15] The procedure was found to work well for some couplings, but suffered from several drawbacks. Forcing conditions were required, with catalyst loadings

of 8 mol% and temperatures of 80–100 °C used. Moreover, the substrate scope was limited to simple aryl iodides and aryl/alkyl thiols, with little functional group tolerance indicated.



Scheme 1: Palladium catalysed coupling of aryl iodides with thiols reported by Migita and co-workers.

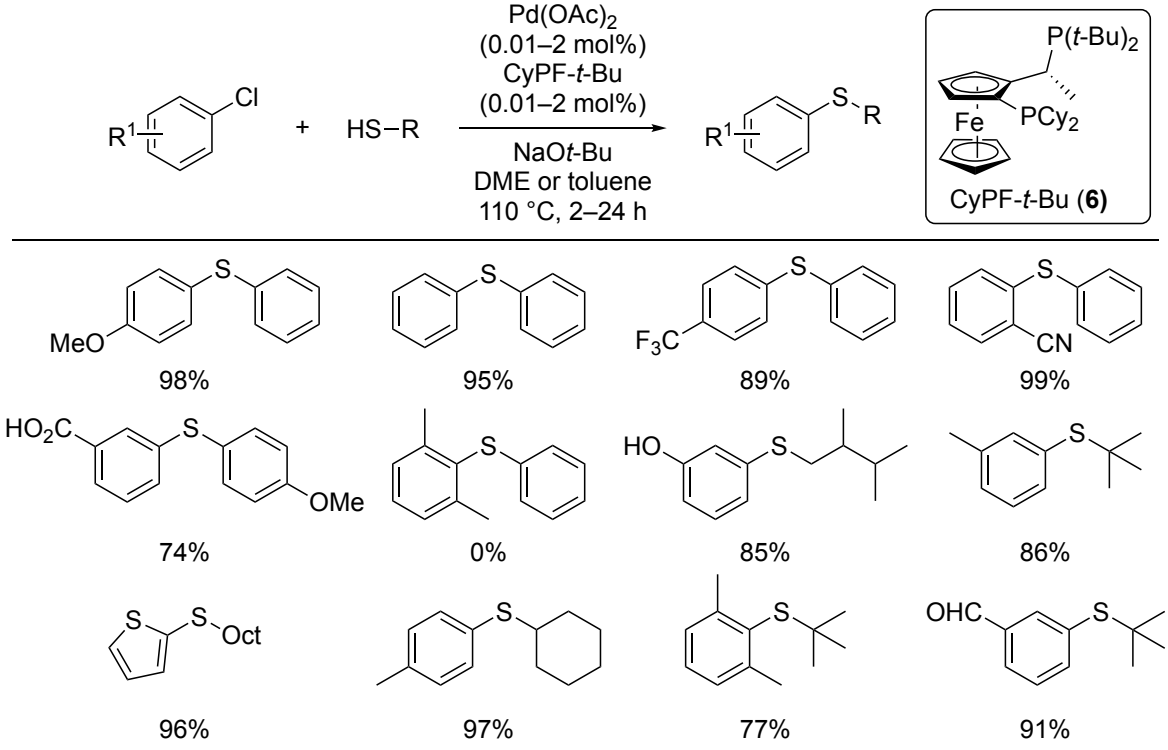
The proposed mechanism involved oxidative addition of the aryl iodide to the palladium catalyst followed by transmetallation of the thiolate and then reductive elimination (Scheme 2).[14,15] Further investigations by Hartwig and co-workers revealed additional mechanistic details.[16–18] It was found that ligands can be readily displaced by thiolates to from anionic complexes **4** or bridging complexes **5**. These pathways are unproductive and can reversibly or irreversibly deactivate the palladium catalyst, explaining the need for high catalyst loadings.



Scheme 2: Proposed mechanism for palladium catalysed C–S bond formation.

Hartwig and co-workers hypothesised that a bulkier biphosphate ligand might inhibit the formation of these unproductive complexes by binding to the metal centre more strongly, while also promoting oxidative addition and reductive elimination.[19,20] Therefore, it was proposed that the CyPF-*t*-Bu ligand **6** could be an efficient ligand for this transformation (Scheme 3). It was found that the reaction with this ligand was extremely efficient, with catalyst loadings of <3 mol% required for reaction with aryl chlorides, which had previously been poor substrates for palladium-catalysed thiolations. A wide substrate scope was established, including electron-poor and electron-rich chlorides, alkyl and aryl thiols and

various functional groups such as esters, ketones, nitriles, amides, phenols and anilines. The products were often isolated in excellent yields of >85%. Some sterically hindered aryl chlorides, such as 2-chloro-1,3-dimethylbenzene, required longer reaction times or did not react at all. Bulky thiols were well tolerated but electron-deficient thiols were poor substrates for this reaction.



Scheme 3: Substrate scope for the palladium-catalysed procedure with CyPF-*t*-Bu (**6**).

Hartwig and co-workers subsequently demonstrated that some of the limitations of this methodology could be addressed by using aryl bromides or iodides, with more sterically hindered aryl halides tolerated.[21] However, electron-poor thiols were still unreactive.

In 2012, Buchwald and co-workers extended the scope of this transformation to the synthesis of aryl trifluoromethylthioethers.[22] The presence of the trifluoromethylsulfenyl group in bioactive compounds often results in improved pharmacokinetic properties due to its high lipophilicity and Hansch parameter (1.44).[23,24] This enables compounds to pass through cell membranes more readily. Some examples of biologically active compounds bearing aryl trifluoromethylthioethers include toltrazuril (**7**), an antiparasitic agent,[25] and tiflorex (**8**), an appetite suppressant (Figure 2).[26] Aryl trifluoromethylthioethers can also be used as precursors for the synthesis of sulfoxides or sulfones such as fipronil (**9**), which has found widespread use as an insecticide for treatment of pets, livestock and crops.[27]

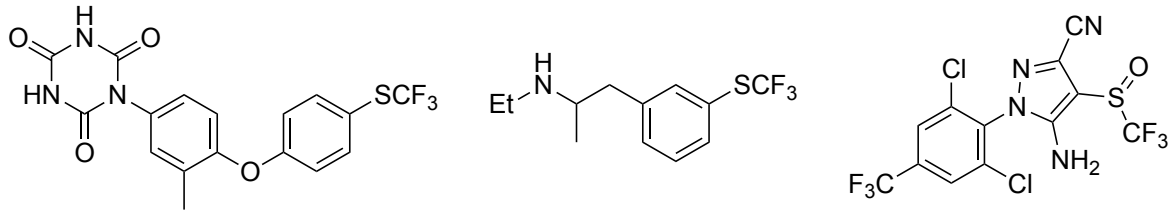
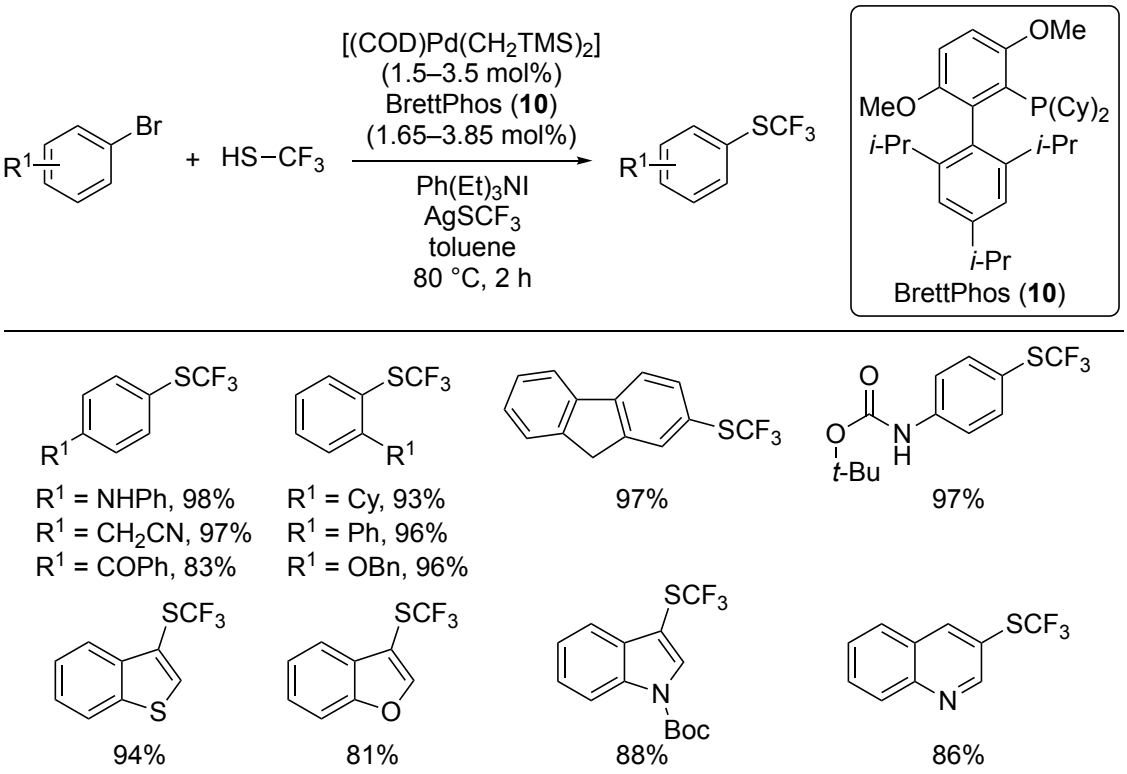


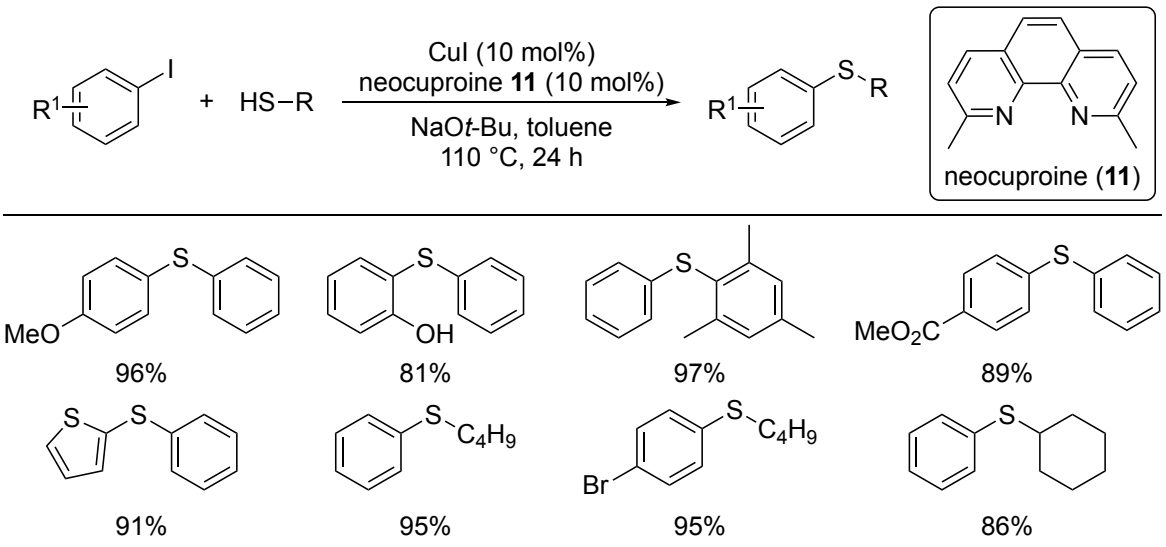
Figure 2: Biologically active compounds bearing aryl trifluoromethylthioethers.

However, the trifluoromethylthiolate anion is a poor nucleophile and it was thought that the main challenge with this transformation would be sluggish transmetallation/reductive elimination steps.[22] It was hypothesised that bulky, electron-rich phosphine ligands such as BrettPhos (**10**) would remediate this issue, having previously been shown to catalyse couplings with less reactive nucleophiles.[28] The combination of $AgSCF_3$ and $Ph(Et)_3NI$ generated $Ph(Et)N_3^+[Ag(SCF_3)I]^-$, which participated in the palladium-catalysed reaction. This complex was more active than only $AgSCF_3$, which was proposed to be due to its anionic nature and superior solubility. Similarly to previously discussed processes, the reaction was insensitive to the electronics of the aryl bromides, furnishing a wide range of products in >80% yield (Scheme 4). Several heterocyclic compounds were also found to be good substrates for this methodology.



Scheme 4: Substrate scope for the palladium-catalysed trifluoromethylthiolation procedure.

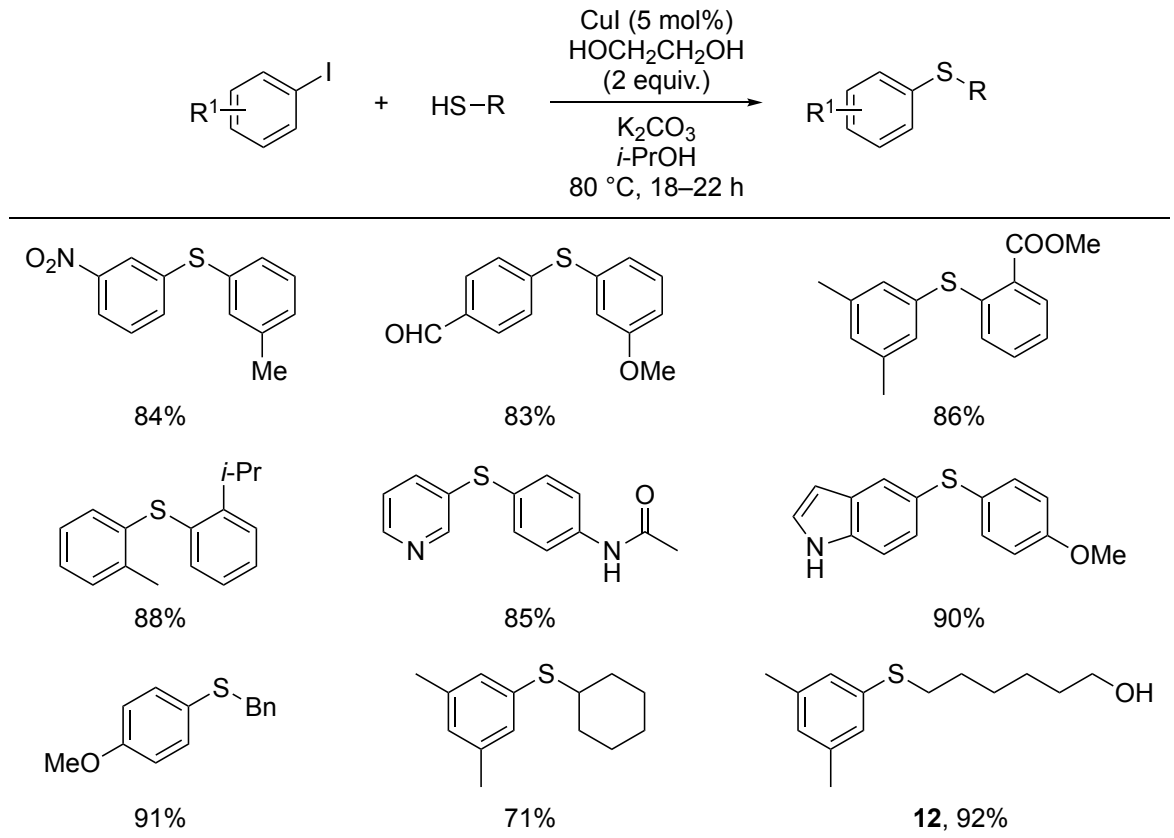
While palladium-catalysed procedures are effective, methods using earth abundant transition-metals are desirable. Copper-catalysis offers an attractive alternative but early methods were hindered by significant limitations including high reaction temperatures, low yields, use of stoichiometric copper and poor functional group tolerance.[29–31] However, in 2002 Venkataraman and co-workers reported a procedure reacting aryl iodides with thiols in the presence of sodium *tert*-butoxide, copper(I) iodide (10 mol%) and neocuproine (**11**) in toluene at 110 °C (Scheme 5).[32] The procedure was effective for electron-poor and electron-rich halides, and aryl and alkyl thiols, with all reported yields >80%. Sterically hindered aryl iodides and thiols were also found to form the desired products in excellent yields. Phenols and esters were tolerated, but no other functional groups were included in the substrate scope.



Scheme 5: Substrate scope for the copper-catalysed procedure with copper(I) iodide and neocuproine (**11**).

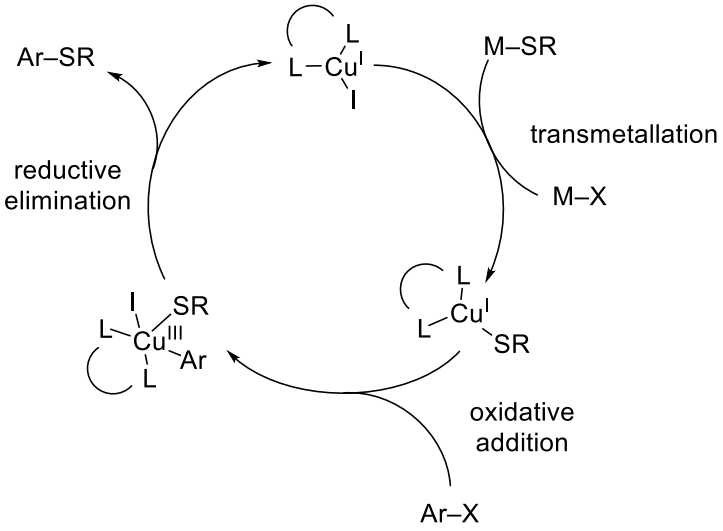
Several months later, Buchwald and co-workers reported an improved procedure.[33] Copper(I) iodide was paired with ethylene glycol as the ligand and potassium carbonate as the base. The use of isopropanol as the solvent resulted in an operationally simple, milder and low-cost protocol. Moreover, a significantly broader substrate scope was demonstrated (Scheme 6). Aryl halides bearing aldehydes, nitriles, carboxylic acids, anilines, alkyl amines, alcohols and esters were all demonstrated as competent substrates. Sterically demanding reactions were also found to be efficient, such as the coupling of 2-isopropylthiophenol with 2-iodotoluene, which proceeded in 88% yield. Impressively, electron-deficient aryl thiols such as 2-chlorothiophenol and methyl thiosalicylate were well tolerated, which compares well to previously discussed palladium-catalysed reactions.[19–21] Selectivity was also observed when alkyl thiols bearing alcohols, and aryl thiols bearing phenols, were used. For example, the reaction of 3,5-dimethylphenyl iodide with 6-hydroxy-1-hexanethiol gave exclusively the desired thioether product **12** in 92% yield. Subsequent contributions by

Guo,[34] Chaudhury[35] and Feng[36] have expanded the transformation to aryl bromides, but practical processes involving aryl chlorides have not yet been reported.



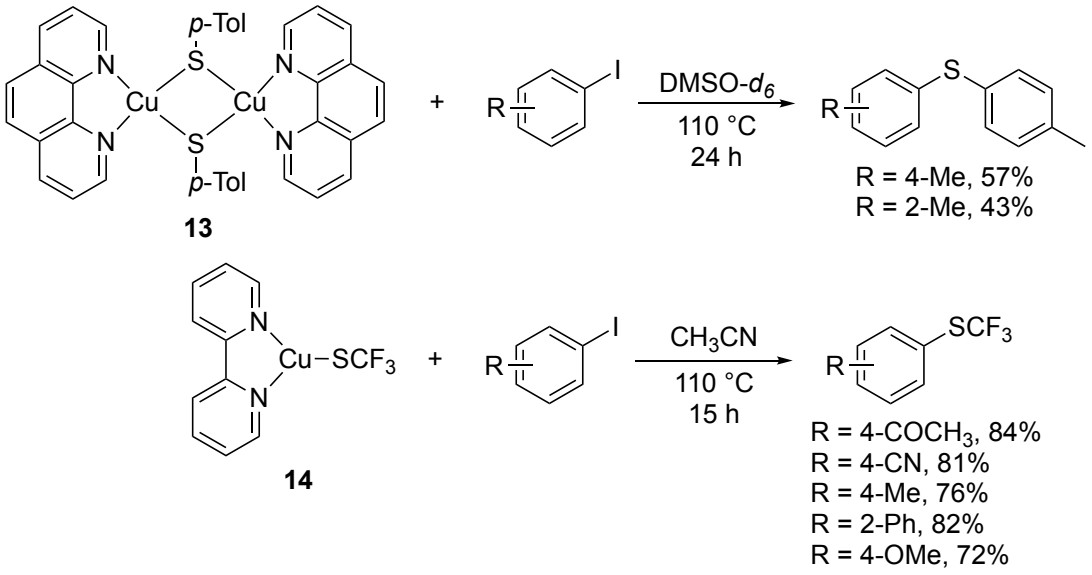
Scheme 6: Substrate scope for the copper-catalysed procedure with copper(I) iodide and ethylene glycol.

The mechanism of copper-catalysed C–S bond forming reactions has received far less attention than the analogous C–N and C–O bond forming procedures, but analogous mechanisms involving Cu(I)/Cu(III) have been proposed.[34–36] First, transmetallation with a thiolate occurs, followed by oxidative addition of the aryl halide and then reductive elimination furnishes the thioether (Scheme 7).



Scheme 7: Proposed mechanism of copper-catalysed reaction using aryl iodides and thiols.

Reports from the Buchwald and Huang groups in 2012 and 2013, respectively, provided evidence for this mechanism.[37,38] Buchwald and co-workers prepared and characterised a series of dimeric Cu(I) complexes, including [Cu(S-*p*-Tol)(phen)]$_2$ (**13**), while Huang and co-workers synthesised trifluoromethylthiolato complexes, including [Cu(SCF$_3$)(bpy)] (**14**) (Scheme 8). These complexes are intermediates in this mechanism following the transmetallation step. It was found that when these were heated in the presence of aryl iodides, the desired thioethers were formed in moderate to excellent yields. These results are consistent with transmetallation occurring before oxidative addition. Further DFT calculations by Huang also provided evidence for the proposed mechanism.[38]

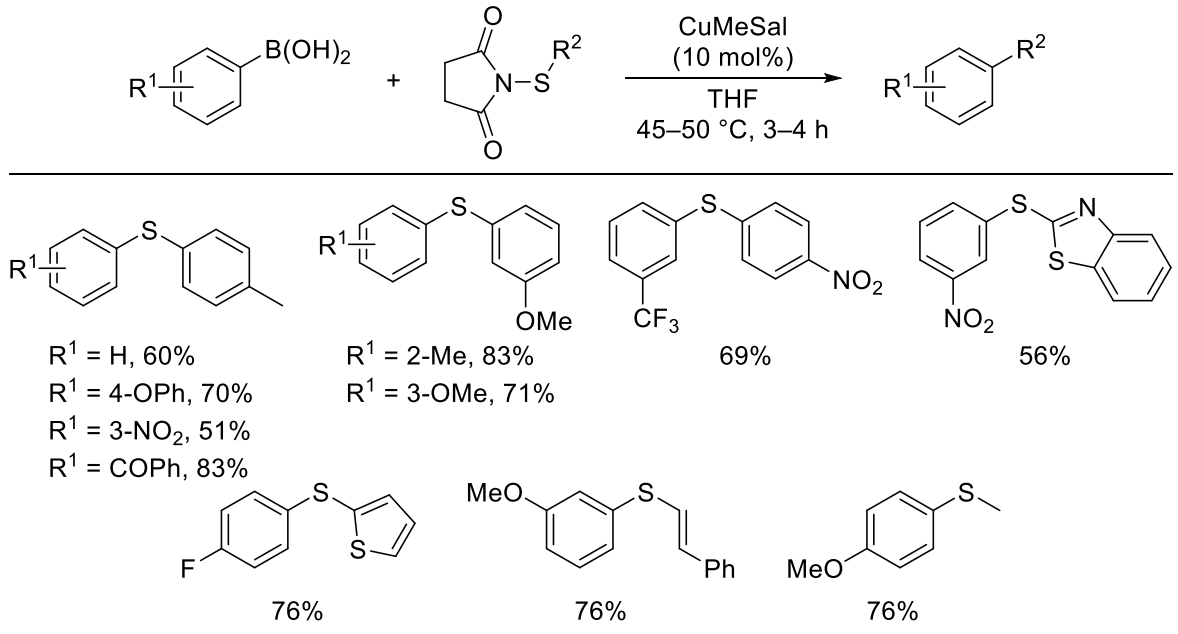


Scheme 8: Mechanistic studies by Buchwald (top) and Huang (bottom).

Copper-catalysed Chan-Lam type reactions have also been explored for C–S bond formation. With the advent of the Suzuki-Miyaura reaction, aryl boronic acids are widely

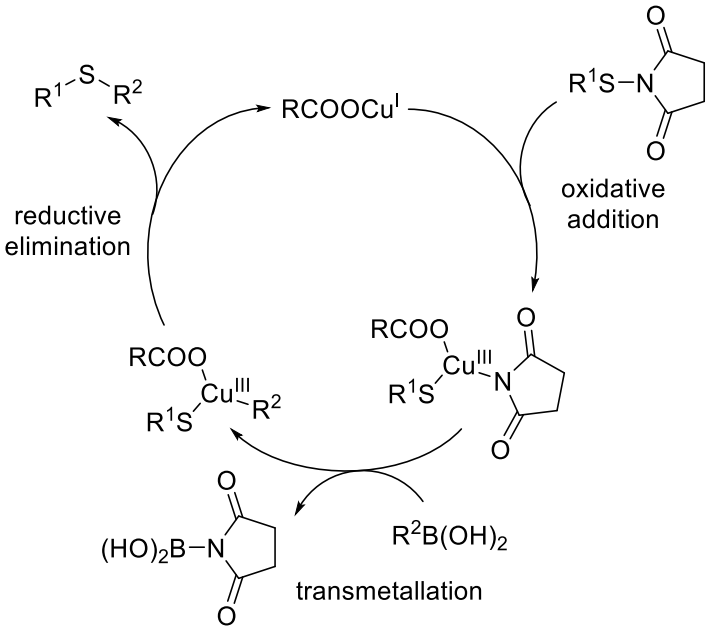
available and inexpensive, so reactions utilising these substrates are convenient. This type of reaction was first reported by Guy and co-workers in 2000, but harsh conditions were required.[39] Alkyl thiols and aryl boronic acids were heated under reflux in dimethylformamide in the presence of stoichiometric copper(II) acetate and pyridine, furnishing alkyl aryl thioethers.

Liebeskind and co-workers hypothesised that the sulfur source was actually disulfides, formed *in situ* from the oxidation of thiols by copper(II) acetate, which was reduced to form an active copper(I) species.[40] Therefore, it was proposed that by using disulfides and a copper(I) source, the reaction could be rendered catalytic and performed under milder conditions. However, the use of disulfides still required stoichiometric quantities of copper(I) methyl salicylate – it was thought that this was due to half of each disulfide equivalent reacting to form copper(I) thiolates. Therefore, alternative thiol surrogates were considered. When *N*-thiosuccinimides were utilised, the reaction proceeded using 20–30 mol% of copper(I) methyl salicylate in tetrahydrofuran using base-free conditions and temperatures of 45–50 °C (Scheme 9). The use of *N*-thiosuccinimides as a sulfur source is desirable as the use of toxic, pungent and sometimes unstable thiols is avoided. By comparison, *N*-thiosuccinimides are usually stable, easily handled solids. The mild procedure was found to be applicable for electron-rich and electron-poor substrates for both the boronic acid and *N*-thiosuccinimide coupling partners. The use of a vinyl boronic acid was also demonstrated. However, it should be noted that no nucleophilic substrates, such as alcohols or amines, were reported. Additionally, the procedure was generally lower yielding (51–79%) than the previously discussed palladium-catalysed methodologies.



Scheme 9: Substrate scope for the copper-catalysed reaction of boronic acids with *N*-thiosuccinimides.

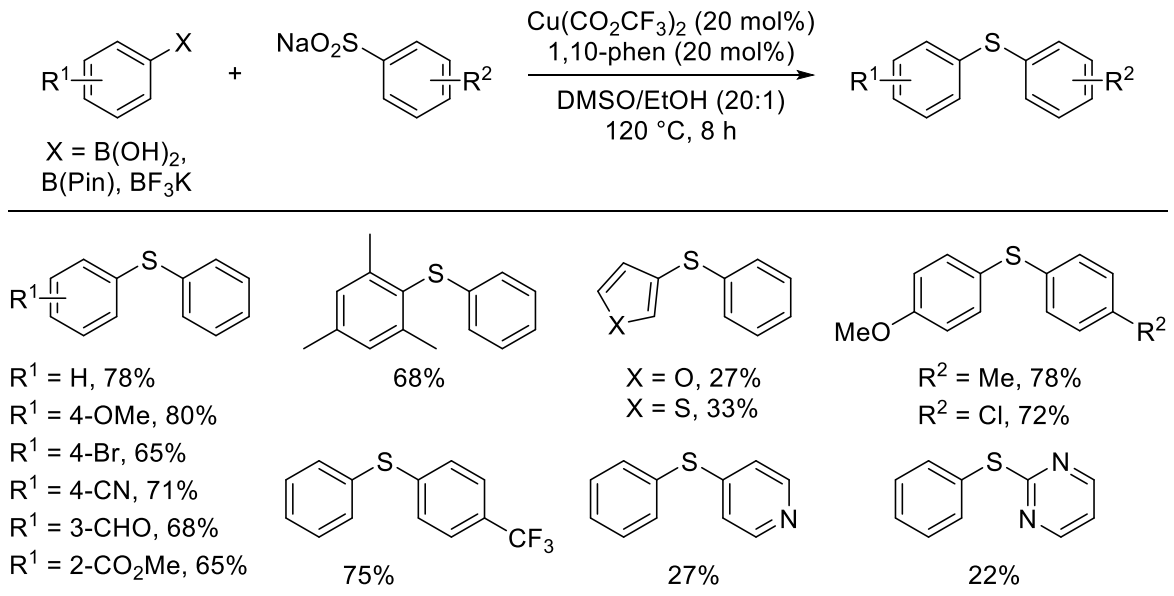
The authors proposed a speculative mechanism involving oxidative addition of the *N*-thiosuccinimide to copper(I) 3-methylsalicylate to form a copper(III) species. This is followed by transmetallation of the boronic acid and reductive elimination to form the desired product, with regeneration of the catalyst (Scheme 10).[40] Other copper(I) carboxylates such as copper(I) acetate and copper(I) thiophene-2-carboxylate were also found to effectively catalyse the process, but other copper(I) sources such as copper(I) oxide and copper(I) chloride were inactive.



Scheme 10: Proposed mechanism of copper-catalysed reaction of boronic acids with *N*-thiosuccinimides.

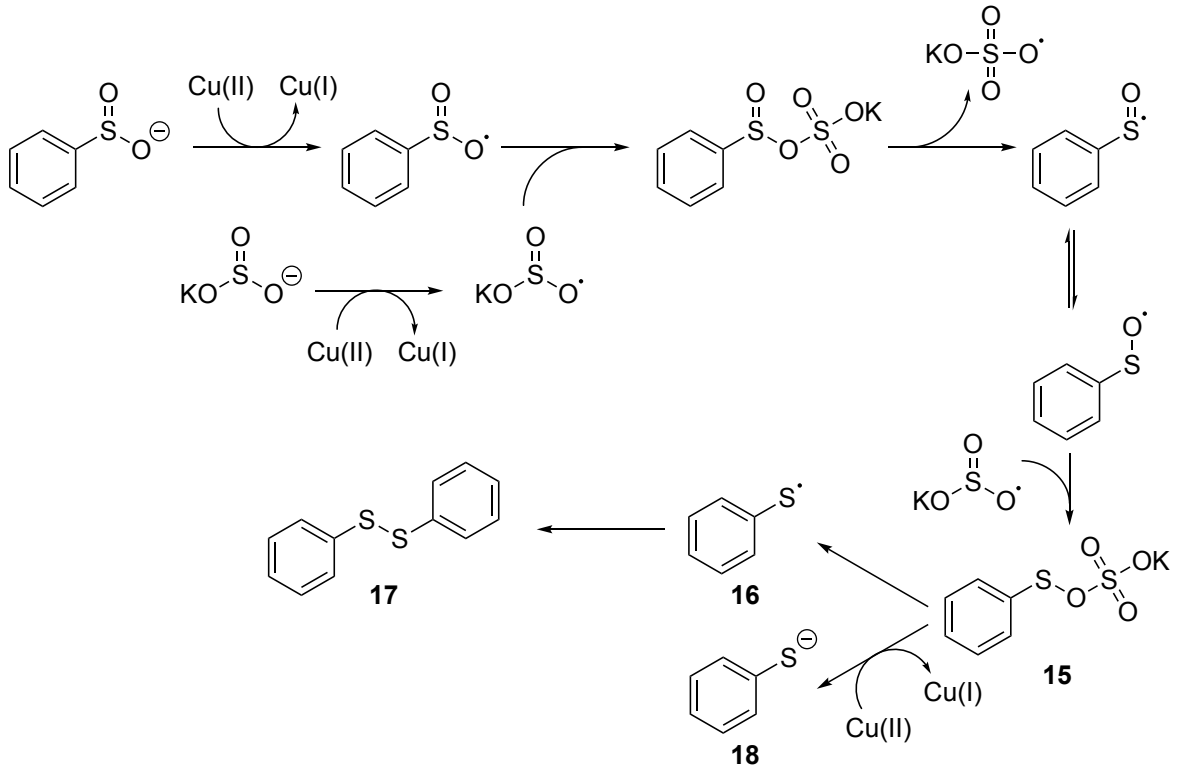
Recently, Ma and co-workers disclosed a procedure utilising sodium sulfinates as thiol surrogates in Chan-Lam-type couplings.[41] Optimisation studies revealed that both copper(I) iodide and copper(II) trifluoroacetate, respectively, were able to catalyse the reaction. 1,10-Phenanthroline was shown to be the optimal ligand and potassium sulfite was used as the base with a 20:1 mixture of dimethyl sulfoxide and ethanol, which was found to effectively solvate all reagents. However, a high temperature of 120 °C was necessary for this reaction. An extensive substate scope study was conducted, with over 50 examples reported (Scheme 11). Regarding the boronic acids, several functional groups were tolerated, including esters, aldehydes, halides, ethers and nitriles. Moreover, the sterically hindered 2,4,6-trimethylphenylboronic acid was coupled with sodium benzenesulfinate in a 68% yield. Other boron sources well also found to be compatible with this procedure, including boronic esters and potassium trifluoroborates. However, the substrate scope of sodium sulfinates was poor. Only halides, alkyl and trifluoromethyl groups were found to participate in reactions giving good or excellent yields, with the use of electron rich sulfinates such as sodium 4-methoxybenzenesulfinate resulting in poor yields. Moreover, heterocycles were generally poorly tolerated in both couplings partners. Nonetheless, given the ease of

handling, stability and commercial availability of sodium sulfinates, this report was a promising development.



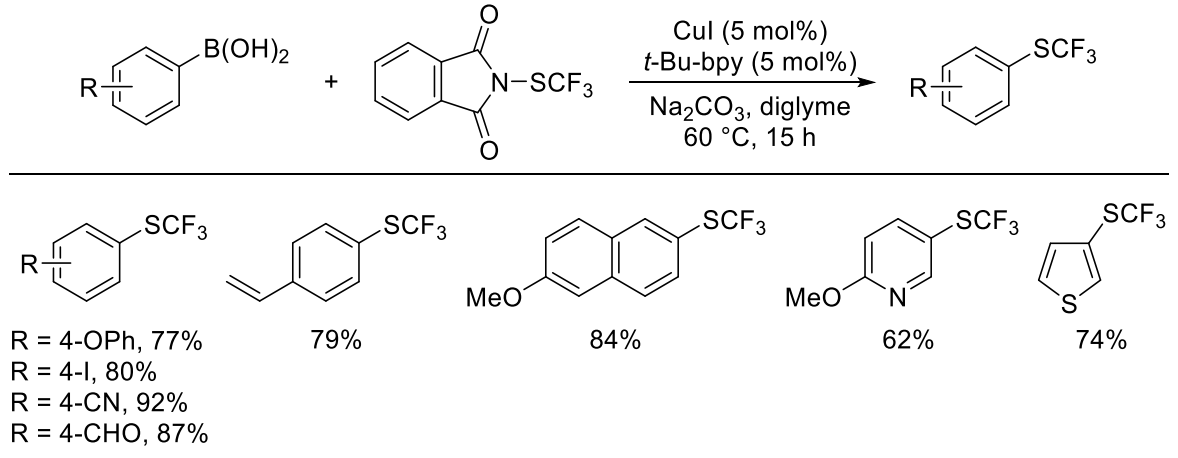
Scheme 11: Substrate scope for the copper-catalysed reaction of boronic acids with sodium sulfinates.

The proposed mechanism in Scheme 12 involves a complex series of radical-mediated steps involving potassium sulfite to form key intermediate **15**, which can then undergo homolytic cleavage to form thiyl radical **16**.[41] It was proposed that this could participate in the coupling directly, or form disulfide **17** which could also be the active species in the reaction. Alternatively, intermediate **15** could be reduced by copper to form sulfenyl anion **18**, which could also participate in the catalytic cycle. The proposed mechanism was supported by a series of experiments. First, the reaction was completely inhibited by TEMPO, indicating a radical pathway for the deoxygenation of the sulfinate. Next, it was shown that disulfide **17** was produced under the reaction conditions in the absence of an organoboron source – this reaction was also inhibited by TEMPO. It was also shown that the reaction proceeds when disulifde **17** was used instead of the sodium sulfinate in a 53% yield. When TEMPO was added to this reaction, partial conversion was still observed, with a 28% yield achieved, indicating multiple coupling mechanisms. Additionally, when the reaction was performed under standard conditions and TEMPO was added after 4 h, the TEMPO adduct of thiyl radical **16** was detected by HRMS. Finally, the reaction didn't proceed under inert conditions. Therefore, it was hypothesised atmospheric oxygen is needed to oxidise copper(I) to copper(II). The authors didn't speculate on the nature of the mechanism with regard to the copper catalytic cycle.



Scheme 12: Proposed mechanism of copper-catalysed reaction of boronic acids with *N*-thiosuccinimides.

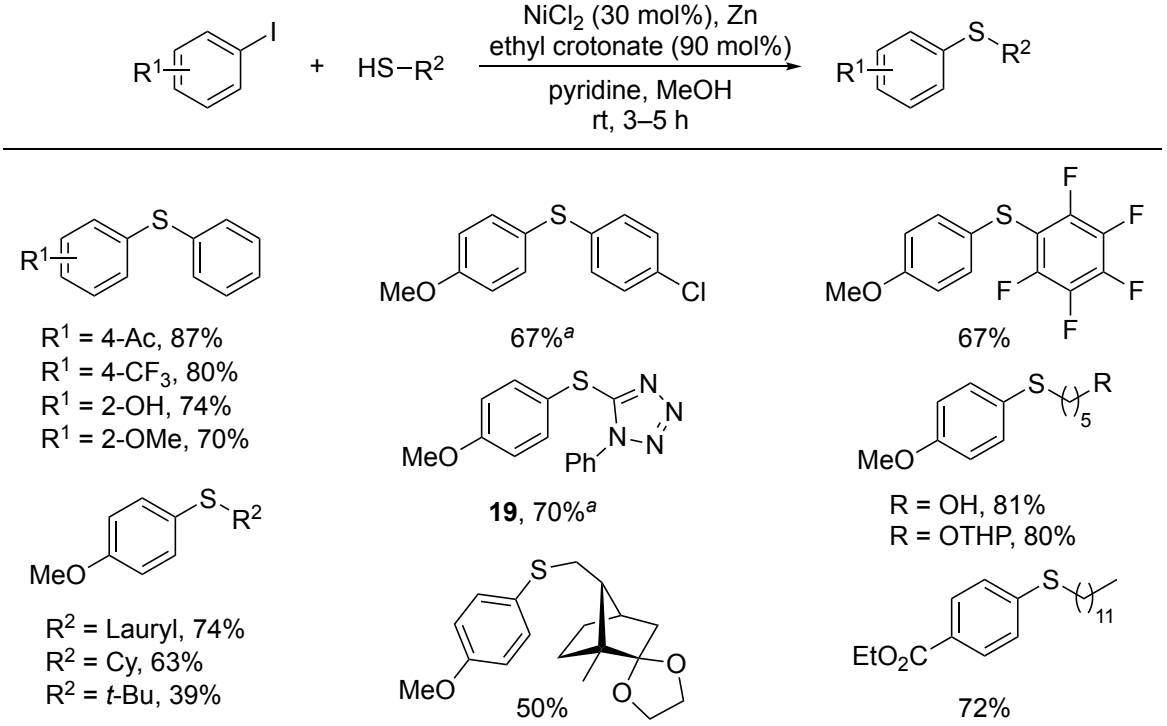
In 2014, Shen reported a Chan-Lam-type procedure for the preparation of aryl trifluoromethylthioethers using *N*-(trifluoromethylthio)phthalimide and aryl boronic acids.[42] This was achieved using copper(I) iodide and 4,4'-di-*tert*-butyl-2,2'-bipyridine (*t*-Bu-bpy) as the catalyst system (5 mol%) in diglyme at 60 °C (Scheme 13). For this method, the use of sodium carbonate as a base was necessary. Electron-donating and electron-withdrawing groups were well tolerated including ethers, halides, esters, aldehydes and nitriles with isolated yields ranging from 50–93%. The use of several heterocycles was also demonstrated. However, there were no examples of sterically hindered boronic acids or unprotected alcohols or amines.



Scheme 13: Substrate scope for the copper-catalysed reaction of boronic acids with *N*-(trifluoromethylthio)phthalimide.

Rueping and co-workers simultaneously published a very similar procedure, also reacting boronic acids with *N*-(trifluoromethylthio)phthalimide under copper-catalysis in the presence of base.[43] Other reports have focused on the use of other trifluoromethylthiol sources in Chan-Lam-type reactions, such as the Rupert-Prakash reagent and elemental sulfur,[44] hypervalent iodine reagents,[45] trifluoromethanesulfenamide,[46] and silver(I) trifluoromethylthiolate.[47]

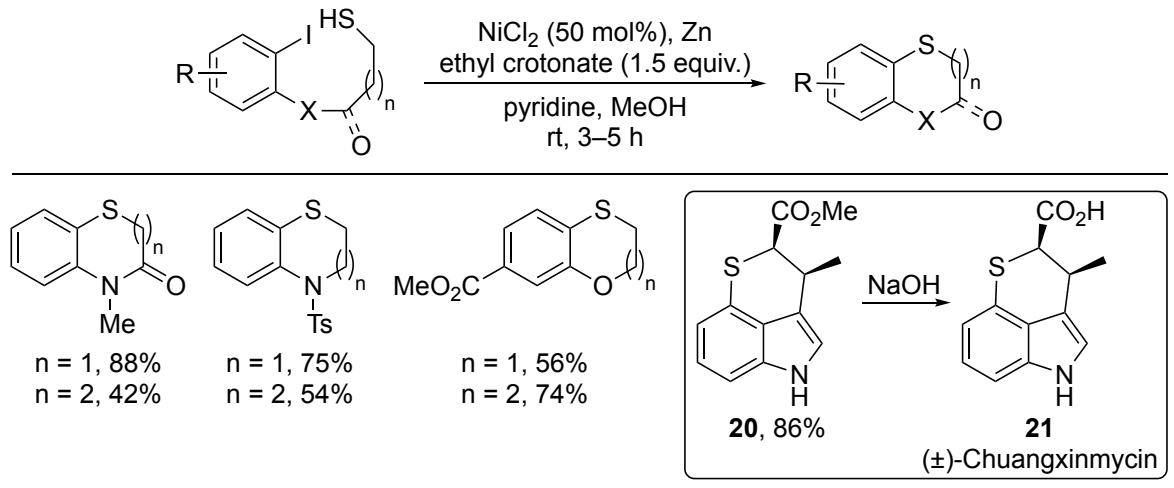
Nickel-catalysis has also been used for the construction of C–S bonds. Early methods reported by Christol[48] and Takagi[49] focused on the coupling of aromatic thiols with aryl halides but had significant drawbacks including high temperatures and/or poor substrate scopes. In 2007, Ying and co-workers reported a procedure which involved a nickel-NHC catalyst that worked well for a variety of aryl halides at 100–110 °C in dimethylformamide.[50] However, the only thiol coupling partner reported was thiophenol. In 2013, Peng and co-workers disclosed a method that could be performed at room temperature in methanol.[51] First, the active catalyst was formed by heating a mixture of zinc (2 equiv.), nickel(II) chloride (30 mol%), ethyl crotonate (90 mol%) and pyridine at 55 °C for 15 minutes. Next, the aryl iodide and alkyl or aryl thiol were added at room temperature and stirred for 3–5 hours (Scheme 14). This protocol was found to be effective for a variety of aryl halides and thiols. There were several examples of primary, secondary and tertiary alkyl thiols participating in the reaction with desired products isolated in moderate to excellent yields. Interestingly, only electron-deficient or neutral aryl thiols were demonstrated to be competent nucleophiles. Upon scale-up, lower catalyst/ligand loadings could be used with improved isolated yields. For example, when the synthesis of tetrazole thioether **19** was performed on a 1 g scale, the yield increased from 70% to 94% and the catalyst loading could be lowered from 30 mol% to 10 mol%.



Scheme 14: Substrate scope for the nickel-catalysed reaction of aryl iodides with thiols.

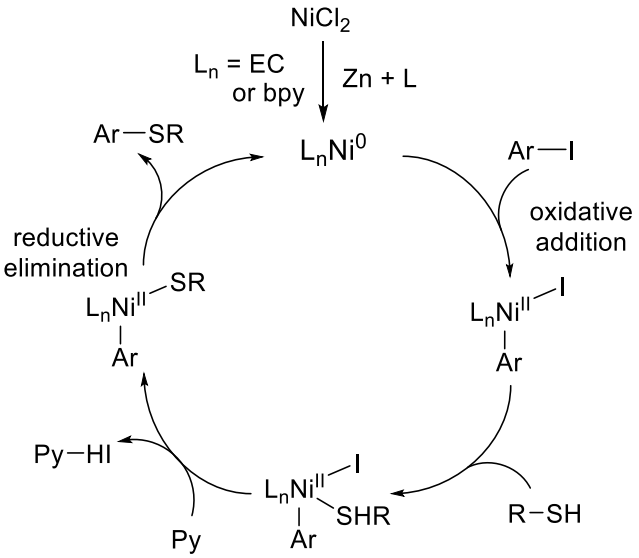
[a] 2,2'-Bipyridine (36 mol%) was used instead of ethyl crotonate.

The authors also showed that the procedure is amenable to intramolecular C–S bond formation to furnish a variety of six and seven-membered rings (Scheme 15).[51] This required an increased loading of nickel(II) chloride to 50 mol%. It was also demonstrated that thioacetates can be used as surrogates for thiols. These cyclic structural units are valuable to the pharmaceutical industry, being present in several drugs including diltiazem and thiazesim. Impressively, this methodology was used in a formal total synthesis of (±)-chuangxinmycin (**21**), a natural product with antibacterial activity.[52] Key intermediate **20** was furnished in 86% yield, which could then be deprotected to give the natural product.



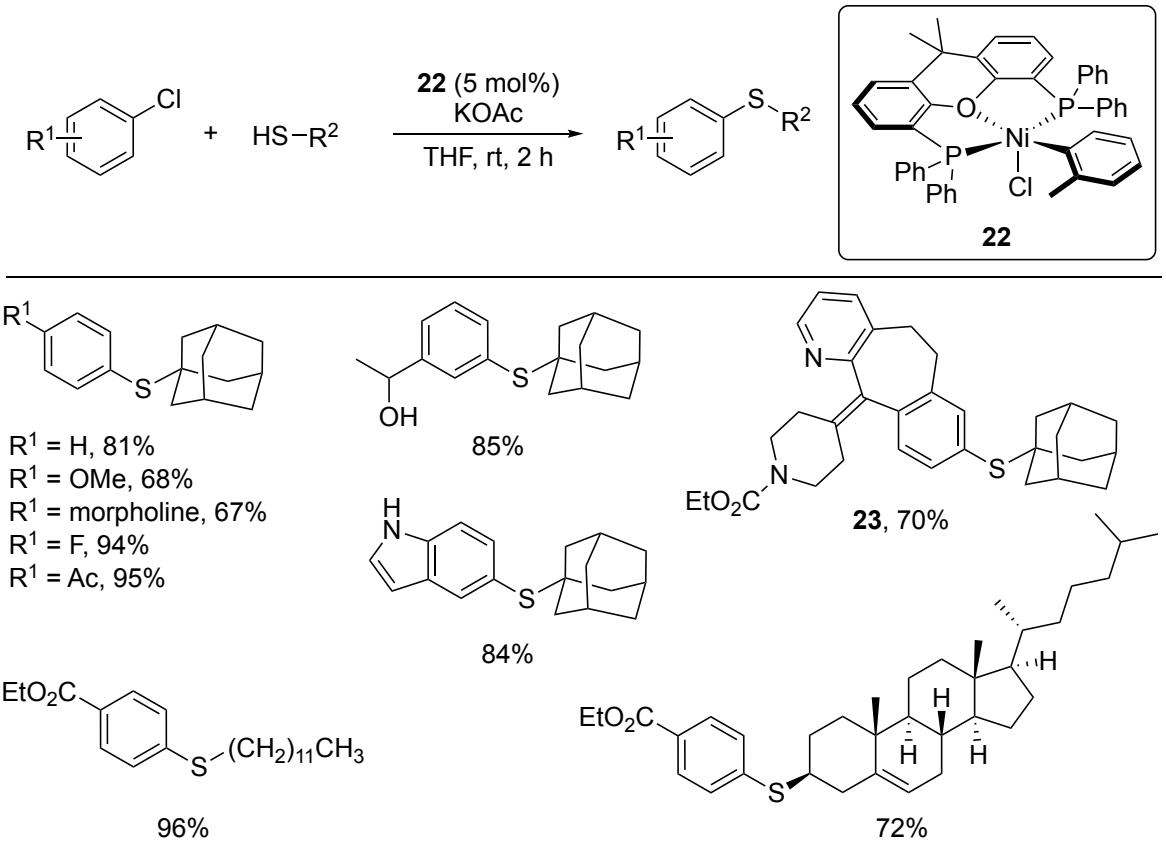
Scheme 15: Nickel-catalysed intramolecular cyclisation and formal synthesis of (±)-chuangxinmycin (**21**).

The authors proposed a mechanism based on previous reports in the literature on nickel-catalysed C–S couplings (Scheme 16).[51] First, nickel(II) chloride is reduced to the active nickel(0) catalyst by zinc powder. Then, there is a sequence of oxidative addition of the aryl iodide, co-ordination of the thiol, pyridine-assisted elimination of hydrogen iodide and reductive elimination of the product.



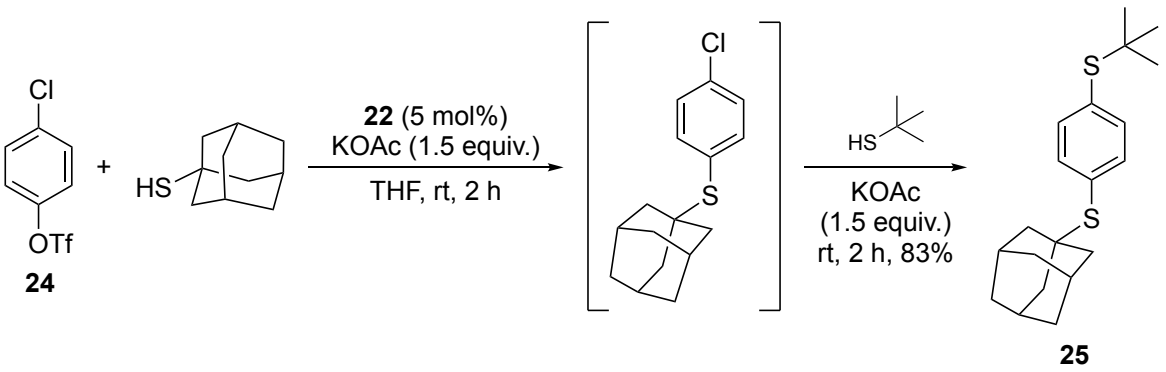
Scheme 16: Proposed mechanism of nickel-mediated reaction of aryl halides with thiols.

In subsequent years, similar transformations with less reactive aryl chlorides have been demonstrated, but these required strong, air-sensitive organometallic bases, elevated temperatures and often gave moderate yields.[53–55] However, in 2022 a procedure was published by Fleischer and co-workers which could be performed rapidly at room temperature in tetrahydrofuran.[56] While the report only covered alkyl thiols, the substrate scope was impressive with fifty examples. This was achieved by the use of the (Xantphos)Ni(*o*-tolyl)Cl precatalyst **22** as an air-stable nickel(II) precursor and potassium acetate as the base, which was found to be crucial in optimisation studies. As well as electron-poor and electron-rich aryl chlorides, several pharmaceutically active compounds or their chloro-derivatives were shown to participate efficiently in the reaction (Scheme 17). Loratidin derivative **23** was furnished in a 70% yield, while thiocholesterol was coupled with ethyl 4-chlorobenzoate in a 72% yield.



Scheme 17: Substrate scope for the nickel-catalysed reaction of aryl chlorides with alkyl thiols.

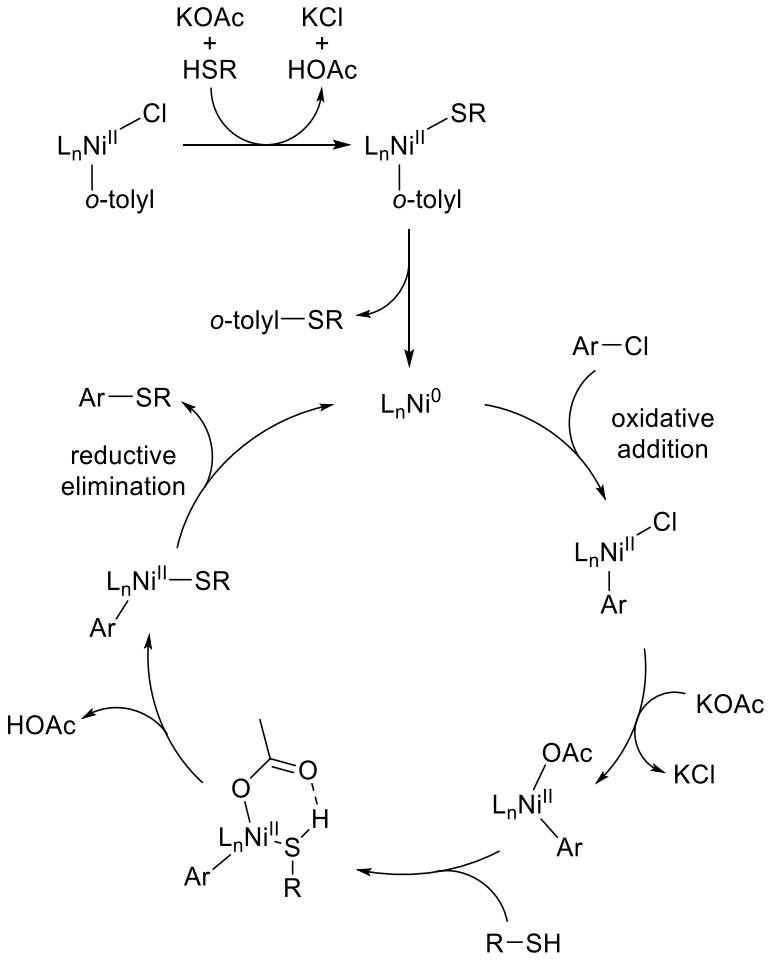
Additionally, an efficient and chemoselective two-step, one-pot procedure from 4-chlorophenyl triflate **24** was demonstrated (Scheme 18). First, the more reactive triflate was reacted with adamantanethiol under the standard conditions for 2 hours. Then, *tert*-butylthiol and an extra 1.5 equivalents of potassium acetate were added. After 2 hours, the desired di-functionalised product **25** was isolated in 83% yield.



Scheme 18: Two-step, one-pot dual thiolation of chlorophenyl tosylate.

Based on detailed DFT calculations and kinetic experiments, the mechanism in Scheme 19 was proposed.[56] First, the precatalyst is activated by co-ordination of the thiol and subsequent reductive elimination of the thiol-*o*-tolyl product, which was detected by mass spectrometry and NMR spectroscopy. Next, the aryl iodide undergoes oxidative addition to

the active catalyst. Ligand exchange with potassium acetate resulted in precipitation of potassium chloride by salt metathesis. Subsequent deprotonation of the thiol, promoted by acetate, then allows reductive elimination to give the desired product. This sequence is analogous to that of the precatalyst activation.



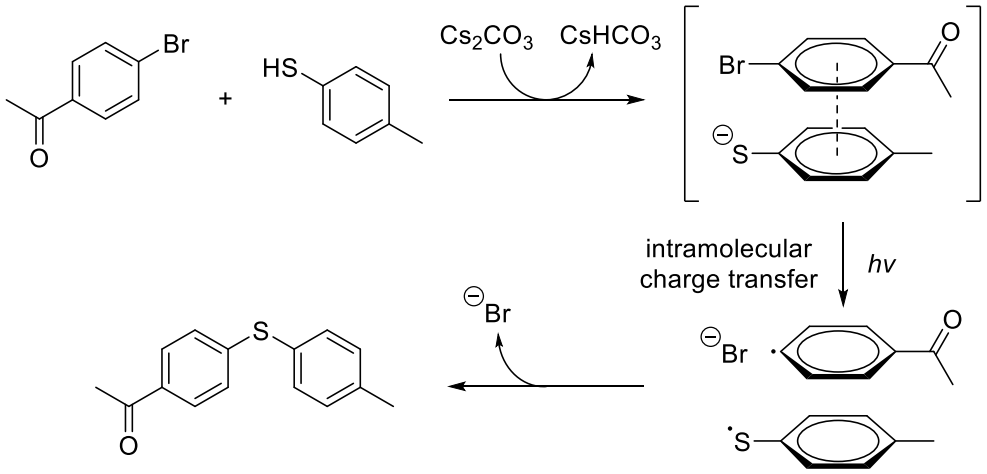
Scheme 19: Proposed mechanism for the nickel-catalysed reaction of aryl chlorides with alkyl thiols.

The scope of nickel-catalysed C–S bond formation has also been expanded to trifluoromethylthiolations. Mild procedures have been published by the groups of Vicic and Schoenebeck using tetramethylammonium trifluoromethanethiolate [$(Me_4N)SCF_3$] with aryl iodides and chlorides, respectively.[57,58] However, for both reports, the substrate scopes were limited compared to previously discussed palladium and copper-catalysed methodologies, with poor tolerance of electron-poor and sterically hindered aryl halides.

1.2 Single-electron approaches to C–S bond formation

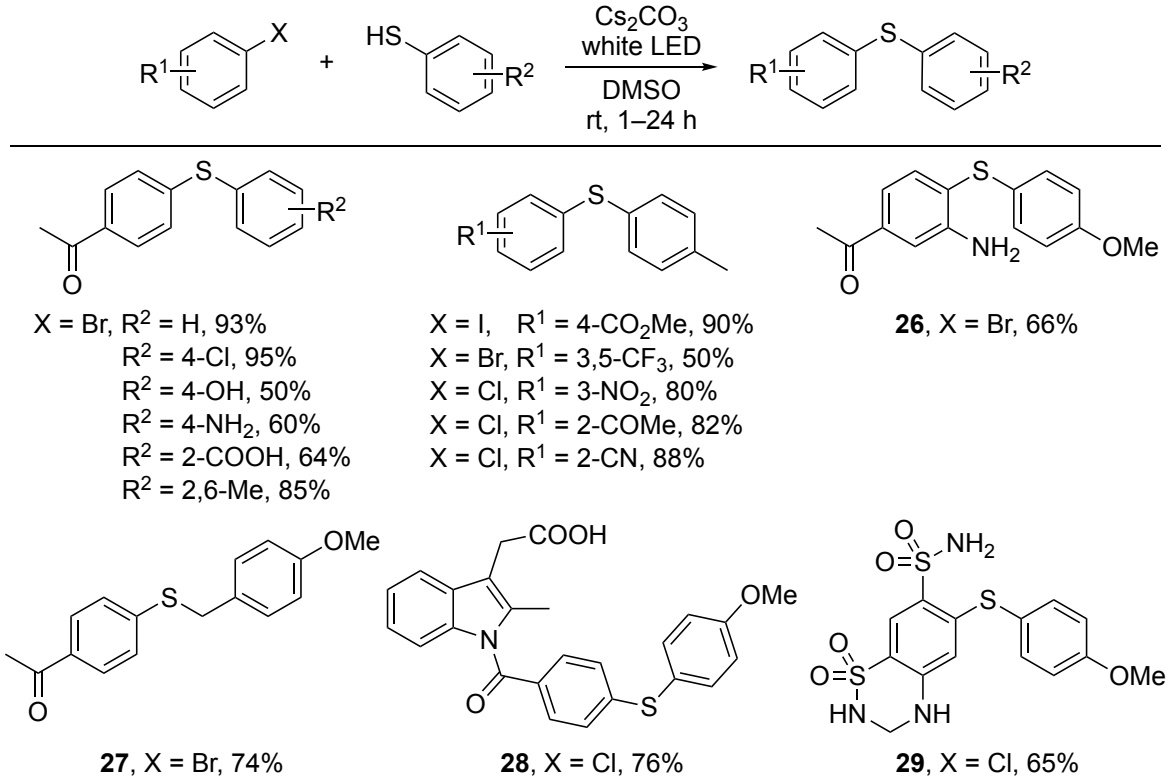
The advent of photochemistry has provided a conceptually new and powerful approach to bond formation in organic chemistry, and in the past decade has been expanded to C–S bond construction.[59] In 2017, Miyake and co-workers reported a simple visible-light

promoted C–S cross-coupling procedure that did not require a catalyst.[60] This procedure, which involved only the coupling partners (aryl halides and aryl thiols), caesium carbonate and dimethyl sulfoxide at room temperature, exploited electron donor acceptor (EDA) complexes (Scheme 20). After deprotonation of the thiol, the resultant electron-rich thiolate can associate with an electron-poor aryl halide to form an EDA complex, which has a charge transfer absorption band in the visible region. Therefore, visible light can induce electron transfer to form thiyl and aryl radical species, which can couple to furnish the diaryl thioether product. This mechanistic proposal was supported by UV-vis and ^{1}H NMR spectra of the reaction mixture of 4-bromoacetophenone and 4-methylbenzenethiol, and DFT calculations.



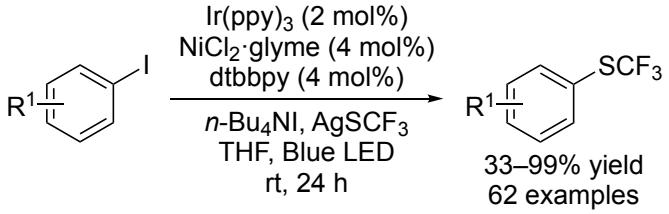
Scheme 20: Proposed mechanism for the light-promoted reaction of aryl halides with thiols.

The substrate scope was largely limited to electron-poor or neutral aryl halides, which is logical given the nature of EDA complexes (Scheme 21).[60] There were some examples of reactions where anilines could be used if an additional electron-withdrawing group was present, such a ketone – in this case the product **26** was isolated in 66% yield. Aryl iodides, bromides and chlorides were all shown to be competent substrates, albeit with longer reaction times for chlorides. Regarding thiols, there was a wide variety of examples including phenols, anilines and carboxylic acids and sterically hindered substrates. The tolerance of nucleophilic substrates is significant as this represents an advantage over many of the previously discussed transition-metal-catalysed processes. One alkyl thiol was also demonstrated to work well, generating thioether **27**. Four FDA-approved drugs bearing aryl chlorides including indomethacin and hydrochlorothiazide were also shown to effectively participate in the methodology, giving functionalised products **28** and **29**, respectively, in good yields.



Scheme 21: Substrate scope for the light-promoted reaction of aryl halides with thiols.

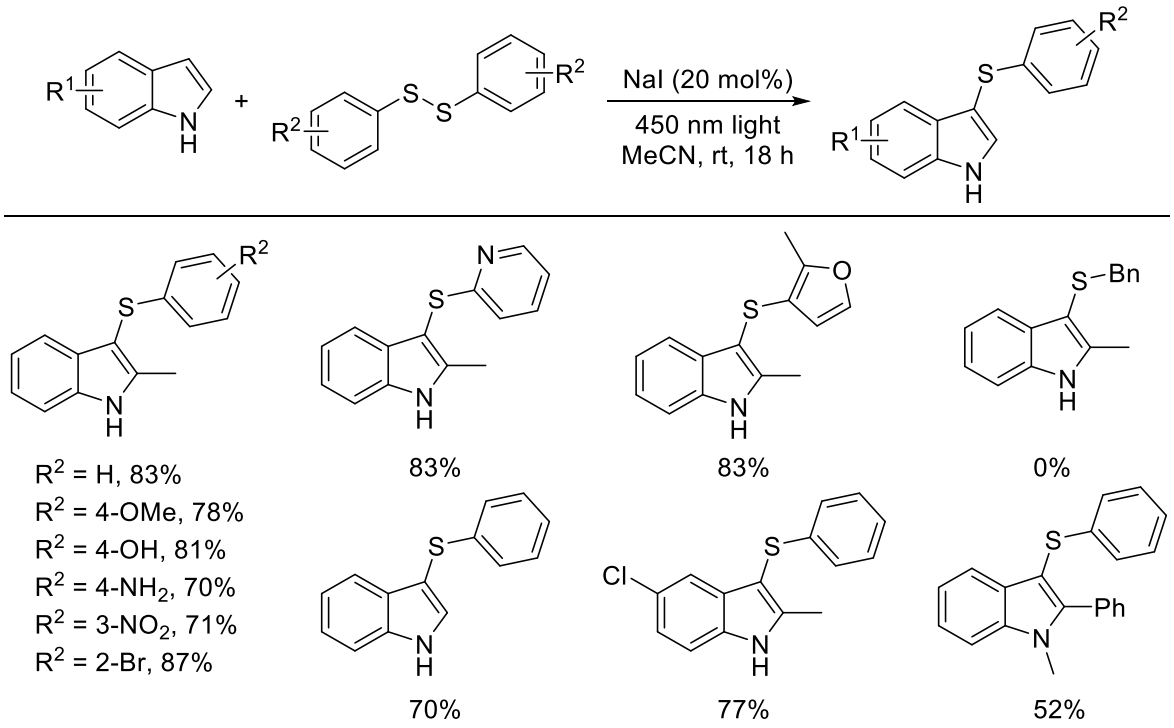
Other methods utilise metal photocatalysts, such as ruthenium or iridium. A popular platform has been the combination of a light-activated iridium photocatalyst with a nickel catalyst, which has been demonstrated to form challenging C–C bonds.[61,62] While this system has been applied to the synthesis of C–S bonds,[63,64] there was no improvement on the previously discussed methodologies in substrate scope or efficiency in terms of yield or atom economy. This makes the use of expensive iridium photocatalysts and elaborate experimental set-ups hard to justify. A recent example from Ghosh and co-workers for the synthesis of aryl trifluoromethylthioethers is depicted in Scheme 22.[64]



Scheme 22: Summary of the light-promoted, Ni/Ir-catalysed synthesis of trifluoromethylthioethers.

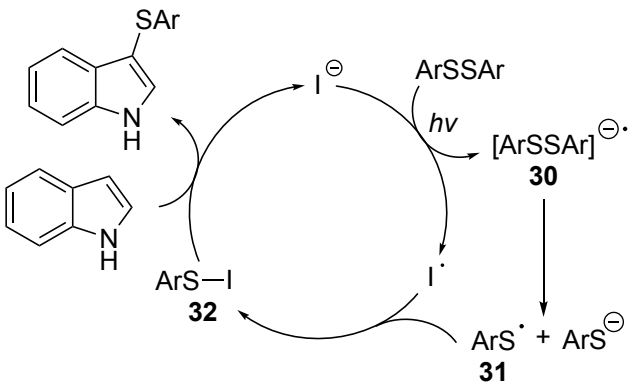
Light-mediated reactions have also been used to effect C–H functionalisation, a topic which has attracted significant attention from organic chemists. In 2017, a method was disclosed by the Yan group on light-promoted thioarylation of indoles using aryl disulfides and sodium iodide. (Scheme 23).[65] The methodology was found to be insensitive to the electronics of the disulfides, with anilines, phenols, heterocycles and arenes bearing nitro groups reacting

with 2-methylindole to furnish the desired products in good to excellent yields. Unfortunately, the use of alkyl disulfides did not result in any conversion. Regarding the indole coupling partner, fewer functional groups were tolerated with only indoles bearing halides and methoxy groups included in the report.



Scheme 23: Substrate scope for the light-promoted C–H thioarylation of indoles.

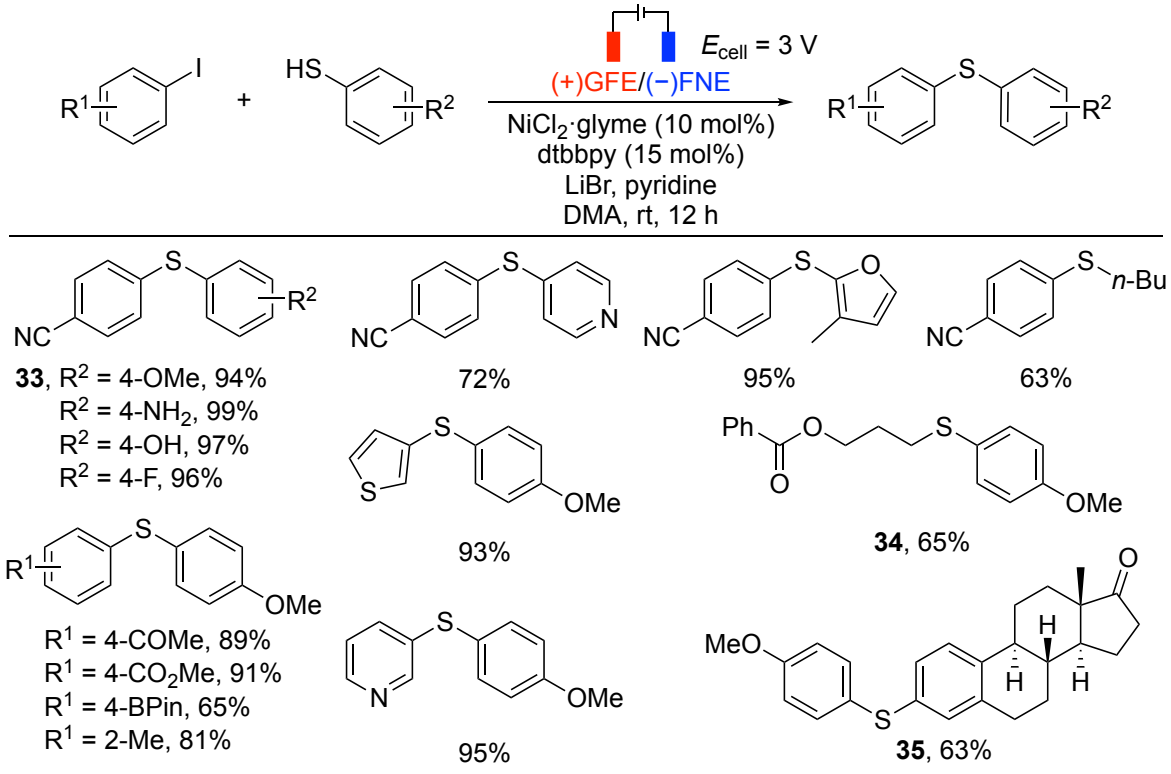
Based on UV-Vis measurements of the reaction mixture, various control experiments, the observations that TEMPO inhibited the reaction and that one equivalent of the disulfide is required, the mechanism in Scheme 24 was proposed.[65] Single electron transfer from the iodide to the photoactivated disulfide generates an iodine radical and disulfide anion radical **30**. Radical **30** fragments to form a thiophenol anion and phenylthiyl radical **31**. The two radicals can then couple to give arylsulfenyl iodide **32**, which undergoes electrophilic aromatic substitution with the electron-rich indole to give the desired product.



Scheme 24: Proposed mechanism for the light-promoted C–H thioarylation of indoles.

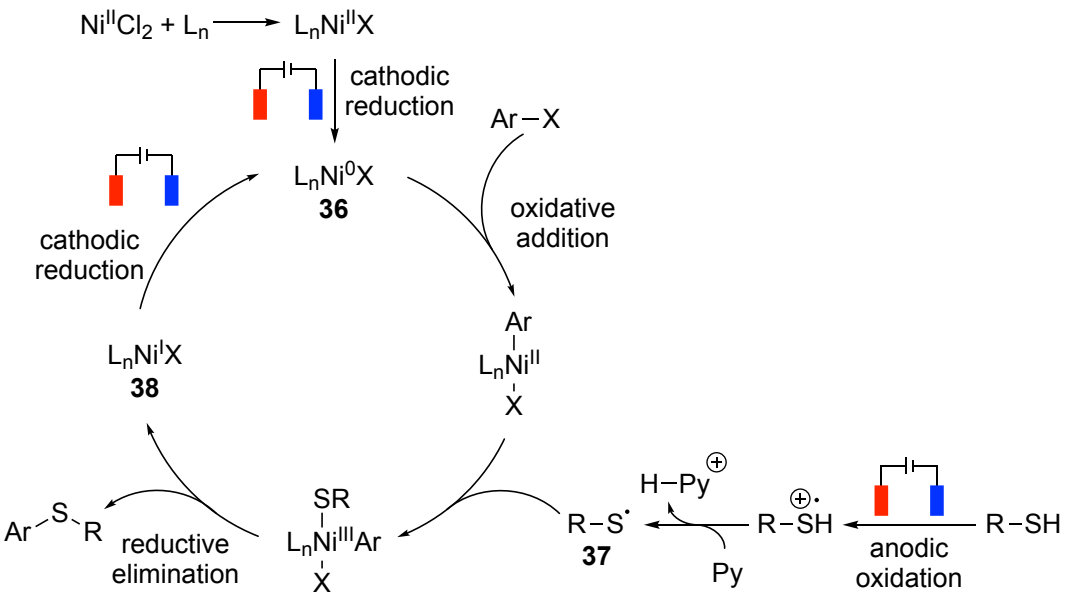
Other light-mediated C–H thiolations have been reported, but they also suffer from limited scope of nucleophiles – usually for only one class of heterocycle. Examples include procedures for imidazopyridines and quinoxaline-2(1*H*)-ones.[66,67]

Electrochemistry has also been explored for C–S bond construction. It presents an attractive alternative to traditional chemistries due to redox-efficiency and avoidance of oxidants. The first coupling of aryl iodides with thiols was reported in 2019 by Zheng and co-workers and bore similarities to previously discussed Ni/Ir photochemical processes.[68] The authors hypothesised that the role of the expensive iridium photocatalyst in manipulating the redox state of the nickel catalyst could be replaced by electrolysis, resulting in a more sustainable procedure. Optimisation studies revealed that the most effective nickel/ligand combination was that of nickel(II) chloride glyme (10 mol%) with 4,4'-bis-(*tert*-butyl)-2-2'-dipyridine (15 mol%). The electrochemical set-up consisted of graphite and nickel electrodes with lithium bromide used as the electrolyte. The methodology was highly effective for the coupling of an impressive variety of aryl thiols with 4-iodobenzonitrile including anilines, phenols and pyridines with isolated yields often exceeding 90% (Scheme 25). Alkyl thiols were also shown to participate in the coupling, albeit in more moderate yields. For the aryl iodide coupling partner, esters, boronic esters, ketones and several electron-rich and electron-poor heterocycles all produced the corresponding product in high yields. An alkyl bromide was also coupled with 4-methoxythiophenol, giving **34** in a 65% yield. Finally, steroid derivative **35** was furnished in 63% yield.



Scheme 25: Substrate scope for the electrochemical thiolation of aryl iodides.

The authors performed several cyclic voltammetry experiments to deduce the mechanism of the reaction.[68] Measurements on the nickel catalyst with and without the aryl iodide indicated that nickel(0) was the active catalyst, with oxidative addition of the iodide resulting in a nickel(II) species. Based on this and radical trapping experiments, the mechanism in Scheme 26 was proposed. First, the active catalytic species **36** is formed by reduction of nickel(II) chloride and co-ordination of the ligand. Next, oxidative addition occurs followed by addition of a thiyl radical **37**. This is generated *via* anodic oxidation of the thiol followed by deprotonation by pyridine. Reductive elimination gives the desired product and nickel(I) species **38**, which is reduced by the cathode to regenerate active catalyst **36**.



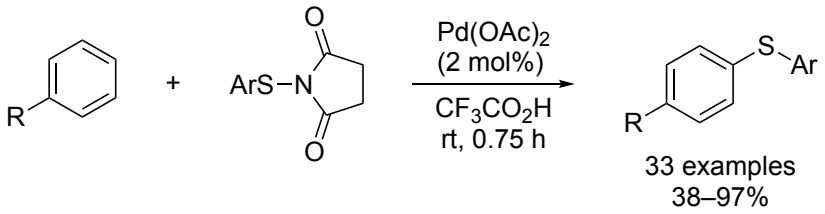
Scheme 26: Proposed mechanism for the electrochemical thiolation of aryl iodides.

While this methodology is an interesting and useful contribution to this area of research, a significant disadvantage is that all experiments were performed in a glovebox.[68] Unfortunately, the authors did not indicate whether the process can be carried out under less stringent conditions. Additionally, when scaled up to 1 g the synthesis of **33** resulted in a significant drop in yield from 94% to 61%. This is representative of a common problem in general for electrochemistry and photochemistry, which is limiting the uptake of these methods in industrial chemistry.

1.3 Brønsted and Lewis Acid Promoted C–S Bond Formation

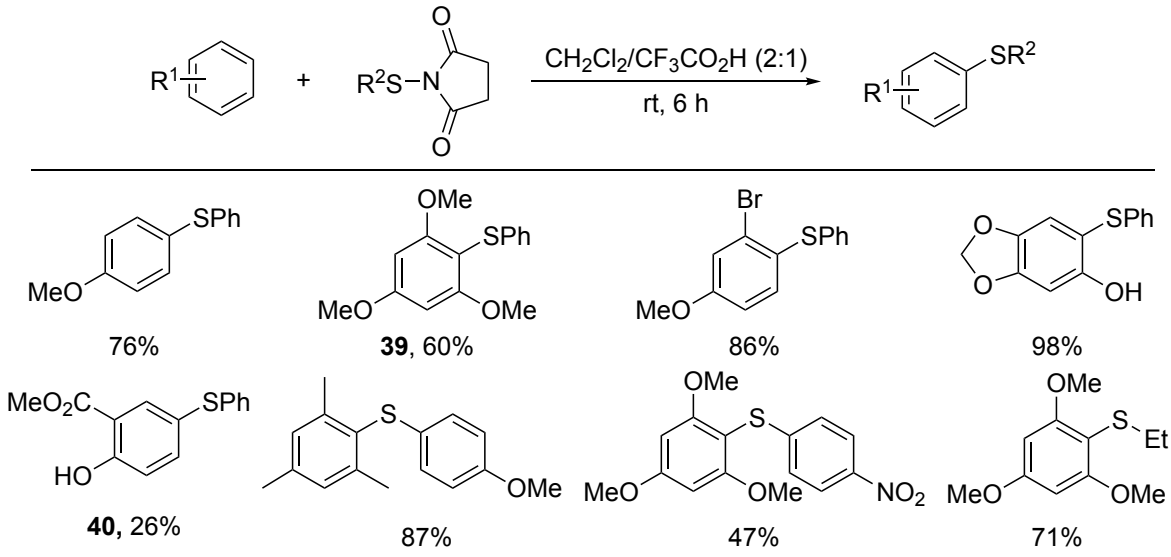
Over the past decade, the use of Brønsted and Lewis acids has emerged as an effective method to promote the thiolation of activated arenes. One of the first reports in this area was by Anbarasan and co-workers in 2014, who disclosed a procedure for the regioselective C–H thioarylation using palladium(II) acetate and trifluoroacetic acid as the

solvent (Scheme 27).[69] While this process had the disadvantage of using a rare-metal palladium catalyst, it was shown in optimisation studies that in the absence of palladium(II) acetate the product was still formed, albeit in low yields. Trifluoroacetic acid was used to activate thioarylsuccimimides, which were used as electrophilic sources of aryl thiols.



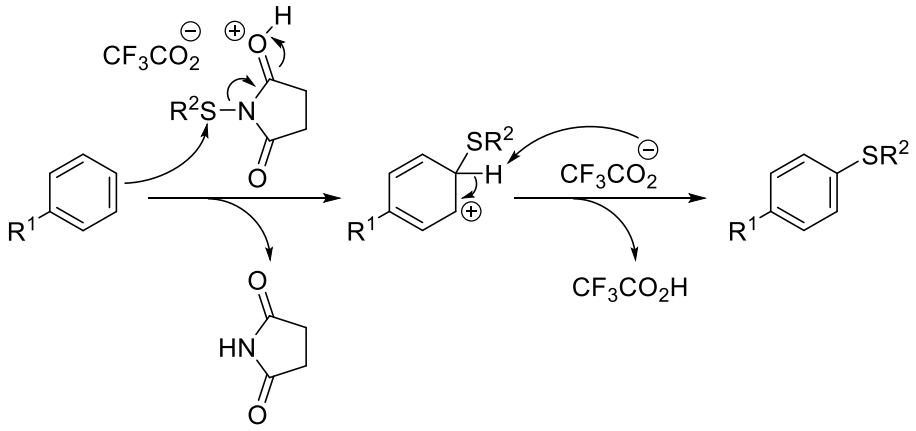
Scheme 27: Summary of the TFA-promoted, Pd-catalysed synthesis of diarylthioethers.

In 2015, Cossy and co-workers reported an improved metal-free procedure (Scheme 28).[70] In this case, trifluoroacetic acid was used as a co-solvent with dichloromethane (1:2). The methodology worked well for some activated arenes, with the thioaryl groups directed to the *para*-position, or the *ortho*-position if the *para*-position was blocked. Phenols and anisoles generally gave the corresponding products in good to excellent yields, and sterically hindered arenes were well tolerated. Some highly activated compounds, such as 1,3,5-trimethoxybenzene, gave lower yields (**39**), presumably due to the formation of poly-substituted side-products. Less activated compounds including those bearing electron-withdrawing groups showed poor reactivity, such as methyl salicylate, which gave product **40** in only 26% yield. The use of several succinimides was demonstrated, including one example of an alkyl succinimide. However, the use of the electron-poor *N*-[(4-nitrophenyl)sulfanyl]succinimide resulted in diminished yields.



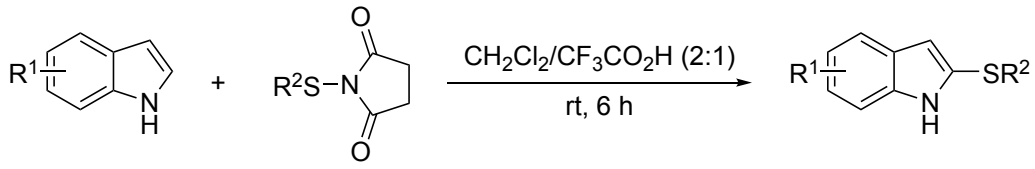
Scheme 28: Substrate scope of the CF_3CO_2H-promoted, metal-free synthesis of aryl thioethers.

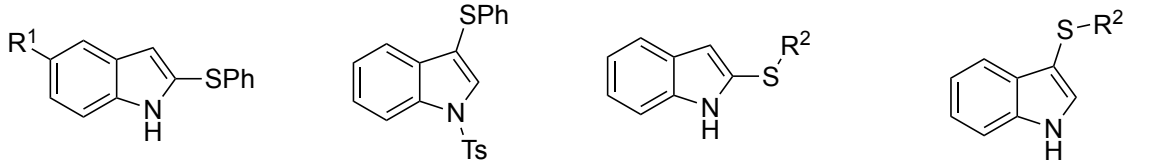
It was proposed that the succinimide reagent is activated by trifluoroactic acid, which can then undergo electrophilic aromatic substitution (Scheme 29).[70] However, while this mechanism explains the requirement for activated arenes, it does not rationalise why electron deficient succinimides such as *N*-[(4-nitrophenyl)sulfanyl]succinimide show poor reactivity – it would be expected that this reagent would be more reactive than the other succinimides used.



Scheme 29: Proposed mechanism of the CF_3CO_2H-promoted, metal-free synthesis of aryl thioethers.

Using the same procedure, Cossy and co-workers then further explored the substrate scope regarding indoles, with interesting results (Scheme 30).[71] They found that instead of substitution occurring at the most nucleophilic C3-position, C2-substituted products were generated. As with the arenes, indoles bearing electron-donating-groups resulted in higher-yielding reactions than those bearing electron-withdrawing groups. The substitution of protected indoles occurred at the C3-position, which enables regioselective control. Again, succinimides with electron deficient thioarenes were less reactive and also resulted in C3-substituted products.





R^1 = OMe, 80%
R^1 = Cl, 83%
R^1 = CF_3, 66%
R^1 = CO_2Me, 60%

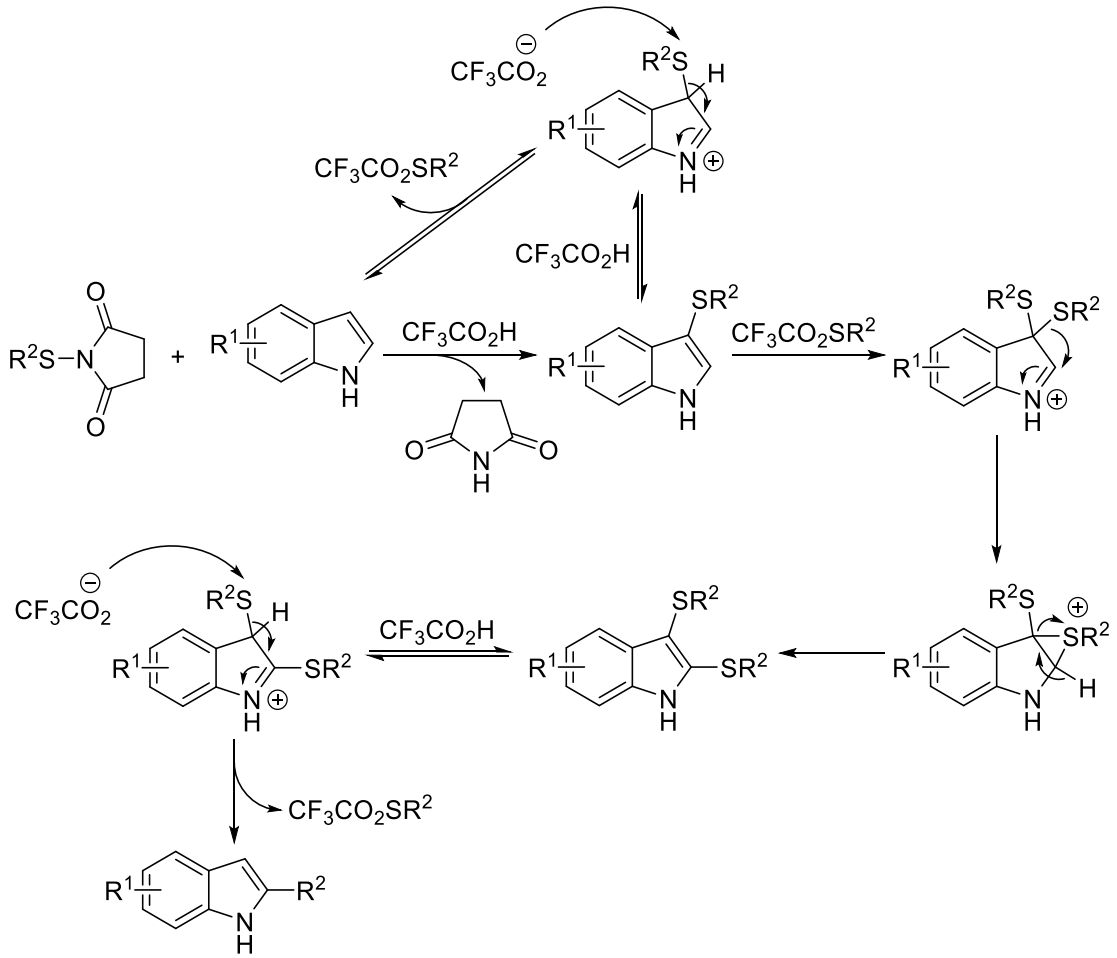
92%

R^2 = 4-PhOMe, 72%
R^2 = 4-PhBr, 93%

R^2 = 4-$PhNO_2$, 30%
R^2 = 2-pyrimidyl, 60%

Scheme 30: Substrate scope of the CF_3CO_2H-promoted, metal-free synthesis of indole thioethers.

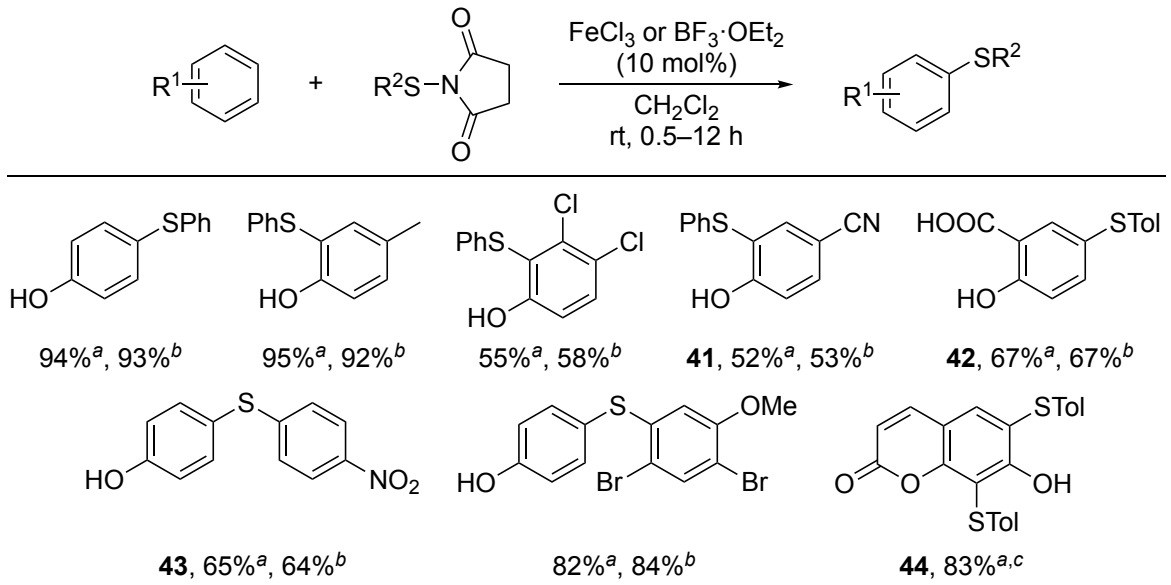
There are relatively few procedures for the direct 2-thiolation of indoles, with other methods involving the treatment of 3-thioindoles with acid,[72] or the use of pyrophoric organolithium reagents to lithiate at the C2-position followed by addition of an electrophile.[73] As such, this method represents a useful alternative. The proposed mechanism is based on previous work by Hamel and co-workers.[71,74] First, an initial C3-substitution is followed by either reversible acid-mediated de-thiolation or a second C3-substitution (Scheme 31). Migration of one of the thioaryl groups through a cyclic three-membered intermediate followed by de-thiolation then gives the final C2-substituted product. The authors hypothesised that the observed substitution pattern of protected indoles, or succinimides bearing electron-poor arenes, is due to the electron-withdrawing groups preventing protonation of the indole nitrogen in the second thiolation.



Scheme 31: Mechanism of the CF_3CO_2H-promoted, metal-free synthesis of indole thioethers.

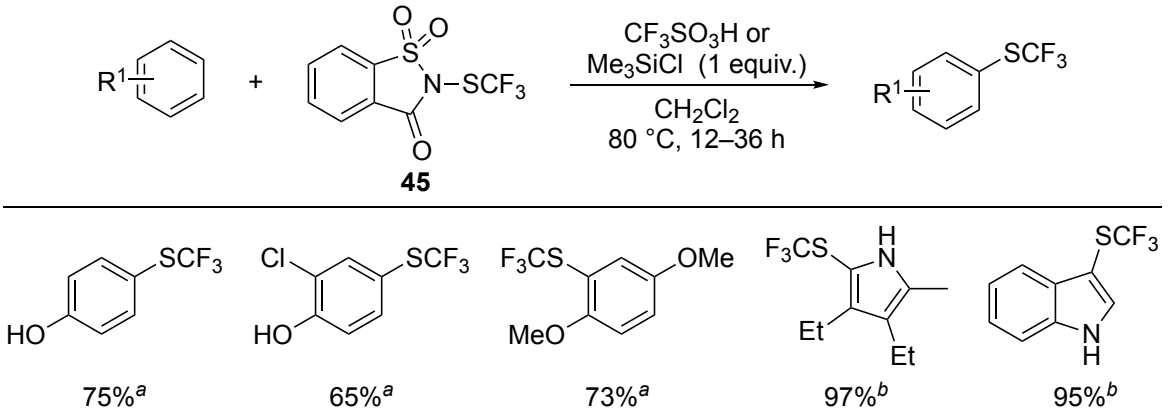
However, a major disadvantage of this methodology is the use of trifluoroacetic acid as a co-solvent. In addition to being highly corrosive, it is incredibly persistent in the environment with no known pathway for its breakdown in nature.[75] Moreover, acid-sensitive functional groups were not compatible with the procedure. Therefore, other groups have focused on the use of milder Lewis acids in catalytic quantities.[76] In 2014, Fu and co-workers reported

a mild, room temperature thioarylation of highly activated arenes such as phenols using only 10 mol% of either iron(III) chloride or boron trifluoride etherate (Scheme 32). The yields and reaction times for both catalysts were very similar. Sterically hindered arenes were tolerated with the desired products isolated in excellent yields. However, the use of phenols with electron-withdrawing groups such as nitriles or carboxylic acids resulted in lower isolated yields (**41** and **42**). As with Cossy's procedure, electron poor succinimide reagents could participate in the reaction in lower yields such as *N*-[(4-nitrophenyl)sulfanyl]succinimide, which gave **43** in 65% yield. The functionalisation of a flavonoid was attempted, but di-substitution was observed. Therefore, two equivalents of the succinimide reagent were used and the di-substituted product **44** was isolated in 83% yield. It was proposed that the Lewis acids could activate the succinimide reagents by co-ordination to one of the carbonyl moieties to generate a more electrophilic intermediate, which would be susceptible to nucleophilic attack by activated arenes.



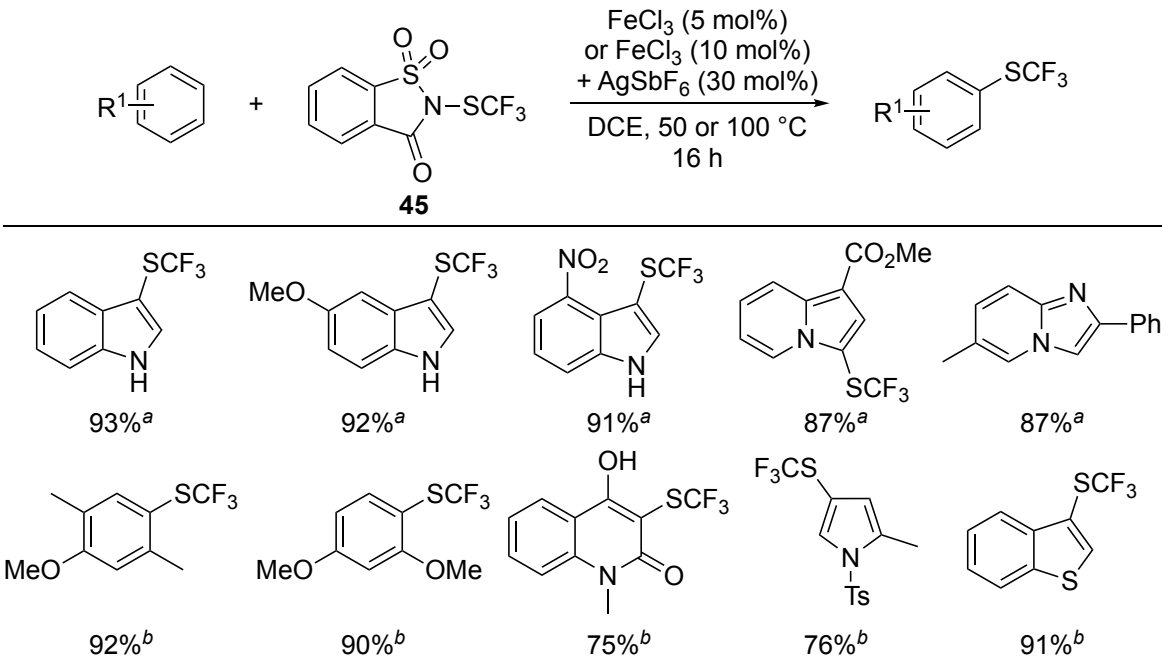
Scheme 32: Substrate scope of the $FeCl_3$ or $BF_3{\cdot}OEt_2$-catalysed synthesis of diaryl thioethers. [a] $FeCl_3$ (10 mol%).[b] $BF_3{\cdot}OEt_2$ (10 mol%). [c] 2.0 equivalents of the succinimide reagent were used.

Similar approaches have also been used for the trifluoromethylthiolation of activated arenes. In 2014, Shen and co-workers reported the synthesis and application of *N*-(trifluoromethyl)saccharin (**45**), a novel and easily synthesised electrophilic reagent.[77] It has since become commercially available. The authors demonstrated that when activated by one equivalent of triflic acid or trimethylsilyl chloride, this reagent could be used for the trifluoromethylthiolation of highly-activated arenes or nitrogen heterocycles such as indoles or substituted pyrroles in moderate to excellent yields (Scheme 33). However, as well as the use of a strong acid, this method suffers from the use of elevated temperatures in a low-boiling point solvent. As such, safety precautions must be taken, and the reaction must be performed in a sealed tube.



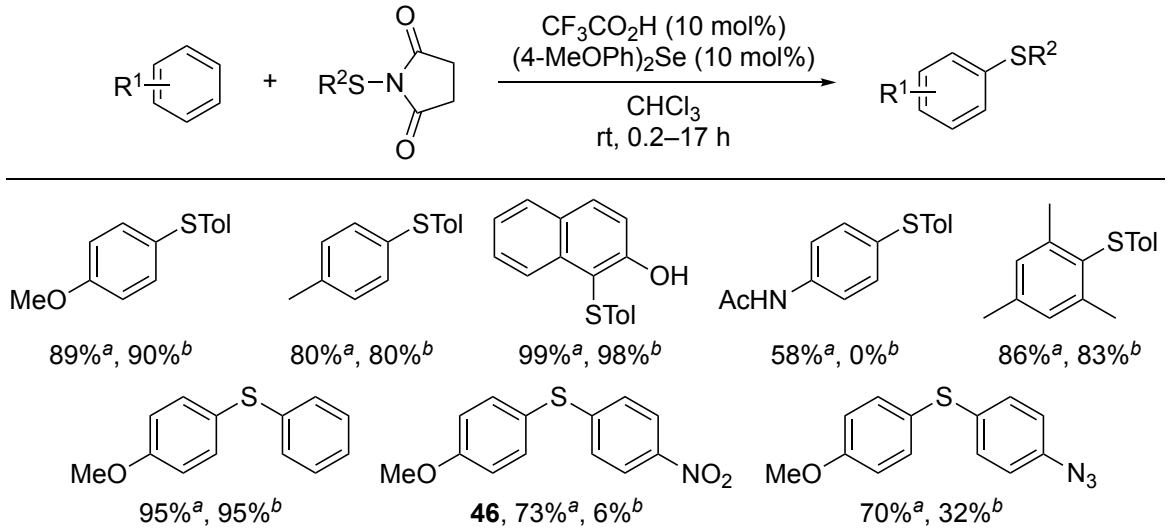
Scheme 33: Substrate scope of the CF_3SO_3H or Me_3SiCl-promoted trifluormomethylthiolation of activated (hetero)arenes. [a] CF_3SO_3H (1 equiv.).[b] Me_3SiCl (1 equiv.).

Almost simultaneously, Li and co-workers reported the same reagent and demonstrated that Lewis acid-catalysis could also be used to enable functionalisation of activated (hetero)arenes, although this procedure also required elevated temperatures.[78] For a wide variety of indoles and imidazole[1,2-*a*]pyridines, iron(III) chloride (5 mol%) at 50 °C in dichloroethane was sufficient to give the desired products in yields often in excess of 90% (Scheme 34). However, for other (hetero)arenes, including various anisoles and other electron-rich heterocycles, temperatures of 100 °C were required, as was the use of a silver(I) hexafluoroantimonate(V) additive (30 mol%). It was proposed that iron(III) hexafluoroantimonate(V), a more Lewis-acidic species, is formed *in situ*.



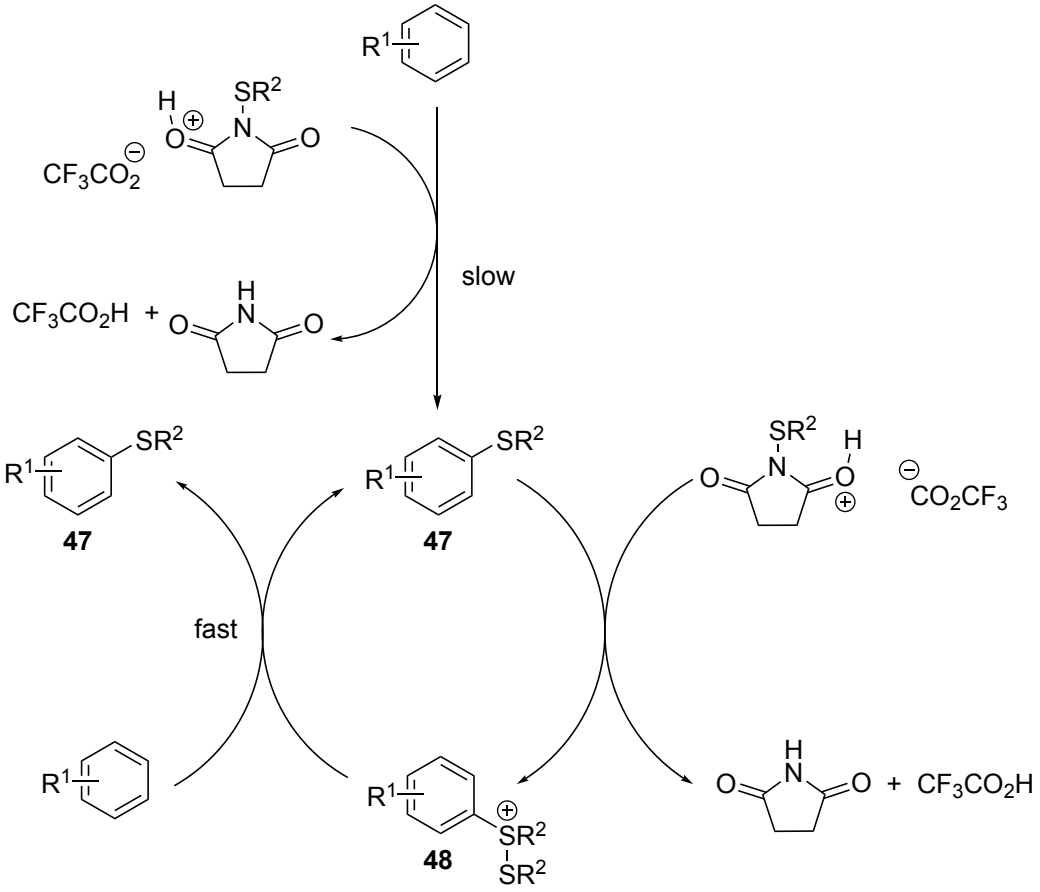
Scheme 34: Substrate scope of the Fe(III)-promoted trifluormomethylthiolation of activated (hetero)arenes. [a] $FeCl_3$ (5 mol%), 50 °C.[b] $FeCl_3$ (10 mol%) and $AgSbF_6$ (30 mol%), 100 °C.

More recently, the combination of Brønsted acid activation with Lewis base-catalysis has been reported to allow C–H thiolations to be performed at room temperature. In 2018, Gustafson and co-workers reported an efficient procedure for the thioarylation of activated arenes using trifluoroacetic acid (10 mol%) and di-(4-methoxyphenyl)selenide (10 mol%) to activate thioaryl succinimides (Scheme 35).[79] While the reported substrate scope was brief, with nine examples, the method was shown to be effective for the thioarylation of phenols, anisoles, protected anilines and even the weakly-activated mesitylene in yields of 58–95%. Regarding the thioaryl succinimide coupling partner, 4-nitro and 4-azidophenyl thiosucccinimides were demonstrated to functionalise anisole. The compatibility of azido groups is significant given its use in biorthogonal chemistry.[80]



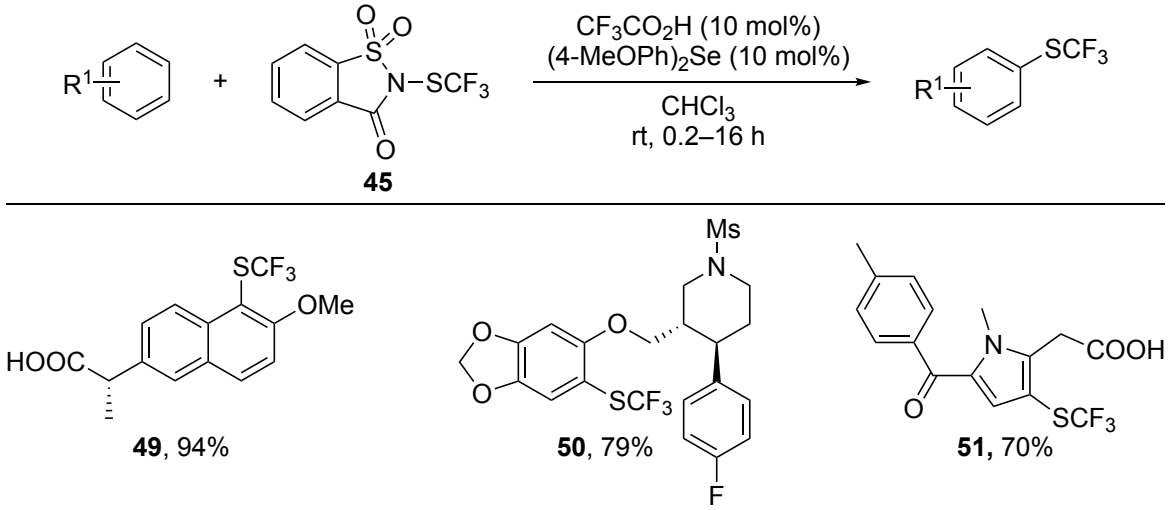
Scheme 35: Substrate scope of the CF_3CO_2H and $(4\text{-MeOPh})_2Se$-catalysed synthesis of diaryl thioethers.
[a] With $(4\text{-MeOPh})_2Se$.[b] Without $(4\text{-MeOPh})_2Se$.

Interestingly, for many substrates the reaction was observed to proceed in a similar yield without the presence of the di-(4-methoxyphenyl)selenide Lewis base.[79] Kinetic studies indicated that when the diaryl thioethers were electron rich, they could act as Lewis bases and induce autocatalysis. As such, the mechanism in Scheme 36 was proposed. After being activated by trifluoroacetic acid, the thioarylsuccinimide participates in an electrophilic aromatic substitution reaction with activated arenes. Once there is a sufficient concentration of product **47** present, a second, faster pathway becomes viable. The electron-rich product **47** can attack the thioaryl succinimide to form cationic intermediate **48**. This species is more electrophilic and therefore can be more readily attacked by arenes to furnish the desired products. For reactions where the product is not sufficiently electron-rich, such as compound **46** bearing a nitro group, the use of di-(4-methoxyphenyl)selenide is still necessary.



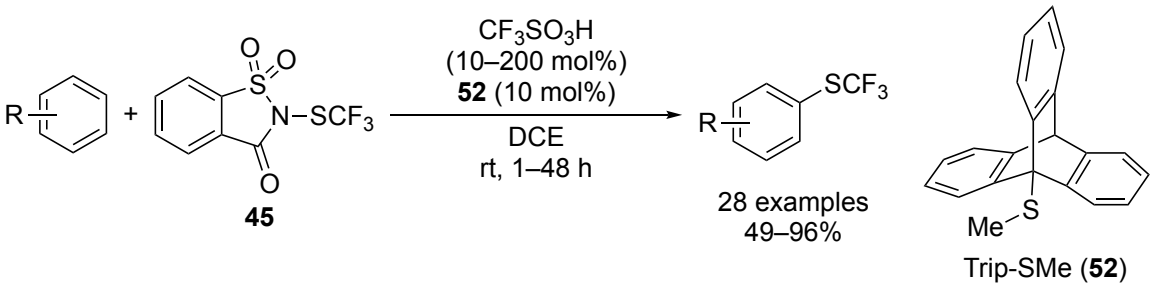
Scheme 36: Proposed mechanism of the CF_3CO_2H and $(4\text{-MeOPh})_2Se$-catalysed synthesis of diaryl thioethers.

This methodology was extended to the trifluoromethylthiolation of activated arenes, with a similar substrate scope shown (Scheme 37).[79] Unsurprisingly, given the electron-withdrawing nature of the trifluoromethylthioether group, the use of di-(4-methoxyphenyl)selenide was necessary for all substrates, with no autocatalysis observed. The functionalisation of several FDA-approved drugs was also demonstrated, with naproxen (**49**), paroxetine (**50**) and tolmetin (**51**) derivatives isolated in 94%, 79% and 70% yields, respectively.



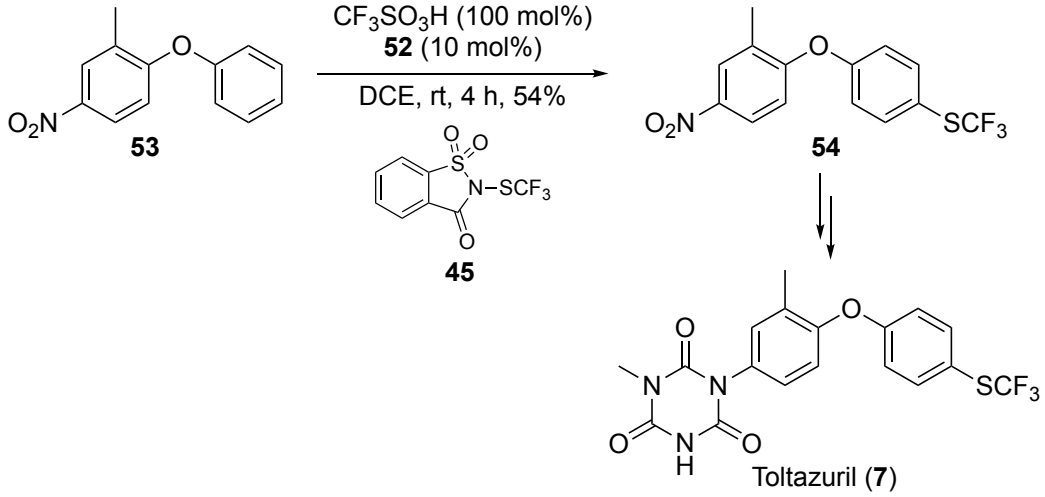
Scheme 37: Substrate scope of the CF_3CO_2H and $(4\text{-MeOPh})_2Se$-catalysed synthesis of aryl trifluoromethylthioethers.

In 2021, Miura and co-workers reported a similar trifluoromethylthiolation procedure using triflic acid and Lewis basic triptycenyl sulfide (**52**) (Scheme 38).[81] A wide variety of activated arenes were efficiently trifluoromethythiolated in moderate to excellent yields, but stoichiometric quantities of triflic acid was necessary for some of the less activated substrates.



Scheme 38: Summary of the CF_3SO_3H and Trip-SMe-catalysed synthesis of aryl trifluoromethylthioethers.

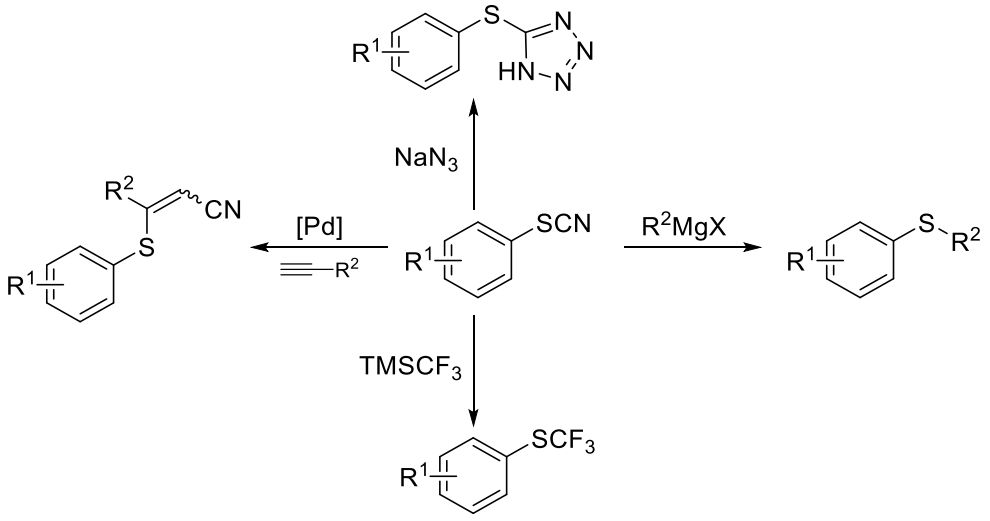
The utility of the procedure was demonstrated in the formal synthesis of toltrazuril (**7**), an antiparasitic agent used for treatment of livestock (Scheme 39).[81] Diaryl ether **53** was subjected to the procedure to give trifluoromethylthiolated product **54**, which is a precursor to toltrazuril. However, stoichiometric quantities of triflic acid were required and the isolated yield was only 54%.



Scheme 39: Formal synthesis of toltrazuril (**7**).

1.4 Aryl Thiocyanates

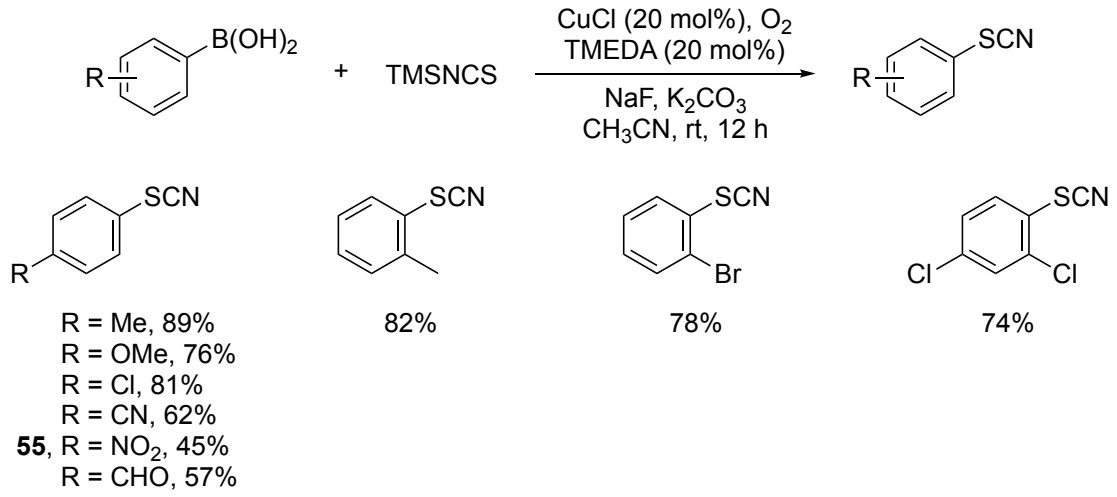
Aryl thiocyanates are present in some natural products and bioactive compounds, but more often they serve as useful and stable precursors to other sulfur containing compounds including the previously discussed aryl/alkyl thioethers[82] and trifluoromethylthioethers,[83] as well as other moieties such as heterocycles (Scheme 40).[84,85] Therefore, there is significant interest in novel, efficient and sustainable methods for the synthesis of these valuable intermediates.



Scheme 40: Synthetic applications of aryl thiocyanates.

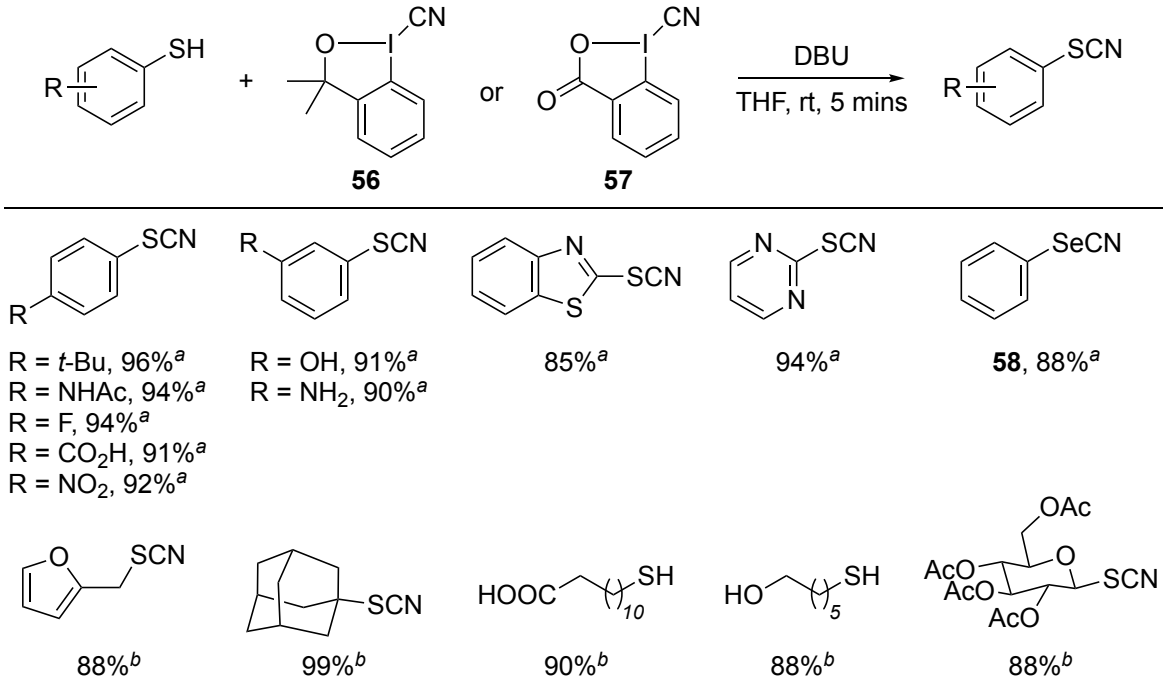
In contrast to thioarylations, thioalkylations and thiotrifluoromethylations, there are few reported methods for transition-metal-catalysed synthesis of aryl thiocyanates. One example is the copper-catalysed synthesis of aryl thiocyanates from aryl boronic acids and trimethylsilyl isothiocyanate in a Chan-Lam-type reaction, reported by Hu and co-workers

(Scheme 41).[86] The procedure was shown to be effective for electron-rich and electron-poor aryl boronic acids, although the use of the strongly deactivated 4-nitroboronic acid gave product **55** in a poor yield of 45%.



Scheme 41: Substrate scope for the copper-catalysed coupling of boronic acids with TMSNCS.

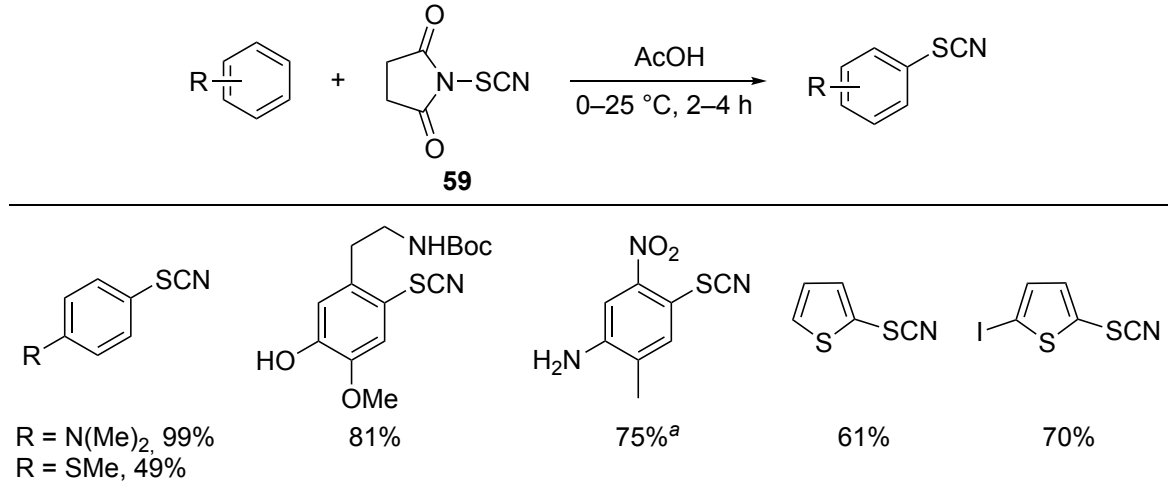
One of the more prominent approaches for the synthesis of aryl thiocyanates is the cyanation of sulfur-containing compounds. Recently, chemists have focused on alternatives to toxic and hard-to-handle reagents such as cyanogen bromide. In 2015, Waser and co-workers reported the use of two hypervalent iodine reagents, 1-cyano-1,2-benziodoxol-3-(1*H*)-one (CBX, **56**) and 1-cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxol (CDBX, **57**), for the cyanation of thiols (Scheme 42).[87] The rapid procedure, taking place at room temperature in only 5 minutes, was found to be very effective for a variety of aryl and alkyl thiols, with yields usually in excess of 85%. Impressively, free amines, alcohols and carboxylic acids were tolerated with no chemoselectivity issues. Furthermore, when phenylselenol was subjected to the procedure, selenocyanate **58** was furnished in 88% yield.



Scheme 42: Substrate scope for the cyanation of thiols with CBX or CDBX.

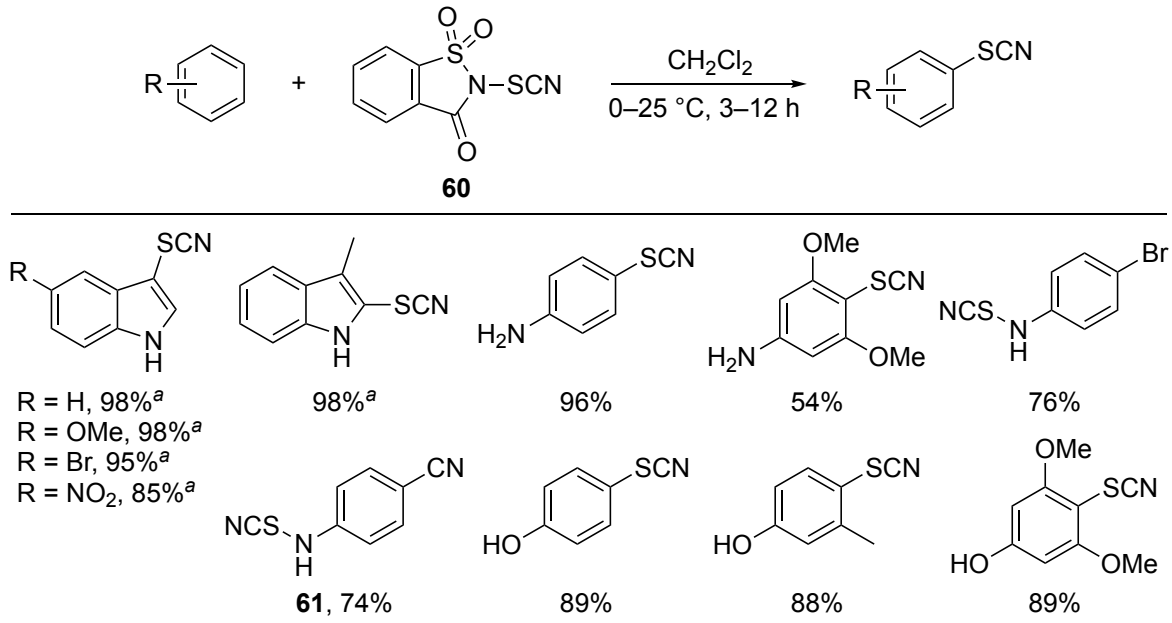
[a] Using CBX **56**.[b] Using CDBX **57**.

However, this process relies on the use of pungent and toxic thiols.[87] Other approaches use disulfides or other sulfur-containing compounds,[88,89] but still require pre-functionalised starting materials. Therefore, the direct C–H thiocyanation of non-functionalized arenes presents an attractive alternative and is the other main approach to the synthesis of aryl thiocyanates. Thiocyanogen chloride was one of the first electrophilic reagents used for this purpose but suffers from the necessity of *in situ* preparation from chlorine gas and thiocyanogen.[90] More stable reagents which can be stored have since been reported such as *N*-thiocyanatosuccinimide (**59**), which was reported by Still and co-workers in 1995 (Scheme 43).[91] It was easily prepared from the commercially available *N*-bromosuccinimide and potassium thiocyanate. The thiocyanation of various arenes was demonstrated in 59–99% yield; however, the substrate scope was limited to highly activated arenes such as anilines, phenols and electron-rich heterocycles. Moreover, for most substrates the use of acetic acid as the solvent was necessary.



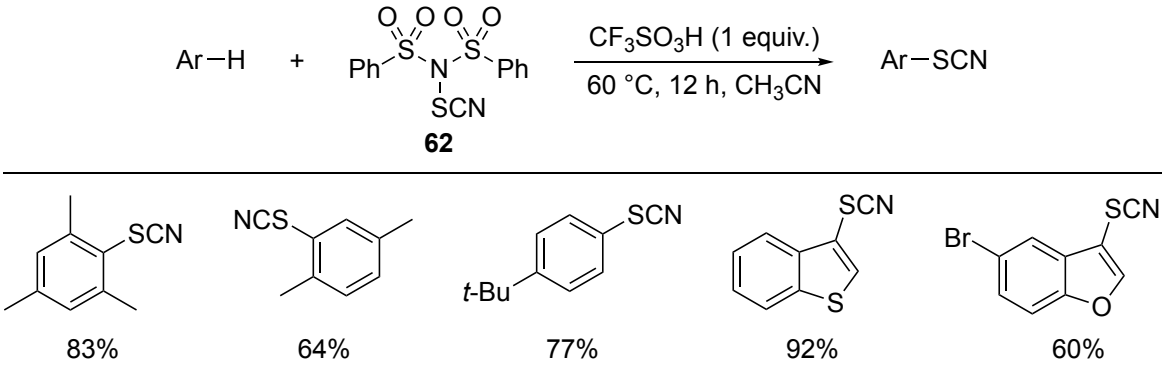
Scheme 43: Substrate scope for the thiocyanation of activated arenes using *N*-thiocyanatosuccinimide.
[a] Using MeOH instead of AcOH as the solvent.

In 2018, Shen and co-workers reported the synthesis and use of *N*-thiocyanatosaccharin (**60**), which was found to be a more active reagent (Scheme 44).[92] Among other transformations, it was demonstrated that it could be used without any additives for the room temperature thiocyanation of activated arenes using tetrahydrofuran or dichloromethane as the solvent. However, the substrate scope was still limited to anilines, phenols and indoles. Indoles bearing electron-withdrawing groups were tolerated, but for anilines the presence of even mildly electron-withdrawing substituents such as nitriles resulted in the formation of *N*-thiocyanated products such as **61**. For phenols, there were no examples of substrates with electron-withdrawing groups.



Scheme 44: Substrate scope for the thiocyanation of activated arenes using *N*-thiocyanatosaccharin (**60**). [a] Using THF instead of CH_2Cl_2 as the solvent.

The following year, Shen and co-workers reported another effective electrophilic thiocyanating reagent, *N*-thiocyanato-dibenzenesulfonimide (**62**) (Scheme 45).[93] While the substrate scope was similar to that of *N*-thiocyanatosaccharin when used without additives, the addition of one equivalent of triflic acid enabled the thiocyanation of relatively unactivated arenes such as mesitylene, *p*-xylene and *t*-butylbenzene. The thiocyanation of heterocycles such as benzothiophene was also demonstrated. However, this method does require the use of stoichiometric amounts of triflic acid.



Scheme 45: Substrate scope for the CF_3SO_3H-mediated thiocyanation of arenes using *N*-thiocyanato-dibenzenesulfonimide.

1.5 Conclusions

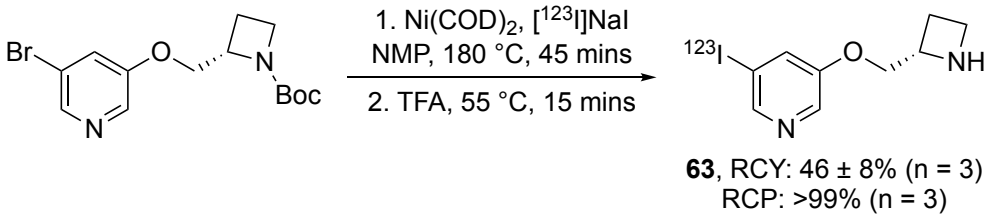
Since 2000, there has been significant progress in the development of new methods for aryl C–S bond formation. In particular, advances in transition-metal-catalysis have allowed for the general synthesis of aryl thiothers from pre-functionalised starting materials such as aryl halides or boronic acids. Photochemistry and electrochemistry, sometimes combined with transition-metal-catalysis, represents a promising new approach. The direct C–H thiolation of arenes has also received significant attention from organic chemists and effective methods have been developed using strong Brønsted acids. However, these are often used in stoichiometric or solvent quantities and are not compatible with some acid-sensitive functional groups. Moreover, these methods can be limited in scope to highly activated arenes such as phenols, anilines and indoles. Therefore, the development of new protocols using milder Lewis acids and conditions is an attractive prospect.

2.0 Novel Methodology for the Functionalisation of Activated Arenes

2.1 Iron-Catalysed Regioselective C–H Thiocyanation of Arenes

2.1.1 Previous Work in the Sutherland Group

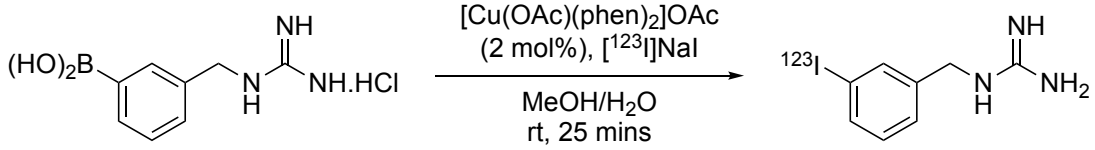
Previously in the Sutherland group, efforts have focused on the development of protocols for the iodination of arenes due to the versatility of aryl halides in various transformations. Moreover, rapid iodination procedures can be used for the preparation of single photon emission computed tomography (SPECT) radiotracers for medical imaging.[94] In 2012, a nickel-catalysed Finkelstein reaction was developed which allowed for the rapid synthesis of aryl iodides from aryl bromides.[95] Further work demonstrated the use of this protocol for the radioiodination of various arenes including the preparation of 5-[^{123}I]A85380 (**63**), a SPECT radiotracer used for imaging neuronal nicotinic acetylcholine receptors (Scheme 46).[96]



63, RCY: 46 ± 8% (n = 3)
RCP: >99% (n = 3)

Scheme 46: Nickel-catalysed radiosynthesis of 5-[^{123}I]-A85380 (**63**).

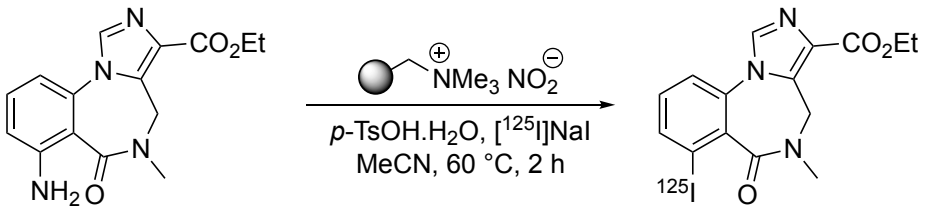
Boronates, which are widely commercially available, have also been utilised in copper- or gold-catalysed iododeboration processes.[97,98] Recently, the group reported a mild and rapid process enabled by a copper precatalyst, [Cu(OAc)(Phen)$_2$]OAc.[99] The methodology was shown to be amenable to the room temperature radioiodination of a wide variety of electron-rich and electron-poor (hetero)arenes. To demonstrate the utility of the procedure, the SPECT neuroendocrine radiotracer [^{123}I]MIBG (**64**) was synthesised in 74 ± 2% radiochemical yield after a reaction time of 25 minutes (Scheme 47).



64, RCY: 74 ± 2% (n = 2)
RCP: 100% (n = 2)

Scheme 47: Copper-catalysed radiosynthesis of [^{123}I]MIBG (**64**).

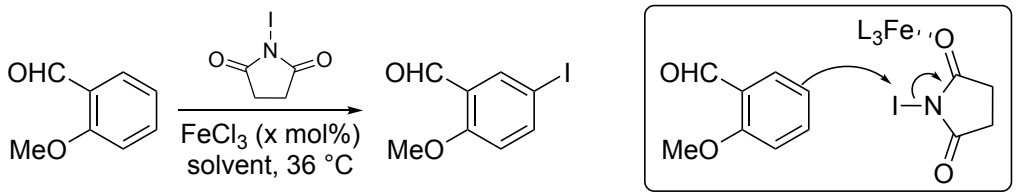
Anilines have also been used in a Sandmeyer-type process for the preparation of aryl iodides.[100] The use of a polymer-supported nitrite resin allowed for the synthesis of stable diazonium salts and avoided potential explosion risks associated with traditional Sandmeyer-type reactions. The process was also demonstrated to be viable for radioiodinations, with various imaging agents prepared including [^{125}]iomazenil (**65**), a SPECT radiotracer for central-type benzodiazepine receptors in brain tissue, in a radiochemical yield of 75 ± 10% (Scheme 48).[101]



65, RCY: 75 ± 10% (n = 2)
RCP: >99% (n = 2)

Scheme 48: Sandmeyer-type radiosynthesis of [^{125}]iomazenil (**65**) using a polymer-supported nitrite resin.

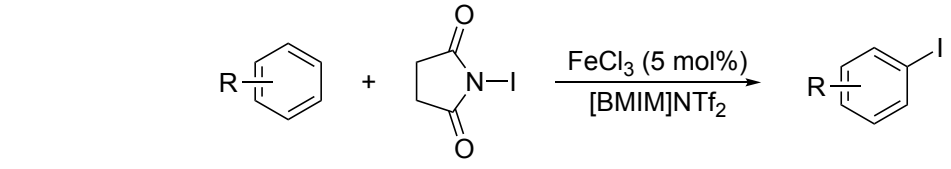
While these methodologies are effective, they rely on pre-functionalised starting materials. Therefore, methods were investigated that would allow for the iodination of non-functionalised starting materials. In 2015, the group developed a mild procedure for the regioselective C–H iodination of activated arenes using *N*-iodosuccinimide (NIS) and Lewis acid-catalysis.[102] Initial optimisation studies screened a variety of transition metal chlorides for the reaction of anisole with NIS in dichloromethane. Iron(III) chloride was found to be the optimal catalyst, with the reaction complete in 1.5 hours using 5 mol% loading. However, for less activated substrates such as 2-methoxybenzaldehyde, it was found that catalyst loadings of 100 mol% were required (Scheme 49). This was deemed excessive, therefore, other iron(III) salts were considered. It was proposed that the use of 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([BMIM]NTf_2), an inexpensive ionic liquid, would result in the *in situ* generation of iron(III) triflimide, a stronger and harder super Lewis acid. Use of [BMIM]NTf_2 as the solvent with an iron(III)-catalyst loading of 5 mol% resulted in full conversion after 2.5 h and an isolated yield of 88%.



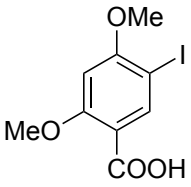
solvent = CH_2Cl_2, 90% (x = 100, 6 h)
solvent = [BMIM]NTf_2, 88% (x = 5, 2.5 h)

Scheme 49: Iodination of 2-methoxybenzaldehyde using $FeCl_3$ or $Fe(NTf_2)_3$.

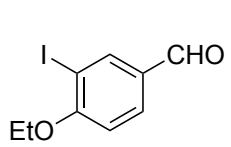
With these optimised conditions, the substrate scope of the transformation was explored (Scheme 50).[102] A wide variety of arenes were iodinated including anisoles, phenols, anilines and electron-rich heterocycles. Substrates bearing electron-withdrawing groups were also tolerated if there was at least one other electron-donating group. For 2-amino-5-chlorobenzophenone, two electron-withdrawing groups were tolerated with the desired product **66** isolated in 88% yield. Several biologically active compounds were prepared, including PIMBA (**67**), a SPECT imaging agent for breast cancer, and 8-iodoharmaline (**68**), a monoamine oxidase inhibitor. For both compounds, temporary protection of the nucleophilic piperidine and imine nitrogens as tetrafluoroborate salts was necessary.



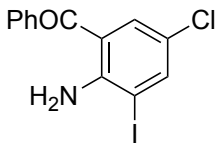
R = OMe, 89% (rt, 0.5 h)
R = OH, 69%, (rt, 0.5 h)
R = NH_2, 79% (rt, 2 h)
R = NHAc, 73% (36°C, 3 h)



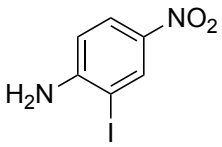
74% (36 °C, 4 h)



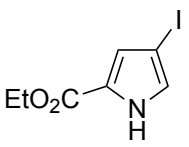
81% (36 °C, 24 h)



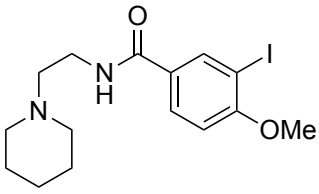
66, 88% (36 °C, 14 h)



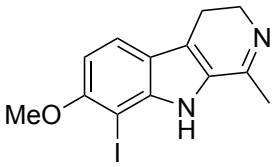
73% (30 °C, 2 h)



76% (36 °C, 1 h)



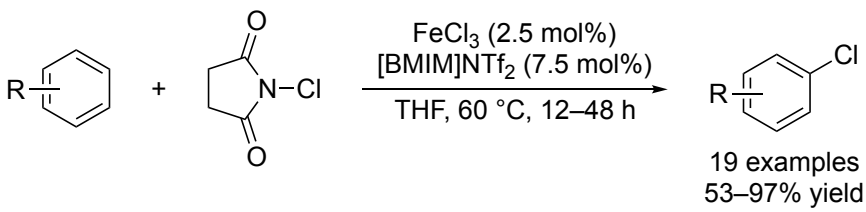
67, 84% (36 °C, 1 h)



68, 73% (36 °C, 2 h)

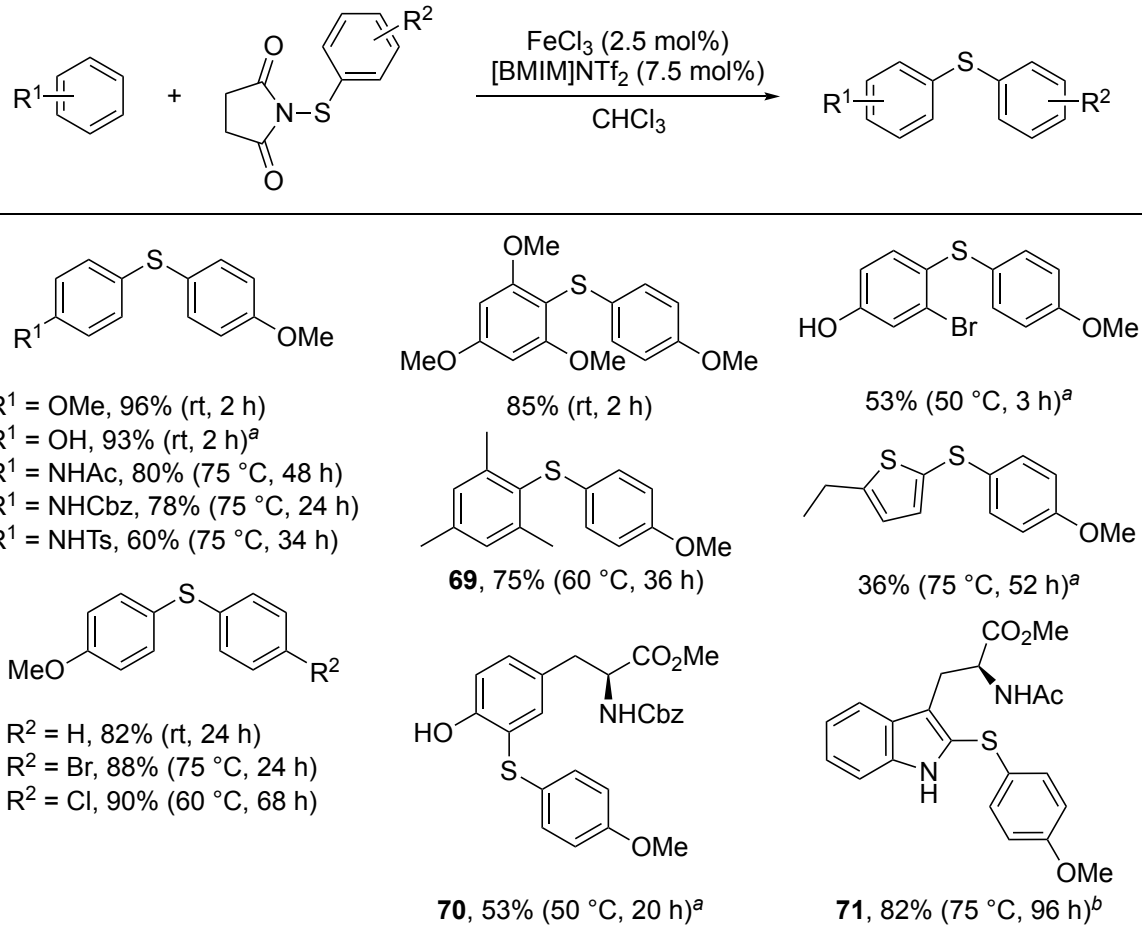
Scheme 50: Substrate scope of the iron(III) triflimide-catalysed iodination of activated arenes.

The group subsequently reported analogous procedures for the bromination and chlorination of activated arenes with similar substrate scopes (Scheme 51).[103,104] Significantly, it was also demonstrated that the halogenations could be performed in common solvents such as tetrahydrofuran using catalytic quantities of [BMIM]NTf_2 to generate iron(III) triflimide.



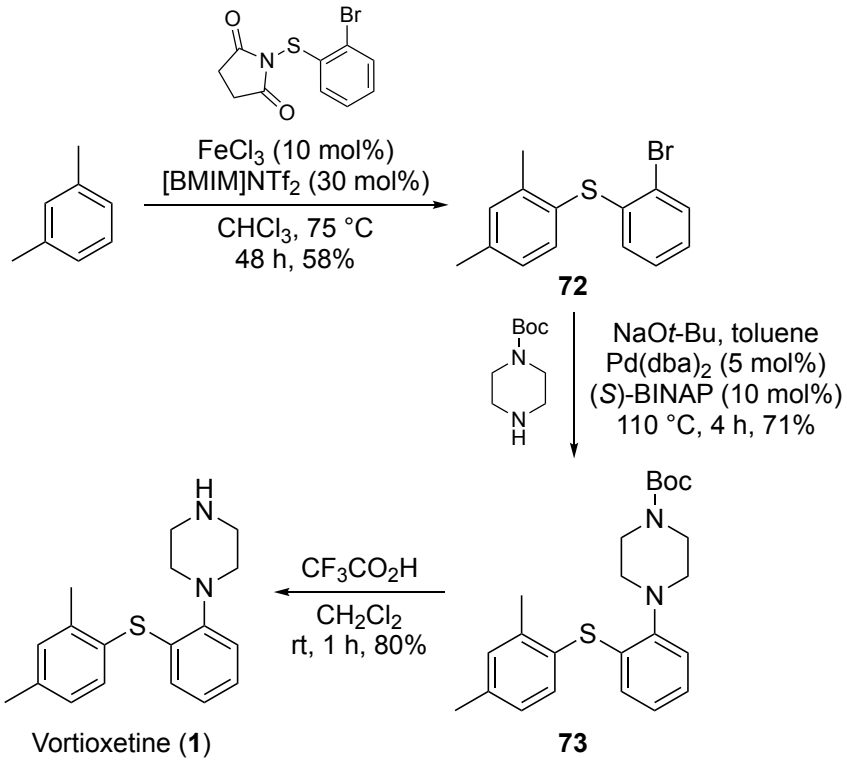
Scheme 51: Summary of the iron(III) triflimide-catalysed chlorination of activated arenes.

More recently, a procedure was developed for the thioarylation of activated arenes using thioarylsuccinimides activated by iron(III) triflimide (Scheme 52).[105] Once again, the procedure had a wide substrate scope with anisoles and phenols often thioarylated in excellent yields. Even the relatively unactivated mesitylene was converted to the desired product **69** in 75% yield. The thioarylation of two protected amino acids, tyrosine and tryptophan, was also successful, giving **70** and **71** in 53% and 82% yields, respectively. Unfortunately, anilines were not tolerated. It was found that instead of electrophilic aromatic substitution, thioarylation occurred on the nitrogen of the aniline.



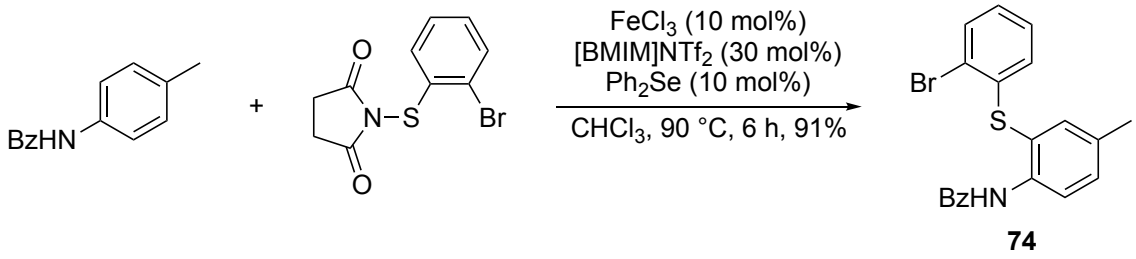
Scheme 52: Substrate scope of the iron(III) triflimide-catalysed thioarylation of activated arenes. [a] $FeCl_3$ (5 mol%) and [BMIM]NTf_2 (15 mol%) was used. [b] $FeCl_3$ (10 mol%) and [BMIM]NTf_2 (30 mol%) was used.

The use of this methodology for the synthesis of biologically active compounds was then investigated, with a key target being antidepressant vortioxetine (**1**) (Scheme 53).[105] *meta*-Xylene, with only two weakly electron-donating methyl groups, was subjected to thioarylation with *N*-(2-bromophenylthio)succinimide to give desired product **72** in 58% yield. For this challenging transformation, a reaction temperature of 75 °C and time of 48 h was required, as well as a higher iron(III) triflimide loading of 10 mol%. The piperidine moiety was then installed using a Buchwald-Hartwig coupling with *N*-Boc-piperadine, followed by deprotection under acidic conditions to furnish vortioxetine (**1**) in 80% yield.



Scheme 53: Synthesis of vortioxetine (**1**).

Finally, the kinetics of the thioarylation were investigated.[105] Similarly to Gustafson and co-workers' findings,[79] the reaction was found to be autocatalytic when the diaryl thioether products were sufficiently electron-rich to act as Lewis bases. Later work in the group investigated the use of an additional Lewis base for challenging thioarylations that were not autocatalytic, such as the reaction depicted in Scheme 54.[106] When the reaction was performed using iron(III) triflimide (10 mol%) at 90 °C, only 22% conversion was observed after 48 h. Several sulfur and selenium Lewis base additives were screened, with diphenyl selenide (10 mol%) giving the best results. After 6 hours, the dual-catalytic reaction was complete with the desired product **74** isolated in 91% yield. These conditions were then used for the thioarylation of several other challenging substrates. It was hypothesised that as the valence electrons of selenium are less tightly bound due to its larger ionic radius, this increases its polarisability and nucleophilicity, resulting in a more effective Lewis base.



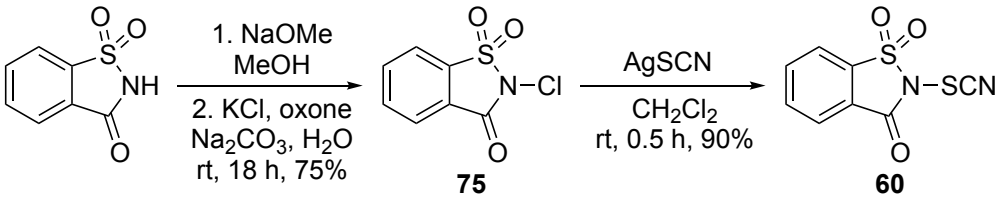
Scheme 54: Lewis acid and Lewis base dual-catalysed synthesised of diaryl thioether **74**.

2.1.2 Project Aims

The aim of this project was to develop a procedure for the thiocyanation of arenes, building on the previous work in the group. It was proposed that iron(III) triflimide would activate *N*-thiocyanatosaccharin in an analogous fashion to the activation of *N*-halosuccinimides and *N*-thioarylsuccinimides. This would enable the mild and regioselective thiocyanation of a wide variety of arenes without the use of a strong Brønsted acid. It was also envisaged that dual Lewis acid and Lewis base-catalysis could be employed for more challenging substrates.

2.1.3 Optimisation and Kinetic Studies

The project began with optimisation studies on the thiocyanation of anisole, which was chosen as the model substrate. *N*-Thiocyanatosaccharin (**60**) was selected as the electrophilic thiocyanating agent due to its high reactivity and ease of synthesis.[92] It was readily prepared in two steps from commercially available saccharin. First, the sodium salt was formed and then converted to *N*-chlorosaccharin (**75**) using potassium chloride in the presence of oxone and sodium carbonate (Scheme 55).[107] Next, nucleophilic substitution with silver(I) thiocyanate generated **60** in 90% yield.[92] For both steps, the best yields were recorded when performing multi gram-scale reactions.

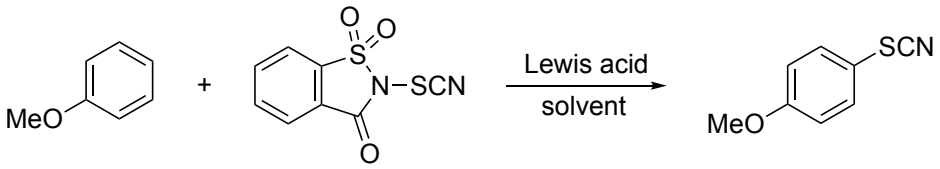


Scheme 55: Two step synthesis of *N*-thiocyanatosaccharin (**60**).

With *N*-thiocyanatosaccharin (**60**) in hand, a brief solvent screen for the thiocyanation of anisole was conducted (Table 1). Previous reports on analogous electrophilic aromatic substitutions from our group and others have found chlorinated solvents, such as dichloromethane or chloroform, as well as tetrahydrofuran and acetonitrile to give good results.[92,93,104,105] For this transformation, the best results were recorded with dichloromethane. At room temperature, 4-thiocyanatoanisole (**76a**) was obtained in 74% yield after a reaction time of 96 hours using iron(III) triflimide (2.5 mol%) as the catalyst (entry 1). To reduce the reaction time and improve conversion, the procedure was performed at 40 °C. This gave a significantly faster reaction with full conversion achieved after 2 hours and an isolated yield of 97% recorded (entry 5). Surprisingly, when iron(III) chloride was used in the absence of [BMIM]NTf_2, the reaction time was only 0.5 h with a

similar isolated yield (entry 6). Thus, these were deemed to be the optimal thiocyanation conditions. This reaction was repeated on a gram scale with an increased 97% yield (entry 7). Several other Lewis acids were screened, and while silver(I) triflimide (entry 8) and indium(III) triflate (entry 10) gave excellent yields, the reaction times were longer at 24 hours for both catalysts.

Table 1: Optimisation of the thiocyanation of anisole.



60, 1.2 equiv. **76a**

Entry	Lewis acid (mol%)	Solvent	Temperature (°C)	Time (h)	Conversion (%)[a]
1	$FeCl_3$ (2.5)/ [BMIM]NTf_2 (7.5)	CH_2Cl_2	20	96	77 (74)
2	$FeCl_3$ (2.5)/ [BMIM]NTf_2 (7.5)	THF	20	6	0
3	$FeCl_3$ (2.5)/ [BMIM]NTf_2 (7.5)	MeCN	20	48	46
4	$FeCl_3$ (2.5)/ [BMIM]NTf_2 (7.5)	$CHCl_3$	20	24	27
5	$FeCl_3$ (2.5)/ [BMIM]NTf_2 (7.5)	CH_2Cl_2	40	2	100 (97)
6	$FeCl_3$ (2.5)	CH_2Cl_2	40	0.5	100 (93)
7[b]	$FeCl_3$ (2.5)	CH_2Cl_2	40	0.5	100 (97)
8	$AgNTf_2$ (2.5)	CH_2Cl_2	40	24	100 (93)
9	$AlCl_3$ (2.5)	CH_2Cl_2	40	24	0
10	$In(OTf_3)$	CH_2Cl_2	40	24	85 (82)

[a] Isolated yields in parentheses. [b] Reaction performed on 1 g scale.

To study the difference between iron(III) triflimide and iron(III) chloride in more detail, a kinetic study was performed using ^{1}H NMR spectroscopy to produce reaction conversion graphs (Figure 3). This confirmed that iron(III) chloride is the superior catalyst and that the reaction is not autocatalytic. Instead, it follows first-order kinetics. Given the electron-withdrawing nature of the thiocyanato group, this was not unexpected. For all previous halogenations and thioarylations developed in the group using succinimide-based reagents, iron(III) triflimide was found to be superior to iron(III) chloride.[102–105] This was proposed to be due to the large volume, low charge density and high electronegativity of the triflimide counter anion, which results in a more Lewis acidic metal centre. However, in this study, a saccharin-based reagent was used. It was hypothesised that this is the reason for the inversion of the previously reported trend between the two Lewis acids. Prior reports in the literature using Brønsted or Lewis acid activation of saccharin-based reagents have

postulated that the catalyst binds to the carbonyl of the amide.[108–110] This carbonyl is more sterically hindered compared to succinimide-based reagents. It is possible that the smaller iron(III) chloride is able to more effectively bind to and activate *N*-thiocyanatosaccharin (**60**) despite being a weaker Lewis acid than the bulkier iron(III) triflimide.

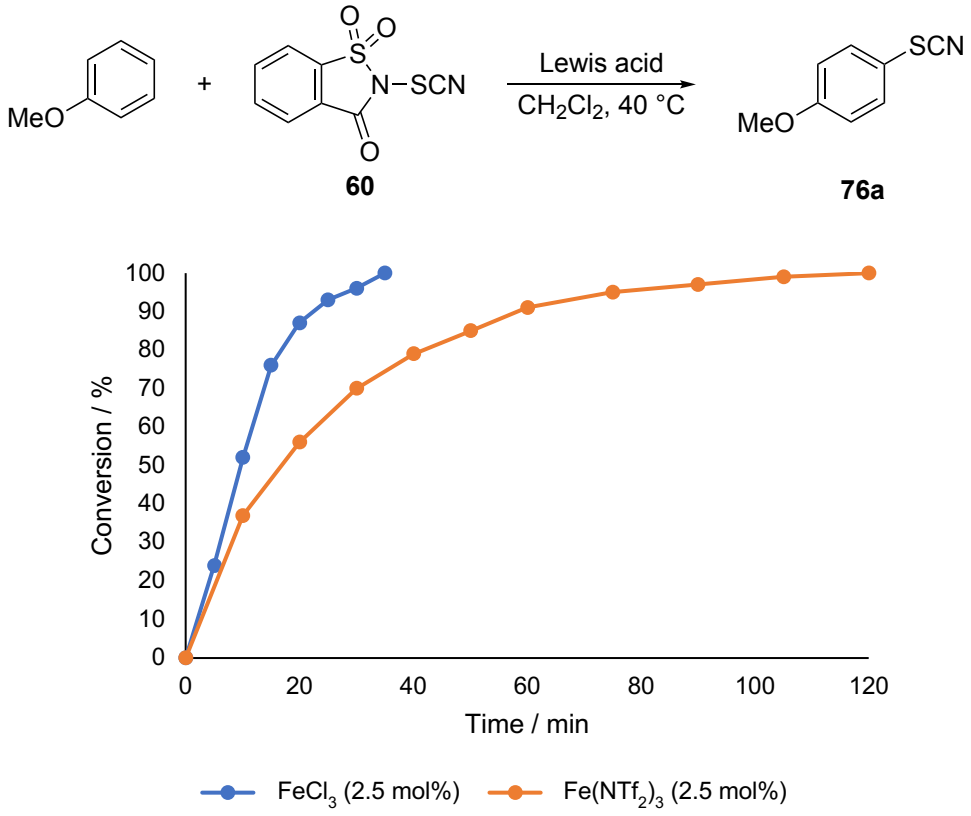
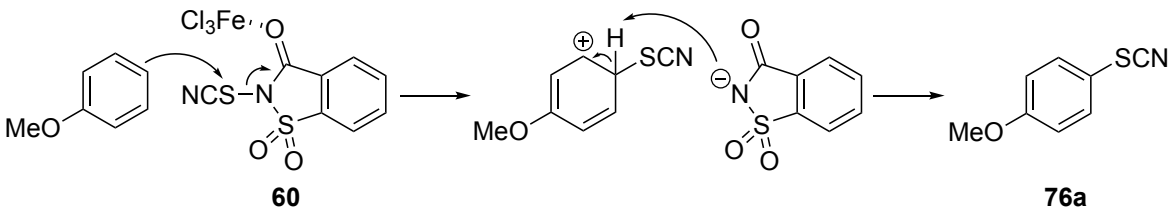


Figure 3: Conversion graph of the reaction of anisole with *N*-thiocyanatosaccharin (**60**) using $FeCl_3$ or $Fe(NTf_2)_3$. Conversion was measured using ^1H NMR spectroscopy. Dimethyl terephthalate was used as an internal standard.

The reaction is proposed to proceed *via* an electrophilic aromatic substitution mechanism, as depicted in Scheme 56. First, iron(III) chloride co-ordinates to the carbonyl oxygen of *N*-thiocyanatosaccharin (**60**). The reagent is then more susceptible to nucleophilic attack by anisole, which results in the formation of a Wheland intermediate. This cationic species is stabilised by the presence of the electron-donating methoxy substituent. Finally, the highly acidic sp^3 proton is abstracted by the saccharinate anion to restore aromaticity, giving 4-thiocyanatoanisole (**76a**) and saccharin.

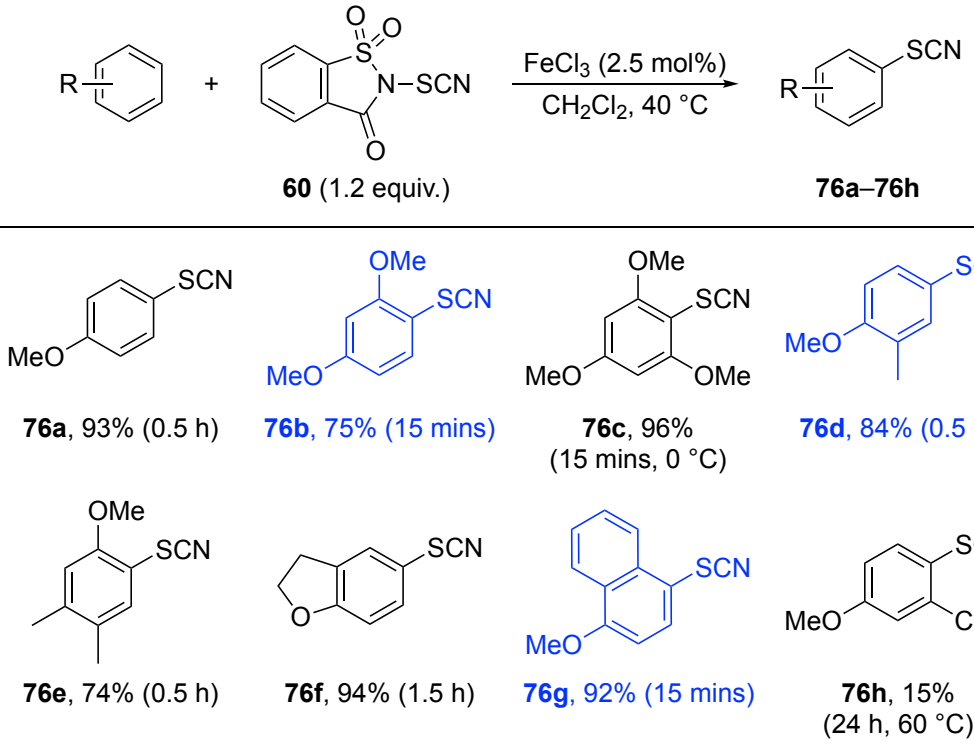


Scheme 56: Proposed mechanism of the $FeCl_3$-catalysed reaction of anisole with *N*-thiocyanatosaccharin (**60**).

For the reaction with anisole, only a small quantity of 2-thiocyanatoanisole (~3%) was observed in the ^{1}H NMR spectrum of the crude reaction mixture. This excellent level of *para*-selectivity is consistent with previous results in the group from halogenation or thioarylation studies.[102–105] The origin of this selectivity was previously investigated regarding the iodination procedure using density functional theory (DFT) calculations.[111] The electrophilic Fukui functions, which indicate the degree to which each atom contributes towards the HOMO and thus is most susceptible to electrophilic attack, were calculated. The results showed that the p_z orbital of the carbon *para* to the directing group was the largest contributor to the HOMO, explaining the observed regioselectivity. Additionally, the sterically hindered nature of the *ortho*-position presumably further enhances *para*-selectivity.

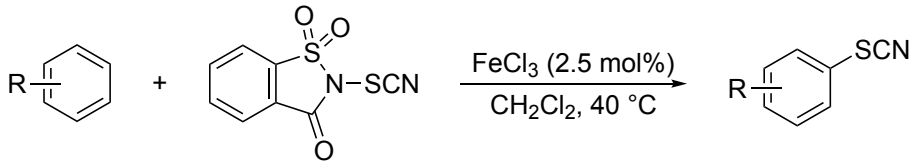
2.1.3 Investigation of the Substrate Scope

Following optimisation of the reaction with anisole, the substrate scope of the methodology was then explored. First, a variety of anisole derivatives were subjected to the thiocyanation procedure (Scheme 57). It was found that these substrates reacted with *N*-thiocyanatosaccharin (**60**) rapidly, with the desired products isolated in excellent yields after reaction times often less than 30 minutes. For the highly activated 1,3,5-trimethoxybenzene, initial attempts at 40 °C resulted in the formation of a mixture of the desired product and the di-substituted product in an 87:13 ratio, measured by ^{1}H NMR spectroscopy. To prevent over-substitution, the reaction was performed at 0 °C with 1.1 equivalents of *N*-thiocyanatosaccharin which resulted in the exclusive formation of the mono-substituted product **76c** in 96% yield. For substrates with a *para*-substituent, such as 3,4-dimethylanisole, the thiocyanation occurred at the *ortho*-position with the desired product **76e** delivered in a 74% yield. In this case, substitution also occurred at the other *ortho*-position, with the 2-thiocyanated side-product isolated in 16% yield. Unfortunately, the thiocyanation with *meta*-anisaldehyde only resulted in a low yield of 15% after an extended reaction time and temperature of 60 °C. The use of 10 mol% iron(III) chloride did not give an improved yield. It is likely that the presence of the electron-withdrawing aldehyde prevents reaction.

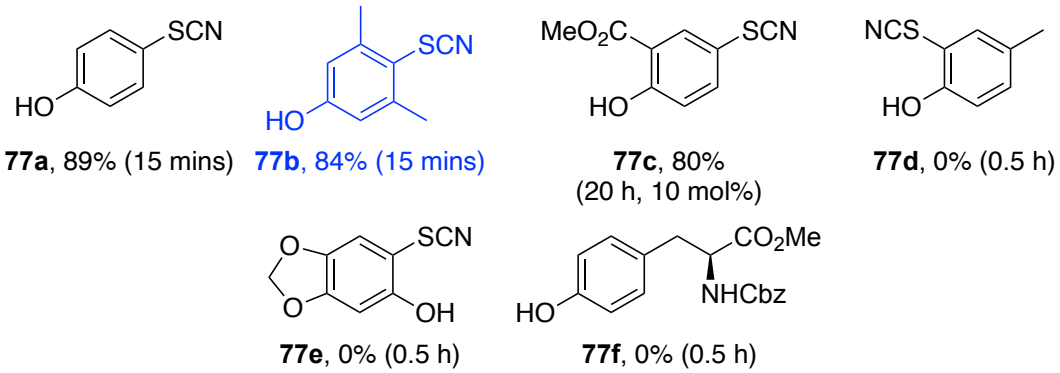


Scheme 57: Substrate scope of the iron(III) chloride-catalysed thiocyanation of anisole derivatives. Products highlighted in blue were synthesised by Maisie Senkans, an MSc student.

Next, the thiocyanation of phenols was investigated (Scheme 58). 4-Thiocyanatophenol (**77a**) was generated in 89% yield after 15 minutes, and the sterically hindered 3,5-dimethylphenol was thiocyanated in a similarly effective reaction. It was demonstrated that electron-withdrawing groups were tolerated with the thiocyanation of methyl salicylate in 80% yield, albeit with a higher catalyst loading (10 mol%) and longer reaction. However, when the *para*-position was blocked, only complex crude mixtures were obtained (**77d**–**77f**). It was hypothesised that for these substrates, *ortho*-thiocyanation occurs followed by reaction with the proximal hydroxy group of the phenol, which results in a variety of products. Attempts to isolate these side-products were unsuccessful. It should also be noted that, to the best of our knowledge, there are no examples of 2-thiocyanatophenols reported in the literature, which gives weight to this hypothesis.



60 (1.2 equiv.) **77a–77c**

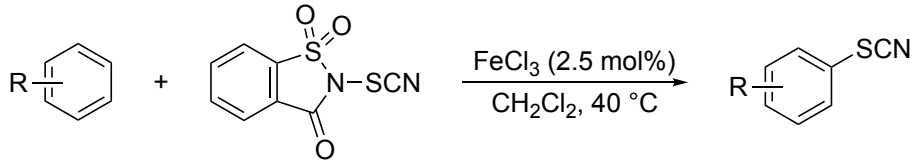


77a, 89% (15 mins) **77b**, 84% (15 mins) **77c**, 80% (20 h, 10 mol%) **77d**, 0% (0.5 h)

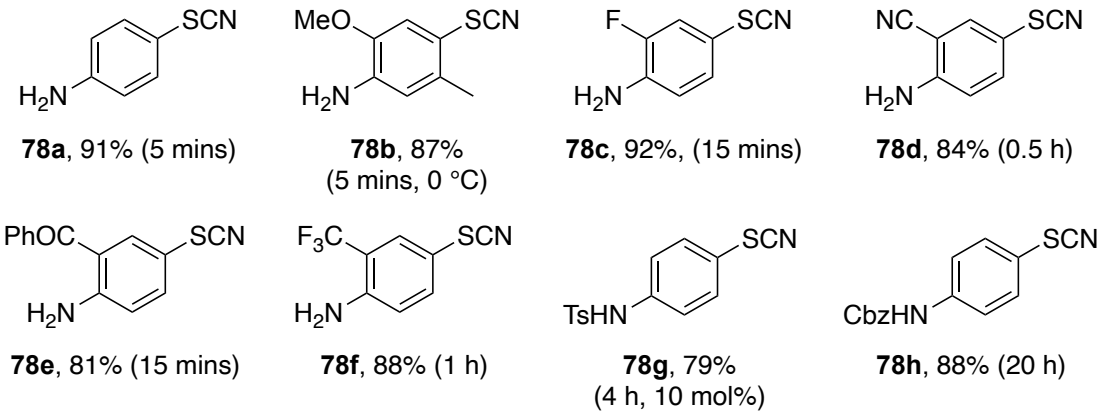
77e, 0% (0.5 h) **77f**, 0% (0.5 h)

Scheme 58: Substrate scope of the iron(III) chloride-catalysed thiocyanation of phenols. Products highlighted in blue were synthesised by Maisie Senkans, an MSc student.

Anilines were found to undergo efficient reactions (Scheme 59). Several substrates bearing electron-withdrawing substituents underwent full conversion in under 1 hour, with excellent isolated yields. For example, 2-trifluoromethyl-4-thiocyanatoaniline (**78f**) was isolated in 88% yield. Halide-, nitrile- and ketone-substituted anilines were also effective substrates, giving products **78c**, **78d** and **78e** in 92%, 84% and 81% yields, respectively. Significantly, no *N*-thiocyanated products were observed for any of these thiocyanations. Protected anilines such as *N*-tosyl and *N*-carboxybenzyl derivatives were also competent substrates, although higher catalyst loadings and longer reaction times were necessary, respectively.



60 (1.2 equiv.) **78a–78h**

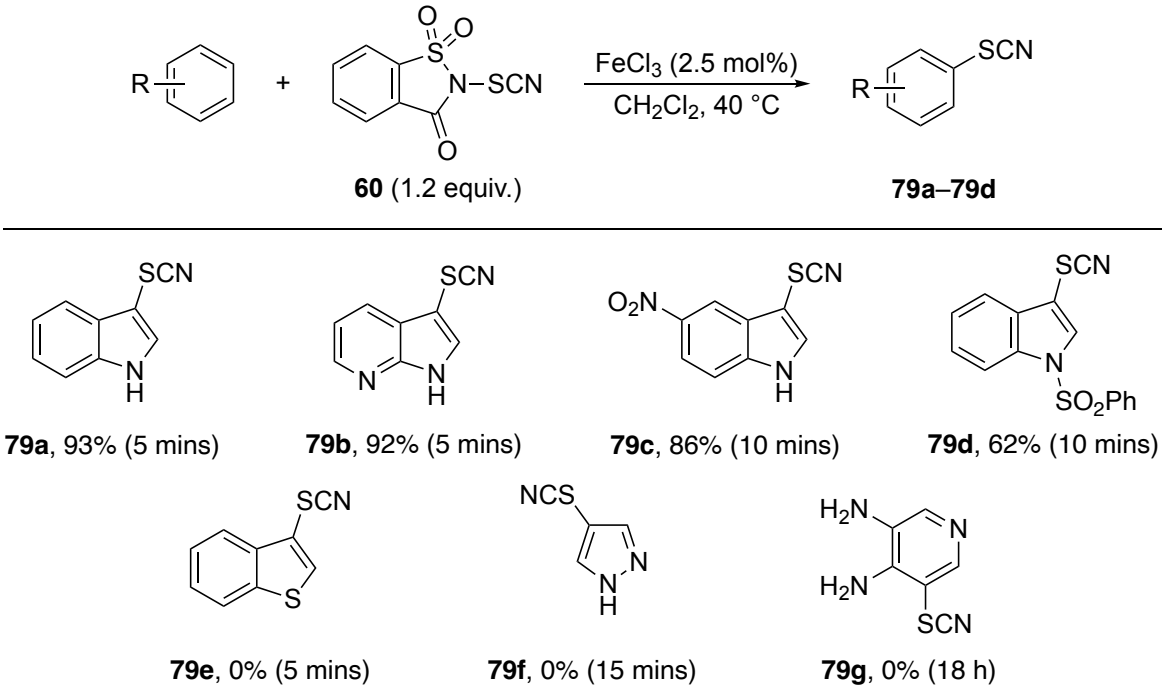


78a, 91% (5 mins) **78b**, 87% (5 mins, 0 °C) **78c**, 92%, (15 mins) **78d**, 84% (0.5 h)

78e, 81% (15 mins) **78f**, 88% (1 h) **78g**, 79% (4 h, 10 mol%) **78h**, 88% (20 h)

Scheme 59: Substrate scope of the iron(III) chloride-catalysed thiocyanation of anilines.

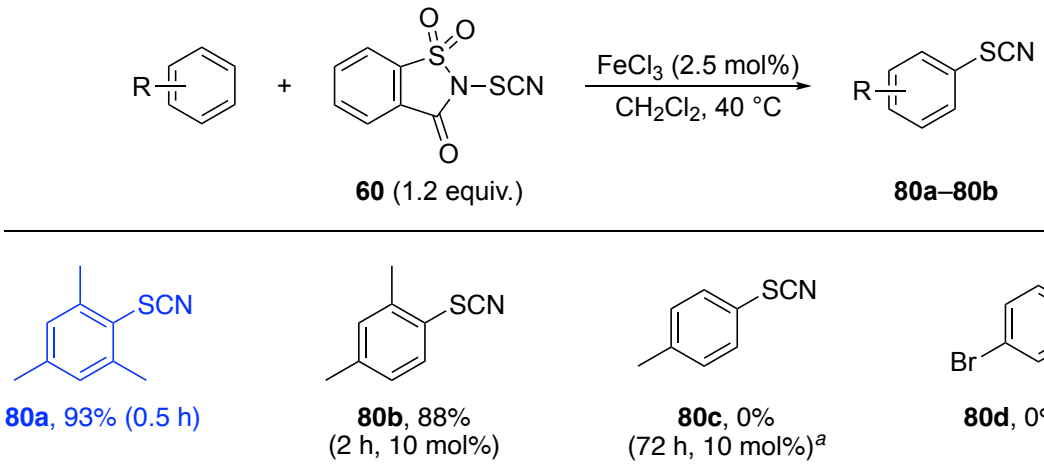
The compatibility of heterocycles with this methodology was also explored (Scheme 60). Indole and 7-azaindole were found to give the desired products **79a** and **79b**, respectively, in excellent yields and rapid reaction times of 5 minutes. Strongly electron-withdrawing substituents were tolerated, with 3-thiocyanto-5-nitroindole (**79c**) furnished in 86% yield after 10 minutes. It was also shown that a sulfonamide-protected indole was able to participate in the process, albeit in a slightly lower yield of 62%. Given Cossy's previous work on thioarylations at the 2-position, structures were conclusively assigned as 3-substituted indoles by comparison of NMR spectra to known compounds. For other electron-rich heterocycles such as benzothiophene and pyrazole, selectivity issues were encountered. While these substrates reacted rapidly, the thiocyanation occurred at a variety of positions and in both cases and it was not possible to isolate the desired products by column chromatography. Attempts to improve selectivity by lowering the reaction temperature to 0 °C were also unsuccessful. For pyridine-3,4-diamine, there was no thiocyanation with only starting material recovered. It was hypothesised that this was due to the basic pyridine nitrogen binding to iron(III) chloride and preventing catalysis.



Scheme 60: Substrate scope of the iron(III) chloride-catalysed thiocyanation of heterocycles.

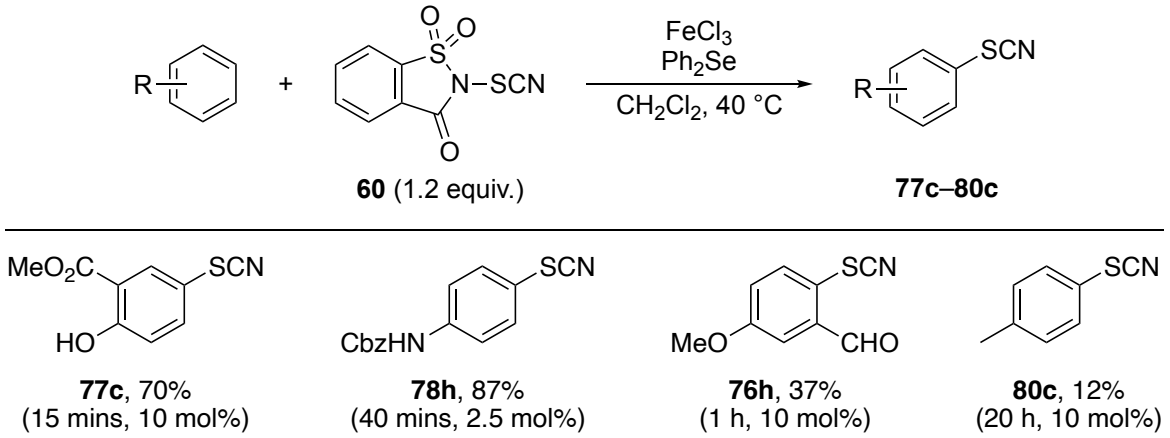
Finally, less activated and unactivated compounds were investigated (Scheme 61). Mesitylene was thiocyanated in only 30 minutes under the standard conditions with the desired product **80a** isolated in an excellent 93% yield. This reaction also demonstrated that di-*ortho*-substituted compounds were well tolerated. Encouraged by this result, other minimally activated compounds were considered. Using the same conditions, the thiocyanation of *meta*-xylene reached 73% conversion after 48 hours. With an increased catalyst loading of 10 mol%, full conversion was observed after 2 h and 1,3-dimethyl-4-

thiocyanatobenzene (**80b**) was isolated in 88% yield. However, when toluene was used no thiocyanation occurred, even under forcing conditions of 72 hours at 60 °C using 10 mol% iron(III) chloride. Given the group's previous work on halogenations and thioarylations,[102–105] it was not expected that substrates bearing only electron-withdrawing groups would give successful reactions. Nonetheless, it was thought worthwhile to consider one such substrate. As expected, bromobenzene did not undergo thiocyanation.



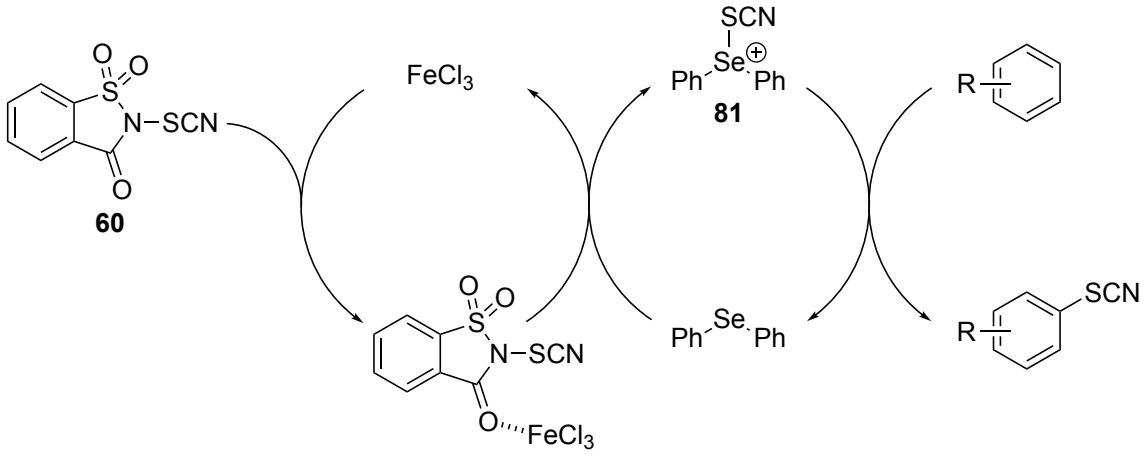
Scheme 61: Substrate scope of the iron(III) chloride-catalysed thiocyanation of minimally activated substrates. Products highlighted in blue were synthesised by Maisie Senkans, an MSc student.[a] Reaction temperature was 60 °C. [b] Reaction temperature was 50 °C.

As the use of diphenyl selenide as a Lewis base in the previous work on dual catalytic Lewis acid/Lewis base promoted thioarylations had been successful,[106] it was proposed that a similar approach could be applied to the thiocyanation of challenging substrates (Scheme 62). Several thiocyanations where the original reaction time was long (>6 h) or the yield was low due to poor conversion were repeated with diphenyl selenide at a catalyst loading equal to the loading of iron(III) chloride. For all substrates, a substantial improvement in reaction rate was observed. The reaction time of methyl salicylate and Cbz-protected aniline improved from 20 hours to 15 and 40 minutes, respectively. Similar isolated yields of products **77c** and **78h** were obtained, compared to the original reactions. For the thiocyanation of *meta*-anisaldehyde, an improved conversion of 45% was observed and the yield of **76h** increased from 15% to 37%. Additionally, the reaction time was reduced from 24 hours to 1 hour. In the case of toluene, the use of the dual-catalytic approach did not substantially improve the outcome. For the latter two reactions, the conversion of diphenyl selenide to di(4-thiocyanatophenyl)selenide was observed. It is clear that for these weakly activated substrates, the thiocyanation of diphenyl selenide competes with the desired thiocyanation of the substrate. Given the electron-withdrawing effect of the thiocyanto group, the Lewis base catalyst is likely de-activated following this transformation, which partly explains the low yields for these compounds.



Scheme 62: Dual-catalytic process involving iron(III) chloride and diphenyl selenide.

The following mechanism was proposed for the dual-catalytic process based on the previous work in the group (Scheme 63).[106] Iron(III) chloride first activates *N*-thiocyanatosaccharin (**60**), which is then attacked by diphenyl selenide to form cationic species **81**. This charged intermediate is significantly more reactive than *N*-thiocyanatosaccharin and is more readily attacked by arenes, producing the desired thiocyanated products and regenerating diphenyl selenide.



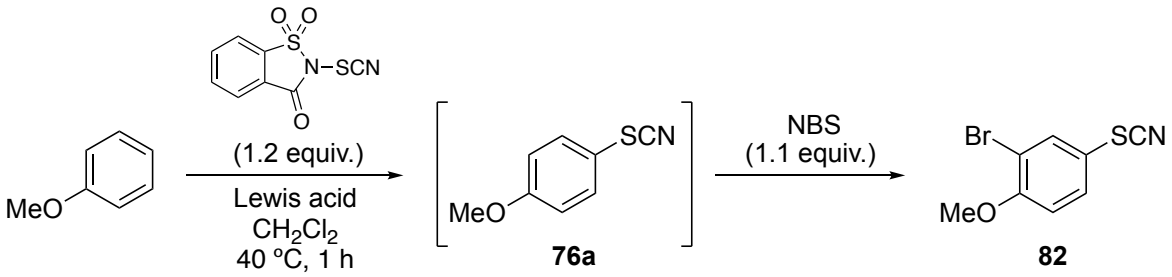
Scheme 63: Proposed mechanism of the dual-catalytic process involving iron(III) chloride and diphenyl selenide.

2.1.4 One-Pot Tandem Thiocyanation-Bromination

Having explored the substrate scope of the procedure, efforts then focused on demonstrating other applications of the process. It was proposed that it would be useful to develop a one-pot procedure for the tandem thiocyanation-halogenation of activated arenes, as this would enable the rapid functionalisation and diversification of simple feedstock chemicals such as anisole. The first attempt used the standard thiocyanation conditions, iron(III) chloride (2.5 mol%) at 40 °C in dichloromethane (Table 2, entry 1). Once the thiocyanation was complete after 1 hour, NBS (1.1 equiv.) was added to the reaction

mixture. Unfortunately, after an extended reaction time of 96 hours, there was no conversion of intermediate **76a** to the 2,4-difunctionalised product **82**. It was hypothesised that the use of iron(III) triflimide, which has previous been demonstrated to be superior to iron(III) chloride for the bromination of arenes,[103] might result in an effective bromination. While this gave a slightly longer thiocyanation of 2 hours, *ortho*-bromination did occur in the 2nd step after the temperature was raised to 55 °C. However, full conversion was not achieved after 40 h and 2-bromo-4-thiocyanatoanisole (**82**) was isolated in only 55% yield. Thus, the reaction was performed using an increased catalyst loading of 10 mol%. This resulted in 92% conversion and a 76% isolated yield of **82** after 18 h. Upon scale-up of the reaction to 0.35 mL of anisole, and a slight increase in the quantity of NBS used to 1.2 equivalents, the yield increased to 87%.

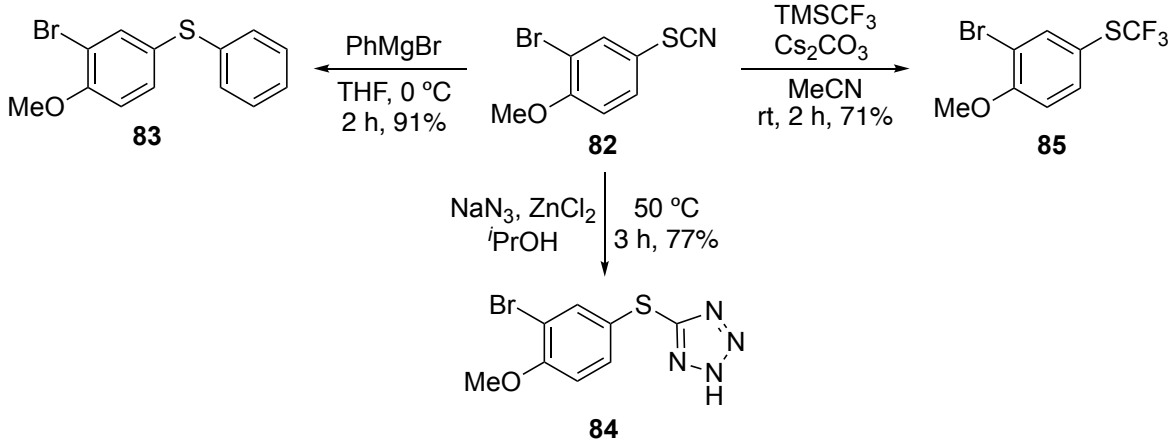
Table 2: Optimisation of the one-pot tandem thiocyanation-bromination of anisole.



Entry	Lewis acid (mol%)	2nd Step Temperature (°C)	2nd Step Time (h)	Yield (%)
1	$FeCl_3$ (2.5)	40	96	0
2[a]	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	55	40	55
3	$FeCl_3$ (10)/[BMIM]NTf_2 (30)	40	18	76
4[b]	$FeCl_3$ (10)/[BMIM]NTf_2 (30)	40	18	87

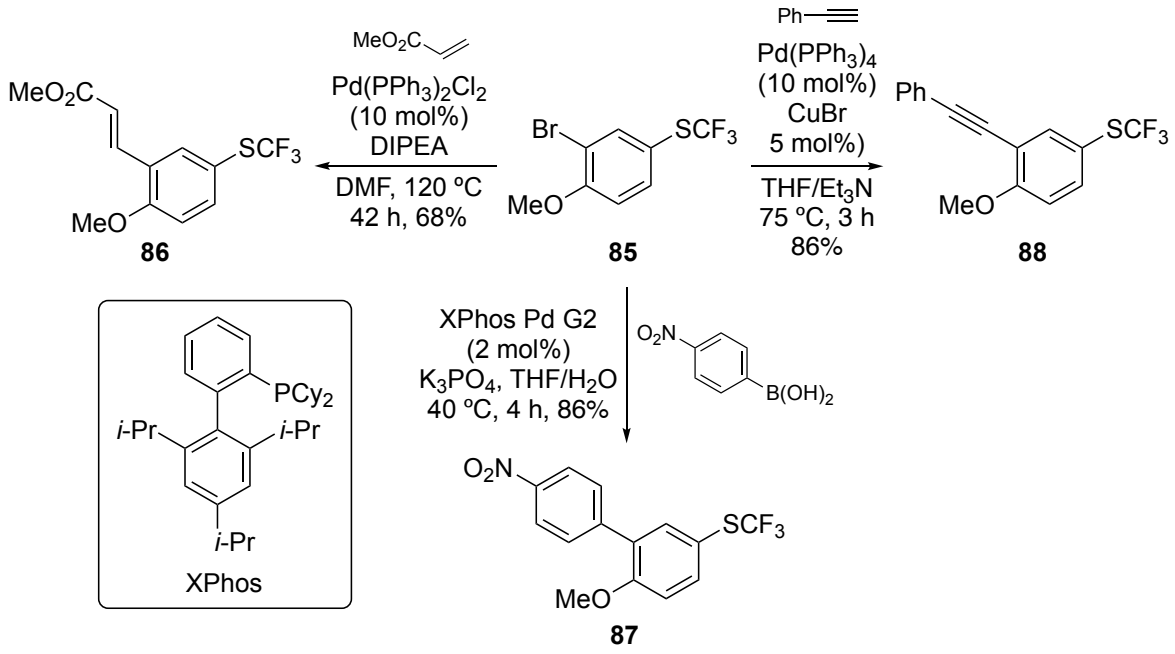
[a] Reaction time for thiocyanation step was 2 h. [b] 1.2 equiv. of NBS were used and reaction was performed at a 0.35 mL scale.

Next, the derivatisation of difunctionalised compound **82** was investigated. Initially, a variety of transformations were attempted on the *para*-thiocyanate moiety (Scheme 64). Nucleophilic substitution with phenylmagnesium bromide gave diaryl thioether **83** in an excellent yield of 91%, while the zinc(II) chloride-mediated reaction with sodium azide in a 1,3-dipolar cycloaddition gave tetrazole **84** in 77% yield. As discussed previously, the trifluoromethylsulfenyl substituent is a privileged motif in medicinal chemistry. Thus, the synthesis of aryl trifluoromethyl thioether **85** was demonstrated. This was achieved using the Ruppert-Prakash reagent, trifluoromethyltrimethylsilane, as a nucleophilic source of the trifluoromethylsulfenly group, which underwent substitution with aryl thiocyanate **82** in the presence of cesium carbonate.[83] The desired product **85** was obtained in 71% yield.



Scheme 64: Diversification of 2,4-difunctionalised compound **82** using the thiocyanato group.

A series of palladium-catalysed functionalisations were then performed at the *ortho*-bromide position of trifluoromethyl thioether **85** (Scheme 65). Heck, Suzuki-Miyaura and Sonogashira reactions were utilised to install methyl carboxyalkenyl, 4-nitrophenyl and phenylalkynyl substituents in 68%, 86% and 86% yields, respectively. Thus, it was demonstrated that simple feedstock chemicals such as anisole can be rapidly and efficiently functionalised and diversified in relatively few steps using the tandem thiocyanation-bromination procedure.

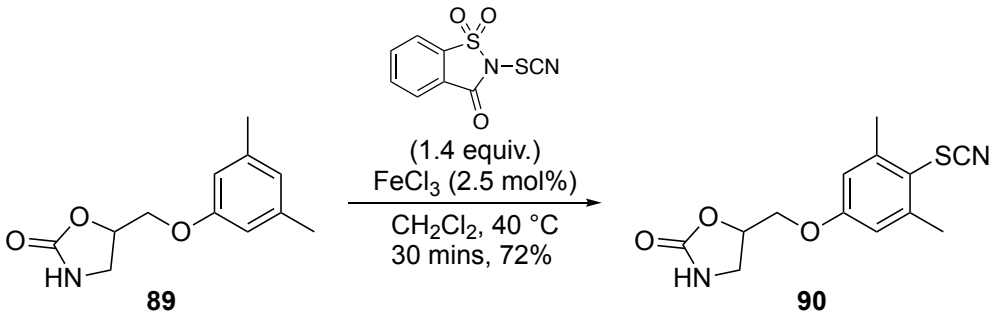


Scheme 65: Diversification of trifluoromethyl thioether **85** using the bromide.

2.1.5 Functionalisation and Synthesis of Biologically Active Compounds

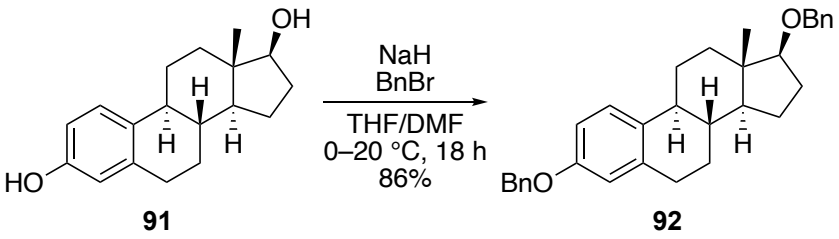
Another major aim of this project was to demonstrate that this process could be used for the late-stage functionalisation of complex molecules. Therefore, two biologically active

compounds were chosen to be subjected to the thiocyanation procedure – metaxalone (**89**) and estradiol (**91**). The thiocyanation of metaxalone (**89**) proceeded smoothly in 30 minutes, although a slightly higher quantity of *N*-thiocyanatosaccharin (1.4 equivalents) was necessary to push the reaction to full conversion (Scheme 66). Unusually for this methodology, the yield was compromised by the formation of a small amount of the *ortho*-substituted product. It was thought that this was due to steric hinderance at the *para*-position. In the crude reaction mixture, there was a 6:1 ratio of *para*:*ortho*-regioisomers, measured by ^{1}H NMR spectroscopy, which were readily separated using column chromatography. The desired *para*-substituted product **90** was isolated in a 72% yield.



Scheme 66: Thiocyanation of metaxalone (**89**).

For estradiol (**91**), the *para*-position is blocked and the thiocyanation is directed to the *ortho*-position. Given that this is adjacent to a hydroxy substituent, it was anticipated that the *ortho*-thiocyanato-product would not be isolable. Therefore, protection of the alcohol was necessary and dibenzyl estradiol derivative **92** was synthesised in 86% yield (Scheme 67).

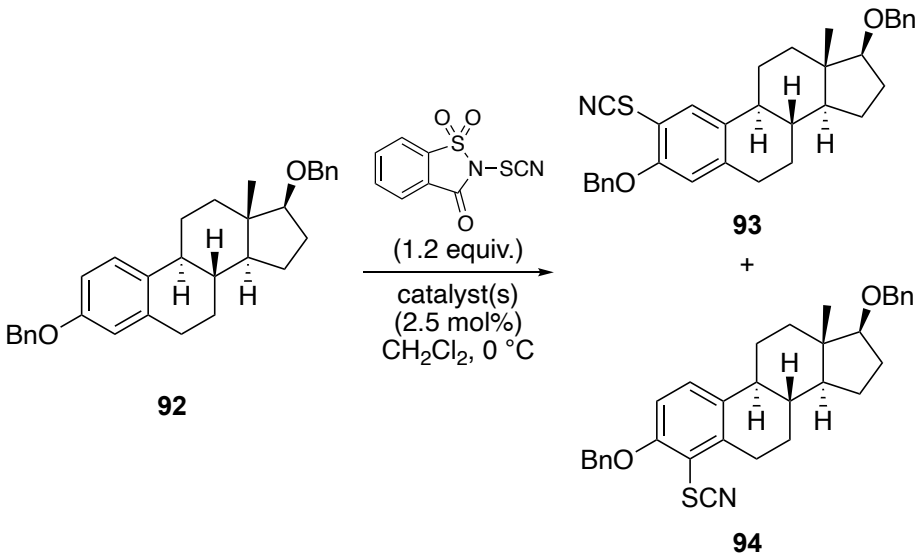


Scheme 67: Synthesis of estradiol derivative **92**.

While the thiocyanation of dibenzyl estradiol derivative **92** resulted in full conversion after 10 minutes under standard conditions, a 1.5:1 mixture of both *ortho*-substituted products **93**:**94** was observed in the crude reaction mixture (Table 3, entry 1). Lowering the reaction temperature to 0 °C did not improve this outcome (entry 2). It was proposed that the use of diphenyl selenide could confer greater regioselectivity due to the increased steric bulk of the diphenyl selenide cationic intermediate **81** compared to *N*-thiocyanatosaccharin, which would lead to improved selectivity for the least sterically hindered *ortho*-position. Using 2.5

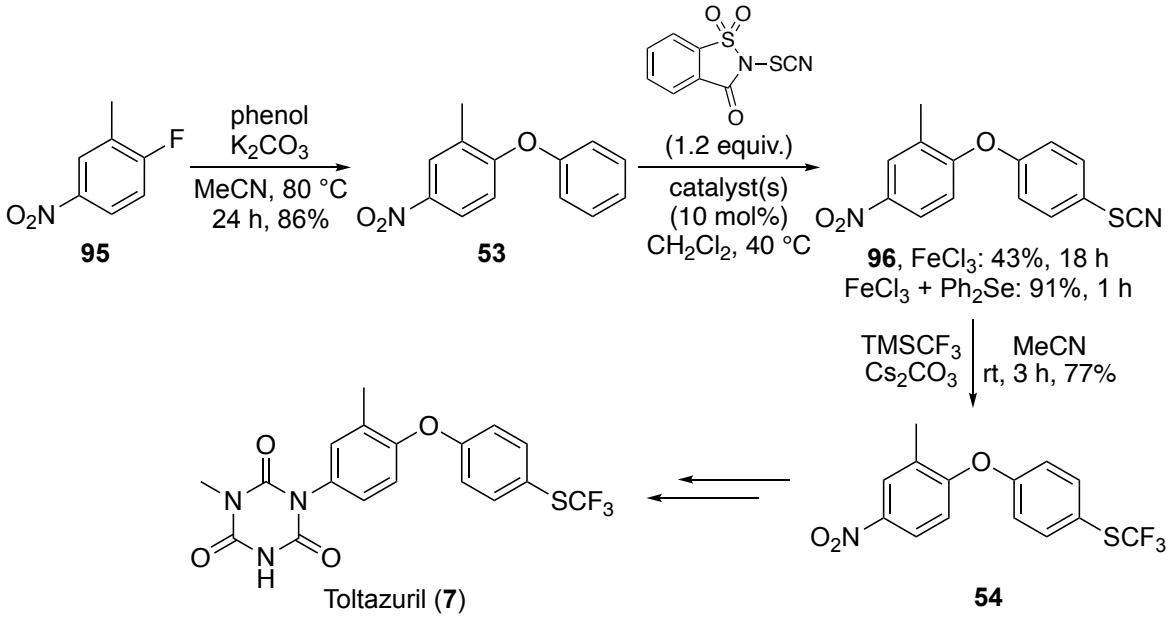
mol% diphenyl selenide, a 9:1 ratio of **93**:**94** was observed and both products were isolated in 86% and 9% yields, respectively (entry 3).

Table 3: Thiocyanation of dibenzyl estradiol derivative **92**.



Entry	Catalyst(s)	Temperature (°C)	Time (mins)	Ratio of 93:94	Yield (%)
1	$FeCl_3$	40	10	1.5:1	-
2	$FeCl_3$	0	60	1.5:1	44 + 15
3	$FeCl_3$ + Ph_2Se	0	10	9:1	86 + 9

Finally, the use of the thiocyanation procedure for the synthesis of a biologically active compound was investigated. The target chosen was toltrazuril **7**, an antiparasitic agent used for treatment of coccidiosis in livestock.[25] First, electron-deficient arene **95** was subjected to nucleophilic aromatic attack by phenol, furnishing diaryl ether **53** in 86% yield (Scheme 68). The thiocyanation of this compound was then attempted, but even the use of 10 mol% iron(III) chloride gave only 43% yield. Presumably, this is due to the presence of the deactivating nitro substituent. However, when the dual-catalytic process using iron(III) chloride and diphenyl selenide was employed, an excellent 91% yield of aryl thiocyanate **96** was recorded after a reaction time of only 1 hour. Finally, conversion of the thiocyanate to trifluoromethyl thioether **54** was achieved in a 77% yield.[83] This compound is an intermediate in the industrial synthesis of toltrazuril (**7**),[25] thus, the formal synthesis was completed.



Scheme 68: Formal synthesis of toltrazuril (**7**).

2.1.6 Conclusions

In conclusion, a rapid and efficient procedure for the thiocyanation of activated arenes has been developed. It was shown that the methodology has a wide substrate scope, is generally extremely regioselective and high-yielding. Significantly, this was achieved without the use of a strong Brønsted acid. The *para*-thiocyanation process was combined with a subsequent one-pot *ortho*-bromination step to rapidly functionalise anisole, which was further elaborated to form more complex products. It was also demonstrated that both the thiocyanation and thiocyanation-bromination processes were amenable to larger scale reactions. Indeed, the yield was slightly improved in both cases. Finally, the thiocyanation of metaxalone and benzyl-protected estradiol was demonstrated, as well as the formal synthesis of toltrazuril.

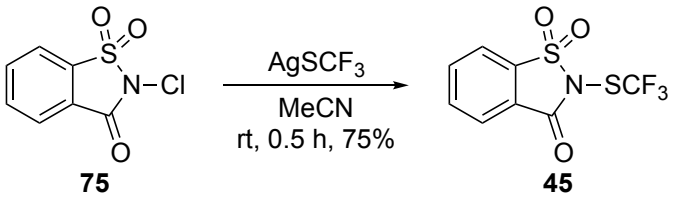
2.2 Iron- and Diphenyl Selenide-Catalysed Regioselective C–H Trifluoromethylthiolation of Arenes

2.2.1 Project Aims

Having successfully developed an efficient and regioselective protocol for the thiocyanation of arenes and demonstrated the conversion of aryl thiocyanates to aryl trifluoromethyl thioethers, it was proposed that this two-step sequence could be achieved in a single step. *N*-(Trifluoromethylthio)saccharin (**45**), an analogous reagent to *N*-thiocyanatosaccharin, would be activated by iron(III) chloride. This would avoid the use of strong Brønsted acids which, as discussed in the introduction, were used in stoichiometric quantities by Gustafson[79] and Miura[81] to effect similar transformations. Li and co-workers previously reported a Lewis acid-promoted procedure involving iron(III) chloride and silver(I) hexafluoroantimonate(V), but high temperatures of 100 °C were required.[78] It was envisaged that the use of a dual-catalytic Lewis base/Lewis acid strategy would allow for the use of milder conditions and result in a wider substrate scope.

2.2.2 Reaction Optimisation

N-(Trifluoromethylthio)saccharin (**45**) was initially prepared from *N*-chlorosaccharin (**75**) and silver(I) trifluoromethanethiolate in 75% yield (Scheme 69).[112] Towards the end of this project, the reagent became commercially available and was purchased from suppliers.



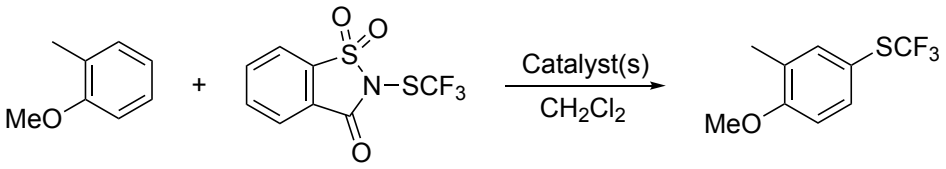
75 **45**

Scheme 69: Synthesis of *N*-(trifluoromethylthio)saccharin (**45**).

Initial optimisation studies were performed using anisole as the model substrate. However, the high volatility of the product, 4-(trifluoromethylthio)anisiole, complicated purification and resulted in low isolated yields. Therefore, 2-methylanisole was considered instead (Table 4). First, a variety of Lewis acids were screened at 10 mol% catalyst loading in dichloromethane at 40 °C. However, after 20 hours, only iron(III) chloride was found to result in any conversion to the desired product **97a**, which was minimal (entry 1). Thus, the dual catalytic Lewis acid/Lewis base strategy was investigated. When both iron(III) chloride (10 mol%) and diphenyl selenide (10 mol%) were used, full conversion was observed after 5 minutes and 2-methyl-4-(trifluoromethylthio)anisole (**97a**) was isolated in 97% yield (entry

5). It was found that the reaction could be performed at room temperature with both catalyst loadings reduced to 2.5 mol%, with a similar yield recorded (entry 7). The reaction time was longer at 2 hours, but this was considered acceptable given the milder conditions. To confirm the necessity of a Lewis acid, the reaction was performed with diphenyl selenide (2.5 mol%) in the absence of iron(III) chloride (entry 8). As expected, no conversion to the desired product was observed.

Table 4: Optimisation of the trifluoromethylthiolation of anisole.



45, 1.1 equiv. **97a**

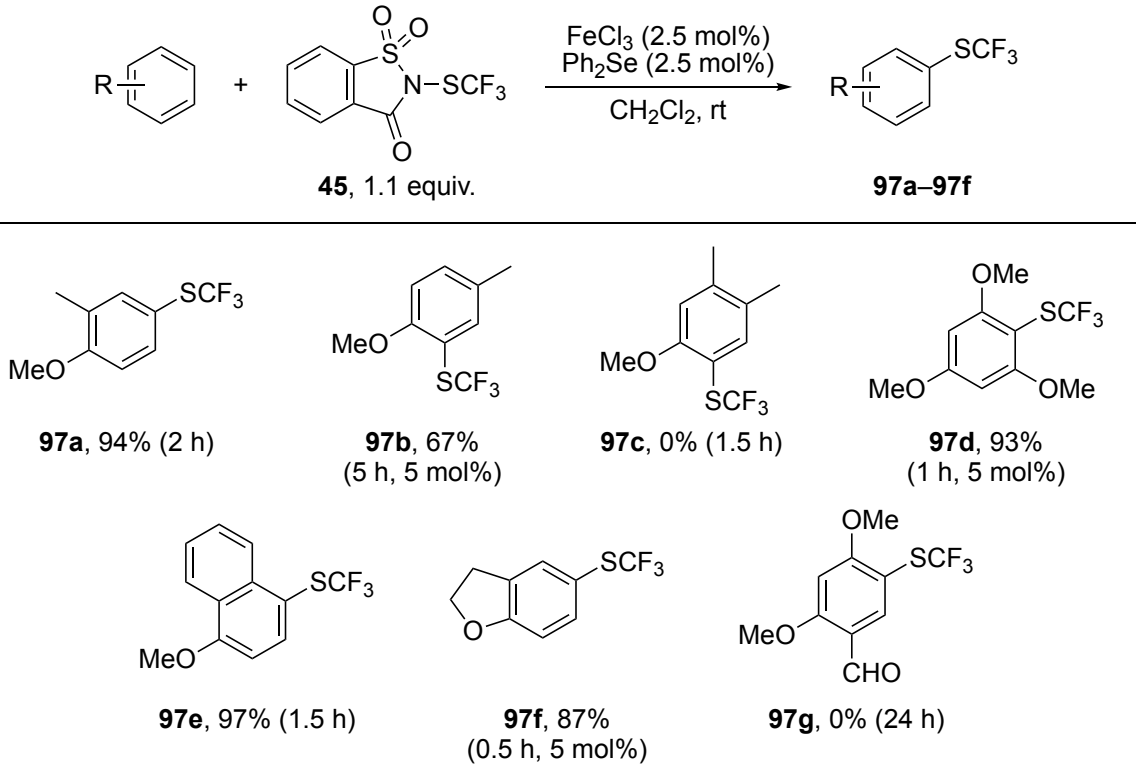
Entry	Catalyst(s) (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	$FeCl_3$ (10)	40	20	3[a]
2	$FeCl_3$ (10)/[BMIM]NTf_2 (30)	40	20	0
3	$AlCl_3$ (10)	40	20	0
4	$AgNTf_2$ (10)	40	20	0
5	$FeCl_3$ (10) + Ph_2Se (10)	40	0.1	97
6	$FeCl_3$ (10) + Ph_2Se (10)	20	0.1	94
7	$FeCl_3$ (2.5) + Ph_2Se (2.5)	20	2	94
8	Ph_2Se (2.5)	20	20	0

[a] Conversion (measured by ^1H NMR spectroscopy).

2.2.3 Substrate Scope

The substrate scope was then explored. Initially, trifluoromethylthiolation of a variety of anisole derivatives was performed (Scheme 70). This worked well for most examples, with short reaction times and yields in excess of 85% recorded. Once again, the reaction was found to be highly regioselective, with most trifluoromethylthiolations giving exclusively the *para*-product. As well as the *para*-carbon being the largest contributor to the HOMO, as previously discussed,[111] this can also be attributed to the sterically hindered nature of the diphenyl selenide cationic intermediate. For some substrates such as 4-methylanisole and 3,4-dimethylanisole where the *para*-position was blocked and the substitution was directed to the *ortho*-position, 5 mol% loadings of each catalyst was necessary to overcome the steric barrier. 2-(Trifluoromethylthio)-4-methylanisole (**97b**) was isolated in 67% yield but for 3,4-dimethylanisole, both *ortho*-products were produced in a 6:1 ratio. These regioisomers were found to be inseparable by column chromatography. In the case of highly

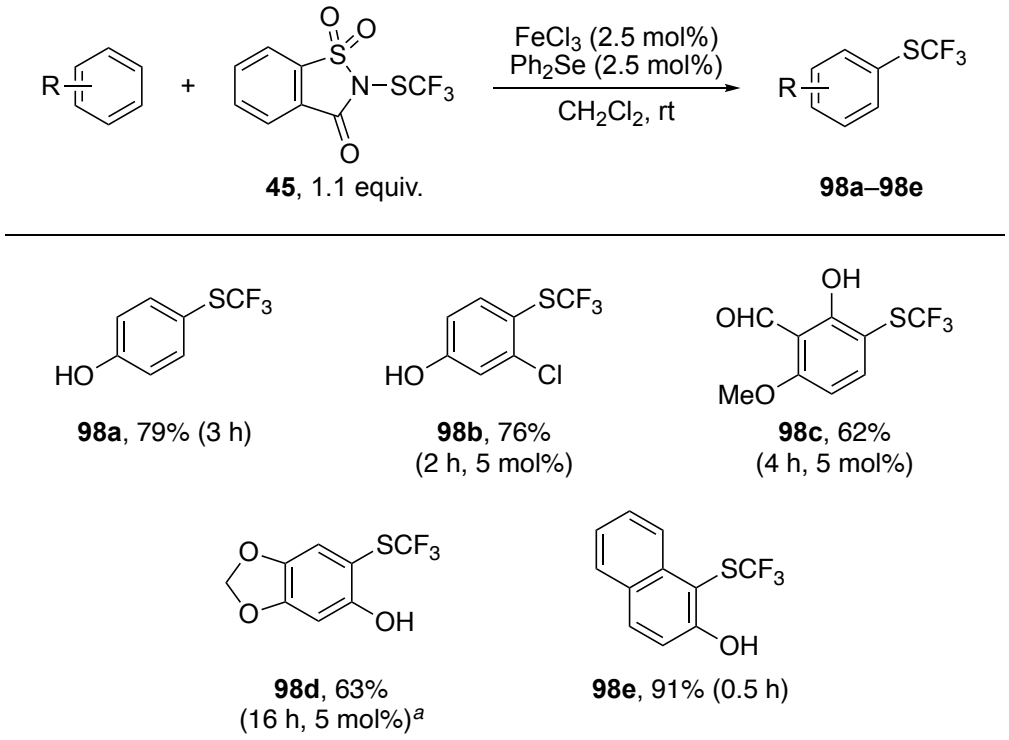
activated 1,3,5-trimethoxyanisole, a selective reaction was observed, with only mono-substituted product **97d** generated in 93% yield. Unlike the analogous thiocyanation reaction, low temperatures were not necessary. Other ethers were also effective substrates. The synthesis of 1-methoxy-4-(trifluoromethylthio)naphthalene (**97e**) proceeded in 97% yield, while the trifluoromethylthiolation of 2,3-dihydrobenzofuran resulted in the isolation of desired product **97f** in 87% yield. Unfortunately, substrates bearing electron-withdrawing groups such as aldehydes were not tolerated, such as 2,4-dimethoxybenzaldehyde. For this compound, no conversion to the desired product **97g** was observed, even after an extended reaction time of 24 hours.



Scheme 70: Substrate scope of the iron(III) chloride and diphenyl selenide-catalysed trifluoromethylthiolation of anisole derivatives.

Next, phenol derivatives were investigated (Scheme 71). The trifluoromethylthiolation of phenol proceeded smoothly, with 4-(trifluoromethylthio)phenol (**98a**) isolated in 79% yield. Significantly, phenols bearing electron-withdrawing groups were able to participate in the reaction, with 3-chlorophenol and 6-methoxysalicaldeyhde functionalised in 76% and 62% yields, respectively. Higher catalyst loadings of 5 mol% were required for these substrates. The structure of **98c** was confirmed by X-ray crystallography, as a conclusive assignment using NMR spectroscopy was not possible (Figure 4). Here, the substitution occurred *para* to the methoxy group and *ortho* to the hydroxy group. It was proposed that this was due to the hydroxy group co-ordinating to the diphenyl selenide cationic intermediate, directing the trifluoromethylthiolation to the *ortho*-position. The less steric hindered nature of this position

could also be a factor in the observed regioselectivity. For sesamol, a longer reaction time (16 hours), higher catalyst loading (5 mol%) and slightly elevated temperature of 40 °C was required, despite the electron-rich nature of this substrate. It was hypothesised that the two oxygen atoms of the dioxolane moiety bind to iron(III) chloride, preventing activation of *N*-(trifluoromethylthio)saccharin (**45**) and necessitating the use of more forcing conditions. Trifluoromethylthiolated product **98d** was isolated in 63% yield. 2-Naphthol also participated effectively in the reaction, giving 1-(trifluoromethylthio)-2-hydroxynaphthalene (**98e**) in 91% yield. It should be noted that, in contrast to the thiocyanation methodology, *para*-substituted phenols were well-tolerated due to the higher stability of 2-(trifluoromethylthio)phenols.



Scheme 71: Substrate scope of the iron(III) chloride and diphenyl selenide-catalysed trifluoromethylthiolation of phenol derivatives. [a] Reaction temperature was 40 °C.

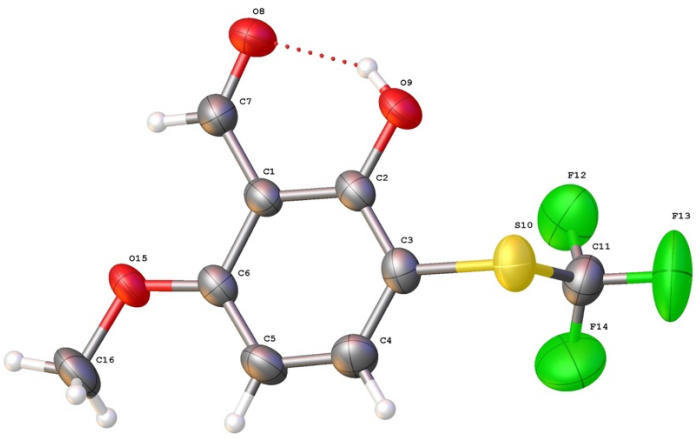
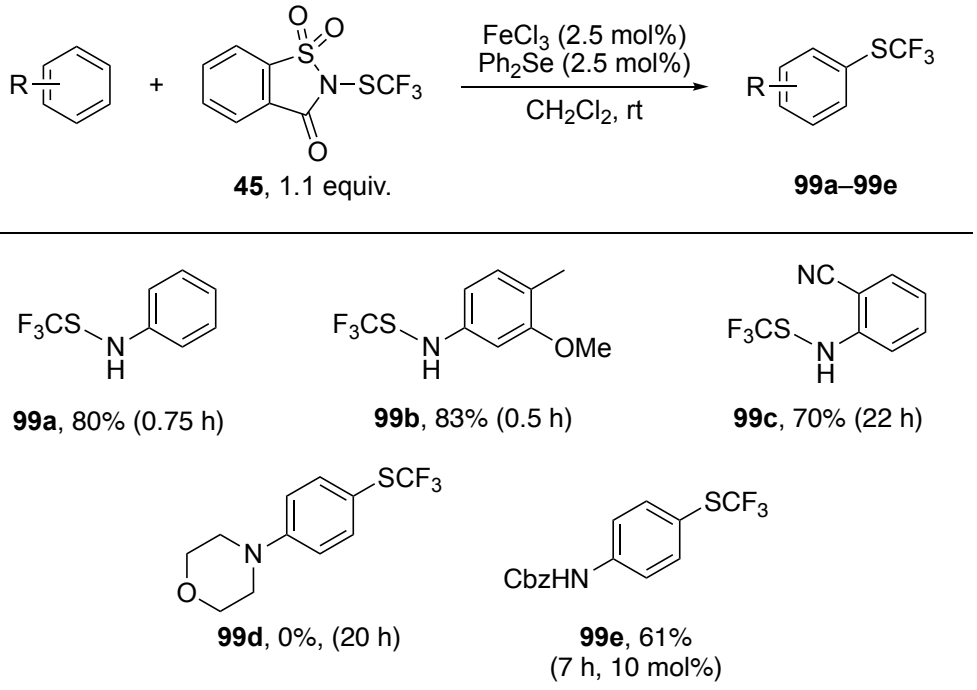


Figure 4: Structure of **98c** determined by X-Ray crystallography. Displacement ellipsoids are drawn at 50% probability level.

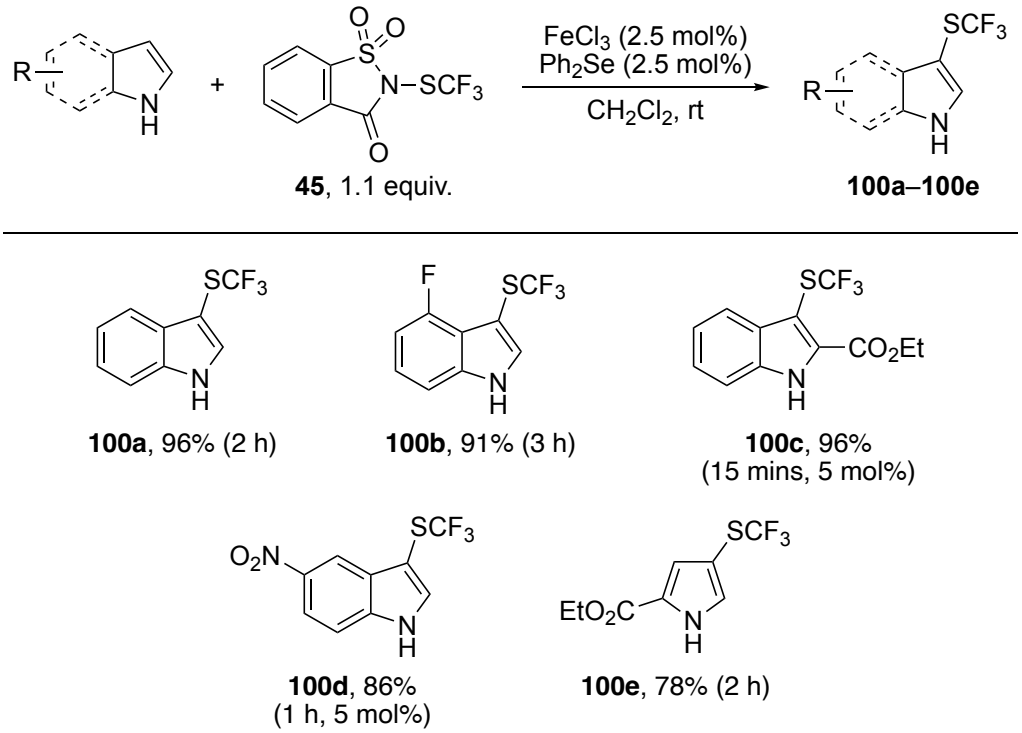
For anilines, another significant difference in reactivity was observed in comparison to the thiocyanation methodology. While the thiocyanation of anilines resulted in the formation of *para*-substituted products, in this project *N*-substituted products were formed. This can be explained using hard and soft acid and base theory.[113] *N*-Thiocyanatosaccharin is a softer reagent than *N*-(trifluoromethylthio)saccharin, partly due to its ability to form multiple resonance forms. Thus, it is attacked by the softer aromatic ring. Conversely, *N*-(trifluoromethylthio)saccharin is harder due to the three electron-withdrawing fluorine atoms and undergoes substitution at the nitrogen.

Aniline underwent trifluoromethylthiolation in only 45 minutes, with **99a** isolated in 80% yield (Scheme 72). The yield was slightly diminished due to the volatility of the product. Highly activated 3-methoxy-4-methylaniline was also a competent substrate and the reaction proceeded in 83% yield in 30 minutes. One example of an aniline bearing an electron-withdrawing substituent was investigated, with *N*-(trifluoromethylthio)-2-cyanoaniline **99c** synthesised in 70% yield, albeit after a longer reaction time of 22 h. It was proposed that a tertiary amine, such as 4-phenylmorpholine, would undergo trifluoromethylthiolation at the *para*-position. However, no conversion to product **99d** was observed. It was hypothesised this was due to the highly electron-rich nitrogen co-ordinating to iron(III) chloride and preventing catalysis. Thus, Cbz-protected aniline was considered due to its more electron-deficient nature. Although 10 mol% of both catalysts were required, the *para*-substituted product **99e** was isolated in 61% yield.



Scheme 72: Substrate scope of the iron(III) chloride and diphenyl selenide-catalysed trifluoromethylthiolation of aniline derivatives.

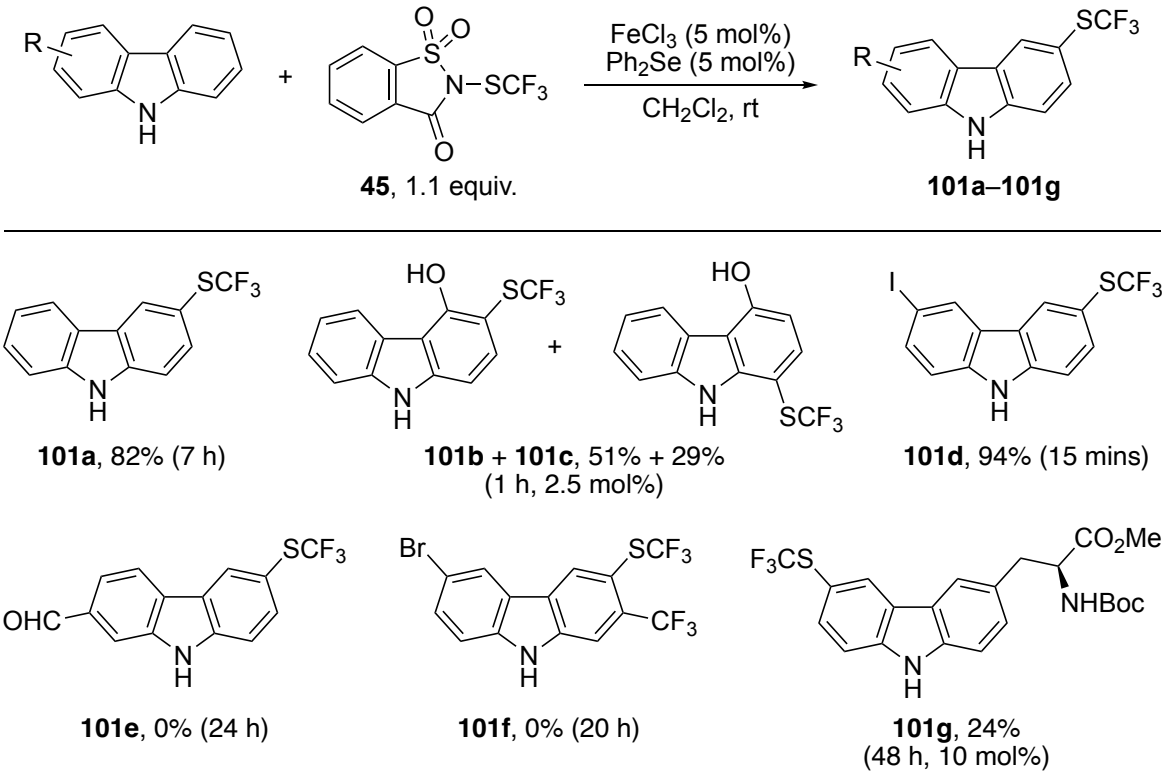
The substrate scope was then expanded by the investigation of nitrogen-containing heterocycles. As indoles had worked well for the thiocyanation project, this was the first class of heterocycles to be evaluated (Scheme 73). The trifluoromethylthiolation of indole was effective and gave product **100a** in 96% yield. Electron-withdrawing substituents in a variety of positions were well tolerated, with 4-fluoro-, ethyl 2-carboxylate- and 5-nitro-substituted indoles functionalised in 91%, 96% and 86% yields, respectively (**100b**, **100c** and **100d**). For the latter two reactions, slightly higher catalyst loadings of 5 mol% were required. In the group's previous work on iodinations and thioarylations,[102,105] pyrrole was found to give unselective reactions, with substitution occurring at various positions. Therefore, the trifluoromethylthiolation of the more electron-deficient ethyl pyrrole-2-carboxylate was instead investigated. While a small quantity of another, unidentified regioisomer was formed (~15% of crude reaction mixture by ^{1}H NMR spectroscopy), the major 4-substituted product **100e** was isolated in 78% yield.



Scheme 73: Substrate scope of the iron(III) chloride and diphenyl selenide-catalysed trifluoromethylthiolation of indole and pyrrole derivatives.

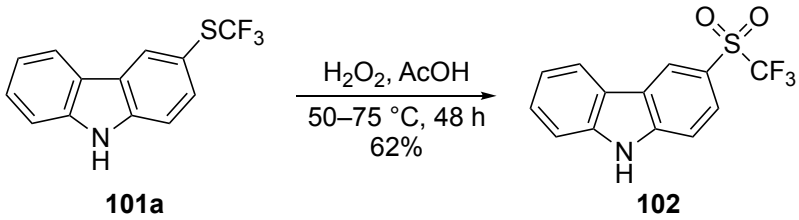
The group recently investigated the fluorescent properties of a variety of carbazole-derived amino acids, with the lead compound featuring a carbazole bearing an electron-withdrawing nitrile group.[114] Therefore, this methodology was investigated for the preparation of trifluoromethylthiolated carbazole derivatives (Scheme 74). For all substrates, the reaction was directed to the more electron-rich ring. The trifluoromethylthiolation of carbazole necessitated a longer reaction time of 7 hours, and a higher catalyst loading of 5 mol%. Only the mono-substituted product **101a** was formed, which was isolated in 82% yield. It is

likely that the de-activating nature of the trifluoromethylsulfenyl group prevents di-substitution from occurring on the opposite ring. While the reaction of 5-hydroxycarbazole with *N*-(trifluoromethylthio)saccharin was faster (1 hour) and only required 2.5 mol% catalyst loadings, regioselectivity issues were observed due to the strongly electron-donating hydroxy substituent, which competed as a directing group. Both 2- and 4-substituted regioisomers, **101b** and **101c**, were isolated in 51% and 29% yields, respectively. When 4-iodocarbazole was subjected to the methodology, the trifluoromethylthiolation was selective for the opposite, more activated ring. The reaction was both rapid (15 minutes) and high yielding (94%). Unfortunately, the use of carbazoles bearing stronger deactivating substituents such as carbazole-3-carboxaldehyde and 3-trifluoromethyl-7-bromocarbazole did not result in any conversion to the desired products **101e** and **101f**. The trifluoromethylthiolation of a Boc-protected carbazole amino acid was attempted, but only 10% conversion was observed after 20 hours. An increased catalyst loading of both iron(III) chloride and diphenyl selenide (10 mol%), and a higher temperature of 40 °C, resulted in an increased conversion of 26% after 48 hours and gave desired product **101g** in 24% yield. It was thought that the numerous heteroatoms in the amino acid moiety are capable of binding to iron(III) chloride and thus, prevent effective activation of *N*-(trifluoromethylthio)saccharin.



Scheme 74: Substrate scope of the iron(III) chloride and diphenyl selenide-catalysed trifluoromethylthiolation of carbazole derivatives.

It was proposed that oxidation of the trifluoromethylsulfenyl substituent of amino acid **101g** to a trifluoromethylsulfone may confer superior fluorescent properties, due to the more electron-withdrawing nature of sulfones compared to thioethers. This would establish a more effective 'push-pull' system, which is a commonly used strategy to improve photophysical properties *via* intramolecular charge transfer. However, the quantity of **101g** produced was not sufficient to perform this step, so studies focused instead on 3-(trifluoromethylthio)carbazole (**101a**), which featured the same substituted carbazole core and thus, would exhibit similar fluorescent properties. Oxidation using hydrogen peroxide and acetic acid at elevated temperatures (50–75 °C) gave trifluoromethylsulfone **102** in 62% yield after 48 hours (Scheme 75).



101a **102**

Scheme 75: Oxidation of trifluoromethylthioether **101a** to trifluoromethylsulfone **102**.

The absorbance and emission spectra of **102** were measured at 5 μM in ethyl acetate (Figure 5). The absorbance maximum was 274 nm and the emission maximum was 379 nm. While this gave a good stokes shift of 105 nm, it was clear from the poor resolution of the emission spectra that this compound exhibited weak fluorescence. As such, further investigation into the photophysical properties of **102** and the trifluoromethylsulfone chromophore was not pursued.

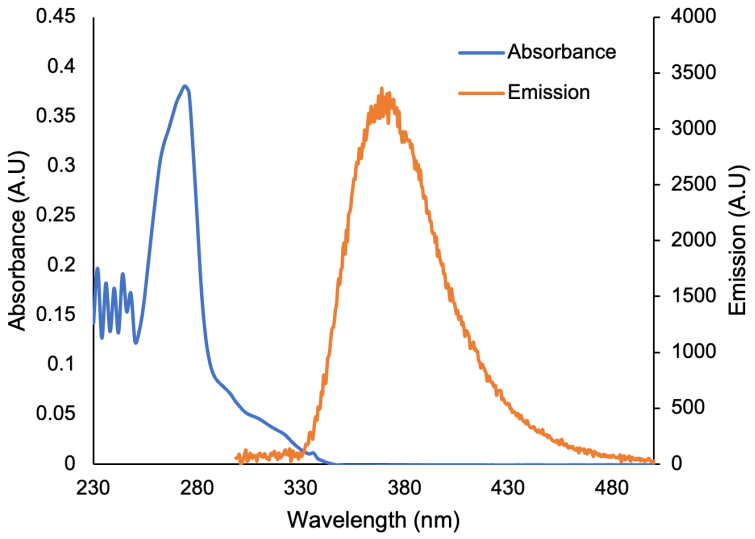
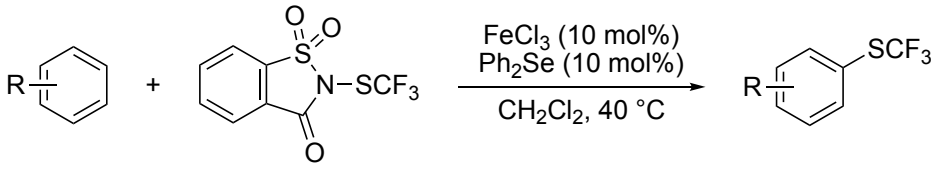


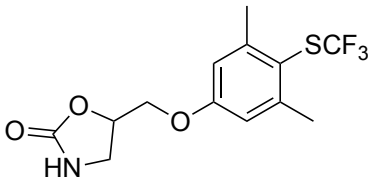
Figure 5: Absorbance and emission spectra of trifluoromethylsulfone **102**. Measured in ethyl acetate at 5 μM concentration, excitation at 274 nm.

2.2.4 Functionalisation and Synthesis of Biologically Active Compounds

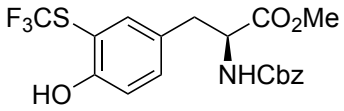
Given the importance of the trifluoromethylsulfenyl group in medicinal chemistry, a key aim of this project was to demonstrate the utility of this methodology for the late-stage functionalisation of biologically-relevant arenes. Thus, the trifluoromethylthiolation of metaxalone, a protected tyrosine derivative and estradiol was investigated (Scheme 76). For these more complex substrates, higher catalyst loadings of 5 or 10 mol%, temperatures of 40 °C and extended reaction times (22 or 48 hours) were required. Given the sterically hindered nature of these compounds and the presence of numerous functional groups capable of competitive binding to iron(III) chloride, this was not surprising. For metaxalone, a 6:1 ratio of *para*:*ortho*-regiosiomers was observed in the crude reaction mixture. This regiochemical outcome was identical to that of the analogous thiocyanation reaction, with a similar isolated yield (69%) of *para*-product **103a**. In the case of the tyrosine derivative, the desired *ortho*-substituted product **103b** was formed in 70% yield. For estradiol, protection of the hydroxy groups was not necessary, which contrasts with the thiocyanation procedure. This was due to the enhanced stability of the *ortho*-trifluoromethylthiolated product, compared to the *ortho*-thiocyanated product. The reaction was somewhat compromised by poorer regioselectivity, but the two *ortho*-products were readily separated using column chromatography, giving **103c** and **103d** in 55% and 27% yield, respectively. The absence of the bulky benzyl protecting group likely contributes to the regiochemical outcome. However, it should be noted that the desired product was generated in a single step. If the same compound was targeted using the thiocyanation methodology, four steps would be needed – protection, thiocyanation, nucleophilic substitution to form the trifluoromethyl thioether, and deprotection.



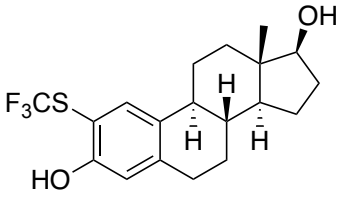
45, 1.1 equiv. **103a**–**103d**

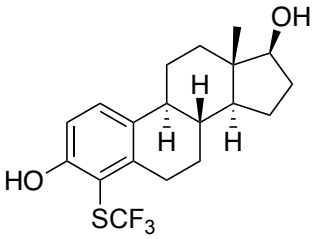


103a, 69% (48 h)



103b, 70% (48 h)

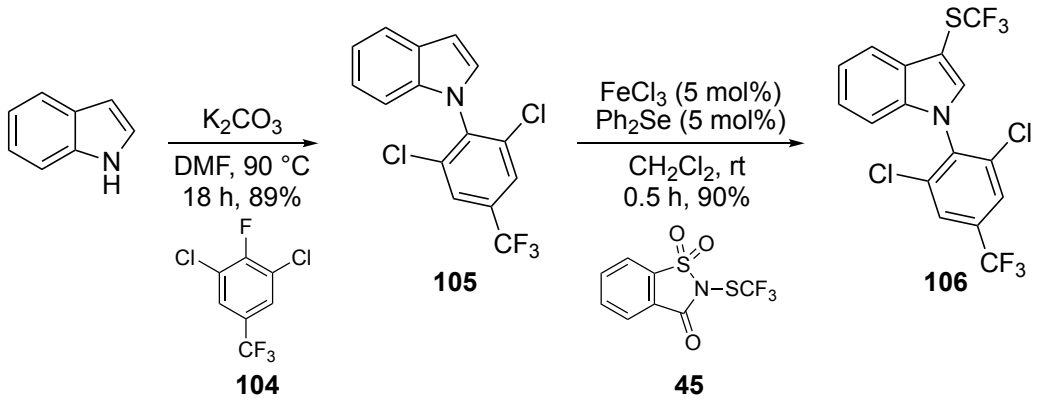




103c + **103d**, 55% + 27% (22 h, 5 mol%)

Scheme 76: Trifluoromethylthiolation of metaxalone, Cbz-Tyr-OMe and estradiol.

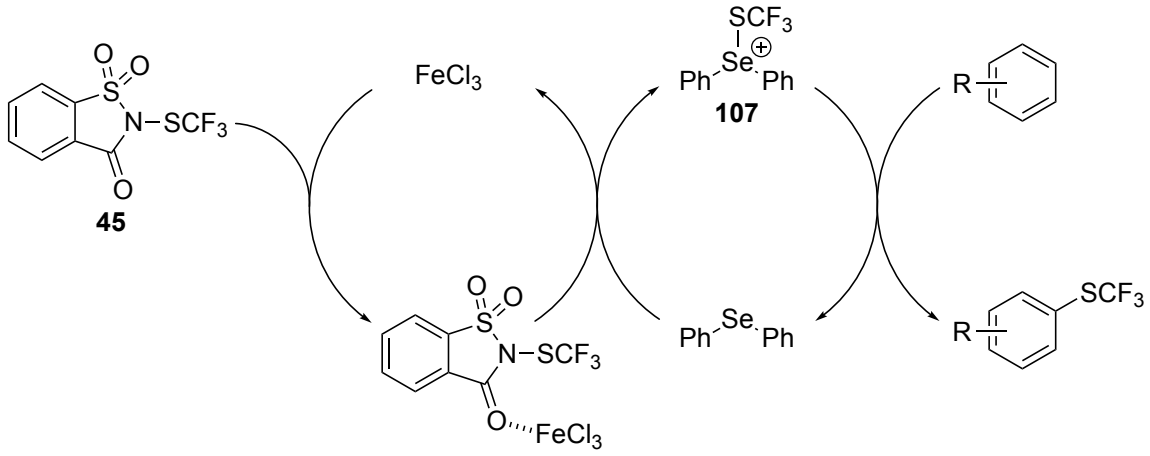
The use of the trifluoromethylthiolation process for the synthesis of *N*-substituted-3-(trifluoromethylthio)indole **106**, a potent insecticide against acarian pests,[115] was also investigated (Scheme 77). It was envisaged that this could be furnished in two steps from indole. First, nucleophilic aromatic substitution with electron deficient arene **104** gave *N*-substituted indole **105** in 89% yield. This was followed by trifluoromethylthiolation, which proceeded in an excellent yield of 90% when 5 mol% of each catalyst was used. The reaction was also rapid, with full conversion to target **106** observed after 30 minutes.



Scheme 77: Synthesis of insecticide **106**.

2.2.5 Reaction Mechanism

The dual-catalytic reaction mechanism was hypothesised to be analogous to the mechanism previously proposed for the thiocyanation process, as this was consistent with the requirement for both Lewis acid and Lewis base catalysts (Scheme 78). Attempts were made to observe key intermediate **107** using NMR spectroscopy, but the incompatibility of iron(III) with NMR spectroscopy, due to its paramagnetic nature, complicated these efforts. Instead of directly analysing a mixture of iron(III) chloride (10 mol%), diphenyl selenide (10 mol%) and *N*-(trifluoromethylthio)saccharin) (**45**), it was necessary to filter the mixture through celite® to remove iron(III) chloride before recording spectra. Only diphenyl selenide and *N*-(trifluoromethylthio)saccharin) (**45**) were visible in the ^{1}H and ^{13}C NMR spectra. It was proposed that intermediate **107** is short-lived and once iron(III) chloride is removed, the concentration of **107** is rapidly reduced. It is also possible that **107** was removed during filtration of iron(III) chloride.



Scheme 78: Proposed mechanism of the dual-catalytic trifluoromethylthiolation involving iron(III) chloride and diphenyl selenide.

2.2.6 Conclusions

In summary, a regioselective and efficient trifluoromethylation protocol of activated arenes has been developed. The utilisation of a dual-catalytic Lewis acid and Lewis base strategy allowed for a mild procedure, avoiding the strong Brønsted acids or high temperatures used in previously reported protocols.[78,79,81] A wide substrate scope was demonstrated, including anisoles, phenols, anilines, pyrroles, indoles and carbazoles. Significant contrasts in reactivity were observed regarding phenols and anilines, compared to the previously discussed thiocyanation protocol. For phenols, substitution at the *ortho*-position was tolerated, while for anilines, *N*-substituted products were obtained. Highly activated substrates were found to undergo selective reactions, often in excellent yields. Electron-withdrawing substituents were also tolerated, depending on the strength of the activating

group. One limitation was the lower reactivity of substrates containing multiple heteroatoms capable of co-ordinating to iron(III) chloride, but this could often be overcome by the use of higher catalyst loadings and/or elevated temperatures. This was demonstrated in the trifluoromethylthiolation of more complex, biologically active substrates such as metaxalone, a protected tyrosine derivative and estradiol. Finally, the highly efficient synthesis of an insecticide was also demonstrated.

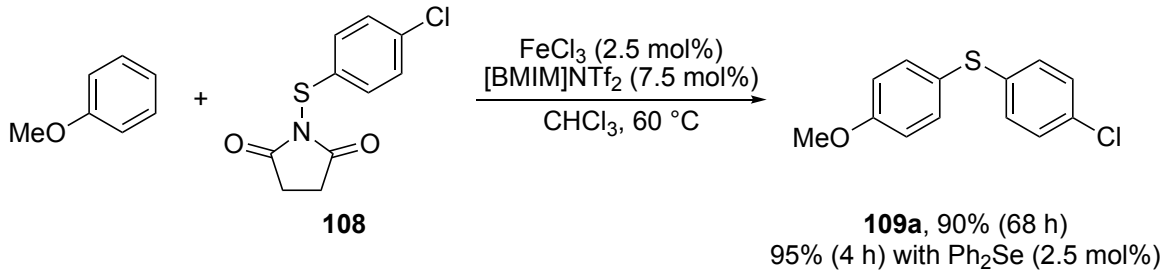
2.3 Iron-Catalysed Regioselective C–H Thioarylation of Arenes

2.3.1 Project Aims

Given the successful use of saccharin-based reagents for the thiocyanation and trifluoromethylthiolation of activated arenes, similar reagents were considered for an improved thioarylation process. While the procedure previously developed in the group using succinimide-based reagents was effective for a wide variety of arenes, limitations were observed, such as the use of high temperatures and extended reaction times for less-activated substrates.[105] Moreover, thioarylations using electron-deficient *N*-(thioaryl)succinimides and thioalkylations were not well tolerated. The use of a dual-catalytic Lewis acid/Lewis base strategy did address some of these issues to an extent, but it was proposed that the use of saccharin-based reagents could further improve the process.

2.3.2 Reaction Optimisation

In the previous studies on thioarylations, one coupling which required forcing conditions was that of anisole with 4-chlorothiophenol-derived succinimide reagent **108** (Scheme 79).[105] Utilising iron(III) triflimide (2.5 mol%), the reaction required a temperature of 60 °C and time of 68 hours, with chloroform used as the solvent. Desired biaryl product **109a** was isolated in 90% yield. When diphenyl selenide (2.5 mol%) was used in a dual-catalytic process with iron(III) triflimide, the reaction was complete after 4 hours, but a temperature of 60 °C was still necessary. Therefore, the analogous reaction with saccharin-based reagent **110** was chosen to optimise the new procedure.

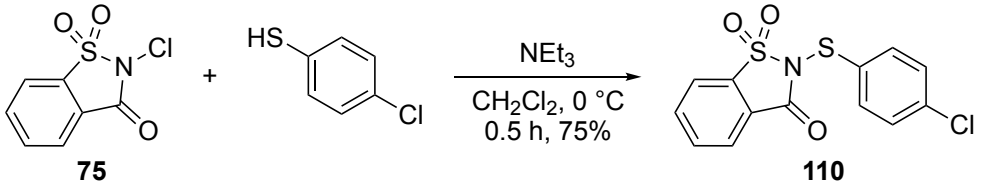


108

109a, 90% (68 h)
95% (4 h) with Ph_2Se (2.5 mol%)

Scheme 79: Reaction of anisole with succinimide reagent **108**.

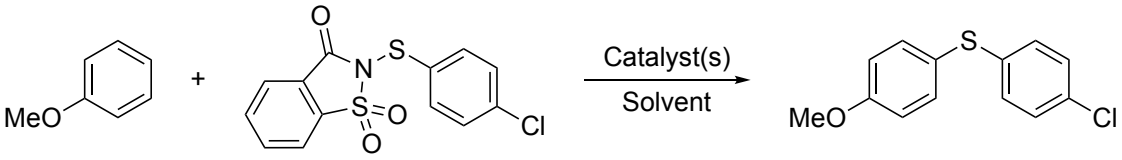
N-(4-Chlorophenylthio)saccharin (**110**) was prepared by the substitution of *N*-chlorosaccharin (**75**) with 4-chlorothiophenol (Scheme 80). Unlike the equivalent succinimide-based reagent, this was not stable to silica gel column chromatography.[105] However, recrystallisation using a 3:2 mixture of toluene:hexane gave desired product **110** in 75% yield.



Scheme 80: Synthesis of *N*-(4-chlorophenylthio)saccharin (**110**).

With *N*-(4-chlorophenylthio)saccharin (**110**) in hand, optimisation of the reaction with anisole was conducted. The previous conditions using *N*-(4-chlorophenylthio)succinimide (**108**) are shown in entries 1 and 2 (Table 5).[105] To enable facile analysis of reaction conversion using ^{1}H NMR spectroscopy, the experiments were performed using $CDCl_3$. First, the thioarylation was performed using the same conditions as before, but with *N*-(4-chlorophenylthio)saccharin (**110**) (entry 3). This reaction was faster than both procedures using the succinimide-based reagent, reaching full conversion after 5 minutes. The isolated yield was similar at 93%. Next, iron(III) chloride was used as the catalyst. Given the previous work on thiocyanation and trifluoromethylthiolation reactions, it was expected that this would be faster than with iron(III) triflimide, but this was not the case. The reaction was both longer (30 minutes) and lower yielding (77%). It is possible that this was due to the use of chloroform, compared to dichloromethane in the previous studies. Iron(III) triflimide was more soluble in chloroform than iron(III) chloride, thus giving a more homogenous and more rapid reaction. Further studies with iron(III) triflimide were then pursued. The thioarylation could be performed at room temperature while still reaching full conversion after 1.5 hours. As a control experiment, the procedure was conducted in non-deuterated chloroform, which surprisingly resulted in a faster reaction time of 30 minutes. Finally, as the thiocyanation and trifluoromethylthiolation methodologies had been effective in dichloromethane, it was considered diligent to investigate this solvent. However, the yield was slightly lower (85%) and the reaction time was longer (3 hours).

Table 5: Optimisation of the thioarylation of anisole.



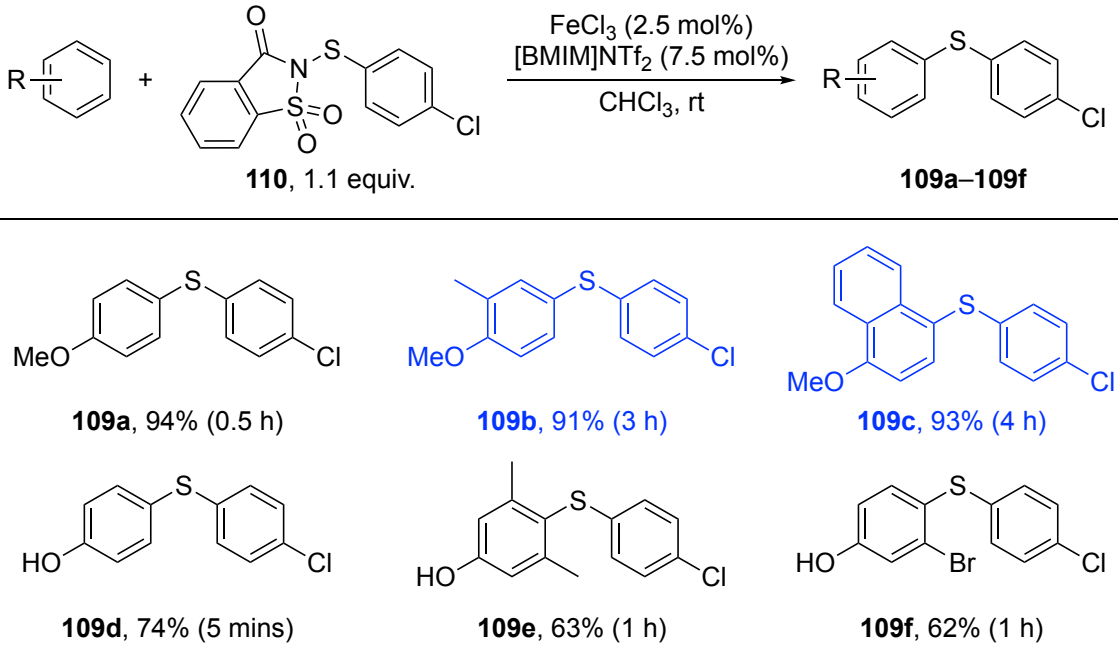
110, 1.1 equiv. **109a**

Entry	Catalyst(s) (mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1[a]	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	$CHCl_3$	60	68	90
2[a]	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5) + Ph_2Se (2.5)	$CHCl_3$	60	4	95
3	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	$CDCl_3$	60	0.1	93
4	$FeCl_3$ (2.5)	$CDCl_3$	60	0.5	77
5	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	$CDCl_3$	20	1.5	91
6	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	$CHCl_3$	20	0.5	94
7	$FeCl_3$ (2.5)/[BMIM]NTf_2 (7.5)	CH_2Cl_2	20	3	85

[a] Reaction was performed using *N*-(4-chlorophenylthio)succinimide (**108**).

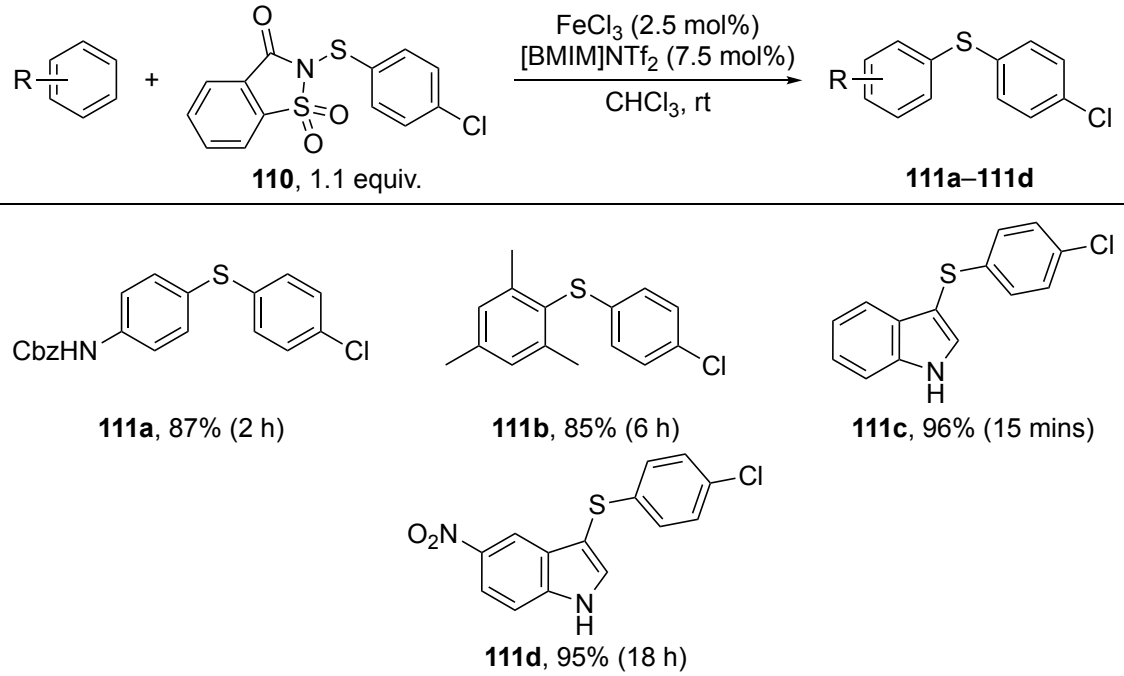
2.3.3 Substrate Scope and Comparison of Saccharin Reagents to Succinimide Reagents

The substrate scope with regard to *N*-(4-chlorophenylthio)saccharin (**110**) was then briefly explored (Scheme 81). Initially, anisoles, naphthalenes and phenols were investigated. For all compounds, the thioarylations proceeded at room temperature using low catalyst loadings of 2.5 mol%, with rapid reactions observed. 2-Methylanisole and 1-methoxynaphthalene were efficiently thioarylated, giving **109b** and **109c** in 91% and 93% yields after 3 and 4 hours, respectively. While phenol was functionalised in a good yield of 74% after only 5 minutes, substituted phenols suffered from regioselectivity issues. For the reaction with 3,5-dimethylphenol and 3-bromophenol, significant quantities of *ortho*-substituted products were formed. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy after reaction times of 1 hour revealed 2:1 and 3:1 ratios of *para*:*ortho*-substituted products, respectively. Nonetheless, these regioisomers were readily separated by column chromatography and the major *para*-products, **109e** and **109f**, were isolated in 63% and 62% yields, respectively. Presumably, the regiochemical outcomes for these reactions were influenced by the sterically-hindered *para*-positions.



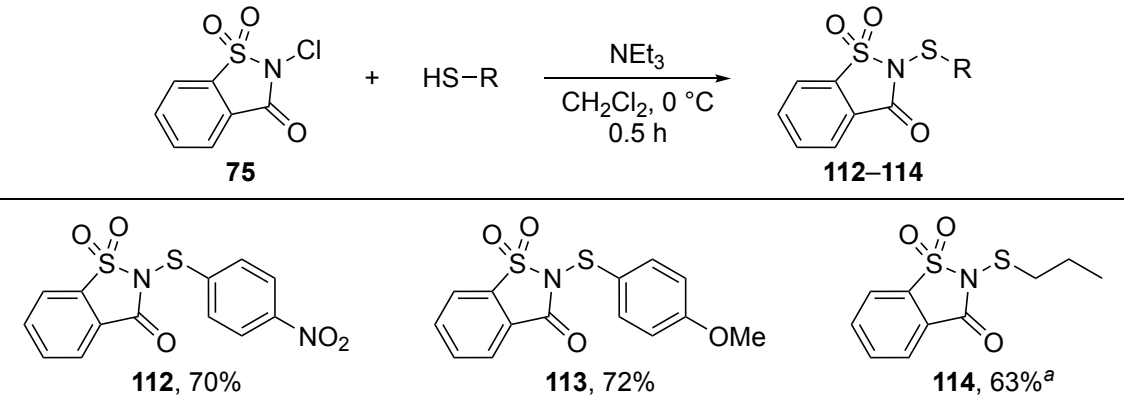
Scheme 81: Substrate scope using *N*-(4-chlorophenylthio)saccharin (**110**) and anisoles, naphthalenes or phenols. Products highlighted in blue were synthesised by Michael Lok, a BSc student.

The thioarylation of Cbz-protected aniline and mesitylene was then demonstrated (Scheme 82). Despite the less activated nature of these substrates, room temperature reactions using 2.5 mol% of iron(III) triflimide were still viable. The reaction of saccharin reagent **110** with Cbz-protected aniline reached full conversion after only 2 hours and gave desired product **111a** in 87% yield. For mesitylene, while a slightly longer reaction time of 6 hours was required, an excellent yield of 85% was achieved. Indoles were also investigated, and were found to be well tolerated, with the thioarylations of indole and 5-nitroindole giving products **111c** and **111d** in excellent yields of 96% and 95%, respectively. For indole, the reaction reached full conversion after 5 minutes. The more deactivated 5-nitroindole required a longer reaction time of 18 hours.



Scheme 82: Substrate scope using *N*-(4-chlorophenylthio)saccharin (**110**) and less activated substrates or indoles.

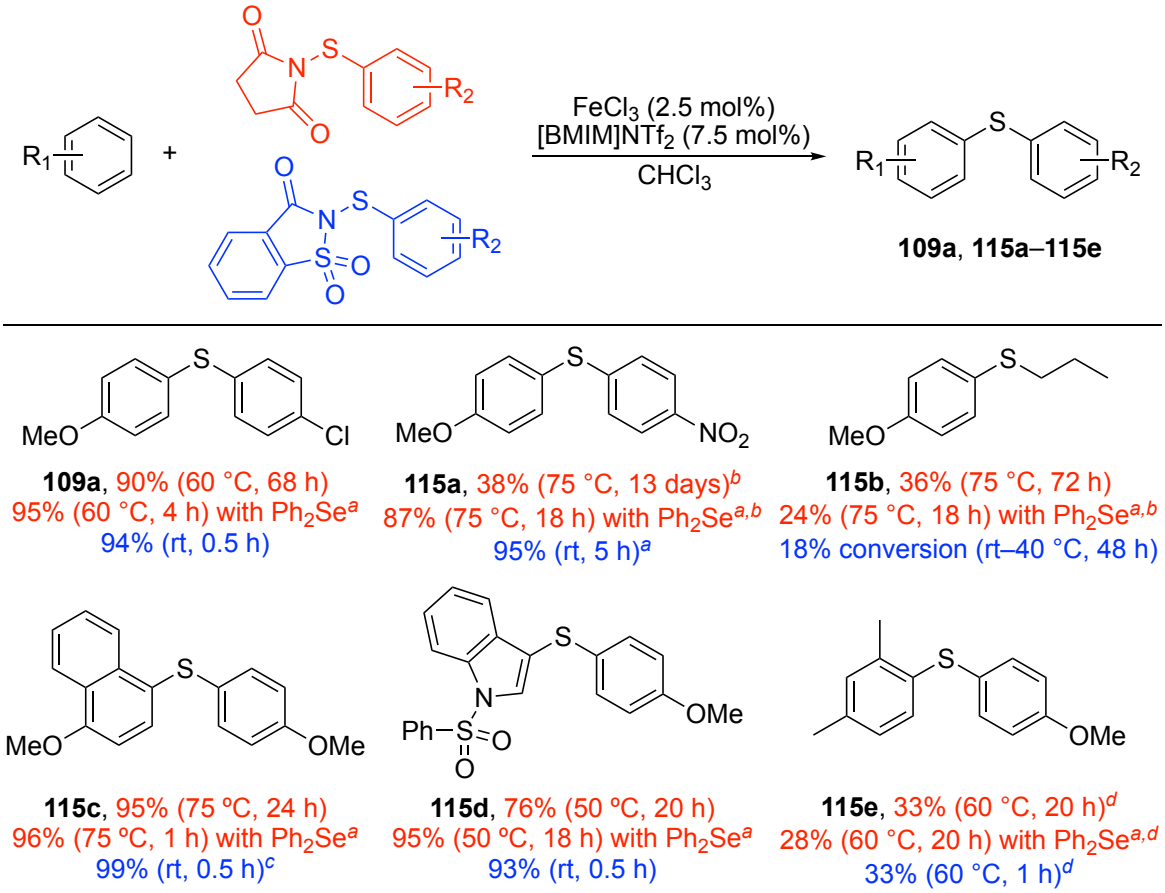
Next, other thioarylations that had previously required high temperatures, long reaction times or gave low yields using succinimide-based reagents were re-investigated.[105] In general, these featured electron-deficient *N*-(thioaryl)succinimides, *N*-(alkylthio)succinimides or minimally activated arenes. Sterically hindered arenes were also challenging in some cases. First, the required *N*-(thioaryl)saccharins were synthesised by the same method used for *N*-(4-chlorophenylthio)saccharin (**110**) in yields of 63–72% (Scheme 83). *N*-(Propanethio)saccharin (**114**) was an oil and purification using recrystallisation was not possible. Partial purification by trituration in hexane was achieved, but two impurities of 5% were still present. One of these impurities was saccharin, and the other was unidentified. Unfortunately, scale-up of this reaction resulted in a crude reaction mixture containing significantly higher quantities of both impurities, and purification was not possible.



Scheme 83: Synthesis of *N*-(aryl/alkylthio)saccharins **112**–**114**.[a] Compound contained two 5% impurities (measured by ^{1}H NMR spectroscopy).

In general, thioarylations using these saccharin-based reagents were found to give significantly faster reactions at reduced temperatures compared to both the iron(III) triflimide and iron(III) triflimide/diphenyl selenide-catalysed processes using succinimide-based reagents (Scheme 84).[105] In most cases yields were similar or slightly increased, especially compared to the previous reactions using only iron(III) triflimide. For example, the reaction of anisole with *N*-(4-nitrophenylthio)saccharin (**112**) was complete in only 5 hours at room temperature using 10 mol% of iron(III) triflimide, with an isolated yield of 95%. This compares to 13 days and 18 hours at 60 °C, and yields of 38% and 87%, using the analogous succinimide reagent with iron(III) triflimide and iron(III) triflimide/diphenyl selenide, respectively. When *N*-(propanethio)saccharin (**114**) was used, only 18% conversion was observed after reaction at room temperature to 40 °C over 48 hours. Previous attempts with the succinimide reagent had used temperatures of 75 °C but still resulted in relatively poor yields, with long reaction times necessary (72 and 18 hours). Unfortunately, the issues encountered in the synthesis of *N*-(propanethio)saccharin (**114**) meant that further attempts at this thioalkylation were not possible.

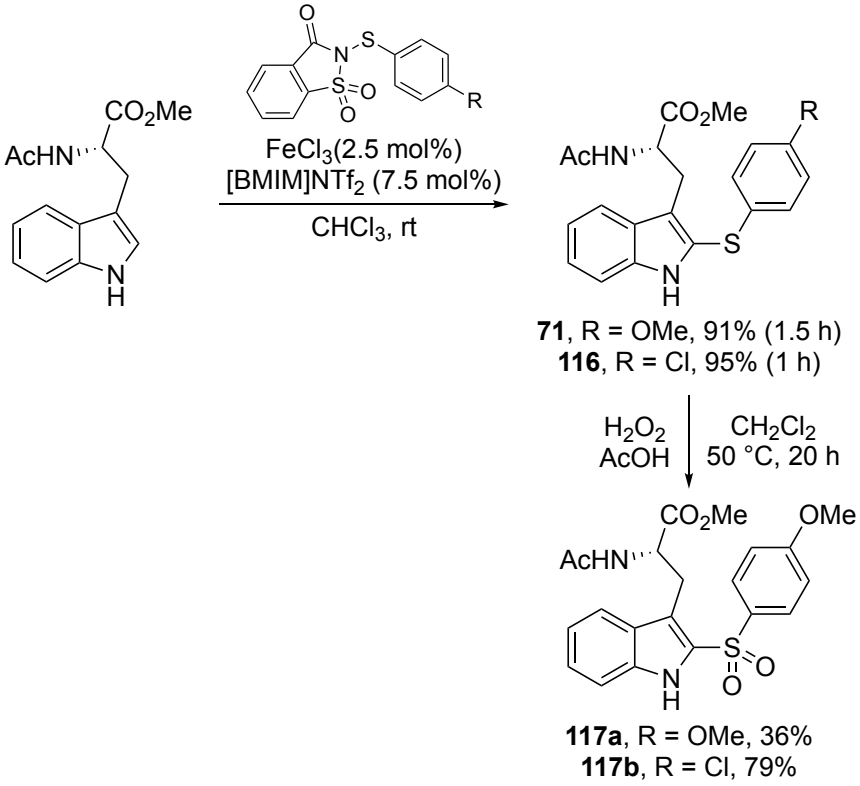
A series of thioarylations with *N*-(4-methoxyphenylthio)saccharin (**113**) were then conducted (Scheme 84). Previously, the reaction with 1-methoxynaphthalene had been high-yielding but even when using diphenyl selenide, a temperature of 75 °C was necessary.[105] In this study, the reaction was complete after 30 minutes at room temperature and the desired product **115c** was isolated in 99% yield. It was found that the temperature and time could also be reduced to room temperature and 30 minutes, respectively, for the thioarylation of 1-benzenesulfonylindole, for which a yield of 93% was recorded. The reactions of the minimally activated *meta*-xylene with *N*-(4-methoxyphenylthio)succinimide had required temperatures of 60 °C, reaction times of 20 hours and poor yields of 33% and 28%. In this case, the use of diphenyl selenide resulted in the lower yield. Here, the reaction time with *N*-(4-methoxyphenylthio)saccharin (**113**) was only 1 hour, but a temperature of 60 °C was still necessary, with **115e** isolated in a similar yield of 33%. The saccharin reagent had been completely consumed so longer reaction times were not considered. For metaxalone, the reaction with *N*-(4-methoxyphenylthio)succinimide had only been attempted with iron(III) triflimide, which required an elevated temperature of 75 °C and catalyst loadings of 10 mol%. The reaction had proceeded in a yield of 72% after 20 hours. With *N*-(4-methoxyphenylthio)saccharin **113**, full conversion was achieved using 2.5 mol% catalyst and a reaction time of 2 hours. The yield was also significantly improved, with product **115f** generated in 90% yield.



Scheme 84: Comparison of previous thioarylations using succinimide-based reagents to thioarylations using saccharin-based reagents. [a] Ph_2Se catalyst loading equal to $FeCl_3$ catalyst loading. [b] $FeCl_3$ (10 mol%) and BMIM[NTf_2] (30 mol%) was used. [c] Reaction was performed by Michael Lok, a BSc student. [d] $FeCl_3$ (5 mol%) and BMIM[NTf_2] (15 mol%) was used.

2.3.4 Synthesis of Tryptophan Derivatives and Fluorescence Studies

Having shown that this procedure is faster and milder, and in some cases higher yielding, than previous methods, it was proposed that it could be used to furnish fluorescent tryptophan derivatives. Tryptophan is naturally fluorescent, but it was proposed that by introducing electron-deficient thioaryl substituents, and then oxidising these compounds to the corresponding sulfones, a charge-transfer chromophore would be created, resulting in amino acids with more favourable photophysical properties. Despite this rationale, it was also considered diligent to evaluate a compound with an electron-donating group. Therefore, a protected tryptophan derivative was subjected to a thioarylation under optimised conditions using the appropriate saccharin reagent to give compound **71** bearing a 4-methoxy group, as well as 4-chloro derivative **116** (Scheme 85). Both reactions proceeded rapidly and efficiently, with the desired products isolated in 91% and 95% yields after 1.5 and 1 hour, respectively. Oxidation of these compounds with hydrogen peroxide was then investigated. While the reaction with 4-chloro-derivative **116** gave sulfone **117b** in 79%, oxidation of 4-methoxy-derivative **71** only resulted in a 36% yield. Nonetheless, enough material was produced to obtain absorption and emission spectra.



Scheme 85: Synthesis of tryptophan derivatives **117a** and **117b**.

The two compounds were found to exhibit red-shifted absorption spectra compared to tryptophan, with maxima at 294 and 296 nm for 4-methoxy-derivative **117a** and 4-chloro-derivative **117b**, respectively. **117a** also exhibited an additional absorption band at 254 nm. Unfortunately, in both cases, there was no significant emission observed (Figure 6). It was hypothesised that the additional degrees of rotational freedom introduced by the aryl sulfone substituents leads to quenching *via* non-radiative decay. More rigid thiazoloindole tryptophan derivatives, recently synthesised in the group, have been shown to have excellent photophysical properties.[116]

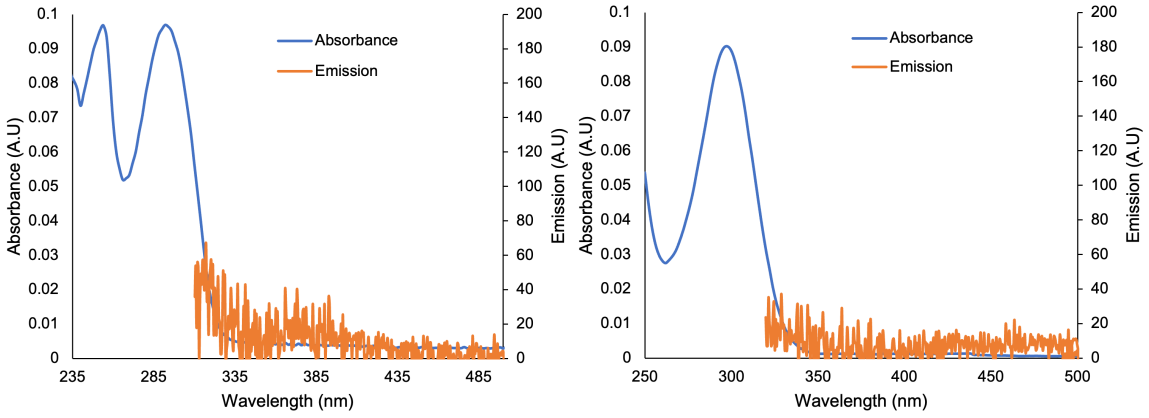
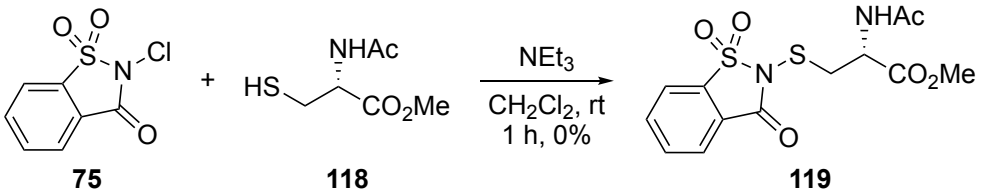


Figure 6: Absorbance and emission spectra of sulfones **117a** (left) and **117b** (right). Measured in methanol at 5 μM concentration, excitation at 294 and 296 nm, respectively.

2.3.5 Investigation of Cysteine-Derived Saccharin Reagents

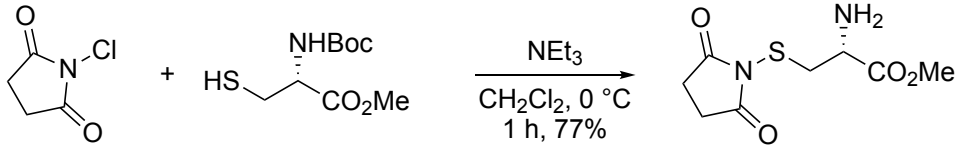
Another aim of this project was to synthesise a cysteine-derived saccharin reagent. It was envisaged that this would allow for the selective functionalisation of arenes and could be used for bioconjugation purposes, or to generate cysteine-based fluorescent amino acids. Protected cysteine **118** was used to prepare this reagent (Scheme 86). Unfortunately, as with *N*-(propanethio)saccharin (**114**), product **119** was not solid and thus, purification was not possible.



75 **118** **119**

Scheme 86: Attempted synthesis of cysteine-derived saccharin reagent **119**.

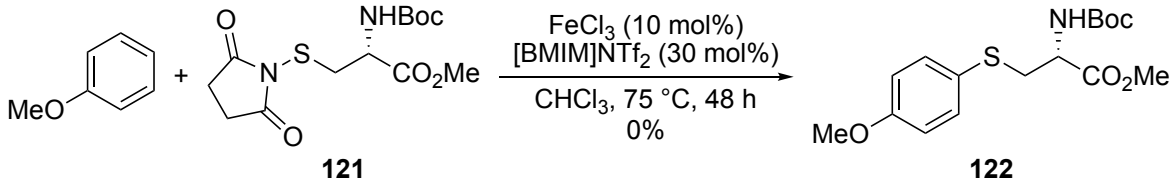
Previously, succinimide-based reagents were found to be stable to silica gel column chromatography.[105] Although a cysteine-derived succinimide reagent would be less reactive than a saccharin-derived reagent, it was still considered worthwhile to investigate. Surprisingly, the analogous succinimide-based reagent was found to decompose during silica gel column chromatography. However, Boc-protected cysteine-derived succinimde **121** has been reported to be stable under these conditions.[117] The synthesis of this compound from *N*-chlorosuccinimide was achieved in 77% yield, with purification by column chromatography successful (Scheme 87).



120 **121**

Scheme 87: Synthesis of cysteine-derived succinimide reagent **121**.

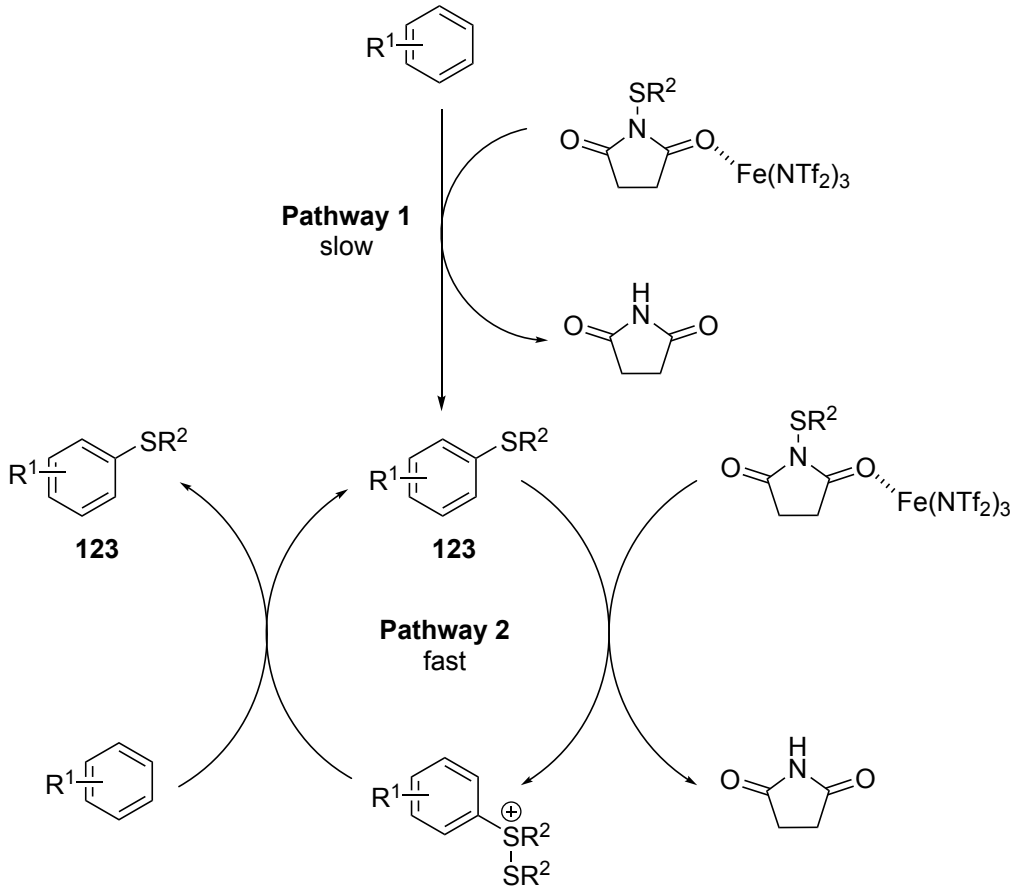
Unfortunately, when this reagent was used for the thiolation of anisole, no conversion to the desired product was observed, even when forcing conditions were utilised (Scheme 88). Thioalkylations had been a limitation of succinimide-based reagents, so this was not entirely unexpected.



Scheme 88: Attempted reaction of anisole with cysteine-derived succinimide reagent **121**.

2.3.6 Mechanistic Investigations

In the previous studies on *N*-(thioaryl)succinimides, the mechanism depicted in Scheme 89 was proposed.[105] Kinetics experiments suggested that the thioarylation was autocatalytic when electron-rich *N*-(thioaryl)succinimides, such as *N*-(4-methoxyphenylthio)succinimde were used.[105] It was hypothesised that products **123** of the electrophilic aromatic substitution in pathway 1 acted as Lewis bases, enabling the faster pathway 2. When electron-poor reagents such as *N*-(4-chlorophenylthio)succinimide were used, no autocatalysis was observed as the products were not sufficiently electron-rich. Thus, only pathway 1 was viable.

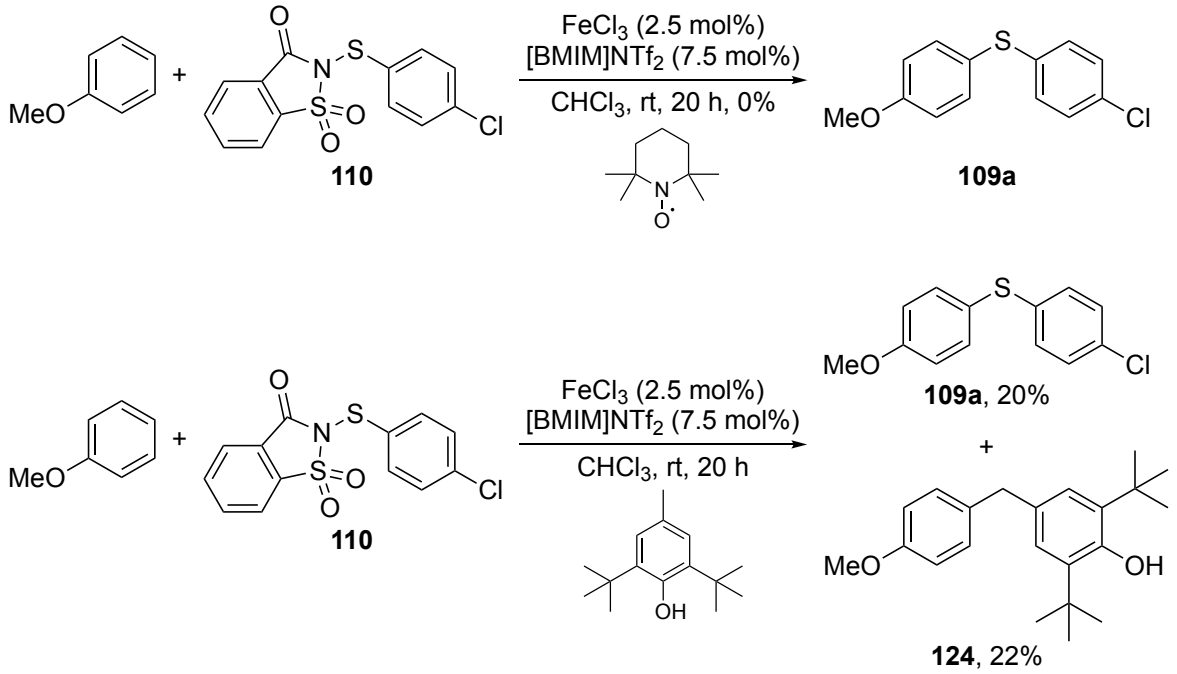


Scheme 89: Previously proposed mechanism for the thioarylation of arenes using succinimide-based reagents.

However, this did not explain the difference in reactivity between *N*-(4-chlorophenylthio)succinimide and *N*-(4-nitrophenylthio)succinimide. The 4-nitro reagent, a

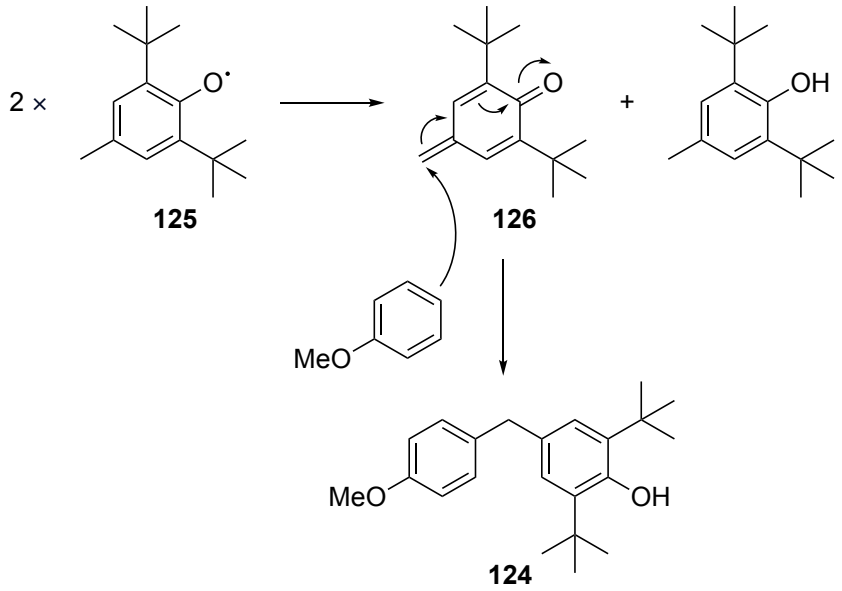
more electron-deficient reagent, was less reactive than the 4-chloro reagent when reacted with anisole, requiring a longer reaction time (13 days vs 68 hours), higher temperature (75 °C vs 60 °C), and resulting in a lower yield (38% vs 90%) as shown in Scheme 84. Given that these reactions were not autocatalytic and were proposed to follow pathway 1, it would be expected that the more electron-deficient succinimide would provide a faster thioarylation. Moreover, while the reaction with electron-rich *N*-(4-methoxyphenylthio)succinimide was faster due to autocatalysis, kinetic studies revealed that the rate was also higher in the initial lag period when product **123** was not at a sufficient concentration for autocatalytic pathway 2 to be viable. It would be expected that the reaction with *N*-(4-chlorophenylthio)succinimide would be faster than the reaction with *N*-(4-methoxyphenylthio)succinimide initially, before autocatalysis becomes viable.

A similar trend was also observed in this work using the analogous saccharin reagents, with more forcing conditions required for *N*-(4-nitrophenylthio)saccharin (**112**) compared to *N*-(4-chlorophenyl)saccharin **110** (Scheme 84). Therefore, further investigations were conducted. It was proposed that if there was a radical species involved, this could be stabilised by electron-donating substituents, which could partially explain the observed reactivity. It should be noted that mechanistic studies during the development of the iron triflimide-catalysed halogenation of arenes showed these did not proceed by a radical pathway.[118] Despite this, radical-trapping experiments were conducted. When the reaction of anisole with *N*-(4-chlorophenylthio)saccharin (**110**) was performed in the presence of TEMPO, a radical scavenger, no reaction was observed (Scheme 90). When TEMPO was replaced with BHT, another radical scavenger, the desired product **109a** was isolated in a low yield of 20% after 20 hours. Significantly, side-product **124** was also isolated in 22% yield. 4,4'-Dichlorodiphenyl disulfide was also observed in the crude reaction mixture using ^{1}H NMR spectroscopy, but attempts at isolation were complicated by co-elution with BHT.



Scheme 90: Radical scavenger experiments.

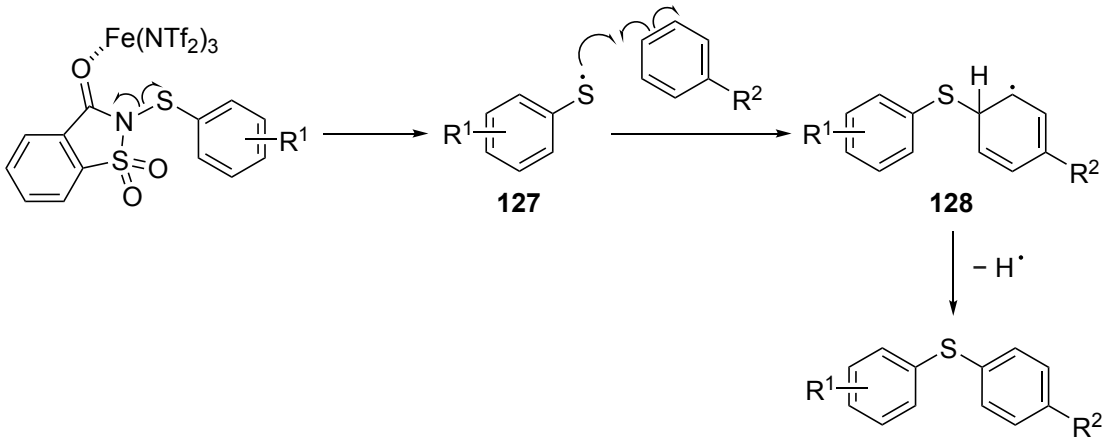
The disproportionation of phenoxy radical **125** to *para*-benzoquinone methide **126** and phenol is well-precedented in the literature.[119–121] Baik and co-workers also reported the electrophilic aromatic substitution of anisole with *para*-benzoquinone methide **126**, forming the same compound **124** isolated here.[121] Thus, it was proposed that this side-product is derived from phenoxy radical **125** in a similar mechanism (Scheme 91).



Scheme 91: Proposed mechanism for the formation of side-product **124**.

These results indicate that the thioarylation may proceed *via* a radical process, but further studies are necessary to provide evidence and elucidate the specific mechanism. Nonetheless, a speculative mechanism is proposed in Scheme 92. First, homolytic

cleavage of the iron(III) triflimide-activated *N*-(thioaryl)saccharin reagent produces thiyl radical **127**, which can participate in a radical aromatic substitution reaction to give radical intermediate **128**. A hydrogen radical is then eliminated to give the aryl thioether product. Iron(III) species are known to mediate radical processes and thus, it is also possible that iron(III) triflimide has another role in this reaction.[122]



Scheme 92: Potential radical thioarylation mechanism.

2.3.7 Conclusions and Future Work

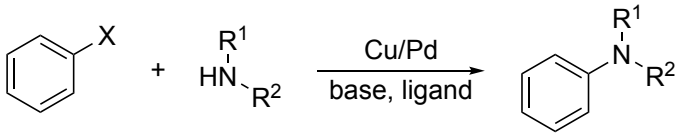
In summary, an improved thioarylation process has been developed using saccharin-based reagents, compared to the previously developed methodology using succinimide-based reagents. Most thioarylations could be performed at significantly lower temperatures and catalyst loadings, while still resulting in faster reactions. In some cases, yields were also higher. Two thioarylated tryptophan derivatives were efficiently synthesised and oxidised to the corresponding sulfones, but these were not fluorescent. A limitation of the methodology was thioalkylations, which had also been the case using succinimide-based reagents. Issues were encountered in the synthesis and purification of *N*-(thioalkyl)saccharins, which hindered optimisation of the subsequent challenging thioalkylations. Radical-trapping studies were performed, which indicated that the reaction may proceed by a radical mechanism.

Future work will involve further evaluation of the substrate scope, particularly regarding highly electron-deficient saccharin reagents, such as *N*-(4-nitrophenylthio)saccharin (**112**). The applications of the methodology regarding the synthesis and functionalisation of biologically active compounds will also be investigated. Finally, further experiments will be performed to probe the mechanism of this transformation.

2.4 Iron- and Copper-Catalysed One-Pot Sulfonamidation of Arenes

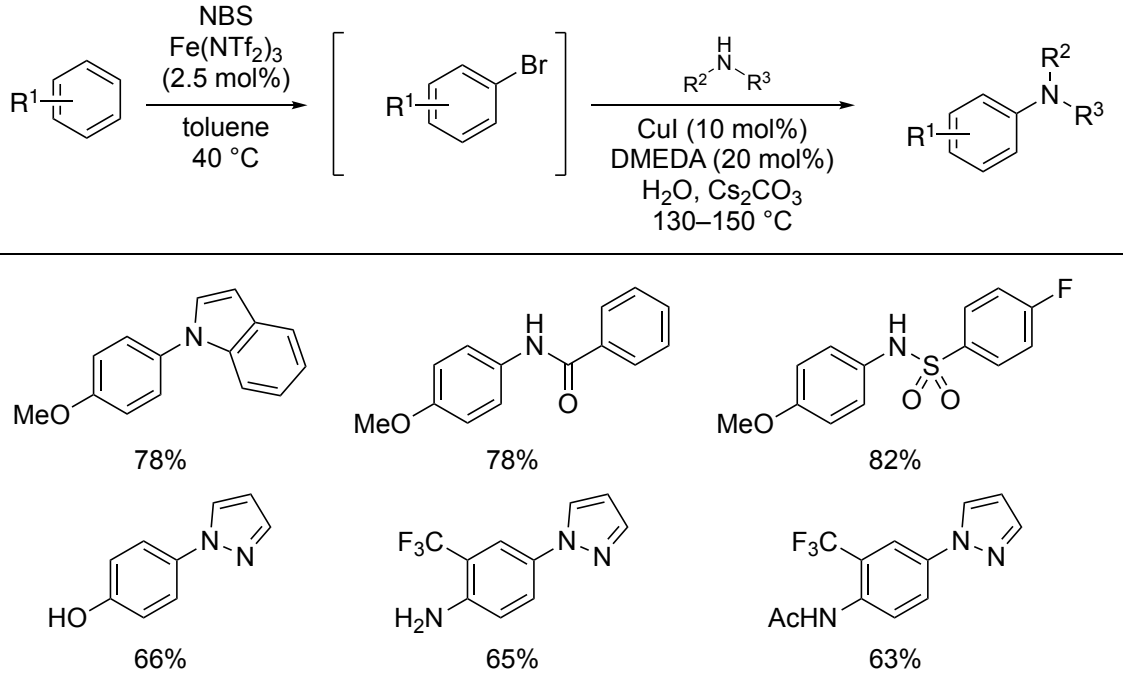
2.4.1 Introduction

The aryl C–N bond is extremely common in organic chemistry and is present in a wide range of pharmaceuticals and natural products. One of the early methods for the formation of this bond was the copper-catalysed coupling of aryl halides with amines, discovered by Ullmann in 1903 (Scheme 93).[123] In its original form, this reaction required high temperatures, often exceeding 200 °C, and stoichiometric quantities of copper. For these reasons, the reaction was not widely utilised. In the past three decades, improvements to the Ullmann-type coupling have enabled the use of much milder reaction conditions. These improvements have involved the use of bidentate N–N, N–O or O–O ligands, which have led to widespread use in both academia and industry.[10] Simultaneously, another powerful method for furnishing these bonds was discovered using palladium catalysis (Scheme 93). In 1994, the groups of Buchwald and Hartwig independently reported the coupling of aryl halides with aminostannanes.[124,125] In the following year, both reported tin-free procedures involving the coupling of amines with aryl halides.[126,127] Subsequent research has revealed bulky phosphines as the optimal ligands for these transformations, allowing for a wide substrate scope and a robust, reliable reaction.[128] Such is the utility of the reaction that in 2014, it was used in 10% of medicinal chemistry publications.[129]



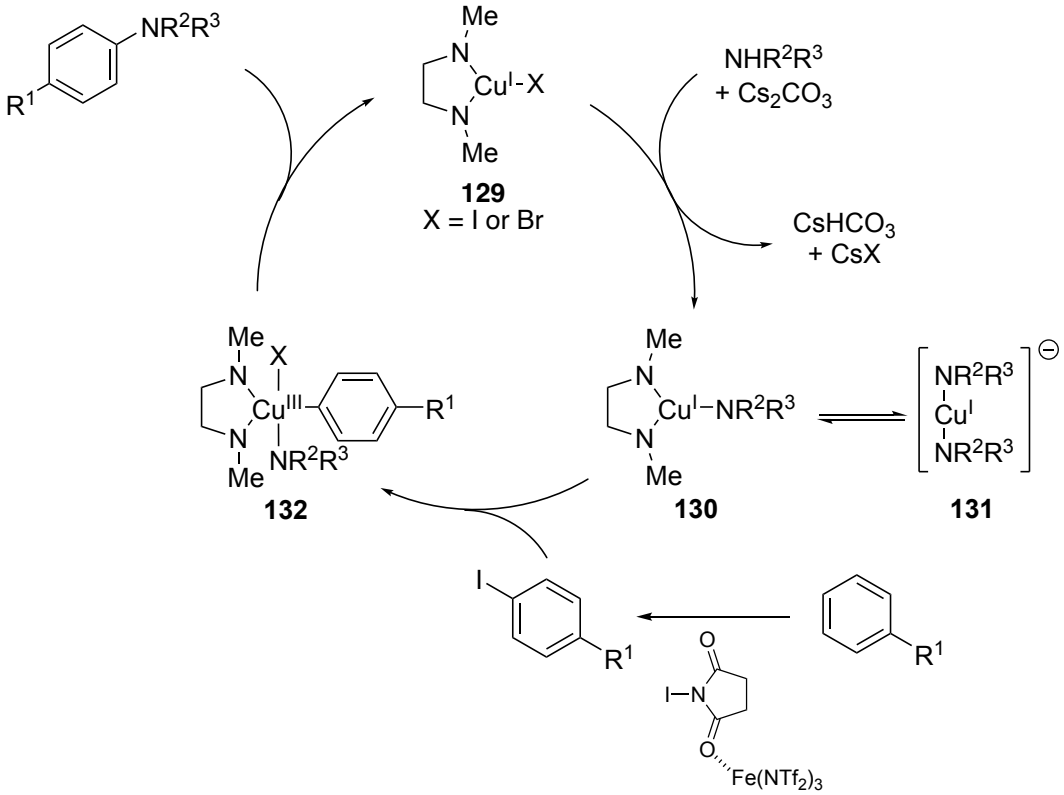
Scheme 93: Ullmann-type and Buchwald-Hartwig couplings.

In 2017, the Sutherland group reported a one-pot process consisting of an initial iron(III) triflimide-catalysed bromination of activated arenes, followed by a copper-catalysed Ullmann-type coupling, allowing for the rapid synthesis aryl C–N bonds in yields of 51–95% (Scheme 94).[103] Toluene was chosen as the solvent as it was compatible with both steps. For the second step, copper(I) iodide (10 mol%) was found to be the optimal copper source when combined with DMEDA (20 mol%) as a bidentate ligand. Caesium carbonate was utilised as the base, while the addition of water as a co-solvent enabled solvation of all reagents. The substrate scope regarding arenes was wide and included various activated arenes such as anisoles, phenols and amines. The amine coupling partners consisted of electron-rich *N*-heterocycles, amides and two sulfonamides.



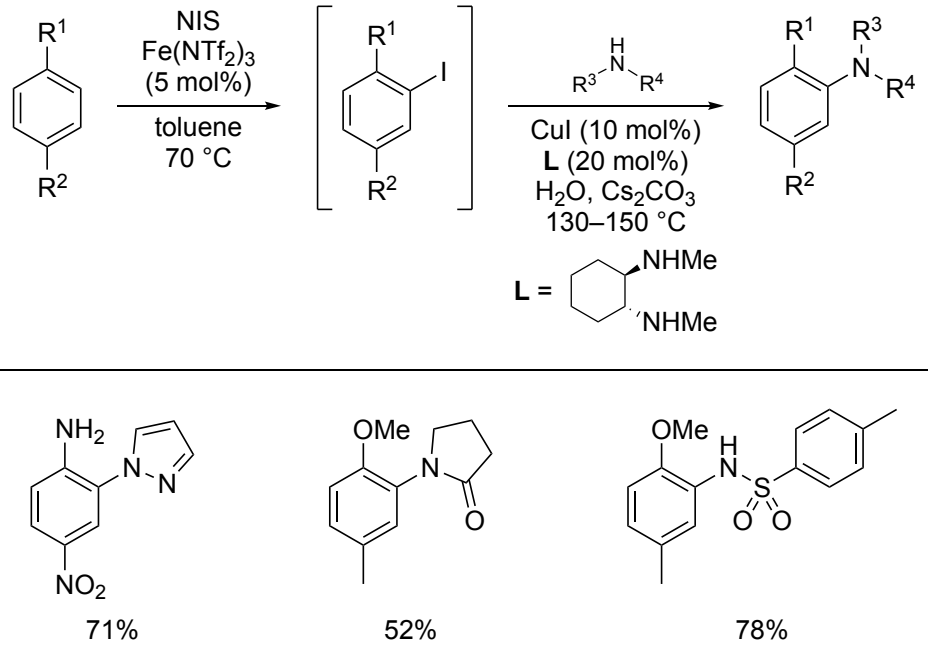
Scheme 94: One-pot amination of activated arenes.

The copper-catalysed Ullmann-type reaction is widely believed to proceed *via* a Cu(I)/Cu(III) mechanism (Scheme 95).[130] DMEDA co-ordinates to copper(I) iodide to form catalytic species **129**, which undergoes substitution with the amine to give intermediate **130**. Studies by Buchwald and co-workers have indicated that this species is in equilibrium with catalytically inactive di-aminated species **131**.[131,132] This equilibrium is shifted towards **130** at higher diamine ligand concentrations. The iodide, formed by reaction with iron(III) triflimide-activated NIS, undergoes oxidative addition, resulting in copper(III) intermediate **132**. Reductive elimination then yields the product.



Scheme 95: Proposed mechanism of the one-pot amination of activated arenes.

Another protocol was developed for *ortho*-amination where the *para*-position is blocked (Scheme 96).[133] This was a more challenging coupling due to steric hindrance, with copper-mediated dehalogenation competing as an alternative pathway during the second step. It was found that this pathway was suppressed when a more reactive iodide was installed in the first step, and trans-*N*,*N*'-dimethylcyclohexane-1,2-diamine was used as the ligand in the second step. The more rigid nature of this ligand has been proposed by Buchwald and co-workers to result in a more stable active catalyst.[134,135] The substrate scope was shown to be similar to the *para*-amination methodology.



Scheme 96: One-pot amination of *para*-substituted arenes.

2.4.2 Project Aims

The diaryl sulfonamide moiety is widespread in medicinal chemistry. As well as being present in a major class of antibiotics, the sulfanilamides, it features in many other biologically active compounds including anti-tumour agent batabulin (**133**),[136] anti-diabetic candidate INT131 (**134**) and a series of bromo and extra C-terminal domain (BET) agonists (**135**) (Figure 7).[137,138]

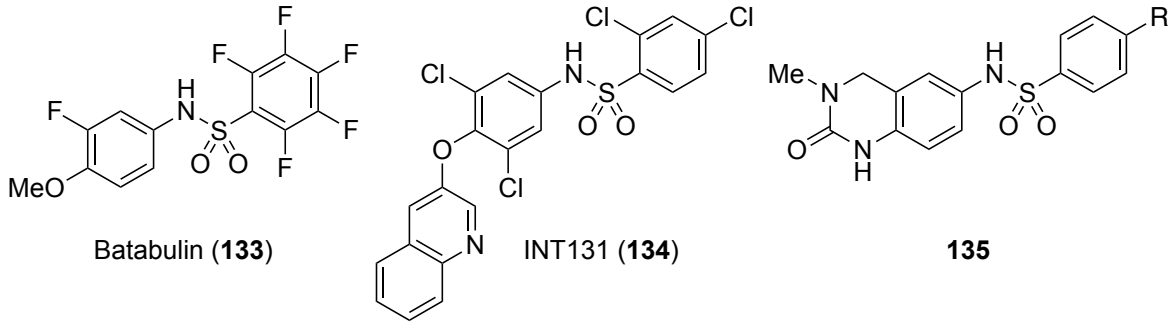
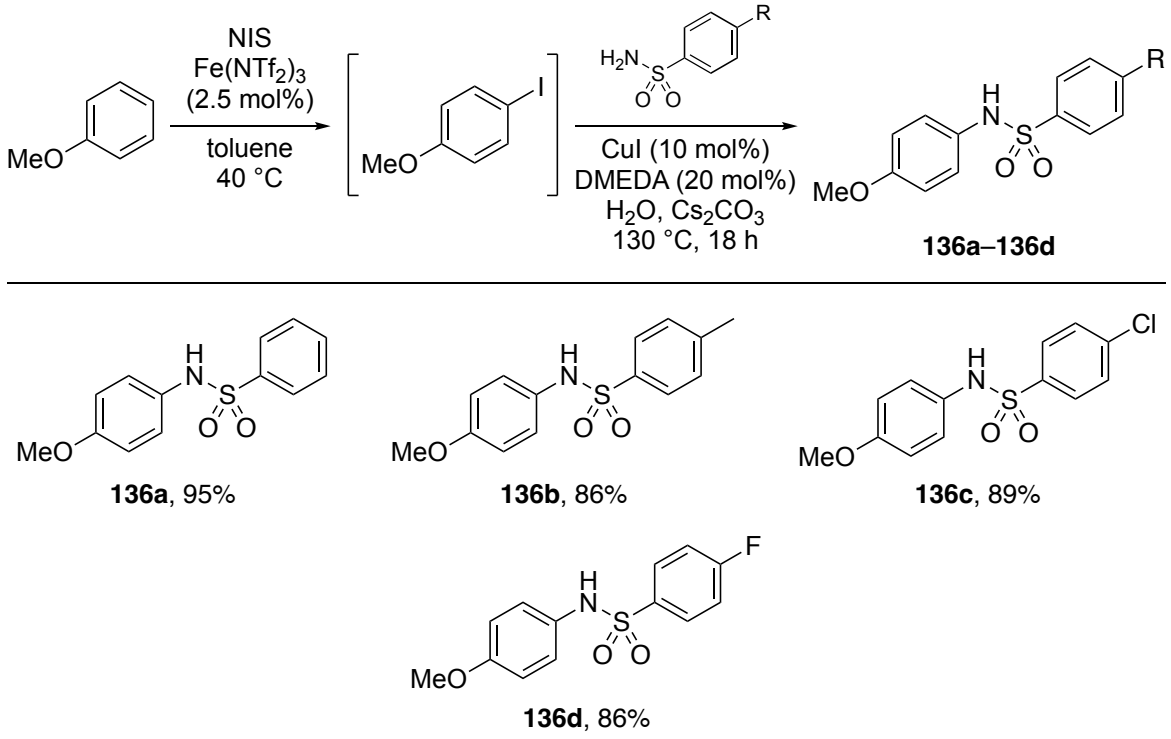


Figure 7: Biologically active diaryl sulfonamides.

Therefore, it was proposed that the substrate scope of the one-pot process could be fully explored and expanded for the preparation of a wider range of diaryl sulfonamides and used for the synthesis of pharmaceutically relevant targets. This would provide an attractive alternative to the reaction of anilines with cyto- and genotoxic sulfonyl chlorides,[139] which is a commonly used approach for the preparation of this valuable motif.

2.4.3 Substrate Scope

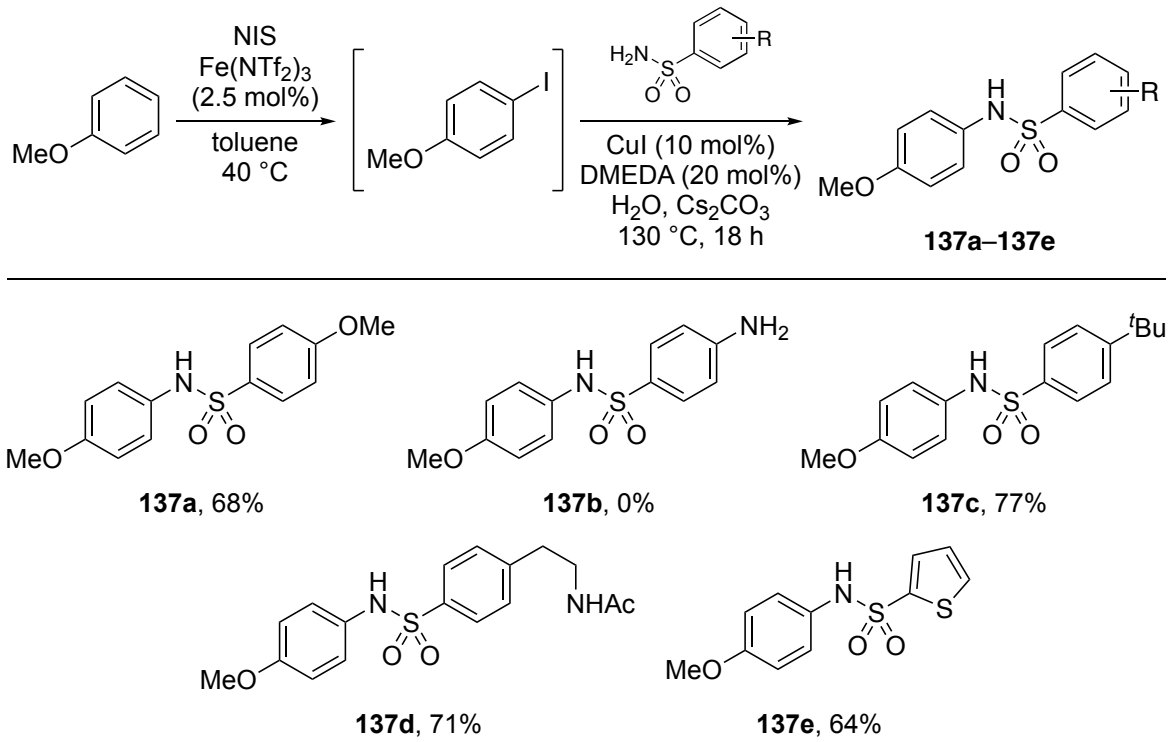
Previously in the group, four diaryl sulfonamides had been synthesised using NIS to iodinate anisole, followed by coupling with benzenesulfonamide, 4-methyl-, 4-chloro- and 4-fluorobenzenesulfonamide (Scheme 97).[140,141] These had been shown to be more efficient compared to analogous couplings using NBS, with isolated yields of 86–95% obtained. Otherwise, the same conditions established for the previous one-pot amination procedure were used.[103]



Scheme 97: One-pot sulfonamidations previously performed in the group.

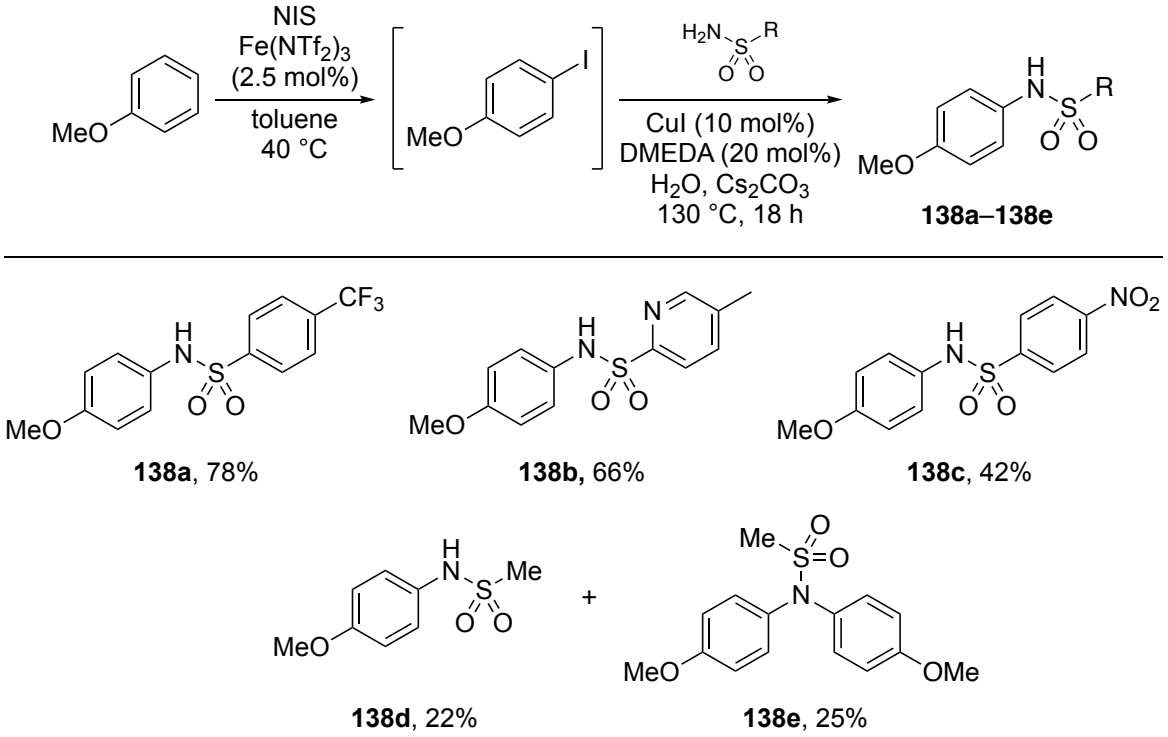
Therefore, the project began by further exploring the substrate scope regarding the sulfonamide partner (Scheme 98). Initially, anisole was coupled with aryl sulfonamides bearing a variety of electron-donating or neutral substituents. The iodination of anisole proceeded smoothly after 4 hours at 40 °C, with a 20:1 ratio of *para*:*ortho*-substituted intermediates observed by ^{1}H NMR spectroscopy. In general, the subsequent copper-catalysed coupling was also effective and all reactions proceeded to full conversion after 18 hours at 130 °C. For the coupling with 4-methoxybenzenesulfonamide, the diaryl product **137a** was isolated in 68% yield. When the highly activated 4-aminobenzenesulfonamide was used, multiple arylations at the sulfonamide nitrogen were observed and both mono- and di-substituted products were present in the crude reaction mixture in an inseparable 1:1 mixture. Sulfonamides with alkyl chains were effective coupling partners, with **137c** and **137d** generated in 77% and 71% yields, respectively. The latter reaction also demonstrated the tolerance of acetamide substituents. One example of a sulfonamide bearing an electron-

rich heterocycle was also investigated, with the coupling of anisole with 2-thiophenesulfonamide proceeding in 64% yield.



Scheme 98: Coupling of anisole with sulfonamides bearing electron-rich and electron-neutral arenes.

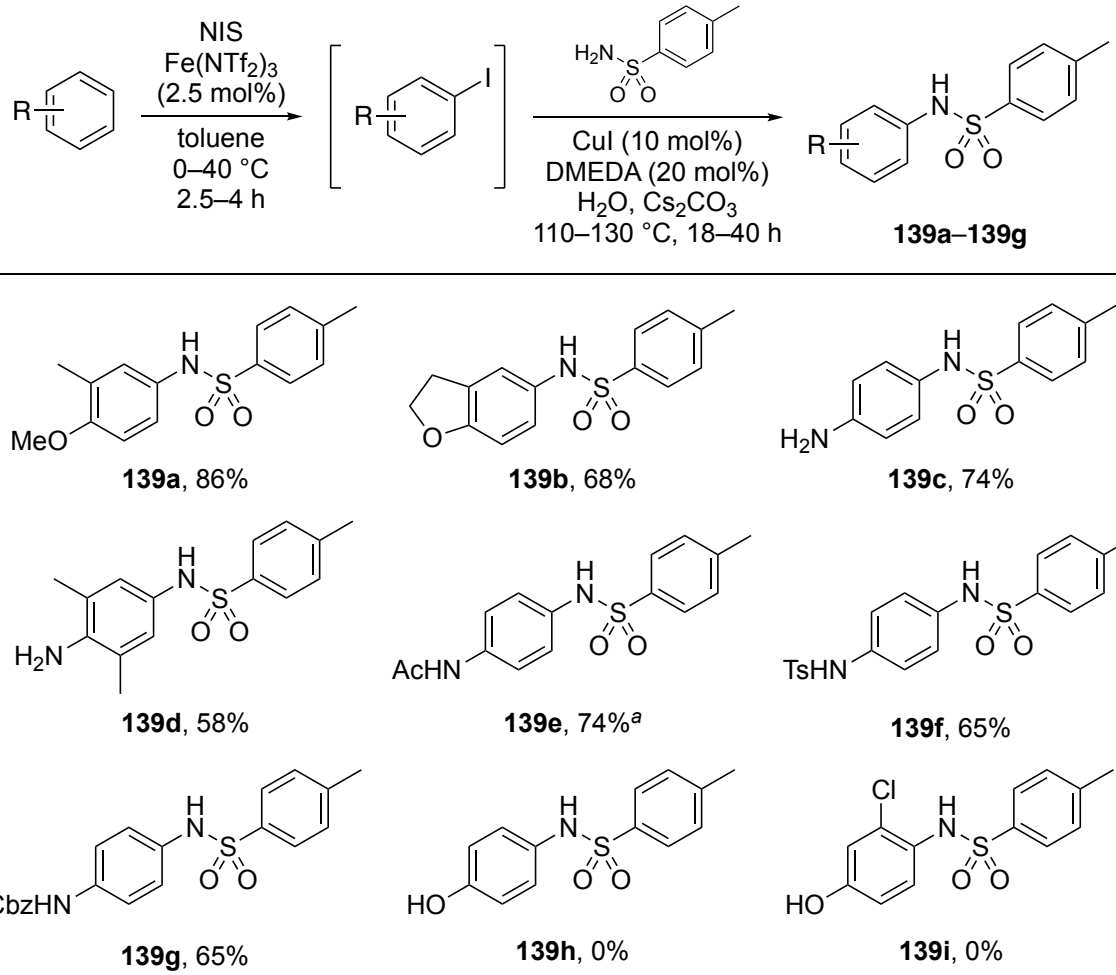
Sulfonamides bearing electron-deficient arenes were then evaluated (Scheme 99). The coupling of anisole with 4-trifluoromethylbenzenesulfonamide proceeded effectively, giving desired product **138a** in 78% yield. Reaction with 5-methyl-2-pyridinesulfonamide was also successful and **138b** was produced in 66% yield. When 4-nitrobenzenesulfonamide was used, the yield was lower (42%) due to incomplete conversion. This can be attributed to the reduced nucleophilicity of the sulfonamide, which is due to the highly electron-withdrawing nitro substituent. An extended reaction time of 48 h in the second step did not result in further conversion. Alkyl sulfonamides were also considered, and while the reaction with methanesulfonamide did proceed, multiple arylations occurred. Both mono- and di-arylated products **138d** and **138e** were isolated in 22% and 25% yields, respectively.



Scheme 99: Coupling of anisole with sulfonamides bearing electron-deficient arenes or an alkyl group.

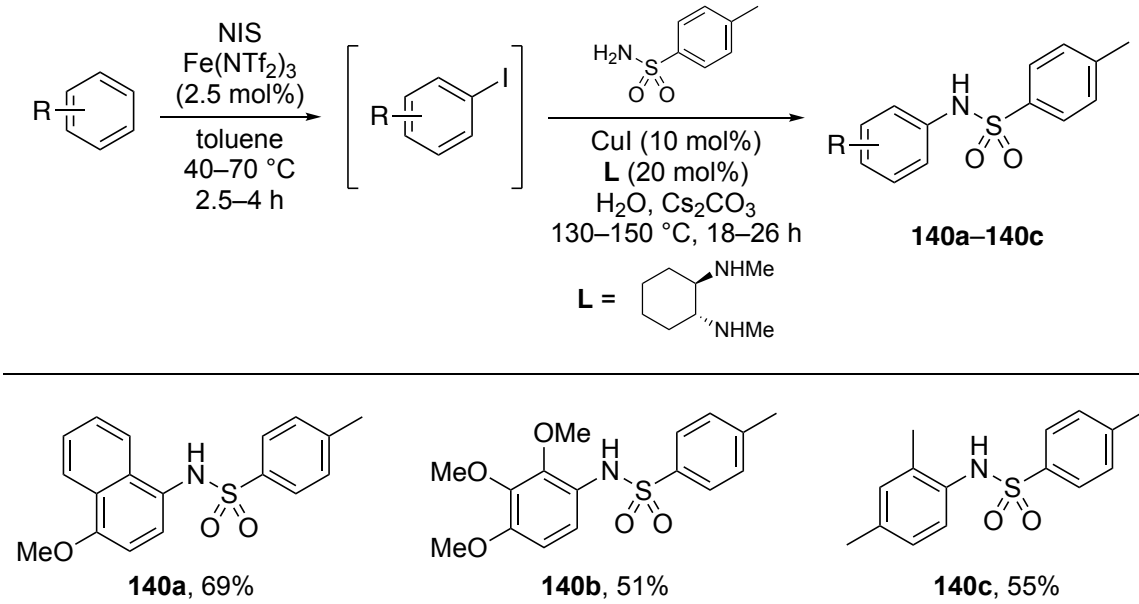
Next, various arenes were subjected to coupling with 4-toluenesulfonamide (Scheme 100). For most substrates, the iodination reached full conversion after 4 hours at 40 °C, while the copper-catalysed second step required reaction conditions of 18 hours at 130 °C. Good to excellent yields were recorded for most reactions, with excellent *para*-selectivity observed. 2-Methylanisole and 2,3-dihydrobenzofuran participated in the coupling to give desired products **139a** and **139b** in yields of 86% and 68%, respectively. Aniline was an effective substrate and diaryl product **139c** was isolated in 74% yield. Due to the highly activated nature of this arene, a lower temperature of 0 °C in the iodination step was required to prevent di-substitution. 2,6-Dimethylaniline was also demonstrated to participate in the reaction, giving **139d** in 58%. The slightly lower yield was attributed to only 86% conversion in the first step, as determined by ^{1}H NMR spectroscopy. It is possible that the greater electron density around the nitrogen atom due to the two methyl groups resulted in stronger coordination to iron(III) triflimide, which hindered NIS activation. Protected anilines also underwent effective sulfonamidation, with acetyl, tosyl- and Cbz-protected anilines giving corresponding products **139e**, **139f** and **139g** in 74%, 65% and 65% yields, respectively. For acetyl-protected aniline, the deactivating effect of the acetyl group necessitated a higher iron(III) triflimide loading of 5 mol%, while for tosyl-protected aniline, a longer iodination time of 24 hours was required. In the case of Cbz-protected aniline, a lower temperature of 110 °C and longer reaction time of 40 hours was necessary to prevent cleavage of the protecting group in the second step. For phenol and 3-chlorophenol, effective iodinations were observed but in the second steps, no conversion to the products **139h** and **139i** were observed. Buchwald and co-workers previously reported similar outcomes with phenols and

other easily deprotonated species such as benzoic acids.[142] This was proposed to be due to co-ordination of these anions to the copper catalyst, which form catalytically inactive species.



Scheme 100: Coupling of arenes with *para*-toluenesulfonamide. [a] Reaction performed using iron(III) triflimide loading of 5 mol%.

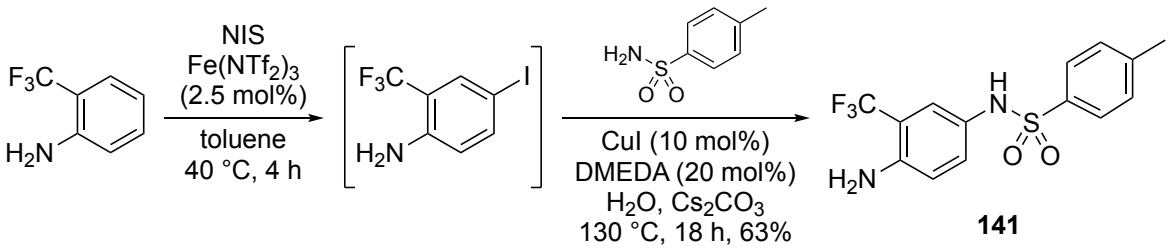
For substrates where the site of the amination had an *ortho*-substituent, the use of conditions developed for the one-pot *ortho*-amination process was found to be necessary to suppress de-iodination during the sulfonamide coupling step.[133] This consisted of using *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine as the ligand, as well as increasing the number of equivalents of the nucleophile from 1.5 to 3.0 (Scheme 101). The coupling with 1-methoxynaphthalene gave **140a** in a 69% yield. Despite the highly activated nature of 1,2,3-trimethoxybenzene, only the mono-aminated product was formed. In the case of the less activated *meta*-xylene, a higher temperature of 70 °C was necessary in the first step. Increased quantities of NIS (1.5 equivalents) were also required, due to competing iodination of the solvent. For both substrates, the second step was performed at 150 °C to overcome the steric barrier. The corresponding products, **140b** and **140c**, were isolated in 51% and 55% yields, respectively.



Scheme 101: Coupling of sterically hindered arenes with *para*-toluenesulfonamide.

2.4.4 Synthesis of Biologically Active Compounds

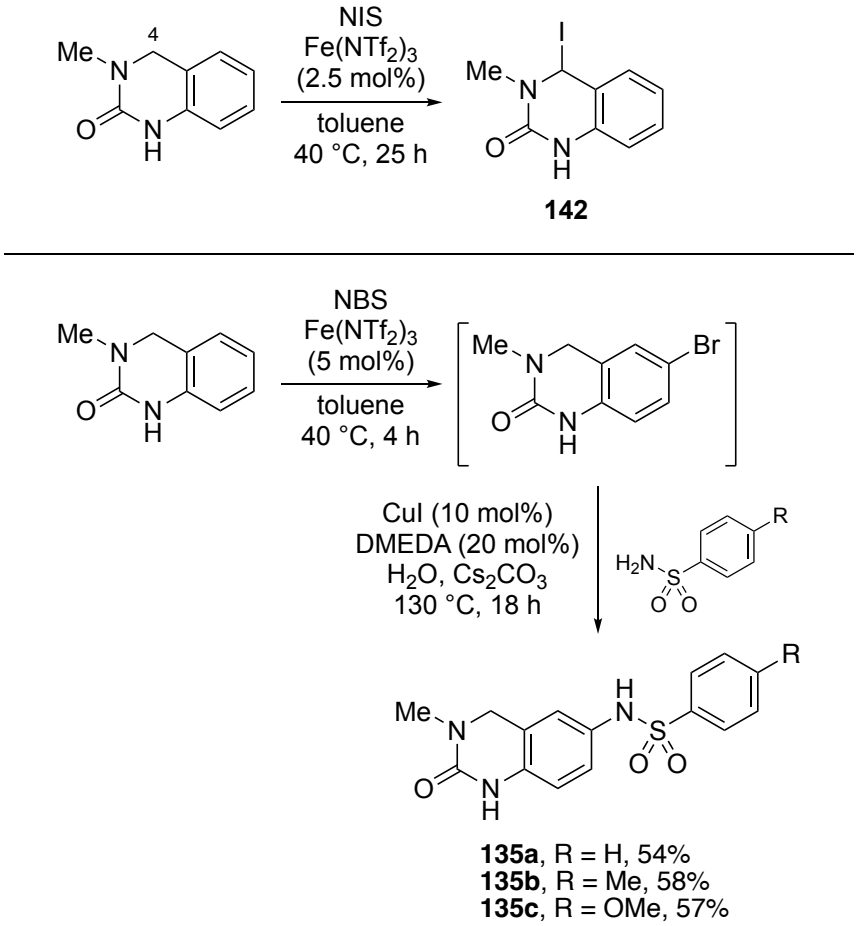
Finally, the use of this methodology for the synthesis of biologically active compounds was investigated. It was proposed that free fatty acid receptor 4 (FFA4) agonist **141** and BET bromodomain inhibitors **135a**–**135c** could be rapidly synthesised from commercially available starting materials. The synthesis of **141** proceeded smoothly using the established standard conditions with a yield of 63% (Scheme 102).



Scheme 102: Synthesis of FFA4 agonist **141**.

Surprisingly, the iodination of 3-methyl-3,4-dihydro-2(1*H*)-quinazolinone did not occur at the expected *para*-position (Scheme 103). Isolation of the undesired product was not successful due to decomposition during silica gel column chromatography, but analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated that 4-substituted compound **142** had been formed. It is possible that this arises from a radical process. However, bromination of this substrate using NBS had previously been reported by Bolm and co-workers.[143] Therefore, NBS was considered instead of NIS. Initially, the bromination was investigated as a single step. Using iron(III) triflimide (5 mol%), the reaction was selective for the *para*-position, with none of the 4-brominated product formed. While two minor, unidentified side-products were

generated (9:1 ratio of product:side-products), the desired bromide was isolated in 71% yield. Following optimisation of an efficient and regioselective halogenation, the two-step, one-pot couplings were performed with benzenesulfonamide, 4-toluenesulfonamide and 4-methoxybenzenesulfonamide, giving desired products **135a**, **135b** and **135c** in 54%, 58% and 57% yields, respectively.



Scheme 103: Attempted iodination of 3-methyl-3,4-dihydro-2(1*H*)-quinazolinone (top). Synthesis of BET bromodomain inhibitors **135a**–**135c** (bottom).

Previously, the synthesis of these compounds required multiple steps with overall yields significantly lower than achieved using this methodology.[138] For example, **135b** and **135c** were prepared by nitration of 3-methyl-3,4-dihydro-2(1*H*)-quinazolinone, reduction and then reaction with a sulfonyl chloride (29% and 24% overall yields, respectively).

2.4.5 Conclusions

In summary, the substrate scope of the one-pot amidation process has been extended for the rapid synthesis of a small library of diaryl sulfonamides. This was found to give good to excellent yields, with excellent selectivity for the *para*-position. Thus, this offers an attractive alternative to other methods involving cyto- and genotoxic sulfonyl chlorides. In the first

step, an iron(III) triflimide-catalysed iodination instead of bromination allowed for a more efficient reaction. For substrates where the amidation site was sterically hindered, the use of *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine instead of DMEDA was found to suppress competing de-iodination. Finally, the utility of this methodology was demonstrated by the rapid synthesis of a FFA4 agonist and three BET bromodomain inhibitors.

3.0 Development of Novel PET Imaging Agents

3.1 New PET Imaging Agents for the Translocator Protein

3.1.1 Introduction

Molecular imaging is a key concept in modern medicine which encompasses several techniques. They can be used to produce real time *in vivo* images in a non-invasive fashion which, among other uses, can facilitate diagnosis and monitoring of disease or damage. Positron emission tomography (PET) is one of these techniques (Figure 8).[144] PET operates by using a compound labelled with an appropriate radionuclide. The radionuclide decays to emit a positron (β^+) which, after travelling a short distance, interacts with an electron to undergo an annihilation event. This produces two 511 keV γ-rays which are emitted in opposite directions. These can be detected in a PET scanner, which converts the energy from the photons into an electric signal. As the two γ-rays are emitted in opposite directions, the location of the annihilation can be determined. Once a large number of annihilation events have been detected, an image can be constructed.

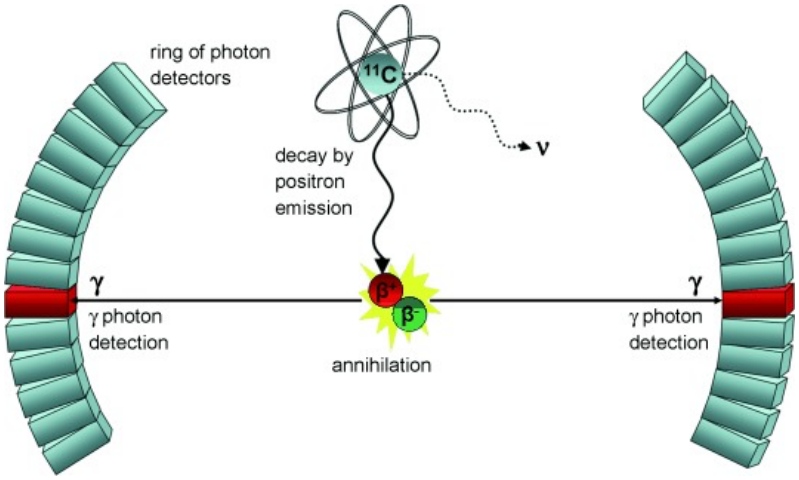


Figure 8: Summary of Positron Emission Tomography.[145] (Reprinted with permission from P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem. Int. Ed.*, 2008, **47**, 8998–9033. Copyright 2008 John Wiley and Sons.)

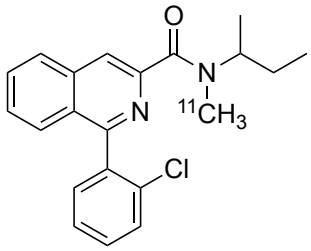
Radionuclide selection is a key consideration for PET imaging.[144] Clearly, the radionuclide must undergo decay by positron emission, but the half-life is also of key importance – it should be comparable to the duration of the imaging experiment so that it is long enough to allow imaging to take place, but short enough that the radionuclide is not present in the body longer than necessary. Radionuclides such as ^{11}C (20 minutes), ^{13}N (10 minutes), ^{15}O (2 minutes) and ^{18}F (110 minutes), among others, can be used for PET imaging, but in practice the most widely used are ^{11}C and ^{18}F. While the short half-life of ^{11}C necessitates an on-site cyclotron to produce the radionuclide, the longer half-life of ^{18}F allows more

flexibility and the tracer can be transported short distances after the radiosynthesis. Longer *in vivo* studies are also possible with ^{18}F.

The translocator protein (TSPO) is an 18 kDa transmembrane protein which is primarily expressed in steroid-synthesising tissues on the outer mitochondrial membrane.[146] Among other functions, it is involved in the transport of cholesterol from the outer to the inner mitochondrial membrane; this is the rate limiting step in the synthesis of steroids. It is highly conserved throughout evolution which indicates that it is essential for tissue development and function.[147] In the past decade, several groups have reported molecular structures of both the wild-type protein and a bacterial mimic of the human rs6791 polymorphism.[148–150] The protein has five transmembrane alpha helices in each monomer unit and exists as a homodimer. A key characteristic of TSPO is the behaviour it exhibits in response to neuroinflammation. In healthy CNS tissues, TSPO expression is limited to microglia cells, the primary resident immune surveillance cell in the brain, in low levels.[151] However, upon brain damage or disease, these microglia are activated and the expression of TSPO is significantly increased. This response is observed with many neurological conditions including Alzheimer's and Parkinson's diseases. It has been proposed that the purpose of this increase is to facilitate mitochondrial proliferation to repair the damaged tissues.[146] This phenomenon makes TSPO a key biomarker for neurological damage and allows it to be targeted by appropriate ligands, or radiotracers, to image these conditions and injuries. Crucially, TSPO also appears to play a role in the response to cardiac damage done by inflammation,[152] and proof-of-concept studies have indicated that TSPO radiotracers can be used to image intraplaque inflammation in carotid atherosclerosis.[153]

The dominant radiotracer used for PET imaging of TSPO is the isoquinoline carboxamide [^{11}C]PK11195 (**143**) (Figure 9).[154] [^{11}C]PK11195 was first discovered by Pharmuka and was one of the first compounds that showed nanomolar binding affinity for TSPO (K_i = 9.3 nM).[155] Moreover, it is not susceptible to interspecies variability.[156] The first radiosynthesis of [^{11}C]PK11195 (**143**) was reported in 1984 by Camsonne and co-workers, using [^{11}C]methyl iodide.[157] This was soon followed in 1986 by Charbonneau and co-workers, with the first study demonstrating that it could be used to image TSPO in the heart of humans.[154] This has since led to [^{11}C]PK11195 (**143**) becoming the prototypical TSPO radiotracer for PET imaging and has been used to image numerous human neurological conditions, including but not limited to multiple sclerosis, Alzheimer's disease and schizophrenia.[156] Despite the widespread use of [^{11}C]PK11195 (**143**), it has a number of suboptimal properties regarding its use as a radiotracer. The use of ^{11}C and the associated short half-life limits its use to locations with an on-site cyclotron and is only suitable for short studies. Moreover, it has poor *in vivo* properties. These mostly stem from its high lipophilicity which results in high

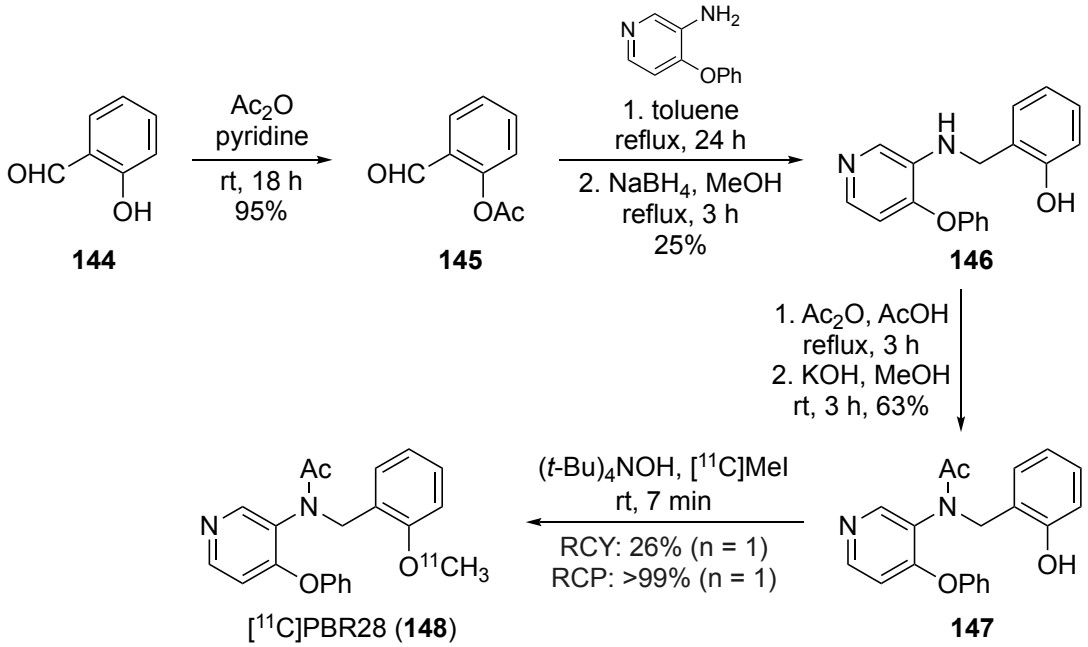
non-specific binding to fats and proteins. This reduces the concentration of free [^{11}C]PK11195 (**143**) in the body and contributes to a high signal-to-noise ratio.[158]



[^{11}C]PK11195 (**143**)

Figure 9: [^{11}C]PK11195 (**143**).

Significant efforts have been directed at developing superior second generation TSPO radiotracers to address these issues. One example is [^{11}C]PBR28 (**148**), synthesised by Pike and co-workers.[159] This was done by treatment of 2-hydroxybenzaldehyde (**144**) with acetic anhydride and pyridine to give acetate **145** in 95% yield (Scheme 104). Reductive amination with 3-amino-4-phenoxypyridine and sodium borohydride then generated **146** in 25% yield. Next, the *N*-acetyl group was installed, along with an unwanted acetate group, which was cleaved under basic conditions to produce radiosynthesis precursor **147** in 63% yield over two steps. The ^{11}C-label was introduced via methylation with [^{11}C]methyl iodide. Reaction at room temperature for 7 minutes gave [^{11}C]PBR28 (**148**) with a yield of 26% and high radiochemical purity. It was found that [^{11}C]PBR28 (**148**) had a roughly tenfold superior TSPO binding affinity compared to [^{11}C]PK11195 (**143**) (K_i = 0.21–0.59 nM and 4.12 nM, respectively).[160] Furthermore, it displayed higher specific binding and lower non-specific binding compared to [^{11}C]PK11195 (**143**), partly due to its lower lipophilicity. Additionally, it had a favourable metabolism profile. All these properties indicated potential for a successful radiotracer.



Scheme 104: Synthesis of [^{11}C]PBR28 (**148**).

However, when [^{11}C]PBR28 (**148**) proceeded to studies in humans, it was found that there was some variability in binding between individuals, with the radiotracer not binding to TSPO at all in ~10% of subjects.[161] Further studies investigated this result in more detail.[162,163] It was found that individuals can be split into three distinct categories – high affinity binders (HAB), mixed affinity binders (MAB) and low affinity binders (LAB). For [^{11}C]PBR28 (**148**), the K_i LAB:HAB ratio was 55:1. Similar results were recorded for almost all other radiotracers investigated. The only ligand found to be insensitive to this phenomenon (LAB:HAB ratio of 1:1) was [^{11}C]PK11195 (**143**). It is now known that this is caused by the TSPO single nucleotide rs6971 genetic polymorphism present in humans.[164] This polymorphism results in an amino acid substitution in TSPO (Ala147Thr) which causes high interindividual variability with regards to binding affinity. High affinity binders have only wild-type TSPO, low affinity binders have only Ala147Thr TSPO while mixed affinity binders have a ~1:1 mixture of the two.[163] This has implications for quantitative comparison between subjects. [^{11}C]PK11195 (**143**) is not sensitive to this polymorphism, binding to both the wild-type and mutant varieties equally well and is a key reason for its continued widespread use.

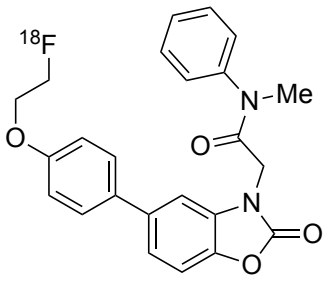
In recent years, there have been several novel radiotracer candidates that have been proposed to be insensitive to the rs6971 polymorphism. [^{18}F]FEBMP (**149**) (Figure 10) was developed by Zhang and co-workers and was shown in a small pilot autoradiography study to be insensitive to the polymorphism.[165] Moreover, due to a suitable lipophilicity (logD = 3.43), it showed excellent blood brain barrier penetration and was used to visualise neuroinflammation in a rat model of focal ischemia. Unfortunately, the radiotracer displayed an undesirable metabolic profile in rats, with 90% metabolism in plasma after 30 minutes.

Furthermore, a metabolite was found in the brain which could have implications for the clarity of PET studies.

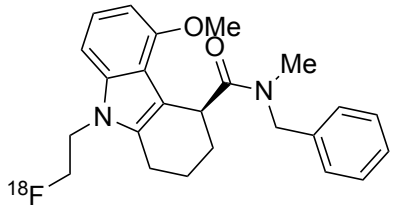
[^{18}F]GE387 (**150**) (Figure 10) was recently synthesised by Aigbirhio and co-workers and was initially reported to be insensitive to the polymorphism, but human tissue was not used in these experiments, which is considered to be the gold standard.[166] Instead, experiments were carried out using human embryonic kidney cell lines overexpressing human TSPO wild-type and TSPO A147T. A later publication reported experiments using human brain tissue, which showed the compound to have a lesser LAB:HAB ratio of 1.8:1.[167] These results demonstrate the importance of method selection for the determination of polymorphism sensitivity.

Using a similar structure to [^{11}C]PK11195 (**143**), Mitterhauser and co-workers reported that (*R*)-[^{18}F]NEBIFQUINIDE (**151**) is insensitive to the polymorphism using human thrombocyte membranes (Figure 10). They demonstrated that it had good metabolic stability in rats and initial results suggested that the compound penetrated the blood brain barrier.[168] However, they have not yet reported the full evaluation of this compound in animal models.

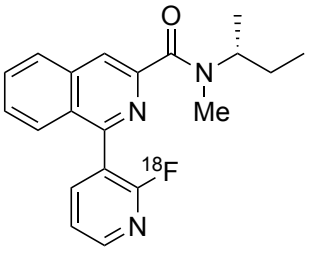
In 2021, [^{18}F]BS224 (**152**) was proposed to be insensitive to the polymorphism by Lee and co-workers (Figure 10).[169] However, it should be noted that to determine this, they used the same method that initially gave over-optimistic figures for [^{18}F]GE387 (**150**). Thus, this result must be confirmed using human tissue. [^{19}F]BS224 (**152**) was evaluated using rat models of ischemic stroke and LPS-induced neuroinflammation and was able to clearly show the inflammatory lesions.



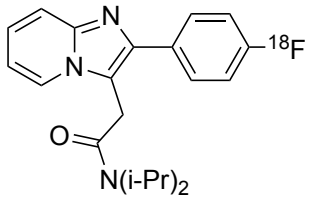
[^{18}F]FEBMP (**149**)



[^{18}F]GE387 (**150**)



(R)-[^{18}F]NEBIFQUINIDE (**151**)



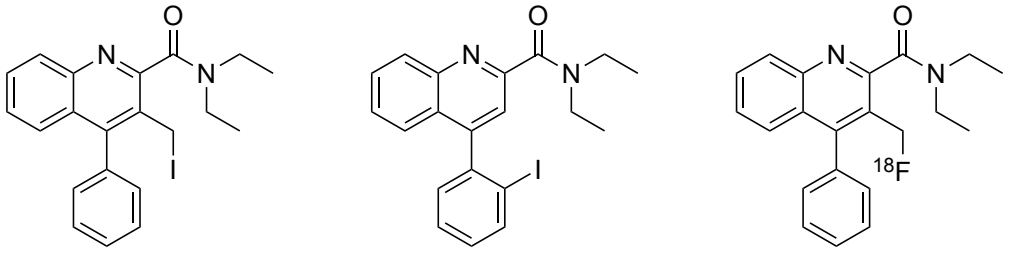
[^{18}F]BS224 (**152**)

Figure 10: [^{18}F]FEBMP (**149**), [^{18}F]GE387 (**150**), (R)-[^{18}F]NEBIFQUINIDE (**151**) and [^{18}F]BS224 (**152**).

3.1.2 Previous Work in the Sutherland Group

The Sutherland group has had a longstanding interest in developing PET radiotracers for TSPO. Given the insensitivity of [^{11}C]PK11195 (**143**) to the rs6971 polymorphism and inspired by the work of Cappelli and co-workers, who performed significant SAR work regarding TSPO,[170–173] efforts focused on the synthesis of analogues with similar core structures. Initial work involved the synthesis of iodinated quinoline carboxamide ligands for SPECT imaging, and 3-iodomethylquinoline (**153**) (Figure 11) was developed, with a K_i of 12.0 nM.[174] This work also revealed that a relatively small amide side chain was key. However, poor physicochemical properties necessitated the development of less lipophilic analogues.

A new analogue **154** (Figure 11) with a diethyl amide side chain further improved the affinity, with the K_i determined to be 5.0 nM.[175] However, this compound still presented sub-optimal physicochemical parameters (P_m = 0.67, K_m = 287 and %PPB = 94%), with comparison to those determined to be ideal by Tavares and co-workers (P_m < 0.5, K_m < 250 and %PPB < 95%).[176] Efforts then turned to developing PET imaging agents using ^{18}F, which would give less lipophilic compounds in comparison with iodinated analogues. Therefore, [^{18}F]AB5186 (**155**) was proposed (Figure 11).[177]

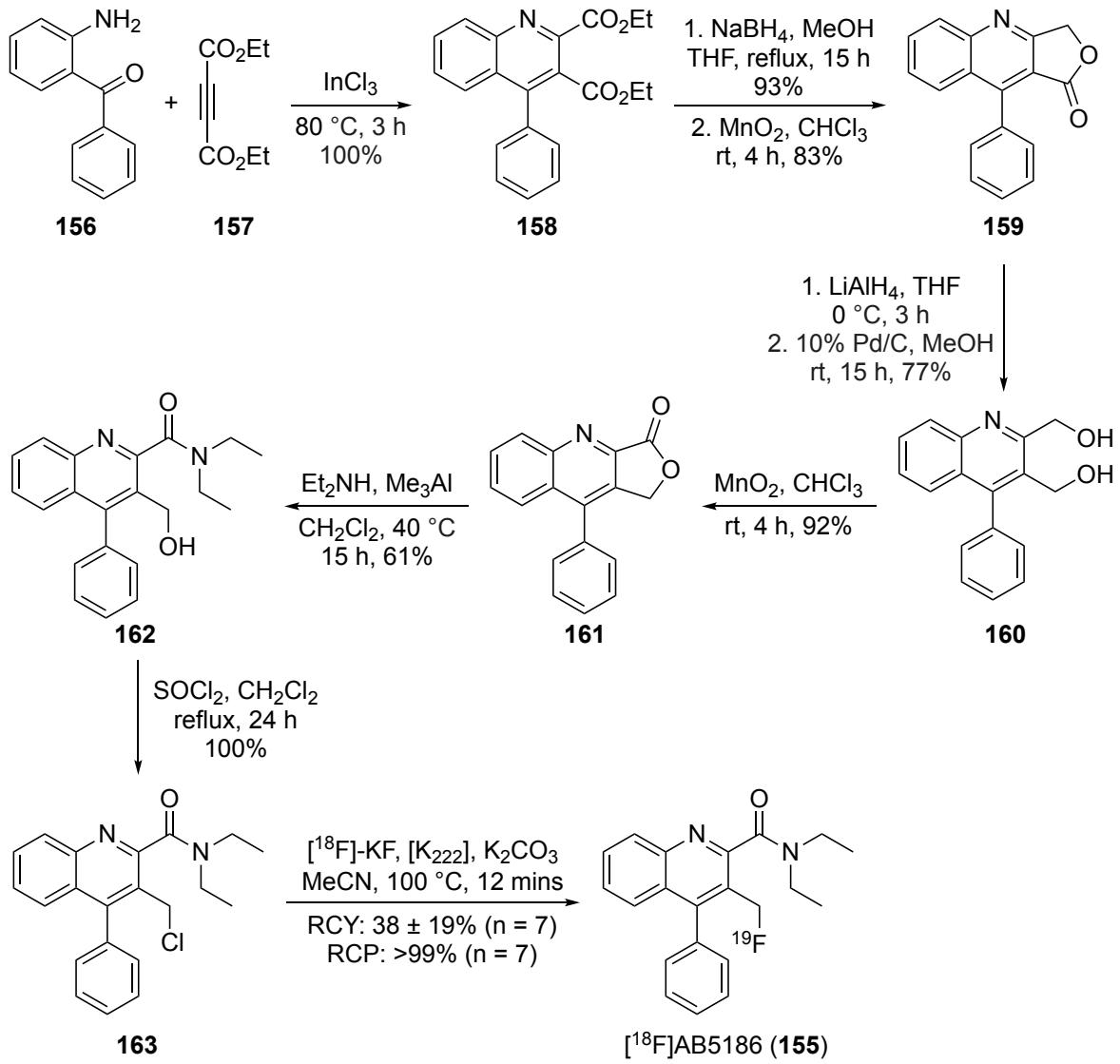


153 **154** AB5186 (**155**)

Figure 11: Iodinated analogues **153** and **154**, and AB5186 (**155**).

The synthesis of [^{18}F]AB5186 (**155**) is outlined in Scheme 105. A one-pot two-component reaction between 2-aminobenzophenone (**156**) and diethyl acetylenedicarboxylate (**157**) furnished diester **158** in quantitative yield.[177] The diester was reduced with sodium borohydride in 93% yield, followed by oxidation with manganese(IV) oxide to give lactone **159** in 83% yield. Ring-opening reduction with lithium aluminium hydride followed by re-oxidation of the C−N bond using palladium on carbon in methanol gave diol **160** in 77% yield over two steps. Using the same conditions as before, lactone **161** was generated in 92% yield by treating diol **160** with manganese(IV) oxide. The diethylamide moiety was installed by a trimethylaluminium mediated reaction in 61% yield to give **162**. This was then treated with thionyl chloride to give radiofluorination precursor **163** in quantitative yield.

Treatment of this precursor with [^{18}F]fluoride, Kryptofix® and potassium carbonate at 100 °C for 12 minutes generated [^{18}F]AB5186 (**155**) in 38 ± 19% RCY.



Scheme 105: Radiosynthesis of [^{18}F]AB5186 (**155**).

As expected, [^{18}F]AB5186 (**155**) had improved physicochemical properties (P_m = 0.50, K_m = 154 and %PPB = 90%).[177] Furthermore, the K_i for TSPO was determined to be 2.8 nM. [^{18}F]AB5186 (**155**) was used to image a glioma in a mouse and also showed the ability to cross the blood brain barrier of a baboon. Unfortunately, it was found that, despite having a similar core structure to [^{11}C]PK11195 (**143**), [^{18}F]AB5186 (**155**) also suffers from sensitivity to the rs6971 polymorphism (Figure 12).[178]

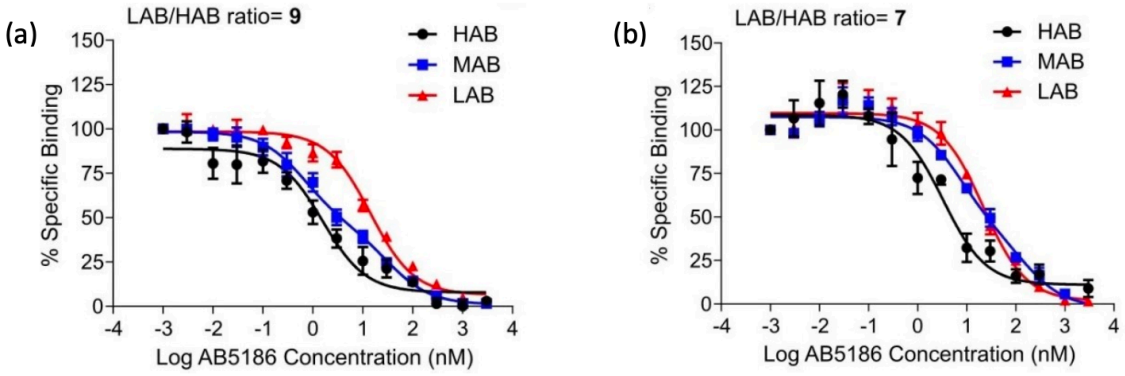
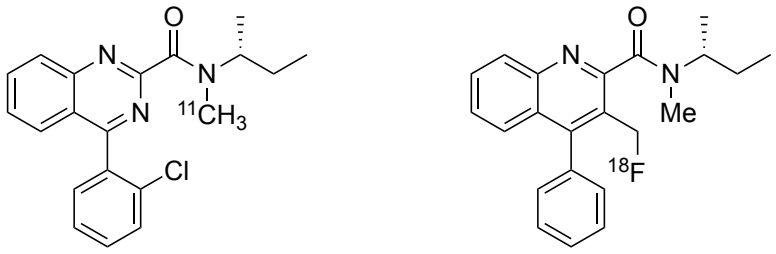


Figure 12: Mean AB5186 (**155**) binding affinity curves in HAB (black), MAB (blue) and LAB (red) human brain (a) and heart (b) tissue. Adapted from *J. Nucl. Med*., 2021, **62**, 536–544.[178]

While the development of [^{18}F]AB5186 (**155**) was in progress, Pike and co-workers reported [^{11}C]-labelled compound **164** (Figure 13), which had a LAB:HAB ratio of 1.3:1.[179] Given the insensitivity of [^{11}C]PK11195 (**143**) and the relative insensitivity of compound **164** to the rs6971 polymorphism, it was proposed that that a switch from the diethyl side chain used for [^{18}F]AB5186 (**155**) to the *sec*-butyl side chain present in [^{11}C]PK11195 (**143**) and **164** could address the sensitivity to the polymorphism. In [^{11}C]PK11195 (**143**), this is present as a racemic mixture, but it had previously been found that the (*R*)-enantiomer has a greater affinity for TSPO than the (*S*)-enantiomer.[180] Given the relative ease of introducing this component *via* amide coupling with the commercially available (*R*)-(−)-*sec*-butylamine, the chiral compound **165** was proposed, which was named [^{18}F]LW223 (Figure 13).[178]

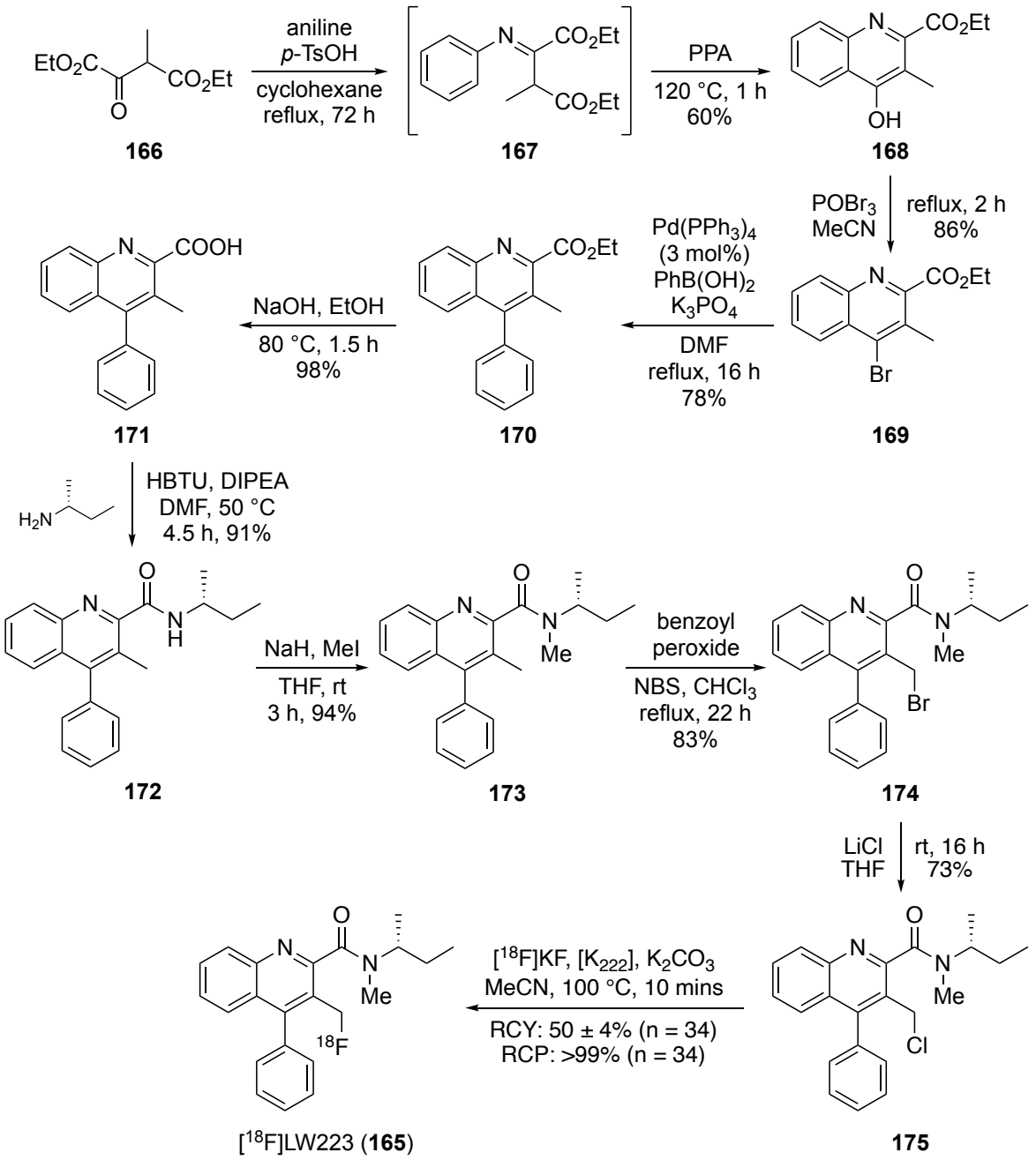


164 [^{18}F]LW223 (**165**)

Figure 13: [^{11}C]-Compound **164** and [^{18}F]LW223 (**165**).

The first stage of this programme focused on the synthesis of LW223 (**165**) (Scheme 106). The heterocyclic core was accessed *via* a Combes quinoline synthesis, with diethyl oxalpropionate (**166**) first reacted with aniline to form imine intermediate **167**.[178] This was immediately subjected to an acid-mediated ring closure with polyphosphoric acid to give quinoline **168** in 60% yield over two steps. In preparation for a Suzuki-Miyaura coupling reaction, **168** was brominated using phosphorus(V) oxybromide to give **169**, which was then coupled with phenylboronic acid to produce biaryl product **170** in 78% yield. The ester was hydrolysed to reveal the carboxylic acid **171** in 98% yield before being subjected to an amide

coupling with (*R*)-(−)-*sec*-butylamine using HBTU as the coupling agent. Amide **172** was isolated in a yield of 91%. Treatment with methyl iodide and sodium hydride gave *N*-methylated product **173** in near quantitative yield. This was followed by a radical bromination with *N*-bromosuccinimide, which proceeded in 83% yield, before substitution with lithium chloride gave **175**, the precursor to the radiosynthesis, in 73% yield. Both the bromide and the chloride were considered for radiosynthesis and it was found that, similar to the radiosynthesis of AB5186, use of the chloride resulted in a more efficient reaction. Treatment of **175** with [^{18}F]fluoride, Kryptofix® and potassium carbonate at 100 °C for 10 minutes yielded [^{18}F]LW223 (**165**) in 50 ± 4% RCY.



Scheme 106: Radiosynthesis of [^{18}F]LW223 (**165**).

Upon the synthesis of [^{18}F]LW223 (**165**), it was found that the compound exists as two rotamers due to restricted rotation about the amide bond.[181] While this was not unexpected, the restriction of rotation was such that these rotamers were separable by HPLC. ^{18}F has a longer half-life than ^{11}C, but it is still relatively short and the avoidance of any delays during radiosynthesis is highly desirable. The existence of two peaks in the HPLC trace means that during purification by semi-preparative HPLC, the product is collected in a larger amount of solvent. This caused complications and delays during purification and reformulation leading to additional decay of the radiotracer.

Despite these issues, LW223 (**165**) was shown in preclinical trials with rats to bind to TSPO specifically and showed excellent *in vivo* characteristics with a favourable metabolism profile.[178] Furthermore, unlike AB5186 (**155**), it was shown to be insensitive to the rs6971 polymorphism and has an excellent K_i of 0.6 nM in human brain and 1.7 nM in human heart (Figure 14). The corresponding values for PK11195 (**143**) are 1.2 nM and 1.7 nM, respectively. [^{18}F]LW223 (**165**) was also evaluated in animal disease models and a package of detailed kinetic *in vivo* kinetic modelling was produced. This data indicated that [^{18}F]LW223 (**165**) is an excellent candidate for progression to human clinical trials. To date, [^{18}F]LW223 (**165**) is the most advanced TSPO radiotracer that is insensitive to the rs6971,[182,183] other than [^{11}C]PK11195 (**143**).

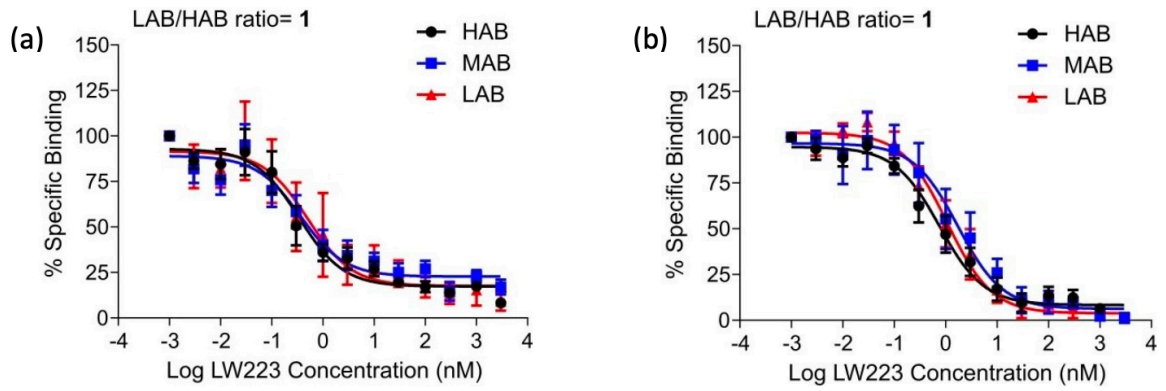


Figure 14: Mean LW223 (**165**) binding affinity curves in HAB (black), MAB (blue) and LAB (red) human brain (a) and heart (b) tissue. Adapted from *J. Nucl. Med.*, 2021, **62**, 536–544.[178]

3.1.3 Project Aims

While [^{18}F]LW223 (**165**) shows significant promise as a TSPO radiotracer, it was considered desirable to remove the rotamers that are observed by HPLC to ease pharmacological development. Additionally, we were keen to further understand the SAR of these compounds towards TSPO. Therefore, the primary aim of this project was to modify the structure of LW223 (**165**) to maintain, and if possible, improve the attractive *in vivo* characteristics while accelerating the rotation about the amide ring such that only one peak

was visible by HPLC. This would be achieved by the synthesis of a library of LW223 analogues with reduced steric bulk at the 3-position of the quinoline. The fluorine would be incorporated at alternative sites on the phenyl and quinoline moieties (Figure 15).

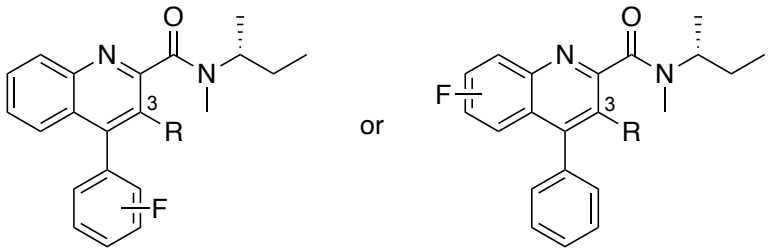
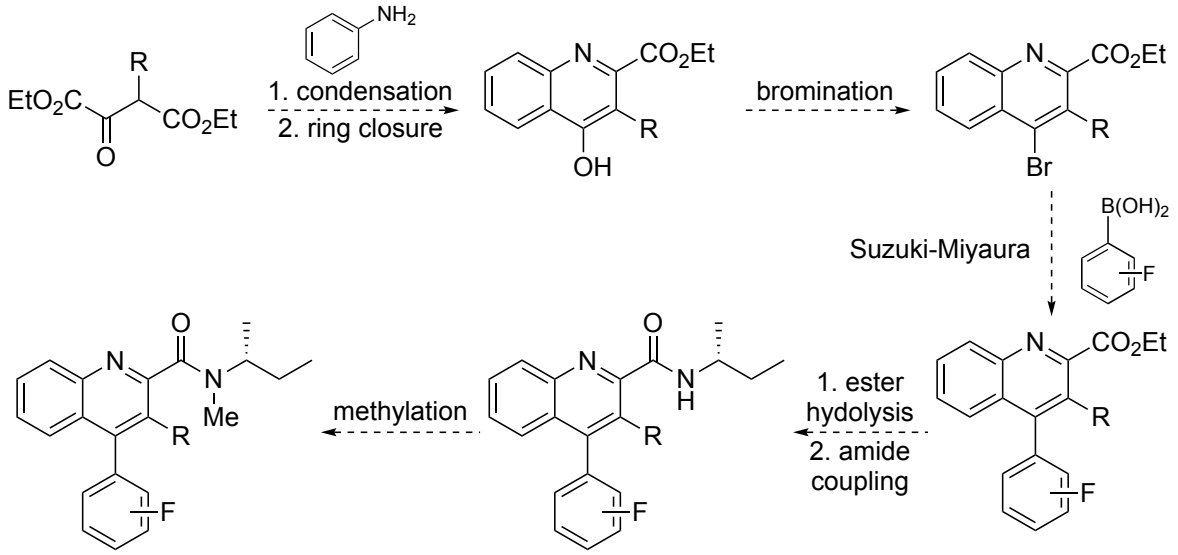


Figure 15: Proposed library of TSPO ligands.

The library of compounds would be ranked by HPLC screening to determine key characteristics such as P_m, K_m and %PPB. Compounds with favourable characteristics (P_m < 0.5, K_m < 250 and %PPB < 95%) would be evaluated in human brain and heart tissues to determine binding affinity to TSPO and the sensitivity of the compounds to the rs6971 polymorphism. For any lead compounds, a radiofluorination method would be devised which would require the synthesis of suitable precursors.

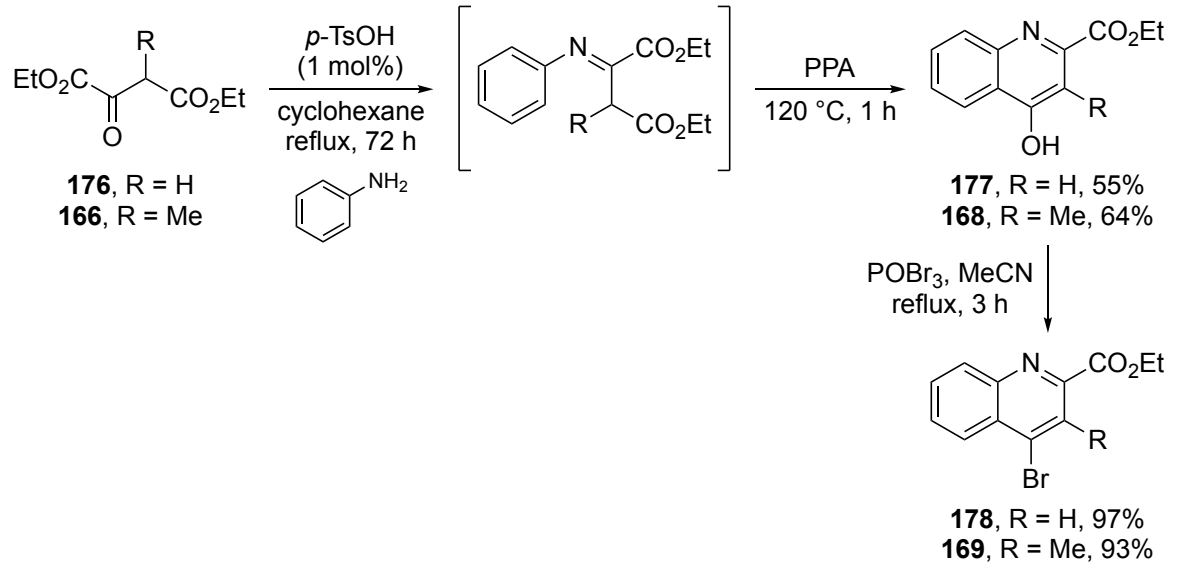
3.1.4 Synthesis and Evaluation of Potential TSPO Radiotracers

It was proposed that a library of LW223 analogues could be synthesised using a similar route to that used for [^{18}F]LW223 (**165**) (Scheme 107).[178] Aniline would be subjected to a condensation reaction with diethyl oxalacetate or diethyl oxalpropionate followed by acid-mediated ring closure and bromination to furnish 4-bromoquinolines. These would be coupled with a variety of boronic acids to give 4-(fluorophenyl)quinoline cores. Ester hydrolysis followed by amide coupling would yield 4-(fluorophenyl)quinoline-2-carboxamides. Finally, *N*-methylation would generate the potential TSPO ligands. The obvious disadvantage of this route, compared to that of [^{18}F]LW223 (**165**), is that the fluoride is not introduced in the final step so any promising compounds would require a separate radiosynthesis route.



Scheme 107: Proposed synthetic route to route to 4-(fluorophenyl)quinolines.

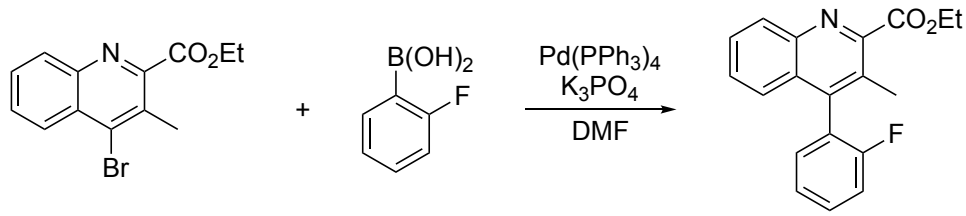
To generate the quinoline cores, the Combes quinoline synthesis was employed.[184,185] Diethyl oxalacetate (**176**) and diethyl oxalpropionate (**166**) were condensed with aniline in the presence of catalytic *p*-tosic acid under Dean-Stark conditions (Scheme 108). From previous work in the group,[174] it was known that these imines are unstable on silica gel and so they were used for the next step without further purification. This involved an acid-mediated cyclisation using neat polyphosphoric acid (PPA) to produce desmethyl and methyl 4-hydroyxquinolines **177** and **168** in 55% and 64% yields over the two steps, respectively. In preparation for the following Suzuki-Miyuara couplings, bromination was achieved by treatment with phosphorus(V) oxybromide to give 4-bromoquinolines **178** and **169** in excellent yields.



Scheme 108: Combes quinoline syntheses and subsequent brominations.

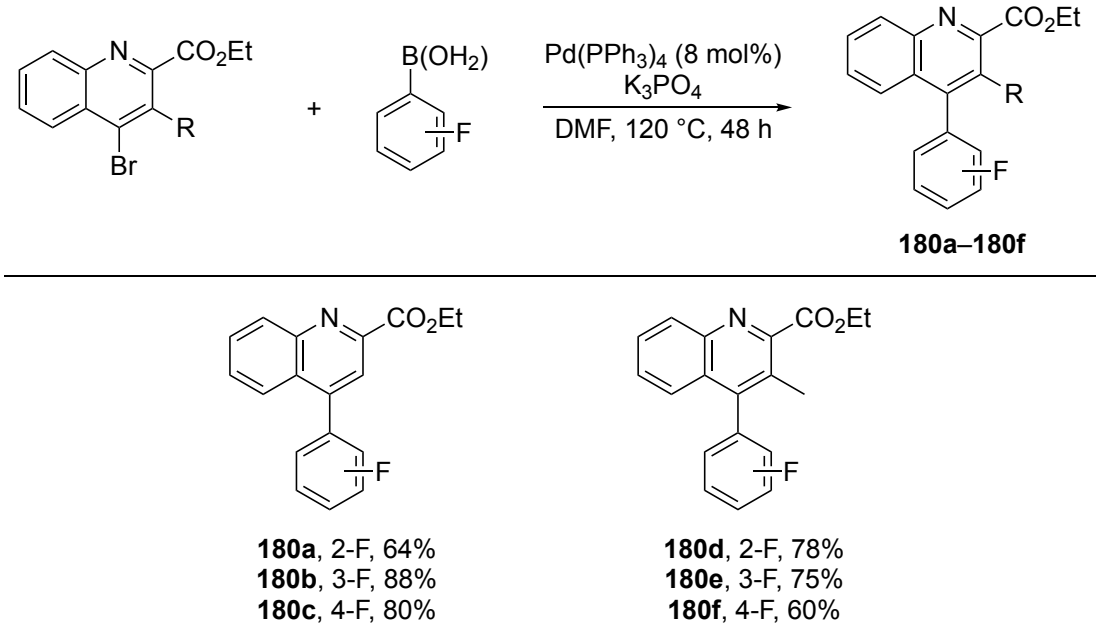
The next step was a Suzuki-Miyaura coupling. In the group, similar couplings had been achieved using *tetrakis*(triphenylphosphine)palladium(0) and potassium phosphate tribasic.[174,178] However, it was found that the use of these conditions for the coupling depicted in Table 6, which involved heating in DMF at 150 °C, resulted in poor yields due to decomposition of the product and starting material (entry 1). It was proposed that a lower temperature would minimise decomposition pathways. Therefore, the reaction was attempted at 95 °C (entry 2). Conversion was measured at 52% after 24 h using ^{1}H NMR spectroscopy, so additional portions of boronic acid (0.5 equiv.), base (0.5 equiv.) and catalyst (1 mol%) were added. This resulted in a minimal increase in conversion to 57% after a further 48 h, and **180d** was isolated in a yield of 46%. Next, the reaction was performed at 120 °C, with additional portions of boronic acid (1.5 equiv.), base (1.5 equiv.) and catalyst (3 mol%) added after 24 h. This gave 94% conversion after 48 h, with **180d** generated in 74% yield (entry 3). Finally, a small increase in initial and additional catalyst loading to 4% mol%, for a total of 8 mol%, gave full conversion and 78% yield (entry 4). With these optimised conditions, 4-bromoquinolines **178** and **169** were coupled with 2-, 3- and 4-fluorophenylboronic acids to furnish 4-(fluorophenyl)quinolines **180a**–**180f** in 64–88% yields (Scheme 109).

Table 6: Optimisation of Suzuki-Miyaura coupling between bromide **169** and boronic acid **179**.



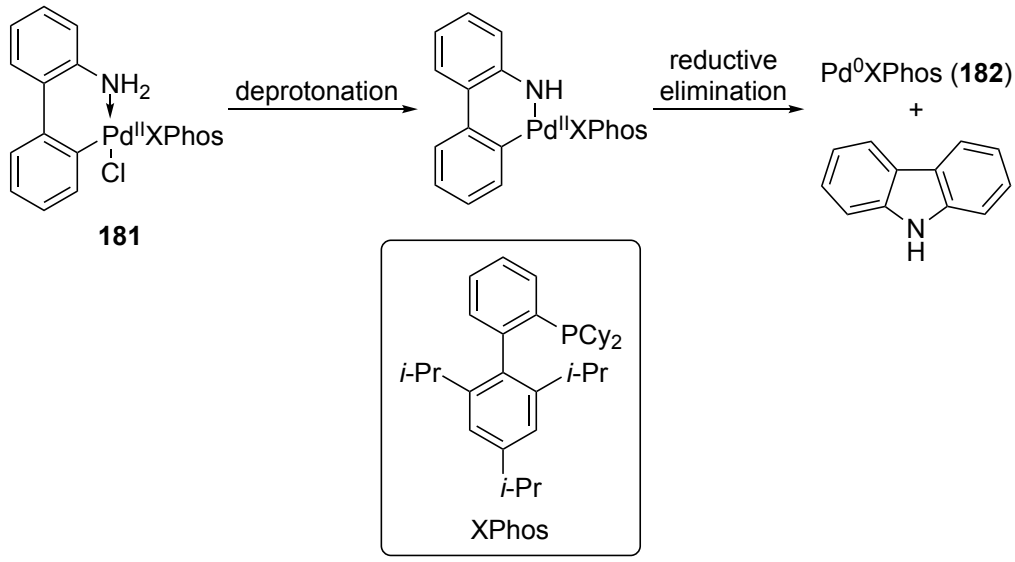
169 **179** **180d**

Entry	Time (h)	Temperature (°C)	Equivalents of 179/K_3PO_4	Catalyst loading (mol%)	Yield (%)
1	18	150	1.5	3	44
2	72	95	2.0	4	46
3	48	120	3.0	6	74
4	48	120	3.0	8	78



Scheme 109: Suzuki-Miyaura couplings using optimised conditions.

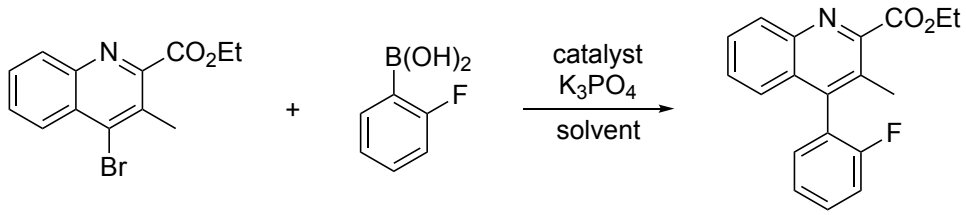
While the conditions reliably gave good to excellent yields, limitations included long reaction times, high temperatures and catalyst loadings and the requirement for 3 equivalents of boronic acid, due to protodeboronation. For these reasons XPhos Pd G2 (**181**), an air stable palladium source developed by Buchwald and co-workers was considered.[186] On exposure to mild base at room temperature, the amine is readily deprotonated and carbazole is reductively eliminated to generate the active XPhosPd(0) species (**182**), which was shown to rapidly catalyse challenging Suzuki-Miyaura couplings at low temperatures (Scheme 110).



Scheme 110: Proposed mechanism of activation of XPhos Pd G2 (**181**).

Buchwald's conditions were tested on a known reaction – the coupling of bromide **169** with 2-fluorophenylboronic acid (**179**). The previous reaction with $Pd(PPh_3)_4$ had given **180d** in 78% yield, (Table 7, entry 1). With only 1.5 equivalents of the boronic acid and 3 mol% of XPhos Pd G2, the reaction was complete after 4 h in THF/water at 40 °C, with **180d** isolated in a similar yield (entry 2).

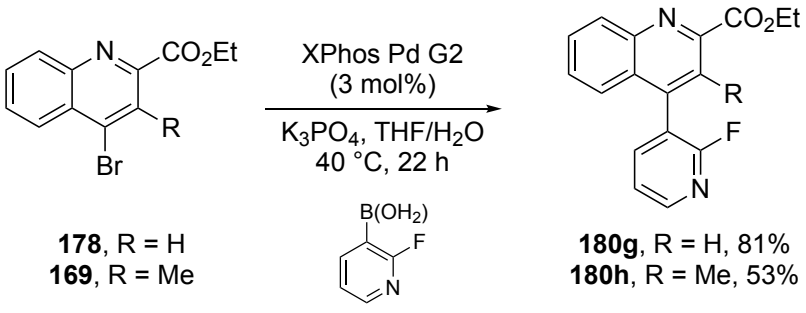
Table 7: Suzuki-Miyaura coupling using $Pd(PPh_3)_4$ or XPhos Pd G2.



169 **179** **180d**

Entry	Catalyst (mol%)	Solvent	Time (h)	Temperature (°C)	Equivalents of 179	Yield (%)
1	$Pd(PPh_3)_4$ (8)	DMF	48	120	3.0	77
2	XPhos Pd G2 (3)	THF/H_2O	4	40	1.5	73

These milder conditions were used for the remaining two couplings. It was proposed that by installing a fluoropyridyl substituent, the lipophilicity of the final compound would be reduced and physicochemical properties improved. Therefore, bromides **178** and **169** were coupled with 2-fluoro-3-pyridineboronic acid. It was found that for these couplings, the optimal results were obtained if the catalyst was added in two portions of 1.5 mol%, 4 h apart, before being stirred for a further 18 h (Scheme 111). For desmethyl compound **180g**, a yield of 81% was recorded while **180h** was generated in a lower yield of 53%, due to incomplete conversion.



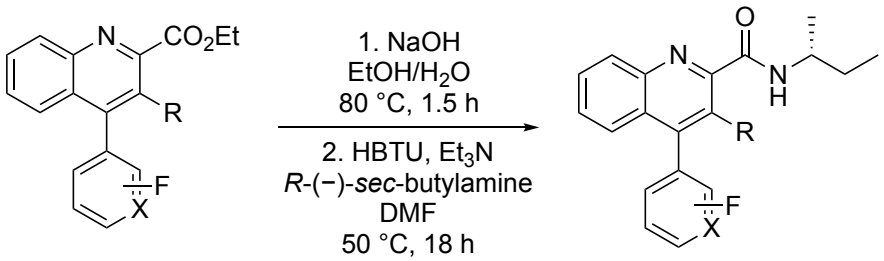
178, R = H
169, R = Me

180g, R = H, 81%
180h, R = Me, 53%

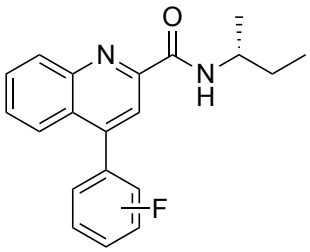
Scheme 111: Suzuki-Miyaura couplings with 2-fluoro-3-pyridineboronic acid.

The 8 esters were then subjected to ester hydrolysis in preparation for amide couplings with (*R*)-(−)-*sec*-butylamine (Scheme 112).[178] Over the two steps, the yields ranged from 61–

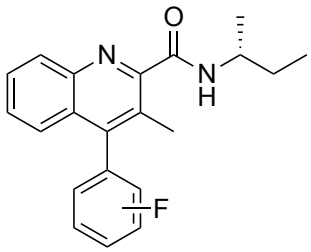
88%. Finally, the amides were *N*-methylated using sodium hydride and methyl iodide to generate final compounds **184a**–**184h** in good to excellent yields (Scheme 113).



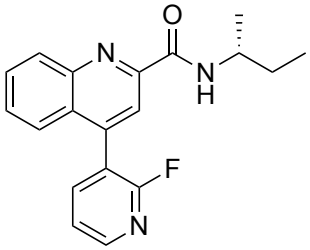
180a–**180h** **183a**–**183h**



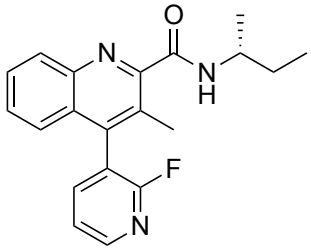
183a, 2-F, 65%
183b, 3-F, 87%
183c, 4-F, 61%



183d, 2-F, 81%
183e, 3-F, 86%
183f, 4-F, 65%

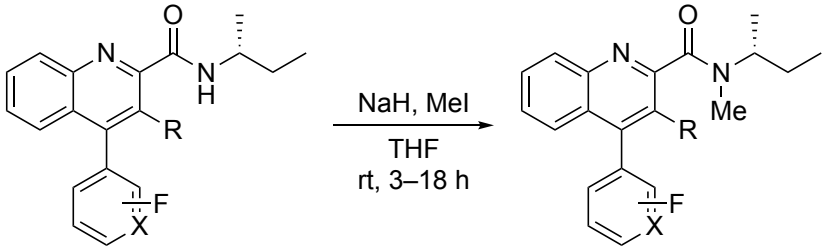


183g, 71%

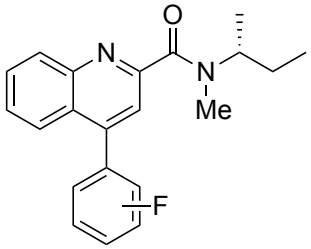


183h, 77%

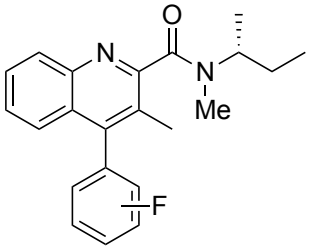
Scheme 112: Ester hydrolysis and amide coupling of esters **180a**–**180h**.



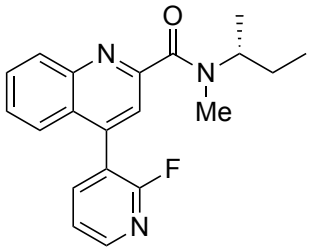
183a–**183h** **184a**–**184h**



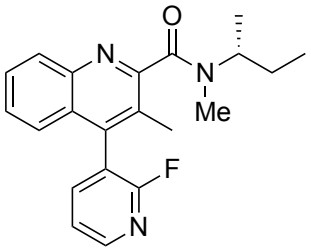
184a, 2-F, 72%
184b, 3-F, 82%
184c, 4-F, 72%



184d, 2-F, 89%
184e, 3-F, 94%
184f, 4-F, 80%



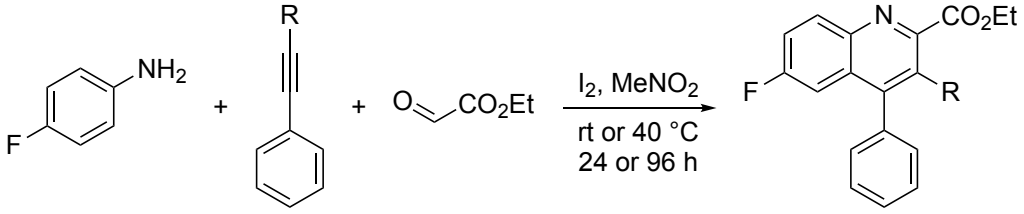
184g, 79%



184h, 86%

Scheme 113: *N*-Methylation of amides **183a**–**183h**.

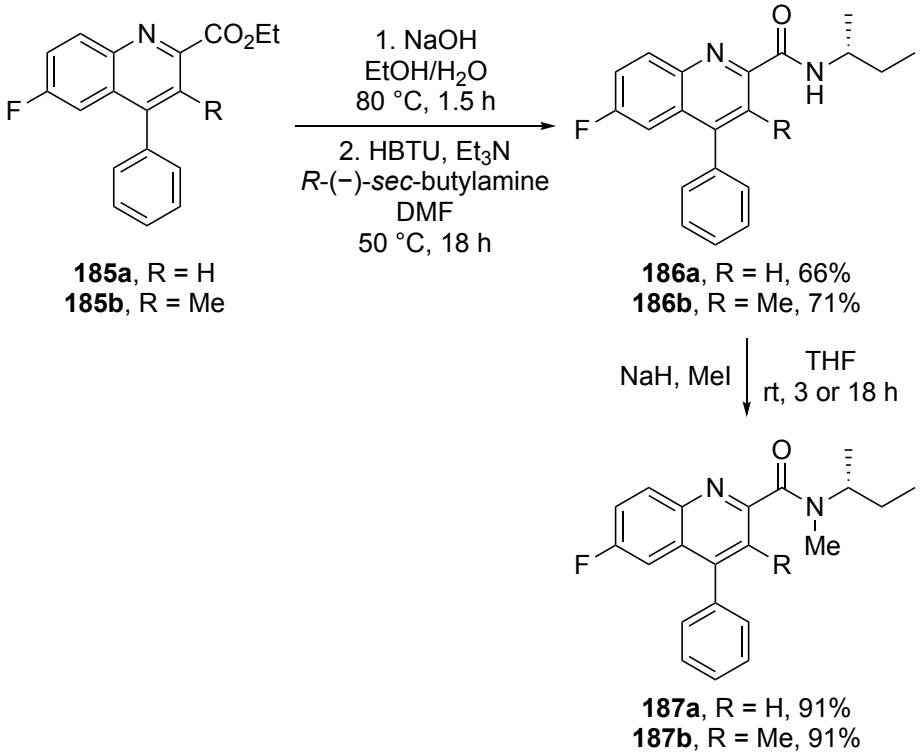
The next step in this project was to synthesise compounds with the fluorine incorporated into the quinoline core. A one-pot reaction involving 4-fluoroaniline, ethyl glyoxylate and phenylacetylene or 1-phenyl-1-propyne catalysed by molecular iodine was utilised to furnish quinoline-2-carboxylates **185a** and **185b** (Scheme 114).[187] This was first attempted with phenylacetylene to give desmethyl compound **185a**. However, this generated a complex mixture containing starting materials, side-products and the desired product, which was isolated in a yield of 21%. Attempts to optimise the reaction involved using higher temperatures, extended reaction times, anhydrous conditions and more equivalents of ethyl glyoxylate. However, none of these variations led to an improvement in the yield of **185a**. The reaction with 1-phenyl-1-propyne was less efficient. It was found that a temperature of 40 °C was necessary to fully convert the imine intermediate to the desired product **185b**, which was isolated in 16% yield. Nonetheless, enough material was obtained to proceed to the later steps. If these compounds prove to be promising, further attempts can be made to optimise this reaction or explore alternative synthetic routes.



185a, R = H, 21%
185b, R = Me, 16%

Scheme 114: Iodine-mediated one-pot synthesis of quinoline-2-carboxylates **185a** and **185b**.

The two compounds were then subjected to the same synthetic sequence previously described (Scheme 115). The hydrolysis and amide coupling proceeded in overall yields of 66% and 71% for **186a** and **186b**, respectively. *N*-Methylation then gave final compounds **187a** and **187b**, both in yields of 91%.



185a, R = H
185b, R = Me

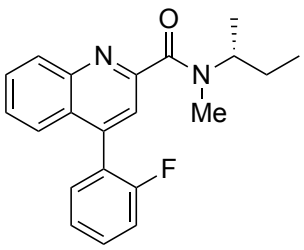
186a, R = H, 66%
186b, R = Me, 71%

187a, R = H, 91%
187b, R = Me, 91%

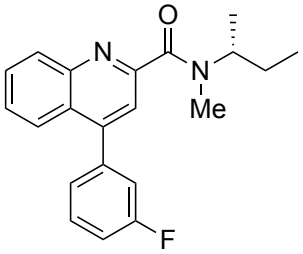
Scheme 115: Synthesis of final compounds **187a** and **187b**.

The physicochemical properties of all ten compounds were then screened by HPLC methodology (Figure 16).[176] Membrane partition coefficient, K_m, represents the distribution of a compound between the aqueous phase and a membrane. This was determined using an immobilised artificial membrane column. Permeability, P_m, is related to K_m and is dependent on the size of the compound. This represents how easily a compound can travel through a membrane *via* passive diffusion – smaller compounds are able to pass through membranes more readily. Finally, the percentage of plasma protein binding, %PPB, was determined using a column coated with human serum albumin. The ideal characteristics for

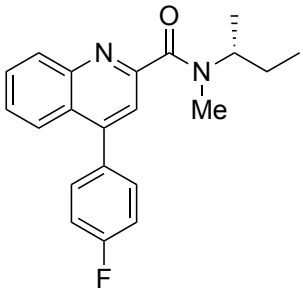
a CNS radiotracer were determined by Tavares and co-workers to be: P_m < 0.5, K_m < 250 and %PPB < 95%.[176] As expected, the two compounds with 2-fluoropyridyl rings, **184g** and **184h**, have the most optimal physicochemical properties, but all compounds have properties within, or close to, the ideal values. This indicates that these candidates are more likely to penetrate the blood brain barrier. In addition, all the desmethyl compounds showed only a single peak by HPLC. This was a key aim of this project and if any compounds prove to be viable radiotracers, some of the issues associated with [^{18}F]LW223 **165** may be avoided.



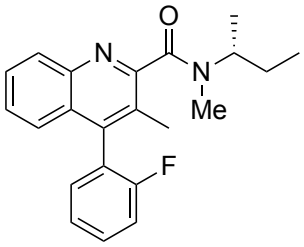
184a
P_m = 0.447
K_m = 150
%PPB = 97.1%
1 peak in HPLC
logP: 4.9



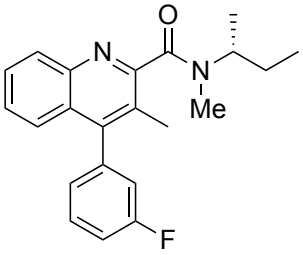
184b
P_m = 0.517
K_m = 173
%PPB = 97.4%
1 peak in HPLC
logP: 4.9



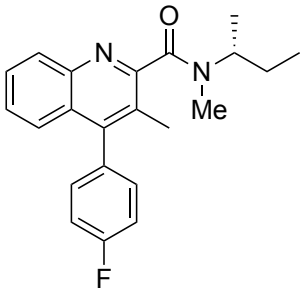
184c
P_m = 0.504
K_m = 169
%PPB = 96.9%
1 peak in HPLC
logP: 4.9



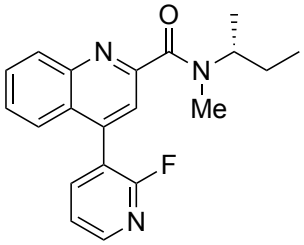
184d
P_m = 0.456
K_m = 160
%PPB = 97.2%
2 peaks in HPLC (64:36)
logP: 5.38



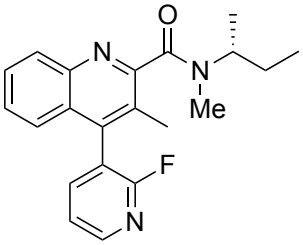
184e
P_m = 0.518
K_m = 181
%PPB = 97.9%
2 peaks in HPLC (60:40)
logP: 5.38



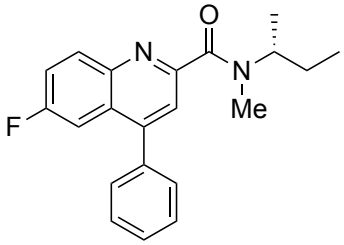
184f
P_m = 0.509
K_m = 178
%PPB = 97.1%
2 peak in HPLC (67:33)
logP: 5.38



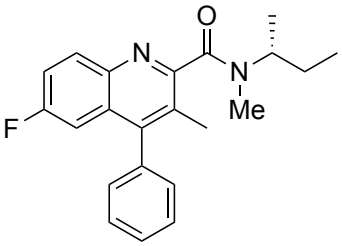
184g
P_m = 0.142
K_m = 48
%PPB = 86.5%
1 peak in HPLC
logP: 4.03



184h
P_m = 0.136
K_m = 48
%PPB = 86.3%
2 peaks in HPLC (51:49)
logP: 4.51



187a
P_m = 0.524
K_m = 176
%PPB = 98.3%
1 peak in HPLC
logP: 4.9



187b
P_m = 0.550
K_m = 193
%PPB = 98.6%
2 peaks in HPLC (62:38)
logP: 5.38

Figure 16: Physicochemical properties of compounds **184a**–**187b**. logP was calculated using ChemDraw 20.0.

Similarly to LW223 (**165**), all compounds showed two rotamers in ^{1}H and ^{13}C NMR spectra. Furthermore, the compounds bearing *meta*- or *ortho*-fluorine atoms in addition to quinoline methyl groups (**184d**, **184e** and **184h**) showed an additional set of peaks (Figure 17). It was proposed that these are the result of restricted rotation about the C–C bonds between the two aryl rings, caused by steric repulsion between the fluorine and methyl substituents. Thus, there are additional sets of diastereomers. This phenomenon has also been observed with [^{11}C]PK11195 (**143**).[188]

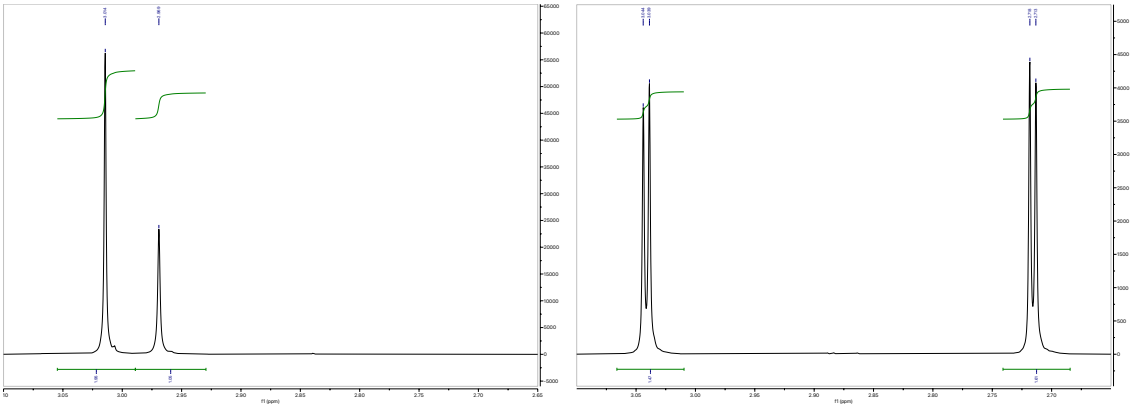
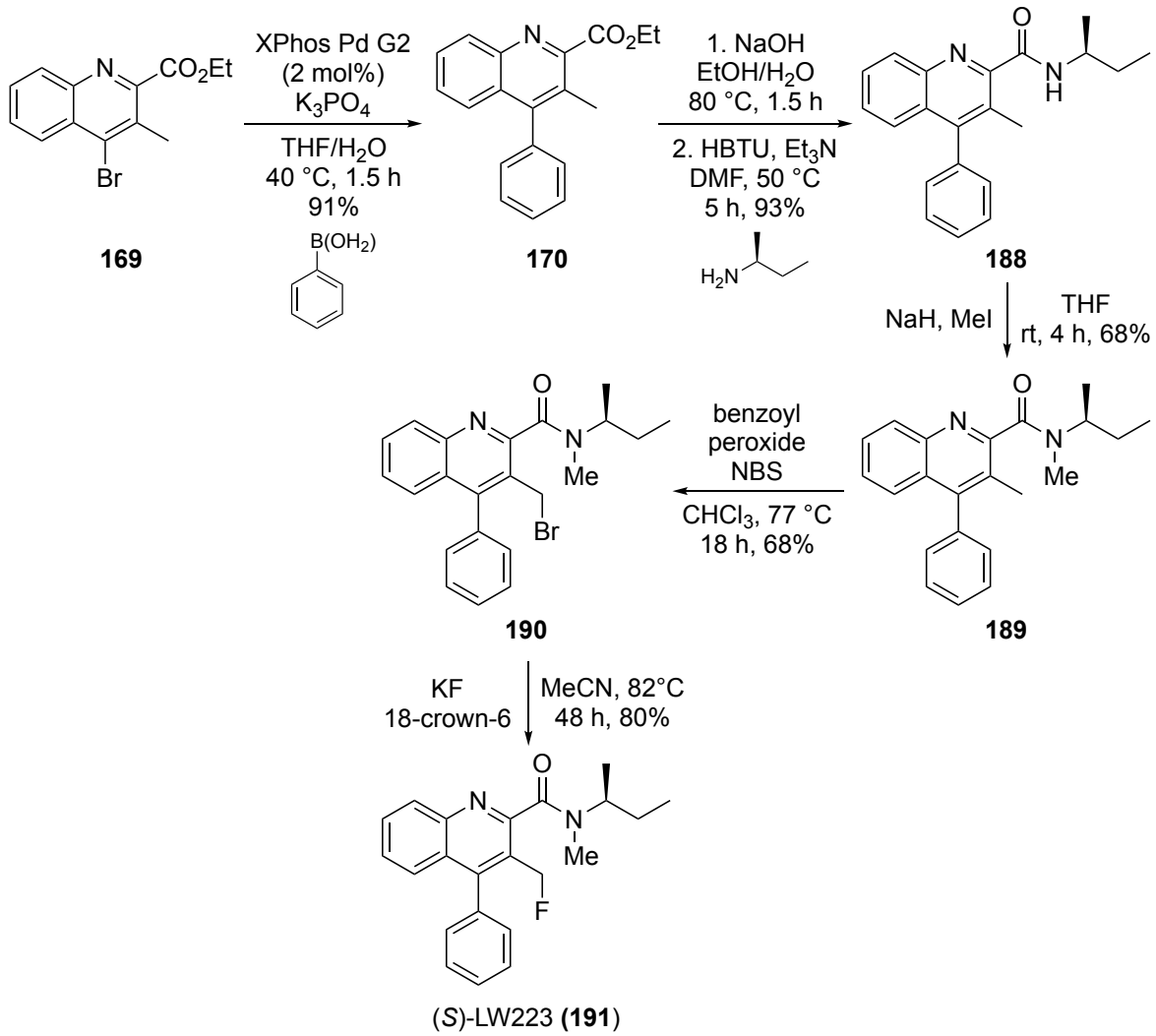


Figure 17: ^{1}H NMR spectra of compounds **184g** (left) and **184h** (right) showing the peaks for the *N*-methyl group.

Future work will determine the binding affinity to TSPO of this library of compounds and sensitivity to the rs6971 polymorphism using human brain and heart tissue. For any lead compound, a new synthetic route for the radiosynthesis of this potential radiotracer will then be devised.

3.1.5 Synthesis of (*S*)-LW223

To support the development of [^{18}F]LW223 (**165**), which is the *R*-enantiomer, it was necessary to synthesise the *S*-enantiomer **191** to establish the difference between the two regarding binding affinity and sensitivity to the rs6791 polymorphism. The first four steps to furnish *N*-methylated amide **189** from bromide **169** were analogous to the previously described synthetic route, with (*S*)-(+)-*sec*-butylamine used instead of (*R*)-(−)-*sec*-butylamine (Scheme 116). Next, a radical bromination using benzoyl peroxide and NBS installed the bromide at the benzylic position in 68% yield.[178] Nucleophilic substitution with potassium fluoride in the presence of 18-crown-6 then produced (*S*)-LW223 (**191**) in 80% yield.



Scheme 116: Synthesis of (*S*)-LW223 (**191**).

Evaluation of (*S*)-LW223 (**191**) in human brain tissue by our collaborators at the University of Edinburgh showed that it had a TSPO K_i of 4.50 and a LAB:HAB 1.5:1 (Figure 18). This compares to values of 0.60 and 1:1, respectively, for (*R*)-LW223 (**165**). Thus, (*R*)-LW223 (**165**) is significantly more potent and less sensitive to the polymorphism than (*S*)-LW223 (**191**).

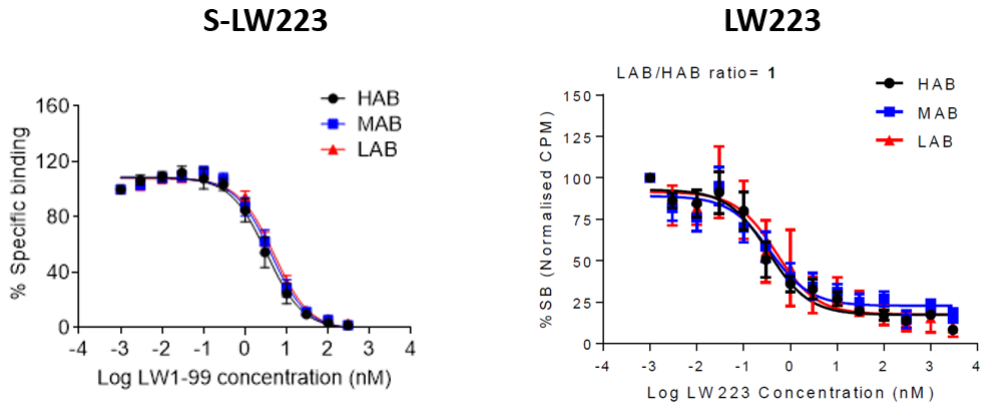


Figure 18: Mean binding affinity curves for (*S*)-LW223 (**191**) (left) and (*R*)-LW223 (**165**) (right) in HAB (black), MAB (blue) and LAB (red) human brain tissue.

3.1.6 Conclusions

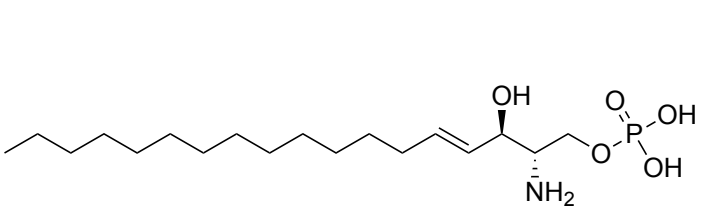
In summary, a library of ten analogues of LW223 have been synthesised, with fluorine incorporated at various positions of the phenyl ring and quinoline core. The physicochemical properties of these compounds have been determined using HPLC methodology and their characteristics regarding rotamers and diastereomers have been probed using ^{1}H NMR spectroscopy. These compounds will be evaluated in human brain and heart tissue to determine binding affinity to TSPO and sensitivity to the rs6971 polymorphism. For any promising ligands, a new route for their radiosynthesis will be devised. The epimer of LW223 was also synthesised and it was found to have a significantly lower binding affinity to TSPO.

3.2 Development of a Novel PET Imaging Agent for the $S1P_5$ Receptor

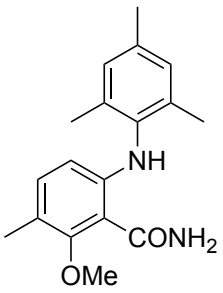
3.2.1 Introduction

Sphingosine-1-phosphate (S1P, **192**) (Figure 19) is a lysophospholipid derived from the cell membrane that acts as an extracellular signal. S1P is involved in several cellular processes including cell growth and apoptosis in the CNS, the cardiovascular system and the immune system.[189] It influences these processes by activation of a set of G-protein coupled receptors (GPCRs): $S1P_1$–$S1P_5$, all of which it binds to with low nanomolar affinities. The five receptors are expressed independently in different cells and tissues. Specifically, $S1P_5$ is expressed in neural and glial cells.[190] Importantly, its distribution indicates that it may play a role in the regulation of the myelination and demyelination processes.[191] The disruption of this process is thought to be one of the key causes of multiple sclerosis (MS).[192] Crucially, activation of $S1P_5$ by S1P (**192**) has been shown to promote the survival of mature oligodendrocytes, which play a key role in the repair of myelin after demyelination. Therefore, selective agonists of $S1P_5$ could potentially be used for the treatment of MS.

In 2010, Mattes and co-workers reported the synthesis of a library of benzamide $S1P_5$ agonists.[193] The most promising candidate **193** (Figure 19) showed an EC_{50} of 2.0 nM for $S1P_5$, and 476 and 373 nM for $S1P_1$ and $S1P_4$, respectively, demonstrating both potency and selectivity for $S1P_5$.



S1P (**192**)

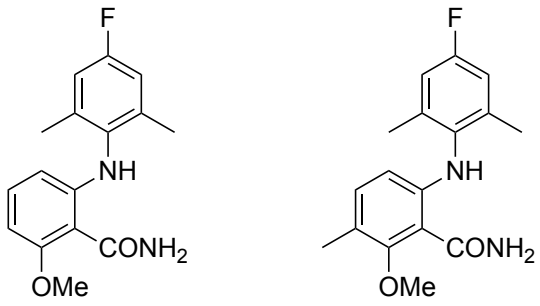


193

Figure 19: Sphingosine-1-phosphate (**192**) and $S1P_5$ agonist **193**.

It was proposed by the Sutherland group that a PET radiotracer for the $S1P_5$ could be developed by modifying the structures of the compounds synthesised by Mattes and co-workers to introduce a fluorine at a suitable location.[181] This radiotracer could be used to further understand the role that the $S1P_5$ receptor plays in the demyelination process. Based on analysis of docking experiments disclosed in the publication, it was hypothesised that the optimal position to incorporate a fluorine would be in the place of the *para*-methyl group in the upper ring. A library of compounds with fluorine at the *para*-position was synthesised,

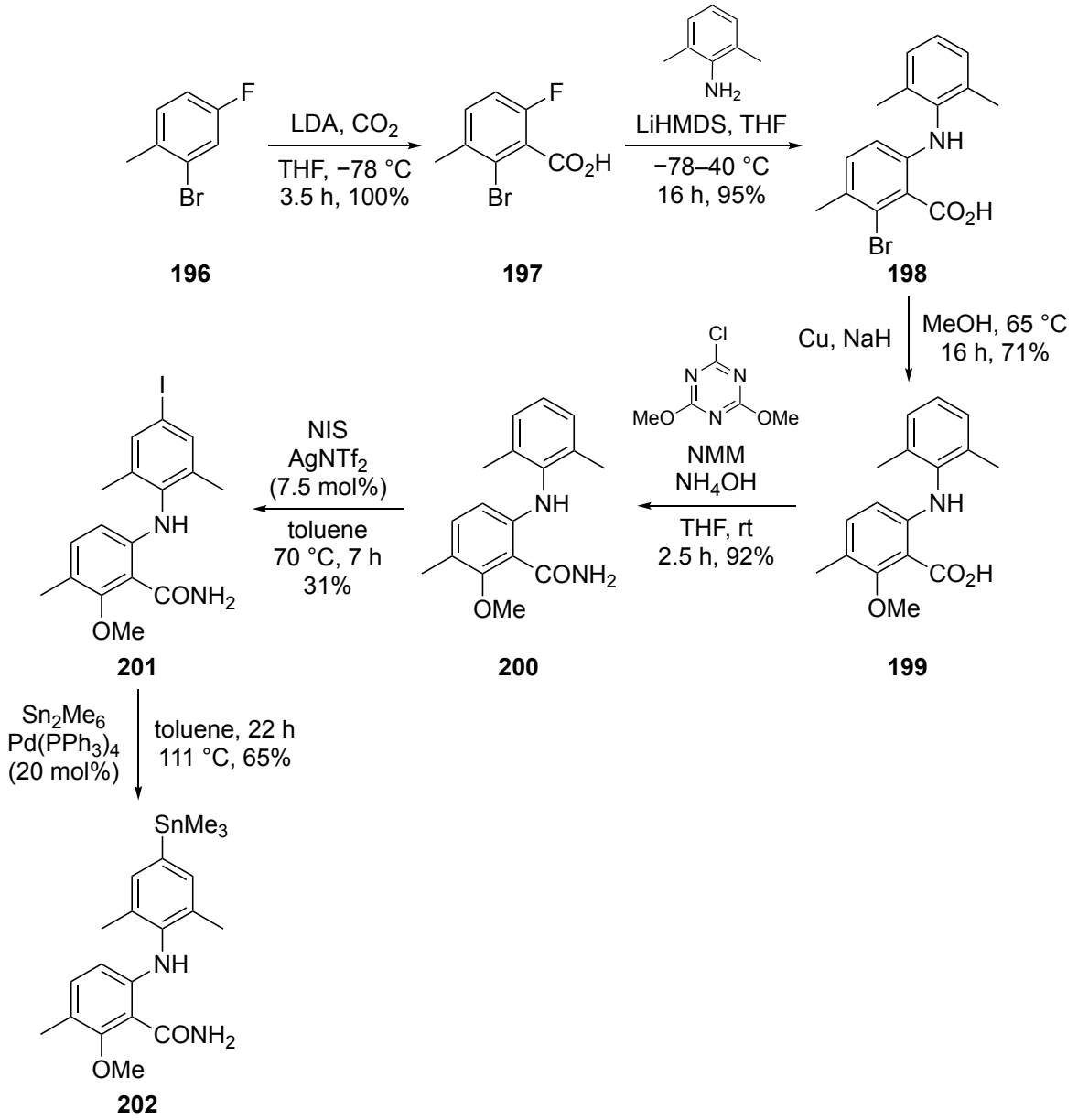
and two compounds, **194** and **195**, (Figure 20) were found to exhibit good potency for $S1P_5$ (EC_{50} = 39.8 nM and 22.3 nM, respectively) and relatively low affinities for other S1P receptors.



194 **195**

Figure 20: $S1P_5$ lead compounds **194** and **195**.

Compound **194** was considered to be the lead compound due to its near-complete lack of affinity for other S1P receptors but attempts to synthesise a precursor for radiosynthesis proved unsuccessful. Compound **195** displayed a EC_{50} of 104 nM for $S1P_1$, but it was still considered to have potential as a radiotracer and thus, a synthetic route to organotin radiofluorination precursor **202** was successfully developed (Scheme 117).[140,181] However, this route suffered from a poor overall yield of 13% over 6 steps, largely due to the inefficiency of the penultimate iodination step. Moreover, this route had not been scaled up, with only 48 mg of organotin compound **202** produced.



Scheme 117: Synthesis of organotin precursor **202**.

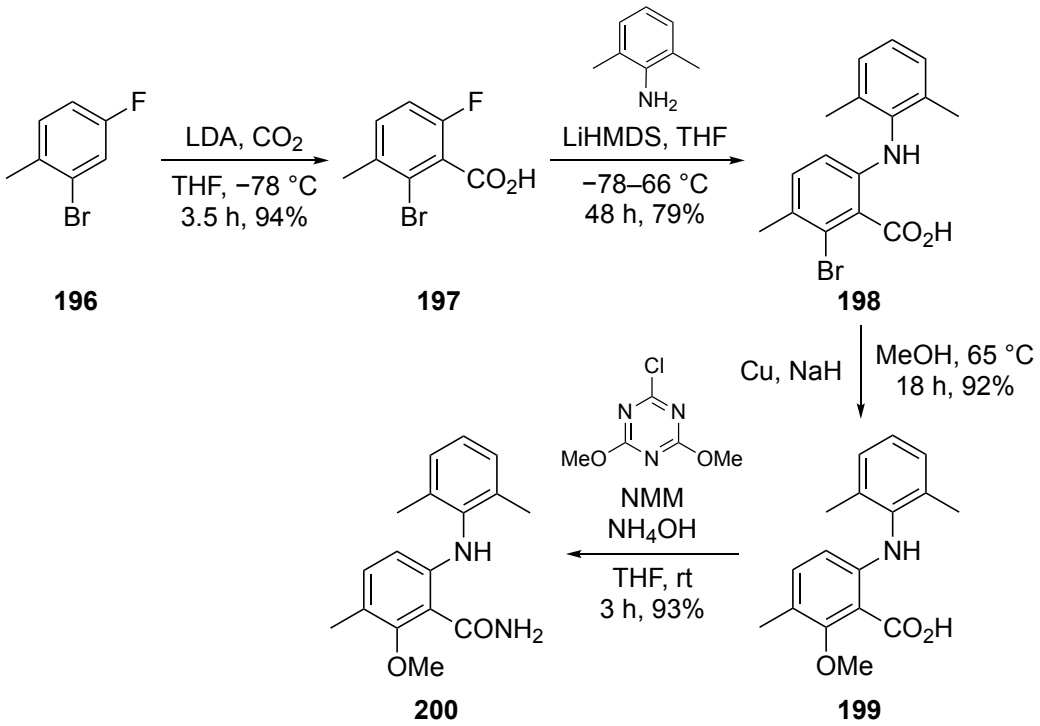
3.2.2 Project Aims

The first aim of this project was to optimise the route to organotin precursor **202**. Once this was achieved, the route would be scaled up to produce sufficient quantities of the precursor to enable comprehensive radiosynthesis studies and PET experiments in rodents. Finally, an alternative boronate precursor would be generated to avoid the use of the potentially toxic organotin precursor and allow the investigation of new radiosynthesis methods.

3.2.3 Synthesis of the Radiosynthesis Precursors

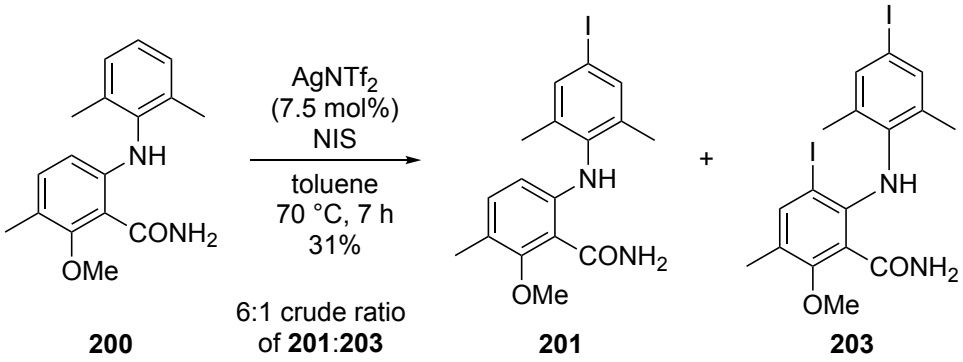
For the first four steps, the conditions previously described were used.[140,181] 2-Bromo-4-fluorotoluene (**196**) was deprotonated using lithium diisopropylamide and reacted with CO_2

to give acid **197** in 94% yield (Scheme 118).[194] An S_NAr reaction with 2,6-dimethylaniline using lithium bis(trimethylsilyl)amide as the base then generated **198** in 79% yield. This was followed by an Ullmann condensation to introduce the methoxy group in 92% yield.[193] Next, amidation with 2-chloro-4,6-dimethoxy-1,3,5-triazine,[193] *N*-methylmorpholine and ammonium hydroxide generated benzamide **200** in 93% yield.



Scheme 118: Synthetic route to amide **200**.

The silver triflimide-catalysed iodination had previously been attempted using methodology developed within the Sutherland group.[195] Unfortunately, the reaction was unselective, forming desired product **201** and di-iodinated side-product **203** in a 6:1 ratio (Scheme 119). Moreover, only 86% conversion was achieved, despite the use of 1.5 equivalents of NIS. The lack of full conversion proved troublesome as the starting material was inseparable from the desired product using flash chromatography. This necessitated the use of an additional recrystallisation step and **201** was isolated in a 31% yield. It was found that using additional equivalents of NIS did not improve conversion and only resulted in the formation of more of the di-iodinated compound.

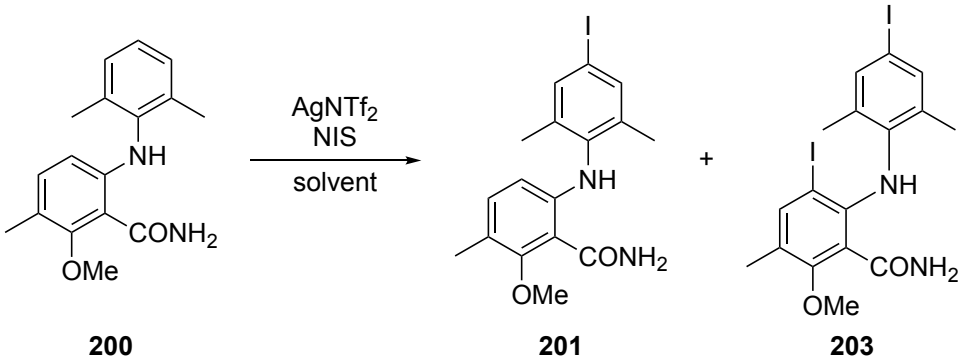


200 **201** **203**

Scheme 119: Previously attempted iodination of **200**.

Initial optimisation varied NIS quantities and catalyst loading. However, these attempts led to no improvement in the yield of **201** or amount of side-product **203** formed. It was thought that the relative insolubility of both the starting material and NIS in toluene was contributing to the low yields. Therefore, alternative solvents were considered. Chloroform was less effective as a solvent and required increased amounts of NIS (1.85 equiv.) to achieve 80% conversion, despite the lack of di-iodination (Table 8, entry 2). This was due to the formation of other unidentified side-products. However, THF resulted in an improved reaction and required only 1.4 equivalents of NIS, which led to 91% conversion in 0.5 h. Iodide **201** was isolated in 53% yield (entry 3). It was found that reducing the temperature from 70 °C to room temperature gave full conversion in 3 h (entry 4). Although the selectivity was poorer using these conditions, the full conversion meant that no recrystallisation step was required and the yield was identical to entry 3. Therefore, these conditions were deemed optimal.

Table 8: Optimisation of the iodination of **200**.

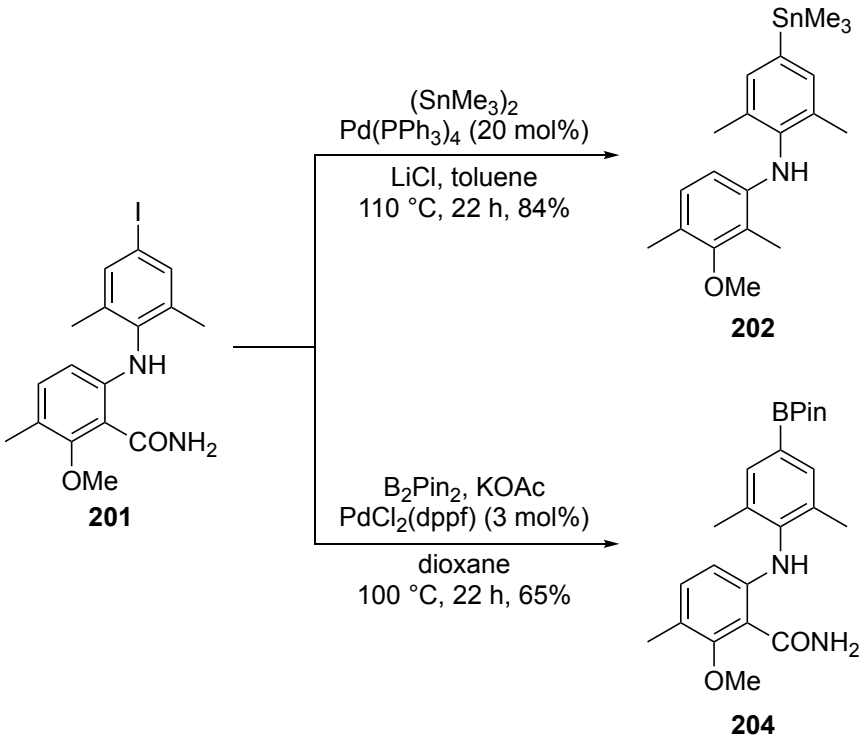


200 **201** **203**

Entry	NIS equiv.	Solvent	Temperature (°C)	Time (h)	Conversion (%)[a]	Ratio of 201:203
1	1.6	Toluene	70	5.5	79 (24)	6:1
2	1.85	$CHCl_3$	70	7	80 (22)	N/A
3	1.4	THF	70	0.5	91 (53)	4:1
4	1.4	THF	20	3	100 (53)	2:1

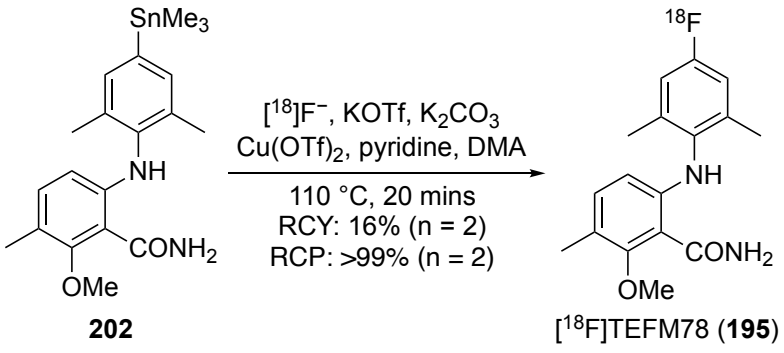
[a] Isolated yields in parentheses

With the iodination optimised, the tin and boron precursors were then synthesised (Scheme 120). Organotin compound **202** was furnished using a stannylation reaction involving $Pd(PPh_3)_4$ (20 mol%) and hexamethylditin in the presence of lithium chloride.[196] This gave **202** in 84% yield. For the synthesis of **204,** a Miyaura borylation was employed.[197] Using $PdCl_2$(dppf) (3 mol%), *bis*(pinacolato)diboron and potassium acetate, the desired product **204** was generated in 65% yield.



Scheme 120: Synthesis of organotin and organoboron precursors **202** and **204**.

The radiofluorination of organotin precursor **202** to produce [^{18}F]**195**, which was named [^{18}F]TEFM78, was performed by our collaborators at the University of Edinburgh in 16% RCY (Scheme 121). The molar activity of 229 GBq/μmol (n = 2) was sufficient to conduct initial experiments in rodents, which showed that [^{18}F]TEFM78 (**195**) is able to penetrate the blood brain barrier (Figure 21).



Scheme 121: Radiosynthesis of [^{18}F]TEFM78 (**195**).

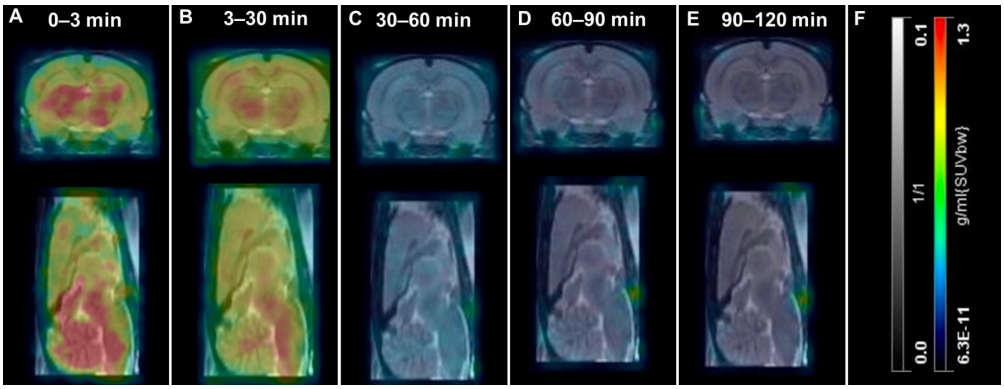
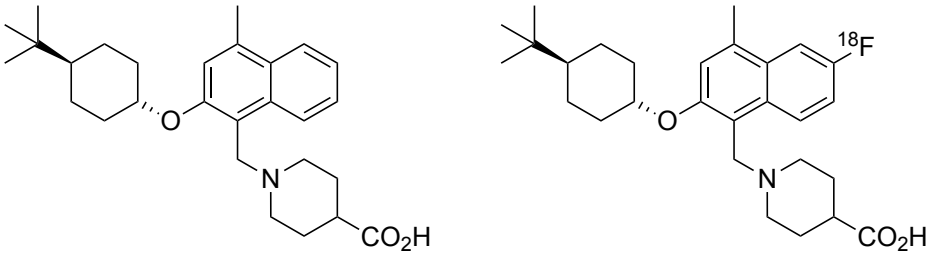


Figure 21: Uptake of [^{18}F]TEFM78 (**195**) in the brain and spine of a rodent. The radiotracer accumulates in the CNS from 0–30 minutes, before being eliminated from 30–120 minutes.

3.2.4 Conclusions and Future Work

In summary, the synthetic route to [^{18}F]TEFM78 (**195**) has been scaled up, with optimisation of the key iodination step achieved. Using the optimised route, organotin and organoboron precursors have been synthesised and are currently being used by our collaborators for radiosynthesis and testing in animals. Future work will involve further development of [^{18}F]TEFM78 as a PET imaging agent, and optimisation of the radiofluorination step using the boronate precursor.

In 2021, the first antagonist **205** for $S1P_5$ was reported by Ma and co-workers (Figure 22).[198] It has been proposed that a fluorinated analogue, such as compound **206**, could provide another valuable tool for studying $S1P_5$ using PET imaging. Synthesis of this compound is underway in our group.



205 **206**

Figure 22: $S1P_5$ antagonist **205** and proposed fluorinated analogue **206**.

4.0 Experimental

4.1 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 performed using Merck Millipore matrix silica gel 60 (40–63 μm). Merck aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) 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 using a Bruker Microtof-q for ESI, Agilent 6125B for ESI and APCI, and JEOL JMS-700 for EI and CI. 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}. 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.

4.2 Thiocyanation Experimental

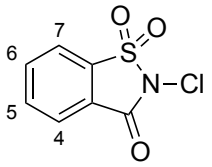
General Procedure A: Thiocyanation of Arenes

To a solution of *N*-thiocyanatosaccharin (**60**) (0.0960 g, 0.400 mmol) and iron(III) chloride (0.0014 g, 0.00832 mmol, 2.5 mol%) in dry dichloromethane (2 mL) under argon was added the arene (0.333 mmol). The reaction mixture was stirred at 40 °C in the absence of light for the required time. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 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 gave the desired product.

Time Dependent NMR Studies

To a solution of *N*-thiocyanatosaccharin (**60**) (0.0960 g, 0.400 mmol) in dry dichloromethane (2 mL) under argon was added anisole (0.036 mL, 0.333 mmol) and dimethyl terephthalate (0.0065 g, 0.0333 mmol). An aliquot was removed and NMR spectrum recorded prior to the addition of catalyst for internal standard calibration. The catalyst was added and the reaction mixture was stirred at 40 °C in the absence of light for the required time. Aliquots (~0.05 mL) were removed at the appropriate time points, diluted in $CDCl_3$ (0.7 mL) and filtered through a short pad of celite. Spectra were recorded and conversion was determined by comparison of the integrals of anisole peaks with dimethyl terephthalate peaks.

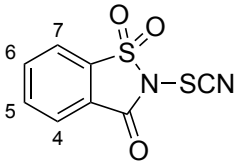
N-Chlorosaccharin (75)[199]



To a solution of saccharin (10.0 g, 54.6 mmol) in methanol (400 mL) was added sodium methoxide (2.95 g, 54.6 mmol). The reaction mixture was stirred at 65 °C for 1 h. The reaction mixture was then concentrated *in vacuo* to give sodium saccharin salt (10.6 g) as a white solid. Sodium carbonate (2.72 g, 25.7 mmol), potassium chloride (3.84 g, 51.4 mmol) and water (250 mL) were added to the saccharin salt. Oxone (31.6 g, 51.4 mmol) was dissolved in water (50 mL) and slowly added at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was filtered, washed with cold water and dried under high vacuum to give *N*-chlorosaccharin (**75**) as a white solid (8.90 g, 79%). Mp 153–156 °C (lit.[199] 146–148 °C); δ_H (400 MHz, $CDCl_3$) 7.87–8.00 (3H, m, 4-H, 5-H and 6-

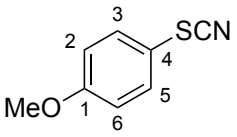
H), 8.10–8.15 (1H, m, 7-H); δ_C (101 MHz, $CDCl_3$) 121.9 (CH), 125.9 (CH), 126.7 (C), 135.1 (CH), 135.6 (CH), 137.9 (C), 156.8 (C); *m/z* (ESI) 182 ([M−Cl]$^-$. 100%).

_N_-Thiocyanatosaccharin (60)[92]



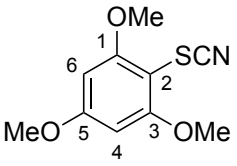
An oven-dried flask was flushed with argon and charged with *N*-chlorosaccharin (**75**) (1.09 g, 5.00 mmol), silver(I) thiocyanate (1.03 g, 6.25 mmol) and dry dichloromethane (50 mL). The reaction mixture was stirred at room temperature in the absence of light for 0.5 h. The reaction mixture was filtered through a short pad of Celite®, washed with dry dichloromethane (2 × 20 mL) and concentrated *in vacuo* to give *N*-thiocyanatosaccharin (**60**) (1.12 g, 93%). Mp 224–226 °C (lit.[92] 227 °C); δ_H (400 MHz, $CDCl_3$) 7.93–7.99 (1H, m, 6-H), 8.00–8.06 (2H, m, 4-H and 5-H), 8.21 (1H, dt, *J* 7.6, 1.0 Hz, 7-H); δ_C (101 MHz, $CDCl_3$) 108.2 (C), 122.3 (CH), 126.3 (C), 126.9 (CH, 135.6 (CH), 136.8 (CH), 138.3 (C), 157.4 (C).

4-Thiocyanatoanisole (76a)[200]



The reaction was performed according to general procedure A using anisole (0.036 mL, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.960 g, 0.400 mmol). The reaction mixture was stirred at 40 °C for 0.5 h. Purification by flash column chromatography (15% diethyl ether in hexane) gave 4-thiocyanatoanisole (**76a**) (0.0514 g, 93%) as a colourless oil. Spectroscopic data were consistent with the literature.[200] δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 6.93–6.97 (2H, m, 2-H and 6-H), 7.48–7.52 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 55.7 (CH_3), 111.7 (C), 113.9 (C), 116.0 (2 × CH), 134.0 (2 × CH), 161.5 (C); *m/z* (ESI) 166 (MH^+. 100%).

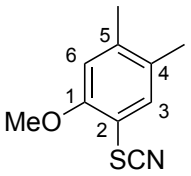
1,3,5-Trimethoxy-2-thiocyanatobenzene (76c)[201]



The reaction was performed according to general procedure A using 1,3,5-trimethoxybenzene (0.0841 g, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g,

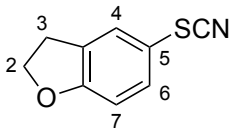
0.600 mmol). The reaction mixture was stirred at 0 °C for 0.25 h. Purification by flash column chromatography (30% ethyl acetate in hexane) gave 1,3,5-trimethoxy-2-thiocyanatobenzene (**76c**) (0.107 g, 95%) as a white solid. Mp 151–153 °C (lit.[201] 151–152 °C); δ_H (400 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 3.91 (6H, s, 2 × OCH_3), 6.15 (2H, s, 4-H and 6-H); δ_C (101 MHz, $CDCl_3$) 55.7 (CH_3), 56.5 (2 × CH_3), 89.9 (C), 91.5 (2 × CH), 112.0 (C), 161.5 (2 × C), 164.4 (C); *m/z* (ESI) 226 (MH^+. 100%).

2-Thiocyanato-4,5-dimethylanisole (76e)



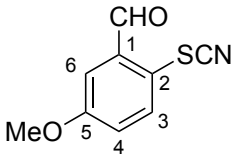
The reaction was performed according to general procedure A using 3,4-dimethylanisole (0.070 mL, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 0.5 h. Purification by flash column chromatography (30% dichloromethane in hexane) gave 2-thiocyanato-4,5-dimethylanisole (**76e**) (0.0719 g, 74%) as a colourless oil. ν_{max}/cm^{-1} (neat) 2942 (CH), 2153 (C≡N), 1594 (C=C), 1473, 1272, 1076, 816; δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 6.73 (1H, s, 5-H), 7.29 (1H, s, 3-H); δ_C (101 MHz, $CDCl_3$) 18.9 (CH_3), 20.3 (CH_3), 56.4 (CH_3), 108.8 (C), 111.2 (C), 113.4 (CH), 130.5 (C), 131.7 (CH), 140.1 (C), 155.1 (C); *m/z* (ESI) 194.0631 (MH^+. $C_{10}H_{12}NOS$ requires 194.0634).

2,3-Dihydro-5-thiocyanatobenzofuran (76f)[202]



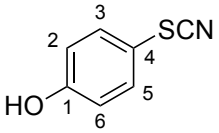
The reaction was performed according to general procedure A using 2,3-dihydrobenzofuran (0.056 mL, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 1.5 h. Purification by flash column chromatography (30% diethyl ether in hexane) gave 2,3-dihydro-5-thiocyanatobenzofuran (**76f**) (0.0831 g, 94%) as a colourless oil. Spectroscopic data were consistent with the literature.[202] δ_H (400 MHz, $CDCl_3$) 3.24 (2H, t, *J* 8.8 Hz, 3-H_2), 4.63 (2H, t, *J* 8.8 Hz, 2-H_2), 6.80 (1H, d, *J* 8.2 Hz, 7-H), 7.32 (1H, dd, *J* 8.2, 1.8 Hz, 6-H), 7.40–7.43 (1H, m, 4-H); δ_C (101 MHz, $CDCl_3$) 29.5 (CH_2), 72.1 (CH_2), 111.1 (CH), 112.1 (C), 113.1 (C), 129.6 (CH), 130.1 (C), 133.3 (CH), 162.4 (C); *m/z* (ESI) 178 (MH^+. 100%).

2-Thiocyanato-5-methoxybenzaldehyde (76h)



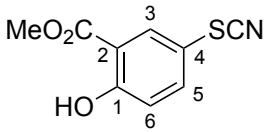
The reaction was performed according to general procedure A using 3-methoxybenzaldehyde (0.058 mL, 0.500 mmol), iron(III) chloride (0.0081 g, 0.0500 mmol, 10 mol%), diphenyl selenide (0.0087 mL, 0.0500 mmol, 10 mol%) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 1 h. Purification by flash column chromatography (7.5–15% ethyl acetate in hexane) gave 2-thiocyanato-5-methoxybenzaldehyde (**76h**) (0.0361 g, 37%) as a white solid. Mp 114–116 °C; ν_{max}/cm^{-1} (neat) 2846 (CH), 2154 (C≡N), 1669 (C=O), 1560 (C=C), 1256, 1021, 916, 815; δ_H (400 MHz, $CDCl_3$) 3.92 (3H, s, OCH_3), 7.25 (1H, dd, *J* 8.8, 2.9 Hz, 4-H), 7.43 (1H, d, *J* 2.9 Hz, 6-H), 7.79 (1H, dd, *J* 8.8, 0.7 Hz, 3-H), 10.03 (1H, d, *J* 0.7 Hz, CHO); δ_C (101 MHz, $CDCl_3$) 56.1 (CH_3), 111.2 (C), 118.9 (C), 120.3 (CH), 121.4 (CH), 130.5 (CH), 133.5 (C), 160.0 (C), 191.4 (CH); *m/z* (ESI) 193.0185 (M^+. $C_9H_7NO_2S$ requires 193.0192).

4-Thiocyanatophenol (77a)[203]



The reaction was performed according to general procedure A using phenol (0.0461 g, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 0.25 h. Purification by flash column chromatography (40% diethyl ether in hexane) gave 4-thiocyanatophenol (**77a**) (0.0669 g, 89%) as a yellow solid. Mp 53–55 °C (lit.[203] 51–53 °C); δ_H (400 MHz, $CDCl_3$) 4.94 (1H, br s, OH), 6.86–6.90 (2H, m, 2-H and 6-H), 7.41–7.46 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 112.4 (C), 113.3 (C), 117.6 (2 × CH), 134.4 (2 × CH), 158.2 (C); *m/z* (ESI) 152 (MH^+. 100%).

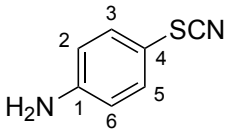
Methyl 2-hydroxy-5-thiocyanatobenzoate (77c)



The reaction was performed according to general procedure A using methyl salicylate (0.043 mL, 0.333 mmol), iron(III) chloride (0.0054 g, 0.0333 mmol, 10 mol%), diphenyl selenide (0.0058 mL, 0.0333 mmol, 10 mol%) and *N*-thiocyanatosaccharin (**60**) (0.160 g, 0.666 mmol). The reaction mixture was stirred at 40 °C for 0.25 h. Purification by flash

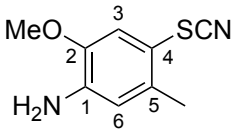
column chromatography (10% ethyl acetate in hexane) gave methyl 2-hydroxy-5-thiocyanatobenzoate (**77c**) (0.0490 g, 70%) as a white solid. Mp 75–77 °C; ν_{max}/cm^{-1} (neat) 3166 (OH), 2955 (CH), 2154 (C≡N), 1674 (C=O), 1571 (C=C), 1388, 1333, 1185, 750; δ_H (400 MHz, $CDCl_3$) 4.00 (3H, s, OCH_3), 7.07 (1H, d, *J* 8.8 Hz, 6-H), 7.65 (1H, dd, *J* 8.8, 2.5 Hz, 4-H), 8.10 (1H, d, *J* 2.5 Hz, 3-H), 11.02 (1H, s, OH); δ_C (101 MHz, $CDCl_3$) 53.0 (CH_3), 111.1 (C), 113.0 (C), 114.1 (C), 120.3 (CH), 134.6 (CH), 139.3 (CH), 163.2 (C), 169.4 (C); *m/z* (ESI) 210.0220 (MH^+. $C_9H_8NO_3S$ requires 210.0219).

4-Thiocyanatoaniline (78a)[204]



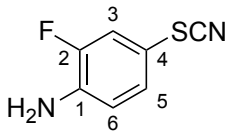
The reaction was performed according to general procedure A using aniline (0.045 mL, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 5 minutes. Purification by flash column chromatography (30% ethyl acetate in hexane) gave 4-thiocyanatoaniline (**78a**) (0.0686 g, 91%) as a yellow solid. Mp 54–55 °C (lit.[204] 50–52 °C); δ_H (400 MHz, $CDCl_3$) 3.97 (2H, br s, NH_2), 6.65–6.68 (2H, m, 2-H and 6-H), 7.33–7.37 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 109.6 (C), 112.5 (C), 116.2 (2 × CH), 134.6 (2 × CH), 148.9 (C); *m/z* (ESI) 151 (MH^+. 100%).

2-Methoxy-4-thiocyanato-5-methylaniline (78b)



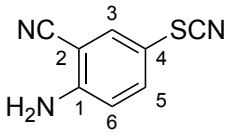
The reaction was performed according to general procedure A using 2-methoxy-5-methylaniline (0.0457 g, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.0961 g, 0.400 mmol). The reaction mixture was stirred at 0 °C for 5 minutes. Purification by flash column chromatography (25% ethyl acetate in hexane) gave 2-methoxy-4-thiocyanato-5-methylaniline (**78b**) (0.0564 g, 87%) as a brown solid. Mp 40–42 °C; ν_{max}/cm^{-1} (neat) 3297 (NH), 2916 (CH), 2148 (C≡N), 1618 (C=C), 1575, 1503, 1260, 1217, 1031, 883; δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s, 5-CH_3), 3.85 (3H, s, OCH_3), 4.03 (2H, br s, NH_2), 6.60 (1H, s, 6-H), 6.96 (1H, s, 3-H); δ_C (101 MHz, $CDCl_3$) 20.2 (CH_3), 56.0 (CH_3), 108.0 (C), 112.1 (C), 116.2 (CH), 116.7 (CH), 135.2 (C), 139.4 (C), 145.9 (C); *m/z* (ESI) 195.0587 (MH^+. $C_9H_{11}N_2OS$ requires 195.0587).

2-Fluoro-4-thiocyanatoaniline (78c)[204]



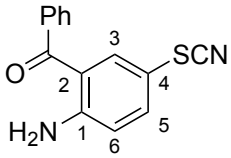
The reaction was performed according to general procedure A using 2-fluoroaniline (0.032 mL, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.0961 g, 0.400 mmol). The reaction mixture was stirred at 40 °C for 0.25 h. Purification by flash column chromatography (30% ethyl acetate in hexane) gave 2-fluoro-4-thiocyanatoaniline (**78c**) (0.0518 g, 92%) as a brown solid. Mp 32–34 °C (lit.[204] 33–34 °C); δ_H (400 MHz, $CDCl_3$) 4.04 (2H, br s, NH_2), 6.78 (1H, dd, *J* 9.0, 8.4 Hz, 6-H), 7.17 (1H, ddd, *J* 8.4, 2.1, 1.0 Hz, 5-H), 7.24 (1H, dd, *J* 10.4, 2.1 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 109.7 (C, d, $^3J_{CF}$ 7.5 Hz), 111.7 (C), 117.4 (CH, d, $^3J_{CF}$ 4.3 Hz), 119.9 (CH, d, $^2J_{CF}$ 20.8 Hz), 129.9 (CH, d, $^4J_{CF}$ 3.3 Hz), 137.5 (C, d, $^2J_{CF}$ 12.5 Hz), 151.1 (C, d, $^1J_{CF}$ 244.4 Hz); *m/z* (ESI) 169 (MH^+. 100%).

2-Cyano-4-thiocyanatoaniline (78d)[204]



The reaction was performed according to general procedure A using 2-cyanoaniline (0.0393 g, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.0961 g, 0.400 mmol). The reaction mixture was stirred at 40 °C for 0.5 h. Purification by flash column chromatography (30% ethyl acetate in hexane) gave 2-cyano-4-thiocyanatoaniline (**78d**) (0.0492 g, 84%) as a white solid. Mp 119–121 °C (lit.[204] 126–127 °C); δ_H (400 MHz, $CDCl_3$) 4.78 (2H, br s, NH_2), 6.80 (1H, d, *J* 8.8 Hz, 6-H), 7.53 (1H, dd, *J* 8.8, 2.3 Hz, 5-H), 7.63 (1H, d, *J* 2.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 97.5 (C), 110.5 (C), 111.0 (C), 115.9 (C), 116.9 (CH), 137.2 (CH), 138.4 (CH), 151.3 (C); *m/z* (ESI) 174 ($[M-H]^-$. 100%).

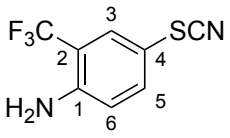
2-Amino-5-thiocyanatobenzophenone (78e)



The reaction was performed according to general procedure A using 2-aminobenzophenone (0.0961 g, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 0.25 h. Purification by flash column chromatography (10–25% ethyl acetate in hexane) gave 2-amino-5-thiocyanatobenzophenone (**78e**) (0.103 g, 81%) as a yellow solid. Mp 84–86 °C. ν_{max}/cm^{-1}

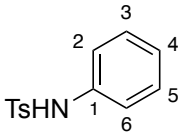
(neat) 3332 (NH), 3029 (CH), 2152 (C≡N), 1635 (C=O), 1572 (C=C), 1249, 943, 829; δ_H (400 MHz, $CDCl_3$) 6.45 (2H, br s, NH_2), 6.79 (1H, d, *J* 8.8 Hz, 6-H), 7.47–7.53 (3H, m, 5-H, 3'-H and 5'-H), 7.56–7.65 (3H, m, 2'-H, 4'-H and 6'-H), 7.71 (1H, d, *J* 2.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 107.0 (C), 112.0 (C), 118.8 (C), 119.1 (CH), 128.6 (2 × CH), 129.2 (2 × CH), 132.0 (CH), 138.5 (CH), 139.0 (C), 140.1 (CH), 152.6 (C), 197.9 (C); *m/z* (ESI) 253.0441 ($[M-H]^-$. $C_{14}H_9N_2OS$ requires 253.0440).

4-Thiocyanato-2-(trifluoromethyl)aniline (78f)[205]



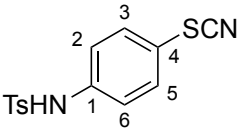
The reaction was performed according to general procedure A using 2-(trifluoromethyl)aniline (0.0806 g, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 1 h. Purification by flash column chromatography (25% ethyl acetate in hexane) gave 4-thiocyanato-2-(trifluoromethyl)aniline (**78f**) (0.0955 g, 88%) as an orange oil. Spectroscopic data were consistent with the literature.[205] δ_H (400 MHz, $CDCl_3$) 4.51 (2H, br s, NH_2), 6.78 (1H, d, *J* 8.7 Hz, 6-H), 7.51 (1H, dd, *J* 8.7, 2.3 Hz, 5-H), 7.66 (1H, d, *J* 2.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 109.6 (C), 111.5 (C), 114.8 (C, q, $^2J_{CF}$ 31.3 Hz), 118.7 (CH), 124.0 (C, q, $^1J_{CF}$ 272.5 Hz), 132.0 (CH, q, $^3J_{CF}$ 5.2 Hz), 137.6 (CH), 146.7 (C); *m/z* (ESI) 219 (MH^+. 100%).

***N*-Tosylaniline**[206]



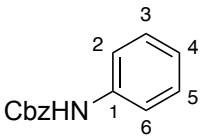
To a mixture of aniline (0.245 mL, 2.69 mmol) and pyridine (2.60 mL, 32.2 mmol) in dichloromethane (10 mL) was added a solution of *p*-toluenesulfonyl chloride (0.615 g, 3.22 mmol) in dichloromethane (5 mL) dropwise. The resulting reaction mixture was left to stir at room temperature for 16 h. The reaction mixture was then washed with a 5% aqueous solution of hydrochloric acid (15 mL). The organic layer was further washed with a saturated aqueous solution of sodium bicarbonate (15 mL) before being dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (30% ethyl acetate in hexane) gave *N*-tosylaniline as a pale-yellow solid (0.584 g, 88%). Mp 100−102 °C (lit.[206] 97−99 °C); δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, 4'-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_-Tosyl-4-thiocyanatoaniline (78g)[207]



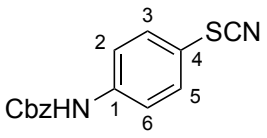
The reaction was performed according to general procedure A using *N*-tosylaniline (0.124 g, 0.500 mmol), iron (III) chloride (0.0081 g, 0.0500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 4 h. Purification by flash column chromatography (20–30% ethyl acetate in hexane) gave *N*-tosyl-4-thiocyanatoaniline (**78g**) (0.120 g, 79%) as a white solid. Mp 114–116 °C (lit.[207] 122–124 °C); δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s, CH_3), 7.13–7.17 (2H, m, 2-H and 6-H), 7.24–7.29 (2H, s, 3'-H and 5'-H); 7.38–7.43 (2H, m, 3-H and 5-H), 7.69–7.73 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 110.8 (C), 119.6 (C), 121.8 (2 × CH), 127.4 (2 × CH), 130.1 (2 × CH), 132.3 (2 × CH), 135.7 (C), 138.7 (C), 144.8 (C); m/z (ESI) 303 ($[M-H]^-$. 100%).

_N_-(Benzyloxycarbonyl)aniline[93]



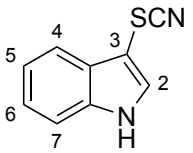
To a solution of aniline (0.245 mL, 2.69 mmol) in tetrahydrofuran (6 mL) at 0 °C was added sodium bicarbonate (0.249 g, 2.96 mmol) followed by benzyl chloroformate (0.415 mL 2.96 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was then quenched with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (10% ethyl acetate in hexane) gave *N*-(benzyloxycarbonyl)aniline as a pale yellow solid (0.340 g, 56%). Mp 70−72 °C (lit.[93] 70−72 °C); δ_H (400 MHz, $CDCl_3$) 5.21 (2H, s, CH_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, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H); (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-thiocyanatobenzene)carbamate (78h)[208]



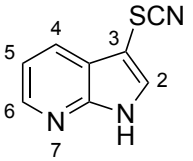
The reaction was performed according to general procedure A using benzyl benzenecarbamate (0.114 g, 0.500 mmol), diphenyl selenide (0.0022 mL, 0.0125 mmol, 2.5 mol%) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 0.75 h. Purification by flash column chromatography (20% ethyl acetate in hexane) gave benzyl (4-thiocyanatobenzene)carbamate (**78h**) (0.123 g, 87%) as a white solid. Mp 75–77 °C (lit.[208] 83–85 °C); δ_H (400 MHz, $CDCl_3$) 5.21 (2H, s, PhCH_2), 6.85 (1H, br s, NH), 7.33–7.43 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 7.48 (4H, br s, 2-H, 3-H, 5-H and 6-H); δ_C (101 MHz, $CDCl_3$) 67.6 (CH_2), 111.2 (C), 117.3 (C), 120.0 (2 × CH), 128.5 (2 × CH), 128.7 (CH), 128.8 (2 × CH), 132.6 (2 × CH), 135.7 (C), 139.9 (C), 153.0 (C); *m/z* (ESI) 307 (MNa^+. 100%).

3-Thiocyanatoindole (79a)[92]



The reaction was performed according to general procedure A using indole (0.0390 g, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.0961 g, 0.400 mmol). The reaction mixture was stirred at 40 °C for 5 minutes. Purification by flash column chromatography (30% ethyl acetate in hexane) gave 3-thiocyanatoindole (**79a**) (0.0540 g, 93%) as a brown solid. Mp 65–67 °C (lit.[92] 72–74 °C); δ_H (400 MHz, $CDCl_3$) 7.29–7.35 (2H, m, 5-H and 6-H), 7.41–7.46 (1H, m, 7-H), 7.51 (1H, d, *J* 2.8 Hz, 2-H), 7.79–7.84 (1H, m, 4-H), 8.65 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 92.5 (C), 112.0 (C), 112.2 (CH), 118.9 (CH), 122.1 (CH), 124.1 (CH), 127.8 (C), 131.1 (CH), 136.1 (C); *m/z* (ESI) 173 ($[M-H]^-$. 100%).

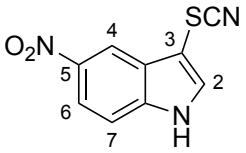
3-Thiocyanato-7-azaindole (79b)[92]



The reaction was performed according to general procedure A using 7-azaindole (0.0393 g, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.0961 g, 0.400 mmol). The reaction mixture was stirred at 40 °C for 5 minutes. Purification by flash column chromatography

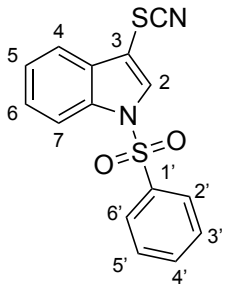
(40% ethyl acetate in hexane) gave 3-thiocyanato-7-azaindole (**79b**) (0.0537 g, 92%) as a white solid. Mp 203–206 °C (lit.[92] 197–199 °C); δ_H (400 MHz, DMSO-d_6) 7.30 (1H, dd, *J* 7.9, 4.7 Hz, 5-H), 8.12 (1H, dd, *J* 7.9, 1.6 Hz, 4-H), 8.17 (1H, d, *J* 2.3 Hz, 2-H), 8.39 (1H, d, *J* 4.7, 1.6 Hz, 6-H), 12.60 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 89.0 (C), 112.1 (C), 117.4 (CH), 119.8 (C), 126.5 (CH), 134.0 (CH), 144.5 (CH), 148.4 (C); *m/z* (ESI) 176 (MH^+. 100%).

3-Thiocyanato-5-nitroindole (79c)[201]



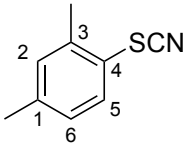
The reaction was performed according to the general procedure using 5-nitroindole (0.0540 g, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.0961 g, 0.400 mmol). The reaction mixture was stirred at 40 °C for 10 minutes. Purification by flash column chromatography (40% ethyl acetate in hexane) gave 3-thiocyanato-5-nitroindole (**79c**) (0.0626 g, 86%) as a pale yellow solid. Mp 210–212 °C (lit.[201] 207–209 °C); δ_H (400 MHz, DMSO-d_6) 7.73 (1H, d, *J* 9.0 Hz, 7-H), 8.15 (1H, dd, *J* 9.0, 2.3 Hz, 6-H), 8.29 (1H, s, 2-H), 8.55 (1H, d, *J* 2.3 Hz, 4-H); δ_C (101 MHz, DMSO-d_6) 93.2 (C), 111.9 (C), 113.7 (CH), 114.4 (CH), 118.2 (CH), 126.9 (C), 137.1 (CH), 139.5 (C), 142.2 (C); *m/z* (ESI) 218 ($[M-H]^-$. 100%).

***N*-Phenylsulfonyl-3-thiocyanatoindole (79d)**



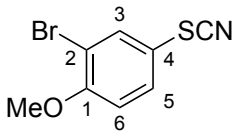
The reaction was performed according to general procedure A using 1-(phenylsulfonyl)indole (0.129 g, 0.500 mmol) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 10 minutes. Purification by flash column chromatography (10% ethyl acetate in petroleum ether) gave *N*-phenylsulfonyl-3-thiocyanatoindole (**79d**) (0.0973 g, 62%) as a white solid. Mp 133–135 °C; ν_{max}/cm^{-1} (neat) 3032 (CH), 2150 (CN), 1582, 1447, 1370, 1269, 1173, 1130, 999; δ_H (400 MHz, $CDCl_3$) 7.38–7.54 (4H, m, 5-H, 6-H, 3'-H and 5'-H), 7.59–7.64 (1H, m, 4'-H), 7.74 (1H, d, *J* 7.6 Hz, 7-H), 7.93–7.97 (3H, m, 2-H, 2'-H and 6'-H), 8.02 (1H, d, *J* 8.4 Hz, 4-H); δ_c (101 MHz, $CDCl_3$) 101.2 (C), 109.7 (C), 113.9 (CH), 119.8 (CH), 124.7 (CH), 126.5 (CH), 127.2 (2 × CH), 129.3 (C), 129.8 (2 × CH), 131.2 (CH), 134.8 (C), 134.9 (CH), 137.5 (C); *m*/*z* (ESI) 315.0259 (MH^+. $C_{15}H_{11}N_2O_2S_2$ requires 315.0256).

1,3-Dimethyl-4-thiocyanatobenzene (80b)[200]



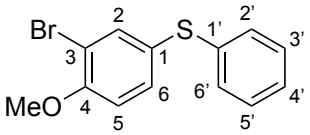
The reaction was performed according to general procedure A using *m*-xylene (0.061 mL, 0.500 mmol), iron(III) chloride (0.0081 g, 0.0500 mmol, 10 mol%) and *N*-thiocyanatosaccharin (**60**) (0.144 g, 0.600 mmol). The reaction mixture was stirred at 40 °C for 2 h. Purification by flash column chromatography (30% dichloromethane in hexane) gave 1,3-dimethyl-4-thiocyanatobenzene (**80b**) (0.0715 g, 88%) as a colourless oil. Spectroscopic data were consistent with the literature.[200] δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, CH_3), 2.46 (3H, s, CH_3), 7.05–7.09 (1H, m, 6-H), 7.12–7.14 (1H, m, 2-H), 7.50 (1H, d, *J* 8.0 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 20.6 (CH_3), 21.2 (CH_3), 111.1 (C), 119.9 (C), 128.6 (CH), 132.4 (CH), 132.9 (CH), 139.9 (C), 141.1 (C); *m/z* (ESI) 164 (MH^+. 100%).

2-Bromo-4-thiocyanatoanisole (82)



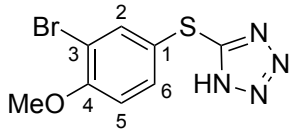
Iron(III) chloride (0.0535 g, 0.330 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.290 mL, 0.990 mmol) and stirred for 0.5 h at room temperature and then added to a solution of *N*-thiocyanatosaccharin (**60**) (0.951 g, 3.96 mmol) in dry dichloromethane (20 mL) under argon. Anisole (0.357 mL, 3.30 mmol) was added and the reaction mixture was stirred in the dark at 40 °C for 1 h. The reaction mixture was then cooled to room temperature and *N*-bromosuccinimide (0.704 g, 3.96 mmol) was added. The reaction mixture was stirred at 40 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (20 mL) and washed with water (20 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL) and the combined organic layers were washed with brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7.5–10% ethyl acetate in hexane) gave 2-bromo-4-thiocyanatoanisole (**82**) (0.701 g, 87%) as a white solid. Mp 61–62 °C; ν_{max}/cm^{-1} (neat) 2944 (CH), 2152 (C≡N), 1577 (C=C), 1483, 1438, 1256, 1010, 810; δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 6.94 (1H, d, *J* 8.7 Hz, 6-H), 7.51 (1H, dd, *J* 8.7, 2.4 Hz, 5-H), 7.77 (1H, d, *J* 2.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 56.7 (CH_3), 111.0 (C), 113.1 (CH), 113.3 (C), 115.2 (C), 132.7 (CH), 136.6 (CH), 157.9 (C); *m/z* (ESI) 243.9427 (MH^+. $C_8H_7{}^{79}BrNOS$ requires 243.9426).

(3-Bromo-4-methoxyphenyl)(phenyl)sulfane (83)[209]



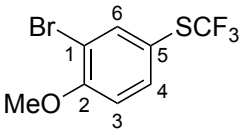
To a solution of 2-bromo-4-thiocyanatoanisole (**82**) (0.0813 g, 0.333 mmol) in dry tetrahydrofuran (1 mL) at 0 °C was added phenylmagnesium bromide (0.500 mL, 0.500 mmol, 1 M in tetrahydrofuran) dropwise and the reaction was stirred for 2 h at 0 °C. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2.5% ethyl acetate in hexane) gave (3-bromo-4-methoxyphenyl)(phenyl)sulfane (**83**) as a white solid (0.0893 g, 91%). Mp 94–96 C (lit.[209] 96–98 °C); δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, OCH_3), 6.87 (1H, d, *J* 8.5 Hz, 5-H), 7.17–7.29 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 7.37 (1H, dd, *J* 8.5, 2.3 Hz, 6-H), 7.65 (1H, d, *J* 2.3 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 56.6 (CH_3), 112.4 (C), 112.6 (CH), 126.6 (CH), 126.8 (C), 129.3 (2 × CH), 129.3 (2 × CH), 133.7 (CH), 137.4 (C), 137.8 (CH), 156.1 (C); *m*/*z* (ESI) 293.9707 (M^+. $C_{13}H_{11}{}^{79}BrOS$ requires 293.9709).

5-(3-Bromo-4-methoxyphenyl)sulfanyl-1H-tetrazole (84)



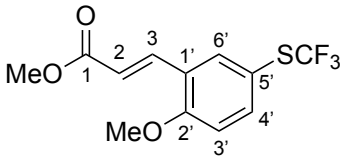
2-Bromo-4-thiocyanatoanisole (**82**) (0.0813 g, 0.333 mmol), sodium nitrite (0.0260 g, 0.400 mmol) and zinc chloride (0.0454 g, 0.333 mmol) were dissolved in propan-2-ol (1 mL) and stirred at 50 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and a 1 M aqueous solution of sodium hydroxide (2.5 mL) was added and stirred for 0.3 h. The reaction mixture was filtered and the filtrate was acidified to pH 1 with a 2 M aqueous solution of hydrochloric acid, which caused the product to precipitate. Filtration followed by washing with a 2 M aqueous solution of hydrochloric acid gave 5-(3-bromo-4-methoxyphenyl)sulfanyl-1H-tetrazole (**84**) as a white solid (0.0739 g, 77%). Mp 151–154; ν_{max}/cm^{-1} (neat) 2976 (CH), 1580 (C=C), 1485, 1254, 1050, 1016, 687; δ_H (400 MHz, DMSO-d_6) 3.89 (3H, s, OCH_3), 7.20 (1H, d, *J* 8.6 Hz, 5-H), 7.61 (1H, dd, *J* 8.6, 2.3 Hz, 6-H), 7.85 (1H, d, *J* 2.3 Hz, 2-H); δ_C (101 MHz, DMSO-d_6) 56.6 (CH_3), 111.4 (C), 113.7 (CH), 119.6 (C), 134.8 (CH), 137.6 (CH), 154.3 (C), 156.7 (C); *m*/*z* (ESI) 286.9591 (MH^+. $C_8H_8{}^{79}BrN_4OS$ requires 286.9597).

2-Bromo-4-(trifluoromethylsulfanyl)anisole (85)[210]



To a suspension of 2-bromo-4-thiocyanatoanisole (**82**) (0.610 g, 2.50 mmol) and caesium carbonate (1.63 g, 5.00 mmol) in dry acetonitrile (5 mL) under argon was added trimethyl(trifluoromethyl)silane (0.739 mL, 5.00 mmol) and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 30 mL) and the combined organic layers were washed with brine (50 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7.5% ethyl acetate in hexane) gave 2-bromo-4-(trifluoromethylsulfanyl)anisole (**85**) (0.513 g, 71%) as a colourless oil. Spectroscopic data were consistent with the literature.[210] δ_H (400 MHz, $CDCl_3$) 3.93 (3H, s, OCH_3), 6.92 (1H, d, *J* 8.6 Hz, 6-H), 7.58 (1H, dd, *J* 8.6, 2.2 Hz, 5-H), 7.84 (1H, d, *J* 2.2 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 56.6 (CH_3), 112.4 (CH), 112.4 (C), 116.2 (C, q, $^3J_{CF}$ 2.4 Hz), 129.5 (C, q, $^1J_{CF}$ 308.5 Hz), 137.4 (CH), 141.1 (CH), 158.4 (C); *m/z* (ESI) (286 MH^+. 100%).

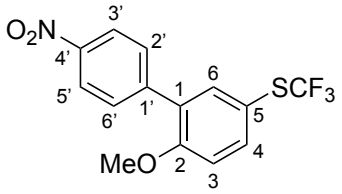
Methyl (2*E*)-3-(2'-methoxy-5'-trifluoromethylsulfanylbenzene)acrylate (86)



To a solution of 2-bromo-4-(trifluoromethylsulfanyl)anisole (**85**) (0.0956 g, 0.333 mmol) in degassed dimethylformamide (4 mL) was added methyl acrylate (0.0750 mL, 0.833 mmol) and *N,N*-diisopropylethylamine (0.174 mL, 1.00 mmol), followed by bis(triphenylphosphine)palladium(II) dichloride (0.0023 g, 0.0333 mmol) and the reaction mixture was stirred under argon at 100 °C for 18 h then 120 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (3 × 25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% ethyl acetate in hexane) gave methyl (2*E*)-3-(2'-methoxy-5'-trifluoromethylsulfanylbenzene)acrylate (**86**) as a white solid (0.0657 g, 68%). Mp 67–68 °C; ν_{max}/cm^{-1} (neat) 2945 (CH), 1711 (C=O), 1586 (C=C), 1484, 1438, 1253, 1093, 814; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 6.55 (1H, d, *J* 16.2 Hz, 2-H), 6.95 (1H, d, *J* 8.7 Hz, 3'-H), 7.62 (1H, dd, *J* 8.7, 2.3 Hz, 4'-H), 7.77 (1H, d, *J* 2.3 Hz, 6'-H), 7.92 (1H, d, *J* 16.2 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 51.9 (CH_3), 56.0 (CH_3), 112.3 (CH), 115.6 (C, q, $^3J_{CF}$ 2.3 Hz), 120.2 (CH), 125.0 (C), 129.6

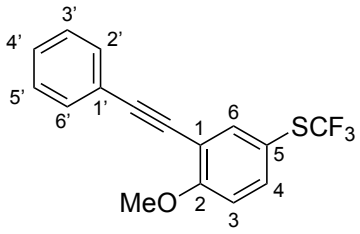
(C, q, $^{1}J_{CF}$ 308.4 Hz), 137.3 (CH), 138.8 (CH), 139.7 (CH), 160.3 (C), 167.6 (C); *m/z* (ESI) 293.0459 (MH^+. $C_{12}H_{12}F_3NO_3S$ requires 293.0454).

2-(4'-Nitrophenyl)-4-(trifluoromethylsulfanyl)anisole (87)



To a solution of 2-bromo-4-(trifluoromethylsulfanyl)anisole (**85**) (0.0851 g, 0.296 mmol), 4-nitrophenylboronic acid (0.0743 g, 0.445 mmol) and potassium phosphate tribasic (0.126 g, 0.593 mmol) in degassed tetrahydrofuran (0.7 mL) and water (1.3 mL) was added XPhos Pd G2 (0.0047 g, 0.00593 mmol) and the reaction mixture was stirred at 40 °C for 4 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of Celite® and washed with ethyl acetate (10 mL). The filtrate was washed with water (10 mL) and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate in hexane) gave 2-(4'-nitrophenyl)-4-trifluoromethylsulfanyl)anisole (**87**) as a brown oil (0.0841 g, 86%). ν_{max}/cm^{-1} (neat) 2950 (CH), 1595 (C=C), 1509, 1345, 1267, 1099, 857; δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s, OCH_3), 7.06 (1H, d, *J* 8.6 Hz, 6-H), 7.62 (1H, d, *J* 2.4 Hz, 3-H), 7.66–7.71 (3H, m, 5-H, 2'-H and 6'-H), 8.26–8.30 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 112.4 (CH), 115.8 (C, q, $^{3}J_{CF}$ 2.3 Hz), 123.5 (2 × CH), 129.6 (C, q, $^{1}J_{CF}$ 308.1 Hz), 129.8 (C), 130.5 (2 × CH), 138.8 (CH), 138.9 (CH), 143.8 (C), 147.2 (C), 158.8 (C); *m/z* (ESI) 330.0405 (MH^+. $C_{14}H_{11}F_3NO_3S$ requires 330.0406).

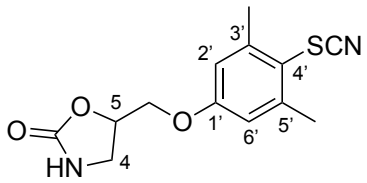
2-(Phenylethynyl)-4-(trifluoromethylsulfanyl)anisole (88)



A reaction vial was charged with 2-bromo-4-(trifluoromethylsulfanyl)anisole (**85**) (0.0956 g, 0.333 mmol), tetrakis(triphenylphosphine)palladium(0) (0.0192 g, 0.0167 mmol) and copper(I) bromide (0.0048 g, 0.0333 mmol). Degassed tetrahydrofuran (0.7 mL) was added and the solution was stirred for 0.1 h. Triethylamine (0.560 mL, 4.00 mmol) and phenylacetylene (0.044 mL, 0.400 mmol) were added and the reaction mixture was stirred at 75 °C under argon for 3 h. The reaction mixture was cooled to room temperature, diluted

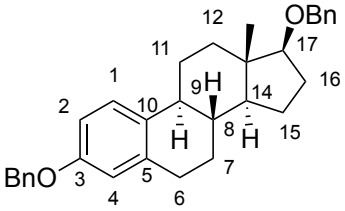
with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate in hexane) gave 2-(phenylethynyl)-4-(trifluoromethylsulfanyl)anisole (**88**) as a white solid (0.0880 g, 86%). Mp 69–71 °C; ν_{max}/cm^{-1} (neat) 2919 (CH), 1585 (C=C), 1479, 1250, 1091, 1015, 750; δ_H (400 MHz, $CDCl_3$) 3.95 (3H, s, OCH_3), 6.93 (1H, d, *J* 8.7 Hz, 6-H), 7.34–7.39 (3H, m, 2'-H, 4'-H and 6'-H), 7.54–7.60 (3H, m, 5-H, 3'-H and 5'-H), 7.79 (1H, d, *J* 2.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 56.3 (CH_3), 84.3 (C), 94.9 (C), 111.7 (CH), 114.4 (C), 115.1 (C, q, $^3J_{CF}$ 2.3 Hz), 123.1 (C), 128.5 (2 × CH), 128.7 (CH), 129.6 (C, q, $^1J_{CF}$ 308.1 Hz), 131.9 (2 × CH), 138.4 (CH), 141.7 (CH), 162.1 (C); *m/z* (ESI) 309.0556 (MH^+. $C_{16}H_{12}F_3NOS$ requires 309.0555).

5-[(3',5'-Dimethyl-4'-thiocyanatophenoxy)methyl]-1,3-oxazolidin-2-one (90)



The reaction was performed according to general procedure A using metaxalone (**89**) (0.0737 g, 0.333 mmol) and *N*-thiocyanatosaccharin (**60**) (0.112 g, 0.466 mmol). The reaction mixture was stirred at 40 °C for 0.5 h. Purification by flash column chromatography (80–90% ethyl acetate in hexane) gave 5-[(3',5'-dimethyl-4'-thiocyanatophenoxy)methyl]-1,3-oxazolidin-2-one (**90**) (0.0668 g, 72%) as a white solid. Mp 174–176 °C; ν_{max}/cm^{-1} (neat) 3246 (NH), 2959 (CH), 2148 (C≡N), 1747 (C=O), 1583 (C=C), 1309, 1244, 1168, 1074, 856; δ_H (400 MHz, $CDCl_3$) 2.57 (6H, s, 2 × CH_3), 3.60 (1H, dd, *J* 8.7, 6.1 Hz, 5-C*H*H), 3.78 (1H, t, *J* 8.7 Hz, 5-CH*H*), 4.15 (2H, d, *J* 4.7 Hz, 4-H_2), 4.93–5.00 (1H, m, 5-H), 5.67 (1H, br s, NH), 6.74 (2H, s, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 22.5 (2 × CH_3), 42.7 (CH_2), 68.1 (CH_2), 74.0 (CH), 111.0 (C), 114.4 (C), 115.4 (2 × CH), 145.1 (2 × C), 159.2 (C), 160.0 (C); *m/z* (ESI) 279.0802 (MH^+. $C_{13}H_{15}N_2O_3S$ requires 279.0798).

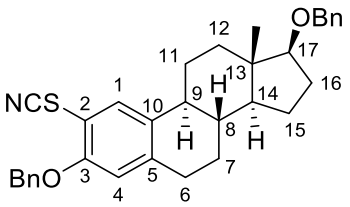
β-Estradiol dibenzyl ether (92)[211]



To a suspension of sodium hydride (0.160 g, 4.00 mmol, 60% dispersion in mineral oil) in dry dimethylformamide (0.5 mL) at 0 °C under argon was added a solution of β-estradiol (**91**) (0.136 g, 0.500 mmol) in dry tetrahydrofuran (0.5 mL) and the resultant mixture was stirred for 1 h. Benzyl bromide (0.148 mL, 1.25 mmol) was then added dropwise and the

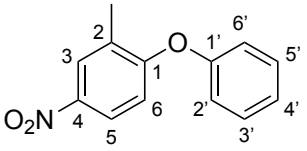
reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water (3 x 10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate in hexane) gave β-estradiol dibenzyl ether (**92**) (0.195 g, 86%) as a white solid. Mp 71–74 °C (lit.[211] 68–70 °C); $[\alpha]_D^{23}$ +43.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s, 13-CH_3), 1.15−1.74 (8H, m, 7-*H*H, 8-H, 11-*H*H, 12-*H*H, 14-H, 15-H_2 and 16-*H*H), 1.84−1.92 (1H, m, 7-H*H*), 2.01−2.13 (2H, m, 12-H*H* and 16-H*H*), 2.14−2.23 (1H, m, 9-H), 2.25−2.33 (1H, m, 11-H*H*), 2.77−2.92 (2H, m, 6-H_2), 3.51 (1H, t, *J* 8.3 Hz, 17-H), 4.58 (2H, s, 17-O*CH*$_2$), 5.04 (2H, s, 3-O*CH*$_2$), 6.72 (1H, d, *J* 2.8 Hz, 4-H), 6.78 (1H, dd, *J* 8.5, 2.8 Hz, 2-H), 7.20 (1H, d, *J* 8.5, 1-H), 7.24−7.45 (10H, m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H); (101 MHz, $CDCl_3$) 12.0 (CH_3), 23.3 (CH_2), 26.6 (CH_2), 27.4 (CH_2), 28.2 (CH_2), 30.0 (CH_2), 38.1 (CH_2), 38.8 (CH), 43.6 (C), 44.1 (CH), 50.4 (CH), 70.1 (CH_2), 71.8 (CH_2), 88.5 (CH), 112.4 (CH), 115.0 (CH), 127.4 (CH), 127.4 (2 × CH), 127.6 (2 × CH), 128.0 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 133.2 (C), 137.5 (C), 138.2 (C), 139.5 (C), 156.9 (C); *m/z* (ESI) (453 MH^+. 100%).

2-Thiocyanato-β-estradiol dibenzyl ether (93)



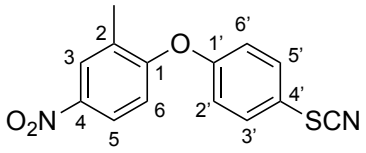
The reaction was performed according to general procedure A using β-estradiol dibenzyl ether (**92**) (0.0453 g, 0.100 mmol), diphenyl selenide (0.0044 mL, 0.00250 mmol, 2.5 mol%) and *N*-thiocyanatosaccharin (**60**) (0.0288 g, 0.120 mmol). The reaction mixture was stirred at 0 °C for 10 minutes. Purification by flash column chromatography (60% dichloromethane in hexane) gave 2-thiocyanato-β-estradiol dibenzyl ether (**93**) (0.0439 g, 86%) as a white solid. Mp 123–125 °C; $[\alpha]_D^{23}$ +63.3 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2926 (CH), 2153 (C≡N), 1596 (C=C), 1496, 1307, 1258, 1078, 738; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s, 13-CH_3), 1.14−1.73 (8H, m, 7-*H*H, 8-H, 11-*H*H, 12-*H*H, 14-H, 15-H_2 and 16-*H*H), 1.84−1.92 (1H, m, 7-H*H*), 2.00−2.22 (3H, m, 9-H, 12-H*H* and 16-H*H*), 2.26−2.35 (1H, m, 11-H*H*), 2.78−2.90 (2H, m, 6-H_2), 3.51 (1H, t, *J* 8.2 Hz, 17-H), 4.58 (2H, s, 17-O*CH*$_2$), 5.13 (2H, s, 3-O*CH*$_2$), 6.71 (1H, s, 4-H), 7.25−7.49 (11H, m, 1-H and 2 × Ph); δ_C (101 MHz, $CDCl_3$) 11.9 (CH_3), 23.3 (CH_2), 26.5 (CH_2), 27.0 (CH_2), 28.2 (CH_2), 29.9 (CH_2), 37.9 (CH_2), 38.4 (CH), 43.5 (C), 44.1 (CH), 50.3 (CH), 71.1 (CH_2), 71.9 (CH_2), 88.3 (CH), 109.9 (C), 111.3 (C), 113.5 (CH), 127.3 (2 × CH), 127.5 (2 × CH), 127.5 (CH), 128.3 (CH), 128.3 (CH), 128.4 (2 × CH), 128.8 (2 × CH), 135.1 (C), 136.2 (C), 139.4 (C), 140.4 (C), 154.0 (C); *m/z* (ESI) 510.2464 (MH^+. $C_{33}H_{36}NO_2S$ requires 510.2461).

2-Methyl-4-nitro-1-phenoxybenzene (53)[212]



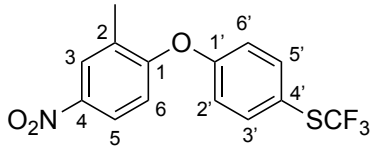
To a solution of 1-fluoro-2-methyl-4-nitrobenzene (**95**) (0.155 g, 1.00 mmol) and phenol (0.104 g, 1.10 mmol) in acetonitrile (2 mL) was added potassium carbonate (0.415 g, 3.00 mmol). The reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was concentrated *in vacuo*, diluted with water (10 mL), extracted with ethyl acetate (3 × 10 mL) and the combined organic layers were washed with saturated sodium carbonate (3 × 20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate in hexane) gave 2-methyl-4-nitro-1-phenoxybenzene (**53**) (0.196 g, 86%) as a colourless oil. Spectroscopic data were consistent with the literature.[212] δ_H (400 MHz, $CDCl_3$) 2.41 (3H, s, 2-CH_3), 6.77 (1H, d, *J* 9.0 Hz, 6-H), 7.02–7.06 (2H, m, 2'-H and 6'-H), 7.20–7.25 (1H, m, 4'-H), 7.38–7.44 (2H, m, 3'-H and 5'-H), 7.99 (1H, dd, *J* 9.0, 2.8 Hz, 5-H), 8.15 (1H, d, *J* 2.8 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 16.5 (CH_3), 116.1 (CH), 120.0 (2 × CH), 123.3 (CH), 125.0 (CH), 126.9 (CH), 129.6 (C), 130.4 (2 × CH), 142.8 (C), 155.5 (C), 161.4 (C); *m/z* (ESI) 230 MH^+. 100%).

1-(2'-Methyl-4'-nitrophenoxy)-4-thiocyanatobenzene (96)



The reaction was performed according to general procedure A using 2-methyl-4-nitro-1-phenoxybenzene (**53**) (0.0763 g, 0.333 mmol), iron(III) chloride (0.0054 g, 0.0333 mmol, 10 mol%), diphenyl selenide (0.0058 mL, 0.0333 mmol, 10 mol%) and *N*-thiocyanatosaccharin (**60**) (0.176 g, 0.733 mmol). The reaction mixture was stirred at 40 °C for 0.25 h. Purification by flash column chromatography (5% diethyl ether in hexane) gave 1-(2'-methyl-4'-nitrophenoxy)-4-thiocyanatobenzene (**96**) (0.0863 g, 91%) as a white solid. Mp 62–64 °C; ν_{max}/cm^{-1} (neat) 2925 (CH), 2156 (C≡N), 1581 (C=C), 1486, 1340, 1244, 1091, 843; δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, 2'-CH_3), 6.90 (1H, d, *J* 9.0 Hz, 6'-H), 7.04–7.09 (2H, m, 2-H and 6-H), 7.56–7.61 (2H, m, 3-H and 5-H), 8.05 (1H, dd, *J* 9.0, 2.7 Hz, 5'-H), 8.18 (1H, d, *J* 2.7 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 16.5 (CH_3), 110.8 (C), 117.9 (CH), 119.1 (C), 120.7 (2 × CH), 123.4 (CH), 127.2 (CH), 130.7 (C), 133.4 (2 × CH), 143.8 (C), 157.6 (C), 159.6 (C); *m/z* (ESI) 287.0484 (MH^+. $C_{14}H_{11}N_2O_3S$ requires 287.0485).

1-(2'-Methyl-4'-nitrophenoxy)-4-(trifluoromethylsulfanyl)benzene (54)[81]



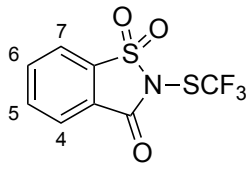
To a suspension of 1-(2'-methyl-4'-nitrophenoxy)-4-thiocyanatobenzene (**96**) (0.106 g, 0.370 mmol) and caesium carbonate (0.241 g, 0.740 mmol) in dry acetonitrile (0.7 mL) under argon was added trimethyl(trifluoromethyl)silane (0.109 mL, 0.740 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate (2 × 10 mL) and the combined organic layers were washed with brine (30 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3% ethyl acetate in hexane) gave 1-(2'-methyl-4'-nitrophenoxy)-4-(trifluoromethylsulfanyl)benzene (**54**) (0.0942 g, 77%) as a colourless oil. Spectroscopic data were consistent with the literature.[81] δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, 2'-CH_3), 6.93 (1H, d, *J* 8.9 Hz, 6'-H), 7.01–7.06 (2H, m, 2-H and 6-H), 7.65–7.70 (2H, m, 3-H and 5-H), 8.06 (1H, dd, *J* 8.9, 2.8 Hz, 5'-H), 8.19 (1H, d, *J* 2.8 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 16.5 (CH_3), 118.2 (CH), 119.6 (C, q, $^3J_{CF}$ 2.5 Hz), 119.7 (2 × CH), 123.4 (CH), 127.2 (CH), 129.6 (C, q, $^3J_{CF}$ 308.4 Hz), 130.9 (C), 138.8 (2 × CH), 143.9 (C), 158.5 (C), 159.6 (C); *m/z* (ESI) (330 MH^+. 100%).

4.3 Trifluoromethylthiolation Experimental

General Procedure B: Trifluoromethylthiolation of Arenes

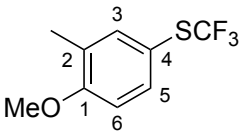
To a solution of *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol) and iron(III) chloride (0.00065 g, 0.00400 mmol, 2.5 mol%) in dry dichloromethane (1 mL) under argon was added the arene (0.160 mmol) and diphenyl selenide (0.0007 mL, 0.00400 mmol, 2.5 mol%). The reaction mixture was stirred at room temperature in the absence of light for the required time. The reaction mixture was then diluted with dichloromethane (10 mL) and washed with water (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 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 gave the desired product.

_N_-(Trifluoromethylthio)saccharin (45)[77]



An oven-dried flask was flushed with argon and charged with *N*-chlorosaccharin (**75**) (0.240 g, 1.10 mmol), silver(I) trifluoromethylthiolate (0.300 g, 1.44 mmol) and dry acetonitrile (3 mL). The reaction mixture was stirred at room temperature in the absence of light for 0.5 h. The reaction mixture was concentrated *in vacuo*, dissolved in dichloromethane (5 mL), filtered through a short pad of Celite® and washed with dichloromethane (2 × 5 mL). The filtrate was concentrated *in vacuo* to give *N*-(trifluoromethyl)saccharin (**45**) (0.211 g, 75%). Mp 111–113 °C (lit.[77] 112–113 °C); δ_H (400 MHz, $CDCl_3$) 7.90–7.96 (1H, m, 6-H), 7.97–8.05 (2H, m, 4-H and 5-H), 8.18–8.22 (1H, m, 7-H); δ_C (101 MHz, $CDCl_3$) 122.1 (CH), 126.3 (C), 126.7 (CH), 127.4 (C, q, $^1J_{CF}$ 316.8 Hz), 135.1 (CH), 136.4 (CH), 138.2 (C), 158.5 (C); *m/z* (ESI) 182 ($[M-SCF_3]^-$. 100%).

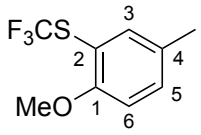
2-Methyl-4-(trifluoromethylthio)anisole (97a)[83]



The reaction was performed according to general procedure B using 2-methylanisole (0.020 mL, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (pentane) gave 2-methyl-4-(trifluoromethylthio)anisole (**97a**) (0.0336 g,

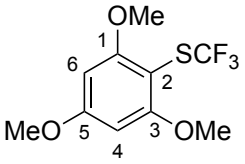
94%) as a colourless oil. Spectroscopic data were consistent with the literature.[83] δ_H (400 MHz, $CDCl_3$) 2.22 (3H, s, 2-CH_3), 3.86 (3H, s, OCH_3), 6.84 (1H, d, *J* 8.5 Hz, 6-H), 7.41 (1H, d, *J* 2.3 Hz, 3-H), 7.47 (1H, dd, *J* 8.5 Hz, 2.3 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 16.2 (CH_3), 55.6 (CH_3), 110.7 (CH), 114.3 (C, q, $^3J_{CF}$ 2.1 Hz), 128.3 (C), 129.9 (C, q, $^1J_{CF}$ 308.2 Hz), 136.0 (CH), 138.8 (CH), 160.2 (C); *m/z* (APCI) 222 (M^+. 100%).

2-(Trifluoromethylthio)-4-methylanisole (97b)[83]



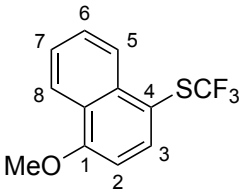
The reaction was performed according to general procedure B using 4-methylanisole (0.020 mL, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 5 h. Purification by flash column chromatography (pentane) gave 2-(trifluoromethylthio)-4-methylanisole (**97b**) (0.0238 g, 67%) as a colourless oil. Spectroscopic data were consistent with the literature.[83] δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, 4-CH_3), 3.88 (3H, s, OCH_3), 6.87 (1H, d, *J* 8.4 Hz, 6-H), 7.23–7.26 (1H, m, 5-H), 7.42 (1H, d, *J* 2.1 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 20.3 (CH_3), 56.3 (CH_3), 111.8 (CH), 112.1 (C), 129.8 (C, q, $^1J_{CF}$ 308.8 Hz), 130.8 (C), 133.5 (CH), 139.0 (CH), 158.7 (C); *m/z* (APCI) 222 (M^+. 100%).

1,3,5-Trimethoxy-2-(trifluoromethylthio)benzene (97d)[213]



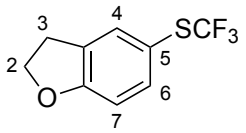
The reaction was performed according to general procedure B using 1,3,5-trimethoxybenzene (0.0269 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0462 g, 0.163 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (20% ethyl acetate in hexane) gave 1,3,5-trimethoxy-4-(trifluoromethylthio)benzene (**97d**) (0.0401 g, 93%) as a white solid. Mp 76–78 °C (lit.[213] 76–77 °C); δ_H (400 MHz, $CDCl_3$) δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 3.88 (6H, s, 2 × OCH_3), 6.16 (2H, s, 4-H and 6-H); δ_C (101 MHz, $CDCl_3$) 55.6 (CH_3), 56.4 (2 × CH_3), 91.2 (2 × CH), 91.9 (C), 129.6 (C, q, $^1J_{CF}$ 310.7 Hz), 163.6 (2 × C), 164.6 (C); *m/z* (APCI) 269 (MH^+. 100%).

1-Methoxy-4-(trifluoromethylthio)naphthalene (97e)[214]



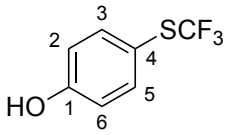
The reaction was performed according to general procedure B using 1-methoxynaphthalene (0.0232 µL, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 1.5 h. Purification by flash column chromatography (hexane) gave 1-methoxy-4-(trifluoromethylthio)naphthalene (**97e**) (0.0403 g, 97%) as a colourless oil. Spectroscopic data were consistent with the literature.[214] δ_H (400 MHz, $CDCl_3$) 4.05 (3H, s, OCH_3), 6.85 (1H, d, *J* 8.1 Hz, 2-H), 7.56 (1H, ddd, *J* 8.4, 6.8, 1.2 Hz, 7-H), 7.66 (1H, ddd, *J* 8.4, 6.8, 1.4 Hz, 6-H), 7.90 (1H, d, *J* 8.1 Hz, 3-H), 8.33 (1H, dd, *J* 8.4, 1.4 Hz, 8-H), 8.48 (1H, br d, *J* 8.4 Hz, 5-H); δ_c (101 MHz, $CDCl_3$) 55.9 (CH_3), 104.0 (CH), 112.4 (C, q, $^3J_{CF}$ 2.2 Hz), 122.7 (CH), 125.9 (CH), 126.1 (CH), 126.6 (C), 128.2 (CH), 129.9 (C, q, $^1J_{CF}$ 309.6 Hz), 136.3 (C), 139.1 (CH), 158.8 (C); *m/z* (APCI) 258 (M^+. 100%).

2,3-Dihydro-5-(trifluoromethylthio)benzofuran (97f)[215]



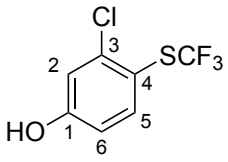
The reaction was performed according to general procedure B using 2,3-dihydrobenzofuran (0.0181 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 0.5 h. Purification by flash column chromatography (hexane–5% diethyl ether in hexane) gave 2,3-dihydro-5-(trifluoromethylthio)benzofuran (**97f**) (0.0306 g, 87%) as a colourless oil. Spectroscopic data were consistent with the literature.[215] δ_H (400 MHz, $CDCl_3$) 3.25 (2H, t, *J* 8.8 Hz, 3-H_2), 4.64 (2H, t, *J* 8.8 Hz, 2-H_2), 6.80 (1H, d, *J* 8.3 Hz, 7-H), 7.41 (1H, dd, *J* 8.3, 1.7 Hz, 6-H), 7.45 (1H, br s, 4-H); δ_C (101 MHz, $CDCl_3$) 29.4 (CH_2), 72.1 (CH_2), 110.5 (CH), 114.4 (C, q, $^3J_{CF}$ 2.1 Hz), 129.0 (C), 129.8 (C, q, $^1J_{CF}$ 308.2 Hz), 133.6 (CH), 137.7 (CH), 162.8 (C); *m/z* (APCI) 220 (M^+. 100%).

4-(Trifluoromethylthio)phenol (98a)[216]



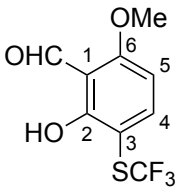
The reaction was performed according to general procedure B using phenol (0.0151 g, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (dichloromethane) gave 4-(trifluoromethylthio)phenol (**98a**) (0.0245 g, 79%) as a white solid. Mp 53–54 °C (lit.[216] 53–54 °C); δ_H (400 MHz, $CDCl_3$) 5.10 (1H, br s, OH), 6.85–6.89 (2H, m, 2-H and 6-H), 7.52–7.56 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 115.4 (C, q, $^3J_{CF}$ 2.2 Hz), 116.7 (2 × CH), 129.7 (C, q, $^1J_{CF}$ 308.1 Hz), 138.7 (2 × CH), 158.2 (C); *m/z* (ESI) 193 ([M−H]$^-$. 100%).

3-Chloro-4-(Trifluoromethylthio)phenol (98b)[77]



The reaction was performed according to general procedure B using 3-chlorophenol (0.0206 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (10% ethyl acetate in hexane) gave 3-chloro-4-(trifluoromethylthio)phenol (**98b**) (0.0278 g, 76%) as a colourless oil. Spectroscopic data were consistent with the literature.[77] δ_H (400 MHz, $CDCl_3$) 5.21 (1H, br s, OH), 6.79 (1H, dd, *J* 8.5, 2.7 Hz, 6-H), 7.05 (1H, d, *J* 2.7 Hz, 2-H), 7.63 (1H, d, *J* 8.5 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 114.8 (C, q, $^3J_{CF}$ 2.3 Hz), 115.3 (CH), 117.9 (CH), 129.4 (C, q, $^1J_{CF}$ 309.6 Hz), 140.7 (CH), 142.2 (C), 158.9 (C); *m/z* (ESI) 227 ([M−H]$^-$. 100%).

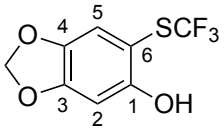
2-Hydroxy-3-(trifluoromethylthio)-6-methoxybenzaldehyde (98c)



The reaction was performed according to general procedure B using 6-methoxysalicyaldehyde (0.0243 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl

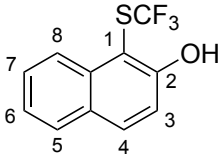
selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 4 h. Purification by flash column chromatography (10% diethyl ether in hexane) gave 2-hydroxy-3-(trifluoromethylthio)-6-methoxybenzaldehyde (**98c**) (0.0251 g, 62%) as a white solid. Mp 118–120 °C; ν_{max}/cm^{-1} (neat) 2896 (CH), 1647 (C=O), 1599 (C=C), 1391, 1233, 1082, 802; δ_H (400 MHz, $CDCl_3$) 3.96 (3H, s, OCH_3), 6.49 (1H, d, *J* 8.8 Hz, 5-H), 7.78 (1H, d, *J* 8.8 Hz, 4-H), 10.33 (1H, s, OH), 12.82 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 56.8 (CH_3), 102.8 (CH), 103.8 (C, q, $^3J_{CF}$ 2.0 Hz), 111.5 (C), 129.8 (C, q, $^1J_{CF}$ 309.7 Hz), 148.4 (CH), 165.7 (C), 165.9 (C), 194.5 (CH); *m/z* (ESI) 253.0142 (MH^+. $C_9H_8F_3O_3S$ requires 253.0141).

3,4-Methylenedioxy-6-(trifluoromethylthio)phenol (98d)[216]



The reaction was performed according to general procedure B using sesamol (0.0221 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 4 h and then 40 °C for 16 h. Purification by flash column chromatography (10% ethyl acetate in hexane) gave 3,4-methylenedioxy-6-(trifluoromethylthio)phenol (**98d**) (0.0241 g, 63%) as a white solid. Mp 80–81 °C (lit.[216] 82–83 °C); δ_H (400 MHz, $CDCl_3$) 5.98 (2H, s, OCH_2O), 6.18 (1H, s, OH), 6.59 (1H, s, 2-H), 6.94 (1H, s, 5-H); δ_C (101 MHz, $CDCl_3$) 97.7 (C), 97.9 (CH), 102.2 (CH_2), 115.1 (CH), 128.8 (C, q, $^1J_{CF}$ 311.6 Hz), 142.1 (C), 152.9 (C), 155.1 (C); *m/z* (ESI) 237 ($[M-H]^-$ 100%).

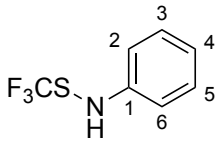
1-(Trifluoromethylthio)-2-hydroxynaphthalene (98e)[77]



The reaction was performed according to general procedure B using 2-hydroxynaphthalene (0.0231 g, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 0.5 h. Purification by flash column chromatography (10% ethyl acetate in hexane) gave 1-(trifluoromethylthio)-2-hydroxynaphthalene (**98e**) (0.0356 g, 91%) as a white solid. Mp 89–90 °C (lit.[77] 89–91 °C); δ_H (400 MHz, $CDCl_3$) 6.92 (1H, s), 7.30 (1H, d, *J* 8.9 Hz, 3-H), 7.43 (1H, ddd, *J* 8.2, 6.9, 1.1 Hz, 7-H), 7.63 (1H, ddd, *J* 8.2, 6.9, 1.3 Hz, 6-H), 7.81 (1H, br d, *J* 8.2 Hz, 8-H), 7.95 (1H, d, *J* 8.9 Hz, 4-H), 8.34 (1H, br d, *J* 8.2 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 101.0 (C), 117.2 (CH),

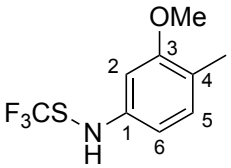
124.4 (CH), 124.5 (CH), 128.5 (CH), 128.7 (CH), 129.0 (C, q, $^1J_{CF}$ 312.8 Hz), 129.6 (C), 135.0 (CH), 136.0 (C), 158.5 (C); *m/z* (ESI) 243 ([M−H]$^-$. 100%).

_N_-(Trifluoromethylthio)aniline (99a)[217]



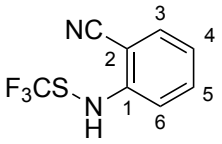
The reaction was performed according to general procedure B using aniline (0.015 mL, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 0.75 h. Purification by flash column chromatography (pentane–5% diethyl ether in pentane) gave *N*-(trifluoromethylthio)aniline (**99a**) (0.0246 g, 80%) as a colourless oil. Spectroscopic data were consistent with the literature.[217] δ_H (400 MHz, $CDCl_3$) 5.08 (1H, br s, NH), 6.94–7.00 (1H, m, 4-H), 7.05–7.11 (1H, m, 2-H and 6-H), 7.24–7.31 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 115.3 (2 × CH), 122.1 (CH), 129.5 (2 × CH), 129.5 (C, q, $^1J_{CF}$ 317.4 Hz), 145.2 (C); *m/z* (ESI) 193 (M^+. 100%).

_N_-(Trifluoromethylthio)-3-methoxy-4-methylaniline (99b)



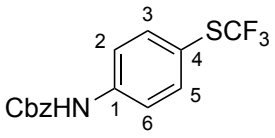
The reaction was performed according to general procedure B using 3-methoxy-4-methylaniline (0.0219 g, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 0.5 h. Purification by flash column chromatography (5% ethyl acetate in hexane) gave *N*-(trifluoromethylthio)-3-methoxy-4-methylaniline (**99b**) (0.0315 g, 83%) as an orange oil. ν_{max}/cm^{-1} (neat) 3360 (OH), 2980 (CH), 1614, 1509 (C=C), 1279, 1108, 1036, 962; δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, 4-CH_3), 3.83 (3H, s, OCH_3), 5.02 (1H, br s, NH), 6.55 (1H, dd, *J* 8.0, 2.4 Hz, 6-H), 6.64 (1H, d, *J* 2.4 Hz, 2-H), 7.00 (1H, d, *J* 8.0 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 15.6 (CH_3), 55.4 (CH_3), 98.2 (CH), 106.9 (CH), 120.2 (C), 129.6 (C, q, $^1J_{CF}$ 317.7 Hz), 131.0 (CH), 144.4 (C), 158.6 (C); *m/z* (ESI) 238.0510 (MH^+. $C_9H_{11}F_3NOS$ requires 238.0508).

_N_-(Trifluoromethylthio)-2-cyanoaniline (99c)



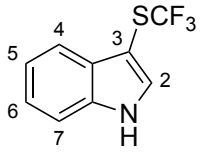
The reaction was performed according to general procedure B using 2-cyanoaniline (0.0189 g, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 22 h. Purification by flash column chromatography (5% ethyl acetate in hexane) gave *N*-(trifluoromethylthio)-2-cyanoaniline (**99c**) (0.0245 g, 70%) as a white solid. Mp 88–90 °C; ν_{max}/cm^{-1} (neat) 3286 (NH), 2821 (CH), 2224 (CN), 1604, 1575 (C=C), 1489, 1286, 1116, 921, 755; δ_H (400 MHz, $CDCl_3$) 5.95 (1H, br s, NH), 6.99–7.06 (1H, m, 6-H), 7.48–7.60 (3H, m, 3H, 4H and 5-H); δ_C (101 MHz, $CDCl_3$) 99.8 (C), 114.7 (CH), 116.5 (C), 122.0 (CH), 129.1 (C, q, $^1J_{CF}$ 316.8 Hz), 132.8 (CH), 134.6 (CH), 148.1 (C); *m/z* (ESI) 219.0200 (MH^+. $C_8H_6F_3N_2S$ requires 219.0198).

Benzyl [4-(trifluoromethylthio)benzene]carbamate (99e)



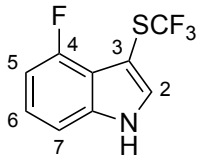
The reaction was performed according to general procedure B using benzyl benzenecarbamate (0.0364 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0026 g, 0.0160 mmol, 10 mol%) and diphenyl selenide (0.0028 mL, 0.0160 mmol, 10 mol%). The reaction mixture was stirred at room temperature for 7 h. Purification by flash column chromatography (40% dichloromethane in hexane) gave benzyl [4-(trifluoromethylthio)benzene]carbamate (**99e**) (0.0320 g, 61%) as a white solid. Mp 104–106 °C; ν_{max}/cm^{-1} (neat) 3262 (NH), 3070 (CH), 1699 (C=O), 1589 (C=C), 1526, 1239, 1115, 830, 739; δ_H (400 MHz, $CDCl_3$) 5.22 (2H, s, PhCH_2), 6.80 (1H, br s, NH), 7.33–7.43 (5H, m, Ph), 7.44–7.48 (2H, m, 2-H and 6-H), 7.56–7.62 (2H, m, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 67.6 (CH_2), 118.1 (C, q, $^3J_{CF}$ 2.3 Hz), 119.1 (2 × CH), 128.6 (2 × CH), 128.7 (CH), 128.9 (2 × CH), 129.7 (C, q, $^1J_{CF}$ 308.1 Hz), 135.8 (C), 137.8 (2 × CH), 140.6 (C), 153.0 (C); *m/z* (APCI) 328.0615 (MH^+. $C_{15}H_{13}F_3NO_2S$ requires 328.0614).

3-(Trifluoromethylthio)indole (100a)[77]



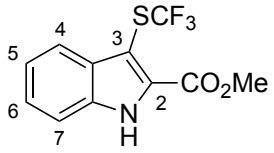
The reaction was performed according to general procedure B using indole (0.0187 g, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (0.0500 g, 0.177 mmol) (**45**). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (30% diethyl ether in hexane) gave 3-(trifluoromethylthio)indole (**100a**) (0.0335 g, 96%) as an orange oil. Spectroscopic data were consistent with the literature.[77] δ_H (400 MHz, $CDCl_3$) 7.26–7.34 (2H, m, 5-H and 6-H), 7.40–7.46 (1H, m, 7-H), 7.55 (1H, d, *J* 2.6 Hz, 2-H), 7.79–7.84 (1H, m, 4-H), 8.50 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 95.8 (C, q, $^3J_{CF}$ 2.4 Hz), 111.8 (CH), 119.5 (CH), 121.8 (CH), 123.6 (CH), 129.6 (C, q, $^1J_{CF}$ 309.9 Hz), 129.6 (C), 132.9 (CH), 136.2 (C); *m/z* (ESI) 216 ([M−H]$^-$. 100%).

3-(Trifluoromethylthio)-4-fluoroindole (100b)



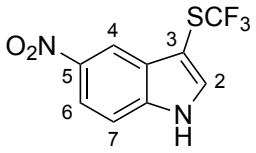
The reaction was performed according to general procedure B using 4-fluoroindole (0.0216 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (0.0500 g, 0.177 mmol) (**45**), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 3 h. Purification by flash column chromatography (10% ethyl acetate in hexane) gave 3-(trifluoromethylthio)-4-fluoroindole (**100b**) (0.0344 g, 91%) as a white solid. Mp 91–93 °C; ν_{max}/cm^{-1} (neat) 3453 (NH), 1577 (C=C), 1509, 1318, 1235, 1092, 1007, 730; δ_H (400 MHz, $CDCl_3$) 6.87–6.96 (1H, m, 5-H), 7.16–7.24 (2H, m, 6-H and 7-H), 7.50 (1H, d, *J* 2.8 Hz, 2-H), 8.62 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 93.6 (C, q, $^3J_{CF}$ 3.0 Hz), 107.4 (CH, d, $^2J_{CF}$ 19.0 Hz), 108.0 (CH, d, $^4J_{CF}$ 4.2 Hz), 118.2 (C, d, $^2J_{CF}$ 19.0 Hz), 124.3 (CH, d, $^3J_{CF}$ 7.8 Hz), 129.4 (C, q, $^1J_{CF}$ 309.4 Hz), 133.7 (CH), 138.9 (C, d, $^3J_{CF}$ 9.5 Hz), 156.8 (C, d, $^1J_{CF}$ 250.7 Hz); *m/z* (APCI) 236.0149 (MH^+. $C_9H_6F_4NS$ requires 236.0152).

3-(Trifluoromethylthio)indole-2-carboxylic acid ethyl ester (100c)



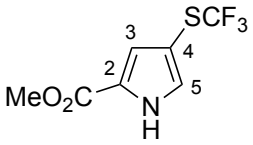
The reaction was performed according to general procedure B using indole-2-carboxylic acid ethyl ester (0.0303 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 15 minutes. Purification by flash column chromatography (5% ethyl acetate in hexane) gave 3-(trifluoromethylthio)indole-2-carboxylic acid ethyl ester (**100c**) (0.0443 g, 96%) as a white solid. Mp 136–137 °C; ν_{max}/cm^{-1} (neat) 3289 (NH), 2992 (CH), 1676 (C=O), 1510 (C=C), 1333, 1260, 1105, 1014, 740; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.50 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 7.32 (1H, ddd, *J* 8.1, 6.8, 1.2 Hz, 6-H), 7.42 (1H, ddd, *J* 8.2, 6.8, 1.2 Hz, 5-H), 7.46 (1H, br d, *J* 8.2 Hz, 4-H), 7.90 (1H, br d, *J* 8.1 Hz, 7-H), 9.47 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 62.1 (CH_2), 100.4 (C, q, $^3J_{CF}$ 2.5 Hz), 112.3 (CH), 121.3 (CH), 122.7 (CH), 126.5 (CH), 129.5 (C, q, $^1J_{CF}$ 310.3 Hz), 131.3 (C), 131.4 (C), 135.2 (C), 160.9 (C); *m/z* (APCI) 290.0458 (MH^+. $C_{12}H_{11}F_3NO_2S$ requires 290.0457).

3-(Trifluoromethylthio)-5-nitroindole (100d)[213]



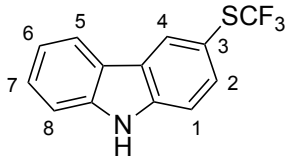
The reaction was performed according to general procedure B using 5-nitroindole (0.0259 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (25% ethyl acetate in hexane) gave 3-(trifluoromethylthio)-4-fluoroindole (**100d**) (0.0395 g, 94%) as a yellow solid. Mp 177–178 °C (lit.[213] 170–172 °C); δ_H (400 MHz, $CDCl_3$) 7.54 (1H, d, *J* 9.0 Hz, 7-H), 7.75 (1H, d, *J* 2.5 Hz, 4-H), 8.22 (1H, dd, *J* 9.0, 2.5 Hz, 6-H), 8.76 (1H, d, *J* 2.2 Hz, 2-H), 8.99 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 99.0 (C, q, $^3J_{CF}$ 2.4 Hz), 112.3 (CH), 116.8 (CH), 119.3 (CH), 129.2 (C, q, $^1J_{CF}$ 309.9 Hz), 129.4 (C), 135.9 (CH), 139.1 (C), 143.7 (C); *m/z* (APCI) 263 (MH^+. 100%).

Methyl 4-(trifluoromethylthio)-1*H*-pyrrole-2-carboxylate (100e)[218]



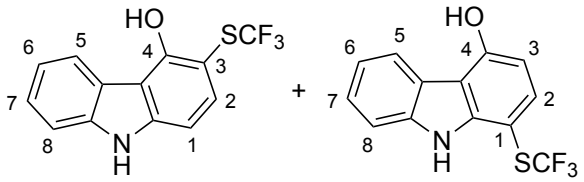
The reaction was performed according to general procedure B using methyl 1*H*-pyrrole-2-carboxylate (0.0300 g, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (0.0500 g, 0.177 mmol) (**45**). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (10%–20% dichloromethane in hexane) gave methyl 4-(trifluoromethylthio)-1*H*-pyrrole-2-carboxylate (**100e**) (0.0282 g, 78%) as an white solid. Mp 106–108 °C (lit.[218] 108–110 °C); δ_H (400 MHz, $CDCl_3$) 3.89 (3H, s, OCH_3), 7.08 (1H, dd, *J* 2.5, 1.6 Hz, 5-H), 7.23 (1H, dd, *J* 3.1, 1.6 Hz, 3-H), 9.64 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 52.1 (CH_3), 104.2 (C, q, $^3J_{CF}$ 2.8 Hz), 121.5 (CH), 124.3 (C), 129.2 (C, q, $^1J_{CF}$ 308.4 Hz), 130.0 (CH), 161.2 (C); *m/z* (ESI) 224 ([M−H]$^-$. 100%).

3-(Trifluoromethylthio)carbazole (101a)[83]



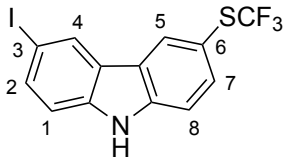
The reaction was performed according to general procedure B using carbazole (0.0268 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 7 h. Purification by flash column chromatography (7.5% ethyl acetate in hexane) gave 3-(trifluoromethylthio)carbazole (**101a**) (0.0351 g, 82%) as a white solid. Mp 143–145 °C (lit.[83] 146–147 °C); δ_H (400 MHz, $CDCl_3$) 7.30 (1H, ddd, *J* 8.0, 6.6, 1.6 Hz, 6-H), 7.42–7.51 (3H, m, 1-H, 7-H and 8-H), 7.68 (1H, dd, *J* 8.4, 1.7 Hz, 2-H), 8.10 (1H, br d, 8.0 Hz, 5-H), 8.19 (1H, br s, NH), 8.38 (1H, d, *J* 1.7 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 111.0 (CH), 111.5 (CH), 113.7 (C, q, $^3J_{CF}$ 2.2 Hz), 120.5 (CH), 120.8 (CH), 122.7 (C), 124.5 (C), 127.0 (CH), 129.7 (CH), 130.0 (C, q, $^1J_{CF}$ 308.2 Hz), 134.1 (CH), 139.9 (C), 140.8 (C); *m/z* (APCI) 268 (MH^+. 100%).

3-(Trifluoromethylthio)-4-hydroxycarbazole (101b) + 1-(trifluoromethylthio)-4-hydroxycarbazole (101c)



The reaction was performed according to general procedure B using 4-hydroxycarbazole (0.0293 g, 0.160 mmol) and *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol). The reaction mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (20% dichloromethane in hexane) gave 3-(trifluoromethylthio)-4-hydroxycarbazole (**101b**) (0.0230 g, 51%) as a white solid. Mp 184–186 °C; ν_{max}/cm^{-1} (neat) 3443 (NH), 3386 (OH), 2919 (CH), 1602 (C=C), 1443, 1247, 1092, 755; δ_H (400 MHz, $CDCl_3$) 7.01 (1H, br s, OH), 7.04 (1H, d, *J* 8.4 Hz, 1-H), 7.32 (1H, ddd, *J* 8.0, 5.5, 2.7 Hz, 6-H), 7.29–7.34 (2H, m, 7-H and 8-H), 7.55 (1H, d, *J* 8.4 Hz, 2-H), 8.23 (1H, br s, NH), 8.34 (1H, d, *J* 8.0 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 96.8 (C), 104.6 (CH), 110.5 (CH), 111.6 (C), 120.9 (CH), 122.3 (C), 123.3 (CH), 126.0 (CH), 129.0 (C, q, $^1J_{CF}$ 311.1 Hz), 135.0 (CH), 139.0 (C), 143.8 (C), 154.9 (C); *m/z* (ESI) 284.0352 (MH^+. $C_{13}H_9F_3NOS$ requires 284.0351). Further elution (50% dichloromethane in hexane) gave 1-(trifluoromethylthio)-4-hydroxycarbazole (**101c**) (0.0132 g, 29%) as a white solid. Mp 153–155 °C; ν_{max}/cm^{-1} (neat) 3473 (NH), 3352 (OH), 2919 (CH), 1584 (C=C), 1442, 1295, 1100, 801, 745; δ_H (400 MHz, $CDCl_3$) 5.91 (1H, br s, OH), 6.63 (1H, d, *J* 8.2 Hz, 3-H), 7.31 (1H, ddd, *J* 7.8, 6.9, 1.3 Hz, 6-H), 7.46 (1H, ddd, *J* 8.2, 6.9, 1.2 Hz, 7-H), 7.51 (1H, ddd, *J* 8.2, 1.3, 0.8 Hz, 8-H), 7.53 (1H, d, *J* 8.2 Hz, 2-H), 8.25–8.30 (1H, m, 5-H), 8.58 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 95.6 (C), 106.9 (CH), 110.7 (CH), 112.3 (C), 120.7 (CH), 122.6 (C), 123.1 (CH), 126.1 (CH), 129.7 (C, q, $^1J_{CF}$ 310.5 Hz), 136.6 (CH), 138.5 (C), 144.8 (C), 155.2 (C); *m/z* (ESI) 284.0353 (MH^+. $C_{13}H_9F_3NOS$ requires 284.0351).

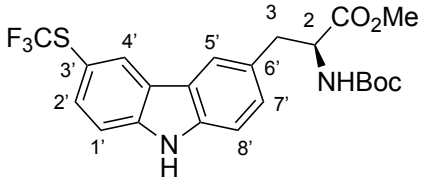
3-Iodo-6-(trifluoromethylthio)carbazole (101d)



The reaction was performed according to general procedure B using 3-iodocarbazole (0.0469 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 15 minutes. Purification by flash column chromatography (10–15% ethyl acetate in hexane) gave 3-iodo-6-(trifluoromethylthio)carbazole (**101d**) (0.0590 g, 94%) as a white solid. Mp

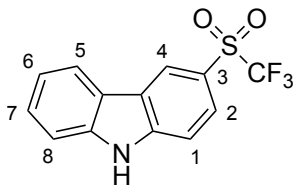
134–136 °C; ν_{max}/cm^{-1} (neat) 3483 (NH), 2918 (CH), 1597 (C=C), 1468, 1287, 1098, 868, 806; δ_H (400 MHz, $CDCl_3$) 7.24 (1H, d, *J* 8.5 Hz, 1-H), 7.44 (1H, d, *J* 8.5 Hz, 8-H), 7.70 (1H, dd, *J* 8.5, 1.8 Hz, 7-H), 7.72 (1H, dd, *J* 8.5, 1.7 Hz, 2-H), 8.22 (1H, br s, NH), 8.31 (1H, br d, *J* 1.8 Hz, 5-H), 8.40 (1H, d, *J* 1.7 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 83.1 (C), 111.7 (CH), 113.0 (CH), 114.4 (C, q, $^3J_{CF}$ 2.3 Hz), 123.2 (C), 125.2 (C), 129.7 (CH), 129.9 (CH), 129.9 (C, q, $^1J_{CF}$ 308.4 Hz), 134.7 (CH), 135.3 (CH), 139.0 (C), 140.7 (C); *m/z* (APCI) 392.9290 (M^+. $C_{13}H_7F_3INS$ requires 392.9290).

Methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(3'-trifluoromethyl-9*H*-carbazol-6'-yl)propanoate (101g)



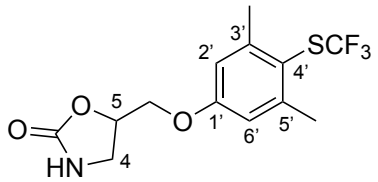
The reaction was performed according to general procedure B using methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(9*H*-carbazol-3'-yl)propanoate (0.0295 g, 0.0800 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0250 g, 0.0880 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 10 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 10 mol%). The reaction mixture was stirred at room temperature for 48 h. Purification by flash column chromatography (50% diethyl ether in hexane) gave methyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-(3'-trifluoromethyl-9*H*-carbazol-6'-yl)propanoate (**101g**) (0.0089 g, 24%) as a white solid. Mp 173–175 °C; $[\alpha]_D^{18}$ +49.9 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3356 (NH), 2918 (CH), 1734 (C=O), 1680 (C=O), 1525 (C=C), 1362, 1246, 1107, 804; (101 MHz, $CDCl_3$) 1.41 (9H, s, 3 × CH_3), 3.05−3.36 (2H, m, 3-H_2), 3.74 (3H, s, OCH_3), 4.43−4.70 (1H, m, 2-H), 5.03 (1H, br d, *J* 8.3 Hz, N*H*Boc), 7.22 (1H, d, *J* 8.4 Hz, 7'-H), 7.36 (1H, d, *J* 8.4 Hz, 8'-H), 7.43 (1H, d, *J* 8.2 Hz, 1'-H), 7.66 (1H, d, *J* 8.2 Hz, 2'-H), 7.83 (1H, s, 5'-H), 8.29 (1H, br s, NH), 8.32 (1H, s, 4'-H); δ_C (101 MHz, $CDCl_3$) 28.4 (3 × CH_3), 38.6 (CH_2), 52.4 (CH_3), 55.1 (CH), 80.2 (C), 111.2 (CH), 111.6 (CH), 113.7 (C, q, $^3J_{CF}$ 1.8 Hz), 121.3 (CH), 123.0 (C), 124.2 (C), 128.2 (CH), 129.7 (CH), 130.0 (C, q, $^1J_{CF}$ 308.1 Hz), 134.2 (CH), 139.1 (C), 141.1 (C), 155.3 (C), 172.7 (C).

3-[(Trifluoromethylthio)sulfonyl]carbazole (102)



To a solution of 3-(trifluoromethylthio)carbazole (**101a**) (0.0250 g, 0.0935 mmol) in glacial acetic acid (0.5 mL) was added 30% hydrogen peroxide in water (0.048 mL, 0.468 mmol) and the reaction mixture was stirred at 50 °C for 5 h and then 75 °C for 19 h. A further portion of 30% % hydrogen peroxide in water (0.019 mL, 0.187 mmol) was added and the reaction mixture was stirred at 75 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL) and washed with water (5 mL). The aqueous layer was further extracted with ethyl acetate (2 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (80–100% dichlomethane in hexane) gave 3-[(trifluoromethylthio)sulfonyl]carbazole (**102**) (0.0174 g, 62%) as a white solid. Mp 200–202 °C; ν_{max}/cm^{-1} (neat) 3390 (NH), 2924 (CH), 1601 (C=C), 1350, 1203, 1126, 1057, 955; δ_H (400 MHz, $CDCl_3$) 7.36–7.42 (1H, m, 6-H), 7.51–7.59 (2H, m, 7-H and 8-H), 7.63 (1H, d, *J* 8.4 Hz, 1-H), 8.04 (1H, br d, *J* 8.4 Hz, 2-H), 8.17 (1H, d, *J* 7.7 Hz, 5-H), 8.62 (1H, br s, NH), 8.76 (1H, br s, 4-H); δ_C (101 MHz, $CDCl_3$) 111.4 (CH), 111.5 (CH), 120.3 (C, q, $^1J_{CF}$ 325.7 Hz), 120.5 (C, q, $^3J_{CF}$ 1.5 Hz), 121.1 (CH), 121.6 (CH), 122.4 (C), 124.0 (C), 124.8 (CH), 127.6 (CH), 128.0 (CH), 140.1 (C), 143.7 (C); *m/z* (ESI) 299.0221 (M^+. $C_{13}H_8F_3NO_2S$ requires 299.0222).

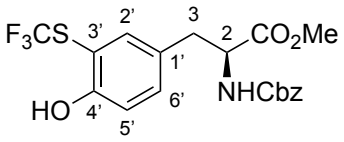
5-[(3',5'-Dimethyl-4'-(trifluoromethylthio)phenoxy)methyl]-1,3-oxazolidin-2-one (103a)



The reaction was performed according to general procedure B using metaxalone (**89**) (0.0354 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0026 g, 0.0160 mmol, 10 mol%) and diphenyl selenide (0.0028 mL, 0.0160 mmol, 10 mol%). The reaction mixture was stirred at 40 °C for 48 h. Purification by flash column chromatography (30% ethyl acetate in hexane) gave 5-[(3',5'-dimethyl-4'-(trifluoromethylthio)phenoxy)methyl]-1,3-oxazolidin-2-one (**103a**) (0.0353 g, 69%) as a white solid. Mp 95–97 °C; ν_{max}/cm^{-1} (neat) 3466 (NH), 2981 (CH), 1748 (C=O), 1591 (C=C), 1311, 1231, 1153, 1095, 964; δ_H (400 MHz, $CDCl_3$) 2.53 (6H, s, 3'- CH_3 and 5'-CH_3), 3.59

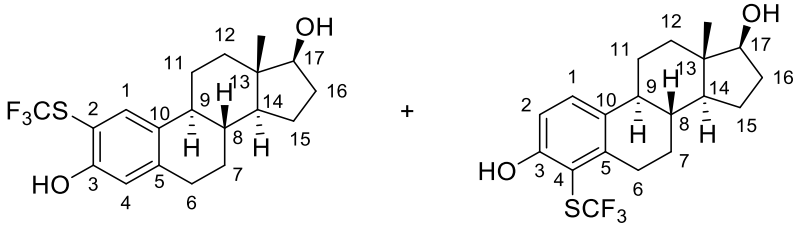
(1H, dd, *J* 8.8, 6.1 Hz, 5-C*H*H), 3.78 (1H, t, *J* 8.8 Hz, 5-CH*H*), 4.15 (2H, d, *J* 4.8 Hz, 4-H_2), 4.92–5.00 (1H, m, 5-H), 6.14 (1H, br s, NH), 6.73 (2H, s, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 22.6 (2 × CH_3), 42.8 (CH_2), 67.9 (CH_2), 74.1 (CH), 114.8 (2 × CH), 115.7 (C, q, $^3J_{CF}$ 1.8 Hz), 130.1 (C, q, $^1J_{CF}$ 309.6 Hz), 147.6 (2 × C), 159.7 (C), 159.9 (C); *m/z* (APCI) 322.0721 (MH^+. $C_{13}H_{15}F_3NO_3S$ requires 322.0719).

_N_-(Benzyloxycarbonyl)-3'-(trifluoromethylthio)-L-tyrosine methyl ester (103b)



The reaction was performed according to general procedure B using *N*-(benzyloxycarbonyl)-L-tyrosine methyl ester (0.0527 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0026 g, 0.0160 mmol, 10 mol%) and diphenyl selenide (0.0028 mL, 0.0160 mmol, 10 mol%). The reaction mixture was stirred at 40 °C for 48 h. Purification by flash column chromatography (30% ethyl acetate in hexane) gave *N*-(benzyloxycarbonyl)-3'-(trifluoromethylthio)-L-tyrosine methyl ester (**103b**) (0.0482 g, 70%) as a white solid. Mp 109–111 °C; $[\alpha]_D^{17}$ +69.6 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3420 (NH), 3301 (OH), 2947 (CH), 1735 (C=O), 1691 (C=O), 1541 (C=C), 1486, 1271, 1190, 1107, 733; δ_H (400 MHz, $CDCl_3$) 3.03 (1H, dd, *J* 14.1, 5.8 Hz, 3-*H*H), 3.11 (1H, dd, *J* 14.1, 5.8 Hz, 3-H*H*), 3.72 (3H, s, OCH_3), 4.60–4.67 (1H, m, 2-H), 5.08 (1H, d, *J* 12.0 Hz, PhC*H*H), 5.13 (1H, d, *J* 12.0 Hz, PhCH*H*), 5.28 (1H, br d, *J* 7.9 Hz, NH), 6.31 (1H, s, OH), 6.96 (1H, d, *J* 8.4 Hz, 5'-H), 7.16 (1H, dd, *J* 8.4, 2.2 Hz, 6'-H), 7.29–7.39 (6H, m, 2'-H and Ph); δ_C (101 MHz, $CDCl_3$) 37.2 (CH_2), 52.6 (CH_3), 54.9 (CH), 67.2 (CH_2), 108.5 (C), 116.6 (CH), 128.3 (2 × CH), 128.4 (CH), 128.7 (2 × CH), 128.8 (C, q, $^1J_{CF}$ 310.6 Hz), 129.1 (C), 135.4 (CH), 136.3 (C), 138.8 (CH), 155.7 (C), 157.4 (C), 171.7 (C); *m/z* (ESI) 430.0934 (MH^+. $C_{19}H_{19}F_3NO_5S$ requires 430.0931).

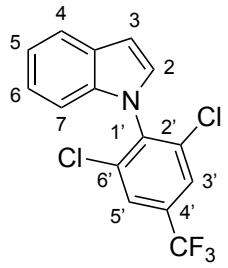
2-(Trifluoromethylthio)-β-estradiol (103c) + 4-(trifluoromethylthio)-β-estradiol (103d)



The reaction was performed according to general procedure B using β-estradiol (0.0436 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at 40 °C for 22 h. Purification by flash column

chromatography (40% diethyl ether in hexane) gave 2-(trifluoromethylthio)-β-estradiol (0.0328 g, 55%) (**103c**) as a white solid. Mp 112–115 °C; $[\alpha]_D^{17}$ +113.7 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3328 (OH), 2928 (CH), 1604 (C=C), 1485, 1103, 905, 733; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, s, 13-CH_3), 1.15−1.55 (7H, m, 7-*H*H, 8-H, 11-*H*H, 12-*H*H, 14-H, 15-*H*H and 16-*H*H), 1.66–1.75 (1H, m, 15-H*H*), 1.85−1.92 (1H, m, 7-H*H*), 1.93–2.00 (1H, m, 12-H*H*), 2.08−2.21 (2H, m, 9-H and 16-H*H*), 2.26−2.35 (1H, m, 11-H*H*), 2.83−2.89 (2H, m, 6-H_2), 3.70–3.77 (1H, m, 17-H), 6.06 (1H, s, 17-OH), 6.79 (1H, s, 4-H), 7.44 (1H, s, 1-H); δ_C (101 MHz, $CDCl_3$) 11.2 (CH_3), 23.3 (CH_2), 26.4 (CH_2), 27.0 (CH_2), 29.8 (CH_2), 30.7 (CH_2), 36.7 (CH_2), 38.6 (CH), 43.4 (C), 43.7 (CH), 50.2 (CH), 81.2 (CH), 105.3 (C, q, $^3J_{CF}$ 2.0 Hz), 116.0 (CH), 129.0 (C, q, $^1J_{CF}$ 310.5 Hz), 134.4 (C), 135.2 (CH), 144.4 (C), 155.8 (C); *m/z* (ESI) 355.1340 (MH^+–H_2O. $C_{19}H_{22}F_3OS$ requires 355.1338). Further elution (40% diethyl ether in hexane) gave 4-(trifluoromethylthio)-β-estradiol (**103d**) as a white solid (0.0160 g, 27%). Mp 88–90 °C; $[\alpha]_D^{18}$ +58.0 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3461 (OH), 2936 (CH), 1470 (C=C), 1284, 1154, 1098, 801; δ_H (400 MHz, $CDCl_3$) 0.79 (3H, s, 13-CH_3), 1.14−1.56 (7H, m, 7-*H*H, 8-H, 11-*H*H, 12-*H*H, 14-H, 15-*H*H and 16-*H*H), 1.66–1.76 (1H, m, 15-H*H*), 1.92–2.00 (1H, m, 7-H*H* and 12-H*H*), 2.08−2.23 (2H, m, 9-H and 16-H*H*), 2.26−2.34 (1H, m, 11-H*H*), 2.90 (1H, ddd, *J* 17.5, 11.1, 6.5 Hz, 6-*H*H), 3.19 (1H, ddd, *J* 17.5, 6.0, 2.2 Hz, 6-H*H*), 3.70–3.78 (1H, m, 17-H), 6.39 (1H, s, 17-OH), 6.91 (1H, d, *J* 8.7 Hz, 2-H), 7.40 (1H, d, *J* 8.7 Hz, 1-H); δ_C (101 MHz, $CDCl_3$) 11.2 (CH_3), 23.2 (CH_2), 26.6 (CH_2), 27.2 (CH_2), 29.3 (CH_2), 30.8 (CH_2), 36.8 (CH_2), 38.2 (CH), 43.4 (C), 44.3 (CH), 50.1 (CH), 82.0 (CH), 108.1 (C), 113.2 (CH), 129.1 (C, q, $^1J_{CF}$ 311.8 Hz), 131.3 (CH), 134.2 (C), 143.4 (C), 156.7 (C); *m/z* (ESI) 355.1337 (MH^+–H_2O. $C_{19}H_{22}F_3OS$ requires 355.1338).

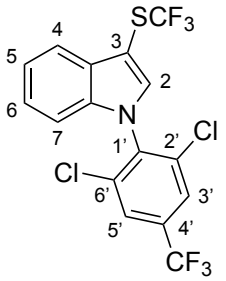
1-[(2',6'-Dichloro-4'-trifluoromethyl)benzene]indole (105)



To a solution of indole (0.0879 g, 0.750 mmol) in dry *N*,*N*'-dimethylformamide (5 mL) under argon was added potassium carbonate (0.124 g, 0.900 mmol) and 1,3-dichloro-2-fluoro-5-(trifluoromethyl)benzene (**104**) (0.135 mL, 0.900 mmol) and the reaction mixture was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (3 × 10 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane–1% ethyl acetate in hexane) gave 1-[(2',6'-dichloro-4'-trifluoromethyl)benzene]indole (**105**) as a yellow oil (0.220 g, 89%). ν_{max}/cm^{-1} (neat) 3079

(CH), 1491, 1453, 1302, 1133, 880, 815, 737; δ_H (400 MHz, $CDCl_3$) 6.79 (1H, dd, *J* 3.3, 0.9 Hz, 3-H), 6.90–6.96 (1H, m, 7-H), 7.10 (1H, d, *J* 3.3 Hz, 2-H), 7.19–7.25 (2H, m, 5-H and 6-H), 7.69–7.75 (1H, m, 4-H), 7.79 (2H, s, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 104.8 (CH), 110.3 (CH), 121.0 (CH), 121.4 (CH), 122.5 (C, q, $^1J_{CF}$ 310.6 Hz), 123.0 (CH), 126.2 (2 × CH, q, $^3J_{CF}$ 3.7 Hz), 127.6 (CH), 128.5 (C), 132.4 (C, q, $^2J_{CF}$ 34.4 Hz), 135.9 (C), 136.6 (2 × C), 138.3 (C); *m/z* (APCI) 330.0057 (MH^+. $C_{15}H_9{}^{35}Cl_2F_3N$ requires 330.0059).

1-[(2',6'-Dichloro-4'-trifluoromethyl)benzene]-3-(trifluoromethylthio)indole (106)



The reaction was performed according to general procedure B using 1-[(2',6'-dichloro-4'-trifluoromethyl)benzene]indole (**105**) (0.0528 g, 0.160 mmol), *N*-(trifluoromethylthio)saccharin (**45**) (0.0500 g, 0.177 mmol), iron(III) chloride (0.0013 g, 0.00800 mmol, 5.0 mol%) and diphenyl selenide (0.0014 mL, 0.00800 mmol, 5.0 mol%). The reaction mixture was stirred at room temperature for 0.5 h. Purification by flash column chromatography (hexane) gave 1-[(2',6'-dichloro-4'-trifluoromethyl)benzene]-3-(trifluoromethylthio)indole (**106**) (0.0622 g, 90%) as a white solid. Mp 76–78 °C; ν_{max}/cm^{-1} (neat) 3115 (CH), 1515 (C=C), 1366, 1305, 1099, 817, 746; δ_H (400 MHz, $CDCl_3$) 6.95–6.99 (1H, m, 7-H), 7.29–7.40 (2H, m, 5-H and 6-H), 7.45 (1H, s, 2-H), 7.82 (2H, s, 3'-H and 5'-H), 7.89 (1H, br d, *J* 7.6 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 98.5 (C, q, $^3J_{CF}$ 2.7 Hz), 110.8 (CH), 120.1 (CH), 122.4 (C, q, $^1J_{CF}$ 273.6 Hz), 122.7 (CH), 124.4 (CH), 126.3 (2 × CH, q, $^3J_{CF}$ 3.7 Hz), 129.4 (C, q, $^1J_{CF}$ 310.0 Hz), 129.8 (C), 133.3 (C, q, $^2J_{CF}$ 34.3 Hz), 135.6 (CH), 136.4 (2 × C), 136.4 (C), 137.0 (C); *m/z* (ESI) 429.9656 (MH^+. $C_{16}H_8{}^{35}Cl_2F_6NS$ requires 429.9653).

4.4 Thioarylation Experimental

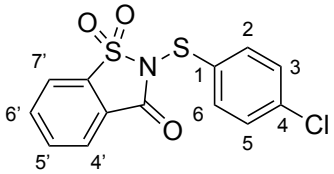
General Procedure C: Preparation of *N*-(Thioaryl)saccharins

A solution of *N*-chlorosaccharin (**75**) (1.0 equiv.) in dry dichloromethane (2 mL/mmol) was added to a stirred solution of thiol (1.0 equiv.) in dry dichloromethane (1 mL/mmol) at 0 °C under argon and stirred for 10 minutes. A solution of triethylamine (1.0 equiv.) in dry dichloromethane (1 mL/mmol) was then added dropwise over a period of 10 minutes. The reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was then diluted with dichloromethane (4 mL/mmol) and washed with water (4 mL/mmol). The aqueous layer was extracted with dichloromethane (2 × 4 mL/mmol) and the combined organic layers were washed with brine (8 mL/mmol). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by recrystallisation gave the desired product.

General Procedure D: Thioarylation of Arenes

Iron(III) chloride (0.0050 g, 0.0300 mmol, 2.5 mol%) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.026 mL, 0.0900 mmol, 7.5 mol%) and stirred for 0.5 h at room temperature and then added to a suspension of the *N*-(thioaryl)saccharin (0.330 mmol) in chloroform (0.6 mL). To the resultant mixture was added the arene (0.300 mmol) and the reaction mixture was stirred at room temperature for the required time. The reaction mixture was then diluted with dichloromethane (10 mL) and washed with water (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 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 gave the desired product.

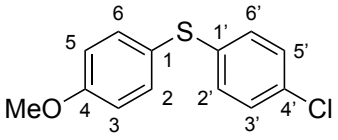
N-(4-Chlorophenylthio)saccharin (110)



The reaction was performed according to general procedure C using *N*-chlorosaccharin (1.09 g, 5.00 mmol), 4-chlorothiophenol (0.723 g, 5.00 mmol), and triethylamine (0.699 mL, 5.00 mmol). Purification by recrystallisation (toluene/hexane, 45 mL/35 mL) gave *N*-(4-chlorophenylthio)saccharin (**110**) (1.22 g, 75%) as a white solid. Mp 193–194 °C; ν_{max}/cm^{-1} (neat) 3090 (CH), 1743 (C=O), 1572 (C=C), 1339, 1220, 1092, 943, 822, 747; δ_H (400 MHz, $CDCl_3$) 7.32–7.37 (2H, m, 2-H and 6-H), 7.76–7.80 (2H, m, 3-H and 5-H), 7.84 (1H, td, *J*

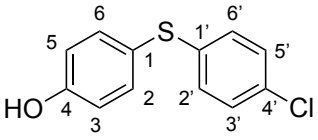
7.5, 1.4 Hz, 6'-H), 7.91 (1H, td, *J* 7.5, 1.2 Hz, 5'-H), 7.94–7.97 (1H, m, 4'-H), 8.10 (1H, br d, *J* 7.5 Hz, 7'-H); δ_C (101 MHz, $CDCl_3$) 121.8 (CH), 126.1 (CH), 127.1 (C), 129.7 (2 × CH), 131.5 (C), 134.6 (CH), 135.0 (2 × CH), 135.7 (CH), 137.4 (C), 138.2 (C), 159.5 (C); *m/z* (ESI) 324.9629 (MH^+. $C_{13}H_8{}^{35}ClNO_3S_2$ requires 324.9629).

(4'-Chlorophenyl)(4-methoxyphenyl)sulfane (109a)[51]



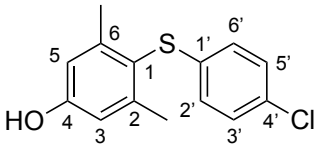
The reaction was performed according to general procedure D using anisole (0.033 mL, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.108 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 0.5 h. Purification by flash column chromatography (hexane/dichloromethane, 4:1) gave (4'-chlorophenyl)(4-methoxyphenyl)sulfane (**109a**) (0.0708 g, 94%) as a white solid. Mp 59−61 °C (lit.[51] 59−61 °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-Hydroxyphenyl)(4'-chlorophenyl)sulfane (109d)[219]



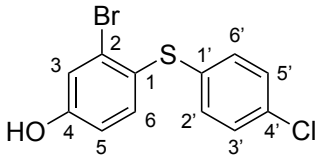
The reaction was performed according to general procedure D using phenol (0.0282 g, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.108 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 5 minutes. Purification by flash column chromatography (10–20% ethyl acetate in hexane) gave (4-hydroxyphenyl)(4'-chlorophenyl)sulfane (**109d**) (0.0526 g, 74%) as a white solid. Mp 64−66 °C (lit.[219] 65−66 °C); δ_H (400 MHz, $CDCl_3$) 5.02 (1H, s, OH), 6.82–6.86 (2H, m, 2'-H and 6'-H), 7.07–7.11 (2H, m, 3-H and 5-H), 7.18–7.22 (2H, m, 2-H and 6-H), 7.33–7.38 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 116.8 (2 × CH), 124.3 (C), 129.2 (2 × CH), 129.6 (2 × CH), 131.9 (C), 135.8 (2 × CH), 137.3 (C), 156.2 (C); *m/z* (ESI) 236 (M^+. 100%).

(2,6-Dimethyl-4-hydroxyphenyl)(4'-chlorophenyl)sulfane (109e)



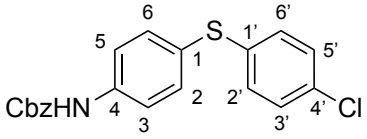
The reaction was performed according to general procedure D using 3,5-dimethylphenol (0.0369 g, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.0977 g, 0.300 mmol). The reaction mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (10% ethyl acetate in hexane) gave (2,6-dimethyl-4-hydroxyphenyl)(4'-chlorophenyl)sulfane (**109e**) (0.0504 g, 63%) as a white solid. Mp 103−104 °C; ν_{max}/cm^{-1} (neat) 3261 (OH), 2921 (CH), 1584 (C=C), 1473, 1299, 1160, 1090, 1008; δ_H (400 MHz, $CDCl_3$) 2.36 (6H, s, 2 × CH_3), 4.98 (1H, br s, OH), 6.69 (2H, br s, 3-H and 5-H), 6.80–6.85 (2H, m, 2'-H and 6'-H), 7.12–7.16 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 22.0 (2 × CH_3), 115.6 (2 × CH), 121.3 (C), 126.5 (2 × CH), 129.1 (2 × CH), 130.3 (C), 137.4 (C), 146.1 (2 × C), 156.5 (C); *m/z* (ESI) 264.0373 (M^+. $C_{14}H_{13}{}^{35}ClOS$ requires 263.0370).

(2-Bromo-4-hydroxyphenyl)(4'-chlorophenyl)sulfane (109f)[219]



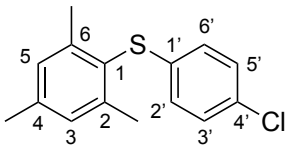
The reaction was performed according to general procedure D using 3-bromophenol (0.032 mL, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.108 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (5–10% ethyl acetate in hexane) gave (2-bromo-4-hydroxyphenyl)(4'-chlorophenyl)sulfane (**109f**) (0.0586 g, 62%) as a colourless oil. Mp 103−104 °C; ν_{max}/cm^{-1} (neat) 3346 (OH), 3082 (CH), 1590 (C=C), 1465, 1212, 1089, 1010; δ_H (400 MHz, $CDCl_3$) 5.26 (1H, s, OH), 6.27 (1H, dd, *J* 8.5, 2.7 Hz, 5-H), 7.11–7.15 (2H, m, 2'-H and 6'-H), 7.18 (1H, d, *J* 2.7 Hz, 3-H), 7.23–7.27 (2H, m, 3'-H and 5'-H), 7.28 (1H, d, *J* 8.5 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 115.9 (CH), 120.9 (CH), 126.3 (C), 128.8 (C), 129.5 (2 × CH), 130.7 (2 × CH), 132.7 (C), 1350 (C), 136.0 (CH), 156.5 (C); *m/z* (ESI) 315.9140 (M^+. $C_{12}H_8{}^{81}Br{}^{35}ClOS$ requires 315.9140).

Benzyl [4-(4'-chlorophenylthio)phenyl]carbamate (111a)



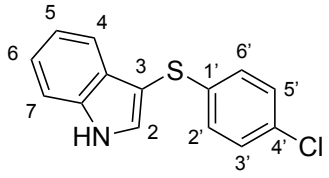
The reaction was performed according to general procedure D using *N*-(benzyloxycarbonyl)aniline (0.0681 g, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.108 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (20% diethyl ether in hexane) gave benzyl [4-(4'-chlorophenylthio)phenyl]carbamate (**111a**) (0.0968 g, 87%) as a colourless oil. Mp 125−126 °C; ν_{max}/cm^{-1} (neat) 3282 (OH), 3066 (CH), 1696 (C=O), 1591 (C=C), 1519, 1250, 1065, 812; δ_H (400 MHz, $CDCl_3$) 5.21 (2H, s, CH_2), 6.72 (1H, br s, NH), 7.12–7.16 (2H, m, 3-H and 5-H), 7.20–7.24 (2H, m, 2-H and 6-H), 7.32–7.43 (9H, m, 2'-H, 3'-H, 5'-H, 6'-H and Ph); δ_C (101 MHz, $CDCl_3$) 67.4 (CH_2), 119.6 (2 × CH), 128.2 (C), 128.5 (2 × CH), 128.6 (CH), 128.8 (2 × CH), 129.3 (2 × CH), 130.6 (2 × CH), 132.4 (C), 134.0 (2 × CH), 136.0 (C), 136.2 (C), 138.1 (C), 153.2 (C); *m/z* (ESI) 370.0667 (M^+. $C_{20}H_{17}{}^{35}ClNO_2S$ requires 370.0663).

Mesityl-(4'-chlorophenyl)sulfane (111b)[220]



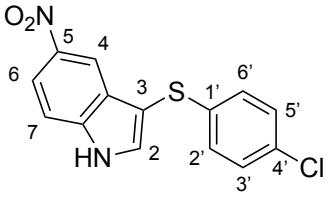
The reaction was performed according to general procedure D using mesitylene (0.042 mL, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.108 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 6 h. Purification by flash column chromatography (hexane) gave mesityl-(4'-chlorophenyl)sulfane (**111b**) (0.0754 g, 85%) as a white solid. Mp 73−75 °C (lit.[220] 78–80 °C); δ_H (400 MHz, $CDCl_3$) 2.33 (3H, s, 4-CH_3), 2.38 (6H, s, 2-CH_3 and 6-CH_3), 6.82–6.86 (2H, m, 2'-H and 6'-H), 7.02 (2H, s, 3-H and 5-H), 7.12–7.16 (2H, m, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 21.3 (CH_3), 21.8 (2 × CH_3), 126.7 (C), 126.8 (2 × CH), 129.1 (2 × CH), 129.6 (2 × CH), 130.4 (C), 137.2 (C), 139.7 (C), 143.8 (2 × C); *m/z* (ESI) 262 (M^+. 100%).

3-(4-Chlorophenylthio)indole (111c)[221]



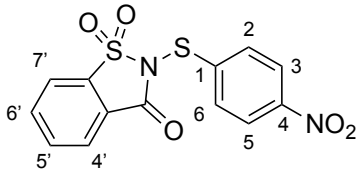
The reaction was performed according to general procedure D using indole (0.0351 g, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.0977 g, 0.300 mmol). The reaction mixture was stirred at room temperature for 15 minutes. Purification by flash column chromatography (10% ethyl acetate hexane) gave 3-(4-chlorophenylthio)indole (**111c**) (0.0751 g, 96%) as a white solid. Mp 132−134 °C (lit.[221] 134–135 °C); δ_H (400 MHz, $CDCl_3$) 7.01−7.05 (2H, m, 2'-H and 6'-H), 7.10−7.15 (2H, m, 3'-H and 5'-H), 7.19 (1H, ddd, *J* 8.0, 7.1, 1.0 Hz, 5-H), 7.29 (1H, ddd, *J* 8.2, 7.1, 1.2 Hz 6-H), 7.45 (1H, dt, *J* 8.2, 1.0 Hz, 7-H), 7.49 (1H, d, *J* 2.6 Hz, 2-H), 7.58 (1H, dd, *J* 8.0, 1.2 Hz, 4-H), 8.40 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 102.6 (C), 111.8 (CH), 119.7 (CH), 121.2 (CH), 123.4 (CH), 127.3 (2 × CH), 128.9 (2 × CH), 128.9 (C), 130.7 (C), 130.8 (CH), 136.7 (C), 138.0 (C); *m/z* (ESI) 260 (MH^+. 100%).

3-(4-Chlorophenylthio)-5-nitroindole (111d)[221]



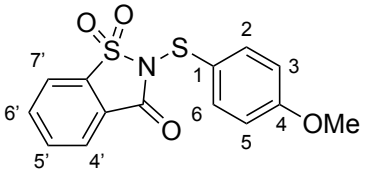
The reaction was performed according to general procedure D using 5-nitroindole (0.0486 g, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**110**) (0.108 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 18 h. Purification by flash column chromatography (40% ethyl acetate in hexane) gave 3-(4-chlorophenylthio)-5-nitroindole (**111d**) (0.0869 g, 95%) as a yellow solid. Mp 213−215 °C (lit.[221] 215–217 °C); δ_H (400 MHz, $CDCl_3$) 7.04 (2H, d, *J* 8.6 Hz, 2'-H and 6'-H), 7.16 (2H, d, *J* 8.6 Hz, 3'-H and 5'-H), 7.52 (1H, d, *J* 8.5 Hz, 7-H), 7.67 (1H, d, *J* 2.3 Hz, 2-H), 8.19 (1H, dd, *J* 8.5, 2.1 Hz, 6-H), 8.54 (1H, d, *J* 2.1 Hz, 4-H), 8.84 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 106.4 (C), 112.1 (CH), 116.9 (CH), 119.1 (CH), 127.8 (2 × CH), 128.8 (C), 129.2 (2 × CH), 131.6 (C), 133.8 (CH), 136.5 (C), 139.6 (C), 143.2 (C); *m/z* (ESI) 304 (M^+. 100%).

N-(4-Nitrophenylthio)saccharin (112)



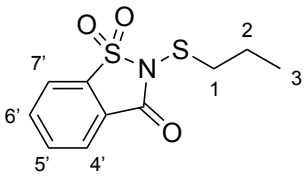
The reaction was performed according to general procedure C using *N*-chlorosaccharin (**75**) (0.435 g, 2.00 mmol), 4-nitrothiophenol (0.310 g, 2.00 mmol), and triethylamine (0.279 mL, 2.00 mmol). Purification by recrystallisation (toluene/hexane, 45 mL/35 mL) gave *N*-(4-nitrophenylthio)saccharin (**112**) (0.470 g, 70%) as a white solid. Mp 164–166 °C; ν_{max}/cm^{-1} (neat) 3106 (CH), 1749 (C=O), 1514 (C=C), 1342, 1189, 941, 839, 737; δ_H (400 MHz, $CDCl_3$) 7.65–7.70 (2H, m, 2-H and 6-H), 7.92 (1H, td, *J* 7.5, 1.5 Hz, 6'-H), 7.99 (1H, td, *J* 7.5, 1.2 Hz, 5'-H), 8.03 (1H, ddd, *J* 7.5, 1.5, 0.7 Hz, 4'-H), 8.16–8.22 (3H, m, 3-H, 5-H and 7'-H); δ_C (101 MHz, $CDCl_3$) 122.0 (CH), 124.6 (2 × CH), 126.4 (CH), 126.7 (C), 128.1 (2 × CH), 135.0 (CH), 136.2 (CH), 138.3 (C), 142.6 (C), 147.8 (C), 159.2 (C); *m/z* (ESI) 358.9779 (MNa^+. $C_{13}H_8N_2NaO_5S_2$ requires 358.9767).

N-(4-Methoxyphenylthio)saccharin (113)



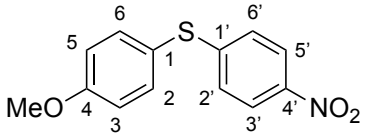
The reaction was performed according to general procedure C using *N*-chlorosaccharin (**75**) (0.326 g, 1.50 mmol), 4-methoxythiophenol (0.184 mL, 1.50 mmol), and triethylamine (0.209 mL, 1.50 mmol). Purification by recrystallisation (toluene/hexane, 30 mL/20 mL) gave *N*-(4-methoxyphenylthio)saccharin (**113**) (0.346 g, 72%) as a white solid. Mp 166–169 °C; ν_{max}/cm^{-1} (neat) 2941 (CH), 1740 (C=O), 1587 (C=C), 1346, 1176, 948, 750; δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, 4-OCH_3), 6.85–6.90 (2H, m, 3-H and 5-H), 7.80 (1H, td, *J* 7.5, 1.3 Hz, 6'-H), 7.86 (1H, td, *J* 7.5, 1.3 Hz, 5'-H), 7.89–7.94 (3H, m, 2-H, 6-H and 4'-H), 8.06 (1H, ddd, *J* 7.5, 1.3, 0.7 Hz, 7'-H); δ_C (101 MHz, $CDCl_3$) 55.6 (CH_3), 114.8 (2 × CH), 121.6 (CH), 123.6 (C), 125.9 (CH), 127.4 (C), 134.4 (CH), 135.4 (CH), 138.3 (2 × CH and C), 159.5 (C), 162.4 (C); *m/z* (ESI) 321.0120 (M^+. $C_{14}H_{11}NO_4S_2$ requires 321.0124).

_N_-(Propanethio)saccharin (114)



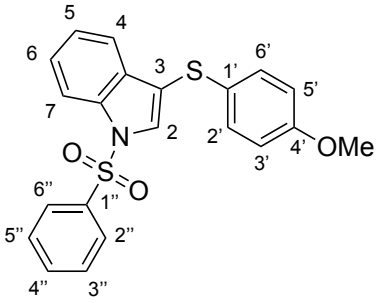
The reaction was performed according to general procedure C using _N_-chlorosaccharin (**75**) (0.109 g, 0.500 mmol), propanethiol (0.0464 g, 0.500 mmol), and triethylamine (0.070 mL, 0.500 mmol). Purification by trituration with cold hexane gave _N_-(propanethio)saccharin (**114**) (0.0812 g, 63%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 1.06 (3H, t, _J_ 7.4 Hz, 3-H_3), 1.72 (2H, sextet, _J_ 7.4 Hz, 2-H_2), 2.99–3.04 (2H, m, 1-H_2), 7.85 (1H, td, _J_ 7.5, 1.5 Hz, 6'-H), 7.91 (1H, td, _J_ 7.5, 1.3 Hz, 5'-H), 7.95–7.98 (1H, m, 4'-H), 8.10–8.13 (1H, m, 7'-H); δ_C (101 MHz, $CDCl_3$) 13.1 (CH_3), 21.8 (CH_2), 41.4 (CH_2), 121.7 (CH), 125.9 (CH), 127.3 (C), 134.6 (CH), 135.5 (CH), 138.3 (C), 160.3 (C).

(4-Methoxyphenyl)(4'-nitrophenyl)sulfane (115a)[222]



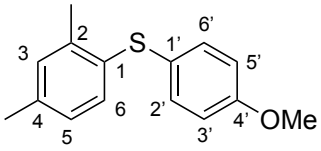
The reaction was performed according to general procedure D using anisole (0.033 mL, 0.300 mmol), _N_-(4-nitrophenylthio)saccharin (**112**) (0.121 g, 0.360 mmol), iron(III) chloride (0.0049 g, 0.0300 mmol, 10 mol%) and 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.026 mL, 0.0900 mmol, 30 mol%). The reaction mixture was stirred at room temperature for 5 h. Purification by flash column chromatography (40% dichloromethane in hexane) gave (4-methoxyphenyl)(4'-nitrophenyl)sulfane (**115a**) (0.0748 g, 95%) as a yellow solid. Mp 63–65 °C (lit.[222] 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%).

[1-(Phenylsulfonyl)indol-3-yl](4'-methoxyphenyl)sulfane (115d)[223]



The reaction was performed according to general procedure D using 1-(phenylsulfonyl)indole (0.0772 g, 0.300 mmol) and *N*-(4-methoxyphenylthio)saccharin (**113**) (0.106 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 0.5 h. Purification by flash column chromatography (50% dichloromethane in hexane) gave [1-(phenylsulfonyl)indol-3-yl](4'-methoxyphenyl)sulfane (**115d**) (0.110 g, 93%) as a white solid. Mp 85−88 °C (lit.[223] 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), 134.2 (C), 135.6 (C), 138.1 (C), 158.9 (C); *m/z* (ESI) 418 (MNa^+. 100%).

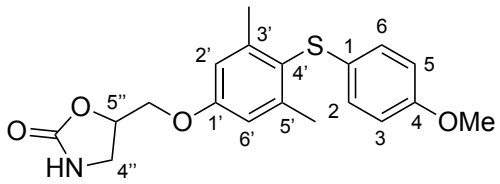
(2,4-Dimethylphenyl)(4'-methoxyphenyl)sulfane (115e)



The reaction was performed according to general procedure D using *meta*-xylene (0.037 mL, 0.300 mmol), *N*-(4-methoxyphenylthio)saccharin (**113**) (0.106 g, 0.330 mmol), iron(III) chloride (0.0024 g, 0.0150 mmol, 5 mol%) and 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.013 mL, 0.0450 mmol, 15 mol%). The reaction mixture was stirred at 60 °C for 1 h. Purification by flash column chromatography (30% dichloromethane in hexane) gave (2,4-dimethylphenyl)(4'-methoxyphenyl)sulfane (**115e**) (0.0239 g, 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, 3-H), 7.00−7.05 (2H, m, 5-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),

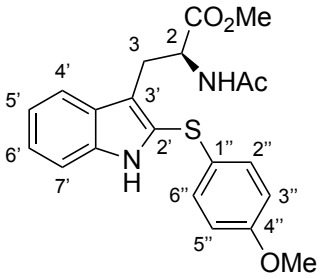
131.4 (CH), 132.7 (C), 133.2 (2 × CH), 136.9 (C), 138.3 (C), 159.2 (C); *m/z* (ESI) 267.0814 (MNa^+. $C_{15}H_{16}NaOS$ requires 267.0814).

5-{[4'-(4-Methoxyphenylthio)-3',5'-dimethylphenoxy]methyl}oxazolidin-2''-one (115f)[224]



The reaction was performed according to general procedure D using metaxalone (0.0664 g, 0.300 mmol) and *N*-(4-methoxyphenylthio)saccharin (**113**) (0.106 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by flash column chromatography (70−100% ethyl acetate in hexane) gave 5-{[4'-(4-methoxyphenylthio)-3',5'-dimethylphenoxy]methyl}oxazolidin-2''-one (**115f**) (0.0969 g, 90%) as a white solid. Mp 38−41 °C (lit.[224] 40−43 °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, 5''-CH_2O), 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%).

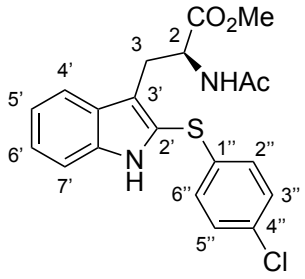
***N*-Acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (71)**



The reaction was performed according to general procedure D using methyl *N*-acetyl-L-tryptophanate (0.0781 g, 0.300 mmol) and *N*-(4-methoxyphenylthio)saccharin (**113**) (0.106 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 1.5 h. Purification by flash column chromatography (50−70% ethyl acetate in hexane) gave *N*-acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (**71**) (0.108 g, 91%) as a white solid. Mp 139−142 °C; $[\alpha]_D^{22}$ +39.1 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3368 (NH), 3281 (NH), 2949 (CH), 1736 (C=O), 1655 (C=O), 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''-

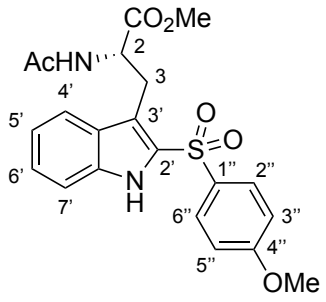
H), 7.17−7.22 (1H, m, 6'-H), 7.26 (2H, d, *J* 8.0 Hz, 7'-H), 7.55 (1H, d, *J* 7.9 Hz, 4'-H), 8.11 (1H, s, NH); δ_C (101 MHz, $CDCl_3$) 23.3 (CH_3), 27.5 (CH_2), 52.6 (CH_3), 53.0 (CH), 55.5 (CH_3), 111.1 (CH), 115.2 (2 × CH), 115.8 (C), 119.1 (CH), 120.3 (CH), 123.5 (CH), 125.8 (C), 125.9 (C), 128.2 (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).

_N_-Acetyl-[2'-(4''-chlorophenylthio)]-L-tryptophan methyl ester (116)



The reaction was performed according to general procedure D using methyl *N*-acetyl-L-tryptophanate (0.0781 g, 0.300 mmol) and *N*-(4-chlorophenylthio)saccharin (**113**) (0.108 g, 0.330 mmol). The reaction mixture was stirred at room temperature for 1 h. Purification by flash column chromatography (60−80% ethyl acetate in hexane) gave *N*-acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (**116**) (0.114 g, 95%) as a white solid. Mp 78−79 °C; $[\alpha]_D^{19}$ +60.7 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3250 (NH), 2951 (CH), 1733 (C=O), 1653 (C=O), 1475, 1216, 1089, 1009, 814; δ_H (400 MHz, $CDCl_3$) 1.84 (3H, s, NHCOC*H*$_3$), 3.33 (1H, dd, *J* 14.5, 5.9 Hz, 3-*H*H), 3.42 (1H, dd, *J* 14.5, 5.9 Hz, 3-H*H*), 3.68 (3H, s, OCH_3), 4.91 (1H, dt, *J* 7.8, 5.9 Hz, 2-H), 6.00 (1H, d, *J* 7.8 Hz, N*H*COCH$_3$), 6.96−7.00 (2H, m, 2''-H and 6''-H), 7.14−7.28 (4H, m, 5'-H, 6'-H, 3''-H and 5''-H), 7.31 (1H, br d, *J* 8.2 Hz, 7'-H), 7.60 (1H, br d, *J* 8.0 Hz, 4'-H), 8.24 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 23.3 (CH_3), 27.6 (CH_2), 52.7 (CH_3), 53.0 (CH), 111.3 (CH), 118.0 (C), 119.4 (CH), 120.5 (CH), 123.0 (C), 124.1 (CH), 128.1 (C), 128.3 (2 × CH), 129.6 (2 × CH), 132.4 (C), 135.0 (C), 137.2 (C), 169.9 (C), 172.3 (C); *m/z* (ESI) 401.0732 ($[M-H]^-$. $C_{20}H_{18}{}^{35}ClN_2O_3S$ requires 401.0732).

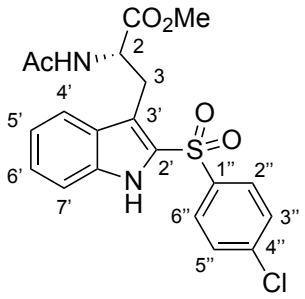
_N_-Acetyl-[2'-(4''-methoxyphenylsulfonyl)]-L-tryptophan methyl ester (117a)



To a solution of *N*-acetyl-[2'-(4''-methoxyphenylthio)]-L-tryptophan methyl ester (**71**) (0.0500 g, 0.136 mmol) in dichloromethane (1 mL) was added glacial acetic acid (0.233 mL, 4.08

mmol) and 30% hydrogen peroxide in water (0.077 mL, 0.679 mmol) and the reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (5 mL) and washed with water (5 mL). The aqueous layer was further extracted with dichloromethane (2 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50–100% ethyl acetate in hexane) gave *N*-acetyl-[2'-(4''-methoxyphenylsulfonyl)]-L-tryptophan methyl ester (**117a**) (0.0195 g, 36%) as a white solid. Mp 80−83 °C; $[\alpha]_D^{19}$ +27.5 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3342 (NH), 2919 (CH), 1733 (C=O), 1652 (C=O), 1593 (C=C), 1496, 1260, 1128, 746, 687; δ_H (400 MHz, $CDCl_3$) 1.96 (3H, s, NHCOC*H*$_3$), 3.32 (1H, dd, *J* 14.2, 9.8 Hz, 3-*H*H), 3.39 (1H, dd, *J* 14.2, 4.6 Hz, 3-H*H*), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.73 (1H, ddd, *J* 9.8, 6.8, 4.6 Hz, 2-H), 6.95−6.99 (2H, m, 3''-H and 5''-H), 7.06 (1H, d, *J* 6.8 Hz, N*H*COCH$_3$), 7.20 (1H, ddd *J* 8.1, 6.8, 1.2 Hz, 5'-H), 7.36 (1H, ddd, *J* 8.4, 6.8, 1.1 Hz, 6'-H), 7.41 (1H, dt, *J* 8.4, 1.2 Hz, 7'-H), 7.70 (1H, dd, *J* 8.1, 1.1 Hz, 4'-H), 7.86−7.91 (2H, m, 2''-H and 6''-H), 8.96 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 23.0 (CH_3), 26.4 (CH_2), 52.7 (CH_3), 53.2 (CH), 55.9 (CH_3), 112.5 (CH), 115.0 (2 × CH), 116.4 (C), 120.8 (CH), 121.7 (CH), 126.7 (CH), 127.4 (C), 129.4 (2 × CH), 131.6 (C), 132.8 (C), 136.0 (C), 164.0 (C), 170.7 (C), 172.4 (C); *m/z* (ESI) 431.1276 (MH^+. $C_{21}H_{21}N_2O_6S$ requires 431.1271).

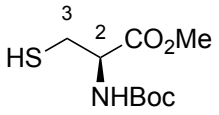
_N_-Acetyl-[2'-(4''-chlorophenylsulfonyl)]-L-tryptophan methyl ester (117b)



To a solution of *N*-acetyl-[2'-(4''-chlorophenylthio)]-L-tryptophan methyl ester (**116**) (0.0500 g, 0.124 mmol) in dichloromethane (1 mL) was added glacial acetic acid (0.212 mL, 3.72 mmol) and 30% hydrogen peroxide in water (0.070 mL, 0.621 mmol) and the reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (5 mL) and washed with water (5 mL). The aqueous layer was further extracted with dichloromethane (2 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% methanol in dichloromethane) gave *N*-acetyl-[2'-(4''-chlorophenylsulfonyl)]-L-tryptophan methyl ester (**117b**) (0.0425 g, 79%) as a white solid. Mp 97−100 °C; $[\alpha]_D^{20}$ +14.3 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3342 (NH), 2924 (CH), 1733 (C=O), 1653 (C=O), 1530 (C=C), 1318, 1154, 754, 635; δ_H (400 MHz, $CDCl_3$) 1.97 (3H, s, NHCOC*H*$_3$), 3.32 (1H, dd, *J* 14.1, 9.7 Hz, 3-*H*H), 3.42 (1H, dd, *J* 14.1, 4.6 Hz, 3-H*H*), 3.75

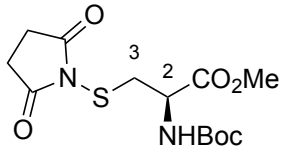
(3H, s, OCH_3), 4.77 (1H, dt, *J* 9.7, 7.0, 4.6 Hz, 2-H), 6.93 (1H, d, *J* 7.0 Hz, N*H*$COCH_3$), 7.21 (1H, ddd, *J* 8.2, 6.5, 1.5 Hz, 5'-H), 7.35−7.43 (2H, m, 6'-H and 7'-H), 7.46−7.51 (2H, m, 3''-H and 5''-H), 7.73 (1H, br d, *J* 8.2 Hz, 4'-H), 7.85−7.90 (2H, m, 2''-H and 6''-H), 9.06 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 23.1 (CH_3), 26.7 (CH_2), 52.7 (CH_3), 53.1 (CH), 112.6 (CH), 117.7 (C), 120.9 (CH), 122.0 (CH), 127.1 (CH), 127.4 (C), 128.5 (2 × CH), 130.0 (2 × CH), 130.2 (C), 136.4 (C), 139.9 (C), 140.7 (C), 170.6 (C), 172.2 (C); *m/z* (ESI) 435.0780 (MH^+. $C_{20}H_{20}{}^{35}ClN_2O_5S$ requires 435.0776).

_N_-[(_tert_-Butoxy)carbonyl]-L-cysteine methyl ester (120)[225]



To a solution of L-cysteine methyl ester hydrochloride (0.858 g, 5.0 mmol) in dichloromethane (5 mL) was added triethylamine (0.767 mL, 5.5 mmol) and the resultant mixture was stirred at room temperature for 5 minutes. Di-*tert*-butyl dicarbonate (1.03 mL, 4.5 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then concentrated *in vacuo*. Purification by flash column chromatography (20% ethyl acetate in hexane) gave *N*-[(*tert*-butoxy)carbonyl]-L-cysteine methyl ester (**120**) (0.918 g, 87%) as a colourless oil. Spectroscopic data were consistent with the literature.[225] $[\alpha]_D{}^{20}$ +29.1 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (1H, t, *J* 8.9 Hz, SH), 1.45 (9H, s, 3 × CH_3), 2.90−3.04 (2H, m, 3-H_2), 3.78 (3H, s, OCH_3), 4.32−4.66 (1H, m, 2-H), 5.01−5.54 (1H, m, NH); δ_C (101 MHz, $CDCl_3$) 27.5 (CH_2), 28.4 (3 × CH_3), 52.8 (CH_3), 55.0 (CH), 80.4 (C), 155.2 (C), 171.0 (C); *m/z* (ESI) 157 ($[M-C_5H_9O_2]Na^+$. 100%).

Methyl _N_-(_tert_-butoxycarbonyl)-_S_-(2,5-dioxopyrrolidin-1-yl)-L-cysteinate (121)[226]



A solution of *N*-chlorosuccinimide (0.140 g, 1.05 mmol) in dry dichloromethane (2 mL) was added to a stirred solution of *N*-[(*tert*-butoxy)carbonyl]-L-cysteine methyl ester (**120**) (0.235 g, 1.00 mmol) in dry dichloromethane (1 mL) at 0 °C under argon. After 10 minutes, a solution of triethylamine (0.153 mL, 1.10 mmol) in dry dichloromethane (1 mL) was then added dropwise over a period of 10 minutes. The reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was then diluted with dichloromethane (4 mL) and washed with water (4 mL). The aqueous layer was extracted with dichloromethane (2 × 4 mL) and the combined organic layers were washed with brine (8 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50% ethyl acetate in hexane) gave methyl *N*-(*tert*-butoxycarbonyl)-*S*-(2,5-dioxopyrrolidin-

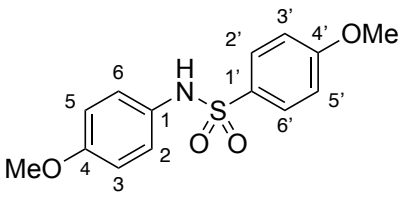
1-yl)-L-cysteinate (**121**) (0.256 g, 77%) as a colourless oil. Spectroscopic data were consistent with the literature.[226] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, 3 × CH_3), 2.79 (4H, s, 2 × CH_2), 3.00 (1H, dd, *J* 14.3, 5.7 Hz, 3-*H*H), 3.55 (1H, br d, *J* 14.3 Hz, 3-H*H*), 3.72 (3H, s, OCH_3), 4.33−4.76 (1H, m, 2-H), 5.25−5.91 (1H, m, NH); δ_C (101 MHz, $CDCl_3$) 28.5 (3 × CH_3), 28.8 (2 × CH_2), 39.5 (CH_2), 52.6 (CH), 53.0 (CH_3), 80.4 (C), 155.3 (C), 171.2 (C), 177.3 (2 × C); *m/z* (ESI) 233 ($[M-C_5H_7O_2]^+$. 100%).

4.5 One-Pot Sulfonamidation Experimental

General Procedure E: Sulfonamidation of Arenes

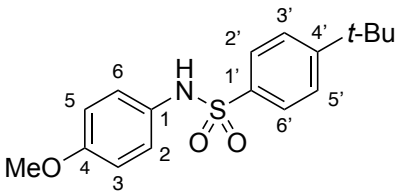
Iron(III) chloride (0.0020 g, 0.0125 mmol, 2.5 mol%) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.011 mL, 0.0375 mmol, 7.5 mol%) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-iodosuccinimide (0.113 g, 0.500 mmol) in toluene (0.5 mL). The arene (0.500 mmol) was added and the mixture was heated to 40 °C for 4 h. Upon completion of the iodination step, the reaction mixture was cooled to room temperature and the primary sulfonamide (0.750 mmol), copper(I) iodide (0.0095 g, 0.0500 mmol), caesium carbonate (0.326 g, 1.00 mmol), *N*,*N'*-dimethylethylenediamine (0.0108 mL, 0.100 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 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 gave the desired product.

4'-Methoxy-*N*-(4-methoxyphenyl)benzenesulfonamide (137a)[227]



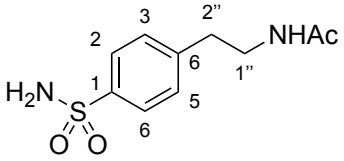
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and 4-methoxybenzenesulfonamide (0.140 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (10–25% ethyl acetate in hexane) gave 4'-methoxy-*N*-(4-methoxyphenyl)benzenesulfonamide (**137a**) as a white solid (0.100 g, 68%). Mp 90–92 °C (lit.[227] 93 °C); δ_H (400 MHz, $CDCl_3$) 3.75 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.63 (1H, br s, NH), 6.73–6.78 (2H, m, 3-H and 5-H), 6.85–6.90 (2H, m, 3'-H and 5'-H), 6.95–7.00 (2H, m, 2-H and 6-H), 7.61–7.67 (2H, m, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 55.7 (CH_3), 114.2 (2 × CH), 114.5 (2 × CH), 125.6 (2 × CH), 129.1 (C), 129.6 (2 × CH), 130.7 (C), 158.1 (C), 163.1 (C); *m/z* (ESI) 316 (MNa^+. 100%).

4'-*tert*-Butyl-*N*-(4-methoxyphenyl)benzenesulfonamide (137c)



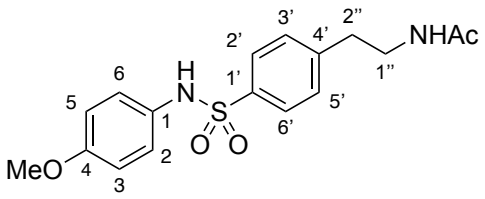
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and 4-*tert*-butylbenzenesulfonamide (0.160 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (40% diethyl ether in hexane) gave 4'-*tert*-butyl-*N*-(4-methoxyphenyl)benzenesulfonamide (**137c**) as a white solid (0.123 g, 77%). Mp 126–129 °C; ν_{max}/cm^{-1} (neat) 3248 (NH), 2962 (CH), 1508, 1400, 1327, 1157, 1130, 1065, 717; δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, $C(CH_3)_3$), 3.76 (3H, s, OCH_3), 6.61 (1H, br s, NH), 6.76 (2H, d, *J* 8.7 Hz, 3-H and 5-H), 6.99 (2H, d, *J* 8.7 Hz, 2-H and 6-H), 7.40–7.46 (2H, m, 3'-H and 5'-H), 7.63 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 31.2 (3 × CH_3), 35.3 (C), 55.6 (CH_3), 114.6 (2 × CH), 125.5 (2 × CH), 126.1 (2 × CH), 127.3 (2 × CH), 129.1 (C), 136.3 (C), 156.8 (C), 158.1 (C); *m/z* (ESI) 320.1310 (MH^+. $C_{17}H_{22}NO_3S$ requires 320.1315).

***N*-(4-Sulfamoylphenethyl)acetamide**[228]



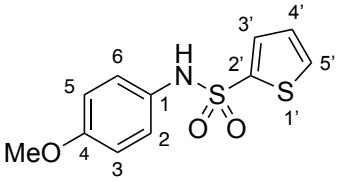
To a solution of 4-(2-aminoethyl)benzenesulfonamide (0.250 g, 1.25 mmol) in dichloromethane (3 mL) at 0 °C was added triethylamine (0.262 mL, 1.88 mmol) followed by acetyl chloride (0.134 mL, 1.88 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then concentrated *in vacuo*. Purification by flash column chromatography (5–6% methanol in dichloromethane) gave *N*-(4-sulfamoylphenethyl)acetamide as a white solid (0.213 g, 70%). Mp 168–169 °C (lit.[228] 166–168 °C); δ_H (400 MHz, CD_3OD) 1.90 (3H, s, $COCH_3$), 2.88 (2H, t, *J* 7.2 Hz, 2''-H_2), 3.42 (2H, t, *J* 7.2 Hz, 1''-H_2), 7.40 (2H, d, *J* 8.5 Hz, 3-H and 5-H), 7.83 (2H, d, *J* 8.5 Hz, 2-H and 6-H); δ_C (101 MHz, CD_3OD) 22.5 (CH_3), 36.2 (CH_2), 41.5 (CH_2), 127.3 (2 × CH), 130.4 (2 × CH), 143.1 (C), 145.3 (C), 173.3 (C); *m/z* (ESI) 241 ($[M-H]^-$. 100%).

***N*-{2''-[4'-(4-Methoxyphenyl)sulfamoylphenyl]ethyl}acetamide (137d)**



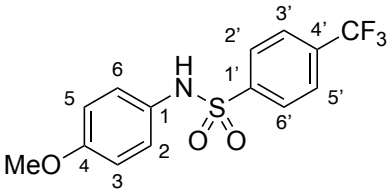
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and *N*-[2'-(4-sulfamoylphenyl)ethyl]acetamide (0.182 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (1.5–4% methanol in dichloromethane) gave *N*-{2''-[4'-(4-methoxyphenyl)sulfamoylphenyl]ethyl}acetamide (**137d**) as a white solid (0.124 g, 71%). Mp 129–131 °C; ν_{max}/cm^{-1} (neat) 3379 (NH), 2974 (CH), 1643 (C=O), 1543, 1504, 1153, 1092, 1030, 837; δ_H (400 MHz, CD_3OD) 1.87 (3H, s, $COCH_3$), 2.83 (2H, t, *J* 7.2 Hz, 2''-H_2), 3.39 (2H, t, *J* 7.2 Hz, 1''-H_2), 3.71 (3H, s, OCH_3), 6.75 (2H, d, *J* 9.0 Hz, 3-H and 5-H), 6.96 (2H, d, *J* 9.0 Hz, 2-H and 6-H), 7.31 (2H, d, *J* 8.3 Hz, 3'-H and 5'-H), 7.60 (2H, d, *J* 8.3 Hz, 2'-H and 6'-H); δ_C (101 MHz, CD_3OD) 22.1 (CH_3), 36.2 (CH_2), 41.3 (CH_2), 55.8 (CH_3), 115.2 (2 × CH), 125.7 (2 × CH), 128.4 (2 × CH), 130.3 (2 × CH), 131.3 (C), 138.9 (C), 146.0 (C), 159.0 (C), 173.2 (C); *m/z* (ESI) 347.1071 ([M−H]$^-$. $C_{17}H_{19}N_2O_4S$ requires 347.1071).

***N*-(4-Methoxyphenyl)-2'-thiophenesulfonamide (137e)**[229]



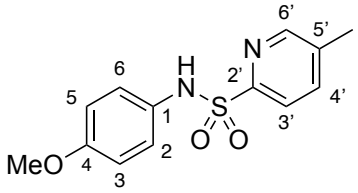
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and 2-thiophenesulfonamide (0.122 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (10–25% ethyl acetate in hexane) gave *N*-(4-methoxyphenyl)-2'-thiophenesulfonamide (**137e**) as a white solid (0.849 g, 68%). Mp 100–103 °C (lit.[229] 104 °C); δ_H (400 MHz, $CDCl_3$) 3.77 (3H, s, OCH_3), 6.59 (1H, br s, NH), 6.77–6.83 (2H, m, 3-H and 5-H), 7.00 (1H, dd, *J* 5.0, 3.8 Hz, 4'-H), 7.01–7.07 (2H, m, 2-H and 6-H), 7.42 (1H, dd, *J* 3.8, 1.3 Hz, 5'-H), 7.53 (1H, dd, *J* 5.0, 1.3 Hz, 3'-H); δ_C (101 MHz, $CDCl_3$) 55.6 (CH_3), 114.6 (2 × CH), 125.8 (2 × CH), 127.4 (CH), 128.6 (C), 132.4 (CH), 133.0 (CH), 139.4 (C), 158.4 (C); *m/z* (ESI) 270 (MH^+. 100%).

***N*-(4-Methoxyphenyl)-4'-(trifluoromethyl)benzenesulfonamide (138a)**[230]



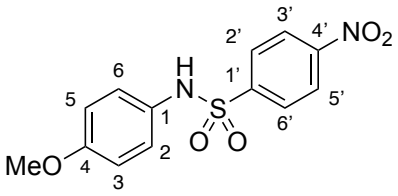
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and 4-(trifluoromethyl)benzenesulfonamide (0.169 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (30–40% diethyl ether in hexane) gave *N*-(4-methoxyphenyl)-4'-(trifluoromethyl)benzenesulfonamide (**138a**) as a white solid (0.130 g, 78%). Mp 137–140 °C (lit.[230] 141–143 °C); δ_H (400 MHz, $CDCl_3$) 3.77 (3H, s, OMe), 6.89 (1H, br s, NH), 6.75–6.82 (2H, m, 3-H and 5-H), 6.96–7.02 (2H, m, 2-H and 6-H), 7.70 (2H, d, *J* 8.3 Hz, 3'-H and 5'-H), 7.83 (2H, d, *J* 8.3 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 55.6 (CH_3), 114.8 (2 × CH), 123.4 (C, q, $^1J_{CF}$ 272.8 Hz), 126.0 (2 × CH), 126.3 (2 × CH, q, $^3J_{CF}$ 3.7 Hz), 128.0 (2 × CH), 128.0 (C), 134.7 (C, q, $^2J_{CF}$ 33.0 Hz), 142.6 (C), 158.6 (C); *m/z* (ESI) 330 ([M−H]$^-$. 100%).

***N*-(4-Methoxyphenyl)-5'-methyl-2'-pyridinesulfonamide (138b)**



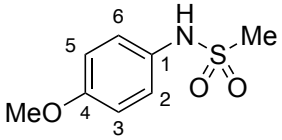
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and 5-methyl-2-pyridinesulfonamide (0.129 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (40% ethyl acetate in hexane) gave *N*-(4-methoxyphenyl)-5'-methyl-2'-pyridinesulfonamide (**138b**) as a white solid (0.0917 g, 66%). Mp 186–189 °C; ν_{max}/cm^{-1} (neat) 3256 (NH), 2924 (CH), 1508, 1339, 1250, 1169, 1107, 1030; δ_H (400 MHz, $CDCl_3$) 2.39 (3H, s, 5'-CH_3), 3.71 (3H, s, OCH_3), 6.68–6.74 (2H, m, 3-H and 5-H), 7.13–7.18 (2H, m, 2-H and 6-H), 7.56 (1H, dd, *J* 8.0, 1.3 Hz, 4'-H), 7.70 (1H, d, *J* 8.0 Hz, 3'-H), 8.51–8.59 (2H, m, NH and 6'-H); δ_C (101 MHz, $CDCl_3$) 18.7 (CH_3), 55.5 (CH_3), 114.4 (2 × CH), 123.1 (CH), 126.0 (2 × CH), 128.8 (C), 137.6 (C), 138.2 (CH), 150.6 (CH), 153.6 (C), 158.0 (C); *m/z* (ESI) 301.0620 (MNa^+. $C_{13}H_{14}N_2NaO_3S$ requires 301.0617).

***N*-(4-Methoxyphenyl)-4'-nitrobenzenesulfonamide (138c)**[231]



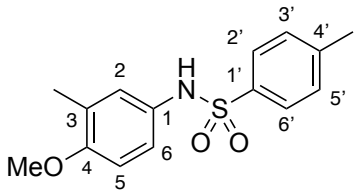
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and 4-nitrobenzenesulfonamide (0.152 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (20–40% ethyl acetate in hexane) gave *N*-(4-methoxyphenyl)-4'-nitrobenzenesulfonamide (**138c**) as a pale-yellow solid (0.0659 g, 42%). Mp 174–176 °C (lit.[231] 173–175 °C); δ_H (400 MHz, $CDCl_3$) 3.78 (3H, s, OMe), 6.41 (1H, br s, NH), 6.80 (2H, d, *J* 9.0 Hz, 3-H and 5-H), 6.97 (2H, d, *J* 9.0 Hz, 2-H and 6-H), 7.86 (2H, d, *J* 9.0 Hz, 2'-H and 6'-H), 8.28 (2H, d, *J* 9.0 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 55.6 (CH_3), 114.9 (2 × CH), 124.3 (2 × CH), 126.4 (2 × CH), 127.6 (C), 128.7 (2 × CH), 144.9 (C), 150.4 (C), 158.9 (C); *m/z* (ESI) 309 (MH^+. 100%).

***N*-(4-Methoxyphenyl)methanesulfonamide (138d)**[232]



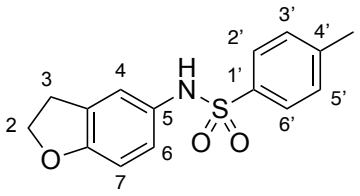
The reaction was performed according to general procedure E using anisole (0.054 mL, 0.500 mmol) and methanesulfonamide (0.0713 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (100% dichloromethane) gave *N*-(4-methoxyphenyl)methanesulfonamide (**138d**) as a yellow solid (0.0224 g, 22%). Mp 109–112 °C (lit.[232] 115 °C); δ_H (400 MHz, $CDCl_3$) 2.95 (3H, s, SO_2CH_3), 3.80 (3H, s, OCH_3), 6.37 (1H, br s, NH), 6.86–6.93 (2H, m, 3-H and 5-H), 7.17–7.23 (2H, m, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 39.1 (CH_3), 55.7 (CH_3), 115.0 (2 × CH), 125.0 (2 × CH), 129.1 (C), 158.4 (C); *m/z* (ESI) 202 (MH^+. 100%).

***N*-(3-Methyl-4-methoxyphenyl)-4'-methylbenzenesulfonamide (139a)**



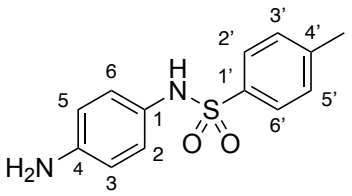
The reaction was performed according to general procedure E using 2-methylanisole (0.122 mL, 1.00 mmol), and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (25–50% diethyl ether in hexane) gave *N*-(3-methyl-4-methoxyphenyl)-4'-methylbenzenesulfonamide (**139a**) as a yellow solid (0.250 g, 86%). Mp 77–79 °C; ν_{max}/cm^{-1} (neat) 3256 (NH), 2951 (CH), 1598, 1501, 1224, 1154, 1091, 812; δ_H (400 MHz, $CDCl_3$) 2.11 (3H, s, 3-CH_3), 2.38 (3H, s, 4'-CH_3), 3.76 (3H, s, OCH_3), 6.38–6.62 (1H, m, NH), 6.65 (1H, d, *J* 9.4 Hz, 5-H), 6.81–6.86 (2H, m, 2-H and 6-H), 7.21 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.61 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 16.3 (CH_3), 21.7 (CH_3), 55.6 (CH_3), 110.3 (CH), 122.4 (CH), 126.7 (CH), 127.5 (2 × CH), 127.7 (C), 128.5 (C), 129.6 (2 × CH), 136.3 (C), 143.7 (C), 156.3 (C); *m/z* (ESI) 314.0817 (MNa^+. $C_{15}H_{17}NNaO_3S$ requires 314.0821).

***N*-(2,3-Dihydrobenzofuran-5-yl)-4'-methylbenzenesulfonamide (139b)**



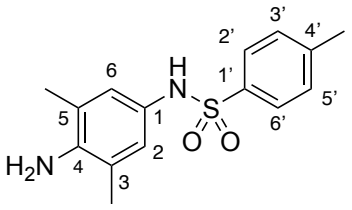
The reaction was performed according to general procedure E using 2,3-dihydrobenzofuran (0.113 mL, 1.00 mmol), and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 22 h. Purification by flash column chromatography (40% diethyl ether in hexane) gave *N*-(2,3-dihydrobenzofuran-5-yl)-4'-methylbenzenesulfonamide (**139b**) as a yellow solid (0.198 g, 68%). Mp 122–125 °C; ν_{max}/cm^{-1} (neat) 3252 (NH), 2896 (CH), 1488, 1327, 1155, 1090, 905, 810; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, 4'-CH_3), 3.13 (2H, t, *J* 8.7 Hz, 3-H_2), 4.53 (2H, t, *J* 8.7 Hz, 2-H_2), 6.57 (1H, d, *J* 8.4 Hz, 7-H), 6.67 (1H, dd, *J* 8.4, 1.4 Hz, 6-H), 6.81 (1H, br s, NH), 7.01 (1H, br s, 4-H), 7.21 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.60 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 29.8 (CH_2), 71.7 (CH_2), 109.4 (CH), 121.9 (CH), 124.3 (CH), 127.5 (2 × CH), 128.2 (C), 128.8 (C), 129.6 (2 × CH), 136.1 (C), 143.7 (C), 158.7 (C); *m/z* (ESI) 312.0666 (MNa^+. $C_{15}H_{15}NNaO_3S$ requires 312.0665).

***N*-(4-Aminophenyl)-4'-methylbenzenesulfonamide (139c)**[233]



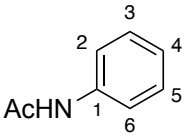
The reaction was performed according to general procedure E using aniline (0.046 mL, 0.500 mmol), *N*-iodosuccinimide (0.124 g, 0.550 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 0 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (35–40% ethyl acetate in hexane) gave *N*-(4-aminophenyl)-4'-methylbenzenesulfonamide (**139c**) as a white solid (0.0969 g, 74%). Mp 182–184 °C (lit.[233] 185–186 °C); δ_H (400 MHz, DMSO-d_6) 2.33 (3H, s, 4'-CH_3), 4.93 (2H, br s, NH_2), 6.35–6.40 (2H, m, 3-H and 5-H), 6.64–6.69 (2H, m, 2-H and 6-H), 7.30 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.51 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 9.38 (1H, s, NH); δ_C (101 MHz, DMSO-d_6) 20.9 (CH_3), 114.0 (2 × CH), 124.5 (2 × CH), 125.5 (C), 126.8 (2 × CH), 129.3 (2 × CH), 136.9 (C), 142.6 (C), 146.4 (C); *m/z* (ESI) 263 (MH^+. 100%).

***N*-(3,5-Dimethyl-4-aminophenyl)-4'-methylbenzenesulfonamide (139d)**



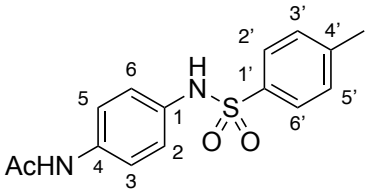
The reaction was performed according to general procedure E using 2,6-dimethylaniline (0.062 mL, 0.500 mmol), and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (60% diethyl ether in hexane) gave *N*-(4-amino-2,6-dimethylphenyl)-4'-methylbenzenesulfonamide (**139d**) as a light-brown solid (0.0843 g, 58%). Mp 120–123 °C; ν_{max}/cm^{-1} (neat) 3252 (NH), 2924 (CH), 1601 (C=C), 1485, 1319, 1153, 1092, 1030, 729; δ_H (400 MHz, $CDCl_3$) 2.06 (6H, s, 3-CH_3 and 5-CH_3), 2.38 (3H, s, 4'-CH_3), 3.52 (2H, br s, NH_2), 6.36 (1H, br s, NH), 6.63 (2H, s, 2-H and 6-H), 7.20 (2H, d, *J* 8.1 Hz, 3'-H and 5'-H), 7.59 (2H, d, *J* 8.1 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 17.7 (2 × CH_3), 21.7 (CH_3), 122.4 (2 × C), 124.7 (2 × CH), 126.1 (C), 127.5 (2 × CH), 129.5 (2 × CH), 136.6 (C), 141.5 (C), 143.5 (C); *m/z* (ESI) 291.1164 (MH^+. $C_{15}H_{19}N_2O_2S$ requires 291.1162).

Acetanilide[234]



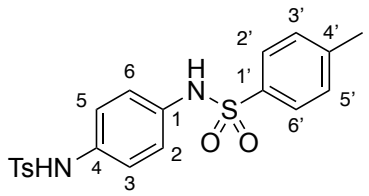
To a solution of aniline (0.489 mL, 5.37 mmol) in dichloromethane (15 mL) was added acetic anhydride (0.762 mL, 8.06 mmol). The resulting reaction mixture was left to stir at room temperature for 3 h. The reaction mixture was washed with a saturated aqueous solution of sodium bicarbonate (30 mL) and the organic layer separated. The aqueous layer was further extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (50% ethyl acetate in hexane) gave acetanilide as a white solid (0.646 g, 89%). Mp 112−114 °C (lit.[234] 111−113 °C); δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, $COCH_3$), 7.10 (1H, t, *J* 7.4 Hz, 4-H), 7.31 (2H, t, *J* 7.8 Hz, 3-H and 5-H), 7.41 (1H, br s, NH), 7.50 (2H, d, *J* 7.8 Hz, 2-H and 6-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'-Methylphenylsulfonamido)phenyl]acetamide (139e)**[235]



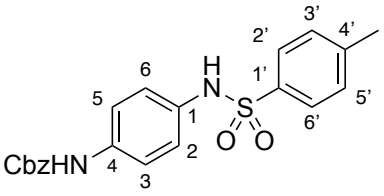
The reaction was performed according to general procedure E using acetanilide (0.135 g, 1.00 mmol), and *p*-toluenesulfonamide (0.256 g, 1.500 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (40–100% ethyl acetate in hexane) gave *N*-[4-(4'-methylphenylsulfonamido)phenyl]acetamide (**139e**) as a white solid (0.225 g, 74%). Mp 179–181 °C (lit.[235] 184–185 °C); δ_H (400 MHz, CD_3OD) 2.07 (3H, s, $COCH_3$), 2.36 (3H, s, 4'-CH_3), 7.00 (2H, d, *J* 9.0 Hz, 3-H and 5-H), 7.26 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.38 (2H, d, *J* 9.0 Hz, 2-H and 6-H), 7.59 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H); δ_C (101 MHz, CD_3OD) 21.4 (CH_3), 23.7 (CH_3), 121.8 (2 × CH), 123.5 (2 × CH), 128.3 (2 × CH), 130.5 (2 × CH), 134.8 (C), 137.0 (C), 138.0 (C), 145.0 (C), 171.5 (C); *m/z* (ESI) 305 (MH^+. 100%).

***N*,*N'*-Ditosyl-1,4-diaminobenzene (139f)**[236]



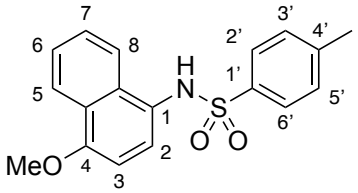
The reaction was performed according to general procedure E using iron(III) chloride (0.0041 g, 0.0250 mmol), 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.022 mL, 0.0750 mmol), *N*-tosylaniline (0.124 g, 0.500 mmol), and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 40 °C for 24 h and the *N*-arylation step at 130 °C for 24 h. Purification by flash column chromatography (80–100% diethyl ether in hexane, and then 100% ethyl acetate) gave *N*,*N'*-ditosyl-1,4-diaminobenzene (**139f**) as a white solid (0.0823 g, 40%). Mp 260–262 °C (lit.[236] 256–258 °C); δ_H (400 MHz, DMSO-d_6) 2.33 (6H, s, 4'-CH_3 and 4''-CH_3), 6.90 (4H, s, 2-H, 3-H, 5-H and 6-H), 7.29 (4H, d, *J* 8.1 Hz, 3'-H, 5'-H, 3''-H and 5''-H), 7.53 (4H, d, *J* 8.1 Hz, 2'-H, 6'-H, 2''-H and 6''-H), 10.01 (2H, br s, NH and NH); δ_C (101 MHz, DMSO-d_6) 20.9 (2 × CH_3), 121.5 (4 × CH), 126.6 (4 × CH), 129.5 (4 × CH), 134.0 (2 × C), 136.5 (2 × C), 143.1 (2 × C); *m/z* (ESI) 417 (MH^+. 100%).

Benzyl [4-(4'-methylphenylsulfonamido)phenyl]carbamate (139g)[237]



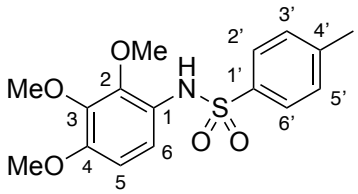
The reaction was performed according to general procedure E using benzyl (4-aminophenyl)carbamate (0.114 g, 0.500 mmol), and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 110 °C for 40 h. Purification by flash column chromatography (10% ethyl acetate in chloroform) gave benzyl [4-(4'-methylphenylsulfonamido)phenyl]carbamate (**139g**) as a white solid (0.130 g, 65%). Mp 161–163 °C (lit.[237] 162–163 °C); δ_H (400 MHz, $CDCl_3$) 2.36 (3H, s, 4'-CH_3), 5.17 (2H, s, OCH_2), 6.78 (1H, br s, NH), 6.90 (1H, br s, NH), 6.98 (2H, d, *J* 9.0 Hz, 3-H and 5-H), 7.19 (2H, d, *J* 8.3 Hz, 3'-H and 5'-H), 7.24 (2H, d, *J* 9.0 Hz, 2-H and 6-H), 7.31–7.41 (5H, m, Ph), 7.60 (2H, d, *J* 8.3 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 67.3 (CH_2), 119.6 (2 × CH), 123.9 (2 × CH), 127.4 (2 × CH), 128.5 (2 × CH), 128.6 (CH), 128.8 (2 × CH), 129.8 (2 × CH), 131.8 (C), 135.9 (C), 136.0 (C), 136.0 (C), 144.0 (C), 153.4 (C); *m/z* (ESI) 397 (MH^+. 100%).

***N*-(4-Methoxynaphthalen-1-yl)-4'-methylbenzenesulfonamide (140a)**



The reaction was performed according to general procedure E using 1-methoxynaphthalene (0.073 mL, 0.500 mmol), and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 50 °C for 5 h and the *N*-arylation step at 130 °C for 22 h, except *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine (0.016 mL, 0.100 mmol) was used. Purification by flash column chromatography (10–20% ethyl acetate in hexane) gave *N*-(4-methoxynaphthalen-1-yl)-4'-methylbenzenesulfonamide (**140a**) as a yellow solid (0.113 g, 69%). Mp 143–144 °C; ν_{max}/cm^{-1} (neat) 3261 (NH), 2936 (CH), 1596, 1465, 1304, 1272, 1185, 1091, 769; δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, 4'-CH_3), 3.98 (3H, s, OCH_3), 6.46 (1H, br s, NH), 6.68 (1H, d, *J* 8.2 Hz, 3-H), 7.15 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.20 (1H, d, *J* 8.2 Hz, 2-H), 7.38–7.46 (2H, m, 6-H and 7-H), 7.58 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H), 7.74 (1H, d, *J* 7.6 Hz, 5-H), 8.22 (1H, d, *J* 7.6 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 55.8 (CH_3), 103.2 (CH), 122.0 (CH), 122.5 (CH), 123.9 (C), 125.7 (CH), 125.7 (CH), 126.1 (C), 127.2 (CH), 127.6 (2 × CH), 129.6 (2 × CH), 131.2 (C), 136.7 (C), 143.7 (C), 155.2 (C); *m/z* (ESI) 350.0817 (MNa^+. $C_{18}H_{17}NNaO_3S$ requires 350.0821).

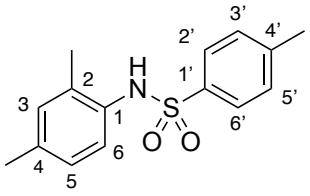
***N*-(2,3,4-Trimethoxyphenyl)-4'-methylbenzenesulfonamide (140b)**



The reaction was performed according to general procedure E using 1,2,3-trimethoxybenzene (0.0841 g, 0.500 mmol), and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 40 °C for 2.5 h and the *N*-arylation step at 150 °C for 18 h, except *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine (0.016 mL, 0.100 mmol) was used. Purification by flash column chromatography (25% ethyl acetate in hexane) gave *N*-(2,3,4-trimethoxyphenyl)-4'-methylbenzenesulfonamide (**140b**) as a white solid (0.0856 g, 51%). Mp 95–97 °C; ν_{max}/cm^{-1} (neat) 3264 (NH), 2943 (CH), 1597 (C=C), 1481, 1335, 1265, 1165, 1096; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, 4'-CH_3), 3.46 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.59 (1H, d, *J* 9.1 Hz, 5-H), 6.78 (1H, br s, NH), 7.19 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.27 (1H, d, *J* 9.1 Hz, 6-H), 7.59 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 21.6 (CH_3), 56.2 (CH_3), 60.8 (CH_3), 61.0 (CH_3), 107.0

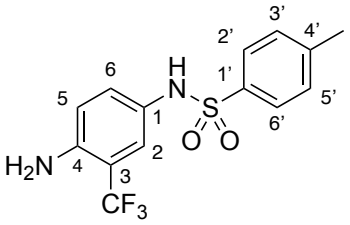
(CH), 116.9 (CH), 123.4 (C), 127.4 (2 × CH), 129.6 (2 × CH), 136.3 (C), 141.7 (C), 143.8 (C), 144.8 (C), 151.3 (C); *m/z* (ESI) 360.0863 (MNa^+. $C_{16}H_{19}NNaO_5S$ requires 360.0876).

N-(2,4-Dimethylphenyl)-4'-methylbenzenesulfonamide (140c)[238]



The reaction was performed according to general procedure E using *m*-xylene (0.061 mL, 0.500 mmol), *N*-iodosuccinimide (0.169 g, 0.750 mmol) and *p*-toluenesulfonamide (0.256 g, 1.50 mmol). The iodination step was carried out at 70 °C for 24 h and the *N*-arylation step at 150 °C for 26 h, except *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine (0.016 mL, 0.100 mmol) was used. Purification by flash column chromatography (25–30% diethyl ether in hexane) gave *N*-(2,4-dimethylphenyl)-4'-methylbenzenesulfonamide (**140c**) as a white solid (0.0760 g, 55%). Mp 89–91 (lit.[238] 93–94 °C); δ_H (400 MHz, $CDCl_3$) 1.95 (3H, s, 2-CH_3), 2.26 (3H, s, 4-CH_3), 2.39 (3H, s, 4'-CH_3), 6.22 (1H, br s, NH), 6.90 (1H, br s, 3-H), 6.93 (1H, br d, *J* 8.1 Hz, 5-H), 7.14 (1H, d, *J* 8.1 Hz, 6-H), 7.21 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.59 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 17.7 (CH_3), 21.0 (CH_3), 21.7 (CH_3), 125.2 (CH), 127.3 (2 × CH), 127.7 (CH), 129.7 (2 × CH), 131.6 (CH), 131.8 (C), 132.1 (C), 136.4 (C), 137.0 (C), 143.8 (C); *m/z* (ESI) 276 (MH^+. 100%).

N-(3-Trifluoromethyl-4-aminophenyl)-4'-methylbenzenesulfonamide (141)[239]



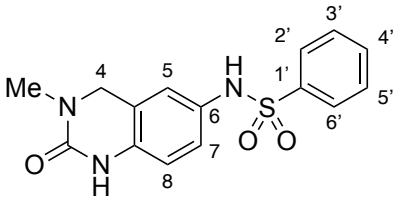
The reaction was performed according to general procedure E using 2-(trifluoromethyl)aniline (0.126 mL, 1.00 mmol), and *p*-toluenesulfonamide (0.258 g, 1.50 mmol). The iodination step was carried out at 40 °C for 4 h and the *N*-arylation step at 130 °C for 18 h. Purification by flash column chromatography (0.5% ethyl acetate in dichloromethane) gave *N*-(3-trifluoromethyl-4-aminophenyl)-4'-methylbenzenesulfonamide (**141**) as a white solid (0.207 g, 63%). Mp 133–135 °C. Spectroscopic data were consistent with the literature.[239] δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s, 4'-CH_3), 4.15 (2H, br s, NH_2), 6.37 (1H, br s, NH), 6.62 (1H, d, *J* 9.9 Hz, 5-H), 6.99–7.05 (2H, m, 2-H and 6-H), 7.23 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.57 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 21.7 (CH_3), 114.1 (C, q, $^2J_{CF}$ 30.6 Hz), 118.0 (CH), 123.4 (CH, q, $^3J_{CF}$ 5.3 Hz), 124.3 (C, q, $^1J_{CF}$

272.6 Hz), 126.1 (C), 127.5 (2 × CH), 129.8 (2 × CH), 130.0 (CH), 135.9 (C), 143.3 (C, q, $^{3}J_{CF}$ 1.8 Hz), 144.1 (C); *m/z* (ESI) 353 (MNa^{+}. 100%).

General Procedure F: One-Pot Sulfonamidation of 3,4-Dihydro-3-methyl-2(1*H*)-quinazolinone

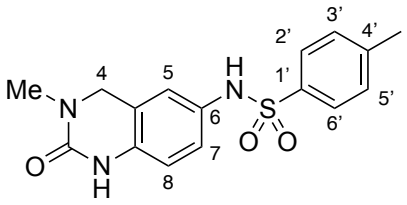
Iron(III) chloride (0.0041 g, 0.0250 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (0.022 mL, 0.0750 mmol) and stirred for 0.5 h at room temperature and then added to a suspension of *N*-bromosuccinimide (0.0979 g, 0.550 mmol) and 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (0.0811 g, 0.500 mmol) in toluene (0.5 ml). The mixture was heated to 40 °C for 4 h. Upon completion of the bromination step, the reaction mixture was cooled to room temperature and the primary sulfonamide (0.750 mmol), copper(I) iodide (0.0095 g, 0.0500 mmol), cesium carbonate (0.326 g, 1.00 mmol), *N*,*N'*-dimethylethylenediamine (0.011 mL, 0.100 mmol) and water (0.4 mL) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 20 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous solution of sodium thiosulfate (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 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 gave the desired product.

N-(3-Methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)benzenesulfonamide (135a)[138]



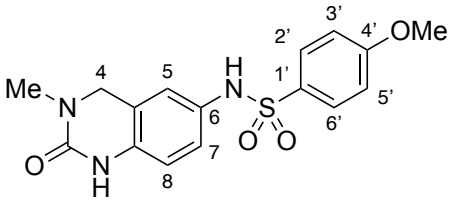
The reaction was performed according to general procedure F using 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (0.0811 g, 0.500 mmol) and benzenesulfonamide (0.118 g, 0.750 mmol). Purification by flash column chromatography (80–100% ethyl acetate in hexane) gave *N*-(3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)benzenesulfonamide (**135a**) as a white solid (0.0854 g, 54%). Mp 200–203 °C (decomposition); Spectroscopic data were consistent with the literature.[138] δ_H (400 MHz, DMSO-d_6) 2.80 (3H, s, NCH_3), 4.28 (2H, s, 4-H_2), 6.59 (1H, d, *J* 8.3 Hz, 8-H), 6.77–6.83 (2H, m, 5-H and 7-H), 7.53 (2H, t, *J* 7.7 Hz, 3'-H and 5'-H), 7.60 (1H, t, *J* 7.7 Hz, 4'-H), 7.69 (2H, d, *J* 7.7 Hz, 2'-H and 6'-H), 9.13 (1H, s, NH), 9.93 (1H, s, NH); δ_C (101 MHz, DMSO-d_6) 33.8 (CH_3), 49.6 (CH_2), 113.7 (CH), 118.4 (C), 119.3 (CH), 121.6 (CH), 126.7 (2 × CH), 129.1 (2 × CH), 130.6 (C), 132.7 (CH), 135.1 (C), 139.5 (C), 153.5 (C); *m/z* (ESI) 318 (MH^{+}. 100%).

***N*-(3-Methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4'-methylbenzenesulfonamide (135b)**[138]



The reaction was performed according to general procedure F using 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (0.0811 g, 0.500 mmol) and 4-methoxybenzenesulfonamide (0.140 g, 0.750 mmol). Purification by flash column chromatography (80–100% ethyl acetate in hexane) gave *N*-(3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4'-methylbenzenesulfonamide (**135b**) as a white solid (0.0957 g, 58%). Mp 180–183 °C (decomposition); Spectroscopic data were consistent with the literature.[138] δ_H (400 MHz, DMSO-d_6) 2.33 (3H, s, 4'-CH_3), 2.80 (3H, s, NCH_3), 4.28 (2H, s, 4-H_2), 6.58 (1H, d, *J* 8.3 Hz, 8-H), 6.76–6.82 (2H, m, 5-H and 7-H), 7.32 (2H, d, *J* 8.2 Hz, 3'-H and 5'-H), 7.57 (2H, d, *J* 8.2 Hz, 2'-H and 6'-H), 9.11 (1H, s, NH), 9.85 (1H, s, NH); δ_C (101 MHz, DMSO-d_6) 21.0 (CH_3), 33.8 (CH_3), 49.6 (CH_2), 113.7 (CH), 118.4 (C), 119.0 (CH), 121.4 (CH), 126.7 (2 × CH), 129.6 (2 × CH), 130.8 (C), 134.9 (C), 136.6 (C), 143.0 (C), 153.6 (C); *m/z* (ESI) 332 (MH^+. 100%).

***N*-(3-Methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4'-methoxybenzenesulfonamide (135c)**[138]



The reaction was performed according to general procedure F using 3,4-dihydro-3-methyl-2(1*H*)-quinazolinone (0.0811 g, 0.500 mmol) and *p*-toluenesulfonamide (0.128 g, 0.750 mmol). Purification by flash column chromatography (80–100% ethyl acetate in hexane) gave *N*-(3-methyl-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)-4'-methoxybenzenesulfonamide (**135c**) as a white solid (0.0985 g, 57%). Mp 165–168 °C (decomposition). Spectroscopic data were consistent with the literature.[138] δ_H (400 MHz, DMSO-d_6) 2.80 (3H, s, NCH_3), 3.79 (OCH_3), 4.28 (2H, s, 4-H_2), 6.59 (1H, d, *J* 8.3 Hz, 8-H), 6.76–6.82 (2H, m, 5-H and 7-H), 7.04 (2H, d, *J* 8.5 Hz, 3'-H and 5'-H), 7.61 (2H, d, *J* 8.5 Hz, 2'-H and 6'-H), 9.12 (1H, s, NH), 9.79 (1H, br s, NH); δ_C (101 MHz, DMSO-d_6) 33.8 (CH_3), 49.6 (CH_2), 55.6 (CH_3), 113.7 (CH), 114.3 (2 × CH), 118.4 (C), 119.1 (CH), 121.4 (CH), 128.9 (2 × CH), 130.9 (C), 131.1 (C), 134.9 (C), 153.6 (C), 162.3 (C); *m/z* (ESI) 348 (MH^+. 100%).

4.6 TSPO Experimental

General Procedure G: Suzuki-Miyaura Coupling of 4-Bromoquinolines and Aryl Boronic Acids

To a solution of the 4-bromoquinoline (1 equiv.) in dry *N,N*-dimethylformamide (15 mL/mmol) under argon was added the boronic acid (1.4 equiv.) and potassium phosphate tribasic (1.4 equiv.) and the reaction mixture degassed under argon for 0.2 h. To this solution was added tetrakis(triphenylphosphine)palladium(0) (0.04 equiv.) and the reaction mixture was stirred at 120 °C for 18 h. After cooling to room temperature, additional portions of boronic acid (1.4 equiv.) and potassium phosphate tribasic (1.4 equiv.) were added, followed by degassing under argon for 0.2 h. Tetrakis(triphenylphosphine)palladium(0) (0.04 equiv.) was added and the reaction mixture was stirred for a further 24 h at 120 °C. After cooling to room temperature, the reaction mixture was filtered through a short pad of Celite®, and washed with ethyl acetate (40 mL/mmol). The filtrate was washed with a 0.1 M aqueous solution of lithium chloride (3 × 40 mL/mmol) and brine (40 mL/mmol). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography to afford the coupled product.

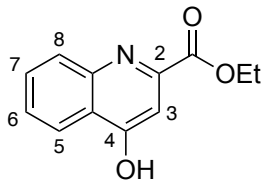
General Procedure H: Ester Hydrolysis and Amide Coupling

To a solution of the ester (1 equiv.) in 50% ethanol/water (15 mL/mmol) was added sodium hydroxide (4 equiv.) and the reaction mixture was stirred at 80 °C for 1.5 h. After cooling to room temperature, the ethanol was removed *in vacuo* and the reaction mixture was acidified to pH 1 with a 2 M aqueous hydrochloric acid solution. The product was extracted with ethyl acetate (3 × 15 mL/mmol), washed with water (15 mL/mmol), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the carboxylic acid, which was used without further purification. The carboxylic acid was dissolved in *N,N*-dimethylformamide (30 mL/mmol) under argon and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (1.5 equiv.) and *N,N*-diisopropylethylamine (2 equiv.) were added. The reaction mixture was stirred at room temperature for 0.75 h. (*R*)-(−)-*sec*-butylamine (1.1 equiv.) was added and the reaction mixture was stirred at 50 °C for 17 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 mL/mmol) and washed with a 2 M aqueous solution of lithium chloride (3 × 50 mL/mmol) and brine (50 mL/mmol). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography gave the amide product.

General Procedure I: *N*-Methylation

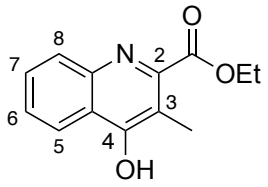
To a solution of the amide (1 equiv.) in dry tetrahydrofuran (20 mL/mmol) under argon was added sodium hydride (60% dispersion in mineral oil) (2 equiv.) and the reaction mixture was stirred at room temperature for 0.5 h. Iodomethane (5 equiv.) was added and the reaction mixture was stirred at room temperature for a further 3 h. The reaction was quenched by the slow addition of water (5 mL/mmol). Tetrahydrofuran was removed *in vacuo*, the aqueous phase was extracted with diethyl ether (3 × 10 mL/mmol) and the combined organic layers were washed with a 1 M aqueous solution of sodium thiosulfate (20 mL/mmol) and brine (20 mL/mmol), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography gave the methylated product.

Ethyl 4-hydroxyquinoline-2-carboxylate (177)[100]



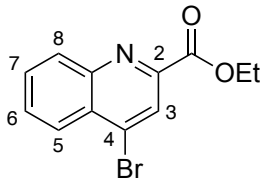
To a solution of aniline (1.00 mL, 11.0 mmol) and diethyl oxalacetate (**176**) (2.06 g, 11.0 mmol) in cyclohexane (80 mL) was added *p*-toluenesulfonic acid (0.0133 g, 0.0699 mmol) and the reaction mixture heated under reflux at 120 °C using a Dean-Stark condenser for 72 h. After cooling to room temperature, the reaction mixture was filtered, washed with hexane (40 mL) and the filtrate concentrated *in vacuo*. To the resulting oil was added polyphosphoric acid (10.0 g) and the mixture stirred at 120 °C for 1.5 h. After cooling to room temperature, a 2.4 M aqueous solution of sodium carbonate (40 mL) was added slowly. The resulting precipitate was extracted with chloroform (3 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50–90% ethyl acetate in hexane) gave ethyl 4-hydroxy-3-methylquinoline-2-carboxylate (**177**) as a pale-yellow solid (1.31 g, 55%). Mp 201–203 °C (lit.[100] 214–215 °C); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, t, *J* 7.1 Hz, $OCH_2\mathit{CH_3}$), 4.49 (2H, q, *J* 7.1 Hz, $O\mathit{CH_2}CH_3$), 7.00 (1H, s, 3-H), 7.39 (1H, ddd, *J* 8.2, 7.1, 0.9 Hz, 6-H), 7.45 (1H, br d *J* 7.9 Hz, 8-H), 7.67 (1H, ddd, *J* 8.3, 7.1, 1.5 Hz, 7-H), 8.35 (1H, dd, *J* 8.2, 1.2 Hz, 5-H), 9.15 (1H, s, OH); δ_C (101 MHz, $CDCl_3$) 14.1 (CH_3), 63.4 (CH_2), 111.7 (CH), 118.0 (CH), 124.5 (CH), 126.4 (CH), 126.4 (C), 133.1 (CH), 136.5 (C), 139.0 (C), 163.0 (C), 179.7 (C); *m/z* (ESI) 240 (MNa^+. 100%).

Ethyl 4-hydroxy-3-methylquinoline-2-carboxylate (168)[174]



To a solution of aniline (1.00 mL, 11.0 mmol) and diethyl oxalpropionate (**166**) (2.07 mL, 11.0 mmol) in cyclohexane (80 mL) was added *p*-toluenesulfonic acid (0.0133 g, 0.0699 mmol) and the reaction mixture was heated under reflux at 120 °C using a Dean-Stark condenser for 72 h. After cooling to room temperature, the reaction mixture was filtered, washed with hexane (40 mL) and the filtrate concentrated *in vacuo*. To the resulting oil was added polyphosphoric acid (10.0 g) and the mixture stirred at 120 °C for 1.5 h. After cooling to room temperature, a 2.4 M aqueous solution of sodium carbonate (40 mL) was added slowly. The resulting precipitate was extracted with chloroform (3 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50–80% ethyl acetate in hexane) gave ethyl 4-hydroxy-3-methylquinoline-2-carboxylate (**168**) as a pale-yellow solid (1.21 g, 55%). Mp 175–177 °C (lit.[174] 176–178 °C); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.2 Hz, $OCH_2\mathit{CH_3}$), 2.48 (3H, s, 3-CH_3), 4.51 (2H, q, *J* 7.2 Hz, $O\mathit{CH_2}CH_3$), 7.32 (1H, ddd, *J* 8.2, 7.0, 1.0 Hz, 6-H), 7.38–7.41 (1H, m, 8-H), 7.62 (1H, ddd, *J* 8.4, 5.5, 1.5 Hz, 7-H), 8.33–8.36 (1H, m, 5-H), 9.25 (1H, s, OH); δ_C (101 MHz, $CDCl_3$) 11.7 (CH_3), 14.2 (CH_3), 63.3 (CH_2), 117.5 (CH), 122.7 (C), 123.7 (C), 123.8 (CH), 126.4 (CH), 132.7 (CH), 132.9 (C), 138.4 (C), 164.3 (C), 179.7 (C); *m/z* (ESI) 254 (MNa^+. 100%).

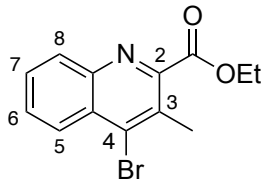
Ethyl 4-bromoquinoline-2-carboxylate (178)[174]



To a solution of ethyl 4-hydroxyquinoline-2-carboxylate (**177**) (0.100 g, 0.460 mmol) in dry acetonitrile (7 mL) under argon was added phosphorous oxybromide (0.396 g, 1.38 mmol) and anhydrous potassium carbonate (0.191 g, 1.38 mmol) and the reaction mixture was heated under reflux for 3 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Water (5 mL) was added to the residue and the product was extracted with ethyl acetate (3 × 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford ethyl 4-bromoquinoline-2-carboxylate (**178**) as a brown solid (0.125 g, 97%). Mp 89–91 °C (lit.[174] 91–92 °C); δ_H (400 MHz, $CDCl_3$) 1.50 (3H, t, *J* 7.1 Hz, $OCH_2\mathit{CH_3}$), 4.57 (2H, q, *J* 7.1 Hz, $O\mathit{CH_2}CH_3$), 7.75 (1H, ddd, *J* 8.3, 7.0, 1.2 Hz, 6-H), 7.84 (1H, ddd, *J* 8.3, 6.9, 1.4 Hz, 7-H), 8.22–8.26 (1H, m, 5-H), 8.30–8.33 (1H, m, 8-H), 8.47 (1H, s, 3-H); δ_C (101 MHz,

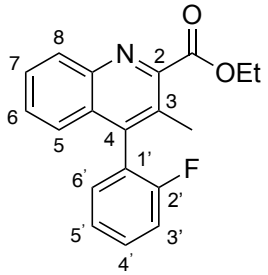
$CDCl_3$) 14.4 (CH_3), 62.6 (CH_2), 125.1 (CH), 126.7 (CH), 128.9 (C), 129.9 (CH), 131.1 (CH), 131.3 (CH), 135.2 (C), 147.9 (C), 148.0 (C), 164.3 (C); *m/z* (ESI) 302 (MNa^+. 100%).

Ethyl 4-bromo-3-methylquinoline-2-carboxylate (169)[174]



To a solution of ethyl 4-hydroxy-3-methylquinoline-2-carboxylate (**168**) (0.768 g, 3.28 mmol) in dry acetonitrile (50 mL) under argon was added phosphorous oxybromide (2.82 g, 9.83 mmol) and anhydrous potassium carbonate (1.36 g, 9.83 mmol) and the reaction mixture was heated under reflux for 3 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Water (25 mL) was added to the residue and the product was extracted with ethyl acetate (3 × 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford ethyl 4-bromo-3-methylquinoline-2-carboxylate (**169**) as a brown solid (0.897 g, 93%). Mp 51–52 °C (lit.[174] 48–50 °C); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.2 Hz, $OCH_2\mathit{CH_3}$), 2.70 (3H, s, 3-CH_3), 4.54 (2H, q, *J* 7.2 Hz, $O\mathit{CH_2}CH_3$), 7.68 (1H, ddd, *J* 8.3, 6.9, 1.4 Hz, 6-H), 7.75 (1H, ddd, *J* 8.3, 6.9, 1.4 Hz, 7-H), 8.12–8.16 (1H, m, 8-H), 8.20–8.23 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 19.9 (CH_3), 62.3 (CH_2), 126.8 (CH), 128.5 (C), 129.2 (CH), 129.4 (C), 129.9 (CH), 130.2 (CH), 137.3 (C), 146.0 (C), 151.1 (C), 166.5 (C); *m/z* (ESI) 316 (MNa^+. 100%).

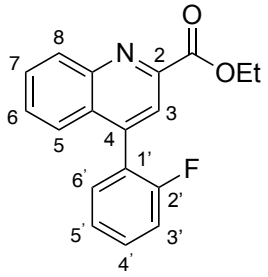
Ethyl 4-(2'-fluorophenyl)-3-methylquinoline-2-carboxylate (180d)[173]



The reaction was performed according to general procedure G using ethyl 4-bromo-3-methylquinoline-2-carboxylate (**169**) (1.33 g, 4.53 mmol), 2-fluorophenylboronic acid (0.950 g, 6.79 mmol), potassium phosphate tribasic (1.44 g, 6.79 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.157 g, 0.136 mmol) in *N,N*-dimethylformamide (70 mL), followed by an additional portion of the same reagents in the same quantities after 18 h. Purification by flash column chromatography (30% diethyl ether in hexane) gave ethyl 4-(2'-fluorophenyl)-3-methylquinoline-2-carboxylate (**180d**) as a light-yellow solid (1.08 g, 77%). Mp 103–105 °C (lit.[173] 107–108 °C); δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.2 Hz,

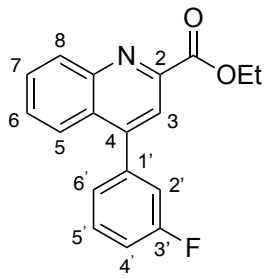
OCH_2CH_3), 2.35 (3H, s, 3-CH_3), 4.55 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 7.21–7.38 (4H, m, 8-H, 3'-H, 5'-H and 6'-H), 7.46–7.54 (2H, m, 7-H and 4'-H), 7.66–7.71 (1H, m, 6-H), 8.22 (1H, br d, *J* 8.5 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 16.6 (CH_3), 62.1 (CH_2), 116.1 (CH, d, $^2J_{CF}$ 21.6 Hz), 124.0 (C, d, $^2J_{CF}$ 17.2 Hz), 124.5 (CH, d, $^4J_{CF}$ 3.6 Hz), 125.4 (CH), 127.5 (C), 128.0 (C), 128.1 (CH), 129.1 (CH), 130.1 (CH), 130.6 (CH, d, $^3J_{CF}$ 7.9 Hz), 131.4 (CH, d, $^3J_{CF}$ 3.3 Hz), 142.6 (C), 145.6 (C), 151.4 (C), 159.6 (C, d, $^1J_{CF}$ 247.2 Hz), 167.2 (C); *m/z* (ESI) 310 (MH^+. 100%).

Ethyl 4-(2'-fluorophenyl)quinoline-2-carboxylate (180a)



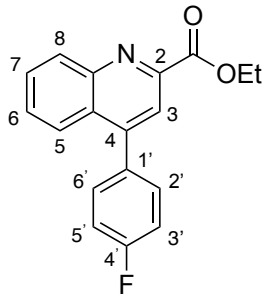
The reaction was performed according to general procedure G using ethyl 4-bromoquinoline-2-carboxylate (**178**) (0.300 g, 1.07 mmol), 2-fluorophenylboronic acid (0.210 g, 1.50 mmol), potassium phosphate tribasic (0.318 g, 1.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.0495 g, 0.0428 mmol) in *N,N*-dimethylformamide (20 mL), followed by an additional portion of the same reagents in the same quantities after 18 h. Purification by flash column chromatography (2.5% ethyl acetate in dichloromethane) gave ethyl 4-(2'-fluorophenyl)quinoline-2-carboxylate (**180a**) as a light-yellow solid (0.201 g, 64%). Mp 138–140 °C; ν_{max}/cm^{-1} (neat) 3065 (CH), 1716 (C=O), 1616 (C=C), 1246, 1107, 759; δ_H (400 MHz, $CDCl_3$) 1.50 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.58 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 7.27 (1H, ddd, *J* 9.6, 8.5, 0.9 Hz, 3'-H), 7.33 (1H, dt, *J* 7.5, 1.1 Hz, 6'-H), 7.43 (1H, dt, *J* 7.5, 1.8 Hz, 5'-H), 7.49–7.55 (1H, m, 4'-H), 7.61 (1H, ddd, *J* 8.4, 6.9, 1.2 Hz, 6-H), 7.74 (1H, m, 5-H), 7.80 (1H, ddd, *J* 8.5, 6.9, 1.4 Hz, 7-H), 8.16 (1H, s, 3-H), 8.39 (1H, br d, *J* 8.5 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 62.3 (CH_2), 116.1 (CH, d, $^2J_{CF}$ 21.7 Hz), 122.1 (CH), 124.5 (CH, d, $^4J_{CF}$ 3.7 Hz), 125.1 (C, d, $^2J_{CF}$ 15.9 Hz), 125.6 (CH), 128.0 (C), 128.8 (CH), 130.1 (CH), 130.9 (CH, d, $^3J_{CF}$ 8.0 Hz), 131.2 (CH), 131.7 (CH, d, $^3J_{CF}$ 3.0 Hz), 144.0 (C), 147.8 (C), 147.9 (C), 159.6 (C, d, $^1J_{CF}$ 248.8 Hz), 165.4 (C); *m/z* (ESI) 318.0901 ([MNa^+]. $C_{18}H_{14}FNNaO_2$ requires 318.0900).

Ethyl 4-(3'-fluorophenyl)quinoline-2-carboxylate (180b)[240]



The reaction was performed according to general procedure G using ethyl 4-bromoquinoline-2-carboxylate (**178**) (0.300 g, 1.07 mmol), 3-fluorophenylboronic acid (0.210 g, 1.50 mmol), potassium phosphate tribasic (0.318 g, 1.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.0495 g, 0.0428 mmol) in *N,N*-dimethylformamide (20 mL), followed by an additional portion of the same reagents in the same quantities after 18 h. Purification by flash column chromatography (10–20% ethyl acetate in hexane) gave ethyl 4-(3'-fluorophenyl)quinoline-2-carboxylate (**180b**) as a white solid (0.280 g, 88%). Mp 125–126 °C (lit.[240] 125–126 °C); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, t, *J* 7.1 Hz, $OCH_2\mathit{CH_3}$), 4.57 (2H, q, *J* 7.1 Hz, $O\mathit{CH_2}CH_3$), 7.19–7.27 (2H, m, 2'-H and 4'-H), 7.31 (1H, br d, *J* 7.7 Hz, 6'-H), 7.52 (1H, td, *J* 7.9, 6.8 Hz, 5'-H), 7.59–7.65 (1H, m, 6-H), 7.78–7.83 (1H, m, 7-H), 7.93 (1H, br d, *J* 8.5 Hz, 5-H), 8.12 (1H, s, 3-H), 8.39 (1H, br d, *J* 8.5 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 62.5 (CH_2), 115.8 (CH, d, $^2J_{CF}$ 21.0 Hz), 116.8 (CH, d, $^2J_{CF}$ 22.3 Hz), 121.3 (CH), 125.5 (CH), 125.5 (CH, d, $^4J_{CF}$ 2.8 Hz), 127.6 (C), 129.0 (CH), 130.3 (CH), 130.5 (CH, d, $^3J_{CF}$ 8.4 Hz), 131.5 (CH), 139.8 (C, d, $^3J_{CF}$ 7.7 Hz), 148.0 (C), 148.3 (C), 148.5 (C, d, $^4J_{CF}$ 2.0 Hz), 162.9 (C, d, $^1J_{CF}$ 247.7 Hz), 165.5 (C); *m/z* (ESI) 296 (MH^+. 100%).

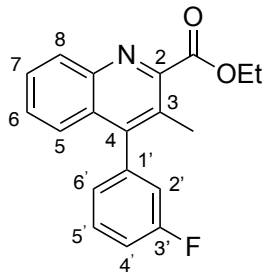
Ethyl 4-(4'-fluorophenyl)quinoline-2-carboxylate (180c)[174]



The reaction was performed according to general procedure G using ethyl 4-bromoquinoline-2-carboxylate (**178**) (0.300 g, 1.07 mmol), 4-fluorophenylboronic acid (0.210 g, 1.50 mmol), potassium phosphate tribasic (0.318 g, 1.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.0495 g, 0.0428 mmol) in *N,N*-dimethylformamide (20 mL), followed by an additional portion of the same reagents in the same quantities after 18 h. Purification by flash column chromatography (15–20% ethyl

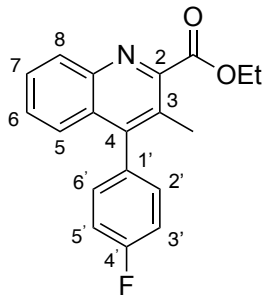
acetate in hexane) gave ethyl 4-(4'-fluorophenyl)quinoline-2-carboxylate (**180c**) as a white solid (0.252 g, 80%). Mp 114–116 °C (lit.[174] 116–118 °C); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.55 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 7.20–7.26 (2H, m, 3'-H, 5'-H), 7.47–7.52 (2H, m, 2'-H, 6'-H), 7.59 (1H, ddd, *J* 8.4, 7.0, 1.2 Hz, 6-H), 7.77 (1H, ddd, *J* 8.3, 7.0, 1.4 Hz, 7-H), 7.90 (1H, br d, *J* 8.4 Hz, 5-H), 8.09 (1H, s, 3-H), 8.36 (1H, br d, *J* 8.3 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 62.4 (CH_2), 115.9 (2 × CH, d, $^2J_{CF}$ 21.6 Hz), 121.4 (CH), 125.5 (CH), 127.8 (C), 128.8 (CH), 130.2 (CH), 131.4 (CH), 131.4 (2 × CH, d, $^3J_{CF}$ 8.3 Hz), 133.6 (C, d, $^4J_{CF}$ 3.4 Hz), 147.9 (C), 148.3 (C), 148.8 (C), 163.2 (C, d, $^1J_{CF}$ 248.8 Hz), 165.5 (C); *m/z* (ESI) 318 (MNa^+. 100%).

Ethyl 4-(3'-fluorophenyl)-3-methylquinoline-2-carboxylate (180e)



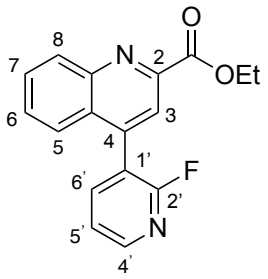
The reaction was performed according to general procedure G using ethyl 4-bromo-3-methylquinoline-2-carboxylate (**169**) (0.315, 1.07 mmol)), 3-fluorophenylboronic acid (0.210 g, 1.50 mmol), potassium phosphate tribasic (0.318 g, 1.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.0495 g, 0.0428 mmol) in *N,N*-dimethylformamide (20 mL), followed by an additional portion of the same reagents in the same quantities after 18 h. Purification by flash column chromatography (20–40% diethyl ether in hexane) gave ethyl 4-(3'-fluorophenyl)-3-methylquinoline-2-carboxylate (**180e**) as a white solid (0.249 g, 75%). Mp 125–126 °C; ν_{max}/cm^{-1} (neat) 2987 (CH), 1727 (C=O), 1582 (C=C), 1373, 1197, 1171, 1123, 765, 739; δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.32 (3H, s, 3-CH_3) 4.55 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.99 (1H, ddd, *J* 9.3, 2.5, 1.5 Hz, 2'-H), 7.04 (1H, ddd, *J* 7.5, 1.5, 1.0 Hz, 6'-H), 7.21 (1H, ddt, *J* 8.6, 2.5, 1.0 Hz, 4'-H), 7.36 (1H, br d *J* 8.6 Hz, 5-H), 7.45–7.55 (2H, m, 6-H and 5'-H), 7.69 (1H, ddd, *J* 8.4, 6.8, 1.4 Hz, 7-H), 8.19 (1H, ddd, *J* 8.4, 1.6, 0.6 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 16.8 (CH_3), 62.3 (CH_2), 115.4 (CH, d, $^2J_{CF}$ 20.9 Hz), 116.6 (CH, d, $^2J_{CF}$ 21.9 Hz), 125.2 (CH, d, $^4J_{CF}$ 3.1 Hz), 125.8 (CH), 126.3 (C), 128.0 (C), 128.1 (CH), 129.3 (CH), 130.1 (CH), 130.6 (CH, d, $^3J_{CF}$ 8.4 Hz), 139.0 (C, d, $^3J_{CF}$ 7.7 Hz), 145.8 (C), 147.3 (C, d, $^4J_{CF}$ 1.8 Hz), 151.7 (C), 163.1 (C, d, $^1J_{CF}$ 248.2 Hz), 167.4 (C); *m/z* (ESI) 322.1057 (MNa^+. $C_{19}H_{16}FNNaO_2$ requires 322.1057).

Ethyl 4-(4'-fluorophenyl)-3-methylquinoline-2-carboxylate (180f)



The reaction was performed according to general procedure G using ethyl 4-bromo-3-methylquinoline-2-carboxylate (**169**) (0.315 g, 1.07 mmol), 4-fluorophenylboronic acid (0.210 g, 1.50 mmol), potassium phosphate tribasic (0.318 g, 1.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.0495 g, 0.0428 mmol) in *N,N*-dimethylformamide (20 mL), followed by an additional portion of the same reagents in the same quantities after 18 h. Purification by flash column chromatography (15–20% ethyl acetate in hexane) followed by extraction with 0.1 M sodium hydroxide gave ethyl 4-(4'-fluorophenyl)-3-methylquinoline-2-carboxylate (**180f**) as a white solid (0.200 g, 60%). Mp 87–90 °C; ν_{max}/cm^{-1} (neat) 3064 (CH), 1723 (C=O), 1602 (C=C), 1512, 1202, 1064, 1014, 763; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.1 Hz, $OCH_2\mathit{CH_3}$), 2.31 (3H, s, 3-CH_3), 4.54 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 7.20–7.27 (4H, m, 2'-H, 3'-H, 5'-H, 6'-H), 7.36 (1H, br d, *J* 8.4 Hz, 5-H), 7.46 (1H, ddd, *J* 8.4, 6.9, 1.1 Hz, 6-H), 7.67 (1H, ddd, *J* 8.4, 6.9, 1.2 Hz, 7-H), 8.18 (1H, br d, *J* 8.4 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 16.8 (CH_3), 62.0 (CH_2), 115.9 (2 × CH, d, $^2J_{CF}$ 21.6 Hz), 125.7 (CH), 126.4 (C), 127.9 (CH), 128.2 (C), 129.1 (CH), 130.0 (CH), 131.1 (2 × CH, d, $^3J_{CF}$ 8.1 Hz), 132.6 (C, d, $^4J_{CF}$ 3.5 Hz), 145.7 (C), 147.6 (C), 151.6 (C), 162.6 (C, d, $^1J_{CF}$ 247.8 Hz), 167.4 (C); *m/z* (ESI) 332.1057 (MNa^+. $C_{19}H_{16}FNNaO_2$ requires 332.1057).

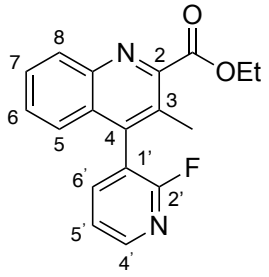
Ethyl 4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxylate (180g)



To a solution of ethyl 4-bromoquinoline-2-carboxylate (**178**) (0.200 g, 0.714 mmol) in tetrahydrofuran (2.7 mL) and water (1.3 mL) was added 2-fluoro-3-pyridineboronic acid (0.151 g, 1.07 mmol) and potassium phosphate tribasic (0.303 g, 1.43 mmol). The reaction mixture was degassed under argon for 0.2 h. To this solution was added XPhos Pd G2

(0.0085 g, 0.0107 mmol) and the reaction mixture was stirred at 40 °C for 4 h. After cooling to room temperature, an additional portion of XPhos Pd G2 (0.0085 g, 0.0107 mmol) was added, and the reaction mixture stirred at 40 °C for a further 18 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of Celite® and washed with ethyl acetate (10 mL). The filtrate was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10% ethyl acetate in hexane) gave ethyl 4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxylate (**180g**) as a white solid (0.180 g, 81%). Mp 168–170 °C; ν_{max}/cm^{-1} (neat) 2936 (CH), 1712 (C=O), 1609 (C=C), 1250, 1207, 1103, 1022, 764; δ_H (400 MHz, $CDCl_3$) 1.49 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.58 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 7.42 (1H, ddd, *J* 7.3, 4.9, 1.8 Hz, 5'-H), 7.62–7.69 (2H, m, 5-H and 6-H), 7.83 (1H, ddd, *J* 8.5, 6.2, 2.1 Hz, 7-H), 7.91 (1H, ddd, *J* 9.3, 7.3, 2.0 Hz, 6'-H), 8.16 (1H, s, 3-H), 8.39–8.44 (2H, m, 8-H and 4'-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 62.6 (CH_2), 120.1 (C, d, $^2J_{CF}$ 31.4 Hz), 121.9 (CH, d, $^4J_{CF}$ 4.5 Hz), 122.3 (CH), 125.0 (CH), 125.5 (C), 129.4 (CH), 130.6 (CH), 131.6 (CH), 141.9 (C, d, $^3J_{CF}$ 4.0 Hz), 142.4 (CH, d, $^3J_{CF}$ 3.9 Hz), 148.0 (C), 148.1 (C), 148.7 (CH, d, $^3J_{CF}$ 14.4 Hz), 160.4 (C, d, $^1J_{CF}$ 240.6 Hz), 165.3 (C); *m/z* (ESI) 319.0851 (MNa^+. $C_{17}H_{13}FN_2NaO_2$ requires 319.0853).

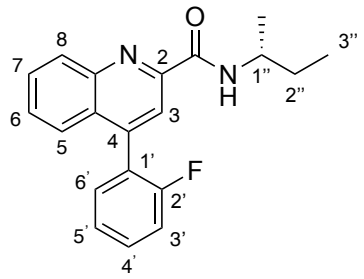
Ethyl 4-(2'-fluoro-3'-pyridyl)-3-methylquinoline-2-carboxylate (180h)



To a solution of ethyl 4-bromo-3-methylquinoline-2-carboxylate (**169**) (0.100 g, 0.340 mmol) in tetrahydrofuran (1.3 mL) and water (0.7 mL) was added 2-fluoro-3-pyridineboronic acid (0.0719 g, 0.510 mmol) and potassium phosphate tribasic (0.303 g, 1.43 mmol). The reaction mixture was degassed under argon for 0.2 h. To this solution was added XPhos Pd G2 (0.0040 g, 0.00560 mmol) and the reaction mixture was stirred at 40 °C for 4 h. After cooling to room temperature, an additional portion of XPhos Pd G2 (0.0040 g, 0.00560 mmol) was added, and the reaction mixture stirred at 40 °C for a further 18 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of Celite®, and washed with ethyl acetate (10 mL). The filtrate was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (15% ethyl acetate in hexane) gave ethyl 4-(2'-fluoro-3'-pyridyl)-3-

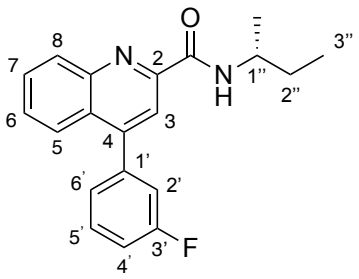
methylquinoline-2-carboxylate (**180h**) as a white solid (0.0554 g, 53%). Mp 139–141 °C; ν_{max}/cm^{-1} (neat) 2994 (CH), 1732 (C=O), 1605 (C=C), 1432, 1248, 1199, 1072, 764; δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.35 (3H, s, 3-CH_3), 4.51–4.59 (2H, m, OCH_2CH_3), 7.29 (1H, br d, *J* 8.5 Hz, 5-H), 7.43 (1H, ddd, *J* 7.3, 4.9, 1.9 Hz, 5'-H), 7.52 (1H, ddd, *J* 8.5, 6.9, 1.2 Hz, 6-H), 7.69–7.76 (2H, m, 7-H and 6'-H), 8.31 (1H, ddd, *J* 8.5, 1.2, 0.6 Hz, 8-H), 8.43 (1H, ddd, *J* 4.9, 2.0, 1.0 Hz, 4'-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 16.8 (CH_3), 62.4 (CH_2), 118.9 (C, d, $^2J_{CF}$ 32.8 Hz), 121.8 (CH, d, $^4J_{CF}$ 4.5 Hz), 124.8 (CH), 127.6 (C), 127.7 (C), 128.7 (CH), 129.6 (CH), 130.5 (CH), 140.3 (C, d, $^3J_{CF}$ 3.6 Hz), 142.5 (CH, d, $^3J_{CF}$ 4.1 Hz), 145.8 (C), 148.6 (CH, d, $^3J_{CF}$ 14.0 Hz), 151.5 (C), 160.5 (C, d, $^1J_{CF}$ 239.7 Hz), 167.1 (C); *m/z* (ESI) 333.1008 (MNa^+. $C_{18}H_{15}FN_2NaO_2$ requires 333.1010).

(*R*)-(*N-sec*-Butyl)-4-(2'-fluorophenyl)quinoline-2-carboxamide (183a)



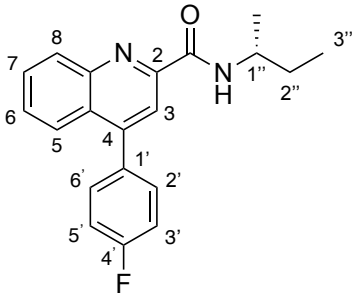
The reaction was performed according to general procedure H using 4-(2'-fluorophenyl)quinoline-2-carboxylate (**180a**) (0.157 g, 0.532 mmol) and sodium hydroxide (0.0848 g, 2.12 mmol) in 50% ethanol/water (11 mL) for the hydrolysis step, and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.255 g, 0.672 mmol), *N,N*-diisopropylethylamine (0.157 mL, 0.898 mmol) and (*R*)-(−)-*sec*-butylamine (0.0500 mL, 0.494 mmol) in *N,N*-dimethylformamide (12 mL) for the amide coupling step. Purification by flash column chromatography (15–20% ethyl acetate in hexane) gave (*R*)-(*N-sec*-butyl)-4-(2'-fluorophenyl)quinoline-2-carboxamide (**183a**) as a white solid (0.105 g, 65%). Mp 120–121 °C; $[\alpha]_D^{21}$ −24.2 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3379 (NH), 3064 (CH), 1667 (CO), 1616 (C=C), 1506, 1450, 1232, 1100, 909, 759; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.33 (3H, d, *J* 6.7 Hz, 1''-CH_3), 1.61–1.76 (2H, m, 2''-H_2), 4.19 (1H, d sextet, *J* 8.9, 6.7 Hz, 1''-H), 7.25 (1H, ddd, *J* 9.5, 8.5, 1.1 Hz, 3'-H), 7.31 (1H, dt, *J* 7.4, 1.1 Hz, 5'-H), 7.42 (1H, dt, *J* 7.4, 1.8 Hz, 6'-H), 7.47–7.53 (1H, m, 4'-H), 7.56 (1H, ddd, *J* 8.1, 7.0, 1.3 Hz, 6-H), 7.70–7.74 (1H, m, 5-H), 7.77 (1H, ddd, *J* 8.4, 7.0, 1.4 Hz, 7-H), 8.13 (1H, br d, *J* 8.9 Hz, NH), 8.17–8.21 (1H, m, 8-H), 8.30 (1H, s, 3-H); δ_C (101 MHz, $CDCl_3$) 10.6 (CH_3), 20.6 (CH_3), 29.9 (CH_2), 46.9 (CH), 116.0 (CH, d, $^2J_{CF}$ 21.7 Hz), 120.1 (CH), 124.4 (CH, d, $^4J_{CF}$ 3.6 Hz), 125.3 (C, d, $^2J_{CF}$ 16.0 Hz), 125.9 (CH), 127.9 (C), 128.0 (CH), 129.9 (CH), 130.1 (CH), 130.7 (CH, d, $^3J_{CF}$ 8.0 Hz), 131.7 (CH, d, $^3J_{CF}$ 3.1 Hz) 144.3 (C), 146.8 (C), 149.6 (C), 159.6 (C, d, $^1J_{CF}$ 248.6 Hz), 163.7 (C); *m/z* (ESI) 345.1368 ([MNa^+]. $C_{20}H_{19}FN_2NaO$ requires 345.1374).

(*R*)-(*N-sec*-Butyl)-4-(3'-fluorophenyl)quinoline-2-carboxamide (183b)



The reaction was performed according to general procedure H using ethyl 4-(3'-fluorophenyl)quinoline-2-carboxylate (**180b**) (0.227 g, 0.768 mmol) and sodium hydroxide (0.110 g, 3.07 mmol) in 50% ethanol/water (15 mL) for the hydrolysis step, and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.361 g, 0.954 mmol), *N,N*-diisopropylethylamine (0.222 mL, 1.27 mmol) and (*R*)-(−)-*sec*-butylamine (0.071 mL, 0.700 mmol) in *N,N*-dimethylformamide (20 mL) for the amide coupling step. Purification by flash column chromatography (10% ethyl acetate in hexane) gave (*R*)-(*N-sec*-butyl)-4-(3'-fluorophenyl)quinoline-2-carboxamide (**183b**) as a white solid (0.192 g, 87%). Mp 97–99 °C; $[\alpha]_D^{25}$ −28.9 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3376 (NH), 2966 (CH), 1668 (C=O), 1580 (C=C), 1522, 1506, 1411, 1198, 764; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.33 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.63–1.75 (2H, m, 2''-H_2), 4.14–4.24 (1H, m, 1''-H), 7.18–7.23 (1H, m, 4'-H), 7.23–7.27 (1H, m, 2'-H), 7.30–7.33 (1H, m, 6'-H), 7.50 (1H, td, *J* 7.9, 6.1 Hz, 5'-H), 7.57–7.61 (1H, m, 6-H), 7.76–7.80 (1H, m, 7-H), 7.94 (1H, br d, *J* 8.5 Hz, 5-H), 8.11 (1H, br d, *J* 8.9 Hz, NH), 8.20 (1H, d, *J* 8.5 Hz, 8-H), 8.27 (1H, s, 3-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 20.7 (CH_3), 30.0 (CH_2), 47.0 (CH), 115.7 (CH, d, $^2J_{CF}$ 21.0 Hz), 116.8 (CH, d, $^2J_{CF}$ 22.1 Hz), 119.2 (CH), 125.5 (CH, d, $^4J_{CF}$ 3.0 Hz), 125.7 (CH), 127.5 (C), 128.2 (CH), 130.1 (CH), 130.3 (CH), 130.4 (CH, d, $^3J_{CF}$ 8.4 Hz), 140.0 (C, d, $^3J_{CF}$ 7.8 Hz), 147.2 (C), 148.6 (C), 149.0 (C), 163.0 (C, d, $^1J_{CF}$ 247.1 Hz), 165.5 (C); *m/z* (ESI) 323.1565 (MH^+. $C_{19}H_{17}FNO_2$ requires 323.1554).

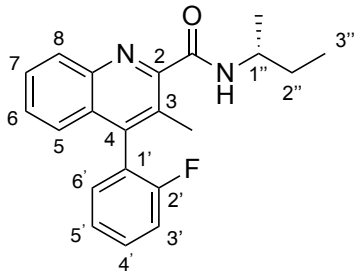
(*R*)-(*N-sec*-Butyl)-4-(4'-fluorophenyl)quinoline-2-carboxamide (183c)



The reaction was performed according to general procedure H using ethyl 4-(4'-fluorophenyl)quinoline-2-carboxylate (**180c**) (0.204 g, 0.691 mmol) and sodium hydroxide (0.110 g, 2.77 mmol) in 50% ethanol/water (14 mL) for the hydrolysis step, and *N,N,N',N'*-

tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.281 g, 0.741 mmol), *N,N*-diisopropylethylamine (0.172 mL, 0.988 mmol) and (*R*)-(−)-*sec*-butylamine (0.055 mL, 0.543 mmol) in *N,N*-dimethylformamide (17 mL) for the amide coupling step. Purification by flash column chromatography (15–20% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-4-(4'-fluorophenyl)quinoline-2-carboxamide (**183c**) as a white solid (0.122 g, 61%). Mp 64–66 °C; $[\alpha]_D^{16}$ −29.4 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3381 (NH), 3066 (CH), 1668 (C=O), 1609 (C=C), 1496, 1456, 1223, 1159, 909, 765; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.33 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.63–1.74 (2H, m, 2''-H_2), 4.19 (1H, d sextet, *J* 8.9, 6.6 Hz, 1''-H), 7.20–7.26 (2H, m, 3'-H and 5'-H), 7.57 (1H, ddd *J* 8.3, 7.0, 0.9 Hz, 6-H), 7.77 (1H, ddd, *J* 8.4, 7.0, 1.2 Hz, 7-H), 7.93 (1H, dd, *J* 8.3, 1.2 Hz, 5-H), 8.12 (1H, br d, *J* 8.8 Hz, NH), 8.19 (1H, dd, *J* 8.4, 0.9 Hz, 8-H), 8.25 (1H, s, 3-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 20.7 (CH_3), 30.0 (CH_2), 47.0 (CH), 115.9 (2 × CH, d, $^2J_{CF}$ 21.6 Hz), 119.4 (CH), 125.8 (CH), 127.8 (C), 128.1 (CH), 130.0 (CH), 130.3 (CH), 131.5 (2 × CH, d, $^3J_{CF}$ 8.2 Hz), 133.9 (C, d, $^4J_{CF}$ 3.4 Hz), 147.3 (C), 149.0 (C), 149.8 (C), 163.2 (C, d, $^1J_{CF}$ 248.7 Hz), 163.9 (C); *m/z* (ESI) 345.1374 (MNa^+. $C_{20}H_{19}FN_2NaO$ requires 345.1374).

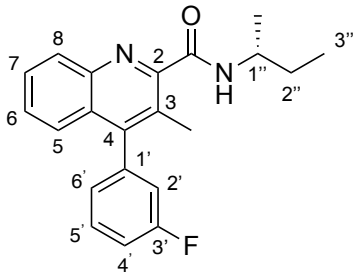
(*R*)-(*N*-*sec*-Butyl)-4-(2'-fluorophenyl)-3-methylquinoline-2-carboxamide (183d)[173]



The reaction was performed according to general procedure H using ethyl 4-(2'-fluorophenyl)-3-methylquinoline-2-carboxylate (**180d**) (0.980 g, 3.17 mmol) and sodium hydroxide (0.510 g, 12.7 mmol) in 50% ethanol/water (50 mL) for the hydrolysis step, and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (1.37 g, 3.61 mmol), *N,N*-diisopropylethylamine (0.842 mL, 2.65 mmol) and (*R*)-(−)-*sec*-butylamine (0.269 mL, 2.65 mmol) in *N,N*-dimethylformamide (70 mL) for the amide coupling step. Purification by flash column chromatography (10–20% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-4-(2'-fluorophenyl)-3-methylquinoline-2-carboxamide (**183d**) as a white solid (0.7435 g, 81%). Mp 148–150 °C. Spectroscopic data is consistent with the literature.[173] $[\alpha]_D^{21}$ −23.7 (*c* 0.1, $CHCl_3$); NMR spectra showed a 1:1 mixture of rotamers. Only signals for one rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.5 Hz, 3''-H_3), 1.32 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.67 (2H, m, 2''-H_2), 2.60 (3H, s, 3-CH_3), 4.14 (1H, d sextet, *J* 8.8, 6.6 Hz, 1''-H), 7.19–7.35 (4H, m, 8-H, 3'-H, 5'-H and 6'-H), 7.44–7.53 (2H, m, 7-H and 4'-H), 7.67 (1H, ddd, *J* 8.4, 6.9, 1.4 Hz, 6-H), 7.86–7.94 (1H, m, NH), 8.11 (1H, br d, *J* 8.4 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 10.6 (CH_3), 17.4 (CH_3), 20.5 (CH_3), 29.9 (CH_2), 46.8 (CH), 116.1

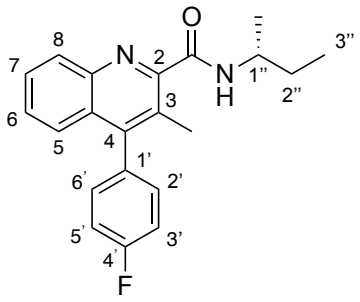
(CH, d, $^{2}J_{CF}$ 21.6 Hz), 124.4 (CH, d, $^{4}J_{CF}$ 3.6 Hz), 124.5 (C, d, $^{2}J_{CF}$ 17.3 Hz), 125.5 (CH), 127.9 (CH), 128.4 (C), 128.9 (CH), 129.7 (CH), 130.0 (C), 130.4 (CH, d, $^{3}J_{CF}$ 7.8 Hz), 131.5 (CH, d, $^{3}J_{CF}$ 3.3 Hz) 143.4 (C), 144.7 (C), 149.9 (C), 159.6 (C, d, $^{1}J_{CF}$ 246.8 Hz), 165.9 (C); *m/z* (ESI) 359 (MNa^{+}. 100%).

(*R*)-(*N-sec*-Butyl)-4-(3'-fluorophenyl)-3-methylquinoline-2-carboxamide (183e)



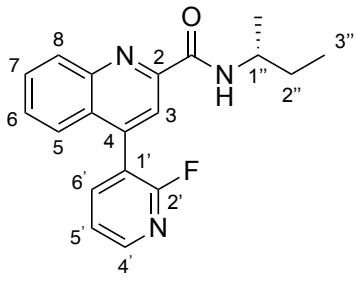
The reaction was performed according to general procedure H using ethyl 4-(3'-fluorophenyl)quinoline-2-carboxylate (**180e**) (0.226 g, 0.731 mmol) and sodium hydroxide (0.117 g, 2.92 mmol) in 50% ethanol/water (16 mL) for the hydrolysis step, and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.340 g, 0.896 mmol), *N,N*-diisopropylethylamine (0.209 mL, 1.20 mmol) and (*R*)-(−)-*sec*-butylamine (0.067 mL, 0.657 mmol) in *N,N*-dimethylformamide (18 mL) for the amide coupling step. Purification by flash column chromatography (10–15% ethyl acetate in hexane) gave (*R*)-(*N-sec*-butyl)-4-(3'-fluorophenyl)-3-methylquinoline-2-carboxamide (**183e**) as a white solid (0.184 g, 86%). Mp 99–100 °C; $[\alpha]_{D}^{26}$ −26.9 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3656 (NH), 2966 (CH), 1667 (C=O), 1511, 1481, 1174, 909, 886, 763; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.33 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.61–1.75 (2H, m, 2''-H_2), 2.57 (3H, s, 3-CH_3), 4.09–4.18 (1H, m, 1''-H), 6.95–6.99 (1H, m, 2'-H), 7.02 (1H, br d, *J* 7.6 Hz, 6'-H), 7.19 (1H, ddt, *J* 8.6, 2.6, 0.9 Hz, 4'-H), 7.33 (1H, br d *J* 8.4 Hz, 5-H), 7.45 (1H, ddd, *J* 8.4, 6.8, 1.3 Hz, 6-H), 7.51 (1H, td, *J* 8.0, 5.9, 5'-H), 7.67 (1H, ddd, *J* 8.4, 6.8, 1.3 Hz, 7-H), 7.87 (1H, d, *J* 8.6 Hz, NH), 8.10 (1H, br d, *J* 8.4 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 11.7 (CH_3), 20.6 (CH_3), 30.0 (CH_2), 46.9 (CH), 115.1 (CH, d, $^{2}J_{CF}$ 20.8 Hz), 116.7 (CH, d, $^{2}J_{CF}$ 21.8 Hz), 125.3 (CH, d, $^{4}J_{CF}$ 3.2 Hz), 125.9 (CH), 127.9 (CH), 128.3 (C), 128.9 (C), 129.0 (CH), 129.7 (CH), 130.5 (CH, d, $^{3}J_{CF}$ 8.6 Hz), 139.6 (C, d, $^{3}J_{CF}$ 7.6 Hz), 144.8 (C), 148.1 (C, d, $^{4}J_{CF}$ 2.2 Hz), 150.2 (C), 163.0 (C, d, $^{1}J_{CF}$ 247.7 Hz), 166.1 (C); *m/z* (ESI) 359.1533 (MNa^{+}. $C_{21}H_{21}FN_2NaO$ requires 359.1530).

(*R*)-(*N-sec*-Butyl)-4-(4'-fluorophenyl)-3-methylquinoline-2-carboxamide (183f)



The reaction was performed according to general procedure H using ethyl 4-(4'-fluorophenyl)-3-methylquinoline-2-carboxylate (**180f**) (0.170 g, 0.550 mmol) and sodium hydroxide (0.0879 g, 2.20 mmol) in 50% ethanol/water (12 mL) for the hydrolysis step, and *N,N,N′,N′*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.232 g, 0.613 mmol), *N,N*-diisopropylethylamine (0.142 mL, 0.808 mmol) and (*R*)-(−)-*sec*-butylamine (0.046 mL, 0.450 mmol) in *N,N*-dimethylformamide (14 mL) for the amide coupling step. Purification by flash column chromatography (15–20% ethyl acetate in hexane) gave (*R*)-(*N-sec*-butyl)-4-(4'-fluorophenyl)-3-methylquinoline-2-carboxamide (**183f**) as a white solid (0.0990 g, 65%). Mp 125–126 °C; $[\alpha]_D^{17}$ −26.6 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3379 (NH), 3067 (CH), 1666 (C=O), 1602 (C=C), 1490, 1455, 1224, 1158, 911, 764; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.32 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.60–1.76 (2H, m, 2''-H_2), 2.56 (3H, s, 3-CH_3), 4.14 (1H, d sextet, *J* 8.7, 6.6 Hz, 1''-H), 7.18–7.26 (4H, m, 2'-H, 3'-H, 5'-H and 6'-H), 7.31 (1H, dd, *J* 8.5, 1.1 Hz, 5-H), 7.45 (1H, ddd, *J* 8.5, 6.8, 1.3 Hz, 6-H), 7.67 (1H, ddd, *J* 8.3, 6.8, 1.1 Hz, 7-H), 7.87 (1H, br d, *J* 8.7 Hz, NH), 8.10 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 20.6 (CH_3), 30.0 (CH_2), 46.9 (CH), 115.9 (2 × CH, d, $^2J_{CF}$ 21.6 Hz), 126.0 (CH), 127.8 (CH), 128.8 (C), 129.0 (CH), 129.1 (C), 129.7 (CH), 131.3 (2 × CH, d, $^3J_{CF}$ 8.0 Hz), 133.2 (C, d, $^4J_{CF}$ 3.6 Hz), 144.8 (C), 148.5 (C), 150.3 (C), 162.6 (C, d, $^1J_{CF}$ 247.4 Hz), 166.2 (C); *m/z* (ESI) 359.1524 (MNa^+. $C_{21}H_{21}FN_2NaO$ requires 359.1530).

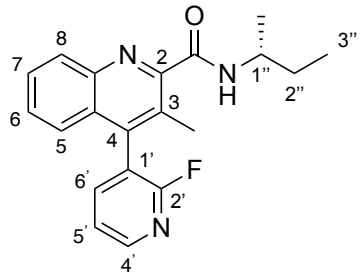
(*R*)-(*N-sec*-Butyl)-4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxamide (183g)



The reaction was performed according to general procedure H using ethyl 4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxylate (**180g**) (0.245 g, 0.827 mmol) and sodium hydroxide (0.132 g, 3.31 mmol) in 50% ethanol/water (16 mL) for the hydrolysis step, and *N,N,N',N'*-

tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.404 g, 1.07 mmol), *N,N*-diisopropylethylamine (0.249 mL, 1.42 mmol) and (*R*)-(−)-*sec*-butylamine (0.080 mL, 0.783 mmol) in *N,N*-dimethylformamide (22 mL) for the amide coupling step. Purification by flash column chromatography (20–40% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxamide (**183g**) as a white solid (0.175 g, 71%). Mp 112–114 °C; $[\alpha]_D^{23}$ −26.2 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3383 (NH), 2967 (CH), 1667 (C=O), 1524, 1435, 1250, 1204, 1103, 756; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.33 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.63–1.75 (2H, m, 2''-H_2), 4.13–4.24 (1H, m, 1''-H), 7.41 (1H, ddd, *J* 7.3, 4.9, 1.8 Hz, 5'-H), 7.58–7.63 (1H, m, 6-H), 7.64–7.68 (1H, m, 5-H), 7.80 (1H, ddd, *J* 8.4, 6.6, 1.6 Hz, 7-H), 7.90 (1H, ddd, *J* 9.3, 7.3, 2.0 Hz, 6'-H), 8.09 (1H, br d, *J* 9.1 Hz, NH), 8.22 (1H, br d, *J* 8.4 Hz, 8-H), 8.29 (1H, s, 3-H), 8.41 (1H, ddd, *J* 4.9, 2.0, 1.1 Hz, 4'-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 20.7 (CH_3), 30.0 (CH_2), 47.1 (CH), 120.2 (CH), 120.4 (C, d, $^2J_{CF}$ 31.1 Hz) 121.9 (CH, d, $^4J_{CF}$ 4.5 Hz), 125.3 (CH), 127.4 (C), 128.6 (CH), 130.4 (CH), 130.4 (CH), 142.2 (C, d, $^3J_{CF}$ 3.9 Hz), 142.3 (CH, d, $^3J_{CF}$ 4.0 Hz), 146.9 (C), 148.6 (CH, d, $^3J_{CF}$ 14.4 Hz), 149.8 (C), 160.4 (C, d, $^1J_{CF}$ 240.6 Hz), 163.5 (C); *m/z* (ESI) 346.1325 (MNa^+. $C_{19}H_{18}FN_3NaO$ requires 346.1326).

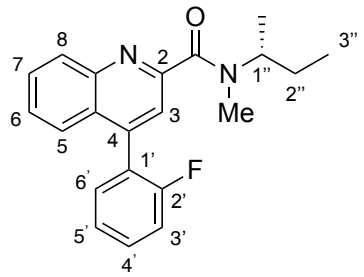
(*R*)-(*N*-*sec*-Butyl)-4-(2'-fluoro-3'-pyridyl)-3-methylquinoline-2-carboxamide (183h)



The reaction was performed according to general procedure H using ethyl 4-(2'-fluoro-3'-pyridyl)-3-methylquinoline-2-carboxylate (**180h**) (0.185 g, 0.596 mmol) and sodium hydroxide (0.110 g, 2.38 mmol) in 50% ethanol/water (12 mL) for the hydrolysis step, and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.274 g, 0.723 mmol), *N,N*-diisopropylethylamine (0.168 mL, 0.964 mmol) and (*R*)-(−)-*sec*-butylamine (0.054 mL, 0.530 mmol) in *N,N*-dimethylformamide (15 mL) for the amide coupling step. Purification by flash column chromatography (20–30% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-4-(2'-fluoro-3'-pyridyl)-3-methylquinoline-2-carboxamide (**183h**) as a yellow oil (0.142 g, 77%). $[\alpha]_D^{21}$ −14.1 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3307 (NH), 2966 (CH), 1651 (C=O), 1513, 1431, 1186, 911, 810, 729; NMR spectra showed a 1:1 mixture of two rotamers. Only signals for one rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.5 Hz, 3''-H_3), 1.31 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.59–1.73 (2H, m, 2''-H_2), 2.59 (3H, s, 3-CH_3), 4.07–4.18 (1H, m, 1''-H), 7.25 (1H, br d, *J* 8.5 Hz, 5-H), 7.41 (1H, ddd, *J* 7.3, 4.9, 1.8, 5'-H), 7.49 (1H, ddd, *J* 8.5, 6.9, 1.2 Hz, 6-H), 7.66–7.73 (2H, m, 7-H

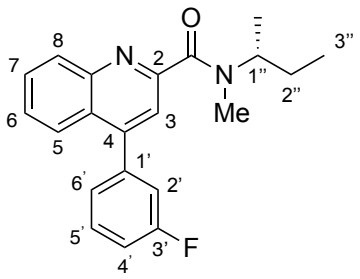
and 6'-H), 7.80–7.95 (1H, m, NH), 8.13 (1H, br d, *J* 8.4, 8-H), 8.41 (1H, ddd, *J* 4.9, 1.9, 1.0 Hz, 4'-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 17.5 (CH_3), 20.6 (CH_3), 30.0 (CH_2), 46.9 (CH), 119.5 (C, d, $^2J_{CF}$ 32.8 Hz), 121.8 (CH, d, $^4J_{CF}$ 4.4 Hz), 124.9 (CH), 127.9 (C), 128.5 (CH), 129.3 (CH), 130.1 (CH), 130.1 (C), 141.1 (C, d, $^3J_{CF}$ 3.5 Hz), 142.5 (CH, d, $^3J_{CF}$ 4.3 Hz), 144.8 (C), 148.4 (CH, d, $^3J_{CF}$ 14.2 Hz), 150.1 (C), 160.1 (C, d, $^1J_{CF}$ 239.4 Hz), 165.8 (C); *m/z* (ESI) 360.1479 (MNa^+. $C_{20}H_{20}FN_3NaO$ requires 360.1483).

(*R*)-(*N*-*sec*-Butyl)-*N*-Methyl-4-(2'-fluorophenyl)quinoline-2-carboxamide (184a)[241]



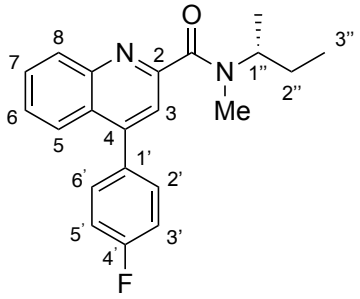
The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(2'-fluorophenyl)quinoline-2-carboxamide (**183a**) (0.0828 g, 0.257 mmol), sodium hydride (0.0206 g, 0.514 mmol, 60% dispersion in mineral oil) and methyl iodide (0.080 mL, 1.29 mmol) in tetrahydrofuran (5 mL). Purification by flash column chromatography (15–20% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(2'-fluorophenyl)quinoline-2-carboxamide **(184a**) as a white solid (0.0619 g, 72%). Mp 78–80 °C (lit.[241] 86 °C); $[\alpha]_D^{22}$ −6.8 (*c* 0.1, $CHCl_3$); NMR spectra showed a 2:1 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.76–0.92 (3H, m, 3''-H_3), 1.26 (3H, d, *J* 6.9 Hz, 1''-CH_3), 1.54–1.77 (2H, m, 2''-H_2), 3.01 (3H, s, NCH_3), 3.87–3.98 (1H, m, 1''-H), 7.21–7.33 (2H, m, 3'-H and 5'-H), 7.40–7.61 (4H, m, 3-H, 6-H, 4'-H and 6'-H), 7.68–7.78 (2H, m, 5-H and 7-H), 8.15–8.20 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 11.2 (CH_3), 18.8 (CH_3), 26.2 (CH_3), 26.7 (CH_2), 50.5 (CH), 116.2 (CH, d, $^2J_{CF}$ 21.8 Hz), 121.5 (CH), 124.6 (CH, d, $^4J_{CF}$ 3.7 Hz), 125.2 (C, d, $^2J_{CF}$ 15.9 Hz), 125.8 (CH), 126.6 (C), 127.6 (CH), 130.0 (CH), 130.3 (CH), 130.9 (CH, d, $^3J_{CF}$ 8.0 Hz), 131.8 (CH, d, $^3J_{CF}$ 3.0 Hz) 143.8 (C), 147.4 (C), 154.8 (C), 159.7 (C, d, $^1J_{CF}$ 248.5 Hz), 169.1 (C); *m/z* (ESI) 359 (MNa^+. 100%).

(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-4-(3'-fluorophenyl)quinoline-2-carboxamide (184b)



The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(3'-fluorophenyl)quinoline-2-carboxamide (**183b**) (0.161 g, 0.499 mmol), sodium hydride (60% dispersion in mineral oil) (0.0499 g, 1.25 mmol) and methyl iodide (0.187 mL, 3.00 mmol) in tetrahydrofuran (10 mL). Purification by flash column chromatography (30% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(3'-fluorophenyl)quinoline-2-carboxamide (**184b**) as a yellow oil (0.1381 g, 82%). $[\alpha]_D^{25}$ −9.7 (*c* 0.1, $CHCl_3$); ν_{max}/ cm^{-1} (neat) 2966 (CH), 1632 (C=O), 1480, 1403, 1208, 1094, 910, 735; δ_H (400 MHz, $CDCl_3$) 0.84 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.28 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.53–1.74 (2H, m, 2''-H_2), 3.02 (3H, s, NCH_3), 3.90–3.98 (1H, m, 1''-H), 7.17–7.27 (2H, m, 4'-H and 2'-H), 7.29–7.33 (1H, m, 6'-H), 7.47–7.59 (3H, m, 3-H, 6-H and 5'-H), 7.74–7.79 (1H, m, 7-H), 7.89–7.93 (1H, m, 5-H), 8.15–8.21 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 11.3 (CH_3), 18.8 (CH_3), 26.3 (CH_3), 27.4 (CH_2), 55.7 (CH), 115.7 (CH, d, $^2J_{CF}$ 21.0 Hz), 116.8 (CH, d, $^2J_{CF}$ 22.2 Hz), 120.5 (CH), 125.5 (CH, d, $^4J_{CF}$ 3.0 Hz), 126.2 (C), 127.7 (CH), 128.2 (CH), 130.1 (CH), 130.5 (CH), 130.5 (CH, d, $^3J_{CF}$ 8.4 Hz), 139.9 (C, d, $^3J_{CF}$ 7.7 Hz), 147.6 (C), 148.2 (C, d, $^4J_{CF}$ 2.0 Hz), 154.8 (C), 162.9 (C, d, $^1J_{CF}$ 247.4 Hz), 169.8 (C); *m/z* (ESI) 337.1715 (MH^+. $C_{21}H_{22}FN_2O$ requires 337.1711).

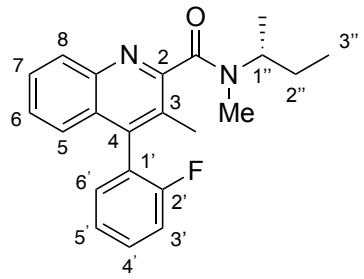
(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-4-(4'-fluorophenyl)quinoline-2-carboxamide (184c)



The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(4'-fluorophenyl)quinoline-2-carboxamide (**183c**) (0.102 g, 0.316 mmol), sodium hydride (0.0316 g, 0.791 mmol, 60% dispersion in mineral oil) and methyl iodide (0.118 mL, 1.90 mmol) in tetrahydrofuran (6 mL). The crude material was purified by flash column chromatography, eluting with 30–50% ethyl acetate in hexane to afford (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(4'-fluorophenyl)quinoline-2-carboxamide (**184c**) as a white solid (0.0762 g, 72%). Mp 89–90 °C; $[\alpha]_D^{16}$ −7.0 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3068 (CH), 1627 (C=O),

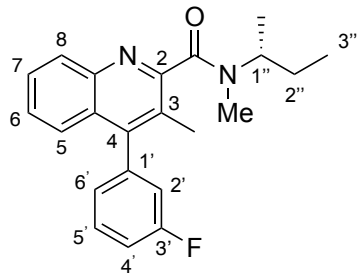
1605 (C=C), 1497, 1470, 1223, 1159, 909, 766; NMR spectra showed a 2:1 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.84 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.28 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.54–1.74 (2H, m, 2''-H_2), 3.01 (3H, s, NCH_3), 3.90–3.98 (1H, m, 1''-H), 7.20–7.25 (2H, m, 3'-H, 5'-H), 7.47–7.57 (4H, m, 3-H, 6-H, 2'-H and 6'-H), 7.73–7.77 (1H, m, 7-H), 7.90 (1H, br d, *J* 8.5 Hz, 5-H), 8.16 (1H, br d, *J* 8.5 Hz, 8-H), δ_C (101 MHz, $CDCl_3$) 11.1 (CH_3), 18.8 (CH_3) 26.3 (CH_3), 27.4 (CH_2), 55.6 (CH), 115.9 (2 × CH, d, $^2J_{CF}$ 21.6 Hz), 120.6 (CH), 125.6 (CH), 126.5 (C), 127.6 (CH), 130.0 (CH), 130.4 (CH), 131.4 (2 × CH, d, $^3J_{CF}$ 8.2 Hz), 133.7 (C, d, $^4J_{CF}$ 3.4 Hz), 147.6 (C), 148.6 (C), 154.8 (C), 163.1 (C, d, $^1J_{CF}$ 248.5 Hz), 169.9 (C); *m/z* (ESI) 359.1527 (MNa^+. $C_{21}H_{20}FN_2NaO$ requires 359.1530).

(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-4-(2'-fluorophenyl)-3-methylquinoline-2-carboxamide (184d)[173]



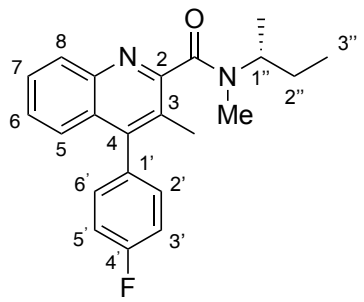
The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(2'-fluorophenyl)-3-methylquinoline-2-carboxamide (**183d**) (0.100 g, 0.297 mmol), sodium hydride (0.0238 g, 0.594 mmol, 60% dispersion in mineral oil) and methyl iodide (0.093 mL, 1.496 mmol) in tetrahydrofuran (6 mL). Purification by flash column chromatography (50–75% diethyl ether in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(2'-fluorophenyl)-3-methylquinoline-2-carboxamide (**184d**) as a white solid (0.0927 g, 89%). Spectroscopic data is consistent with the literature.[173] Mp 42–44 °C; $[\alpha]_D^{18}$ −5.6 (*c* 0.1, $CHCl_3$); NMR spectra showed a 2:2:3:3 mixture of two rotamers and two diastereomers. Only signals for the major diastereomer and rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.20 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.54–1.72 (2H, m, 2''-H_2), 2.24 (3H, s, 3-CH_3), 3.04 (3H, s, NCH_3), 3.38–3.50 (1H, m, 1''-H), 7.22–7.54 (6H, m, 7-H, 8-H, 3'-H, 4'-H, 5'-H and 6'-H), 7.63–7.68 (1H, m, 6-H), 8.09–8.15 (1H, m, 5-H); δ_C (101 MHz, $CDCl_3$) 11.2 (CH_3), 16.1 (CH_3), 18.4 (CH_3), 25.5 (CH_3), 26.6 (CH_2), 55.6 (CH), 116.1 (CH, d, $^2J_{CF}$ 21.7 Hz), 124.0 (C, d, $^2J_{CF}$ 17.2 Hz), 124.5 (CH, d, $^4J_{CF}$ 3.6 Hz), 125.3 (CH), 125.9 (C), 127.2 (CH), 128.8 (CH), 129.6 (CH), 130.5 (CH, d, $^3J_{CF}$ 7.7 Hz), 131.4 (CH, $^3J_{CF}$ 3.3 Hz), 141.9 (C), 145.8 (C), 155.9 (C), 156.5 (C), 159.6 (C, d, $^1J_{CF}$ 247.2 Hz), 169.4 (C); *m/z* (ESI) 373 (MNa^+. 100%).

(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-4-(3'-fluorophenyl)-3-methylquinoline-2-carboxamide (184e)



The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(3'-fluorophenyl)-3-methylquinoline-2-carboxamide (**183e**) (0.161 g, 0.479 mmol), sodium hydride (60% dispersion in mineral oil) (0.0478 g, 1.20 mmol) and methyl iodide (0.168 mL, 2.87 mmol) in tetrahydrofuran (10 mL). Purification by flash column chromatography (30% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(3'-fluorophenyl)3-methylquinoline-2-carboxamide (**184e**) as a colourless oil (0.158 g, 94%). $[\alpha]_D^{26}$ −3.6 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2969 (CH), 1633 (C=O), 1582, 1479, 1330, 1231, 909, 764; NMR spectra showed a 3:3:2:2 mixture of two rotamers and two diastereomers. Only signals for the major diastereomer and rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.85 (3H, t, *J* 7.3 Hz, 3''-H_3), 1.25 (3H, d, *J* 6.4 Hz, 1''-CH_3), 1.37–1.47 (2H, m, 2''-H_2), 2.23 (3H, s, 3-CH_3), 3.04 (3H, s, NCH_3), 3.43–3.51 (1H, m, 1''-H), 6.97–7.08 (2H, m, 2'-H and 6'-H), 7.19 (1H, ddt, *J* 8.6, 2.6, 0.9 Hz, 4'-H), 7.35–7.39 (1H, m, 5-H), 7.41–7.45 (1H, m, 6-H), 7.48–7.54 (1H, m, 5'-H), 7.65 (1H, ddd, *J* 8.3, 6.7, 1.4 Hz, 7-H), 8.09 (1H, br d, *J* 8.3 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 11.3 (CH_3), 16.4 (CH_3), 18.7 (CH_3), 25.6 (CH_3), 27.3 (CH_2), 55.9 (CH), 115.2 (CH, d, $^2J_{CF}$ 20.9 Hz), 116.6 (CH, d, $^2J_{CF}$ 21.8 Hz), 124.8 (C), 125.2 (CH, d, $^4J_{CF}$ 3.1 Hz), 125.4 (C), 125.7 (CH), 127.2 (C), 127.2 (CH), 129.0 (CH), 129.6 (CH), 130.5 (CH, d, $^3J_{CF}$ 8.5 Hz), 139.0 (C, d, $^3J_{CF}$ 7.7 Hz), 145.9 (C), 156.2 (C), 163.0 (C, d, $^1J_{CF}$ 247.8 Hz), 169.6 (C); *m/z* (ESI) 373.1683 (MNa^+. $C_{22}H_{23}FN_2NaO$ requires 373.1687).

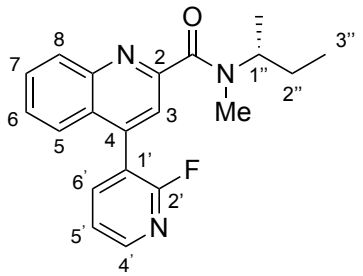
(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-4-(4'-fluorophenyl)-3-methylquinoline-2-carboxamide (184f)



The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(4'-fluorophenyl)-3-methylquinoline-2-carboxamide (**183f**) (0.0968 g, 0.288 mmol), sodium

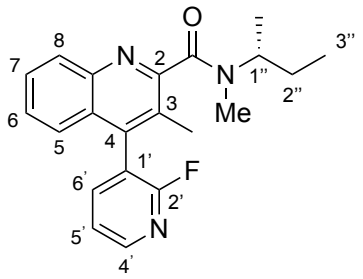
hydride (0.0306 g, 0.765 mmol, 60% dispersion in mineral oil) and methyl iodide (0.114 mL, 1.84 mmol) in tetrahydrofuran (6 mL). Purification by flash column chromatography (30% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(4'-fluorophenyl)-3-methylquinoline-2-carboxamide (**184f**) as a white solid (0.0804 g, 80%). Mp 124–125 °C; $[\alpha]_D^{17}$ −8.6 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3062 (CH), 1634 (C=O), 1490, 1464, 1223, 1158, 904, 765; NMR spectra showed a 2:1 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.24 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.55–1.74 (2H, m, 2''-H_2), 2.22 (3H, s, 3-CH_3), 3.04 (3H, s, NCH_3), 3.44–3.52 (1H, m, 1''-H), 7.21–7.27 (4H, m, 2'-H, 3'-H, 5'-H and 6'-H), 7.35–7.45 (2H, m, 5-H and 6-H), 7.65 (1H, ddd, *J* 8.3, 6.9, 1.5 Hz, 7-H), 8.07–8.13 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 11.3 (CH_3), 16.5 (CH_3), 18.7 (CH_3), 25.7 (CH_3), 26.7 (CH_2), 56.0 (CH), 115.9 (2 × CH, d, $^2J_{CF}$ 21.5 Hz), 125.1 (C), 125.8 (CH), 127.2 (CH), 127.6 (C), 128.9 (CH), 129.7 (CH), 131.2 (2 × CH, d, $^3J_{CF}$ 8.1 Hz), 132.8 (C, d, $^4J_{CF}$ 3.6 Hz), 146.0 (C), 147.1 (C), 156.3 (C), 162.7 (C, d, $^1J_{CF}$ 247.5 Hz), 169.7 (C); *m/z* (ESI) 373.1687 (MNa^+. $C_{22}H_{23}FN_2NaO$ requires 373.1686).

(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxamide (184g)



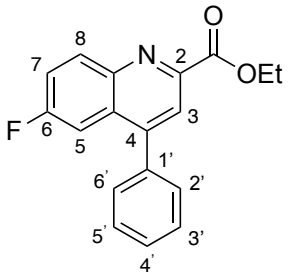
The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxamide (**183g**) (0.159 g, 0.493 mmol), sodium hydride (60% dispersion in mineral oil) (0.0493 g, 1.23 mmol) and methyl iodide (0.184 mL, 2.96 mmol) in tetrahydrofuran (12 mL). Purification by flash column chromatography (40–50% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(2'-fluoro-3'-pyridyl)quinoline-2-carboxamide (**184g**) as a white solid (0.131 g, 79%). Mp 96–98 °C; $[\alpha]_D^{23}$ −7.8 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2970 (CH), 1609 (C=O), 1431, 1404, 1096, 810, 760; NMR spectra showed a 2:1 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.5 Hz, 3''-H_3), 1.17–1.37 (3H, m, 1''-CH_3), 1.53–1.76 (2H, m, 2''-H_2), 3.01 (3H, s, NCH_3), 3.84–4.04 (1H, m, 1''-H), 7.37–7.43 (1H, m, 5'-H), 7.55–7.67 (3H, m, 3-H, 5-H and 6-H), 7.76–7.82 (1H, m, 7-H), 7.87–7.94 (1H, m, 6'-H), 8.15–8.22 (1H, m, 8-H), 8.38–8.42 (1H, m, 4'-H); δ_C (101 MHz, $CDCl_3$) 11.2 (CH_3), 18.8 (CH_3), 26.3 (CH_3), 26.7 (CH_2), 50.7 (CH), 120.2 (C, d, $^2J_{CF}$ 31.3 Hz), 121.6 (CH), 121.9 (CH, d, $^4J_{CF}$ 4.5 Hz), 125.0 (CH), 126.1 (C), 128.1 (CH), 130.3 (CH), 130.6 (CH), 141.6 (C, d, $^3J_{CF}$ 3.9 Hz), 142.4 (CH, d, $^3J_{CF}$ 4.0 Hz), 147.3 (C), 148.6 (CH, d, $^3J_{CF}$ 14.5 Hz), 154.7 (C), 160.5 (C, d, $^1J_{CF}$ 240.3 Hz), 168.8 (C); *m/z* (ESI) 338.1662 (MH^+. $C_{20}H_{21}FN_3O$ requires 338.1663).

(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-4-(2'-fluoro-3'-pyridyl)-3-methylquinoline-2-carboxamide (184h)



The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-4-(2'-fluoro-3'-pyridyl)-3-methylquinoline-2-carboxamide (**183h**) (0.125 g, 0.370 mmol), sodium hydride (60% dispersion in mineral oil) (0.0370 g, 0.926 mmol) and methyl iodide (0.138 mL, 2.22 mmol) in tetrahydrofuran (9 mL). Purification by flash column chromatography (50–75% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-4-(2'-fluoro-3'-pyridyl)-3-methylquinoline-2-carboxamide (**184h**) as a white solid (0.112 g, 86%). Mp 144–147 °C; $[\alpha]_D^{22}$ −6.1 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2940 (CH), 1633 (C=O), 1462, 1329, 1249, 1126, 905, 766; NMR spectra showed a 2:1 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.19 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.36–1.47 (2H, m, 2''-H_2), 2.22 (3H, s, 3-CH_3), 2.71 (3H, s, NCH_3), 3.37–3.52 (1H, m, 1''-H), 7.30 (1H, dd, *J* 8.4, 3.7 Hz, 5-H), 7.38–7.52 (2H, m, 6-H and 5'-H), 7.66–7.78 (2H, m, 7-H and 6'-H), 8.10–8.17 (1H, m, 8-H), 8.42 (1H, ddd, *J* 4.9, 2.0, 1.0 Hz, 4'-H); δ_C (101 MHz, $CDCl_3$) 11.3 (CH_3), 15.9 (CH_3), 17.5 (CH_3), 25.7 (CH_3), 26.7 (CH_2), 55.7 (CH), 119.0 (C, d, $^2J_{CF}$ 32.3 Hz), 121.8 (CH, d, $^4J_{CF}$ 4.7 Hz), 124.7 (CH), 126.1 (C), 126.7 (C), 127.7 (CH), 129.3 (CH), 130.0 (CH), 139.8 (C, d, $^3J_{CF}$ 3.7 Hz), 142.5 (CH, d, $^3J_{CF}$ 4.4 Hz), 145.9 (C), 148.5 (CH, d, $^3J_{CF}$ 14.3 Hz), 156.1 (C), 160.6 (C, d, $^1J_{CF}$ 239.2 Hz), 169.0 (C); *m/z* (ESI) 374.1641 (MNa^+. $C_{21}H_{22}FN_3NaO$ requires 374.1639).

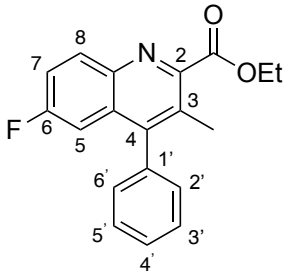
Ethyl 6'-fluoro-4-phenylquinoline-2-carboxylate (185a)[175]



To a solution of 4-fluoroaniline (0.095 mL, 1.00 mmol) in nitromethane (2 mL) was added phenylacetylene (0.165 mL, 1.50 mmol), ethyl glyoxalate solution (50% in toluene) (0.204 mL, 1.00 mmol) and iodine (0.0506 g, 0.200 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with ethyl acetate (10 mL) and washed with a 1 M

aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 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 (15% diethyl ether in hexane) followed by trituration with diethyl ether gave ethyl 6-fluoro-4-phenylquinoline-2-carboxylate (**185a**) as a white solid (0.0624 g, 21%). Mp 151–153 °C (lit.[175] 154–155 °C); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, t, *J* 7.1 Hz, $OCH_2\mathit{CH_3}$), 4.57 (2H, q, *J* 7.1 Hz, $O\mathit{CH_2}CH_3$), 7.49–7.60 (7H, m, 5-H, 7-H, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 8.15 (1H, s, 3-H), 8.35–8.42 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 62.5 (CH_2), 109.3 (CH, d, $^2J_{CF}$ 23.3 Hz), 120.7 (CH, d, $^2J_{CF}$ 26.0 Hz), 121.9 (CH), 129.0 (C, d, $^3J_{CF}$ 9.7 Hz), 129.0 (2 × CH), 129.1 (CH), 129.5 (2 × CH), 134.0 (CH, d, $^3J_{CF}$ 9.4 Hz), 137.3 (C), 145.5 (C), 147.5 (C, d, $^4J_{CF}$ 2.9 Hz), 149.5 (C, d, $^4J_{CF}$ 5.9 Hz), 162.1 (C, d, $^1J_{CF}$ 251.2 Hz), 165.4 (C); *m/z* (ESI) 296 (MH^+. 100%).

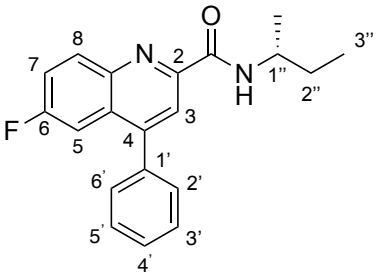
Ethyl 6-fluoro-4-phenyl-3-methylquinoline-2-carboxylate (185b)



To a solution of 4-fluoroaniline (0.095 mL, 1.00 mmol) in dry nitromethane (2 mL) was added 1-phenyl-1-propyne (0.187 mL, 1.50 mmol), ethyl glyoxalate solution (50% in toluene) (0.204 mL, 1.00 mmol) and iodine (0.0506 g, 0.200 mmol). The reaction mixture was stirred at room temperature for 4 h, and then stirred at 40 °C for 92 h. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 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 (15% diethyl ether in hexane) followed by trituration with diethyl ether gave ethyl 6-fluoro-4-phenyl-3-methylquinoline-2-carboxylate (**185b**) as a white solid (0.0481 g, 16%). Mp 102–105 °C. ν_{max}/cm^{-1} (neat) 2936 (CH), 1724 (C=O), 1624 (C=C), 1489, 1281, 1242, 1069, 833; δ_H (400 MHz, $CDCl_3$) 1.47 (3H, t, *J* 7.1 Hz, $OCH_2\mathit{CH_3}$), 2.32 (3H, s, 3-CH_3), 4.54 (2H, q, *J* 7.1 Hz, $O\mathit{CH_2}CH_3$), 6.98 (1H, dd, *J* 10.1, 2.8 Hz, 5-H), 7.21–7.26 (2H, m, 2'-H and 6'-H), 7.44 (1H, ddd, *J* 9.3, 8.0, 2.8 Hz, 7-H), 7.48–7.58 (3H, m, 3'-H, 4'-H and 5'-H), 8.19 (1H, dd, *J* 9.3, 5.5 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 17.0 (CH_3), 62.3 (CH_2), 109.5 (CH, d, $^2J_{CF}$ 23.3 Hz), 119.5 (CH, d, $^2J_{CF}$ 26.1 Hz), 127.3 (C), 128.5 (CH), 129.0 (2 × CH), 129.2 (2 × CH), 129.4 (C, d, $^3J_{CF}$ 9.9 Hz), 132.6 (CH, d, $^3J_{CF}$ 9.5 Hz), 136.4 (C), 142.9 (C), 148.3 (C,

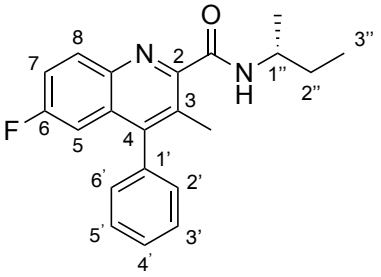
d, $^{4}J_{CF}$ 5.8 Hz), 151.1 (C, d, $^{4}J_{CF}$ 2.9 Hz), 161.5 (C, d, $^{1}J_{CF}$ 249.3 Hz), 167.4 (C); *m/z* (ESI) 310.1243 (MH^+. $C_{19}H_{17}FNO_2$ requires 310.1238).

(*R*)-(*N-sec*-Butyl)-6-fluoro-4-phenylquinoline-2-carboxamide (186a)



The reaction was performed according to general procedure H using ethyl 6-fluoro-4-phenylquinoline-2-carboxylate (**185a**) (0.163 g, 0.550 mmol) and sodium hydroxide (0.0881 g, 2.20 mmol) in 50% ethanol/water (10 mL) for the hydrolysis step, and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.268 g, 0.707 mmol), *N,N*-diisopropylethylamine (0.165 mL, 0.943 mmol) and (*R*)-(−)-*sec*-butylamine (0.053 mL, 0.519 mmol) in *N,N*-dimethylformamide (15 mL) for the amide coupling step. Purification by flash column chromatography (10% ethyl acetate in hexane) gave (*R*)-(*N-sec*-butyl)-6-fluoro-4-phenylquinoline-2-carboxamide (**186a**) as a colourless oil (0.142 g, 66%). $[\alpha]_D^{15}$ −19.1 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3387 (NH), 2967 (CH), 1670 (C=O), 1512, 1462, 1196, 833, 702; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.33 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.63–1.74 (2H, m, 2''-H_2), 4.13–4.24 (1H, m, 1''-H), 7.48–7.61 (7H, m, 5-H, 7-H, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 8.05 (1H, d, *J* 8.9 Hz, NH), 8.19 (1H, dd, *J* 9.3, 5.5 Hz, 8-H), 8.30 (1H, s, 3-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 20.7 (CH_3), 30.0 (CH_2), 47.0 (CH), 109.5 (CH, d, $^{2}J_{CF}$ 23.3 Hz), 119.1 (CH), 120.3 (CH, d, $^{2}J_{CF}$ 26.1 Hz), 128.8 (C, d, $^{3}J_{CF}$ 9.8 Hz) 128.9 (2 × CH), 129.0 (CH), 129.5 (2 × CH), 132.8 (CH, d, $^{3}J_{CF}$ 9.3 Hz), 137.5 (C), 144.3 (C), 149.3 (C, d, $^{4}J_{CF}$ 2.9 Hz), 149.6 (C, d, $^{4}J_{CF}$ 5.7 Hz), 161.6 (C, d, $^{1}J_{CF}$ 249.7 Hz), 163.8 (C); *m/z* (ESI) 323.1564 (MH^+. $C_{20}H_{20}FN_2O$ requires 323.1554).

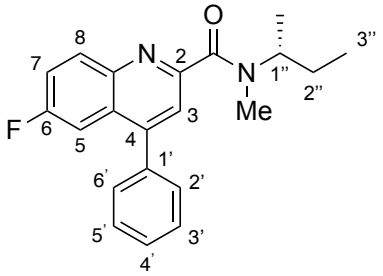
(*R*)-(*N-sec*-Butyl)-6-fluoro-4-phenyl-3-methylquinoline-2-carboxamide (186b)



The reaction was performed according to general procedure H using ethyl 6-fluoro-4-phenyl-3-methylquinoline-2-carboxylate (**185b**) (0.125 g, 0.404 mmol) and sodium

hydroxide (0.0646 g, 1.62 mmol) in 50% ethanol/water (8 mL) for the hydrolysis step, and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.184 g, 0.485 mmol), *N,N*-diisopropylethylamine (0.113 mL, 0.647 mmol) and (*R*)-(−)-*sec*-butylamine (0.036 mL, 0.355 mmol) in *N,N*-dimethylformamide (11 mL) for the amide coupling step. Purification by flash column chromatography (15% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-6-fluoro-4-phenyl-3-methylquinoline-2-carboxamide (**186b**) as a white solid (0.0917 g, 71%). Mp 139–141 °C; $[\alpha]_D^{16}$ −25.1 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3298 (NH), 2966 (CH), 1663 (C=O), 1485, 1381, 1196, 829, 733; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.32 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.62–1.75 (2H, m, 2''-H_2), 2.56 (3H, s, 3-CH_3), 4.09–4.18 (1H, m, 1''-H), 6.95 (1H, dd, *J* 10.2, 2.8 Hz, 5-H), 7.19–7.23 (2H, m, 2'-H and 6'-H), 7.42 (1H, ddd, *J* 9.2, 8.0, 2.8 Hz, 7-H), 7.47–7.57 (3H, m, 3'-H, 4'-H and 5'-H), 7.80 (1H, br d, *J* 8.7 Hz, NH), 8.09 (1H, dd, *J* 9.2, 5.5 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 17.8 (CH_3), 20.6 (CH_3), 30.0 (CH_2), 46.9 (CH), 109.6 (CH, d, $^2J_{CF}$ 23.3 Hz), 119.3 (CH, d, $^2J_{CF}$ 26.2 Hz), 128.3 (CH), 129.0 (2 × CH), 129.3 (2 × CH), 129.7 (C, d, $^3J_{CF}$ 10.0 Hz), 129.8 (C), 132.2 (CH, d, $^3J_{CF}$ 9.5 Hz), 136.9 (C), 141.9 (C), 149.1 (C, d, $^4J_{CF}$ 5.8 Hz), 149.8 (C, d, $^4J_{CF}$ 2.9 Hz), 161.4 (C, d, $^1J_{CF}$ 249.0 Hz), 168.1 (C); *m/z* (ESI) 337.1714 (MH^+. $C_{21}H_{22}FN_2O$ requires 337.1711).

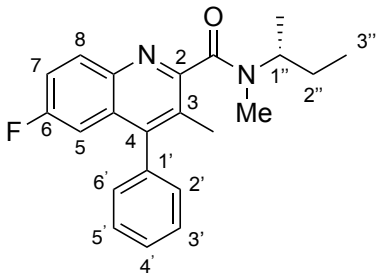
(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-6-fluoro-4-phenylquinoline-2-carboxamide (187a)



The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-6-fluoro-4-phenylquinoline-2-carboxamide (**186a**) (0.100 g, 0.310 mmol), sodium hydride (60% dispersion in mineral oil) (0.0310 g, 0.775 mmol) and methyl iodide (0.116 mL, 1.86 mmol) in tetrahydrofuran (8 mL). Purification by flash column chromatography (30% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-6-fluoro-4-phenylquinoline-2-carboxamide (**187a**) as a colourless oil (0.0951 g, 91%). $[\alpha]_D^{15}$ −4.8 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2967 (CH), 1628 (C=O), 1485, 1402, 1200, 1092, 833; NMR spectra showed a 2:1 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.84 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.27 (3H, d, *J* 6.7 Hz, 1''-CH_3), 1.53–1.74 (2H, m, 2''-H_2), 3.01 (3H, s, NCH_3), 3.88–3.97 (1H, m, 1''-H), 7.48–7.60 (8H, m, 3-H, 5-H, 7-H, 2'-H, 3'-H, 4'-H, 5'-H and 6'-H), 8.16 (1H, dd, *J* 9.3, 5.5 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 11.3 (CH_3), 18.8 (CH_3), 26.3 (CH_3), 27.4 (CH_2), 55.7 (CH), 109.4 (CH, d, $^2J_{CF}$ 23.7 Hz),120.2 (CH, d, $^2J_{CF}$ 25.8 Hz), 121.2 (CH), 127.5 (C, d, $^3J_{CF}$ 9.7 Hz) 129.0 (2 × CH), 129.0 (CH), 129.5 (2 ×

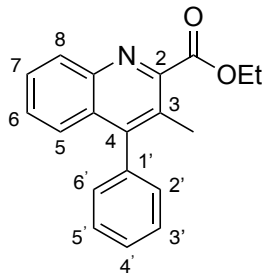
CH), 132.8 (CH, d, $^{3}J_{CF}$ 9.2 Hz), 137.4 (C), 144.7 (C), 149.2 (C, d, $^{4}J_{CF}$ 5.6 Hz), 154.2 (C, d, $^{4}J_{CF}$ 2.9 Hz), 161.3 (C, d, $^{1}J_{CF}$ 248.7 Hz), 169.8 (C); *m/z* (ESI) 337.1714 (MH^+. $C_{21}H_{22}FN_2O$ requires 337.1711).

(*R*)-(*N*-*sec*-Butyl)-*N*-methyl-6-fluoro-4-phenyl-3-methylquinoline-2-carboxamide (187b)



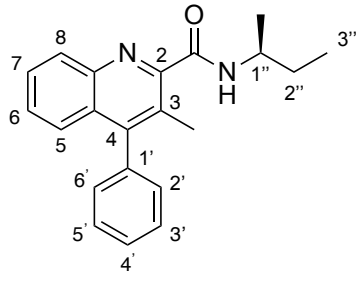
The reaction was performed according to general procedure I using (*R*)-(*N*-*sec*-butyl)-6-fluoro-4-phenyl-3-methylquinoline-2-carboxamide (**186b**) (0.0799 g, 0.238 mmol), sodium hydride (60% dispersion in mineral oil) (0.0238 g, 0.595 mmol) and methyl iodide (0.089 mL, 1.43 mmol) in tetrahydrofuran (7 mL). Purification by flash column chromatography (30% ethyl acetate in hexane) gave (*R*)-(*N*-*sec*-butyl)-*N*-methyl-6-fluoro-4-phenyl-3-methylquinoline-2-carboxamide (**187b**) as a white solid (0.0761 g, 91%). Mp 88–90 °C; $[\alpha]_D^{17}$ −13.2 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2970 (CH), 1632 (C=O), 1489, 1215, 1200, 1072, 833, 702; NMR spectra showed a 3:2 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.24 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.53–1.72 (2H, m, 2''-H_2), 2.22 (3H, s, 3-CH_3), 3.04 (3H, s, NCH_3), 3.42–3.51 (1H, m, 1''-H), 6.97–7.01 (1H, m, 5-H), 7.22–7.28 (2H, m, 2'-H and 6'-H), 7.40 (1H, ddd, *J* 9.2, 8.0, 2.8 Hz, 7-H), 7.47–7.57 (3H, m, 3'-H, 4'-H and 5'-H), 8.07 (1H, dd, *J* 9.2, 5.5 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 11.5 (CH_3), 16.6 (CH_3), 18.7 (CH_3), 25.7 (CH_3), 27.3 (CH_2), 56.0 (CH), 109.5 (CH, d, $^{2}J_{CF}$ 23.1 Hz), 119.1 (CH, d, $^{2}J_{CF}$ 26.0 Hz), 126.4 (C), 128.4 (CH), 128.5 (C, d, $^{3}J_{CF}$ 10.0 Hz), 129.0 (2 × CH), 129.3 (2 × CH), 132.1 (CH, d, $^{3}J_{CF}$ 9.2 Hz), 136.5 (C), 143.0 (C), 147.7 (C, d, $^{4}J_{CF}$ 5.7 Hz), 155.6 (C, d, $^{4}J_{CF}$ 2.9 Hz), 161.0 (C, d, $^{1}J_{CF}$ 247.8 Hz), 169.6 (C); *m/z* (ESI) 351.1883 (MH^+. $C_{22}H_{24}FN_2O$ requires 351.1867).

Ethyl 3-methyl-4-phenylquinoline-2-carboxylate (170)[174]



To a solution of ethyl 4-bromo-3-methylquinoline-2-carboxylate (**169**) (1.77 g, 6.02 mmol) in tetrahydrofuran (15 mL) and water (30 mL) was added phenylboronic acid (1.10 g, 9.03 mmol) and potassium phosphate tribasic (2.54 g, 12.0 mmol). The reaction mixture was degassed under argon for 0.2 h. To this solution was added XPhos Pd G2 (0.0944 g, 0.120 mmol) and the reaction mixture was stirred at 40 °C for 1.5 h. After cooling to room temperature, the reaction mixture was filtered through a short pad of Celite® and washed with ethyl acetate (50 mL). The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% ethyl acetate in hexane) gave ethyl 3-methyl-4-phenylquinoline-2-carboxylate (**170**) as a white solid (1.60 g, 91%). Mp 110–112 °C (lit.[174] 110–112 °C); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.32 (3H, s, 3-CH_3), 4.55 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 7.23–7.27 (2H, m, 2 × ArH), 7.37–7.56 (5H, m, 3 × ArH, 5-H and 6-H), 7.67 (1H, ddd, *J* 8.3, 6.7, 1.4 Hz, 7-H), 8.19 (1H, br d, J 8.3 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 16.8 (CH_3), 62.1 (CH_2), 126.0 (CH), 126.2 (C), 127.7 (CH), 128.1 (CH), 128.2 (C), 128.7 (2 × CH), 129.0 (CH), 129.2 (2 × CH), 129.8 (CH), 136.7 (C), 145.6 (C), 148.7 (C), 151.5 (C), 167.4 (C); *m/z* (CI) 292 (MH^+. 100%), 220 (48), 137 (3), 113 (9), 85 (19).

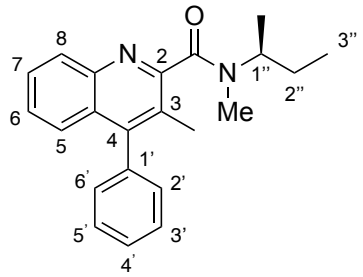
(*S*)-(*N*-*sec*-Butyl)-3-methyl-4-phenylquinoline-2-carboxamide (188)



The reaction was performed according to general procedure H using ethyl 3-methyl-4-phenylquinoline-2-carboxylate (**170**) (1.60 g, 5.49 mmol) and sodium hydroxide (0.879 g, 22.0 mmol) in 50% ethanol/water (100 mL) for the hydrolysis step. 3-Methyl-4-phenylquinoline-2-carboxylic acid (0.527 g, 2.00 mmol), *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (1.14 g, 3.00 mmol), *N,N*-diisopropylethylamine (0.699 mL, 4.00 mmol) and (*S*)-(+)-*sec*-butylamine (0.223 mL, 2.20

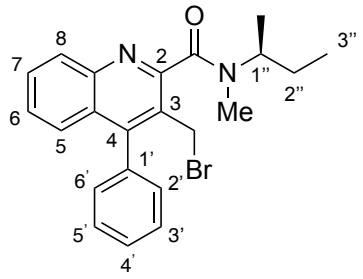
mmol) in *N,N*-dimethylformamide (20 mL) were used for the amide coupling step. Purification by flash column chromatography (20% ethyl acetate in hexane) gave (*S*)-(*N*-*sec*-butyl)-3-methyl-4-phenylquinoline-2-carboxamide (**188**) as a white solid (0.602 g, 93%). Mp 149–151 °C; $[\alpha]_D^{16}$ +23.5 (c 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 3282 (NH), 2967 (CH), 1638 (C=O), 1537 (C=C), 1442, 1380, 1156, 885, 760; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.33 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.61–1.76 (2H, m, 2''-H_2), 2.56 (3H, s, 3-CH_3), 4.08–4.21 (1H, m, 1''-H), 7.21–7.25 (2H, m, 2 × ArH), 7.35 (1H, ddd, *J* 8.4, 1.5, 0.7 Hz, 5-H), 7.43 (1H, ddd, *J* 8.4, 6.7, 1.3 Hz, 6-H), 7.46–7.56 (3H, m, 3 × ArH), 7.66 (1H, ddd, *J* 8.4, 6.7, 1.5 Hz, 7-H), 7.88 (1H, d, *J* 8.6 Hz, NH), 8.09 (1H, ddd, *J* 8.4, 1.3, 0.7 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 10.7 (CH_3), 17.7 (CH_3), 20.6 (CH_3), 30.0 (CH_2), 46.9 (CH), 126.3 (CH), 127.7 (CH), 128.1 (CH), 128.7 (C), 128.8 (2 × CH), 128.9 (CH), 128.9 (C), 129.5 (2 × CH), 129.6 (CH), 137.5 (C), 144.8 (C), 149.6 (C), 150.3 (C), 166.3 (C); *m/z* (ESI) 319.1811 (MH^+. $C_{21}H_{22}N_2O$ requires 319.1805).

(*S*)-(*N*-*sec*-Butyl)-*N*-methyl-3-methyl-4-phenylquinoline-2-carboxamide (189)



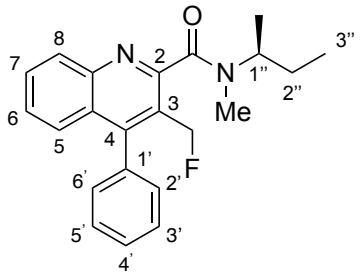
The reaction was performed according to general procedure I using (*S*)-(*N*-*sec*-butyl)-3-methyl-4-phenylquinoline-2-carboxamide (**188**) (0.726 g, 2.28 mmol), sodium hydride (60% dispersion in mineral oil) (0.182 g, 4.56 mmol) and methyl iodide (0.710 mL, 11.4 mmol) in tetrahydrofuran (45 mL). Purification by flash column chromatography (20–50% ethyl acetate in hexane) gave (*S*)-(*N*-*sec*-butyl)-*N*-methyl-3-methyl-4-phenylquinoline-2-carboxamide (**189**) as a white solid (0.513 g, 68%). Mp 112–113 °C; $[\alpha]_D^{17}$ +9.3 (c 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2967 (CH), 1622 (C=O), 1442, 1326, 1071, 1017, 768, 703; NMR spectra showed a 5:1 mixture of two rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.24 (3H, d, *J* 6.6 Hz, 1''-CH_3), 1.36–1.48 (1H, m, 2''-*H*H), 1.54–1.70 (1H, m, 2''-H*H*), 2.22 (3H, s, 3-CH_3), 3.04 (3H, s, NCH_3), 4.43–4.53 (1H, m, 1''-H), 7.24–7.30 (2H, m, 2 × ArH), 7.37–7.43 (2H, m, 5-H and 6-H), 7.46–7.56 (3H, m, 3 × ArH), 7.64 (1H, ddd, *J* 8.4, 5.0, 3.2 Hz, 7-H), 8.09 (1H, br d, *J* 8.4 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 11.3 (CH_3), 16.5 (CH_3), 18.7 (CH_3), 25.7 (CH_3), 27.3 (CH_2), 49.7 (CH), 125.6 (C), 126.1 (CH), 127.0 (CH), 127.6 (C), 128.2 (CH), 128.8 (2 × CH), 128.8 (CH), 129.5 (2 × CH), 129.6 (CH), 137.0 (C), 146.0 (C), 148.2 (C), 156.3 (C), 169.8 (C); *m/z* (ESI) 333.1972 (MH^+. $C_{22}H_{24}N_2O$ requires 333.1961).

(*S*)-3-Bromomethyl-(*N*-*sec*-butyl)-*N*-methyl-4-phenylquinoline-2-carboxamide (190)



A solution of (*S*)-(*N*-*sec*-butyl)-*N*-methyl-3-methyl-4-phenylquinoline-2-carboxamide (**189**) (0.440 g, 1.32 mmol) in chloroform (10 mL) was degassed under argon for 0.2 h. To this was added *N*-bromosuccinimide (0.353 g, 1.99 mmol) and dibenzoyl peroxide (0.0426 g, 0.132 mmol) and the solution heated under reflux for 3 h. A further portion of *N*-bromosuccinimide (0.295 g, 1.66 mmol) was then added and the solution heated under reflux for a further 18 h. After cooling to room temperature, the reaction mixture was filtered, and the solvent removed *in vacuo*. The crude residue was then diluted with ethyl acetate (15 mL) and washed with water (3 × 15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2.5–5% ethyl acetate in dichloromethane) gave (*S*)-3-bromomethyl-(*N*-*sec*-butyl)-*N*-methyl-4-phenylquinoline-2-carboxamide (**190**) as a white solid (0.371 g, 68%). Mp 160–162 °C; $[\alpha]_D^{17}$ +11.4 (c 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2969 (CH), 1626 (C=O), 1482, 1395, 1044, 758, 700; NMR spectra showed a 3:2 mixture of rotamers. Only signals for the major rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.32 (3H, d, *J* 6.7 Hz, 1''-CH_3), 1.51–1.80 (1H, m, 2''-H_2), 3.08 (3H, s, NCH_3), 4.56–4.71 (2H, m, 3-CH_2), 4.82–4.92 (1H, m, 1''-H), 7.35–7.49 (4H, m, 2 × ArH, 5-H and 6-H), 7.51–7.62 (3H, m, 3 × ArH), 7.71 (1H, ddd, *J* 8.4, 6,8, 1.6 Hz, 7-H), 8.03–8.21 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 11.3 (CH_3), 17.2 (CH_3), 26.7 (CH_2), 27.8 (CH_2), 30.7 (CH_3), 50.4 (CH), 126.5 (C), 126.9 (2 × CH), 127.5 (C), 127.6 (CH), 128.7 (2 × CH), 128.8 (CH), 129.2 (CH), 129.3 (CH), 130.3 (CH), 135.1 (C), 146.2 (C), 149.7 (C), 155.3 (C), 168.4 (C); *m/z* (ESI) 411.1072 (M^+. $C_{22}H_{24}{}^{79}BrN_2O$ requires 411.1067).

(*S*)-(*N*-*sec*-Butyl)-3-(fluoromethyl)-*N*-methyl-4-phenylquinoline-2-carboxamide (191)



To a solution of 18-crown-6 (0.188 g, 0.713 mmol) in acetonitrile (15 mL) under argon was added potassium fluoride (0.207 g, 3.57 mmol) and the suspension stirred at room temperature for 0.5 h. A solution of (*S*)-(*N*-*sec*-butyl)-3-bromomethyl-*N*-methyl-4-phenylquinoline-2-carboxamide (**190**) (0.259 g, 0.630 mmol) in acetonitrile (13 mL) and dichloromethane (7 mL) was then added dropwise to the reaction mixture. The mixture was stirred under reflux for 24 h. Further portions of 18-crown-6 (0.188 g, 0.713 mmol) and potassium fluoride (0.138 g, 2.38 mmol) were then added and the reaction mixture heated under reflux for a further 24 h. On cooling to room temperature, water (20 mL) was added to the mixture and the product extracted using dichloromethane (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% ethyl acetate in hexane) gave (*S*)-(*N*-*sec*-butyl)-3-(fluoromethyl)-*N*-methyl-4-phenylquinoline-2-carboxamide (**191**) as a white solid (0.176 g, 80%). Mp 140–142 °C; $[\alpha]_D^{17}$ +14.1 (c 0.1, $CHCl_3$); ν_{max}/cm^{-1} (neat) 2976 (CH), 1625 (C=O), 1485, 1399, 1048, 969, 764; NMR spectra showed a 1:1 mixture of rotamers. Only signals for one rotamer are recorded. δ_H (400 MHz, $CDCl_3$) 1.04 (3H, t, *J* 7.4 Hz, 3''-H_3), 1.28 (3H, d, *J* 6.8 Hz, 1''-CH_3), 1.41–1.79 (1H, m, 2''-H_2), 3.06 (3H, s, NCH_3), 4.82–4.92 (1H, m, 1''-H), 5.24–5.47 (2H, m, 3-CH_2), 7.30–7.39 (2H, m, 2 × ArH), 7.43–7.59 (5H, m, 3 × ArH, 5-H and 6-H), 7.71–7.78 (1H, m, 7-H), 8.15 (1H, d, *J* 8.4 Hz, 8-H); δ_C (101 MHz, $CDCl_3$) 11.1 (CH_3), 17.5 (CH_3), 26.1 (CH_3), 27.5 (CH_2), 50.1 (CH), 79.2 (CH_2, $^1J_{CF}$ 162.7 Hz), 123.1 (C, $^2J_{CF}$ 15.3 Hz), 127.1 (CH), 127.2 (C, $^4J_{CF}$ 2.3 Hz), 127.4 (CH), 128.6 (2 × CH), 128.8 (CH), 129.8 (2 × CH), 129.8 (CH), 130.5 (CH), 135.0 (C, $^3J_{CF}$ 4.4 Hz), 147.3 (C, $^4J_{CF}$ 2.5 Hz), 151.1 (C, $^3J_{CF}$ 4.7 Hz), 156.0 (C), 169.0 (C); *m/z* (ESI) 351.1876 (M^+. $C_{22}H_{24}FN_2O$ requires 351.1867).

HPLC Methods for Physicochemical Properties Analysis[176]

All physicochemical analyses were performed using a Dionex™ UltiMate™ 3000 series, and data acquisition and processing performed using Chromeleon 6.8 chromatography software. Standard and novel compounds were dissolved in 1:1 organic and aqueous phase mixture, prepared to a concentration of 0.5 mg/mL. The HPLC system oven was set to 25

°C, and UV detection achieved using a diode array detector (190–800 nm). Analysis was performed using 5 µL sample injections.

P_m and K_m values were determined using previously developed methodology on a Registech IAM.PC.DD2 (15 cm × 4.6 mm) column. Acetonitrile and 0.01 mM phosphate buffered saline at pH 7.4 was used as the mobile phase, with a flow rate of 1.0 mL/min. The retention time of each compound of interest was measured under an isocratic mobile phase with the percentage acetonitrile ranging from 30–70%. The retention time of citric acid, as an unretained compound, under an isocratic mobile phase of 100% phosphate buffered saline was used for system corrections. The following equations were used to calculate P_m and K_m of the compounds of interest using Microsoft Excel software.

$$k_{IAM} = \frac{(t_r - t_0)}{t_0}$$

Where k_{IAM} = solute capacity factor on the column, t_r = compound retention time and t_0 = unretained compound retention time.

$$k_{IAM} = \left(\frac{V_s}{V_m}\right) \times K_m$$

Where V_s = volume of the IAM interphase created by the immobilised phospholipids, V_m = total volume of the solvent within the IAM column and K_m = membrane partition coefficient.

$$V_m = \frac{W_{PhC}}{\partial_{PhC}} + \frac{W_{C10}}{\partial_{C10}} + \frac{W_{C3}}{\partial_{C3}}$$

Where the specific weight of PhC (∂_{PhC}) = 1.01779 g/mL and C_{10}/C_3 ($\partial_{C10/C3}$) = 0.86 g/mL; W_{PhC} = 133 mg, W_{C10} = 12.73 mg and W_{C3} = 2.28 mg.

$$V_m = f_r \times t_0$$

Where f_r = flow rate.

$$P_m = \frac{K_m}{MW}$$

Where P_m = permeability and MW = molecular weight.

%PPB values were determined using previously developed methodology on a ChromTech HSA 5 µm (3.0 × 50 mm) column. Isopropanol and 0.01 mM phosphate buffered saline at pH 7.4 was used as the mobile phase, with a flow rate of 1.8 mL/min. The retention time of each compound of interest was measured under the following mobile phase conditions: 0–3 min, 0–30% isopropanol; 3–10 min, 30% isopropanol; 10.5–11.0 min, 30–0% isopropanol; 11.0–15.0 min, 0% isopropanol. System calibration was achieved using the following compounds and plotting %PPB values against their mean retention times: warfarin (%PPB

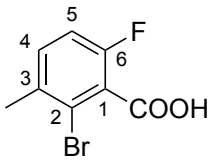
= 98.0), nizatidine (%PPB = 35.0), bromazepam (%PPB = 60.0), carbamazepine (%PPB = 75.0), nicardipine (%PPB = 95.0), ketoprofen (%PPB = 98.7), indomethacin (%PPB = 99.0) and diclofenac (%PPB = 99.8). For each standard compound, the literature %PPB value was converted to its corresponding log *K* value, which when plotted against t_r on the HSA column, afforded a line equation from which the log *K* value of the unknown compounds could be extracted. The log *K* values of the unknown compounds could then be converted to %PPB. Log *K* and subsequent %PPB calculations for the compounds of interest were performed using Excel 2019 Software.

$$\log K = \log\left[\frac{\%PPB}{101 - \%PPB}\right]$$

$$\%PPB = \left[\frac{(101 - 10^{\log K})}{(1 + 10^{\log K})}\right]$$

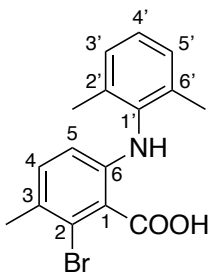
4.7 S1P$_5$ Experimental

2-Bromo-6-fluoro-3-methylbenzoic acid (197)[193]



To a solution of freshly distilled diisopropylamine (1.90 mL, 13.8 mmol) in tetrahydrofuran (20 mL) under argon at −10 °C was added *n*-butyllithium (5.2 mL, 13.0 mmol, 2.5 M in hexanes). The mixture was stirred for 0.5 h, before cooling to −78 °C. 2-Bromo-4-fluorotoluene (**196**) (1.00 mL, 8.09 mmol) was then added dropwise. After 1 h of stirring, carbon dioxide was bubbled into the reaction via syringe (a pellet of dry ice was added to a 10 mL syringe). The addition was continued for 0.3 h and then the reaction mixture was allowed to reach room temperature over 2 h. The mixture was diluted with water (15 mL) and extracted with a 1 M aqueous solution of sodium hydroxide (15 mL). The aqueous layers were then washed with ethyl acetate (30 mL) and the organic layer discarded. The aqueous layers were acidified to pH 1 using a 1 M aqueous solution of hydrochloric acid and subsequently extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2-bromo-6-fluoro-3-methylbenzoic acid (**197**) as a white solid (1.78 g, 94%). The spectroscopic data were consistent with the literature.[193] Mp 104–106 °C; δ_H (500 MHz, $CDCl_3$) 2.42 (3H, s, 3-CH_3), 7.05 (1H, t, *J* 8.6 Hz, 5-H), 7.31 (1H, dd, *J* 8.6, 5.9 Hz, 4-H), 11.39 (1H, br s, OH); δ_C (101 MHz, $CDCl_3$) 22.7 (CH_3), 114.7 (CH, d, $^2J_{CF}$ 20.8 Hz), 121.7 (C, d, $^3J_{CF}$ 4.0 Hz), 123.7 (C, d, $^2J_{CF}$ 19.4 Hz), 132.8 (CH, d, $^3J_{CF}$ 8.3 Hz), 134.9 (C, d, $^4J_{CF}$ 3.7 Hz), 157.6 (C, d, $^1J_{CF}$ 252.6 Hz), 169.8 (C); *m/z* (EI) 232 (M^+. 100%), 215 (55), 153 (38), 107 (38), 84 (34).

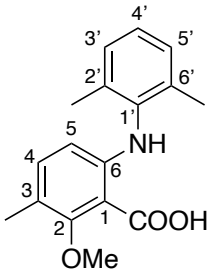
2-Bromo-6-[(2',6'-dimethylphenyl)amino]-3-methylbenzoic acid (198)



To a solution of 2-bromo-6-fluoro-3-methylbenzoic acid (**197**) (2.39 g, 10.2 mmol) in tetrahydrofuran (50 mL) under argon was added 2,6-dimethylaniline (2.53 mL, 20.5 mmol) and the mixture cooled to −78 °C. Lithium bis(trimethylsilyl)amide (32.7 mL, 32.7 mmol, 1.0 M in tetrahydrofuran) was then slowly added over 0.1 h. The reaction mixture was stirred at

−78 °C for 1 h then allowed to reach room temperature before heating to 60 °C and stirring for 72 h. The reaction was quenched with water (30 mL) and acidified to pH 2 with 10% aqueous hydrochloric acid. The mixture was then extracted with ethyl acetate (3 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30–50% ethyl acetate in petroleum ether (40–60)) followed by trituration with hexane gave 2-bromo-6-[(2',6'-dimethylphenyl)amino]-3-methylbenzoic acid (**198**) as a brown solid (2.69 g, 79%). Mp 126–128 °C; ν_{max}/cm^{-1} (neat) 3389 (NH), 2918 (OH/CH), 1690 (CO), 1661, 1489, 1234, 773; δ_H (500 MHz, $CDCl_3$) 2.20 (6H, s, 2'-CH_3 and 6'-CH_3), 2.34 (3H, s, 3-CH_3), 6.14 (1H, d, *J* 8.5 Hz, 5-H), 7.02 (1H, d, *J* 8.5 Hz, 4-H), 7.07–7.17 (3H, m, 3'-H, 4'-H and 5'-H), 10.29 (1H, br s, OH); δ_C (126 MHz, $CDCl_3$) 18.2 (2 × CH_3), 23.0 (CH_3), 112.5 (CH), 116.9 (C), 124.0 (C), 126.4 (CH), 128.0 (C), 128.6 (2 × CH), 134.0 (CH), 136.0 (2 × C), 137.1 (C), 146.0 (C), 173.4 (C); *m/z* (ESI) 356.0250 (MNa^+. $C_{16}H_{16}{}^{79}BrNNaO_2$ requires 356.0257).

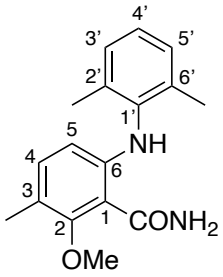
6-[(2',6'-Dimethylphenyl)amino]-2-methoxy-3-methylbenzoic acid (199)



Sodium hydride (0.968 g, 24.2 mmol, 60% in mineral oil) was added to an oven-dried flask under argon and washed with hexane (2 × 10 mL) to remove the oil. The flask was cooled to 0 °C, methanol (13 mL) was added to the reaction vessel carefully over 0.1 h and then stirred for 0.5 h. 2-Bromo-6-[(2',6'-dimethylphenyl)amino]-3-methylbenzoic acid (**198**) (2.69 g, 8.06 mmol) in methanol (12 mL) was added followed by copper powder (0.204 g, 3.22 mmol) and the reaction mixture heated under reflux for 18 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* and water (30 mL) was added. The mixture was acidified to pH 2 using 10% aqueous hydrochloric acid and extracted with dichloromethane (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (40–50% ethyl acetate in petroleum ether (40–60)) gave 6-[(2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzoic acid (**199**) as a brown solid (2.11 g, 92%). Mp 92–94 °C; ν_{max}/cm^{-1} (neat) 3289 (NH), 3094 (OH), 2945 (CH), 1699 (CO), 1570 (C=C), 1501, 1414, 1385, 1223, 1040, 818, 770; δ_H (500 MHz, $CDCl_3$) 2.18 (6H, s, 2'-CH_3 and 6'-CH_3), 2.20 (3H, s, 3-CH_3), 3.93 (3H, s, OCH_3), 6.03 (1H, d, *J* 8.7 Hz, 5-H), 7.01 (1H, d, *J* 8.7 Hz, 4-H), 7.06–7.18 (3H, m, 3'-H, 4'-H and 5'-H), 9.59 (1H, br s, NH), 12.15 (1H, br s, OH); δ_C (126 MHz, $CDCl_3$) 15.1 (CH_3), 18.2 (2 × CH_3), 62.2 (CH_3), 102.1 (C), 110.0 (CH),

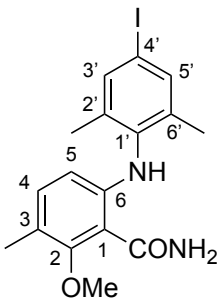
116.3 (C), 126.7 (CH), 128.5 (2 × CH), 136.7 (2 × C), 137.1 (C), 137.1 (CH), 150.2 (C), 158.2 (C), 168.7 (C); *m/z* (ESI) 308.1248 (MNa^+. $C_{17}H_{19}NNaO_3$ requires 308.1257).

6-[(2',6'-Dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (200)



To a solution of 6-[(2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzoic acid (**199**) (2.01 g, 7.05 mmol) in tetrahydrofuran (20 mL) was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.49 g, 8.47 mmol) and *N*-methylmorpholine (2.33 mL, 21.2 mmol) and the reaction mixture was stirred for 2 h at room temperature. The precipitate was filtered and ammonium hydroxide (60 mL) was added to the filtrate. The reaction mixture was stirred for 0.5 h at room temperature and then filtered. 2 M Sodium hydroxide (75 mL) was added to the filtrate and the crude product was extracted with ethyl acetate (3 × 75 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (15–30% ethyl acetate in hexane) gave 6-[(2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**200**) as a white solid (1.86 g, 93%). Mp 116–118 °C; ν_{max}/cm^{-1} (neat) 3443 (NH), 3184 (NH), 2936 (CH), 1645 (CO), 1570 (C=C), 1497, 1366, 1261, 1047, 816, 731; δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s, 3-CH_3), 2.21 (6H, s, 2'-CH_3 and 6'-CH_3), 3.79 (3H, s, OCH_3), 5.96 (1H, d, *J* 8.6 Hz, 5-H), 6.04 (1H, br s, NH), 6.94 (1H, d, *J* 8.6 Hz, 4-H), 7.03–7.19 (3H, m, 3'-H, 4'-H and 5'-H), 7.93 (1H, br s, NH), 9.47 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 15.2 (CH_3), 18.4 (2 × CH_3), 61.1 (CH_3), 107.0 (C), 109.3 (CH), 117.5 (C), 126.0 (CH), 128.3 (2 × CH), 134.9 (CH), 136.6 (2 × C), 138.1 (C), 148.9 (C), 158.1 (C), 170.9 (C); *m/z* (ESI) 307.1409 (MNa^+. $C_{17}H_{20}N_2NaO_2$ requires 307.1417).

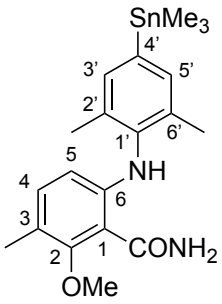
6-[(4'-Iodo-2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (201)



To a solution of 6-[(2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**200**) (0.500 g, 1.76 mmol) and silver bis(trifluoromethanesulfonyl)imide (0.0512 g, 0.132 mmol)

in dry tetrahydrofuran (7 mL) under argon was slowly added *N*-iodosuccinimide (0.554 g, 2.46 mmol) in dry tetrahydrofuran (2.0 mL). The reaction mixture was stirred at room temperature for 3 h in the dark. The reaction mixture was filtered through a short pad of Celite®, washed with ethyl acetate and concentrated *in vacuo*. Purification by flash column chromatography (20–25% diethyl ether in hexane) gave 6-[(4'-iodo-2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**201**) as a white solid (0.382 g, 53%). Mp 141–143 °C; ν_{max}/cm^{-1} (neat) 3447 (NH), 3202 (NH), 2934 (CH), 1645 (C=O), 1572 (C=C), 1497, 1468, 1398, 1366, 1265, 1215, 1047, 851, 733; δ_H (500 MHz, $CDCl_3$) 2.13 (6H, s, 2'-CH_3 and 6'-CH_3), 2.17 (3H, s, 3-CH_3), 3.78 (3H, s, OCH_3), 5.66 (1H, br s, NH), 5.92 (1H, d, *J* 8.6 Hz, 5-H), 6.95 (1H, d, *J* 8.6 Hz, 4-H), 7.45 (2H, s, 3'-H and 5'-H), 7.92 (1H, br s, NH), 9.41 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 15.2 (CH_3), 18.0 (2 × CH_3), 61.2 (CH_3), 90.8 (C), 107.2 (C), 109.3 (CH), 118.1 (C), 135.0 (CH), 137.2 (2 × CH), 138.2 (C), 139.0 (2 × C), 148.4 (C), 158.2 (C), 170.6 (C); *m/z* (ESI) 433.0385 (MNa^+. $C_{17}H_{19}IN_2NaO_2$ requires 433.0383).

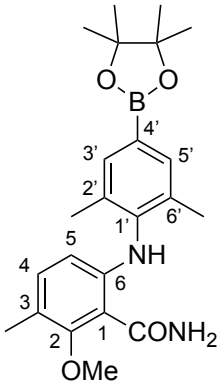
6-[(4'-(Trimethylstannyl)-2'-6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (202)



An oven-dried microwave vial was flushed with argon and charged with 6-[(4'-iodo-2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**201**) (0.0800 g, 0.195 mmol) in dry toluene (3.0 mL). Lithium chloride (0.0413 g, 0.975 mmol) was added and the mixture was degassed under argon for 0.2 h. Tetrakis(triphenylphosphine)palladium(0) (0.0451 g, 0.0390 mmol) and hexamethylditin (0.0806 mL, 0.390 mmol) were added under argon and the reaction mixture was stirred under reflux for 21 h. After cooling to room temperature, the reaction mixture was quenched by the addition of 30% aqueous potassium fluoride solution (2.0 mL) and stirred at room temperature for 0.5 h. The mixture was filtered through a short pad of Celite®, washed with ethyl acetate and concentrated *in vacuo*. Purification by neutral alumina (Brockmann grade V) flash column chromatography (20% diethyl ether in hexane) gave 6-[(4'-(trimethylstannyl)-2'-6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**202**) as a colourless oil (0.0734 g, 84%). ν_{max}/cm^{-1} (neat) 3445 (NH), 3188 (NH), 2918 (CH), 1651 (C=O), 1576, 1497, 1267, 1258, 1049, 765; δ_H (500 MHz, $CDCl_3$) 0.29 (9H, s, $Sn(CH_3)_3$), 2.16 (3H, s, 3-CH_3), 2.19 (6H, s, 2'-CH_3 and 6'-CH_3), 3.78 (3H, s, OCH_3), 5.68 (1H, br s, NH), 5.97 (1H, d, *J* 8.6 Hz, 5-H), 6.93 (1H, d, *J* 8.6 Hz, 4-H),

7.21 (2H, s, 3'-H and 5'-H), 7.92 (1H, br s, NH), 9.46 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) −9.5 (3 × CH_3), 15.2 (CH_3), 18.3 (2 × CH_3), 61.2 (CH_3), 106.9 (C), 109.5 (CH), 117.5 (C), 134.9 (CH), 135.8 (2 × CH), 136.0 (2 × C), 138.4 (C), 139.4 (C), 148.9 (C), 158.1 (C), 170.8 (C); *m/z* (ESI) 471.1056 (MNa^+. $C_{20}H_{28}N_2NaO_2Sn$ requires 471.1065).

6-[(4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2'-6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (204)



An oven-dried microwave vial was flushed with argon and charged with 6-[(4'-iodo-2',6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**201**) (0.0500 g, 0.122 mmol), bis(pinacolato)diboron (0.0371 g, 0.146 mmol), potassium acetate (0.0359 g, 0.366 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (complex with dichloromethane) (0.0030 g, 0.00366 mmol) and dry dioxane (1 mL). The reaction mixture was degassed under argon for 0.2 h and stirred at 100 °C for 22 h. The reaction mixture was filtered through a short pad of Celite®, washed with ethyl acetate and concentrated *in vacuo*. Purification by flash column chromatography (15% ethyl acetate in hexane) gave 6-[(4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2'-6'-dimethylphenyl)amino]-2-methoxy-3-methylbenzamide (**204**) as a white solid (0.0326 g, 65%). Mp 204–205 °C; ν_{max}/cm^{-1} (neat) 3444 (NH), 3208 (NH), 2976 (CH), 2933 (CH), 1650 (C=O), 1574, 1498, 1363, 1214, 1143, 732; δ_H (500 MHz, $CDCl_3$) 1.36 (12H, s, $C_2(CH_3)_4$), 2.16 (3H, s, 3-CH_3), 2.19 (6H, s, 2'-CH_3 and 6'-CH_3), 3.78 (3H, s, OCH_3), 5.79 (1H, br s, NH), 5.95 (1H, d, *J* 8.6 Hz, 5-H), 6.92 (1H, d, *J* 8.6 Hz, 4-H), 7.57 (2H, s, 3'-H and 5'-H), 7.89 (1H, br s, NH), 9.49 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 15.2 (CH_3), 18.3 (2 × CH_3), 25.0 (4 × CH_3), 61.3 (CH_3), 83.9 (2 × C), 107.5 (C), 109.8 (CH), 118.0 (C), 135.0 (CH), 135.0 (2 × CH), 135.6 (2 × C), 141.4 (C), 148.4 (C), 148.9 (C), 158.2 (C), 170.9 (C); *m/z* (ESI) 433.2269 (MNa^+. $C_{23}H_{31}BN_2NaO_4$ requires 433.2269).

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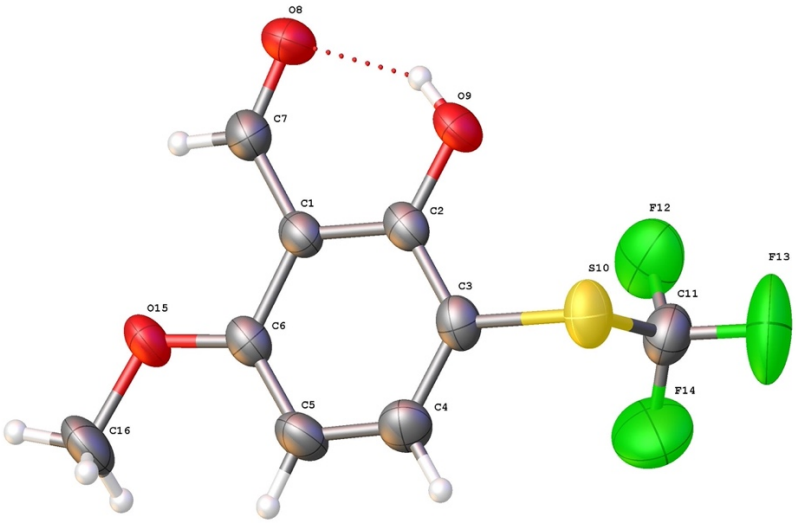
Appendix I – Crystal Structure Data for 98c

2-Hydroxy-3-(trifluoromethylthio)-6-methoxybenzaldehyde (**98c**) was recrystallised from diethyl ether. Following crystallisation, the solvent was allowed to evaporate at room temperature over 18 hours. The crystals were collected and X-ray crystallography analysis was performed.



View showing the structure and atom labelling scheme for **98c** (CCDC 2305671). Displacement ellipsoids are drawn at 50% probability level.

Computing details: Data collection: *APEX3* Ver. 2016.9-0 (Bruker-AXS, 2016); cell refinement: *SAINT* V8.37A (Bruker-AXS, 2016); data reduction: *APEX3* Ver. 2016.9-0 (Bruker-AXS, 2016); program(s) used to solve structure: SHELXT 2018/2; program(s) used to refine structure: *SHELXL* 2018/3; molecular graphics: Olex2 1.5; software used to prepare material for publication: Olex2 1.5.

Crystal data

$C_9H_7F_3O_3S$	$F(000)$ = 512
M_r = 252.21	D_x = 1.649 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 7.9284 (8) Å	Cell parameters from 6104 reflections
b = 4.8567 (5) Å	θ = 2.8–26.3°
c = 26.543 (3) Å	μ = 0.35 mm^{-1}
β = 96.455 (3)°	T = 295 K
V = 1015.58 (18) Å^3	Block, colourless
Z = 4	0.28 × 0.16 × 0.1 mm

Data collection

Bruker D8 VENTURE diffractometer	2065 independent reflections
Radiation source: microfocus sealed tube, INCOATEC Iμs 3.0	1825 reflections with $I > 2\sigma(I)$
Multilayer mirror optics monochromator	$R_{int} = 0.036$
Detector resolution: 7.4074 pixels mm^{-1}	$\theta_{max} = 26.4°$, $\theta_{min} = 2.6°$
ϕ and ω scans	$h = -9 \rightarrow 9$
Absorption correction: multi-scan *SADABS2016/2* (Bruker, 2016/2) was used for absorption correction. wR2(int) was 0.0657 before and 0.0560 after correction. The Ratio of minimum to maximum transmission is 0.8373. The l/2 correction factor is not present.	$k = -6 \rightarrow 6$
$T_{min} = 0.624$, $T_{max} = 0.745$	$l = -33 \rightarrow 33$
11249 measured reflections	

Refinement

Refinement on F^2	Primary atom site location: dual
Least-squares matrix: full	Hydrogen site location: inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.054$	H-atom parameters constrained
$wR(F^2) = 0.125$	$w = 1/[\sigma^2(F_o^2) + (0.024P)^2 + 1.4201P]$ where $P = (F_o^2 + 2F_c^2)/3$
$S = 1.18$	$(\Delta/\sigma)_{max} < 0.001$
2065 reflections	$\Delta\rangle_{max} = 0.28$ e $Å^{-3}$
147 parameters	$\Delta\rangle_{min} = -0.29$ e $Å^{-3}$
0 restraints	