New Iodination Reactions for the Synthesis of SPECT Imaging Agents

Nikki L Sloan, M.Sci

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School of Chemistry

College of Science & Engineering

University of Glasgow

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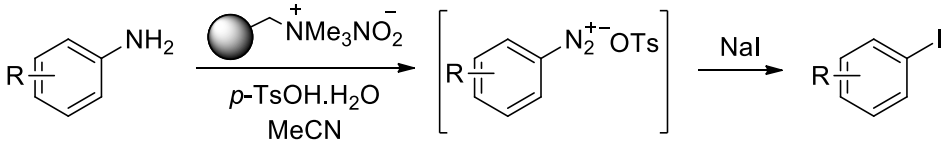
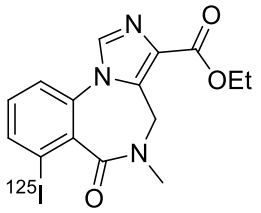
Abstract

This thesis describes the development of a mild, one-pot, diazotisation-iodination reaction, *via* a stable diazonium salt intermediate. The reaction is tolerant of various functional groups and substitution patterns, and was used as the final step in the synthesis of six potential or currently used radiotracers for SPECT imaging.

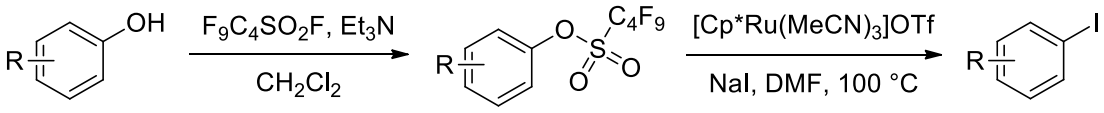


The transformation was also adapted for use with sodium [^{125}I]iodide as a mild, operationally simple method to access ^{125}I-labelled SPECT radiotracers. The full radiosynthesis of the imaging agent iomazenil is described with iodine-125 and iodine-123. This one-pot reaction was then utilised for the development of new SPECT imaging agents for the N-methyl-D-aspartate (NMDA) receptor. A small library of analogues based on the SPECT imaging agent CNS1261 were synthesised.



Iomazenil

The final project describes the development of a metal-catalysed iodination reaction from non-halide starting materials. The use of a highly active ruthenium catalyst and a nonaflate leaving group gave promising results for a number of substrates.



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Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis represents the original work of Nikki L. Sloan 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 Dr Andrew Sutherland between October 2013 to March 2017. Aspects of the work described herein have been published elsewhere as listed below.

N. L. Sloan, S. K. Luthra, G. McRobbie, S. L. Pimlott and A. Sutherland, *Chem. Commun.*, 2017, **53**, 11008.

N. L. Sloan, S. K. Luthra, G. McRobbie, S. L. Pimlott and A. Sutherland, *RSC Adv.*, 2017, **7**, 54881.

Abbreviations

Aß	*beta*-amyloid
Ac	acetyl
Ar	aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BOC	*tert*-butyloxycarbonyl
br	broad
CI	chemical ionisation
cod	1,5-cyclooctadiene
conc.	Concentrated
COSY	correlation spectroscopy
COX	cyclooxygenase
CNS	central nervous system
D	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*'-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone

DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EDCI	ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron-donating group
EI	electron ionisation
equiv.	equivalents
ESI	electrospray ionisation
EWG	electron-withdrawing group
g	grams
GABA	gamma-aminobutyric acid
GBq	gigabecquerel
h	hours
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
5-I-A-85380	5-[^{123}I]iodo-3-[2(S)-2-azetidinylmethoxy]pyridine
IBOX	2-(4'-dimethylaminophenyl)-6-iodobenzoxazole
IC_{50}	half maximal inhibitory concentration

keV	kilo-electron volts
K_i	inhibition constant
KI	potassium iodide
m	multiplet
M	molar
MBq	megabecquerel
mg	milligrams
mL	millilitres
mmol	millimoles
Mp	melting point
MS	molecular sieves
MW	molecular weight
MTBE	methyl *tert*-butyl ether
nAChR	nicotinic acetylcholine receptors
n.c.a	non-carrier added
nM	nanomolar
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide

NIMI	*N*-iodomorpholinium iodide
NMDA	*N*-methyl-D-aspartate
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NfO	nonafluorobutanesulfonate
nonaflate	nonafluorobutanesulfonate
PARP	poly(ADP-ribose) polymerase
PBR	peripheral benzodiazepine receptor
PCP	phencyclidine
PET	positron emission tomography
ppm	parts per million
q	quartet
rt	room temperature
s	singlet
SM	starting material
S_NAr	nucleophilic aromatic substitution
SPECT	single photon emission computed tomography
t	triplet
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
triflate	trifluoromethanesulfonate
TfO	trifluoromethanesulfonate
Ts	*para*-toluenesulfonyl
TSPO	translocator protein
μM	micromolar
UV	ultraviolet

1.0 Introduction

1.1 Molecular Imaging

Molecular imaging allows the visualisation of biological processes, non-invasively, at the molecular, cellular, organ and whole body level. This includes techniques such as Magnetic Resonance Imaging (MRI), Optical Imaging, Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). PET and SPECT are the most sensitive of these techniques.[1] They require the use of a molecular imaging probe to visualise biological processes, and can be used for the diagnosis and prognosis of diseases such as cancers, neurological disease and cardiovascular disease. They can also be used in drug development and can aid in understanding drug action, help in establishing drug dosage and treatment strategies.

1.1.1 PET Imaging

PET imaging requires an imaging agent that contains a radionuclide that decays by emission of a positron.[2] This positively charged positron is radiated from the nucleus and travels a short distance in the surrounding tissue in the body before annihilating with an electron to emit two 511 keV γ-rays at 180° to one another. These γ-rays are detected by surrounding detectors and allow a 3D image to be constructed which can give information on biological processes in the body. The radionuclides used for PET imaging have short half-lives (Table 1)[1a] and as such, syntheses and purification must be fast. Due to the short half-lives of the radioisotopes, an on-site cyclotron is generally required for production of these, making PET an expensive technique. The most commonly used radionuclides in PET imaging are carbon-11 (^{11}C) and fluorine-18 (^{18}F). The advantages of these radionuclides are that the isotope can be incorporated into the ligand easily without substantially altering the molecule. Stable carbon-12 is the main constituent of biologically active compounds and can be replaced with carbon-11 with minimal structural alteration. A hydrogen atom can be replaced with fluorine-18 without causing steric change and has actually been known to improve the potency of molecular probes.[3] Imaging agents labelled with fluorine-18 are important in PET analysis due to its slightly longer half-life of 110

minutes. This allows for longer synthesis and purification times as well as longer in vivo studies compared to other PET radionuclides.

Table 1. Radionuclides used for PET imaging.

Nuclide	Half-life (mins)	Type of emission
^{11}C	20	β^+
^{13}N	10	β^+
^{15}O	2	β^+
^{18}F	110	β^+
^{68}Ga	68	β^+/electron capture

1.1.2 SPECT Imaging

SPECT imaging is a similar technique to PET, except that it utilises radionuclides that directly emit γ-radiation by photon emission. These radionuclides have longer half-lives than those used for PET (Table 2), and are of a lower energy. Typically, iodine-123 (^{123}I) or technetium-99m (^{99m}Tc) are used as radionuclides for SPECT. SPECT is a less sensitive technique than PET; however the longer half-lives of the radionuclides result in easier handling of the radioisotope and allows for the study of longer biological processes. With SPECT imaging, longer radiosynthesis times are possible, as is transportation of the imaging agent to the site of injection, meaning equipment is less expensive at the injection site.

Table 2. Radionuclides used for SPECT imaging.

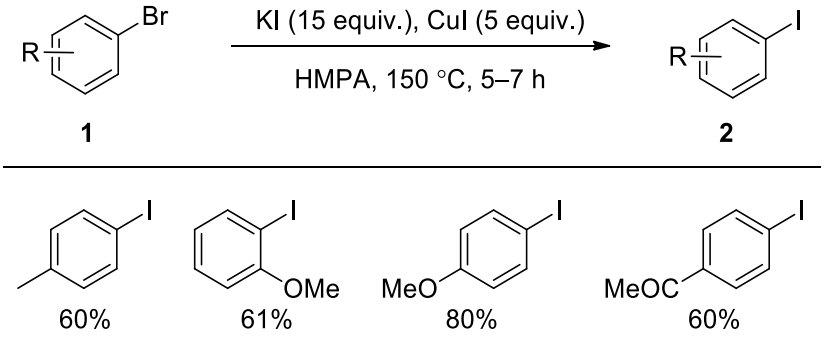
Nuclide	Half-life (h)	Type of emission
^{123}I	13.2	Electron capture
^{99m}Tc	6	Isomeric transition
^{111}In	67.9	Electron capture
^{67}Ga	78.3	Electron capture

1.2 Iodination of Aromatic Rings

Aryl iodides are not only important for the synthesis of SPECT imaging agents. They are also components in a number of medicinally important compounds[4] and are used as precursors for key transformations, including metal-catalysed cross-coupling reactions[5] and the generation of aryl magnesium or lithium reagents. There are a number of different approaches for the synthesis of aryl iodides. These include electrophilic aromatic substitution reactions,[6] metal-catalysed halogen exchange[7] and the Sandmeyer reaction,[8] which is a nucleophilic aromatic substitution where iodide replaces a diazo group. Issues with these methods include harsh conditions, high loadings of reagents or poly-iodination. The development of more mild reaction conditions with high regioselectivity has been investigated more recently and there are a number of methods now available.

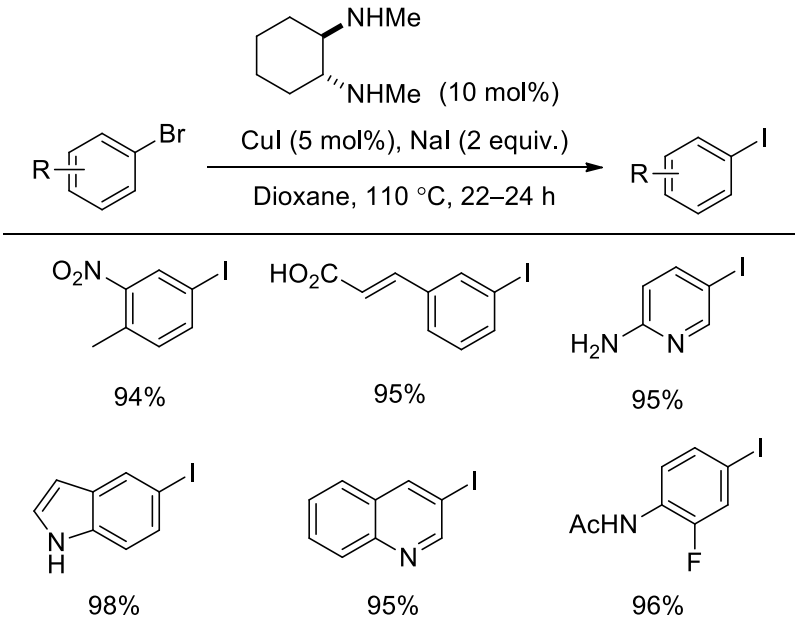
1.2.1 Halogen Exchange Reactions

A common method for synthesis of aryl iodides involve a halogen exchange reaction from aryl bromides or, less frequently, aryl chlorides. As aryl iodides are more reactive than aryl bromides and aryl chlorides, the reaction from aryl iodides from bromides and chlorides can be more difficult than the reverse reaction. Successful examples of halogen exchange reactions giving the aryl iodide product in high yields are most commonly catalysed by nickel or copper catalysts.[9] Halogen exchange reactions using copper catalysts were first reported in 1964,[10] using copper(I) halide salts in pyridine. Aryl chlorides could be prepared from aryl bromides or aryl iodides. Aryl bromides could also be prepared from aryl iodides. However, the reaction was not suitable for the synthesis of aryl iodides. Suzuki *et al*[11] obtained aryl iodides (**2**) from aryl bromides (**1**) when using a copper(I) iodide catalyst with potassium iodide in hexamethylphosphoramide (HMPA), although both reagents were required in a large excess for the reaction to go to completion (Scheme 1). Yields of 60—80% were achieved, exploring a narrow substrate scope.



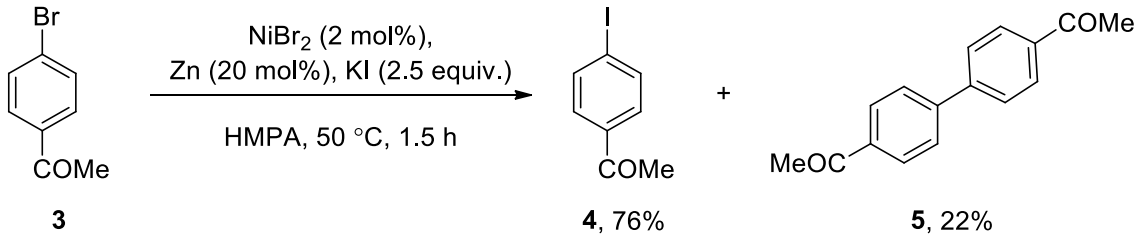
Scheme 1. Cu(I)-catalysed halogen exchange.

The first general reaction conditions for the synthesis of aryl iodides from aryl bromides in high yields was reported by Klapars and Buchwald in an aromatic Finkelstein reaction, using a copper(I)-catalyst with diamine ligands (Scheme 2).[12] As well as aryl iodides, a number of heteroaryl iodides were synthesised. The synthesis of heteroaryl iodides is even less commonly reported than aryl iodides, and is not a trivial process. The use of dioxane as solvent gave higher conversion in the reaction than DMF, which is typically employed for halogen-exchange reactions.[13] This was hypothesised to be due to the formation of unreactive halo-cuprate complexes when the sodium iodide was fully soluble in solvent, halting the reaction. Reaction times of 22—40 hours were required at temperatures of 110—130 °C. The use of higher temperatures and long reaction times can cause difficulties in the synthesis of more complex structures and is problematic for the synthesis of SPECT imaging agents.



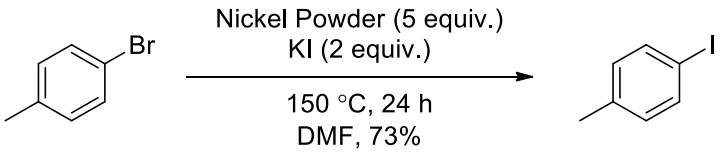
Scheme 2. Copper(I)-catalysed iodination of arenes.

The other most commonly used transition metal for iodination *via* halogen exchange is nickel. A nickel-mediated halogen exchange reaction to form aryl iodides was first reported by Takagi *et al*[14] by in situ formation of nickel(0) from nickel(II) bromide by reduction with zinc powder. In the presence of potassium iodide, in polar solvents such as HMPA, the reaction of aryl bromide **3** gave a mixture of the aryl iodide **4** and the biaryl product **5** (Scheme 3). The nickel(0) formed in situ is believed to insert into the aryl bromide bond, before implementing the Finkelstein-type displacement reaction to give the aryl iodide. However, due to the large excess of zinc required to initiate the reaction, Ullmann-type biaryl by-products were formed in high yield also, *via* the aryl iodide product. To obtain the best yields, the reaction had to be stopped before completion to minimise formation of the biaryl product. Other early methods involving the in-situ reduction of nickel(II) to nickel(0) also encountered issues with the formation of these biaryl species.[15]



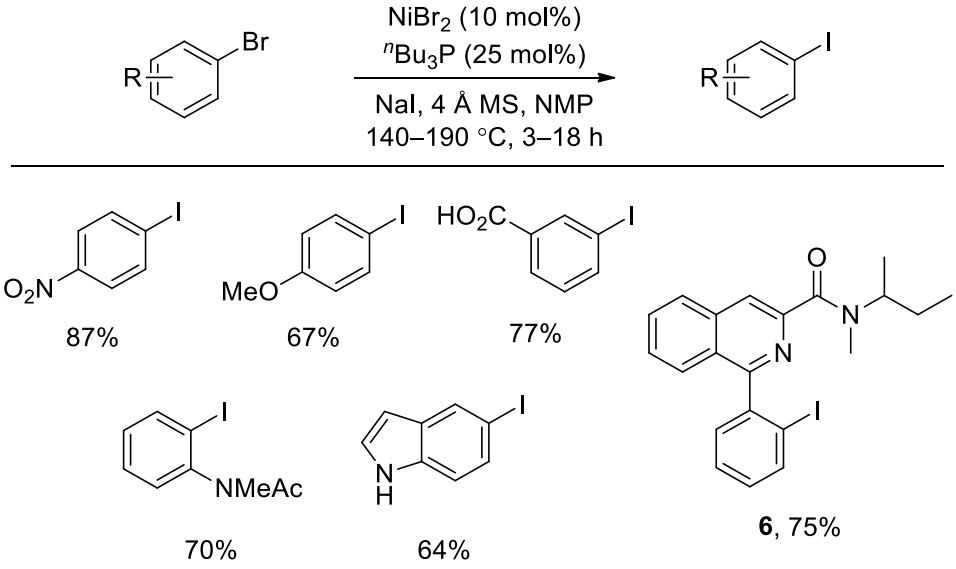
Scheme 3. Halogen exchange reaction using nickel(II) bromide, zinc and potassium iodide.

Cheng and co-workers[16] found that using nickel(0) powder rather than in situ generated nickel(0) stopped formation of the biaryl by-products in the synthesis of aryl iodides from aryl bromides. However, high temperatures and a large excess of the nickel catalyst were required to increase the reaction rate to drive the reaction to completion in 24 hours (Scheme 4).



Scheme 4. Halogen exchange using stoichiometric nickel(0).

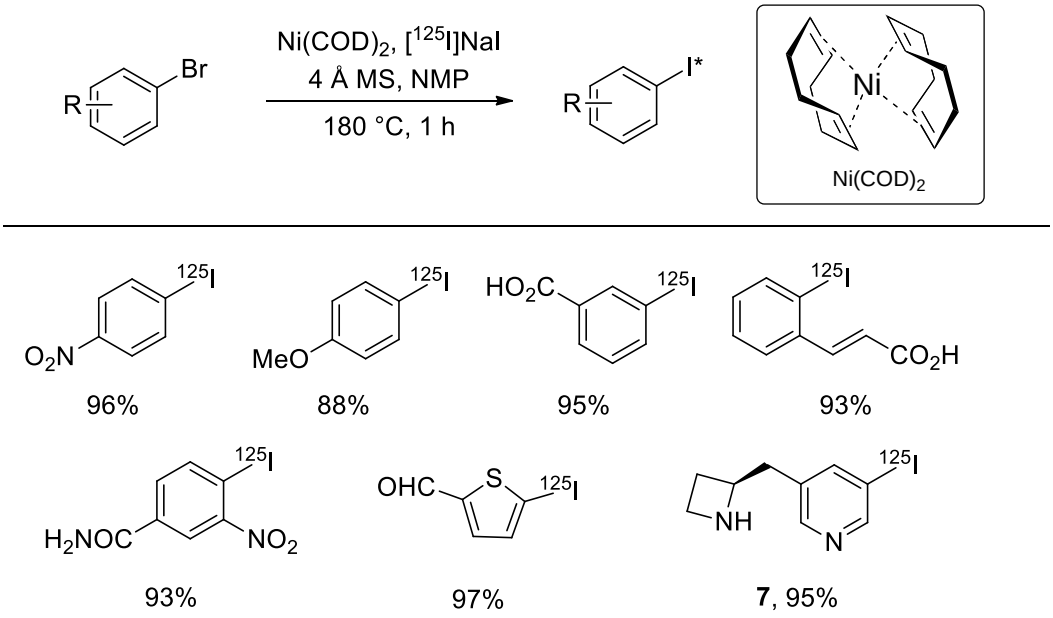
A more general nickel-catalysed halogen exchange reaction has been developed more recently in the Sutherland group for the synthesis of aryl iodides.[17] Using nickel(II) bromide as catalyst and tri-*n*-butylphosphine as ligand at temperatures of 140—190 °C, a number of electron-deficient and electron-rich aryl bromides were converted to aryl iodides in high yields (Scheme 5). Reaction times could also be shortened to 10—30 minutes using microwave heating. Despite the high temperatures, minimal decomposition was observed and the reaction could be used for the synthesis of the translocator protein (TSPO) ligand, I-PK11195 (**6**).



Scheme 5. Nickel-catalysed halogen exchange reaction.

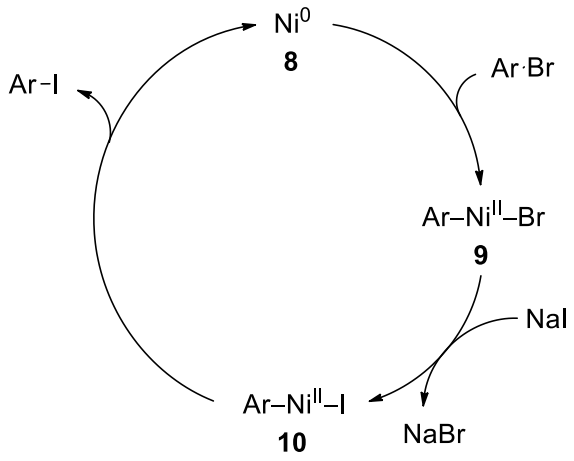
The nickel catalysed reaction was also successfully adapted for the radioiodination of aryl and heteroaryl bromides (Scheme 6). Nickel(II) bromide

was not suitable for the radioiodination, due to the presence of the bromide ion directing the equilibrium towards the bromide starting material. This was not found to be an issue in the cold aryl iodination reactions, as sodium iodide was used in excess (6 equivalents). However, in the radioiodination reaction, sodium [^{125}I]iodide is the limiting reagent and the use of nickel(II) bromide catalyst was found to give low radiochemical yield. Use of the non-halogen-containing bis(1,5-cyclooctadiene)nickel(0) [Ni(COD)$_2$] gave high yields for a range of electron-rich and electron-deficient ^{125}I-labelled aryl and heteroaryl compounds.[18] The reaction was also shown to be applicable to the synthesis of the imaging agent 5-[^{123}I]iodo-3-[2(S)-2-azetidinylmethoxy]pyridine (5-I-A-85380, **7**), which is used for imaging neuronal nicotinic acetylcholine receptors (nAChR) in humans.



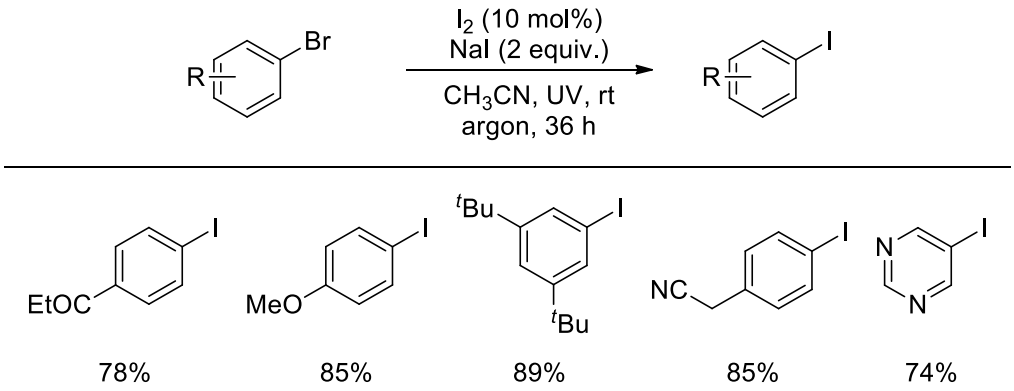
Scheme 6. Nickel-catalysed radioiodination of aryl bromides.

The mechanism is believed to proceed *via* a typical cross-coupling pathway (Scheme 7). Oxidative addition of the electron-rich nickel(0) (**8**) into the aryl bromide bond gives the nickel(II) species **9**. This is followed by ligand exchange resulting in the nickel(II) species **10** and finally reductive elimination of the aryl iodide product to regenerate the nickel(0) catalyst.



Scheme 7. Mechanism for iodination of aryl bromides with nickel(0).

There has also been an interesting report of a photo-induced, metal-catalyst-free iodination of aryl bromides by Li *et al.*[19] The reaction takes place under mild conditions, with 10 mol% molecular iodine and sodium iodide as the iodinating reagent at room temperature, albeit in a longer reaction time of 36 hours (Scheme 8). Electron-rich and electron-poor rings were compatible with the reaction conditions, as were heterocyclic bromides.



Scheme 8. Photo-induced metal-catalyst-free iodination.

1.2.2 Pseudo-halides as Leaving Groups

Halides are most commonly used as the electrophilic partner in cross-coupling reactions and aromatic halogenation reactions; however more recent studies have focused on phenol-based electrophiles. These phenol derivatives act as pseudo-halides and are readily available as a broad range of inexpensive substrates. One of the key advantages to using phenol-derived electrophiles is

the availability of the substrates. The use of phenol derivatives as opposed to halogens as starting materials in aromatic iodinations is advantageous as they should allow an increase in substrate scope, as well as easier separation of product from substrate. Methods for the synthesis of aryl halides directly from phenols generally require forcing conditions.[20] One of the reasons for this is the higher C—O bond strength compared to C—Br or C—Cl. The C—O bond can be activated by conversion of the phenol to a better leaving group, such as ethers (**11**), sulfonates (**12**), sulfamates (**13**), esters (**14**), carbonates (**15**) and carbamates (**16**) (Figure 1).[21] An issue with these groups is that the bond dissociation energy of the aryl C—O bond is higher than that of the acyl C—O bond, implying selectivity with the majority of these electrophiles should be a challenge. However, nickel catalysts have been shown to be more efficient in their activation of aryl and benzyl C—O bonds than palladium catalysts and these bonds can be selectively cleaved depending on reaction conditions.[22] Nickel exists in the oxidation states $Ni^{(0)}/Ni^{(II)}$ and $Ni^{(I)}/Ni^{(III)}$ compared to palladium $Pd^{(0)}/Pd^{(II)}$ and $Pd^{(III)}/Pd^{(IV)}$ and is more nucleophilic than palladium, due to its smaller size, which allows for reaction of less reactive electrophiles. The nickel-catalysed cross-coupling reactions of phenol derivatives, such as those shown in Figure 1, have been studied extensively by Percec and co-workers.[23] They found that the nickel-catalysed reactions were sensitive to small changes in reaction conditions, making it difficult to predict the best conditions for reactions. Generally it was found that aryl sulfonates (**12**) and aryl sulfamates (**13**) were the more reactive of the phenol derived electrophiles, with aryl carbamates (**16**) being less reactive and requiring harsher conditions. Despite the work done on the use of phenol derivatives in metal-catalysed cross-coupling reactions, currently there is a lack of general metal-catalysed methods for the synthesis of aryl halogens, especially aryl iodides.

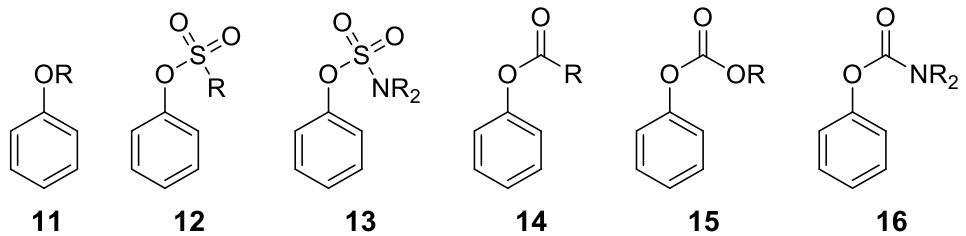
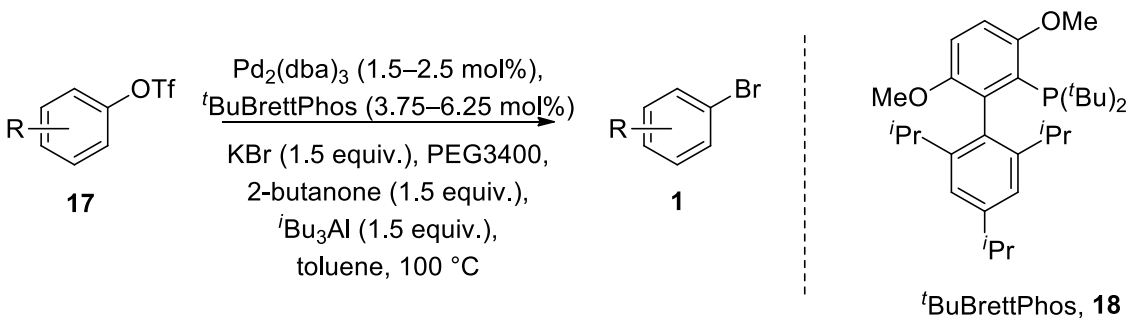


Figure 1. Phenol derivatives used as electrophiles in nickel-catalysed cross-coupling reactions.

1.2.2.1 Sulfonates

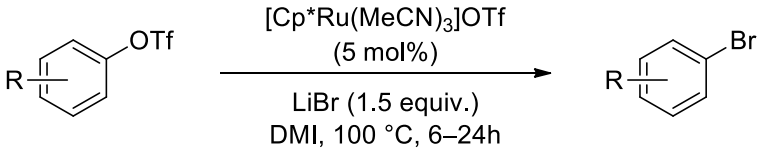
Buchwald and co-workers first reported the use of aryl triflates (ArOTf) as electrophiles in palladium(0)-catalysed halogenation of arenes. They showed that aryl triflates could be converted to the aryl fluorides in high yields.[24] They later showed aryl triflates (**17**) could also be converted to the corresponding aryl bromides (**1**) and chlorides using a palladium(0)-catalyst (Scheme 9).[25] The reaction was complete in 20—24 hours, giving yields of 60—80% for a range of substrates. The reaction however required a number of additives. The bulky biarylphosphine ^{t}BuBrettPhos ligand **18**, as well as additives polyethylene glycol (PEG3400), tri-*iso*-butylaluminium and 2-butanone were required. PEG3400 was added as a phase transfer catalyst, due to potassium bromides low solubility in toluene. Tri-*iso*-butylaluminium was added as a Lewis acid to prevent reactions of potassium triflate, however the side-product from the carbon-carbon cross-coupling reaction of the bromide product with tri-iso-butylaluminium was formed. This meant 2-butanone was required to form a dialkylaluminium alkoxide which suppressed the formation of coupled and reduced products. This was the first palladium-catalysed direct conversion of aryl sulfonate esters to aryl bromides and chlorides. However the reaction was not applicable to iodides.



Scheme 9. Palladium(0)-catalysed synthesis of aryl bromides from aryl triflates.

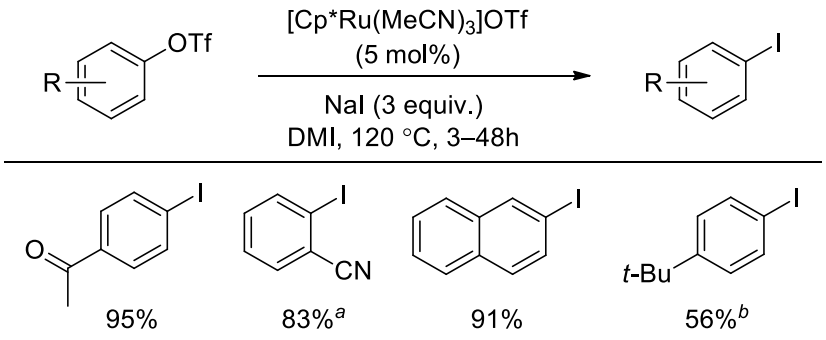
Electron-rich ruthenium catalysts have also been found to effectively catalyse the formation of aryl bromides from aryl triflates.[26] Strongly electron-donating Cp* ligands (Cp* = $C_5Me_5^-$) were able to activate the ruthenium catalyst [Cp*Ru(MeCN)$_3$]OTf and facilitate the oxidative addition of aryl triflates more readily than previously attempted ruthenium catalysts.[27] The use of additives was not required and the bromination occurred under mild conditions of 100 °C, with 5 mol% catalyst in short reaction times (Scheme 10). Electron-deficient

arenes reacted in high yields, while electron-rich arenes required a higher catalyst loading (10 mol%) and 3 equivalents of lithium bromide to allow high conversion in suitable reaction times.



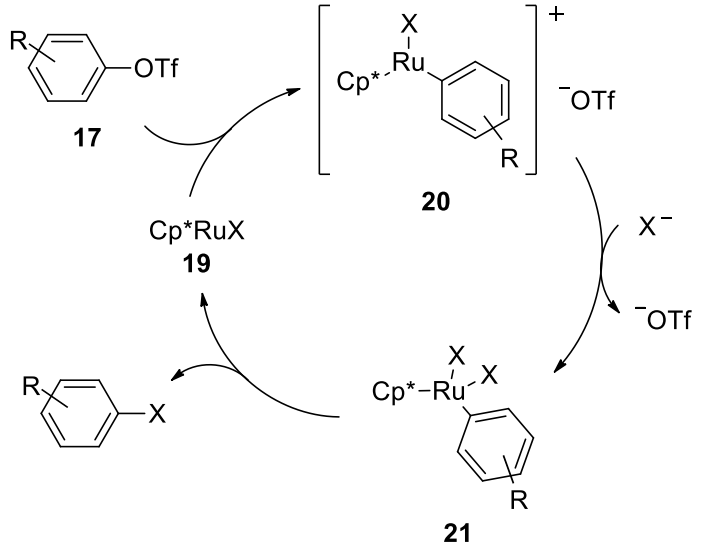
Scheme 10. Ruthenium-catalysed bromination of aryl triflates.

Interestingly, the iodination of aryl triflates was also reported using the same ruthenium catalyst. Iodination required more forcing conditions of 120 °C, with 5—15 mol% catalyst and 3—6 equivalents of sodium iodide. The reaction was only compatible with electron-deficient substrates with a small substrate scope being explored (Scheme 11). The moderately electron-rich 4-*tert*-butyliodobenzene could be synthesised in 48 hours, however the reaction required more forcing conditions of 15 mol% catalyst and 6 equivalents of sodium iodide to give the product in 56% yield.



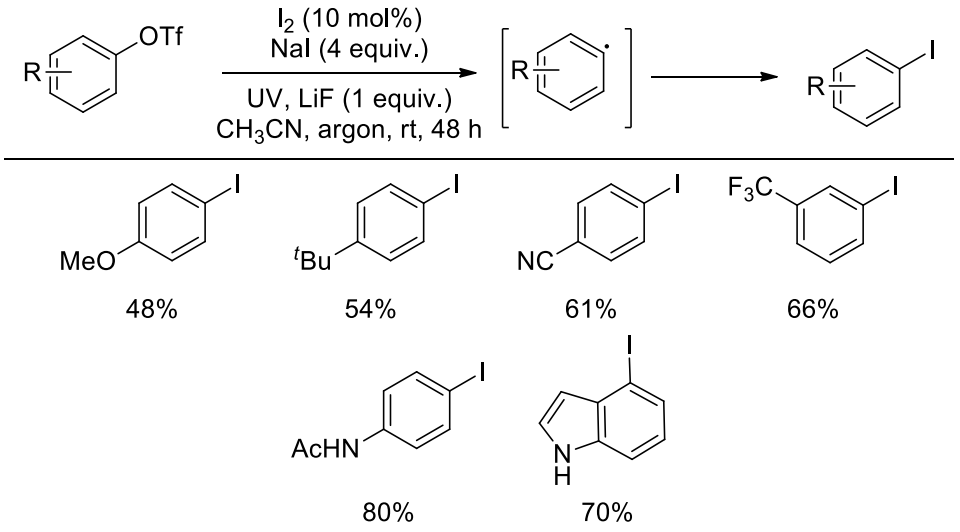
Scheme 11. Ruthenium-catalysed iodination of aryl triflates. [a] Reaction required 10 mol% catalyst. [b] Reaction required 15 mol% catalyst and 6 equivalents of sodium iodide.

The paper proposed a catalytic cycle involving η^1-arylruthenium(IV) triflate intermediate **20** (Scheme 12). Oxidative addition of the aryl triflate (**17**) to the ruthenium catalyst **19** gives η^1-arylruthenium(IV) triflate **20**, followed by coordination of X^- to give the η^1-arylruthenium(IV) complex **21**. Reductive elimination of the aryl halide product regenerates the ruthenium catalyst **19**. This type of mechanism would also explain the higher reactivity of electron-deficient arenes compared to electron-rich arenes.



Scheme 12. Plausible mechanism for transformation of aryl triflates to halides.

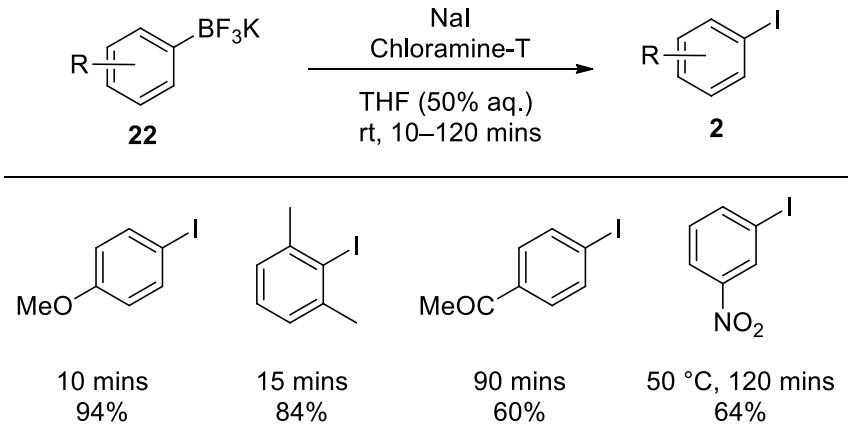
The metal-catalyst-free iodination of aryl triflates has also been reported this year *via* aryl radicals (Scheme 13).[28] The reaction used sodium iodide as an electron donor to generate the aryl radical under photoirradiation, with addition of lithium fluoride and iodine as iodinating reagent. This gave a broad scope of electron-deficient and electron-rich arenes as well as heteroarenes in moderate to good yields. The authors believed this to be the first demonstration of the generation of radicals from phenol-derivatives and also showed this to be applicable to the synthesis of aryl boronates.



Scheme 13. Iodination of aryl triflates *via* aryl radicals.

1.2.2.2 Boronates

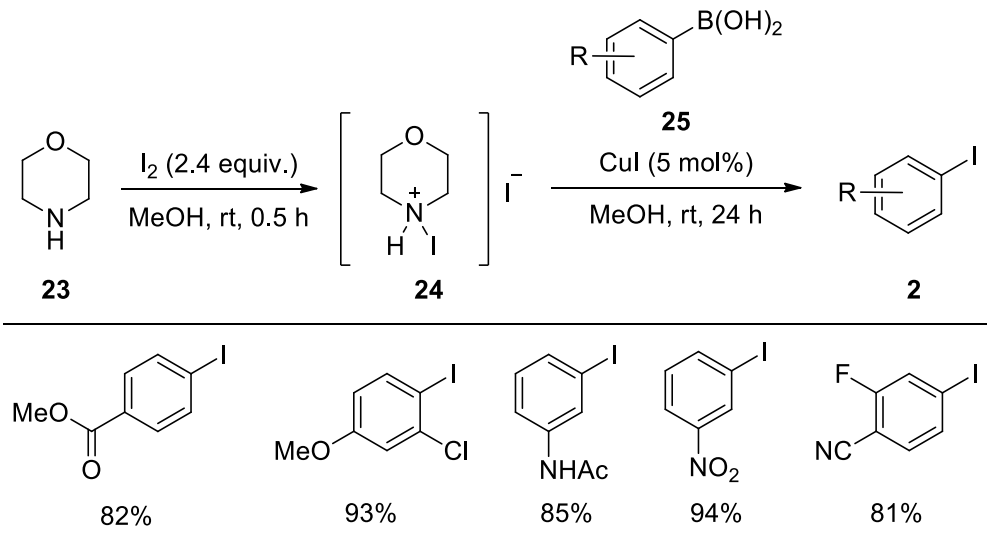
Aryl boronates have been used more recently in the iodination of arenes. The iodination of arylboronic acids as precursors is appealing due to their availability; however, earlier reports of iodination of these substrates required inert conditions and were not compatible with electron-deficient rings.[29] Potassium aryltrifluoroborates ($ArBF_3K$, **22**) are readily prepared from arylboronic acids and have been shown to be suitable for the metal-catalyst-free electrophilic iodination of aromatic rings by Kabalka *et al* (Scheme 14).[30] The sodium iodide is oxidised by chloramine-T to give an iodonium ion (I^+) before the *ipso*-substitution of the corresponding aryl boronate. The reaction enabled the iodination of electron-rich arenes in excellent yields in short reaction times. However, electron-deficient arenes proved more challenging in the reaction. A small number of arenes containing electron-withdrawing groups could be iodinated, albeit with slightly higher reaction temperatures and longer reaction times.



Scheme 14. Synthesis of aryl iodides from potassium aryltrifluoroborates.

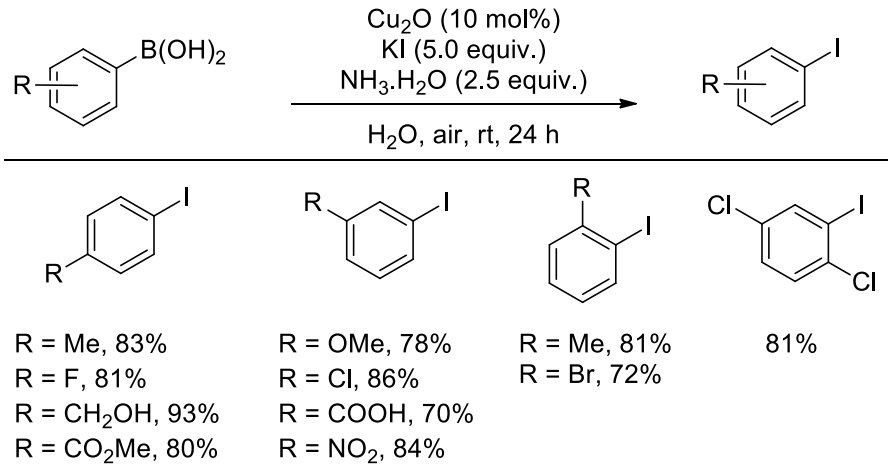
A copper-catalysed iodination of arylboronic acids has been reported using *N*-iodomorpholinium iodide (NIMI) (**24**) as a novel iodination reagent (Scheme 15).[31] This was generated by reaction of iodine and morpholine (**23**), to give the highly electrophilic iodinating reagent *in situ* and allow attack on the boronic acid (**25**). The activation of the boronic acid by the iodide ion is also required, giving a more nucleophilic boron species. The combination of the activation of the organoboron species and the highly electrophilic NIMI reagent allowed for a mild iodination reaction at room temperature with only 5 mol% copper catalyst. The

reaction was general, allowing the iodination of a number of electron-rich arenes, as well as giving high yields of electron-deficient arenes, unlike previous *ipso*-iodination of boronates.



Scheme 15. Copper-catalysed iodination of arylboronic acids *via* *N*-iodomorpholinium iodide.

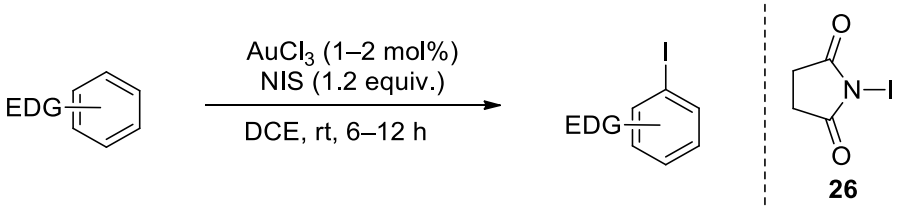
A general procedure for iodination of arylboronic acids *via* a copper-catalyst has also been developed by Yang *et al*,[32] including the iodination of electron-deficient rings (Scheme 16). The reaction is under very mild conditions, at room temperature, with water as solvent and oxygen in air as the oxidant. A number of electron-rich and electron-deficient aryl iodides were prepared in high yields with the reaction showing excellent functional group compatibility.



Scheme 16. Copper-catalysed iodination of arylboronic acids.

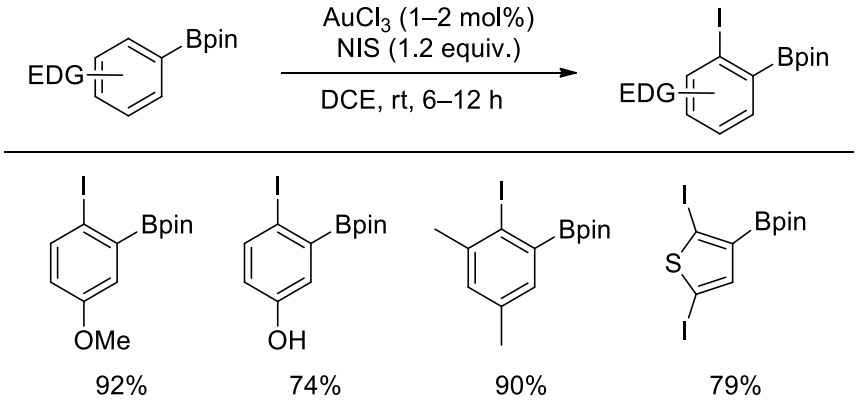
1.2.3 Electrophilic Aromatic Substitution

Another method commonly used for iodination of aromatic rings is an electrophilic aromatic substitution reaction, using electron-donating groups in the ring to control the regioselectivity. Issues with this method include problems with regioselectivity and poly-iodination, as well as it being limited to electron-rich aromatic rings. Wang *et al*[33] investigated the gold(III)-catalysed electrophilic aromatic halogenation reaction with the use of *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS, **26**) for the chlorination, bromination and iodination of arenes, respectively (Scheme 17). They found they could improve reactivity and regioselectivity by the dual activation of both the halogenating reagent, NXS, as well as the aromatic ring by use of the Lewis acidic gold(III) chloride, giving high yields.



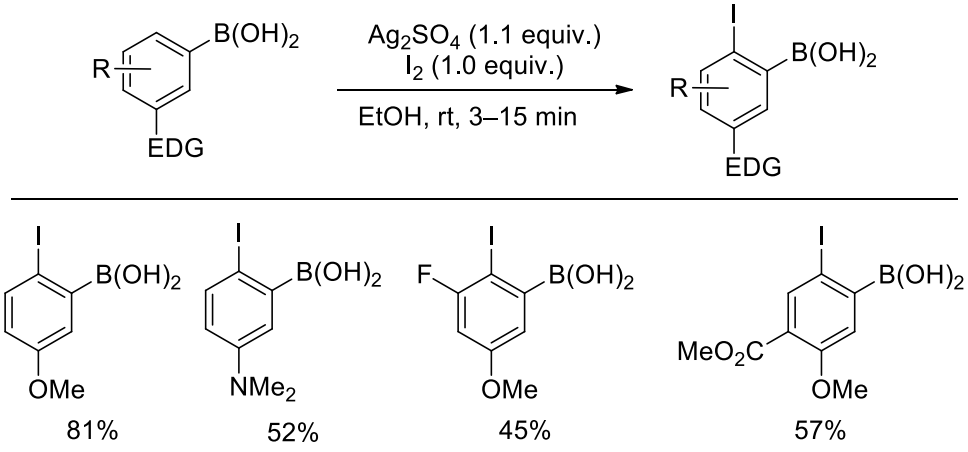
Scheme 17. Gold-catalysed iodination of electron-rich arenes.

The same group later demonstrated the halogenation of pinacol arylboronates using the same gold(III) chloride catalyst (Scheme 18).[34] Interestingly, the group could control the halogenation of the arylboronates with no product from the *ipso*-substitution of the boronate group. With the use of electron-donating groups, an electrophilic aromatic substitution took place, rather than the product from *ipso*-substitution of the boronate group. The paper focused mainly on the bromination of pinacol arylboronates, with a small number of electron-rich substrates suitable for the iodination reaction. Mild conditions of room temperature with a low catalyst loading of gold(III) chloride was able to activate both the arene ring, by forming an arylgold(III) species, and the NIS reagent, by coordination as a Lewis acid. However, the reaction was limited to electron-rich substrates.



Scheme 18. Gold-catalysed iodination of pinacol arylboronates.

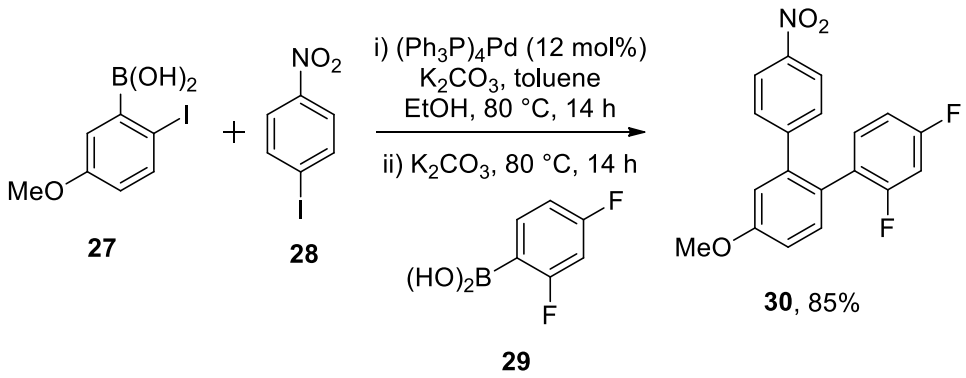
Al-Zoubi *et al*[35] have reported a silver(I)-mediated iodination method which incorporates iodine *ortho* to boronic acid groups, with the use of an electron-donating directing group on the ring to enable mono-iodination (Scheme 19). The combination of silver(I) sulfate and iodine in ethanol meant mono-iodination was possible at room temperature and none of the *ipso*-substituted product was observed. However, the reaction required the use of stoichiometric silver(I)-catalyst and was restricted to electron-rich arenes, giving moderate to good yields. The reaction was stopped after 3—15 minutes, with decomposition observed when the reaction was left for longer.



Scheme 19. Silver-catalysed *ortho*-iodination of boronic acids.

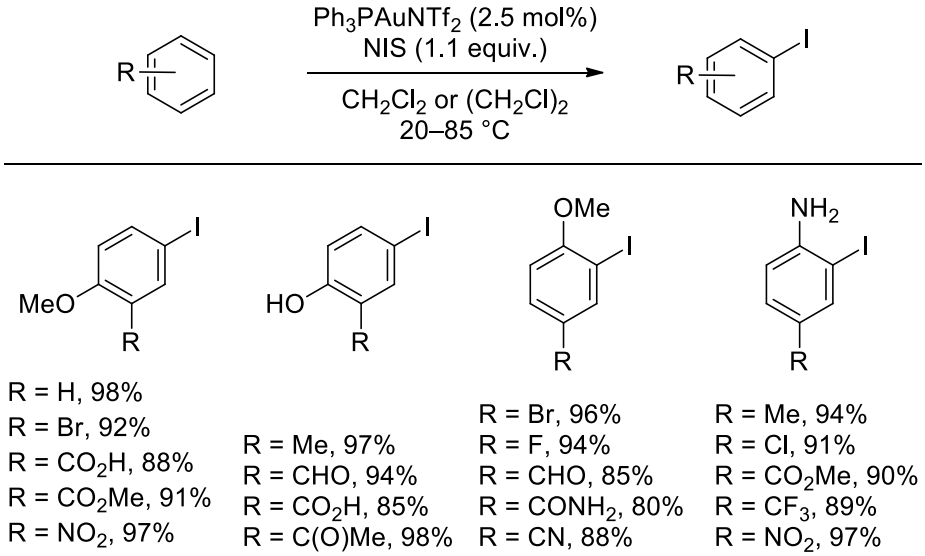
To demonstrate the utility of the products as intermediates in cross-coupling reactions, the group also converted 5-methoxy-2-iodophenylboronic acid (**27**) into several *ortho,ortho*-triaryl products *via* two chemoselective Suzuki couplings in high yields (Scheme 20). Reaction first with 4-iodonitrobenzene

(**28**), followed by addition of 2,4-difluorophenylboronic acid (**29**) gave the product **30** in 85% yield.



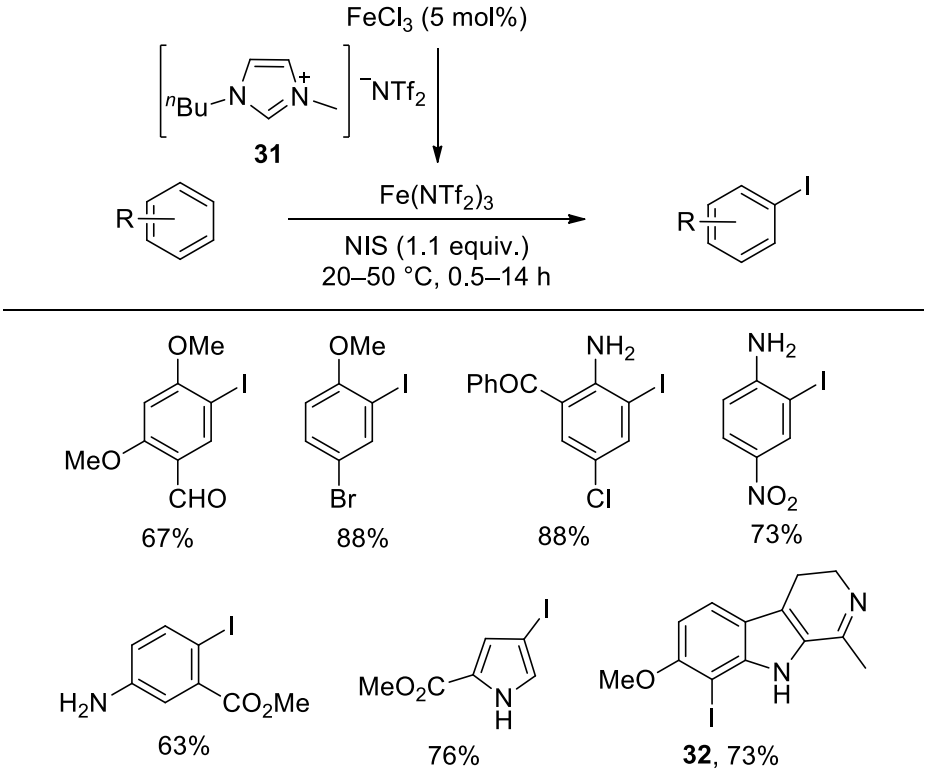
Scheme 20. One-pot chemoselective double Suzuki coupling.

A more general method of electrophilic aromatic substitution has been reported by Leboeuf *et al*[36] using a gold(I)-catalyst and NIS (Scheme 21). The Lewis-acidic catalyst $Ph_3PAuNTf_2$ containing the highly delocalised triflimide ligand is highly active and allows for the iodination of electron-rich arenes which also contained a number of electron-withdrawing groups. For disubstituted arenes containing a substituent *ortho* or *meta* to the electron-donating group, the iodine was installed *para* to the electron-donating group in excellent yields and regioselectivity, even when the ring contained strongly electron-withdrawing groups or mildly electron-donating groups (Scheme 21, columns 1 and 2). When the disubstituted arene contained a group *para* to the electron-donating group, the iodine was installed *ortho* to the electron-donating group, again in excellent yields and regioselectivity (Scheme 21, columns 3 and 4). Mild reaction conditions of 2.5 mol% catalyst at room temperature was possible for the majority of substrates, with those containing strong electron-withdrawing groups (i.e. CF_3, NO_2, $CONH_2$, CN and CHO) requiring heating under reflux in 1,2-dichloroethane. The group investigated the possibility of dual activation of the aromatic ring and NIS in the same mechanism proposed by Wang *et al*,[33] however they found no evidence of the gold arene intermediate in the absence of NIS. They therefore suggested the reaction proceeded *via* a Friedel-Crafts-type mechanism, with the gold(I)-catalyst activating NIS before attack by the aromatic ring. This allowed for a much more broad substrate scope compared to previously reported electrophilic substitution methods.[33–35]



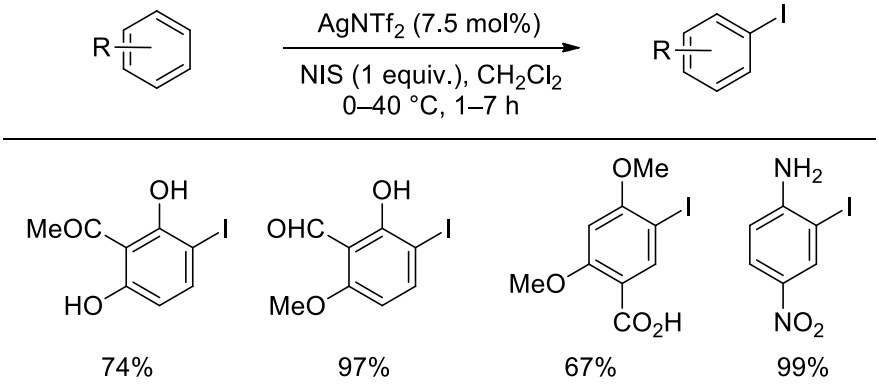
Scheme 21. Gold(I)-catalysed iodination of arenes with NIS.

The iodination of arenes has also been reported with a cheaper, more sustainable iron(III)-catalyst, using NIS as the iodinating reagent and a triflimide-based ionic liquid.[37] Using iron(III) chloride as catalyst in the ionic liquid 1-butyl-3-methyl-imidazolium bis(trifluoromethylsulfonyl)imide ([BMIM]NTf_2, **31**) gave *in situ* formation of the highly Lewis acidic catalyst iron(III) triflimide which allowed for activation of NIS and iodination of a number of substrates containing electron-donating groups as well as deactivating groups (Scheme 22). This allowed for low temperatures and low catalyst loading at shorter reaction times than previous iodination reactions with NIS. The reaction was also applied to several medicinally important compounds such as 8-iodoharmaline (**32**), which is a monoamine oxidase inhibitor.[38] However, di-iodinated products were formed for highly active substrates such as phenols, resulting in lower yields of the mono-iodinated products.



Scheme 22. Iron(III)-catalysed iodination using NIS in an ionic liquid solvent.

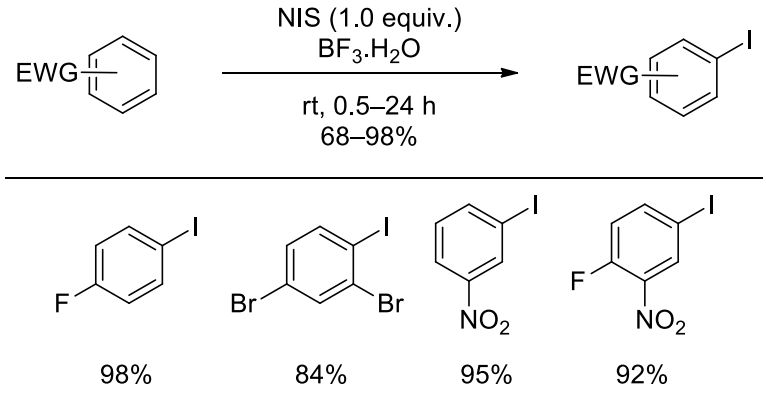
The issue of di-iodination of highly activated arenes could be overcome by the use of a less active metal centre. Silver(I) triflimide was shown to be a general catalyst for the iodination of electron-rich arenes containing electron-donating and electron-withdrawing groups, as well as allowing for the mono-iodination of highly activated arenes (Scheme 23).[39]



Scheme 23. Silver(I) triflimide-catalysed iodination of electron-rich arenes.

The iodination of deactivated rings with NIS has also been reported. Olah and co-workers[40] found that deactivated rings reacted with NIS in

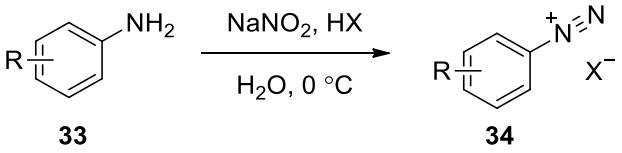
trifluoromethanesulfonic acid (triflic acid).[40a] Nitrobenzene and *α,α,α*-trifluorotoluene gave exclusively the *meta*-iodinated product in 86% and 91% yield respectively. The group also reported that reaction of deactivated arenes with NIS could take place in boron trifluoride monohydrate (BF_3—H_2O) (Scheme 24).[40b] These reactions allowed access to more difficult deactivated aryl iodides. However using triflic acid or boron trifluoride as solvent in the reaction would make these methods unsuitable for acid sensitive or more complex structures.



Scheme 24. Iodination of deactivated rings with NIS and trifluoride monohydrate.

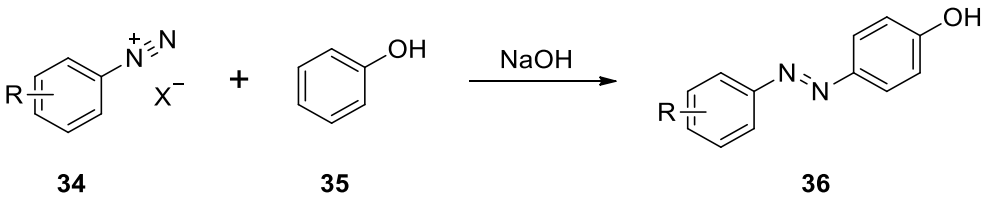
1.3 Diazonium salts

Diazonium salts are organic compounds with the formula RN_2X, where R can be an alkyl or aryl group and X is an organic or inorganic anion.[41] Diazonium salts are very reactive due to the excellent dinitrogen leaving group and are usually not isolable. Aryl diazonium salts (**34**) are more stable than alkyl diazonium salts due to the delocalisation between the aromatic ring and dinitrogen and can be used as intermediates in a number of reactions.[42] The standard formation of diazonium salts occurs by reaction of an aniline (**33**) with sodium nitrite and a strong acid, such as sulfuric acid or hydrochloric acid (Scheme 25). The acid used in the reaction is important, as this defines the nature of the counteranion, which affects the stability of the diazonium salt. Diazonium salts with a low nucleophilic counteranion, such as tetrafluoroborate[43] or tosylate,[44] are stable enough to be isolated, even though they contain the dinitrogen leaving group. For example, Filiminov and co-workers[44] have shown that aryl diazonium tosylate salts are stable up to 600 °C, due to the strong affinity between the counteranion and diazonium salt.



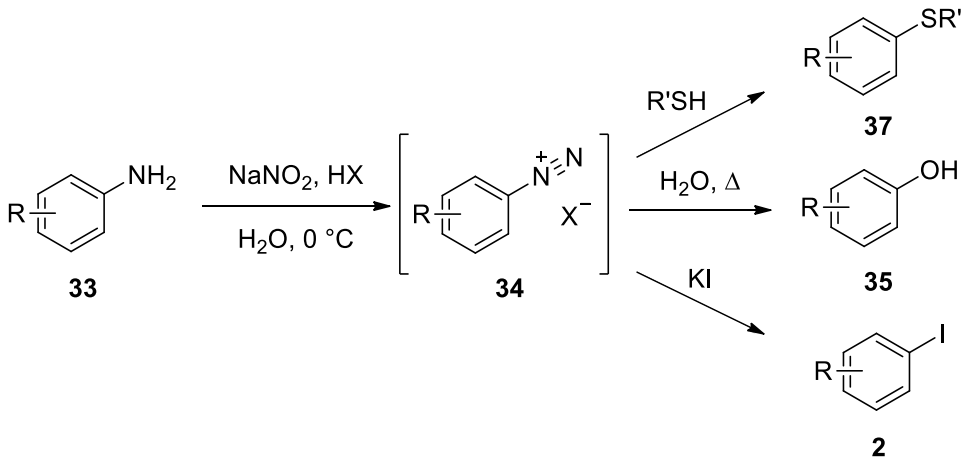
Scheme 25. Formation of diazonium salts.

Diazonium salts can be used as intermediates in the synthesis of halides and azo compounds. They can also be used in cross-coupling reactions as pseudo-halide type electrophiles.[45] One common reaction of diazonium salts is the synthesis of aryl azo compounds (**36**), where the diazonium ion (**34**) acts as an electrophile in coupling reactions with activated aromatic rings, such as phenols (**35**) and anilines, to give the aryl azo product **36** (Scheme 26).[46]



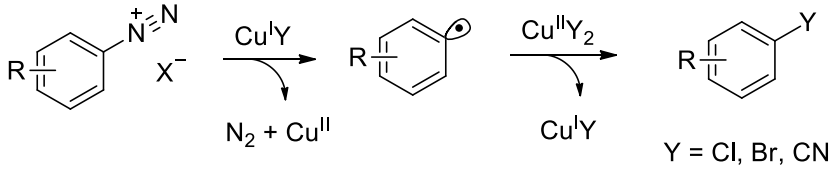
Scheme 26. Cross coupling of aryl diazonium salt and phenol to form azo compounds.

Diazonium ions also undergo reactions where the dinitrogen group is lost and replaced by a nucleophile, known as the Sandmeyer reaction (Scheme 27). The reaction of diazonium salts (**34**) with thiols, water or potassium iodide will give the aromatic thiol (**37**), phenol (**35**) or aryl iodide (**2**) respectively with loss of nitrogen gas.



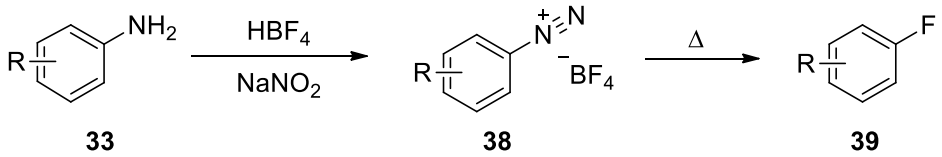
Scheme 27. Nucleophilic substitution of diazonium salts.

The synthesis of aryl chlorides and bromides can also be achieved by the Sandmeyer reaction, but requires the addition of a copper(I) catalyst, which induces elimination of the dinitrogen. This forms an aryl radical intermediate, which reacts with the halide ion of the copper(I) salt (Scheme 28).[47] Benzonitrile can also be obtained in this way by the use of copper(I) cyanide.



Scheme 28. Synthesis of aryl chlorides/bromides and cyanides *via* diazonium salts.

Aromatic fluorination is possible *via* diazonium salts by reaction with fluoroboric acid, in a reaction known as the Balz-Schiemann reaction (Scheme 29).[48] A diazonium fluoroborate intermediate (**38**) is formed, which, on heating, undergoes thermal decomposition to give the aryl fluoride (**39**).



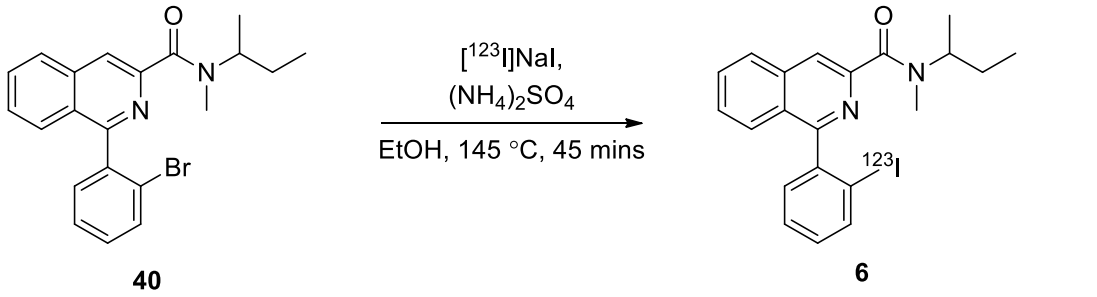
Scheme 29. Synthesis of aryl fluorides *via* diazonium salts.

The Sandmeyer reaction is a very important transformation in aromatic chemistry, because it can result in substitution patterns that are not achievable by direct transformation. However, the Sandmeyer halogenation reaction is often accompanied by unwanted side reactions due to the intermediate aryl cation being highly unstable and reactive. The reaction is also associated with harsh reaction conditions and reagents. Diazonium salts are not currently used as intermediates in the synthesis of SPECT imaging agents for these reasons.

1.4 Radioiodination of SPECT Imaging Agents

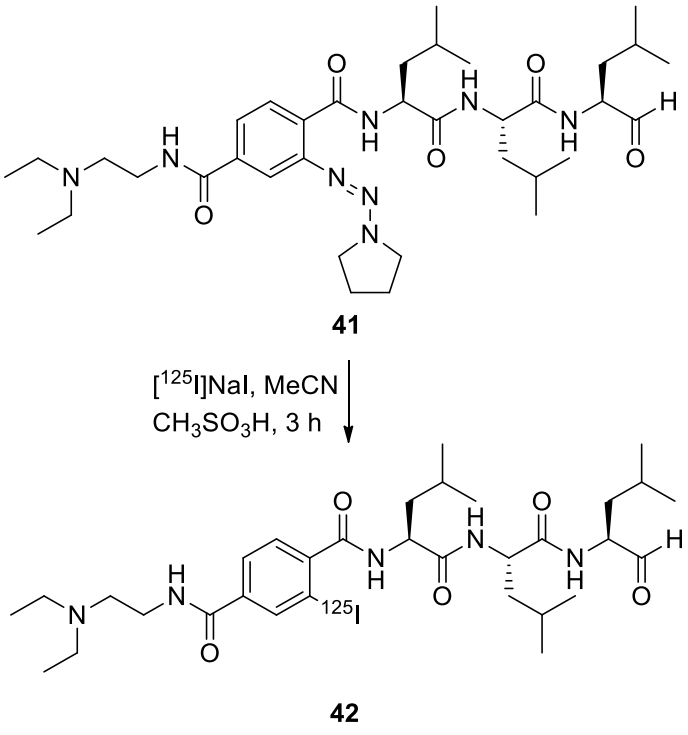
The chemistry required to incorporate radioiodine into organic molecules is similar to that used for cold iodination reactions,[49] although the reaction with radioiodine can present some further challenges including working with high levels of radioactivity. For high radiochemical yields, reaction times and purification must be fast due to the short half-lives of the radionuclides. A large excess of unlabelled precursor or microwave heating can be used to speed up reaction times. Products must also be easily separated from precursors and impurities to allow for high radiochemical purity and high specific activity. All this must be achieved on a small scale, with microgram concentrations of reactants, which are still in large excess to the radioiodine. The position of the iodination is also important to avoid metabolism of the carbon-iodine bond *in vivo*, with aromatic C—I bonds more stable then aliphatic C—I bonds.[50]

Both nucleophilic and electrophilic substitution methods can be used for radioiodination. An advantage of nucleophilic substitution methods are that sodium [^{123}I]iodide and sodium [^{125}I]iodide are already in iodide ion form, therefore there is no need for oxidising agents. The most common nucleophilic reaction used is a halogen exchange reaction. This can be direct exchange of the stable iodine-127 for the radioisotope; however this results in low specific activity due to competition between the radioactive iodine and stable iodine-127.[51] Aryl bromides, or chlorides, are more convenient as precursors and result in higher specific activity, but often require harsh reaction conditions and can result in the time consuming separation of the starting material from product. The synthesis of [^{123}I]I-PK11195 (**6**), an imaging agent for neuroinflammation,[52] has been achieved *via* a halogen exchange reaction from the aryl bromide precursor **40** in the presence of ammonium sulfate, giving the product in an isolated radiochemical yield of 41.3 ± 11.2% (n = 2) (Scheme 30).



Scheme 30. Synthesis of [^{123}I]I-PK11195 *via* a nucleophilic halogen exchange reaction.

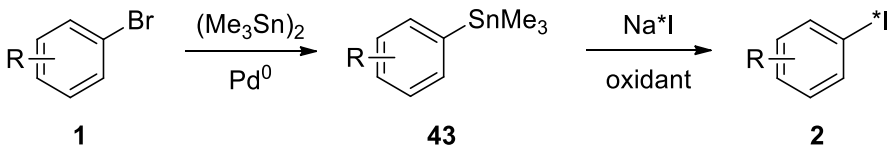
Diazonium salts can be used in radioiodination reactions by reaction with secondary amines to form more stable triazenes, which decompose in acidic conditions in the presence of radioiodide to give the aromatic iodide product. The synthesis of leucine peptide derivative **42** from triazene **41** gave a radiochemical yield of 41% and radiochemical purity of over 99% (Scheme 31).[53]



Scheme 31. Radioiodo-dediazonisation of a leucine-derived peptide.

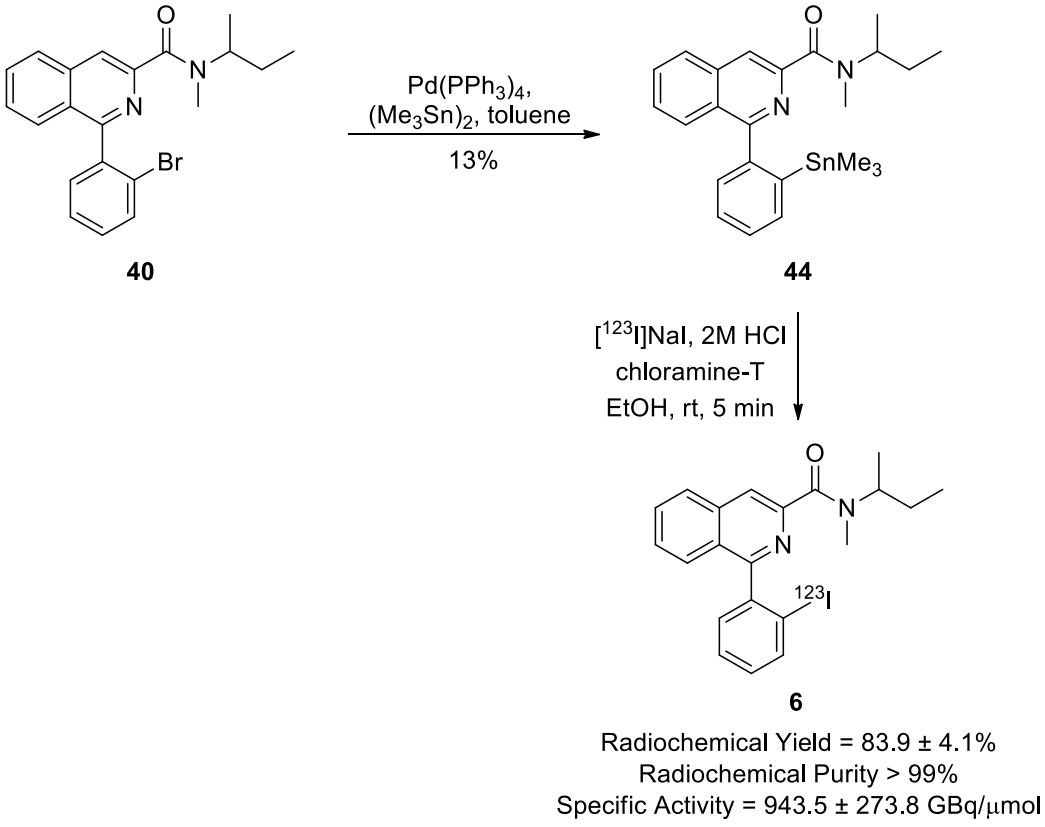
Electrophilic substitution methods for radioiodination require the use of an oxidising agent, such as chloramine-T,[54] Iodogen,[55] or peracetic acid,[56] to oxidise the iodine to give a positively charged iodine cation (I^+) which can act as an

electrophile. Direct radioiodination where a hydrogen atom is substituted for a radioiodine atom can be possible for electron-rich arenes that are already activated for electrophilic substitution.[57] For non-activated arenes, a leaving group is generally required that can be replaced with radioiodine, to allow a regioselective reaction. An organometallic intermediate is commonly used, as these can accommodate a positive charge. The most commonly used technique for the synthesis of radioiodoarenes uses an organotin intermediate (**43**) (Scheme 32).[49] The first step is the palladium(0)-catalysed stannylation of an aryl bromide (**1**) to give the organotin intermediate (**43**), followed by an oxidative iododestannylation reaction by the oxidised iodine to give the radioiodinated product (**2**).



Scheme 32. Radioiodination *via* organostannyl precursor.

This method allows for regioselective labelling, and typically generates SPECT imaging agents in high radiochemical yields with high specific activity. For example, previously in the group, the successful synthesis of [^{123}I]I-PK11195 (**6**) has also been achieved *via* an electrophilic iododestannylation reaction in very high radiochemical yield and purity (Scheme 33).[58] However, the synthesis of the organotin intermediate **44** was problematic, with a low yield of 13%. As well as the difficult synthesis of organotin intermediates, organotin compounds are highly toxic, and removal of organotin residues after the iododestannylation reaction can be problematic. This raises toxicology issues in the synthesis of these clinical imaging agents. Organotin compounds can also be unstable, so long-term storage and transportation of these precursors can be problematic.[59]



Scheme 33. Synthesis of [^{123}I]I-PK11195 *via* an organotin intermediate.

1.5 Proposed Research

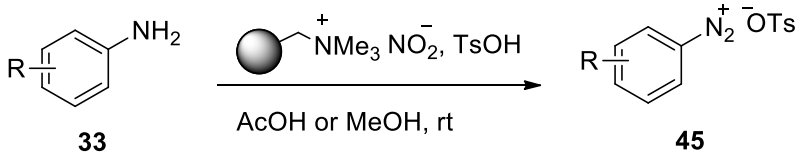
The main aim of this PhD was to develop new iodination reactions that could be performed under mild reaction conditions from readily available starting materials. The reaction would use simple procedures with easy to handle reagents, to allow the general synthesis of aryl iododes. Upon development of a general, mild reaction, the method would then be used in the synthesis of medicinally important compounds, including current or potential SPECT imaging agents. The developed method would also be used for the radioiodination of arenes with iodine-125 for preclinical trials and iodine-123 for use in diagnostic imaging. A common problem in the synthesis of radioiodinated tracers is the purification of these. The iodination method will therefore utilise non-halogen starting materials, allowing for easier separation of the final radioiodinated product from starting materials.

2.0 One-pot diazotisation-iodination reaction for the synthesis of aromatic iodides.

2.1 Background

Radioiodination reactions for SPECT imaging require a method to be developed that allows the fast, efficient and mild synthesis of aryl iodides, using readily available starting materials. The preparation of diazonium salts from aryl amines (anilines) followed by a Sandmeyer-type reaction is one of the most common approaches for the preparation of aryl iodides.[60] However, diazonium salts are not generally used as precursors for radioiodination of SPECT tracers. The harsh acidic conditions required for the formation of diazonium salts and their unstable, potentially explosive nature has led to by-products and low radiochemical yields in previous attempts.[61] However, more stable diazonium salts have been prepared using a non-nucleophilic counterion, such as *p*-toluenesulfonic acid for the preparation of the stable aryldiazonium tosylate **45**.[44] It was hypothesised that these more stable diazonium salts may be used for radioiodination, without the past problems of by-products and low yields.

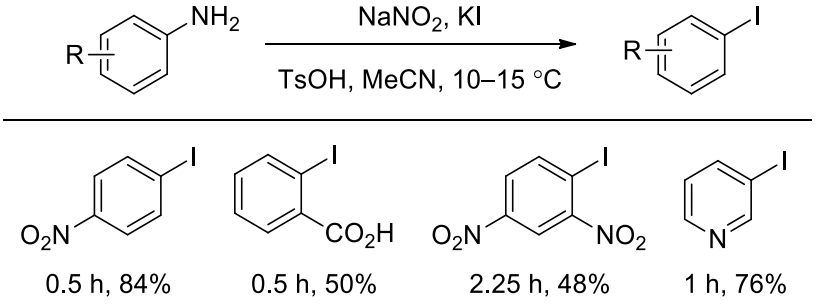
More recently, it has also been shown that these stable aryldiazonium tosylate salts **45** can be prepared from a polymer-supported diazotisation reagent (Scheme 34).[44] The polymer-supported nitrite was prepared simply by ion exchange of porous tetramethylammonium hydroxide resin AV-17-86 or Amberlyst A26 with sodium nitrite in water. Addition of the polymer-supported nitrite and *p*-toluenesulfonic acid to aromatic amines in acetic acid or methanol at room temperature gave the diazonium salts **45** in fast reaction times of 5—20 minutes.



Scheme 34. Synthesis of stable diazonium salts via polymer supported nitrite.

The diazonium salts were found to be highly stable, allowing storage at room temperature, in the dark, for several months and in sunlight for two weeks without loss of activity. They were also found to have excellent thermal stability at temperatures up to 600 °C without risk of explosion. The use of acetic acid as solvent is one condition in this reaction that would be undesirable for radiohalogenations, with a milder solvent being preferable, especially for iodination of more complex imaging agents. These conditions would be unsuitable for anilines containing acid sensitive functional groups and would also require a neutralisation work-up.

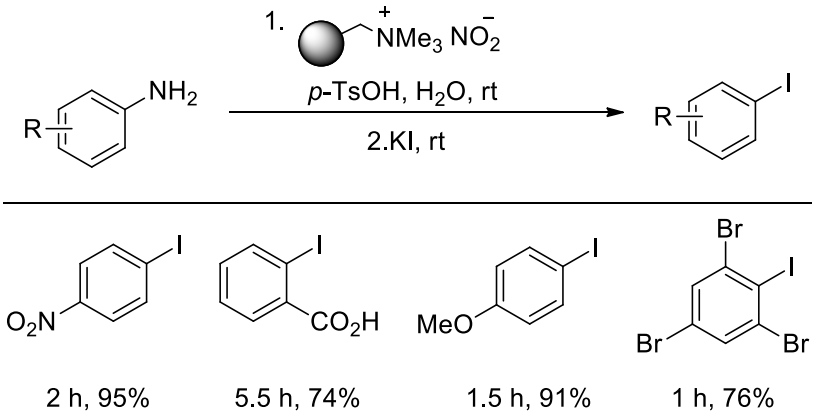
Filimonov *et al*[62] have also reported a one-pot diazotisation-iodination, in acetonitrile using sodium nitrite and *p*-toluenesulfonic acid for formation of the diazonium tosylate salt intermediate and potassium iodide for the subsequent iodination (Scheme 35). The method was found to be general for a number of electron-rich and electron-deficient substituted aryl amines, with reaction times of 0.5—2 hours. The authors reported one limitation of the reaction was that it was affected by sterics, with *ortho*-substituents retarding the reaction rate.



Scheme 35. One-pot iodination via diazonium tosylate salt.

The same group also reported the reaction in a water paste, by grinding the reactants together in a mortar with a pestle.[63] The reactions proceeded at room temperature in 20—30 minutes, however grinding the reaction mixture with mortar and pestle is not possible on a large scale and would not be applicable to radiochemistry. The reactants had to be added in a stepwise manner to stop the formation of side products. The same group repeated the reaction in water using a polymer-supported nitrite reagent as opposed to sodium nitrite (Scheme 36).[64] The first step was formation of the diazonium salt by stirring *p*-toluenesulfonic acid, polymer-supported nitrite and the aniline in water for 0.5 hours. This was

followed by filtration of the polymer-support, before addition of potassium iodide to the reaction mixture and stirring for 1—5 hours, to give a small number of aromatic iodides in good yields. The reactants could not be added in one step. The addition of the polymer-supported nitrite, *p*-toluenesulfonic acid and potassium iodide in one-pot, led to incomplete conversion of the aniline, and formation of elemental iodine. They believed this was due to intermediates from the diazotisation step being consumed by oxidation of the iodide ion to iodine.

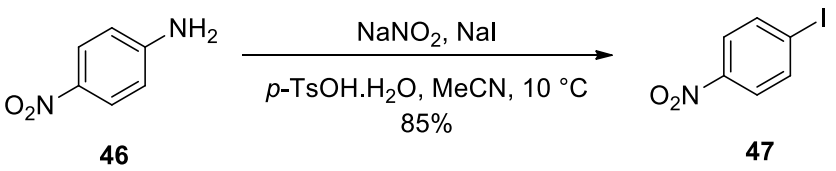


Scheme 36. Aromatic iodination by use of polymer-supported nitrite reagent.

2.2 Optimisation

It was decided to investigate the use of polymer-supported diazotisation reagents in the presence of *p*-toluenesulfonic acid for the preparation of diazonium tosylate salts. These intermediates would then be studied for halogenation under mild conditions, in a one-pot diazotisation-iodination reaction. Preparation of the stable diazonium tosylate salts and the use of these as intermediates in radiohalogenation reactions is attractive due to the general availability of aromatic amines and the mild conditions of the halogenation reaction. Using a polymer-supported reagent is also advantageous for radioiodinations, as a large excess of reagent is commonly used to push the reaction to completion in a fast reaction time. The polymer-support can enable easy removal of the reagents by filtration. The use of a polymer-supported nitrite reagent also removes some of the limitations associated with standard conditions of diazonium salt formation, such as the use of sodium nitrite, which can lead to the release of nitrogen oxides. The reaction reported by Filimonov *et*

al[62] was initially repeated using 4-nitroaniline (**46**), to give an 85% yield of 4-nitro-1-iodobenzene (**47**) (Scheme 37).

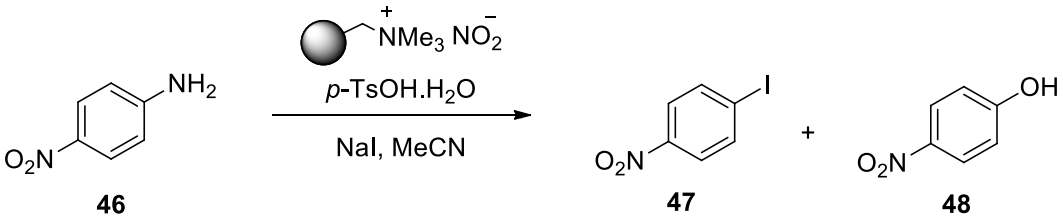


46 **47**

Scheme 37. Initial diazotisation-iodination reaction.

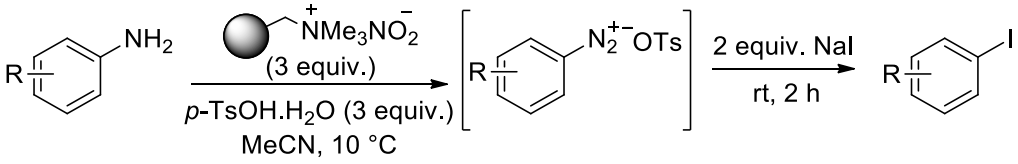
The sodium nitrite was then replaced with a polymer-supported nitrite reagent in the reaction. The polymer-supported nitrite was prepared by ion exchange of porous tetramethylammonium hydroxide resin Amberlyst A26 with sodium nitrite in water.[44] This could be prepared in a large batch and stored at room temperature for several months with no loss of activity. This was added to 4-nitroaniline (**46**) in the presence of *p*-toluenesulfonic acid, followed by the addition of sodium iodide in water dropwise (Table 3). The reaction was first attempted with addition of reactants at room temperature, as only 3—5% formation of the phenol by-product had been reported at this temperature.[62] However, addition of the polymer-supported nitrite reagent and sodium iodide at room temperature gave a low yield of 15%, with the phenol **48** found to be the major product at 60% yield (Table 3, entry 1). Addition of the reagents at 10 °C minimises the formation of the phenol side product. The reaction was followed to assess the time taken for each step, with the amine substrate shown to be consumed after 20 minutes (followed by TLC). The reaction could be worked up after this time to give a modest yield of 53% of iodinated product (Table 3, entry 2). The diazonium salt intermediate had been formed, but more time was required for the iodination step in the reaction. The reaction gave a high yield of 75% after 1 hour (Table 3, entry 3), with the highest yield of 85% after 2 hours (Table 3, entry 5). The consumption of the diazonium salt intermediate could also be followed by the *β*-naphthol test, which would give a negative result when the diazonium salt had fully reacted.

Table 3. Temperature and time screen



Entry	Temperature (°C)	Time (h)	Yield 47 (%)	Yield 48 (%)
1	rt	2	15	60
2	10 to rt	0.5	53	n/a
3	10 to rt	1	75	n/a
4	10 to rt	1.5	70	n/a
5	10 to rt	2	85	n/a

The optimum conditions were found to be addition of the polymer-supported nitrite and sodium iodide to the reaction mixure at 10 °C, after which the reaction was warmed to room temperature and stirred for 2 hours in total. The reagents were used in excess, with 3 equivalents of polymer-supported nitrite, 3 equivalents of *p*-toluenesulfonic acid and 2 equivalents of sodium iodide (Scheme 38).



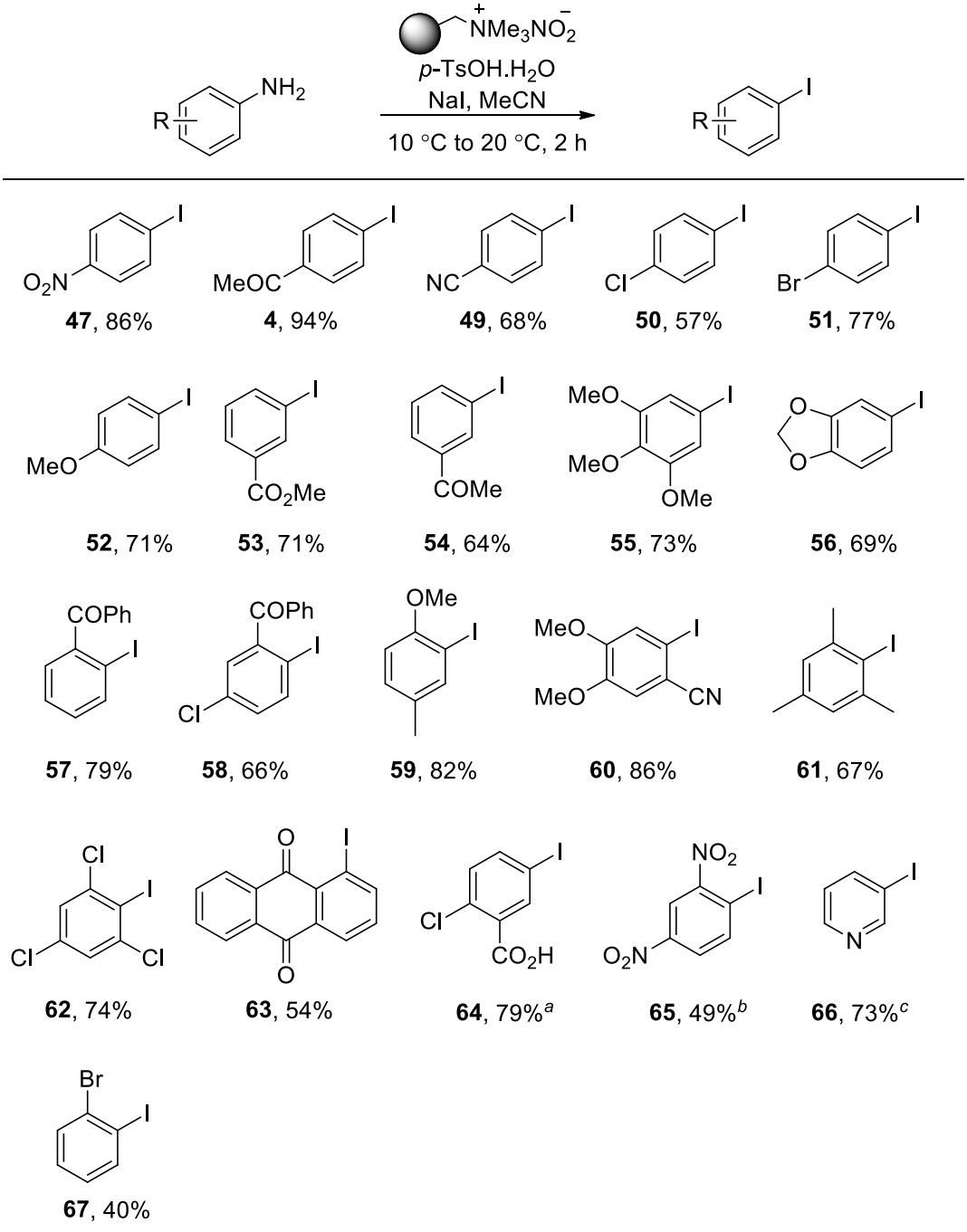
Scheme 38. Optimum diazotisation-iodination reaction conditions.

2.3 Substrate Scope

Using these optimised conditions, the scope of reaction was evaluated, with the results shown in Scheme 39. Electron-deficient *meta*- and *para*-substituted aryl compounds (**4**, **47**, **49**, **53** and **54**) were converted in excellent yields, as were electron-rich *meta*- and *para*-substituted aryl compounds (**52**, **55** and **56**). More sterically demanding *ortho*-substituted electron-rich and electron-deficient aryl compounds were also converted in excellent yields (**59**, **61** and **62**). Lastly, a

number of multi substituted electron-rich and electron-poor rings gave good yields (**58**, **60**, **63** and **64**).

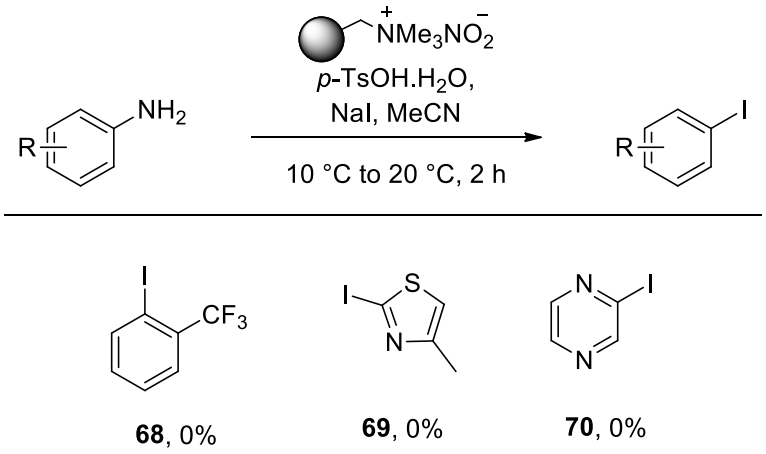
Some more demanding structures gave low yields under the standard conditions, but by either increasing the reaction time, or the temperature, the yields could be improved. 2-Chloro-5-iodobenzoic acid (**64**) was prepared in a low yield of 38% yield under standard conditions. Full conversion of the aniline starting material had occurred, but the substitution of the diazo group for iodine required more time in the reaction. Increasing the reaction time to 24 hours increased this yield considerably to 79%. 2,4-Dinitroiodobenzene (**65**) was prepared in 35% under standard conditions at room temperature for 2 hours, with 50% of starting material recovered. Increasing this time to 16 hours increased the yield to 49%, with complete consumption of starting material. The yield could also be increased by increasing the temperature to 60 °C, giving a yield of 42% after 2 hours. However, leaving the reaction for 16 hours at this temperature did not increase the yield, with a small amount of starting material still visible in the ^{1}H NMR spectrum of the reaction mixture. This lower yield can be explained by the very electron-deficient nature of the aryl ring, with the two nitro groups restricting the reactivity of the amine. The heteroaromatic compound 3-iodopyridine (**66**) was synthesised in only 7% yield under standard conditions. The substrate is also highly electron-deficient and required heating to 60 °C for 16 hours, which increased the yield to 73%.



Scheme 39. Scope of one-pot diazonisation-iodination. For each reaction 3 eq. of polymer-supported nitrite/*p*-TsOH and 2 eq. NaI were used. [a] Reaction required 24 h. [b] Reaction required 16 h. [c] Reaction was performed at 60 °C for 16 h.

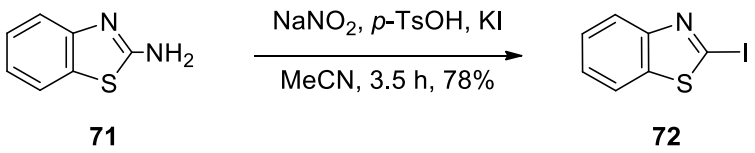
Some substrates gave no product even when increasing temperature or reaction time (Scheme 40). 2-(Trifluoromethyl)aniline (**68**) resulted in no reaction at all, even after increasing the reaction temperature to 60 °C for a reaction time of 2 hours. A small amount of mass was recovered after work-up of the reaction mixture, which gave a mess of peaks by ^{1}H NMR spectroscopy. This was surprising, as 2,4-dinitroaniline (**65**) had been successfully iodinated in the

reaction. This may be due to a combination of steric bulk and the electron-deficient nature of the trifluoromethyl group, which in the *ortho*-position would make it difficult for the large iodide ion to approach. Heteroaromatic substrates were mostly unsuccessful in the reaction. Other than 3-aminopyridine (**66**), other heteroaromatics attempted gave no conversion to product (**69** and **70**). 2-Aminopyrazine (**70**) formed the diazonium salt, which could be detected by ^{1}H NMR spectroscopy. However, the iodination did not take place. As well as the diazonium salt, the ^{1}H NMR spectrum contained an impurity which was not isolated in a 2.2:1 ratio of diazonium salt to unknown.



Scheme 40. Unsuccessful substrates in the reaction.

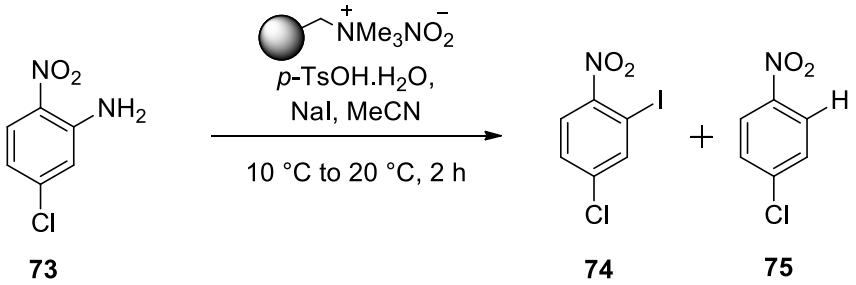
Heteroaromatics attempted in the reaction containing the amino group in the 2-position made the formation of the diazonium salt extremely difficult due to electronics. There are few examples of diazotisation reactions taking place in the 2-position of aromatic heterocycles. One successful example (Scheme 41) was the synthesis of 2-iodobenzothiazole (**72**) *via* similar conditions to our method in 78% yield.[62] However, the synthesis of similar structure 2-iodo-4-methylthiazole (**69**) gave no conversion to product using this method.



Scheme 41. Synthesis of 2-iodobenzothiazole.

5-Chloro-2-nitroaniline (**73**) gave a mixture of products which could not be separated. From analysis of the ^{1}H NMR spectrum of the reaction mixture, these were believed to be the iodinated product **74** and the reduced product **75**. The side product was believed to be **75** due to the observed pair of doublets with coupling constants of 9.1 Hz. The reaction under standard conditions of room temperature for 2 hours gave a 2:1 mixture of the reduced product **75** and the iodinated product **74** (Table 4, entry 1). Extra equivalents of sodium iodide were added to the reaction in the hope this would push the formation of the iodinated product, however this had no effect (Table 4, entry 2). The reaction was also heated to 60 °C with 6 equivalents of sodium iodide in an attempt to increase the rate of formation of the iodinated product, however this only increased the formation of the side product, giving this in a now 5:1 ratio of **75** over **74** (Table 4, entries 3 and 4). Lastly, the reaction was attempted at 0 °C for the full 2 hours to halt the formation of the reduced product (Table 4, entry 5). This increased the ratio of **74** to **75** slightly, giving the product in a 1:1 ratio, however as these could not be separated by column chromatography or by other purification methods attempted, iodination of this substrate was abandoned.

Table 4. Conditions for iodination of 5-chloro-2-nitroaniline and ratio of products.



73 **74** **75**

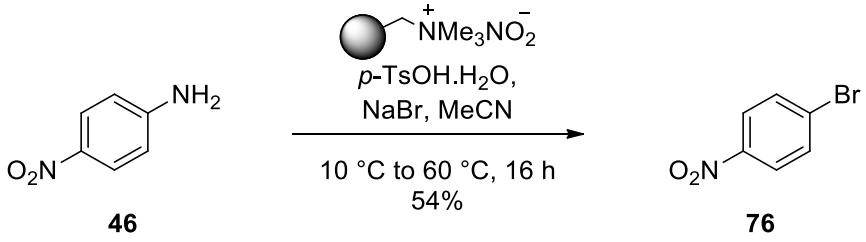
Entry	Temperature (°C)	Equiv. NaI	Time (h)	Ratio of 74	Ratio of 75
1	10 to rt	2	2	1	2
2	10 to rt	6	2	1	2.5
3	10 to 60	2	2	1	5
4	10 to 60	6	2	1	4
5	0	2	2	1	1

The reduced product was not a problem for the majority of substrates, and was only detected for substrates with an electron-withdrawing group in the *ortho*-

position to the diazo group. The substrate 2-amino-4,5-dimethoxybenzonitrile (**60**) also gave a small amount of the reduced side-product (~5%), however this could be separated from the iodinated product by column chromatography.

2.4 Attempted bromination and fluorination

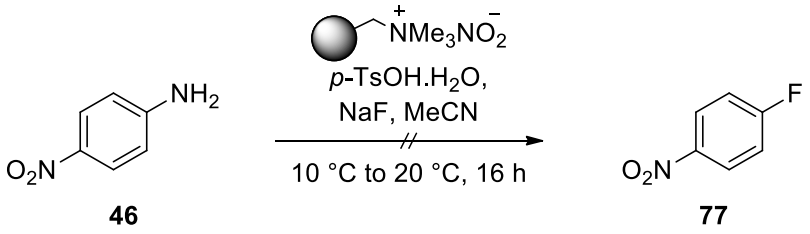
The reaction conditions were also explored for use in a bromination reaction. The synthesis of aryl bromides is valuable as these are used extensively in cross-coupling reactions. The bromination reaction required more harsh conditions than for the iodination reaction. 4-Nitroaniline (**46**) was used as the substrate due to the high yield of 86% achieved in the iodination reaction, under mild conditions of room temperature in 2 hours. The bromination reaction at room temperature gave an isolated yield of 13% product **76** under the same conditions. Increasing the reaction time to 16 hours saw no improvement in yield. Complete conversion of 4-nitroaniline (**46**) to the diazonium salt was detected; however the bromination would not occur readily at this temperature. The reaction required higher temperatures of 60 °C for 16 hours; to give the brominated product **76** in 54% yield (Scheme 42). The Sandmeyer reaction for the bromination of diazonium salts usually includes the addition of a copper(I) catalyst, which initiates the reaction by a one-electron transfer mechanism.[65] However, this was not further pursued at this stage.



Scheme 42. Aromatic diazotisation-bromination reaction.

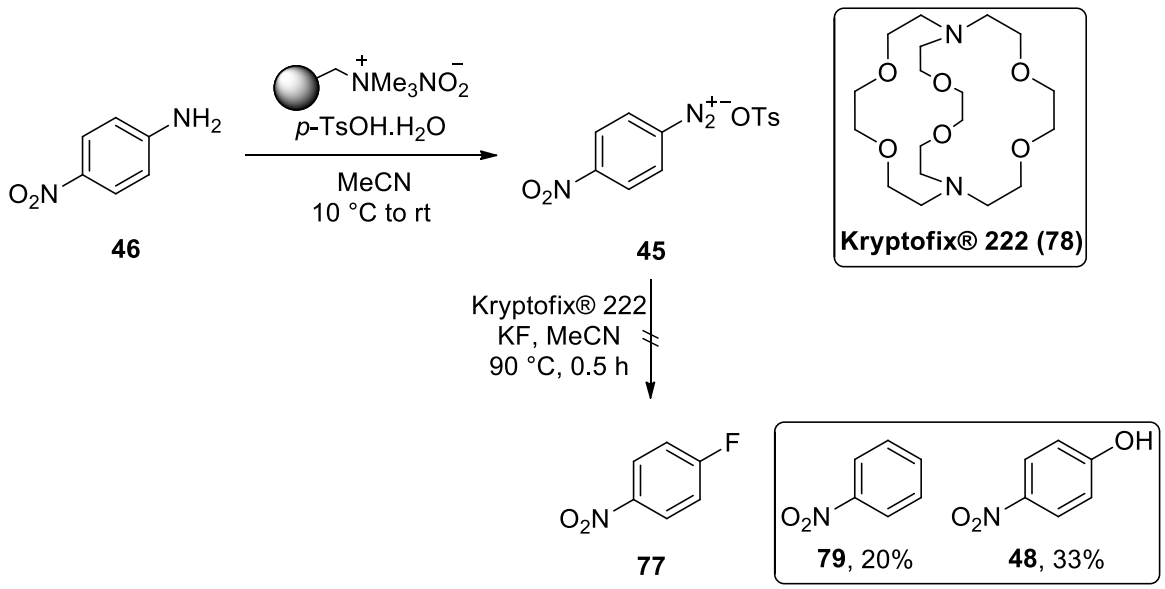
A mild synthesis of aryl fluorides is also highly desirable as these can be used for the synthesis of PET imaging agents. Aromatic fluorination is a challenging reaction, as the fluoride ion forms strong hydrogen bonds with a variety of hydrogen bond donors and is only weakly nucleophilic.[66] The fluorination reaction was attempted under the standard conditions used for iodination, replacing sodium iodide with sodium fluoride, to assess whether this could result

in any product. *p*-Nitroaniline (**46**) was again used as substrate, but this gave none of the fluorinated product **77** under the conditions attempted (Scheme 43).



Scheme 43. Attempted diazotisation-fluorination reaction.

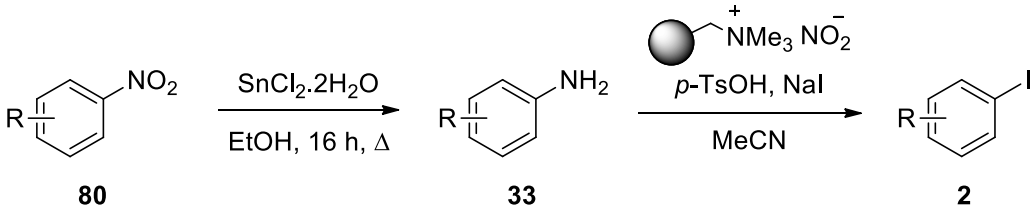
The reaction was also attempted in two steps (Scheme 44). The diazonium salt was first prepared and isolated to enable this to be dried for the fluorination reaction. A chelating agent additive was used in the second step to increase the nucleophilicity of the fluoride ion. Chelating agents work by trapping the cation and freeing the nucleophilic fluorine to increase reactivity. Kryptofix® 222 (**78**) was added to the reaction mixture, with potassium fluoride as the fluorinating reagent. Molecular sieves were also added to the reaction to ensure dry conditions. The reaction was heated to 90 °C under argon for 1 hour; however this gave a mixture of the reduced compound **79** and 4-nitrophenol **48**, with no fluorination detected.



Scheme 44. Attempted aromatic diazotisation-fluorination reaction with cryptand.

2.5 Imaging Agents

After the diazotisation-iodination reaction was shown to have a general scope, it was applied to the synthesis of more complex, potential or current molecular imaging agents used for SPECT imaging. The aromatic iodination would be the final step in all the syntheses, which would be hugely beneficial for the radioiodination reaction due to the short half-life of radioiodine, as well as minimising handling of radioactive material. The amino precursor **33** would be masked throughout the synthesis as the less reactive nitrophenyl **80**. This would allow the mild reduction of the nitro group, using a tin(II) chloride reduction, followed by the one-pot diazotisation-iodination reaction as the final two steps in the synthesis (Scheme 45).



Scheme 45. General Scheme for Iodination of aryl compounds.

The imaging agents investigated were chosen due to their varying structures, to show the reaction could successfully be applied to more complex structures, as well as tolerating a number of functional groups (Figure 2). The current method of radioiodination for these ligands is the two-step stannylation and iododestannylation reaction. Each substrate will be discussed in more detail below.

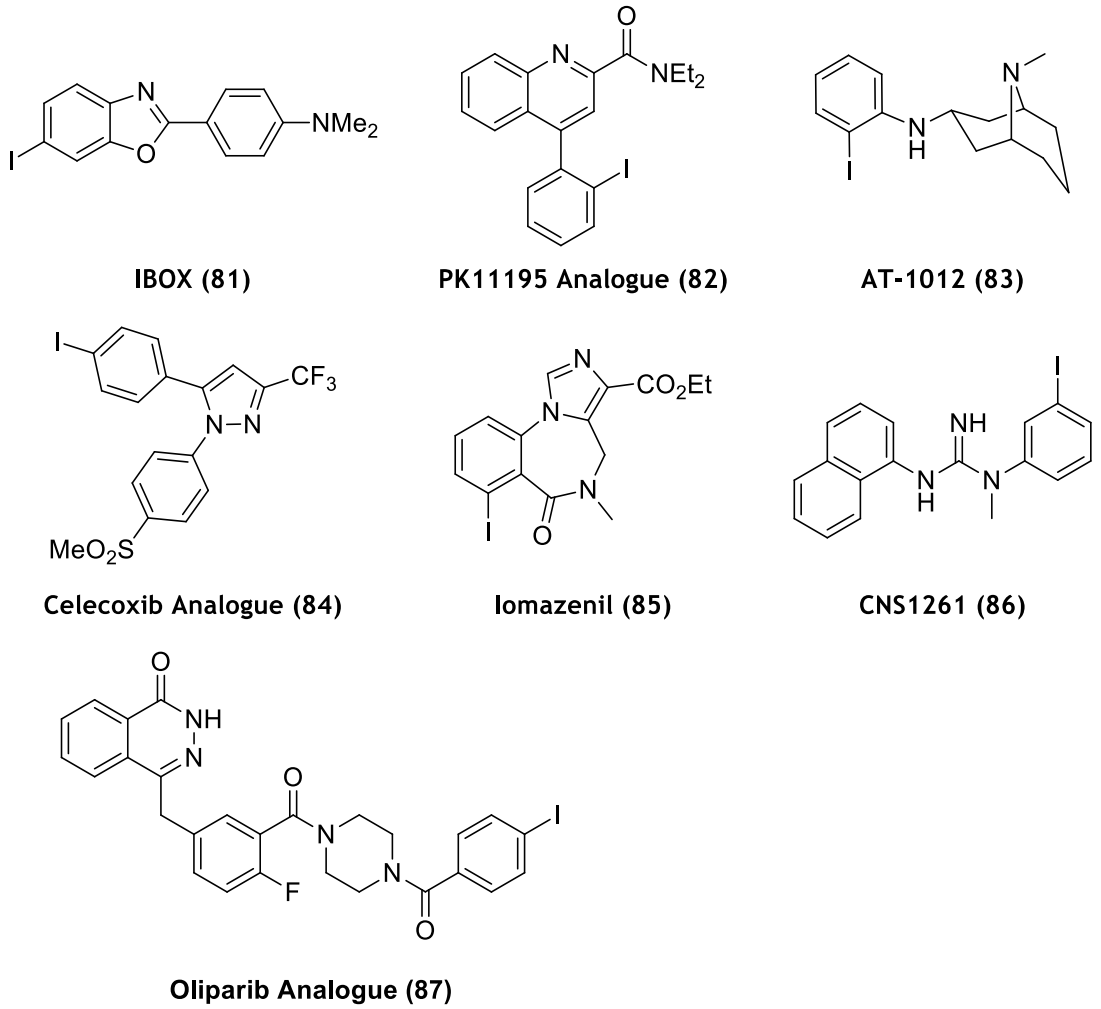


Figure 2. Biologically active ligands synthesised using the one-pot diazotisation-iodination reaction.

2.5.1 Synthesis of 2-(4'-Dimethylaminophenyl)-6-iodobenzoxazole (IBOX)

2.5.1.1 Introduction

The first ligand to be iodinated via the developed diazotisation-iodination reaction was the imaging agent IBOX (**81**). IBOX is a radioligand for the imaging of β-amyloid plaques and is an analogue of thioflavin T (Figure 3).

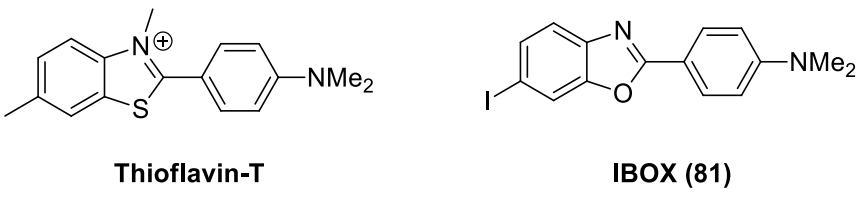
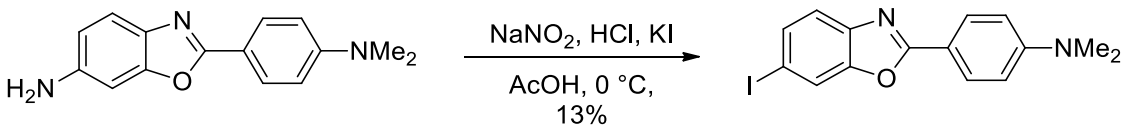


Figure 3. Thioflavin-T and its analogue, IBOX.

Thioflavin T is a dye that displays enhanced fluorescence when binding to misfolded protein aggregates, known as amyloids.[67] The formation of amyloids not only causes the previously healthy protein to lose its normal physiological function, but they also clump together to form amyloid fibrils, which build up around cells as amyloid plaques. This can disrupt the function of tissues and organs and as such, amyloids are linked to a large number of diseases. *beta*-Amyloid (Aß) is a polypeptide that forms amyloid fibrils in the brain. These are the main component of amyloid plaques found in the brains of patients with Alzheimer's disease. The overproduction and accumulation of Aß plaques in the brain is therefore believed to be a key event in the development of Alzheimer's disease.[68] As Aß plaques precede the onset of dementia and cognitive decline in patients with Alzheimer's disease, monitoring the formation of these with Aß plaque-selective ligands is important for its diagnosis and prognosis.

Zhuang *et al*[69] have shown that IBOX has high *in vitro* binding affinity for Aß plaques (K_i = 0.8 nM), as well as high selectivity for Aß aggregates in post-mortem Alzheimer's brain sections. It was also shown to have high brain uptake, with a relatively fast brain washout. This makes IBOX a promising candidate for the imaging of Alzheimer's disease. Previous synthesis of IBOX (**81**) also uses a diazotisation-iodination reaction from the aniline precursor **88** as the final step in the synthesis. However, more traditional, strongly acidic conditions were used in the reaction. Using a 1:10 mixture of concentrated hydrochloric acid to acetic acid as solvent, the reaction gave a yield of 13% (Scheme 46).[69]



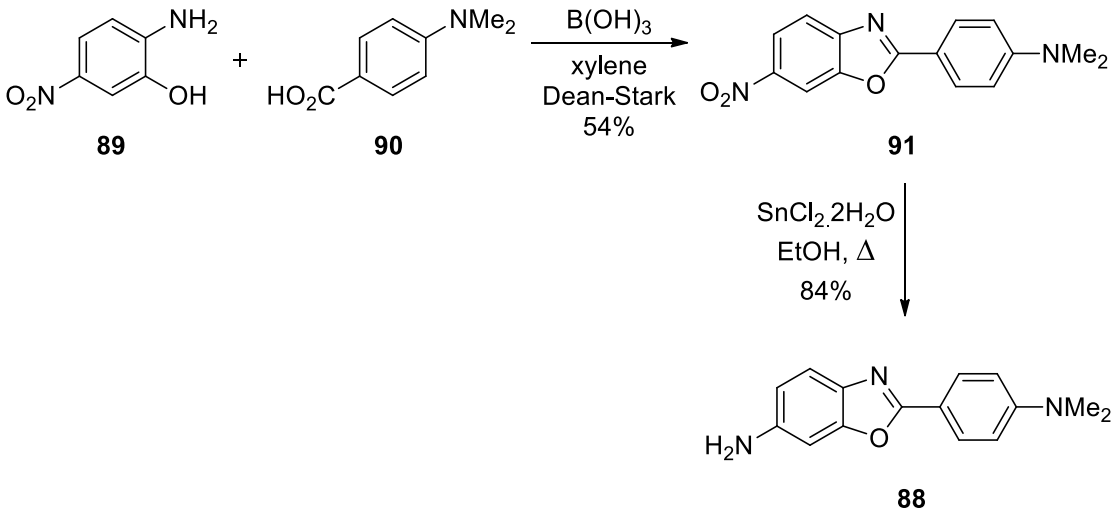
88 **81**

Scheme 46. Previous synthesis of IBOX.

2.5.1.2 Synthesis

The first step in the synthesis of IBOX (**81**) was the literature reported condensation of 5-nitro-2-aminophenol (**89**) with 4-dimethylaminobenzoic acid (**90**), with boric acid acting as a Lewis acid (Scheme 47).[69] This gave the coupled

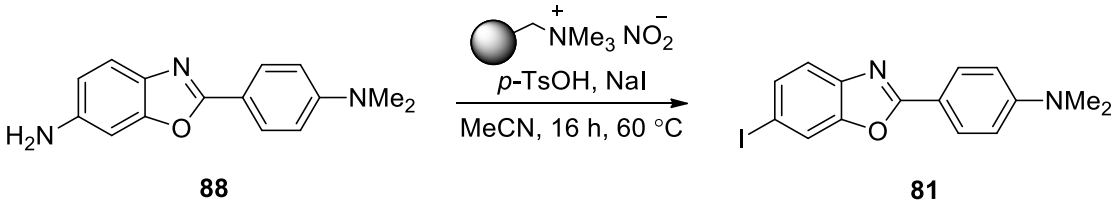
product **91** in 54% yield. The next step in the synthesis was the reduction of the nitro group with tin(II) chloride dihydrate, which gave the amine precursor **88** in 84% yield.



Scheme 47. Synthesis of IBOX.

The final step in the synthesis was the one-pot diazotisation-iodination reaction. This was first attempted under the standard reaction conditions of room temperature for 2 hours, which gave the final iodinated product **81** in a low yield of 17% (Table 5, entry 1). The reaction time was next increased to 16 hours; however this only increased the yield slightly to 32% (Table 5, entry 2). The radioiodination reaction requires fast reaction times, meaning a reaction time of more than 16 hours was not suitable. To increase the yield further, the reaction was heated to 60 °C for 16 hours to give an optimum yield of 59% (Table 5, entry 3).

Table 5. Optimised conditions for the iodination of IBOX.



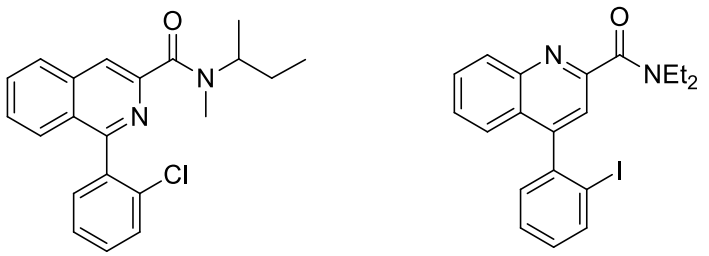
88 81

Entry	Temperature (°C)	Time (h)	Yield (%)
1	rt	2	17
2	rt	16	32
3	60	16	59

2.5.2 Synthesis of PK11195 Analogue

2.5.2.1 Introduction

The next imaging agent investigated was 4-(2-iodophenyl)quinoline-2-*N*-diethylcarboxamide (**82**), which is an analogue of PK11195 (**92**), an imaging agent for the translocator protein (TSPO) (Figure 4).

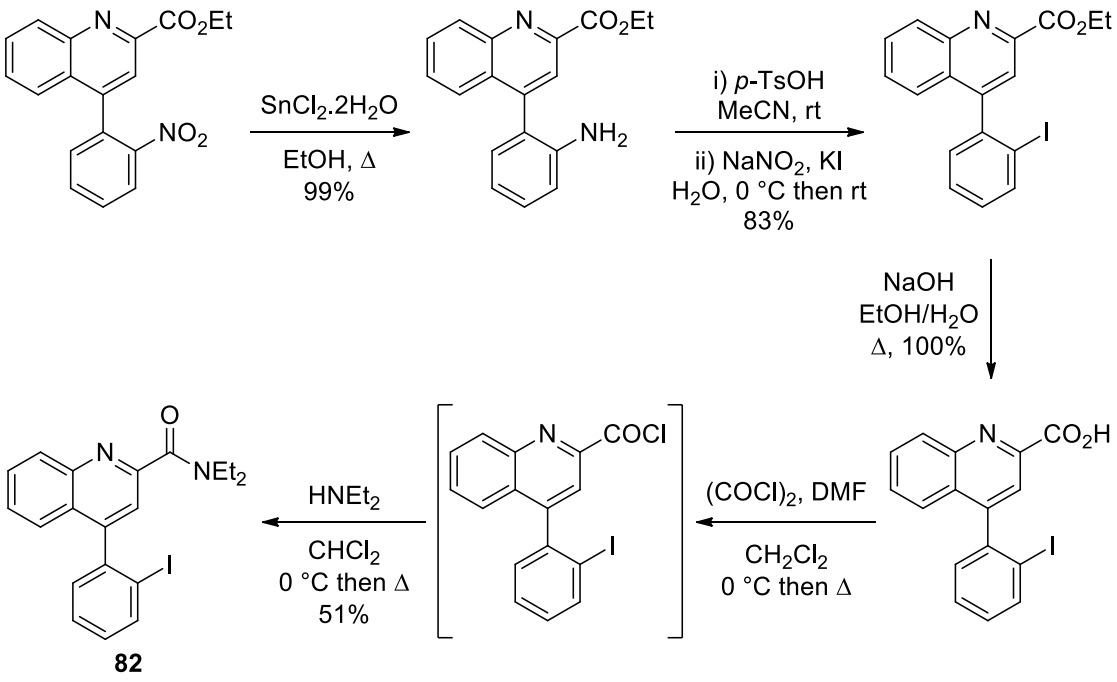


PK11195 (92) 82

Figure 4. Radioligands for TSPO.

The TSPO, formerly known as the peripheral benzodiazepine receptor (PBR), is mainly found on the outer mitochondrial membrane and is expressed on the peripheral organs throughout the body. It is also found in low concentrations in the brain; however after brain injury or neurodegeneration, TSPO levels are dramatically increased.[70] This makes the TSPO a valuable target for PET and SPECT imaging of diseases associated with neuroinflammation, such as Parkinson's disease,[71] Alzheimer's disease[72] and strokes.[73]

The isoquinoline carboxamide PK11195 is a ligand for the TSPO and has been shown to have high selectivity and high binding affinity (K_i = 9.3 nM) for the TSPO.[74] However, PK11195 has limitations, such as its high level of non-specific binding, causing low brain uptake and low sensitivity.[75] New radioligands for TSPO have been investigated in the group previously, with the analogue **82** found to have a higher affinity (K_i = 5.01 nM) for TSPO, as well as similar physicochemical properties to PK11195.[76] The previous synthesis of analogue **82** had the iodination step taking place 3 steps before the end of the synthesis, which is not applicable for radioiodination (Scheme 48).[76] It was believed that the mild diazotisation-iodination method would allow a more rapid synthesis to analogue **82** and allow for a potential method for radioiodination, with iodination being the final step in the synthesis.

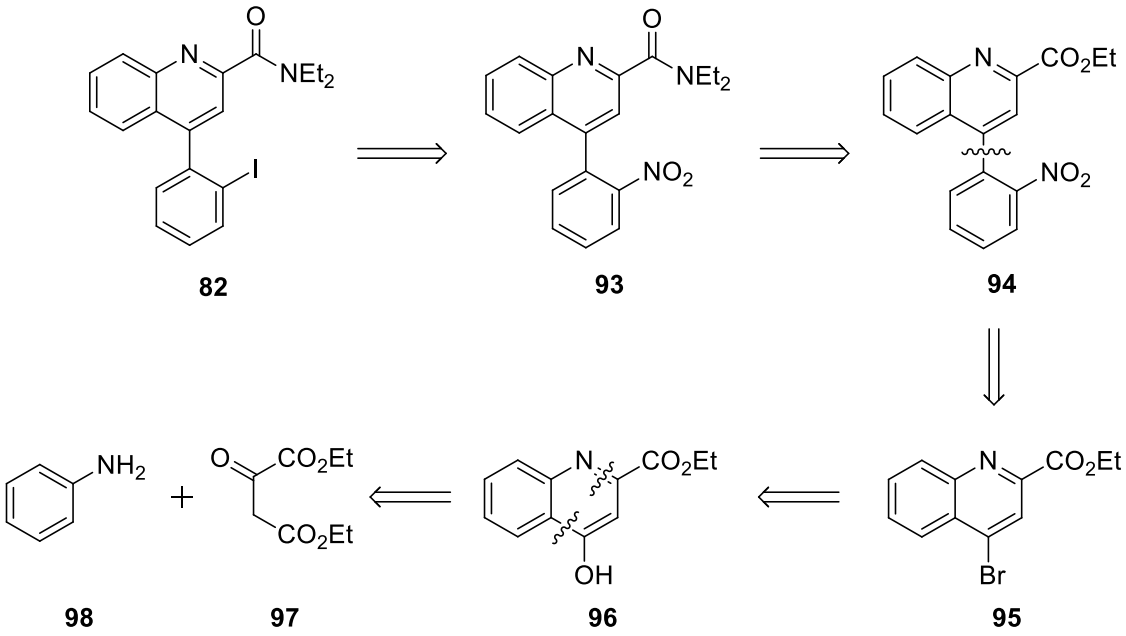


Scheme 48. Previous synthesis of PK11195 analogue 82.

2.5.2.2 Synthesis

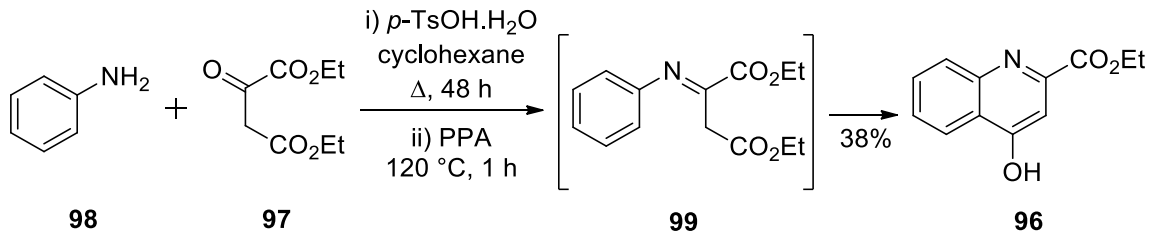
A retrosynthetic synthesis of the desired PK11195 analogue **82** is shown in Scheme 49. The final iodinated compound **82** would be synthesised from nitro precursor **93** *via* the reduction of the nitro to the amine, followed by the developed one-pot diazotisation-iodination reaction. Synthesis of the aromatic nitro precursor **93** would be achieved *via* an amide coupling reaction of the

carboxylic acid, after hydrolysis of the ethyl ester **94**. Coupled product **94** would be obtained by a palladium catalysed cross-coupling reaction between bromoquinoline **95** with 2-nitrophenylboronic acid. Functional group interconversion to hyroxyquinoline **96** would allow synthesis from commercially available starting materials. Disonnection of hydroxyquinoline **96** as shown gives the cheap starting materials diethyl oxaloacetate (**97**) and aniline (**98**).



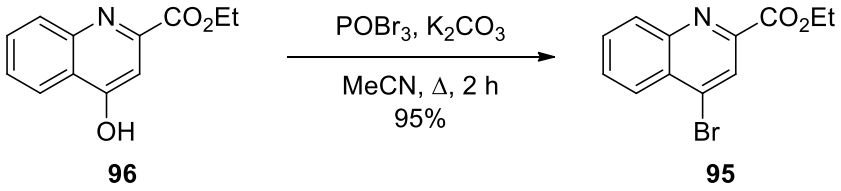
Scheme 49. Retrosynthesis of PK11195 analogue 82.

The first step in the synthesis of the TSPO ligand **82** was the formation of the hydroxyquinoline ring, which was achieved via the Combes quinolone synthesis.[77] The condensation of aniline (**98**) with diethyl oxaloacetate (**97**) in the presence of *p*-toluenesulfonic acid under Dean-Stark conditions gave imine intermediate **99**, followed by ring closure of the imine mediated by polyphosphoric acid to give 4-hydroxyquinoline carboxylate (**96**) in 38% yield (Scheme 50). The reaction had been optimised previously in the group[76] giving a similar yield of 37% and could be prepared on a large scale, with cheap starting materials, to allow progression onto the next step in the synthesis.



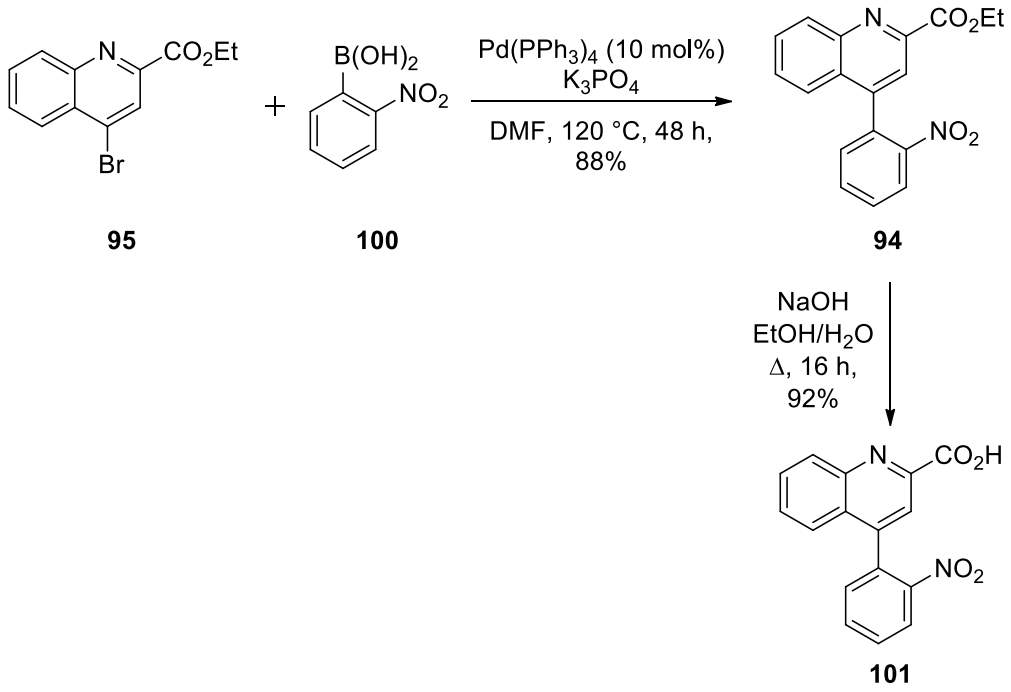
Scheme 50. Combes quinolone synthesis of hydroxyquinoline 96.

The next step was bromination of **96** *via* an aromatic nucleophilic substitution (S_NAr) reaction with phosphorus oxybromide to give 4-bromoquinoline carboxylate (**95**) in 95% yield (Scheme 51).



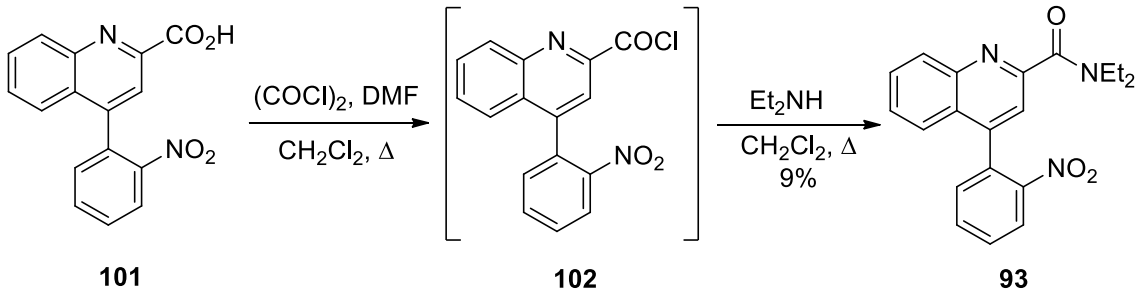
Scheme 51. Substitution of hydroxyl group by bromine *via* an S_NAr reaction.

Product **95** was then used in a Suzuki-Miyaura coupling reaction with 2-nitrophenyl boronic acid (**100**), in the presence of tetrakis(triphenylphosphine)palladium(0) as catalyst and potassium phosphate as base to give the coupled product ethyl 4-(2-nitrophenyl)quinoline-2-carboxylate (**94**) in a yield of 88% after 48 hours at 120 °C (Scheme 52). This was followed by the hydrolysis of the ester group with sodium hydroxide, which gave carboxylic acid **101** in 92% yield.



Scheme 52. Synthesis of 4-(2-nitrophenyl)quinoline-2-carboxylic acid (101).

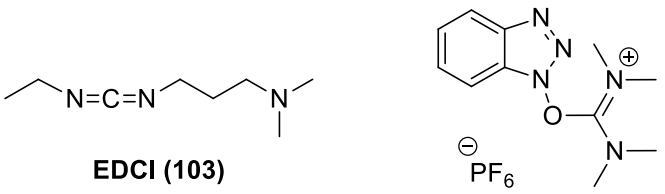
Formation of the quinolone-2-carboxamide **93** from the carboxylic acid **101** was the next step in the synthesis. It was envisioned that the amide could be synthesised from the carboxylic acid by activation *via* the acyl chloride. This was attempted by reaction with oxalyl chloride to form the acyl chloride intermediate **102**, before an amide coupling by addition with diethylamine (Scheme 53). The reaction gave a complicated mixture by ^{1}H NMR spectroscopy, which was difficult to interpret. The product could be separated by column chromatography, but only gave low yields of approximately 9%, even with long reaction times. These conditions had been successful in the group previously for similar analogues of PK11195,[76] but had not been attempted for an analogue containing the bulky, strongly deactivating nitro group, which may be causing the decreased reactivity of the carboxylic acid.



101 **102** **93**

Scheme 53. Attempted synthesis of amide 93 *via* acyl chloride 102.

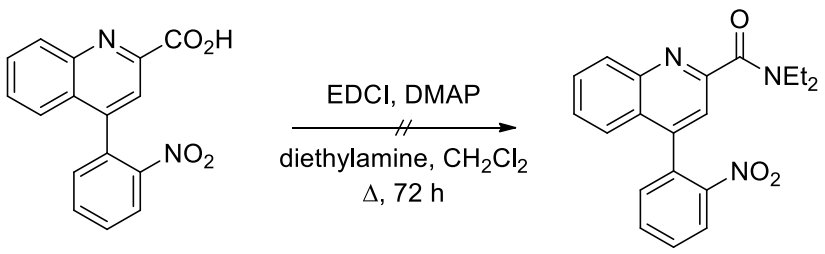
Other methods of activating the carboxylic acid for amidation were then investigated. The linking of amino acid monomers by peptide, or amide, bonds to form peptides has resulted in a large variety of peptide coupling reagents for activation of carboxylic acids. Figure 5 shows the peptide coupling reagents used.



EDCI (103) **HBTU (104)**

Figure 5. Peptide coupling reagents.

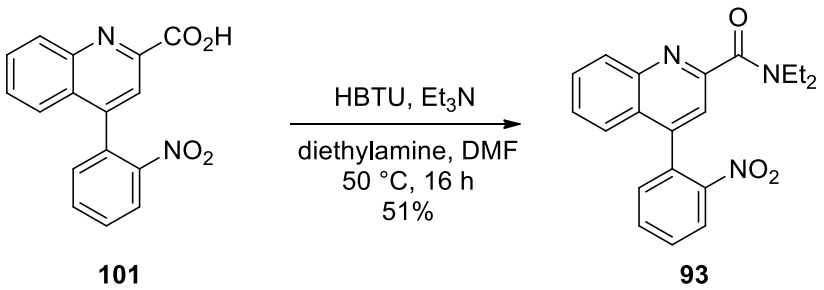
The amide coupling reagent EDCI (**103**) was used first in the attempted preparation of amide **93**, with catalytic DMAP at room temperature (Scheme 54). After 2 hours, there was still no conversion of starting material shown by TLC, therefore the reaction was heated under reflux. Long reaction times of 72 hours still resulted in recovery of starting material **101** and no product.



101 **93**

Scheme 54. Attempted amide synthesis with EDCI.

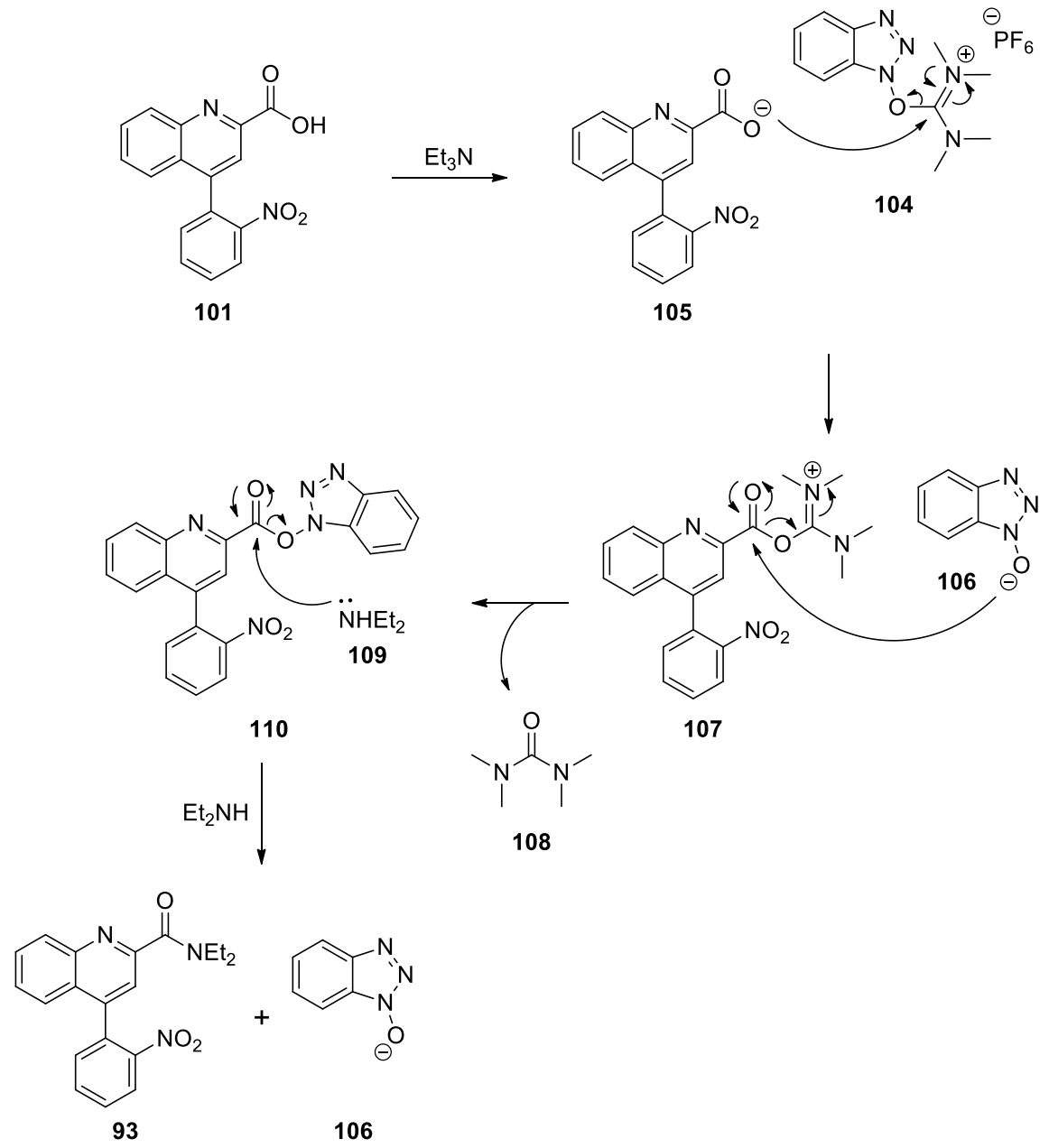
The amide coupling reagent HBTU (**104**) was next attempted in the reaction. The reaction was heated to 50 °C for 16 hours with triethylamine as base, before addition of diethylamine and gave the required amide in a yield of 51% (Scheme 55).



101 **93**

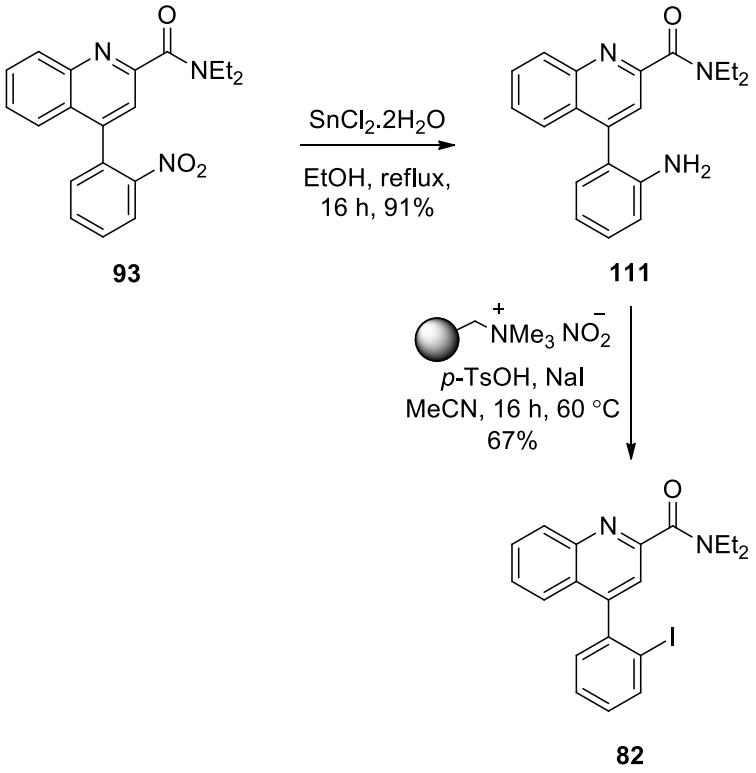
Scheme 55. Amide synthesis with HBTU.

The mechanism is shown in Scheme 56. The first step is deprotonation of the carboxylic acid **101** by triethylamine, followed by attack on HBTU (**104**) by the carboxylate ion **105** to form the oxygen anion of benzotriazole (**106**) and the highly reactive *O*-acylisourea **107**. *O*-acylisourea **107** is activated for attack by a nucleophile due to the stable urea leaving group **108**. The benzotriazole anion **106** then reacts with the *O*-acylisourea **107** to form an activated ester species **110** and urea **108.** Diethylamine (**109**) can then attack the reactive OBt ester **110**, which gives product **93** and regenerates 1-hydroxybenzotriazole (**106**).



Scheme 56. Amide coupling mechanism with HBTU.

With the amide product **93** in hand, the final two steps in the synthesis were reduction of the nitro group, followed by the one-pot diazotisation-iodination reaction. The reduction of the nitro group with tin(II) chloride dihydrate gave the amine **111** in 91% yield (Scheme 57). This was following by the diazotisation-iodination reaction which, at 60 °C for 16 hours, gave the iodinated final product **82** in 67% yield.



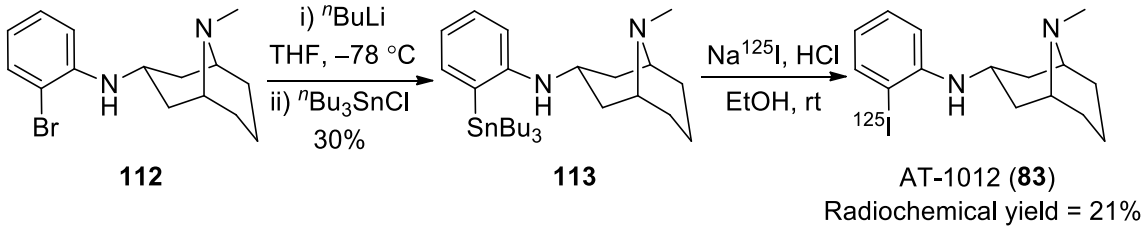
Scheme 57. Final two steps in the synthesis of PK11195 analogue 82.

2.5.3 Synthesis of AT-1012

2.5.3.1 Introduction

AT-1012 (**83**) is a highly selective antagonist for the α3β4 nicotinic acetylcholine receptor (nAChR). nAChRs are ligand-gated ion channels that mediate cation influx when activated by the binding of the neurotransmitter acetylcholine.[78] They are also activated by nicotine and are believed to cause the addictive effects from this drug. nAChRs are present in the CNS as well as the periphery nervous system and are involved in a number of physiological processes. There are several subunits of nAChRs in the brain, α4β2 and α7 nAChRs being the most prominent.[79] The $\alpha 3\beta 4$ nAChR subtype is only present in small amounts in the brain; however it is predominant in certain areas, such as the sensory and autonomic ganglia, and has been shown to play an important role in drug addiction, especially with nicotine.[80] Antagonism of this receptor could be important in reducing addictive effects in several abused drugs. Selective ligands for the $\alpha 3\beta 4$ nAChR are highly desirable to enable the study of the role of the receptor in drug addiction and to better understand the link between addiction

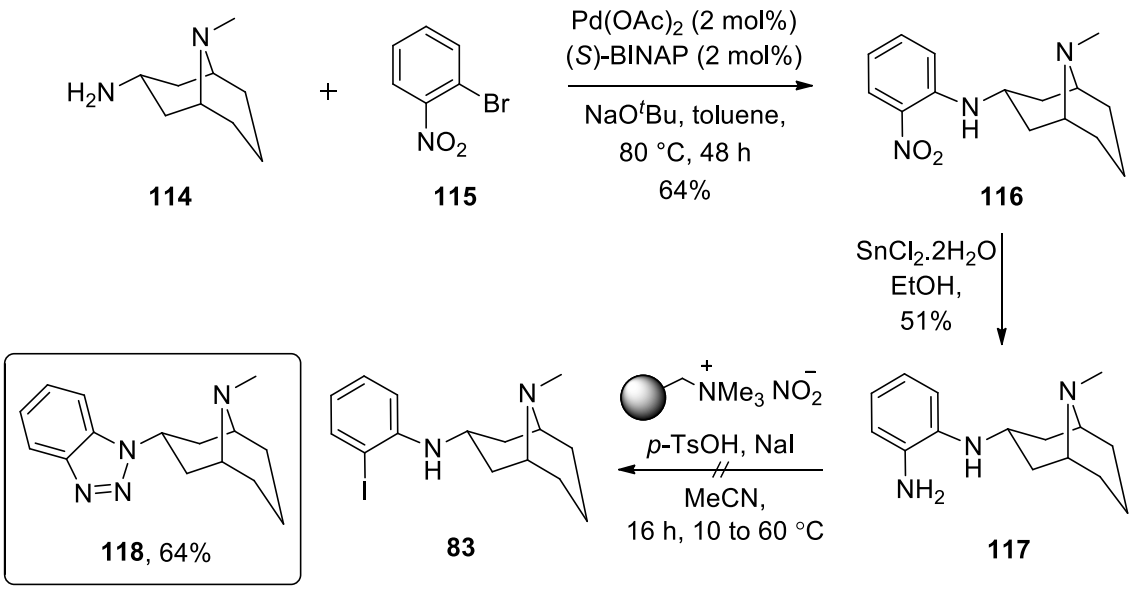
and this receptor. AT-1012 (**83**) has high binding affinity for the α3β4 subtype nAChR (K_i = 0.93 nM) and has been shown to have very high selectivity for α3β4 over the more prominent α4β2 nAChR in the brain (~144 fold). The method currently used for radioiodination of **83** is *via* an iododestannylation reaction of the organotin intermediate **113**, prepared from the bromide-precursor **112** (Scheme 58). The reaction with iodine-125 gave a radiochemical yield of 21%.[81]



Scheme 58. Labelling of AT-1012 with iodine-125.

2.5.3.2 Synthesis

The first step in our synthesis of **83** was a Buchwald-Hartwig coupling of the azabicyclononane **114** with 1-bromo-2-nitrobenzene (**115**) in the presence of palladium(II) acetate (2 mol%) and (*S*)-BINAP ligand (2 mol%) to give **116** in 64% yield. This was followed by the reduction of the nitro group with tin(II) chloride dihydrate to give the amine precursor **117** in 51% yield (Scheme 59). The one-pot diazotisation-iodination reaction was attempted at room temperature for 16 hours, but gave no conversion to product. The reaction was then repeated with heating to 60 °C and stirred for 16 hours in the hope this would push the iodination reaction. This resulted in full conversion of starting material; however, this was not converted to the desired iodinated product **83**. Full analysis found this to be the triazole product **118**, which was synthesised in 64% yield. Diazo-nitrogen bond formation from diazonium salts is known[82] and this may suggest that a limitation of the reaction is that it cannot take place in the presence of an amino group alpha to the diazonium salt. Protection of the amine could be a potential way of solving this issue in future syntheses of ligands containing an alpha amino group. However, the sterically hindered secondary amine in AT-1012 would be difficult to protect and deprotect in the synthesis and it was decided to leave the synthesis of **83** at this point.



Scheme 59. Synthesis of AT-1012.

2.5.4 Synthesis of Celecoxib Analogue

2.5.4.1 Introduction

Cyclooxygenase (COX) is an enzyme responsible for the formation of prostaglandins, which are important biological mediators of pain and inflammation in the body.[83] Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the activity of COX, most inhibiting both COX-1 and COX-2. COX-1 is expressed in normal cells, with COX-2 only being expressed in response to physiological stimuli in elevated levels during inflammation, where prostaglandins are unregulated. As well as being responsible for inflammation and pain, COX-2 has also been shown to play a role in the growth of tumour cells.[84] Drugs which inhibit both COX-1 and COX-2 non-selectively not only inhibit the inflammatory response of COX-2, but also the beneficial prostaglandin regulatory processes.[83] Drugs which are selective inhibitors of COX-2 can be used to treat pain and inflammation without some of the side effects observed when inhibiting COX non-selectively.

Celecoxib (**119**) is a drug used for the treatment of acute pain by acting as an inhibitor of COX-2 selectively. Analogues of celecoxib, such as **84** (Figure 6), are

investigated as imaging agents for COX-2, and are useful in the imaging of inflammation as well as being important for the imaging and detection of cancers.[85] Celecoxib analogue **84** has been reported as having a high binding affinity for COX-2 (IC_{50} = 5.2 μM) compared to COX-1 (IC_{50} > 100 μM),[86] with a more recent paper reporting this being as high as 0.05 μM for COX-2.[87]

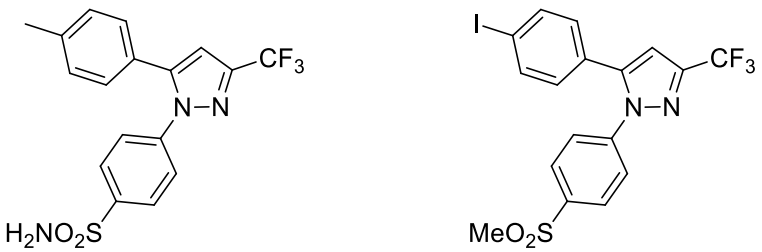
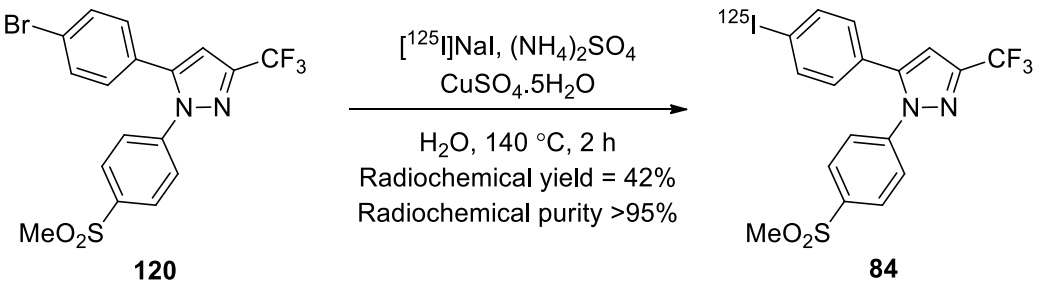


Figure 6. Celecoxib analogue 84.

Celecoxib analogue **84** has been labelled with iodine-125 previously by Kuge *et al*[86] using the halogen exchange reaction shown in Scheme 60. The reaction gave a radiochemical yield of 42%, with a long HPLC method required to separate the bromide-precursor **120** from the iodinated product **84**, with the product eluting after 64 minutes. An iodination method with a non-halogen starting material could result in much faster purification methods.

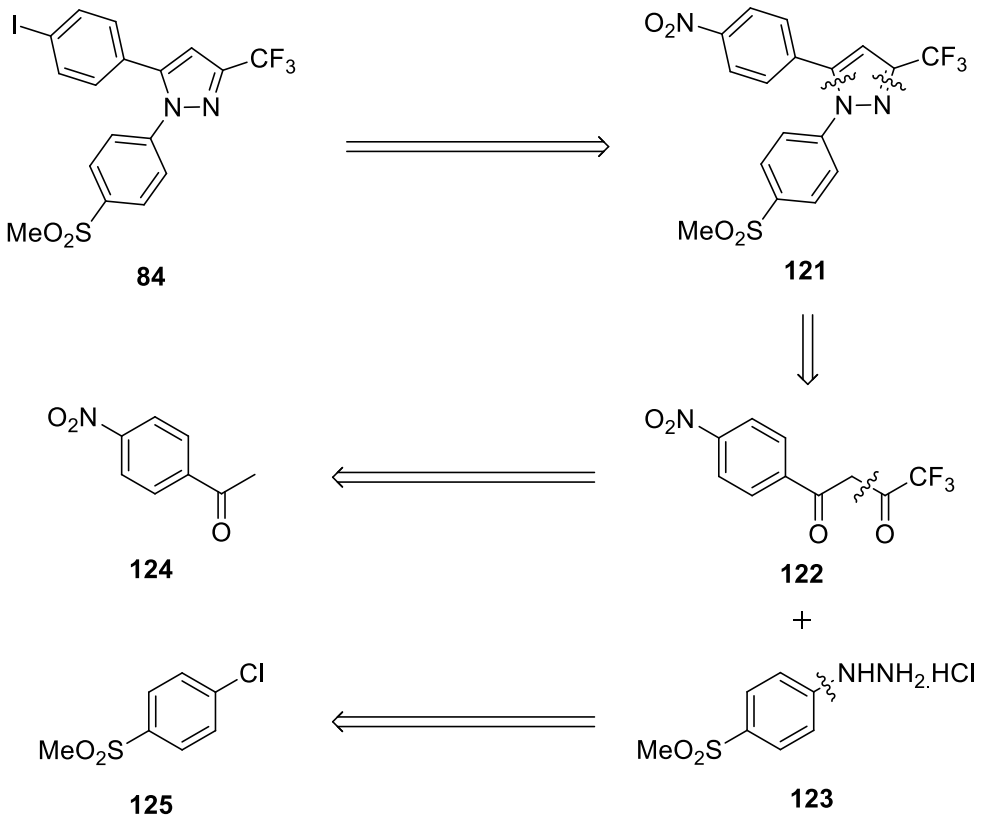


Scheme 60. Radioiodination of imaging agent 84 with iodine-125.

2.5.4.2 Synthesis

The retrosynthetic analysis of the COX-2 imaging agent **84** is shown in Scheme 61. The final iodinated product would be synthesised by the reduction of the nitro group followed by the diazotisation-iodination reaction as for the previous imaging agents. The nitro precursor **121** would be prepared by disconnection of

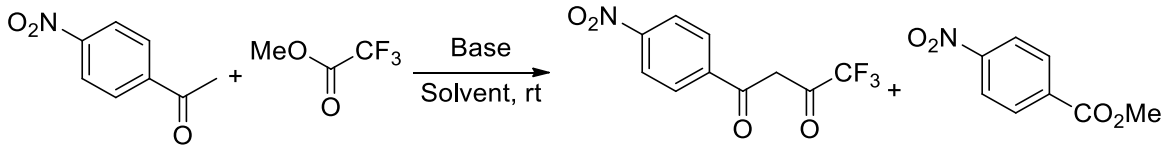
the pyrazole ring, which could be formed from the reaction between β-diketone **122** with phenyl hydrazine **123.** β-Diketone **122** could be made in one step from the commercially available 4-nitroacetophenone (**124**), and phenyl hydrazine **123** could be prepared in one step from the commercially available 4-chlorophenyl methyl sulfonyl (**125**).



Scheme 61. Retrosynthetic route to the COX-2 imaging agent 84.

The first step in the forward synthesis was a Claisen condensation of 4-nitroacetophenone (**124**) with methyl trifluoroacetate (**126**) (Table 6). Reaction with 25% sodium methoxide in methanol as base using a literature procedure resulted in recovery of starting material only (Table 6, entry 1).[87] Potassium *tert*-butoxide was next used as base in the reaction, with varying equivalents of base, methyl trifluoroacetate (**126**) and reaction times attempted. Methyl 4-nitrobenzoate (**127**) was isolated as the major product when 1.2 equivalents of base was used (Table 6, entries 3 and 4). Using 3 equivalents of potassium *tert*-butoxide as base with 2.5 equivalents of **126**, for 24 hours gave the desired β-diketone product **122** in 19% yield (Table 6, entry 5), with an optimised yield of 75% obtained when the reaction was left for 48 hours (Table 6, entry 6).

Table 6. Conditions for synthesis of ß-diketone 122.

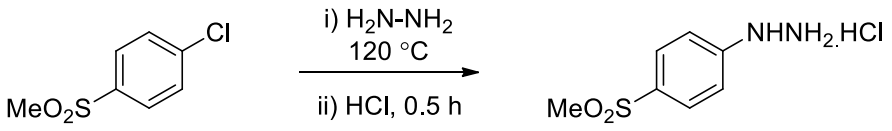


124 **126** **122** **127**

Entry	Base	Base (equiv.)	126 (equiv.)	Solvent	Time (h)	124 (%)	122 (%)	127 (%)
1	25% NaOMe in MeOH	1.3	1.1	MTBE	48	42	0	0
2	NaOMe	1.3	1.1	MTBE	48	54	0	0
3	^{t}BuOK	1.2	1.2	Toluene	18	62	0	25
4	^{t}BuOK	3	1.2	Toluene	48	16	0	46
5	^{t}BuOK	3	2.5	Toluene	24	14	19	11
6	^{t}BuOK	3	2.5	Toluene	48	0	75	0

The hydrazine starting material **123** was made in one step by reaction of 4-chlorophenyl methyl sulfonyl (**125**) with hydrazine (Table 7). The literature procedure for the reaction took place in a hydrogenation Parr shaker,[88] to give a yield of 73%. The reaction of **125** and hydrazine was therefore firstly attempted with microwave heating at 160 °C but this resulted in decomposition (Table 7, entry 1). Lowering the temperature to 120 °C gave quantitative yield (Table 7, entry 2). The reaction was also attempted with regular heating at 120 °C and 150 °C. This gave the product in 22% yield (Table 7, entry 3) and quantitative yield (Table 7, entry 4) respectively.

Table 7. Conditions for synthesis of phenyl hydrazine (123).

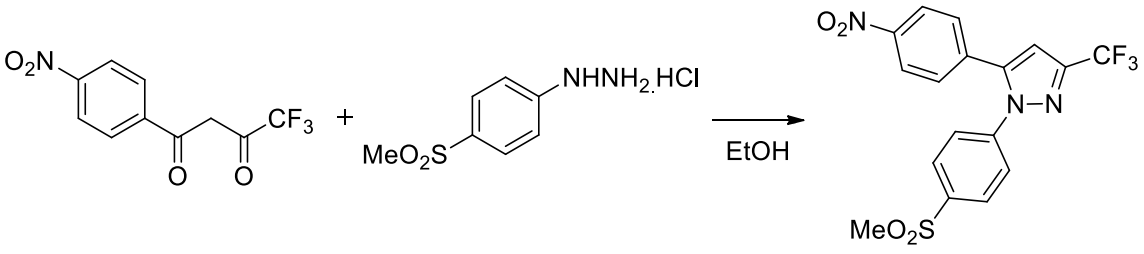


125 **123**

Entry	Temperature (°C)	Time (h)	Microwave heating	Yield (%)
1	160	1	yes	decomposition
2	120	1	yes	100
3	120	16	no	22
4	150	16	no	100

With both starting materials in hand, the next step in the synthesis was the reaction of β-diketone **122** and phenylhydrazine **123** to give pyrazole **121.** Standard literature conditions,[87] under reflux in ethanol, gave no product after 16 hours (Table 8, entry 1). Reaction in toluene for 48 hours to give an increase in reflux temperature gave only 5% yield of pyrazole **121** (Table 8, entry 2). The reaction in ethanol was stirred for a longer reaction time of 72 hours, which gave pyrazole **121** in the highest yield (Table 8, entry 3). Although this only gave an optimised yield of 27%, the reaction was repeated on a large scale to have enough material for the final reduction and diazotisation-iodination steps in the synthesis. A further increase in reaction time to 120 hours did not give an increase in yield (Table 8, entry 4).

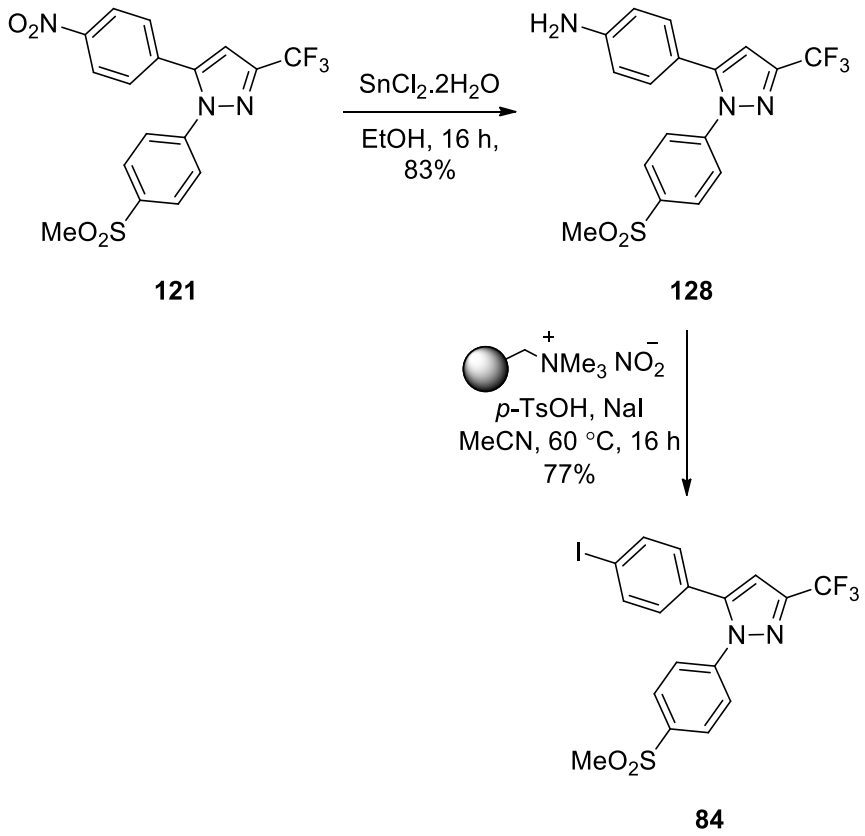
Table 8. Conditions for pyrazole formation.



122 **123** **121**

Entry	Time (h)	Solvent	Yield (%)
1	16	EtOH	0
2	48	toluene	5
3	72	EtOH	27
4	120	EtOH	19

The synthesis of the celecoxib analogue **84** was completed by reduction of the nitro group with tin(II) chloride dihydrate to give the amine precursor **128** in 83% yield. This was followed by the diazotisation-iodination reaction, at 60 °C for 16 hours, which gave the final product **84** in an excellent yield of 77% (Scheme 62).



Scheme 62. Synthesis of celecoxib analogue 84.

2.5.5 Synthesis of Iomazenil

2.5.5.1 Introduction

Iomazenil (**85**) is an antagonist for the benzodiazepine site on the $GABA_A$ receptor and is used as a SPECT imaging agent. The $GABA_A$ receptor is a ligand-gated ion channel, which is activated by the neurotransmitter GABA (γ-aminobutyric acid). When activated, the $GABA_A$ receptor facilitates the flow of Cl^- ions into the neuron, which causes an inhibitory effect on neurotransmission and has a calming effect in the brain. The $GABA_A$ receptor also has a number of allosteric binding sites, one of which is the benzodiazepine receptor. Agonistic action on this receptor increases the affinity of $GABA_A$ for the GABA

neurotransmitter, which increases this calming effect. Antagonistic action on this receptor has the opposite effect and the GABA-benzodiazepine receptor in the brain is linked to a variety of neuropsychiatric disorders such as epileptic seizure, anxiety and schizophrenia.[89] Imaging of the benzodiazepine site is also useful in measuring *in vivo* effects of benzodiazepine drugs.[90] Flumazenil (**129**), labelled with fluorine-18 or carbon-11 and iomazenil (**85**), labelled with iodine-123, are both antagonists for the GABA-benzodiazepine receptor and are the most commonly used imaging agents for the receptor (Figure 7).

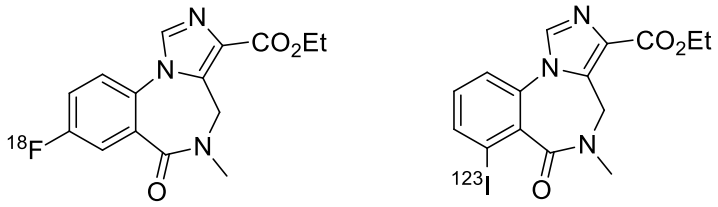
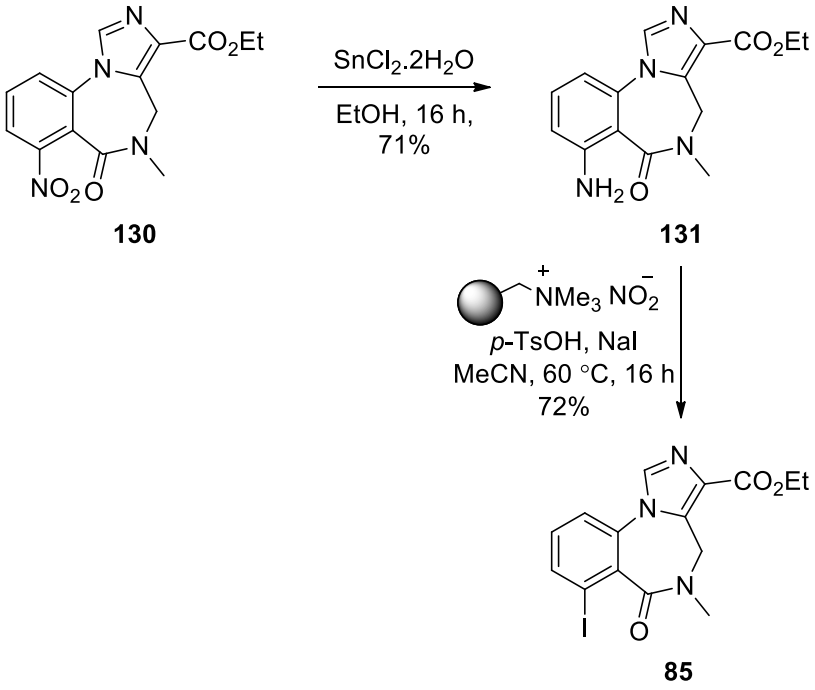


Figure 7. Imaging agents for the central benzodiazepine receptor.

[^{123}I]Iomazenil has been shown to have a high brain uptake and high affinity (K_d = 0.5 nM) *in vitro* for the central benzodiazepine receptor, with high specific binding.[91] [^{123}I]Iomazenil has also been used in SPECT imaging of the benzodiazepine site in clinical studies of Alzheimer's disease and epilepsy.[92]

2.5.5.2 Synthesis

The synthesis of iomazenil was undertaken *via* the nitro precursor **130**, which was provided by GE Healthcare. The nitro group was reduced with tin(II) chloride dihydrate to the amino precursor **131** in 71% yield. This was followed by the one pot diazotisation-iodination reaction, which was carried out at 60 °C for 16 hours to give the final product **85** in 72% yield (Scheme 63). The reaction was not further optimised or attempted under milder conditions due to the small amount of nitro precursor available.



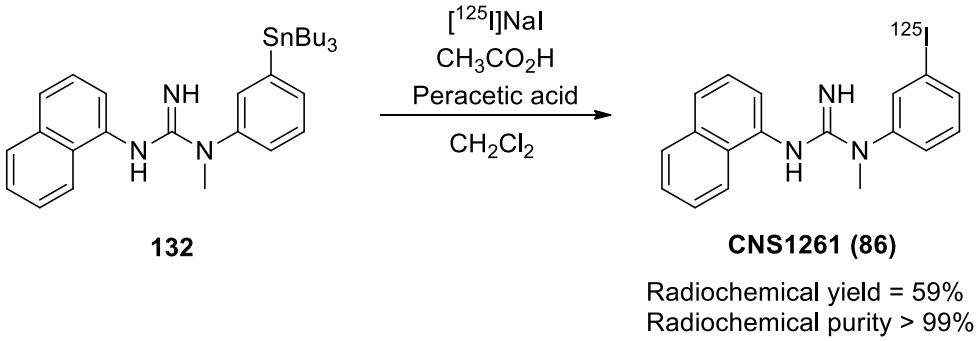
Scheme 63. Synthesis of Iomazenil.

2.5.6 Synthesis of CNS1261

2.5.6.1 Introduction

The synthesis of CNS1261, for the imaging of the *N*-methyl-D-aspartate (NMDA) receptor, was also investigated. The NMDA receptor is a ligand gated ion channel found in neurons, similar to $GABA_A$, that allows the influx of cations into the synapse.[93] The receptor is regulated by binding of glutamate and the co-agonist glycine, [94] which control the frequency and duration of the ion channel opening. Excessive simulation of the NMDA receptor due to high glutamate binding allows for a high influx of cations into cells, which causes neuronal death and is linked to a number of neurodegenerative diseases, such as Alzheimer's disease, epilepsy, schizophrenia and Parkinson's disease.[95] The neurotransmitter glutamate binds at the NMDA receptor's ion channel binding site, known as the phencyclidine (PCP) binding site. The PCP binding site is located within the open ion channel; therefore ligands which act at this binding site only bind when the channel is open, allowing a novel approach for imaging of neurodegenerative diseases.

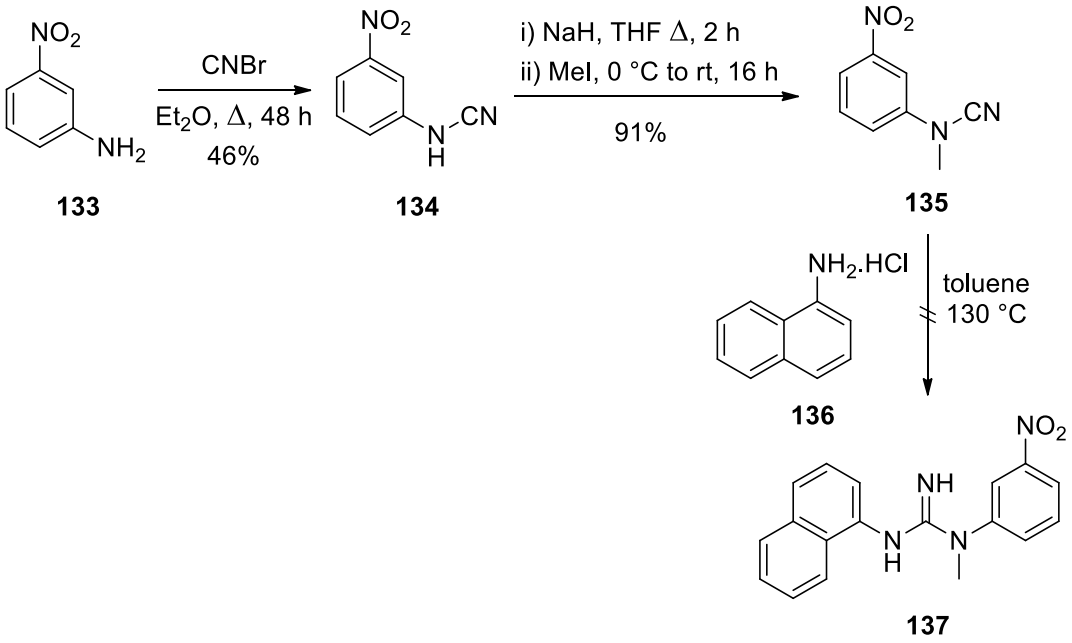
CNS1261 has been shown to have a high binding affinity (K_i = 4.2 nM) and high specificity for the phencyclidine binding site inside the ion channel of NMDA.[96] This is an important binding site as it is only accessible when the NMDA receptor is activated and the ion channel open. CNS1261 (**86**) has been labelled with iodine-125 by an iododestannylation reaction from the organotin precursor **132**, giving the final product in a radioactivity yield of 59% yield (Scheme 64).[96]



Scheme 64. Synthesis of [^{125}I]CNS1261.

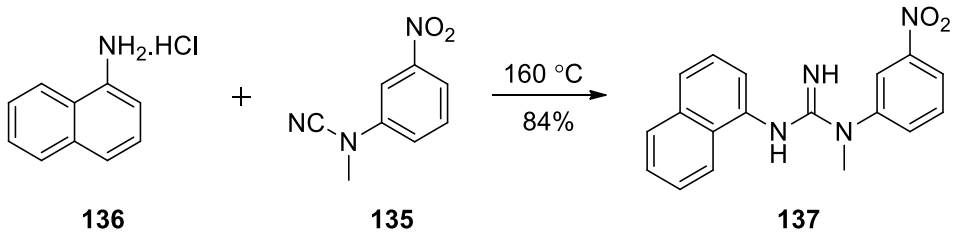
2.5.6.2 Synthesis

In our synthesis, CNS1261 would be prepared from 3-nitroaniline and 1-naphthylamine, allowing for the reduction of the nitro group and the key one-pot diazotisation-iodination reaction to take place as the final steps. As shown in Scheme 65, 3-nitroaniline (**133**) was first reacted with cyanogen bromide to give *N*-(3-nitrophenyl)cyanamide (**134**) in 46% yield, followed by methylation with sodium hydride and methyl iodide to give *N*-methyl-(3-nitrophenyl)cyanamide (**135**) in 91% yield. Attempts to couple cyanamide **135** with 1-naphthylamine hydrochloride (**136**) in toluene were not successful, giving back only starting material after 48 hours at 130 °C.[97]



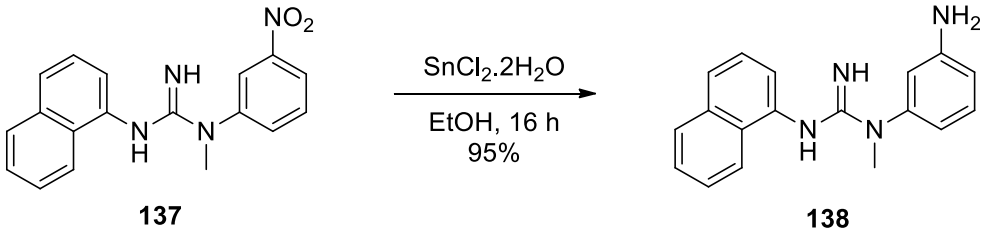
Scheme 65. Attempted synthesis of guanidine 137.

The reaction of 1-naphthylamine hydrochloride (**136**) and *N*-methyl-(3-nitrophenyl)cyanamide (**135**) was next attempted neat at 160 °C, as per a method by Dumont and co-workers,[98] which successfully gave the guanidine **137** in 84% yield after 3 hours (Scheme 66).



Scheme 66. Synthesis of guanidine 137 by neat reaction at 160 °C.

The final two steps in the synthesis were reduction of the nitro group, followed by the one-pot diazotisation-iodination reaction. Reduction of the nitro group with tin(II) chloride dihydrate gave the amine **138** in 95% yield (Scheme 67).

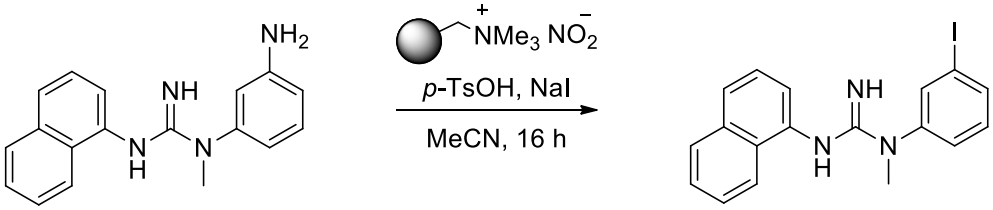


137 138

Scheme 67. Reduction of nitro group to give amine 138.

The one-pot diazotisation-iodination reaction of amino precursor **138** gave the iodinated product **86** in the highest yield of 58% at room temperature for 16 hours (Table 9, entry 1). The reaction was also attempted at 40 °C for 16 hours, which gave a similar yield of 54% (Table 9, entry 2), and 60 °C, with the higher temperature giving a lower yield of 33% (Table 9, entry 3).

Table 9. Conditions for iodination of CNS1261.



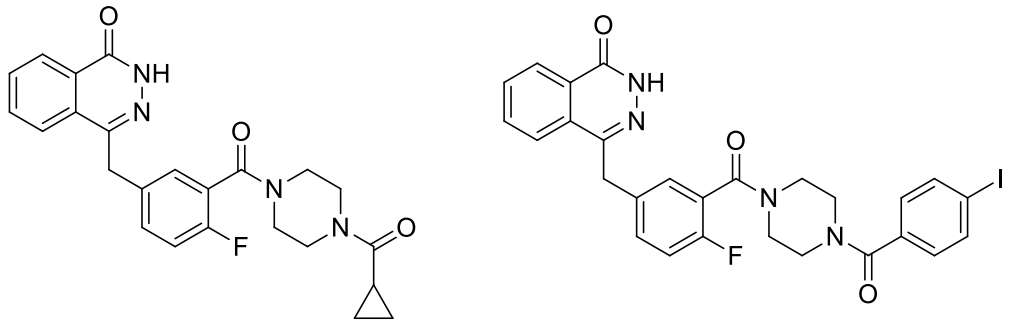
138 86

Entry	Temperature (°C)	Yield (%)
1	rt	58
2	40	54
3	60	33

2.5.7 Synthesis of a ligand for PARP-1

The final compound investigated was an analogue of Olaparib (**139**) (Figure 8). Olaparib is a drug for certain cancers, which blocks the growth of cancer cells by acting as an inhibitor of poly(ADP-ribose) polymerase-1 (PARP-1).[99] PARP-1 is an important target for cancer treatment and imaging of cancer, due to its involvement in the repair of DNA single-strand breaks (SSB). After detecting a SSB, PARP-1 will bind to the DNA and begin the synthesis of a poly(ADP-ribose) chain. It does this by addition of ADP-ribose in a posttranslational modification process known as ADP-ribosylation. This poly(ADP-ribose) chain can then signal

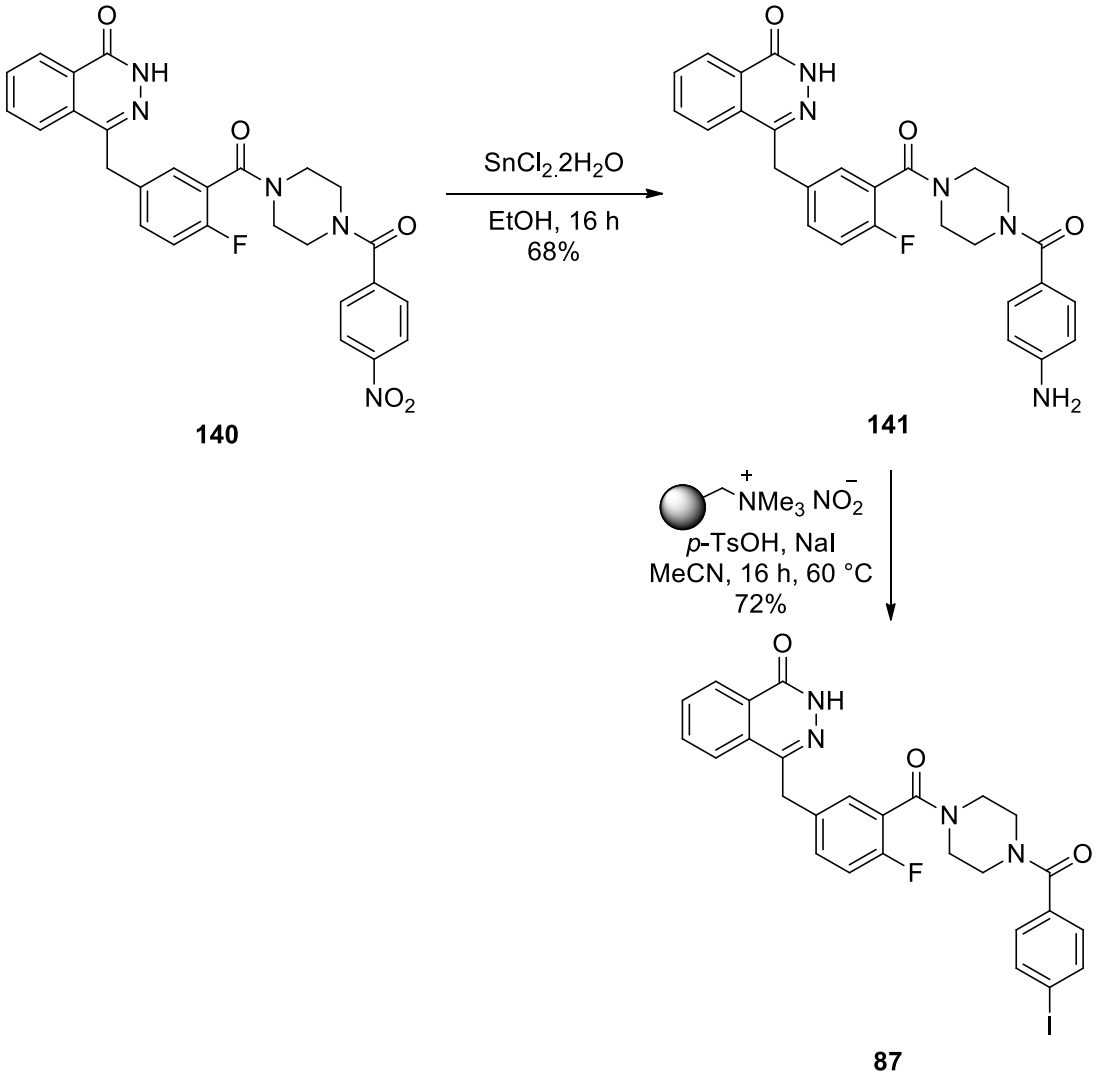
for base excision repair (BER) to begin. The olaparib analogue **87** had been synthesised previously in the group by Filip Zmuda and developed as a SPECT imaging agent of PARP-1.[100]



Olaparib (139) **87**

Figure 8. Olaparib and the imaging agent analogue 87.

The nitro precursor **140** was available from Filip Zmuda's previous synthesis. The reduction of the nitro group of **140** with tin(II) chloride dihydrate, as for the previous targets, gave the aniline precursor **141** in 68% yield (Scheme 68). The one-pot diazotisation-iodination reaction proceeded to give iodinated product **87** in 72% yield, after 16 hours at 60 °C. The reaction may proceed at room temperature, but was not optimised due to the small amount of nitro precursor **140** available.



Scheme 68. Iodination of oliparib analogue 87 for imaging of PARP-1.

2.6 Radioiodination

There are four isotopes of iodine that are currently used as therapeutic agents in medicine (Table 10). Iodine-123 and iodine-125 are gamma-emitting radioisotopes that are used as nuclear imaging tracers. Iodine-123 has a half-life of 13 hours and is used in clinical in vivo SPECT imaging.[1] Iodine-125 is more commonly used in preclinical, in vitro measurements due to its longer half-life of 59 days.[101] Iodine-124 on the other hand can be used for PET imaging. Although it primarily decays by electron capture, ~25% of decay is by positron emission. It is mainly used to image the thyroid using PET, but can also be used as a PET radiotracer with a longer half-life than typical PET radionuclides.[102] Lastly, iodine-131 decays by beta minus decay, where a neutron is converted to a

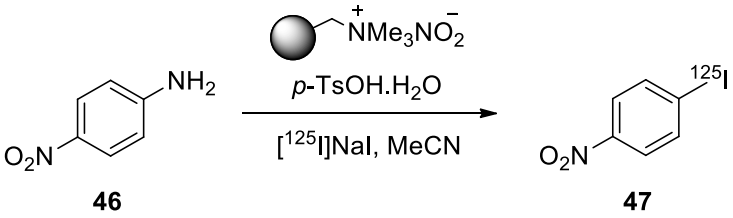
proton with release of an energetic electron. It can be used in imaging and radiation therapy where tissue damage is desired, for example for the treatment of hyperthyroidism or certain cancers.[103]

Table 10. Imaging isotopes of iodine.

Isotope	Half-life ($t_{1/2}$)	Mode of decay	Product of decay
^{123}I	13 h	Electron capture	^{123}Te
^{124}I	4.2 days	Electron capture/ β^+	^{124}Te
^{125}I	59.4 days	Electron capture	^{125}Te
^{131}I	8.0 days	β^-	^{131}Xe

The iodination reaction was shown to be general and gave high yields for a number of more complex imaging agents. The next stage in the project was to develop the reaction for iodine-125 incorporation. The translation to radiochemistry, using the radioactive nuclide, usually requires alteration of the method. The small scale of radiochemical procedures can alter expected behaviour. Initially, 4-nitroaniline (**46**) was used as the substrate to optimise the reaction conditions with iodine-125. Standard conditions from the developed non-radioactive iodination reaction with iodine-127 were first attempted, with sodium [^{125}I]iodide as the limiting reagent. The highest radiochemical yield of 4-[^{125}I]iodonitrobenzene (**47**) was given when 0.5 mg of substrate in 200 μL of solvent was used, with three equivalents of both *p*-toluenesulfonic acid and polymer-supported nitrite, stirring for 2 hours at room temperature (Table 11, entry 1). The reaction mixture was removed from the reaction vial after 2 hours with syringe and injected onto the analytical HPLC. The use of the polymer support allows for minimum work up, with this left behind in the reaction vial. The reaction gave an excellent radiochemical yield of 93%. Decreasing the reagent loading did not affect the radiochemical yield considerably (Table 11, entries 2 and 3). Different reaction temperatures and other loadings of *p*-toluenesulfonic acid and polymer-supported nitrite were also investigated in the reaction. Increasing the temperature resulted in lower radiochemical yield, likely due to the formation of the phenol by-product (Table 11, entries 4 and 5). The reaction was also checked after 1 hour (Table 11, entry 6), but only gave a radiochemical yield of 37%, showing the 2 hours to be necessary under these reaction conditions.

Table 11. Optimisation of the one-pot diazotisation-radioiodination of 4-nitroaniline.



46 47

Entry	Concentration	Equiv. of reagents	Temperature (°C)	Time (h)	RCY (%)
1	0.5 mg/200 µL	3	20	2	93
2	0.5 mg/200 µL	2	20	2	83
3	0.5 mg/200 µL	1	20	2	86
4	0.5 mg/200 µL	3	40	2	65
5	0.5 mg/200 µL	3	60	2	54
6	0.5 mg/200 µL	3	20	1	37

The reaction with 4-nitroaniline (**46**) was repeated under the same optimum conditions and was also found to be reproducible, with a radiochemical yield of 86 ± 8% (n = 6). The reactions gave a particularly clean radio-HPLC (Figure 9), with no sign of radioactive side products.

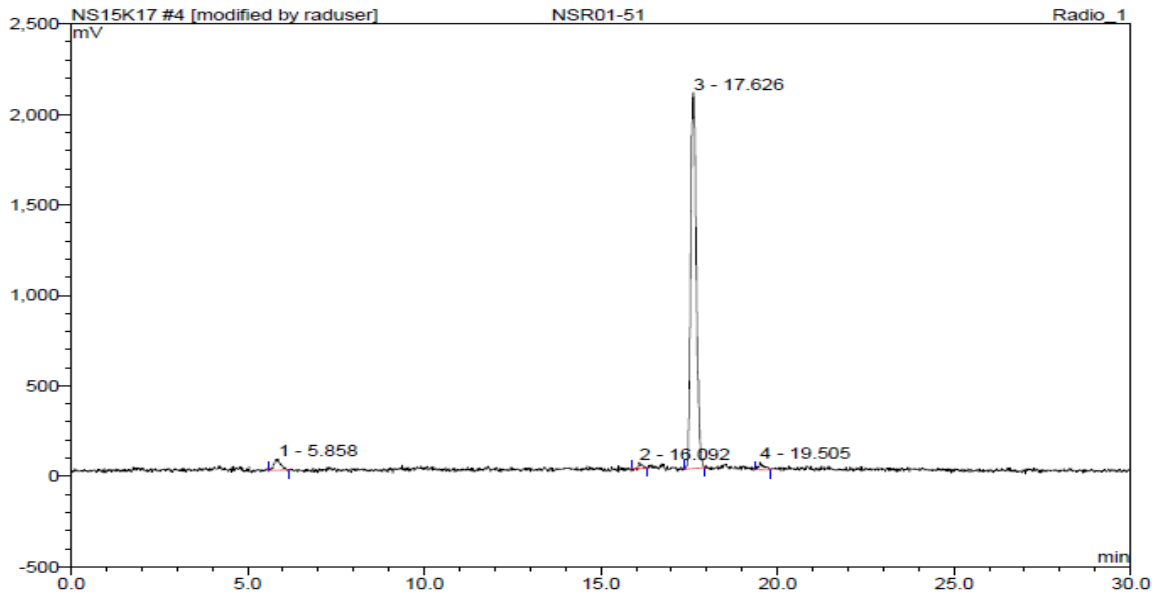
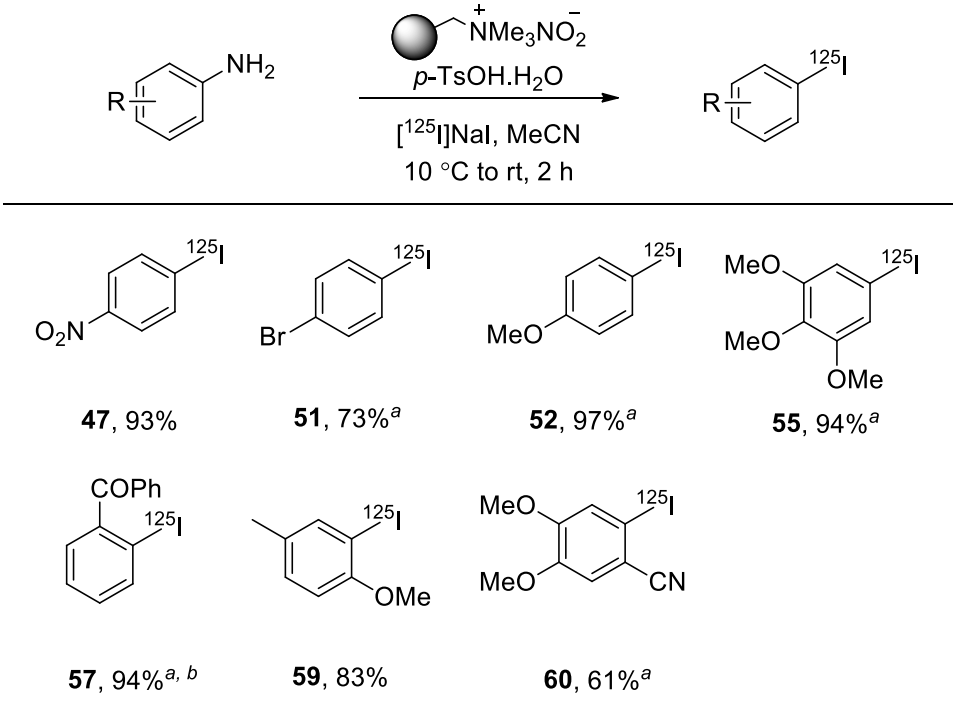


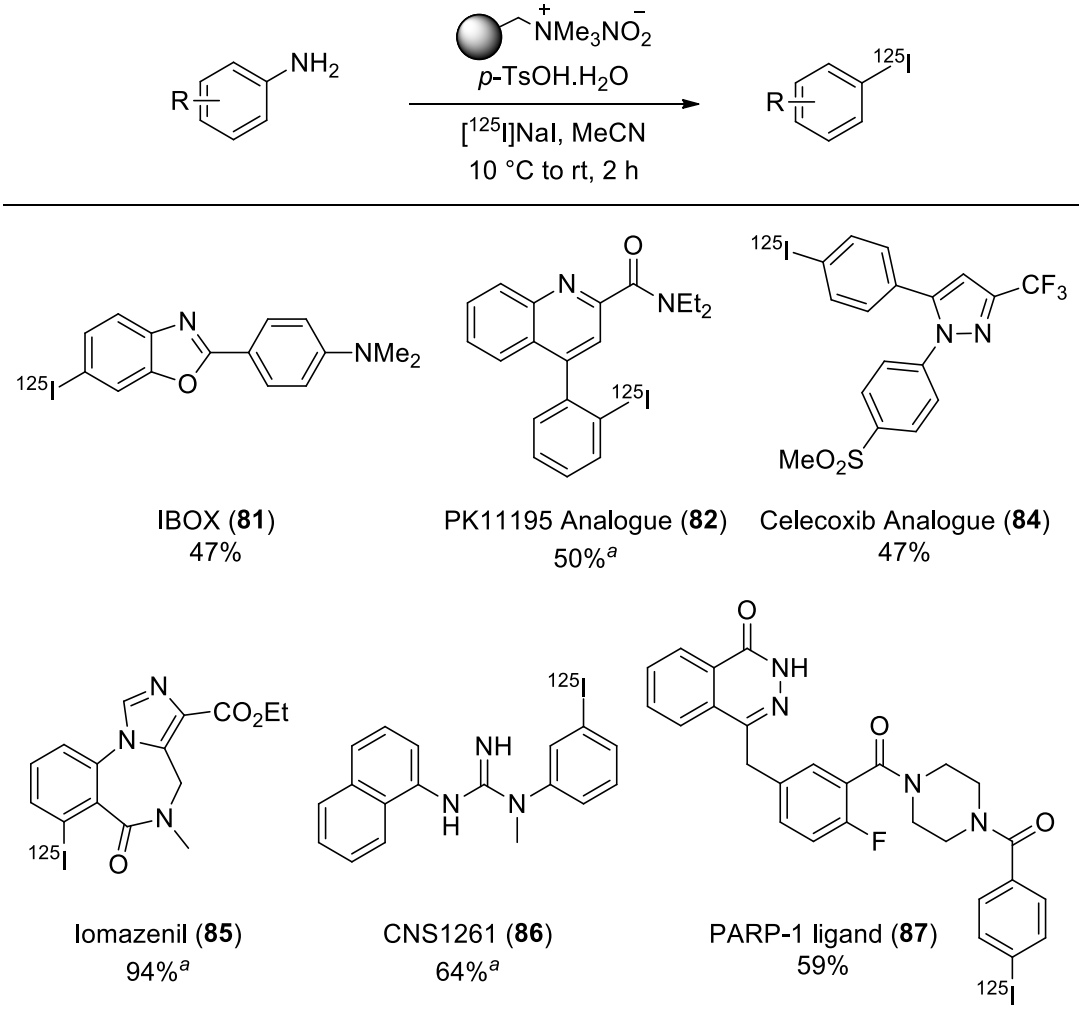
Figure 9. Analytical radio-HPLC of the reaction mixture from the radioiodination of 4-nitroaniline.

The optimised radioiodination reaction was evaluated for the preparation of a number of substrates (Scheme 69). Electron-deficient and electron-rich multi-substituted aryl compounds were converted in good to excellent radiochemical yields. The use of six equivalents of *p*-toluenesulfonic acid and polymer-supported nitrite was found to increase the radiochemical yield for a number of substrates that gave lower yields using standard conditions (Scheme 69, **51**, **52**, **55**, **57** and **60**). For example, 4-[^{125}I]Iodobromobenzene (**51**) only gave an 8% radiochemical yield under standard conditions, however this could be increased to 73% with six equivalents of reagents. Only two substrates required further optimisation. 4-[^{125}I]Iodoanisole (**52**) was prepared in 34% radiochemical yield under standard conditions. Six equivalents of *p*-toluenesulfonic acid and polymer-supported nitrite increased the radiochemical yield to 84%, however the highest radiochemical yield (97%) was achieved when the reaction was conducted at 40 ºC. 2-[^{125}I]Iodobenzophenone (**57**) gave a radiochemical yield of 70% under the standard conditions, with the highest radiochemical yield (94%) when the reaction time was increased to four hours.



Scheme 69. Substrate scope for one-pot diazotisation-iodination reaction with sodium [^{125}I]iodide. Standard conditions were 3 eq. of polymer-supported nitrite/*p*-TsOH. [a] 6 eq. polymer-supported nitrite/*p*-TsOH were used. [b] Reaction required 4 hours.

A number of SPECT imaging agents were also successfully labelled with iodine-125 (Scheme 70). Six equivalents of *p*-toluenesulfonic acid and polymer-supported nitrite were again used as the optimum conditions for all synthesised SPECT imaging agents. The reaction could be performed at room temperature for several of the substrates. For those that gave modest radiochemical yields at room temperature, increasing the reaction temperature to 60 °C gave higher radiochemical yields (Scheme 70, **82**, **85** and **86**).



Scheme 70. Radioiodination of imaging agents with sodium [^{125}I]iodide. [a] Reaction was performed at 60 °C.

The SPECT imaging agent [^{125}I]iomazenil (**85**) gave a particularly high radiochemical yield of 94%, with a clean radio-HPLC (Figure 10). The methodology was also shown to be reproducible, with a radiochemical yield for [^{125}I]iomazenil (**85**) of 89 ± 8% (n = 9).

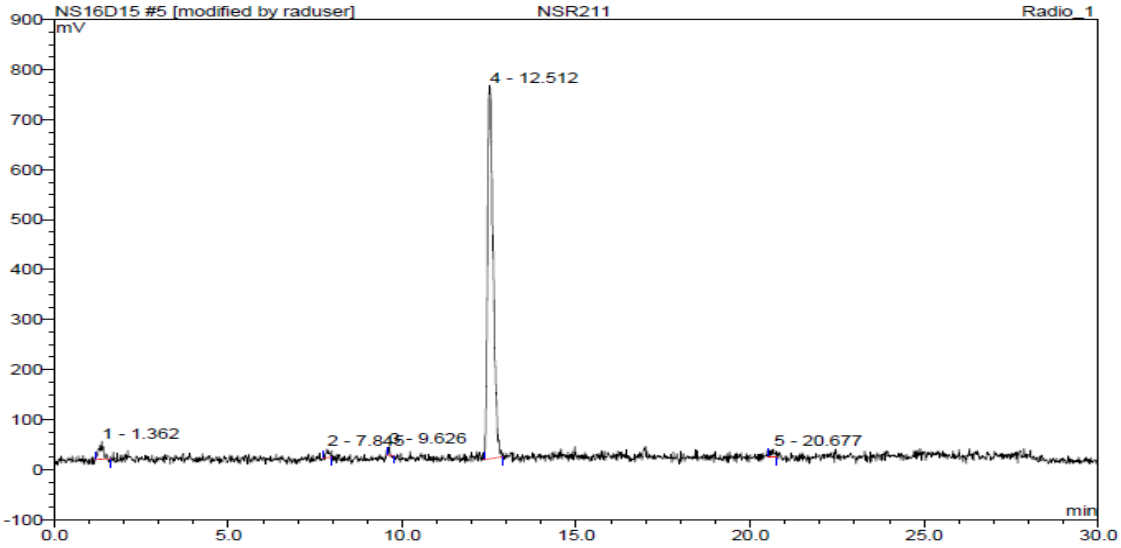
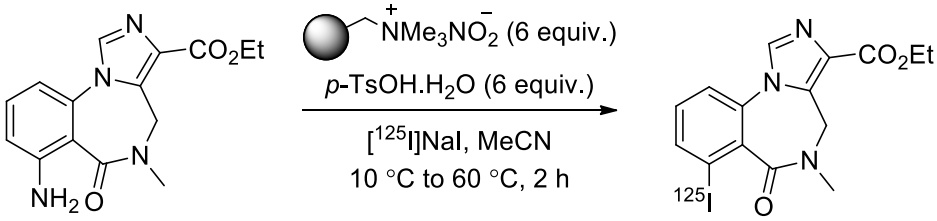


Figure 10. Radio-HPLC trace for [^{125}I]iomazenil.

Preparative runs using 6–7 MBq of sodium [^{125}I]iodide gave [^{125}I]iomazenil (**85**) in 75 ± 9.9% (n = 2) radioactivity yield after HPLC purification, in 3.5 hours from start of synthesis to end of formulation (Scheme 71). The molar activity of [^{125}I]iomazenil (**85**) was calculated from the UV-HPLC product peak in the reaction mixture, calculated against a UV concentration response curve which was prepared using non-labelled iomazenil. The molar activity was found to be 16.2 ± 1.22 GBq/μmol at the end of synthesis. Quality control was performed on a semi-preparative HPLC and the radiochemical purity was calculated at >99%.



131 **85**

Radioactivity yield = 75 ± 9.9% (n = 2)
Radiochemical purity > 99% (n = 2)
Molar activity = 16.2 ± 1.22 GBq/μmol (n = 2)

Scheme 71. Optimised conditions for labelling of [^{125}I]iomazenil.

Having shown that the reaction of **85** with iodine-125 worked well and gave high radiochemical yield and purity, the method was investigated with iodine-123, which would give a new synthesis for the preparation of [^{123}I]iomazenil for clinical applications. The radioiodination reaction was performed using the same

optimised conditions for iodine-125 labelling of **85** shown in Scheme 71. Using no-carrier-added sodium [^{123}I]iodide (30–40 MBq), the reaction resulted in a messy radio-HPLC with a number of peaks, which looked as though decomposition may have taken place. The [^{123}I]iomazenil product could be purified by HPLC and formulated, with an end of synthesis radioactivity yield of 22 ± 9% (n = 4). The radiochemical purity after HPLC purification was still high (>99%). The molar activity was high (>298 ± 42 GBq/μmol), however as the amount of [^{123}I]iomazenil produced fell below the limit of detection of the UV detector for this particular compound (<6.1 × 10^{-5} μmol), an absolute value for molar activity could not be determined. The molar activity for no-carrier-added sodium [^{123}I]iodide is very high, at 8780 GBq/μmol. This means a very small amount of reagent is used in the reaction. Difficulties due to this can be overcome by adding non-radioactive sodium [^{127}I]iodide, known as addition of a carrier. The reaction was attempted with carrier-added sodium [^{123}I]iodide as the lower molar activity due to the addition of stable sodium [^{127}I]iodide would hopefully help the reaction to proceed at higher radioactivity yields. The molar activity for the carrier-added sodium [^{123}I]iodide was still high at >200 GBq/μmol, which, although lower than that for no-carrier-added sodium [^{123}I]iodide (8780 GBq/μmol), it is still higher than the molar activity of no-carrier-added sodium [^{125}I]iodide (96 GBq/μmol).

The results from the initial preparative run using carrier-added sodium [^{123}I]iodide (30–40 MBq) were promising, giving similar results to the work with sodium [^{125}I]iodide, with a radiochemical yield of 94% and an end of synthesis radioactivity yield of 72% after purification and formulation. The problem with the synthesis was that the results were not reproducible, with the next batch of carrier-added sodium [^{123}I]iodide giving a radiochemical yield of 53% and an end of synthesis radioactivity yield of 38%. Overall, the results with carrier-added sodium [^{123}I]iodide were higher than the reaction with no-carrier-added sodium [^{123}I]iodide, giving an end of synthesis radioactivity yield of 52.0 ± 17.8% (n = 3). Quality control was again performed on the analytical HPLC (Figure 11) and the radiochemical purity after formulation was >99% (n = 3). The molar activity was still high (>298 ± 42 GBq/μmol). The amount of [^{123}I]iomazenil produced again fell below the limit of detection of the UV detector for this compound (<6.1 × 10^{-5} μmol), therefore an absolute value for molar activity could not be

determined. One of the reactions performed used 73 MBq carrier-added sodium [^{123}I]iodide, allowed for a more accurate calculation of molar activity. For this reaction, the molar activity was calculated to be 634 GBq/μmol.

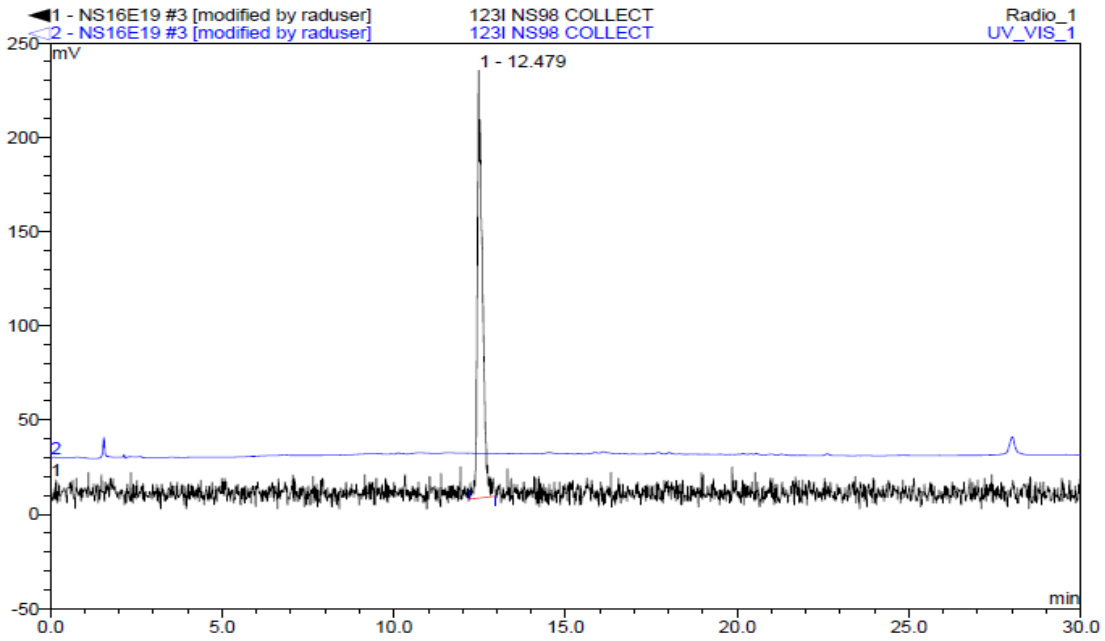


Figure 11. Analytical QC chromatogram of [^{123}I]iomazenil. Radio-HPLC (black) and UV-HPLC (blue) both shown.

2.7 Conclusions

A one-pot diazotisation-iodination reaction was developed for the mild iodination of readily available aromatic amines. This was shown to have a broad substrate scope, with the reaction being compatible with a variety of functional groups. The reaction is also applicable for the iodination of a number of SPECT imaging agents, with a mild reduction of the aromatic nitro group followed by a final-stage mild iodination making this method suitable for radioiodination of these imaging agents for SPECT imaging.

The transformation was successfully adapted for reaction with sodium [^{125}I]iodide, giving high radiochemical yields for a number of substrates and imaging agents, including a new radiosynthesis for the SPECT imaging agents [^{125}I]IBOX (**81**), [^{125}I]iomazenil (**85**) and [^{125}I]CNS1261 (**86**). A preparative run of [^{125}I]iomazenil (**85**) gave the final product in high radioactivity yield of 75 ± 9.9% (n = 2), with high radiochemical purity. The reaction with carrier-added sodium

[^{123}I]iodide for the synthesis of [^{123}I]iomazenil (**85**) gave an end of synthesis radioactivity yield of 52.0 ± 17.8% (n = 3).

2.8 Future Work

Ways of improving the end of synthesis radioactivity yield for the synthesis of [^{123}I]iomazenil could be investigated to give more reproducible results with carrier-added sodium [^{123}I]iodide. The specific activity for carrier-added sodium [^{123}I]iodide when purchased aims to be at >200 GBq/μmol. Addition of extra stable sodium [^{127}I]iodide would lower the specific activity, but would possibly increase the radiochemical yield to similar results observed with sodium [^{125}I]iodide.

The synthesis of [^{125}I]**82** is the first radioiodination of this potential SPECT imaging agent for TSPO. Previous studies in the group has shown this to have a higher affinity (K_i = 5.01 nM) for TSPO than the current standard SPECT imaging agent PK11195, as well as similar physicochemical properties.[104] This can now be explored as a potential SPECT imaging agent for neuroinflammation.

3.0 Synthesis of CNS1261 Analogues

3.1 Introduction

After the successful synthesis of imaging agent CNS1261 (**86**), it was decided to investigate the synthesis of analogues of this imaging agent which may increase selective binding for the NMDA receptor. A number of imaging agents have been designed that bind at the PCP binding site and act as non-competitive antagonists of the NMDA receptor. These include the radioiodinated agent MK-801 (Figure 12, **142**), however its high lipophilicity results in high nonspecific uptake in white matter in the brain.[105] *N*-(1-Naphthyl)-*N'*-(3-iodophenyl)-*N'*-methylguanidine (CNS1261) (**86**) is one of the more promising of these ligands, showing high affinity (K_i 4.2 nM against [^{3}H]MK-801) and high specificity to the NMDA receptor, as well as moderate lipophilicity (Log *D* 2.19).[106] However, CNS1261 (**86**) has been shown to suffer from a considerable amount of nonspecific binding, meaning small changes in receptor availability are unlikely to be detected.[107] There are several groups who have worked on the synthesis and testing of analogues of CNS1261 (**86**) in an attempt to reduce the level of nonspecific binding, or allow imaging with PET by labelling with fluorine-18 or carbon-11. Structure activity relationship (SAR) studies have shown that, for unsymmetrical guanidines, a naphthyl group is beneficial for the potency of the ligand. A number of *N*-(1-naphthyl)-*N'*-aryl-*N*'-methylguanidines have been shown to act at the NMDA receptor, with a 2,5-disubstituted phenyl ring on the other side enhancing this further.[108] Furthermore, a bromo, iodo, trifluoromethyl, methylthio or ethyl group have been shown to be the best substituents on the phenyl ring for enhancing activity, with this being correlated with the substituent size and hydrophobicity. Dumont *et al*[109] found that, for *N*,*N'*-diphenyl derivatives, a *N*-(2-chloro-5-methylthiophenyl) group on one side of the guanidine gave the highest affinity for PCP binding on the NMDA receptor *in vitro*. Some of the more promising ligands developed from this work include CNS5161 (**143**) (K_i 1.87 nM),[106] GMOM (**144**) (K_i 5.20 nM),[109] and GE-179 (**145**) (K_i 2.4 nM)[110] which have all shown promise for PET imaging of the activated NMDA receptor. However, further investigation is necessary before these can be used as PET radioligands in humans.

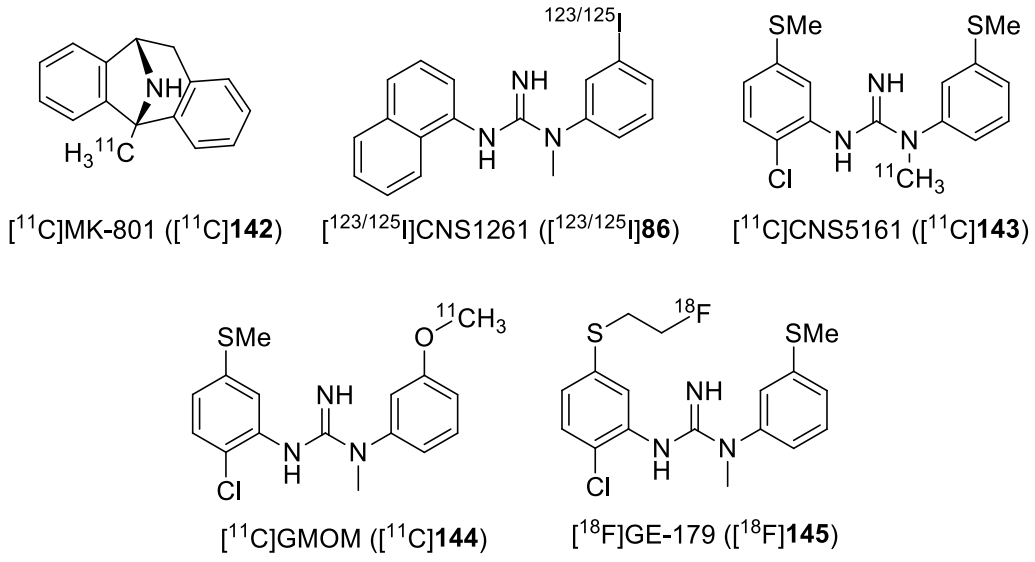


Figure 12. Structures of radiolabelled *N,N'*-diaryl-*N*-methylguanidines.

More recent studies by Windhorst and co-workers[111] also found highest affinity with a (2-chloro-5-methylthiophenyl) group at one side of the guanidine, with a substituent at the 3-aryl position of the other side enhancing this further (Figure 13, column 1). Pike and co-workers[112] have found that affinity for the NMDA receptor was not improved when changes were made to the *N*-naphthyl side of CNS1261, however, alteration of the substituent at the 3-position of the *N'*-phenyl group could lead to higher affinity, with multiple substituents enhancing the binding affinity even further (Figure 13, columns 2 and 3).

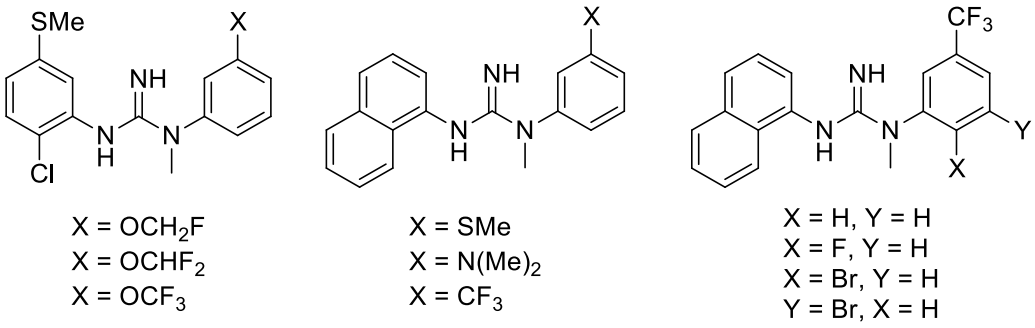


Figure 13. Recent analogues found to give highest binding affinity for NMDA receptor.

3.1.1 Proposed Research

The aim of this project was to generate a small library of novel NMDA inhibitors based on the imaging agent CNS1261. Compounds with the *N,N'*-diaryl-*N'*-methylguanidine general structure were chosen, with the aryl substituents

chosen based on the previously described studies. One side would contain either a *N*-naphthyl group (as shown in Figure 14, analogues **146**, **147** and **148**) or *N*-(2-chloro-5-methylthiophenyl) group (Figure 14, **149**, **150** and **151**) as analogues containing either of these as one side of the guanidine have been shown to give high binding affinity. The second key objective of this project was to show that the strategy of reduction of a nitroaryl group to an amine followed by one-pot diazonium/iodination process could be used to access these compounds both cold and radiolabelled.

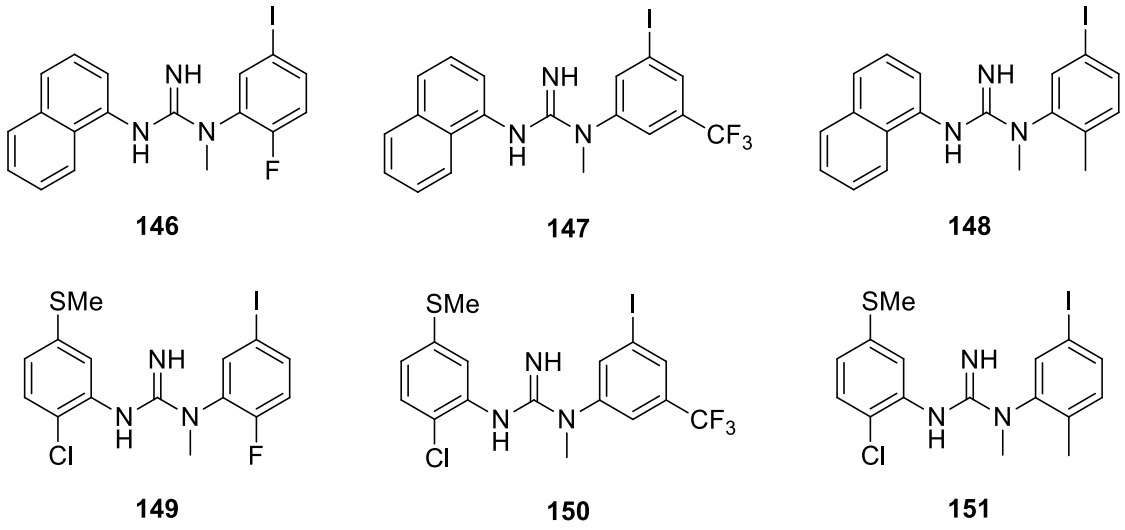


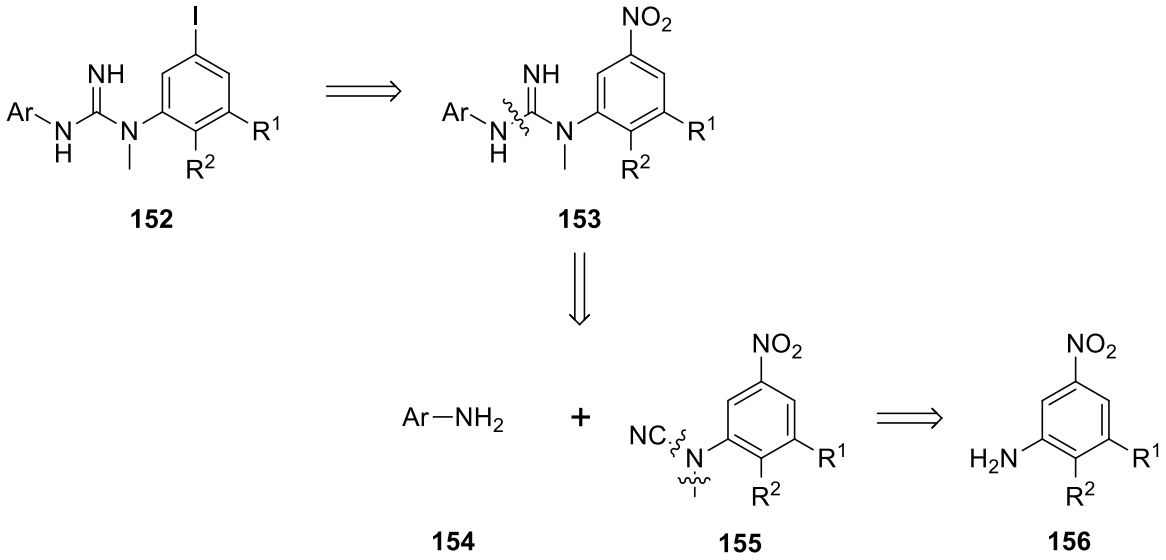
Figure 14. Structure of CNS1261 analogues.

Following the synthesis of a small library of compounds with stable iodine-127, testing to investigate the ligands physicochemical properties and their binding affinity for the NMDA receptor would be investigated. The best analogue/s identified following testing would be radiolabelled and evaluated as a potential radiotracers for SPECT imaging of the NMDA receptor.

3.1.2 Retrosynthetic Analysis

A retrosynthetic analysis of the potential NMDA inhibitors is shown in Scheme 72. The syntheses of these would follow the same method used previously in the synthesis of CNS1261 (**86**). The final step in the synthesis would be the one-pot diazotisation-iodination reaction to enable radioiodination of analogues showing promising physicochemical properties. Therefore, functional group interconversion of the iodine in the target compound **152** would lead to the

nitro precursor **153**. Disconnection of the guanidine as shown would afford the aniline **154** and the *N*-methyl-*N*-arylcyanamide **155**. Finally, disconnection of the *N*-methyl and *N*-cyanide groups would yield the aniline **156**.

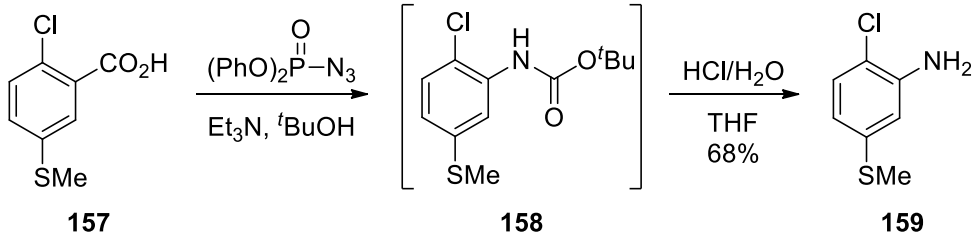


Scheme 72. Retrosynthesis of CNS1261 analogues.

3.2. Synthesis of Analogues

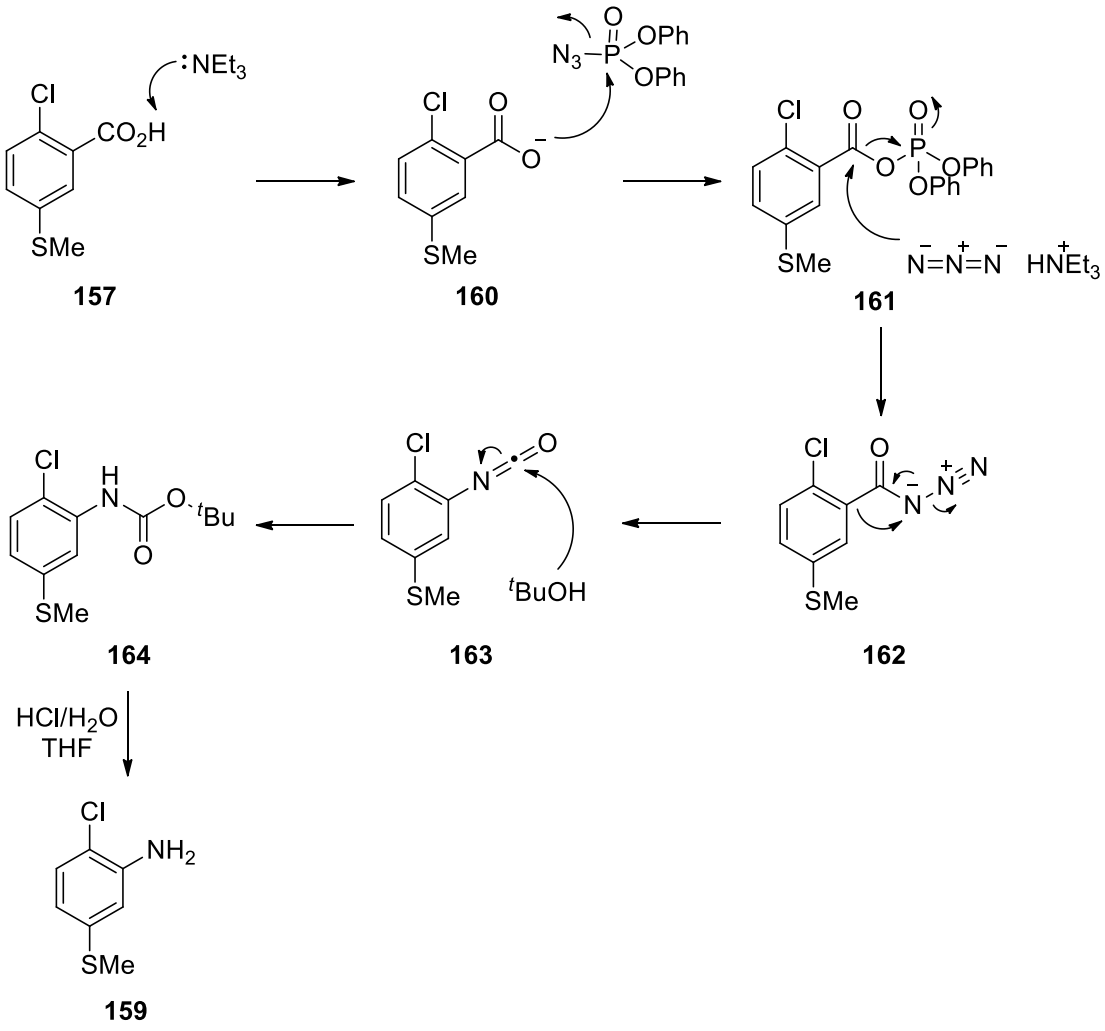
3.2.1. Synthesis of Starting Materials

2-Chloro-5-(methylthio)aniline (**159**) was not commercially available and so was synthesised. This was prepared from 2-chloro-5-(methylthio)benzoic acid (**157**) by reaction with diphenylphosphoryl azide and triethylamine in *t*-butanol as solvent to give the *tert*-butyloxycabonyl (BOC) protected aniline **158** in a modified Curtius reaction (Scheme 73).[113] Immediate removal of the BOC protecting group by 50% hydrochloric acid in tetrahydrofuran in one-pot gave 2-chloro-5-(methylthio)aniline (**159**) in 68% overall yield.



Scheme 73. Synthesis of 2-chloro-5-(methylthio)aniline (159).

The reaction mechanism is shown in Scheme 74. This proceeds by deprotonation of carboxylic acid **157** to give the carboxylate ion **160**, before attack on the phosphorus of diphenylphosphoryl azide to form intermediate **161**. Attack of the carbonyl group by the azide gives acyl azide **162**, which decomposes to isocyanate **163**. *tert*-Butanol then attacks isocyanate **163** to give BOC protected aniline **164**. Addition of aqueous hydrochloric acid deprotects **164** to give the aniline product **159**.

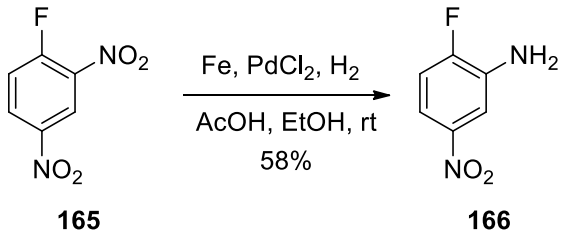


Scheme 74. Mechanism of amine 159 formation from carboxylic acid 157.

3.2.2 2-Fluoro-5-iodophenyl Analogue

The first aniline to be coupled with 1-naphthylamine (**137**) and 2-chloro-5-(methylthio)aniline (**159**) was 2-fluoro-5-nitroaniline (**166**). The fluorine in the molecule could also potentially be used as a labelling site with fluorine-18, allowing for imaging with PET as well as SPECT. The first step would be the

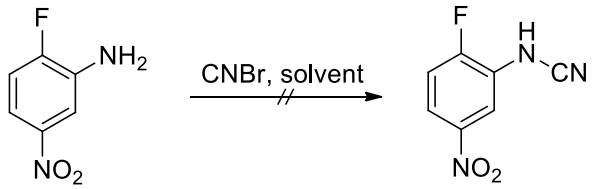
selective reduction of the *ortho*-nitro group over the *para*-nitro group in the commercially available 1-fluoro-2,4-dinitrobenzene (**165**). This was selectively reduced by use of an iron-catalysed hydrogenation method (Scheme 75).[114] The literature reaction used a Parr hydrogenation reactor to control pressure, however bubbling hydrogen through the reaction using a balloon was found to successfully reduce the *ortho*-nitro group. As soon as reduction of the *ortho*-nitro group was complete, reduction of the *para*-nitro group would begin, therefore reaction monitoring was essential. Following the reaction by TLC and quenching this as soon as starting material was converted, after about 2 hours, allowed for the highest yield of 58%.



165 **166**

Scheme 75. Synthesis of 2-fluoro-5-nitroaniline.

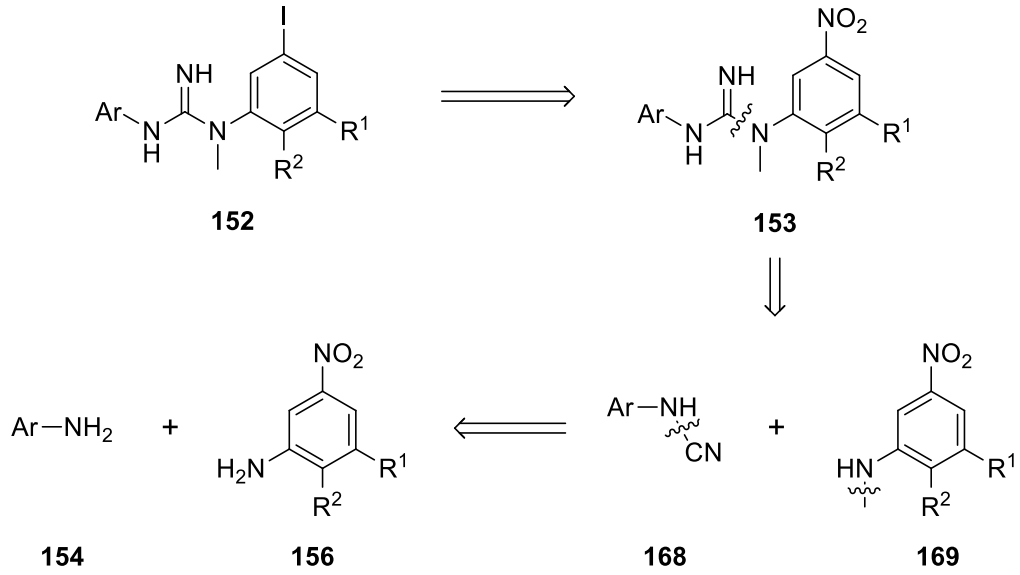
The next step in the synthesis was the cyanation of the amine group (Scheme 76). Reaction of **166** with cyanogen bromide was attempted in various solvents and temperatures, with none giving the desired product **167**.



166 **167**

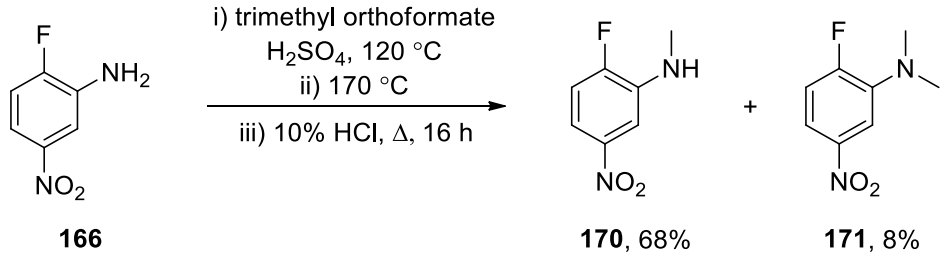
Scheme 76. Attempted synthesis of *N*-(2-fluoro-5-nitrophenyl)cyanamide (167).

A different synthesis was then explored, the retrosynthesis for this shown in Scheme 77. The guanidine disconnection would give cyanamide **168** and *N*-methylaniline **169**. These could again be formed from anilines **154** and **156**.



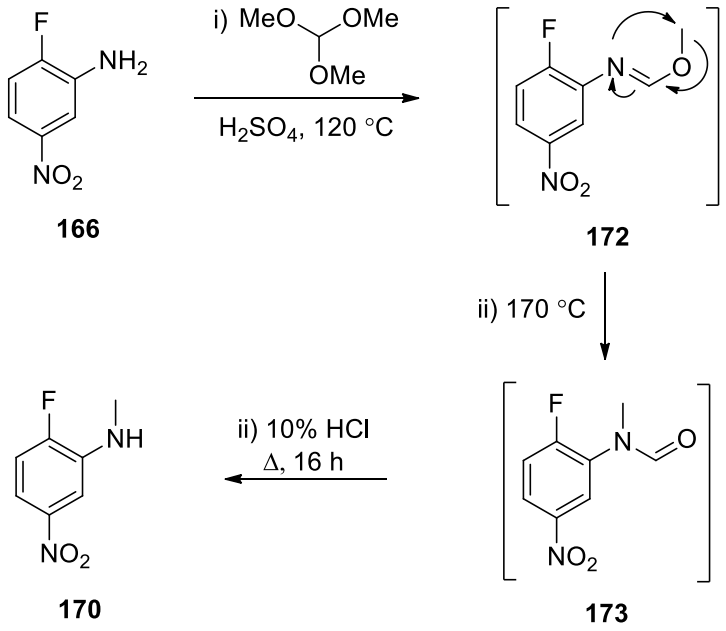
Scheme 77. Alternative retrosynthesis.

The methylation of 2-fluoro-5-nitroaniline (**166**) was achieved using a one-pot method with trimethyl orthoformate and catalytic amounts of sulfuric acid, followed by aqueous hydrochloric acid (Scheme 78).[115] This method was chosen with the aim of reducing any dimethylation of the amine, which was foreseen to be a possible issue with the synthesis. The reaction gave the desired product, *N*-methyl-2-fluoro-5-nitroaniline (**170**), in 68% yield, with only 8% of the dimethylated product **171**.



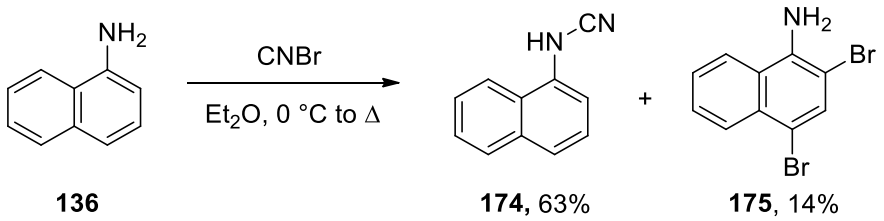
Scheme 78. Methylation of 2-fluoro-5-nitroaniline.

The reaction proceeds by attack of trimethyl orthoformate by the aniline **166** to give intermediate **172**, before heating to 170 °C to effect a sigmatropic rearrangement and give *N*-methylformanilide intermediate **173** (Scheme 79). Hydrolysis of this in aqueous hydrochloric acid gives *N*-methyl-2-fluoro-5-nitroaniline (**170**).



Scheme 79. Methylation reaction of 166 mechanism.

With the methylated amine in place for the right hand side of the coupling, cyanation of 1-naphthylamine (**136**) and 2-chloro-(5-methylthio)aniline (**159**) was required before coupling of the two sides. Cyanation of **136** was achieved by reaction with cyanogen bromide in diethyl ether to give 1-naphthylcyanamide (**174**) in 63% yield (Scheme 80). The reaction also gave 2,4-dibromo-1-naphthylamine (**175**) as a side product, but as this was only in 14% yield this was not seen as a problem.

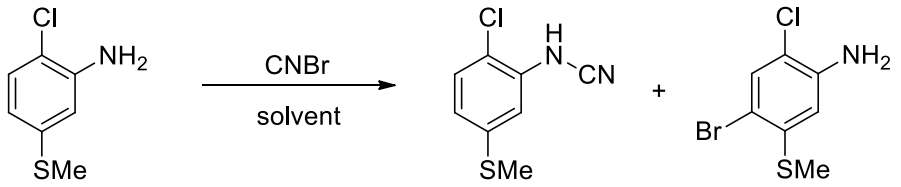


Scheme 80. Cyanation of 1-naphthylamine.

Cyanation of 2-chloro-(5-methylthio)aniline (**159**) was attempted under the same conditions of cyanogen bromide in diethyl ether under reflux. However, these conditions returned only starting material after 3 days (Table 12, entry 1). The reaction was next attempted in tetrahydrofuran under reflux to allow an increase in temperature to push the reaction. This again only resulted in a return of mostly starting material with some decomposition after longer reaction

times (Table 12, entry 2). The reaction was also run in acetonitrile under reflux, to allow for a further increase in temperature to 82 °C. At this temperature the starting material was fully converted in the reaction, but this gave the brominated product **177** in 45% yield (Table 12, entry 3). Search of the literature found a method with cyanogen bromide in water, however this did not specify conditions for the reaction.[113] The reaction was attempted first under reflux, to increase the solubility of the starting material in the solvent. However, this gave a complex spectrum by ^{1}H NMR spectroscopy (Table 12, entry 4). The temperature was next lowered to 40 °C and the reaction stirred for 16 hours, which gave the desired product **176** in 57% yield (Table 12, entry 5).

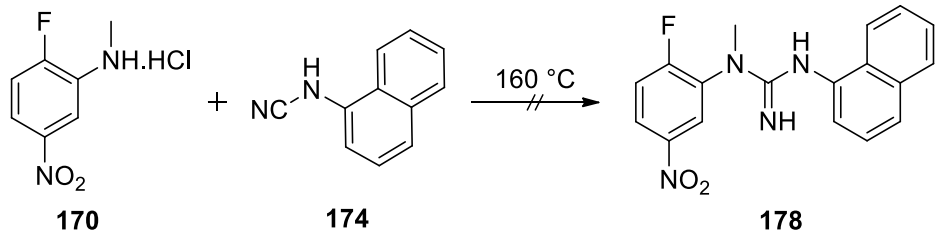
Table 12. Conditions for cyanation of 2-chloro-(5-methylthio)aniline (158).



159 **176** **177**

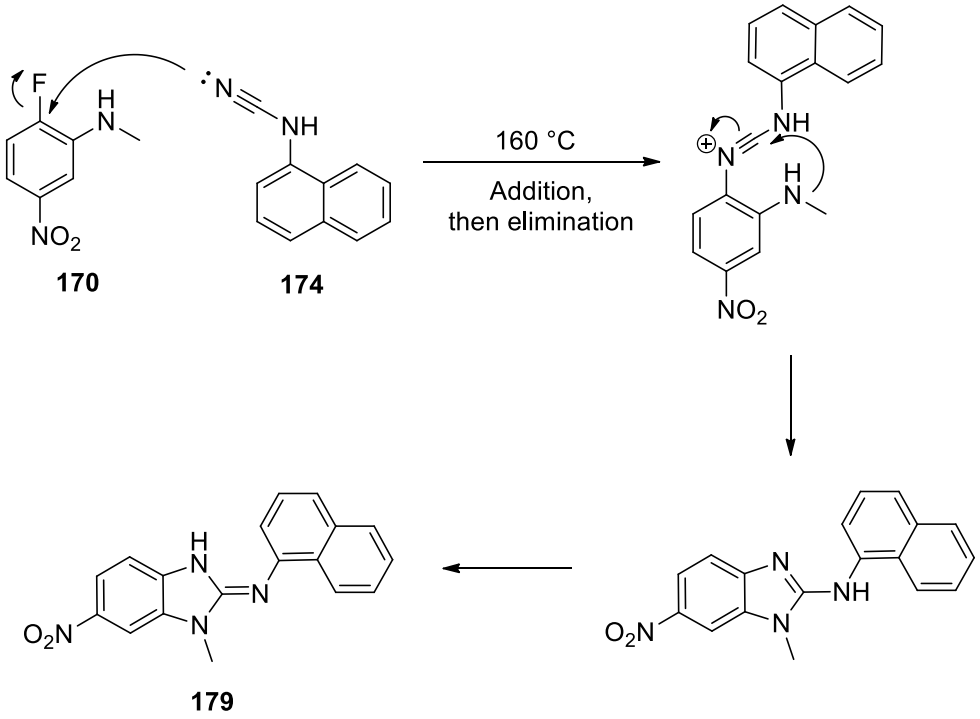
Entry	Solvent	Temperature (°C)	Result (% yield)
1	Et_2O	Reflux (35)	SM only
2	THF	Reflux (66)	SM only
3	MeCN	Reflux (82)	Brominated product **177** (45)
4	H_2O	Reflux (100)	Complex mixture
5	H_2O	40	Product **176** (57)

The coupling reaction between *N*-methyl-2-fluoro-5-nitroaniline (**170**) and 1-naphthylcyanamide (**174**) was next attempted using the same conditions as the reaction for CNS1261 (**86**), neat at 160 °C (Scheme 81). However, the major product in the reaction was not the desired guanidine **178**.



Scheme 81. Attempted coupling reaction between *N*-methyl-2-fluoro-5-nitroaniline (170) and 1-naphthylcyanamide (174).

Full analysis of the product showed loss of the fluorine atom. Due to the *para*-nitro group, the fluorine atom is an excellent leaving group for a nucleophilic aromatic substitution reaction, and as such the benzimidazoline **179** was formed (Scheme 82).



Scheme 82. Formation of benzimidazoline 179.

For SPECT imaging, iodination must be the final step in the synthesis. As we were interested in using the one-pot diazotisation-iodination reaction reaction as the final step in the synthesis, the 2-fluorobenzene analogues **146** and **149** could not be prepared using this method and focus was moved to other CNS1261 analogues.

3.2.3 3-Trifluoromethyl-5-iodophenyl Analogues

A trifluoromethyl group has been shown to be one of the most beneficial for binding affinity to the NMDA receptor. Due to this, an aryl ring containing a trifluoromethyl group was next investigated for coupling with both the 2-chloro-(5-methylthio)aniline group (**159**), to give *N*-(2-chloro-(5-methylthio)phenyl)-*N'*-[3-iodo-5-(trifluoromethyl)phenyl]-*N'*-methylguanidine (**150**) and 1-naphthylamine (**136**) to give *N*-(1-naphthyl)-*N'*-[3-iodo-5-(trifluoromethyl)phenyl]-*N'*-methylguanidine (**147**) (Figure 15).

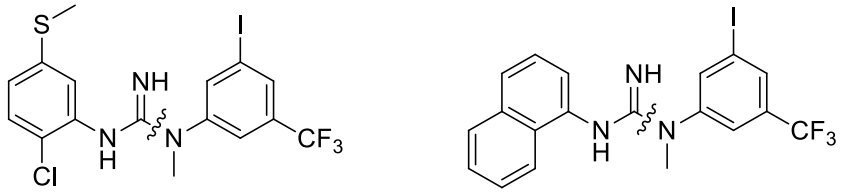
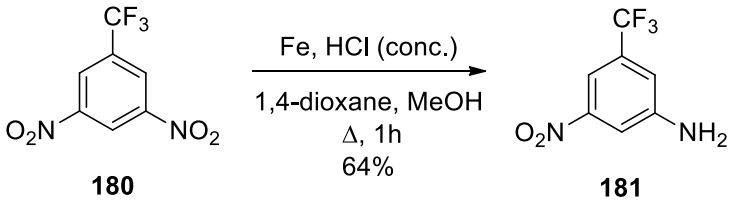


Figure 15. CNS1261 analogues containing a trifluoromethyl group.

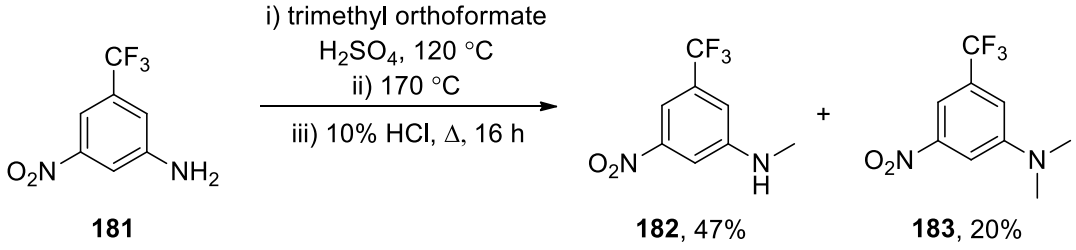
3-Nitro-5-(trifluoromethyl)aniline (**181**) was prepared from the selective reduction of one nitro group from commercially available 3,5-dinitrobenzotrifluoride (**180**). A method was found in the literature for the same analogue which gave the product in 57% yield.[116] 3,5-Dinitrobenzotrifluoride (**180**), concentrated sulfuric acid and iron powder were heated under reflux in 1,4-dioxane and methanol for 1 hour to give 3-nitro-5-(trifluoromethyl)aniline (**181**) in 64% yield (Scheme 83).



Scheme 83. Selective reduction of nitro group.

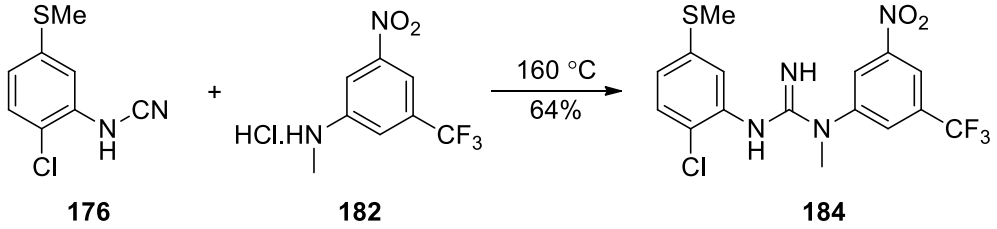
The methylation of 3-nitro-5-(trifluoromethyl)aniline (**181**) was achieved using the same method used for 2-fluoro-5-nitroaniline (**166**) (Scheme 78). Reaction with trimethyl orthoformate in sulfuric acid gave 3-nitro-5-

(trifluoromethyl)aniline (**182**) in 47% yield with 20% of the dimethylated product **183** (Scheme 84).



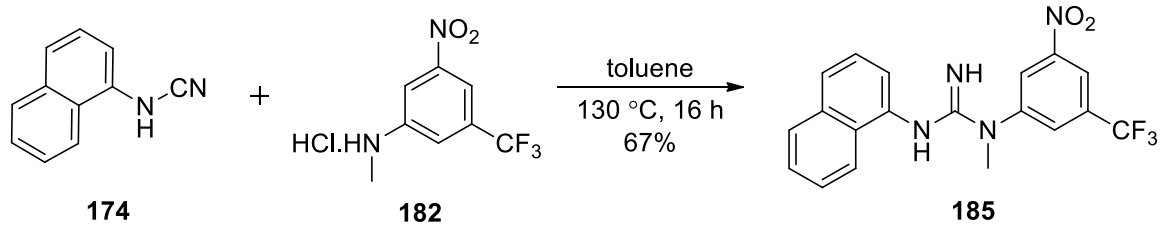
Scheme 84. Methylation of 3-nitro-5-(trifluoromethyl)aniline.

The coupling of 2-chloro-(5-methylthio)cyanamide (**176**) and 3-nitro-5-(trifluoromethyl)aniline hydrochloride (**182**), neat at 160 °C overnight, which gave guanidine product **184** in 64% yield (Scheme 85). However, yields for the coupling were found to not be reproducible, with the repeat reaction under the same conditions giving a yield of 39%.



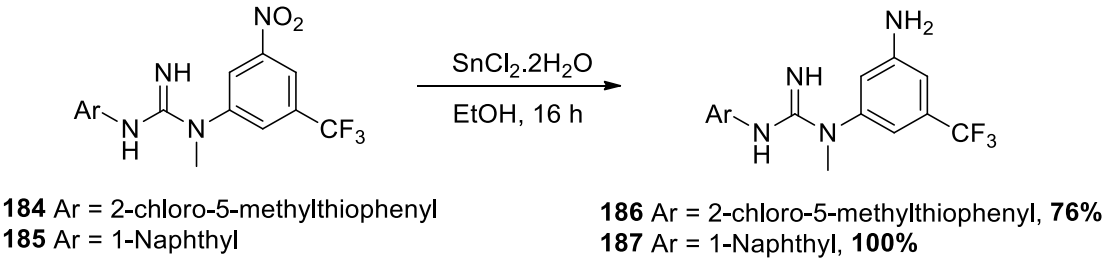
Scheme 85. Guanidine coupling of 176 and 182.HCl.

The coupling of 3-nitro-5-(trifluoromethyl)aniline hydrochloride (**182**) with 1-naphthylcyanamide (**174**) to give guanidine **185** was next investigated. Due to the difficulty in reproducibility with the guanidine coupling for guanidine **184**, it was decided to attempt the reaction in solvent, as this would hopefully allow for less decomposition of the reaction mixture and more reliable reaction yields. The reaction was run in anhydrous toluene at 130 °C overnight and gave guanidine product **185** in 61% yield (Scheme 86). This was also more consistent than the previously used neat method, giving yields of 60% and 67% in the two repeat reactions.



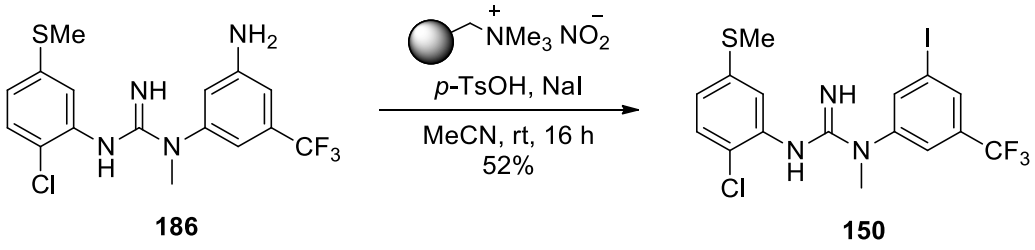
Scheme 86. Guanidine coupling of 174 and 182.HCl.

The final two steps in the synthesis were the reduction of the nitro group with tin(II) chloride dihydrate, followed by the one-pot diazotisation-iodination reaction. The reduction of the nitro group proceeded smoothly for both analogues **184** and **185** to give amine products **186** and **187** in 76% yield and quantitative yield respectively (Scheme 87).



Scheme 87. Reduction of nitro group to give amine precursors 186 and 187.

The one-pot diazotisation-iodination reaction was first investigated for 2-chloro-5-(methylthio)phenyl analogue **186**. Using the same conditions as for the iodination of CNS1261 (**86**), the reaction gave 52% yield of **150** after 16 hours (Scheme 88).

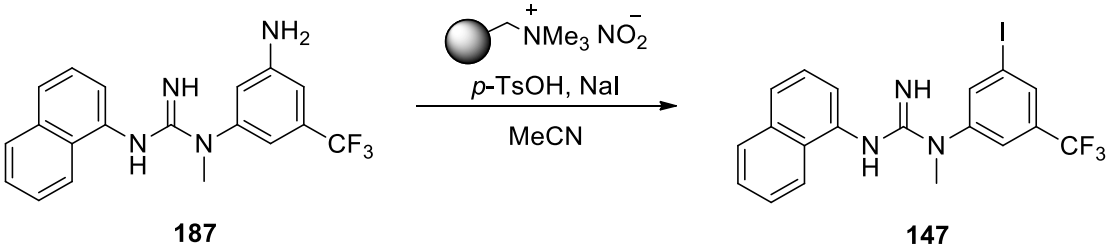


Scheme 88. Reduction and iodination of guanidine 186.

The one-pot diazotisation-iodination reaction of 1-naphthyl analogue **187** was also attempted at room temperature for 16 hours. These conditions gave the

final iodinated product **147** in only 21% yield (Table 13, entry 1). Therefore the reaction temperature was increased to 60 °C for 16 hours which increased the yield slightly to 33% (Table 13, entry 2). Finally, the reaction time was increased to 24 hours at the higher temperature of 60 °C, which gave the highest yield of 43% (Table 13, entry 3).

Table 13. Iodination of guanidine 187.

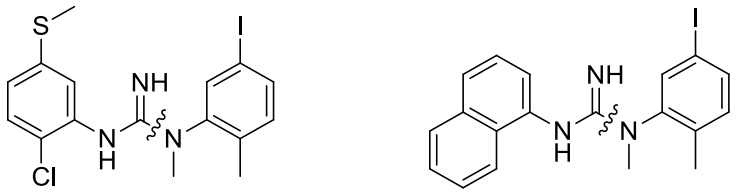


187 **147**

Entry	Temperature (°C)	Time (h)	Yield (%)
1	rt	16	21
2	60	16	33
3	60	24	43

3.2.4 2-Methyl-5-iodophenyl Analogues

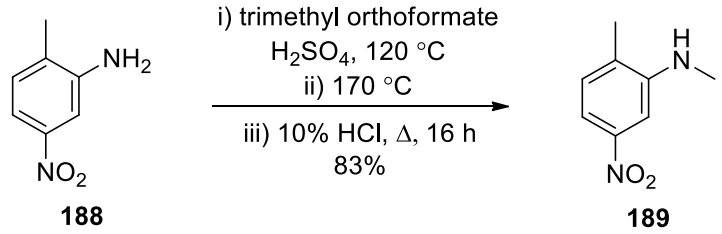
The third aryl ring to be coupled to both cyanamides contained a methyl group in the 2-position of the ring (Figure 16). This would allow for carbon-11 labelling for PET imaging as well as iodine-123 labelling for SPECT if either analogue was shown to have high affinity for the NMDA receptor. Coupling with 2-chloro-(5-methylthio)aniline (**159**) would give *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(2-methyl-5-iodophenyl)-*N'*-methylguanidine (**151**), while the coupling with 1-naphthylamine (**136**) would give *N*-(1-naphthyl)-*N'*-(2-methyl-5-iodophenyl)-*N'*-methylguanidine (**148**).



151 **148**

Figure 16. CNS1261 analogues containing the 2-methyl-5-iodoaryl group.

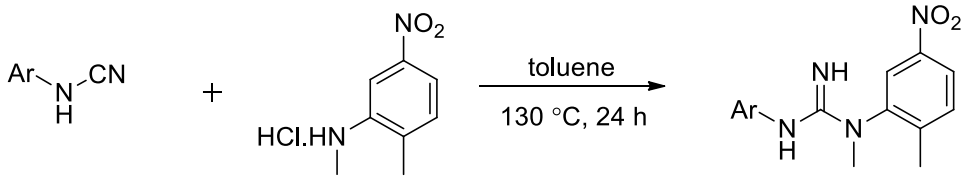
2-Methyl-5-nitroaniline (**188**) was commercially available, therefore the first step in the synthesis was methylation of the aniline starting material **188** (Scheme 89). The same method was used for the methylation as in the previous syntheses, with trimethyl orthoformate and catalytic sulfuric acid neat, at 120 °C for 16 hours, before heating to 170 °C for one hour to enact the rearrangement. This was followed by addition of 10% hydrochloric acid at 100 °C, before heating under reflux for 16 hours. This gave methylated product **189** in 83% yield, with the dimethylated side product observed for other analogues not detected.



188 **189**

Scheme 89. Methylation of 2-methyl-5-nitroaniline.

The coupling of *N*-methyl-2-methyl-5-nitroaniline hydrochloride (**189**) with 2-chloro-5-(methylthio)cyanamide (**176**) in toluene at 130 °C gave guanidine **190** in 78% yield after 16 hours (Scheme 90). The coupling with 1-naphthylcyanamide (**174**) also proceeded smoothly to give guanidine **191** in quantitative yield.



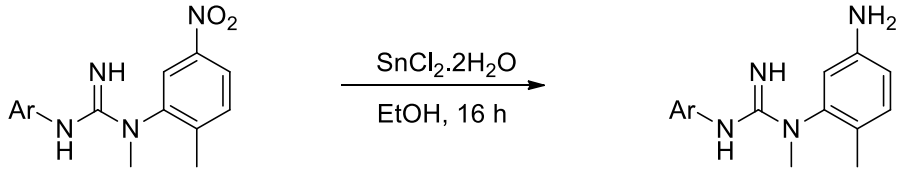
176 Ar = 2-chloro-5-(methylthio)-phenyl
174 Ar = 1-Naphthyl

189

190 Ar = 2-chloro-5-(methylthio)-phenyl, **78%**
191 Ar = 1-Naphthyl, **100%**

Scheme 90. Synthesis of guanidines 190 and 191.

Reduction of the nitro compounds **190** and **191** with tin(II) chloride dihydrate gave the amino precursors **192** and **193** in 66% and 88% yield, respectively (Scheme 91).

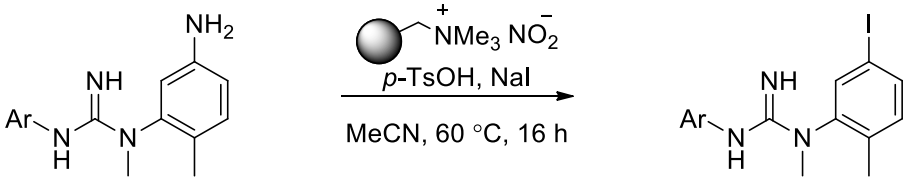


190 Ar = 2-chloro-5-(methylthio)phenyl
191 Ar = 1-Naphthyl

192 Ar = 2-chloro-5-(methylthio)phenyl, **66%**
193 Ar = 1-Naphthyl, **88%**

Scheme 91. Reduction of nitro group to give anilines 192 and 193.

This was followed by the one-pot diazotisation-iodination reaction (Scheme 92). The iodination reaction of 2-chloro-5-(methylthio)phenyl analogue **192** was conducted at 60 °C for 16 hours which gave the final iodinated product **151** in 77% yield. The iodination reaction of the 1-naphthyl analogue **193** was first attempted at room teperature for 16 hours. These conditions gave the iodinated product **148** in only 26% yield. The reaction temperature was then increased to 60 °C for 16 hours which increased the yield of **148** to 59%.



192 Ar = 2-chloro-5-(methylthio)phenyl
193 Ar = 1-Naphthyl

151 Ar = 2-chloro-5-(methylthio)phenyl, **77%**
148 Ar = 1-Naphthyl, **59%**

Scheme 92. Iodination of anilines 192 and 193.

3.3 Conclusions

Initial attempts to prepare the guanidine targets *via* the same key reaction as that used for the CNS1261 synthesis in Chapter 2.5.6 were not successful due to the failure of the cyanation of 2-fluoro-5-nitroaniline (**166**). Instead, cyanation of the coupling partner allowed for a more efficient synthesis of these cyanamides. The 2-fluorobenzene analogues **146** and **149** were not synthesised as coupling of *N*-methyl-2-fluoro-5-nitroaniline (**170**) and 1-naphthylcyanamide (**174**) gave benzimidazoline **179** as major product. The coupling reactions for the 3-(trifluoromethyl)benzene analogues successfully took place, followed by reduction of the nitro group and the one-pot diazotisation-iodination reaction to give the guanidine products **150** and **147** (Figure 17). The 2-methylbenzene

analogues were also successfully synthesised by this method to give the guanidines **151** and **148**.

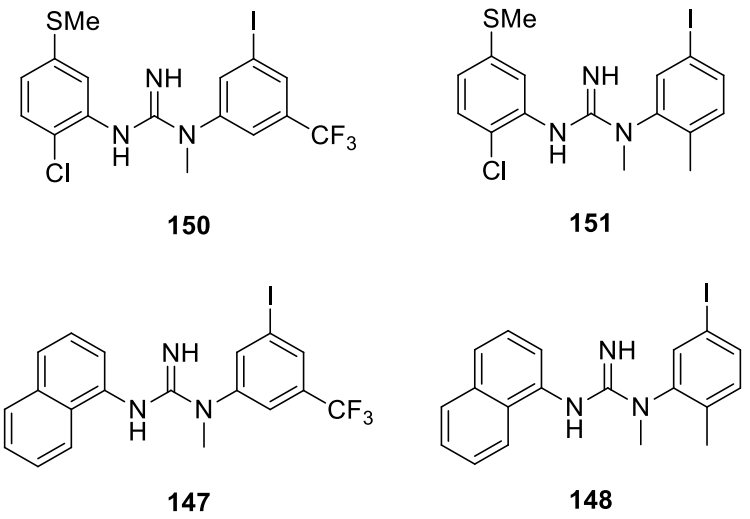


Figure 17. Successfully synthesised CNS1261 analogues.

3.4 Future Work

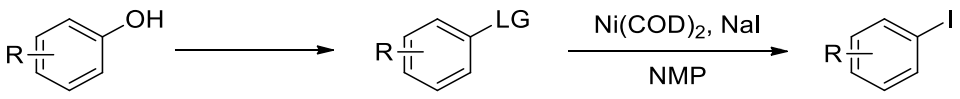
Future work will increase the number of analogues of CNS1261 for testing. Work will then investigate the physicochemical properties of the analogues, including the lipophilicity from the partition coefficient (Log*P*), the permeability from the membrane partition coefficient (K_m) and the plasma protein binding. The binding affinity for the NMDA receptor will also be determined. From these results, the compounds can be ranked relative to CNS1261, and any showing promising properties can be progressed for further testing as potential imaging agents for the NMDA receptor.

4.0 Metal-Catalysed Iodinations

4.1 Nickel-Catalysis

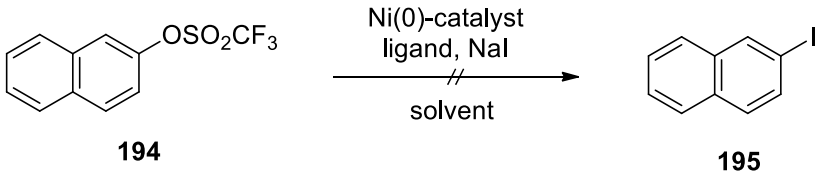
4.1.1 Background/aims

Previously in the group, the nickel-catalysed iodination of aryl bromides was found to undergo complete conversion and thus caused no issues with purification.[117] However, as the transformation is a halogen exchange, if complete conversion was not achieved then separation of the bromide starting material and the iodide product could be problematic. A metal-catalysed iodination from a non-halogen starting material would result in easier separation of starting material from product. Using a more common starting material than an aryl bromide, such as a phenol, would also have the added advantage of expanding the scope of reaction. The ruthenium-catalysed iodination of aryl triflates by Imazaki *et al*[118] is the only metal-catalysed iodination of aromatic rings from sulfonates currently in the literature, to the best of my knowledge. The method however is only applicable to electron-deficient rings. Therefore, the synthesis of aryl iodides from non-halogen starting materials under mild conditions is an important area to study. Following on from the successful radioiodination of a number of aryl bromides using bis(1,5-cyclooctadiene)nickel(0) ($Ni(COD)_2$) as catalyst,[119] it was decided to investigate the use of this highly active catalyst in the iodination reaction with pseudo-halides as leaving groups. The proposed two step iodination reaction is shown in Scheme 93. There are a number of pseudo-halide groups which could be used as intermediates in the reaction, as discussed in Section 1.3. The use of a nickel catalyst in the reaction with a non-halogen starting material makes sense due to the increasing demonstration that nickel is a more active catalyst than palladium for cross-coupling reactions with phenol derived pseudo-halides.[120]



Scheme 93. Metal-catalysed Iodination Reaction.

Previously, 2-naphthyl triflate (**194**) was prepared in the group by Alasdair Cant and the $Ni(COD)_2$ catalysed iodination method was attempted for the conversion of this to the corresponding iodide (Scheme 94). However, no conversion to 2-iodonaphthalene (**195**) was detected. Various temperatures, nickel catalysts, ligands and solvents were also attempted in the reaction, but the iodinated product **195** was not detected in any of the reactions. After the lack of success with the triflate group, a number of alternative leaving groups were investigated in the reaction.



Scheme 94. Attempted synthesis of 193 from 2-naphthyl triflate 192.

4.1.2 Nonafluorobutanesulfonate leaving group

Sulfonates are commonly used substrates for nucleophilic substitution reactions and metal-catalysed cross-coupling reactions, due to the sulfonate ion (RSO_3^-) being an excellent leaving group.[121] Triflates (**196**) also have a strongly electron-withdrawing trifluoromethyl group, which reduces electron density at the adjacent carbon atom to the sulfonate. More recently, nonafluorobutanesulfonates (nonaflates, **197**), which have a C_4F_9 perfluoroalkyl chain, have been shown to be better leaving groups in a number of cross-coupling reactions than triflates.[122] It is proposed that the additional fluorine atoms increase the electron withdrawing effect of the perfluoroalkyl chain even more than in the case of the triflate group. Nonaflates are easily prepared by the reaction of a nucleophile with nonafluorobutanesulfonyl fluoride, which is a cheaper reagent than reagents commonly used for the synthesis of triflates.

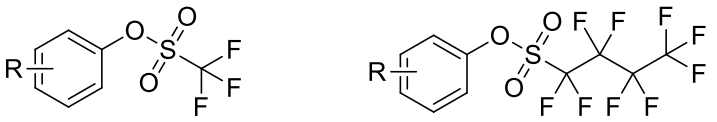
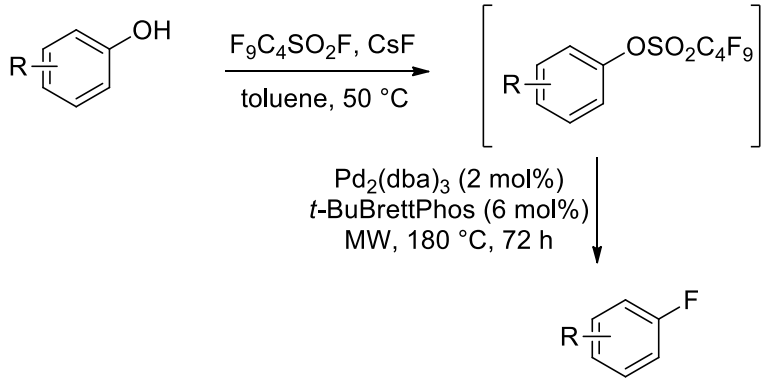


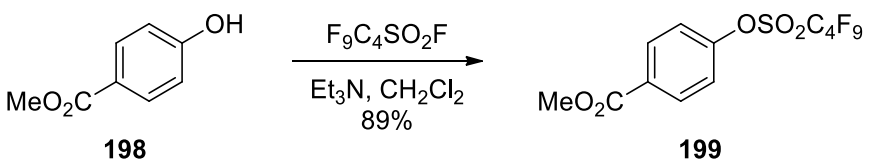
Figure 18. Triflate and Nonaflate leaving groups.

Work by Larhed and co-workers[123] examined the use of nonaflates as leaving groups in a one-pot, two-step palladium-catalysed aryl fluorination reaction (Scheme 95). The reaction was only applicable to a small substrate scope and could not be applied to electron-rich substrates or substrates containing protic functionalities. Another limitation of the reaction was that only aryl fluorides could be prepared using this method, with low conversion (>10%) of aryl chlorides, only traces of aryl bromides and no reactivity for aryl iodides. This is the first example of aryl nonaflates being used as substrates in halogenation reactions.



Scheme 95. Palladium-catalysed fluorinations using a nonaflate leaving group.

Based on the Larhed work, we decided to investigate the combination of aryl nonaflate starting materials and nickel catalysts in an iodination reaction. The reaction of methyl 4-hydroxybenzoate (**198**) with nonafluorobutanesulfonyl fluoride and triethylamine as base gave methyl 4-nonafluorobutanesulfonoxybenzoate (**199**) in 89% yield (Scheme 96). This substrate was chosen as the electron-withdrawing *para*-methyl ester group should activate the ring towards the oxidative addition step in the synthesis.

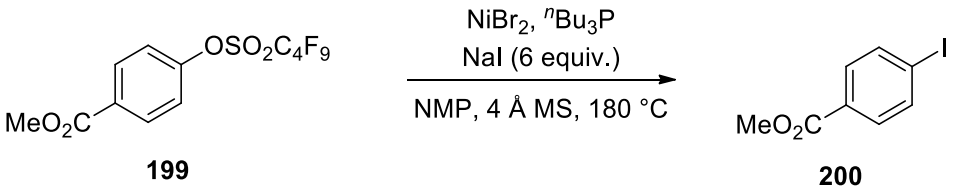


Scheme 96. Synthesis of methyl 4-nonafluorobutanesulfonoxybenzoate (199)

The iodination reaction was then attempted with nickel(II) bromide (10 mol%), with *n*-tributylphosphine ligand (25 mol%) to reduce this in situ to the required

nickel(0) catalyst. This gave a yield of 14% of **200** after 16 hours at 180 °C (Table 14, entry 1). Increasing the catalyst and ligand loading did not result in an increased yield (Table 14, entry 2). Increasing the time of reaction resulted in almost full conversion of **199** after 120 hours, but this did not result in an increase of iodinated product **200** (Table 14, entries 3 and 4). After 24 hours, an extra 10 mol% nickel(II) bromide catalyst, with 25 mol% *n*-tributylphosphine ligand were added, but after 48 hours there was still no increase in yield (Table 14, entry 5). Lastly, the temperature was reduced as it was believed decomposition may be taking place, however these lower temperatures did not increase the yield, but only worked to decrease the rate of the reaction (Table 14, entries 6 and 7).

Table 14. Screen of conditions for nickel(II) bromide-catalysed iodination.

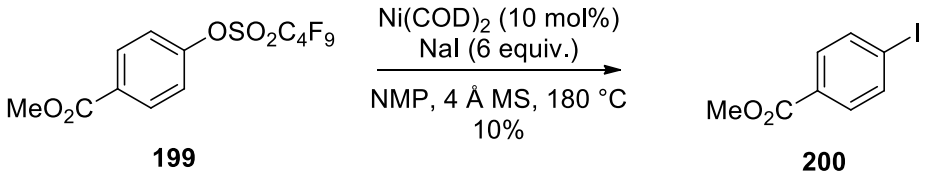


199 **200**

Entry	$NiBr_2$ (mol%)	$^nBu_3P$ (mol%)	Time (h)	Temperature (°C)	Yield 200 (%)	Recovered 199 (%)
1	10	25	16	180	14	19
2	20	50	16	180	6	12
3	10	25	48	180	11	12
4	10	25	120	180	5	8
5	10 + 10	25 + 25	48	180	12	8
6	10	25	16	160	2	23
7	10	25	16	140	0	14

The iodination was also attempted using the nickel(0) catalyst, $Ni(COD)_2$, as it was believed the catalyst would be more active in the reaction. $Ni(COD)_2$ (10 mol%) and sodium iodide were used in the reaction at 180 °C (Scheme 97). $Ni(COD)_2$ is highly sensitive to air and moisture, however initial efforts focussed on running the reaction without use of a glovebox. Following the reaction by TLC showed that nearly full conversion of the starting material had taken place after 20 hours. However, after purification by column chromatography, only 10% yield of the iodinated product **200** was isolated, with similar recovery of starting

material **199**. The major product in the reaction was found to be the nonaflate of 4-hydroxybenzoic acid **201** (Figure 19) in 48% yield. Small levels of methyl 4-hydroxybenzoate (**202**) and 4-iodobenzoic acid (**203**) were also observed in the ^{1}H NMR spectrum, however these were not isolated due to the small scale of reaction. It was believed that **201** would have been the major product in the reactions with nickel(II) bromide also, although this was not isolated in the reactions.



Scheme 97. Nonaflate leaving group in iodination reaction.

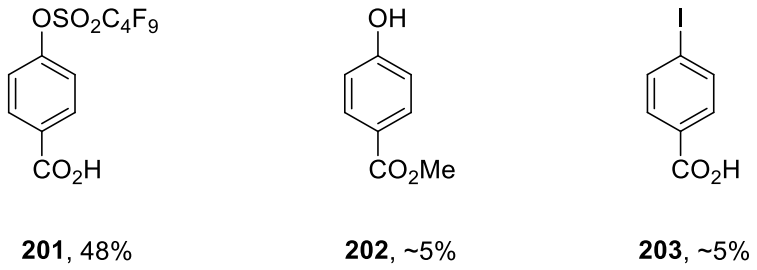


Figure 19. Products formed in the attempted iodination of 199.

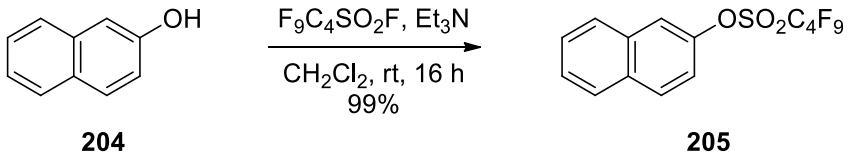
To ensure completely inert conditions for the reaction, sodium iodide and molecular sieves were dried in an oven overnight and the reaction was set up in an inert argon glovebox in a sealed reaction vial. The reaction vial was then stored in a dry atmosphere until use, at which time the nonaflate substrate was added in dry NMP. It was hoped this would increase the conversion to **200**. However, the rigorous exclusion of air and moisture from the reaction did not increase the yield of **200**, or decreased yields of the carboxylic acid **201** (Table 15, entry 2). At high temperatures of 180 °C, side reactions may be expected to take place, so the reaction was repeated at lower temperatures in the hope this would halt the formation of some of the observed side products. The reaction was attempted at 160 °C (Table 15, entry 3) and 140 °C (Table 15, entry 4), however these lower temperatures did not affect the ratio of products, but only decreased the rate of reaction. The reaction was also repeated with addition of

potassium carbonate base to neutralise any acid formed which may be catalysing hydrolysis of ester **199**, however 49% of the nonaflate of 4-hydroxybenzoic acid (**201**) was still isolated (Table 15, entry 5).

Table 15. Conditions for iodination of methyl 4-nonafluorobutanesulfonoxybenzoate (199).

Entry	Base	Temperature (°C)	Time (h)	Glovebox	Recovered 199 (%)	Yield 200 (%)	Yield 201 (%)
1	none	180	20	No	10	5	48
2	none	180	24	Yes	8	10	50
3	none	160	48	Yes	14	8	52
4	none	140	96	Yes	22	5	45
5	K_2CO_3	180	24	Yes	10	10	49

Although the carboxylic acid **201** was formed as the major product in the reaction, it was promising that some iodinated product had been isolated. Therefore, it was decided to investigate the iodination of a substrate with less functionality, to reduce the possibility of side reactions. As such, 2-naphthol (**204**) was converted to 2-naphyl nonaflate (**205**) by reaction with nonafluorobutanesulfonyl fluoride and triethylamine to give the product **205** in 99% yield after 16 hours at room temperature (Scheme 98).



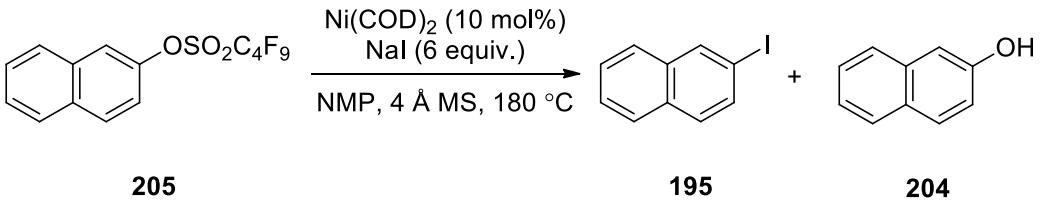
204 **205**

Scheme 98. Synthesis of 2-naphyl nonaflate (205).

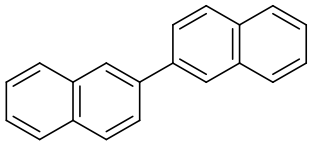
Nonaflate **205** was then dried and used in the reaction with $Ni(COD)_2$ and sodium iodide. A number of reaction conditions were attempted for the iodination reaction, with the key results shown in Table 16. Initial reactions with $Ni(COD)_2$ gave a yield of only 10% of **195** after 48 hours (Table 16, entry 1). The *in situ* reduction of nickel(II) bromide with tributylphosphine as ligand gave no conversion to product **195** (Table 16, entry 2). The rigorous exclusion of air and moisture from the $Ni(COD)_2$ catalyst was found to be key to generation of the iodinated product **195**. Handling the catalyst and dried sodium iodide in an inert argon glovebox increased the yield of **195** to 33% after 24 hours (Table 16, entry

3). However, increasing the time to 96 hours did not increase the yield further (Table 16, entries 4 and 5). Small levels of the phenol product **204** and coupled biaryl product **206** were also observed by ^{1}H NMR spectroscopy, but were not isolated due to the small scale of the reaction.

Table 16. Reaction conditions for the iodination of 2-naphthyl nonaflate (205).



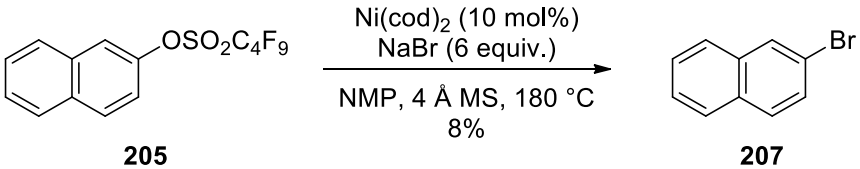
205 **195** **204**



206

Entry	Catalyst	Ligand	Time (h)	Glovebox	Yield 195 (%)	Recovered 205 (%)
1	$Ni(COD)_2$	none	48	No	10	28
2	$NiBr_2$	$^nBu_3P$	24	No	0	34
3	$Ni(COD)_2$	none	24	Yes	33	24
4	$Ni(COD)_2$	none	48	Yes	24	25
5	$Ni(COD)_2$	none	96	Yes	28	18

The reaction was also attempted for the bromination of aryl nonaflates, using sodium bromide (Scheme 99). The reaction of 2-naphthyl nonaflate (**205**) with $Ni(COD)_2$ (10 mol%) and sodium bromide at 180 °C gave only an 8% yield of 2-bromonaphthalene (**207**) after 22 hours, with 50% of the 2-naphthyl nonaflate starting material (**205**) recovered after column chromatography. The bromination reaction was not investigated further after the initial poor result and efforts were focussed on the development of an iodination reaction.

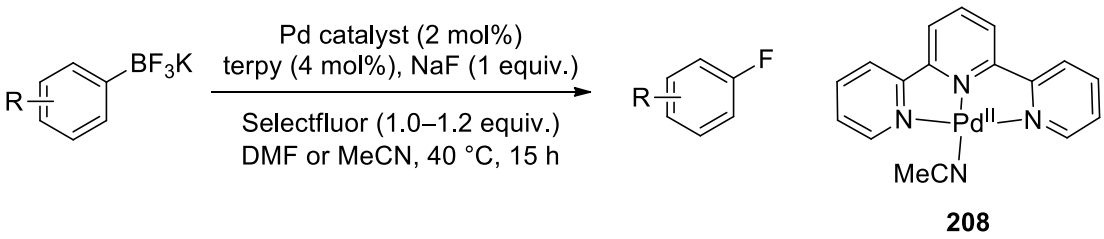


205 **207**

Scheme 99. Bromination of 2-naphthyl nonaflate (205) using nickel(0)-catalyst.

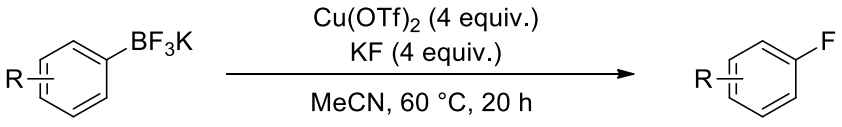
4.1.3 Trifluoroborate leaving group

The potassium trifluoroborate group has been used as a leaving group more recently in aryl fluorinations.[125,126] Metal-mediated fluorination reactions of arylboronic acid derivatives have previously required the use of stoichiometric amounts of transition metal complexes.[124] Making these reactions catalytic can be an issue due to the slow transmetalation of the arene from boron to the transition metal. However, the first catalytic metal-catalysed fluorination of arylboronic acid derivatives has recently been reported.[125] Using aryl trifluoroborates as substrate, a palladium(II)-catalysed process gave the aryl fluorides in excellent yields (Scheme 100). Side products from protodeborylation are often an issue with the fluorination of arylboronic acid derivatives, however these were not seen in the reaction.[124] The reaction required palladium catalyst **208**, as well as the ligand terpyridine (terpy), sodium fluoride and selectfluor to give good yields.



Scheme 100. Palladium-catalysed fluorination of aryl trifluoroborates.

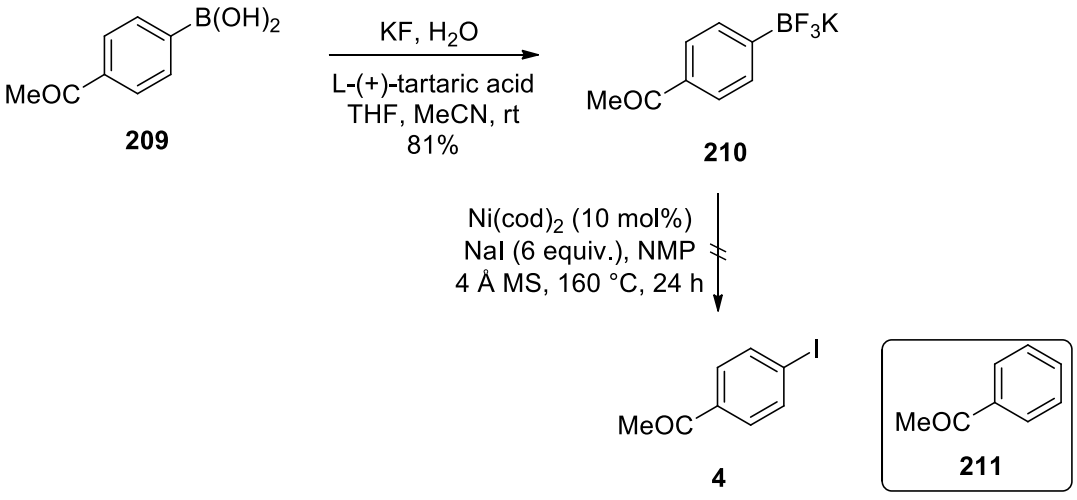
A copper(III)-mediated fluorination of aryl trifluoroborates has also been reported.[126] The reaction did not require the use of expensive transition metal complexes or additives and gave good yields under mild conditions (Scheme 101). This was applicable to electron-rich and electron-deficient substrates, with preliminary studies showing that the reactions did not require the exclusion of air and moisture. One of the limitations of these reactions is that they were unable to utilise this for the synthesis of aryl iodides.



Scheme 101. Copper-mediated fluorination of aryl trifluoroborates.

As discussed in section 1.2, the iodination of aryltrifluoroborates and arylboronic acids has also been achieved by copper-catalysed and non-metal-catalysed electrophilic iodination methods. With this in mind, potassium 4-acetylphenyltrifluoroborate (**210**) was prepared from (4-acetylphenyl)boronic acid (**209**) with L-(+)-tartaric acid and potassium fluoride to give **210** in 81% yield. The trifuoroborate **210** was dried and added to a microwave vial with 10 mol% $Ni(COD)_2$ and 6 equivalents of sodium iodide and the reaction mixture was heated to 160 °C for 24 h. The acetophenone product (**211**) from protodeborylation was the major product at 41% yield, with no iodination detected. As the trifluoroborate group had been removed, it appeared that the nickel catalyst could be participating in an oxidative addition reaction, followed by protodeboronation rather than the iodination reaction. It was believed lowering the temperature may allow the iodination reaction to take place before the protodeboronation step. A temperature screen was undertaken to establish whether this was the case (Table 17). Lowering the temperature was found to decrease the yield of the reduced product **211** slightly. Boronic acid **209** was recovered at lower temperatures. No iodinated product was detected in any of the reactions.

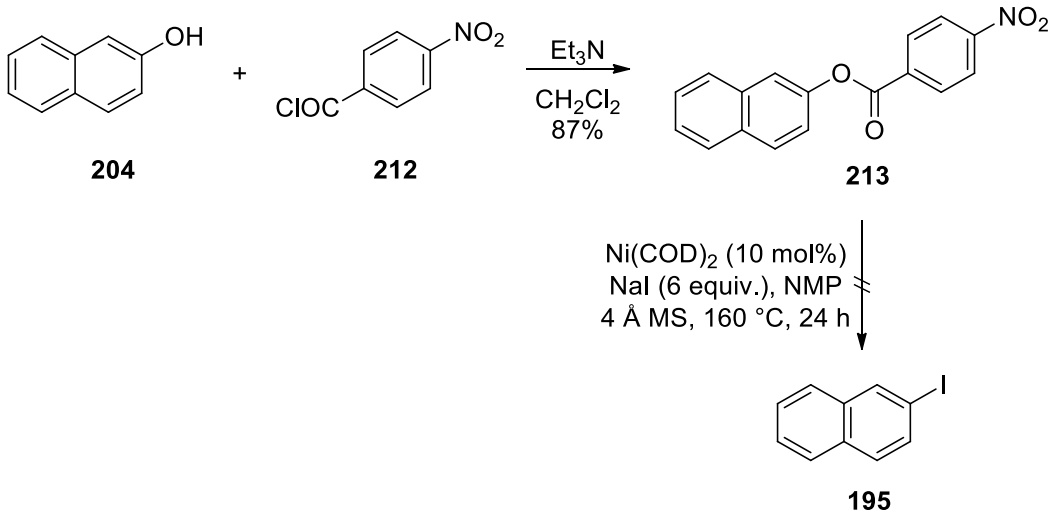
Table 17. Temperature screen for iodination of potassium trifluoroborate.



Entry	Temperature (°C)	Product 211 yield (%)	SM 209 Recovered (%)
1	160	41	0
2	140	34	12
3	120	22	47
4	100	20	62

4.1.4 *para*-Nitrobenzoate leaving group

Esters are commonly employed as effective leaving groups in nickel-catalysed cross-coupling reactions.[127] *para*-Nitrobenzoate has also recently been shown to be a successful leaving group in a palladium catalysed allylic fluorination reaction.[128] Therefore, investigation into whether this could be utilised in the aromatic iodination reaction was undertaken. The esterification reaction of 2-naphthol (**204**) with 4-nitrobenzoyl chloride (**212**) formed 2-naphthyl 4-nitrobenzoate (**213**) in 87% yield (Scheme 102). This was then attempted in the nickel(0)-catalysed reaction with $Ni(COD)_2$ (10 mol%) and sodium iodide at 160 °C. However, no conversion to **195** was observed after 24 hours, with 86% of **204** recovered.



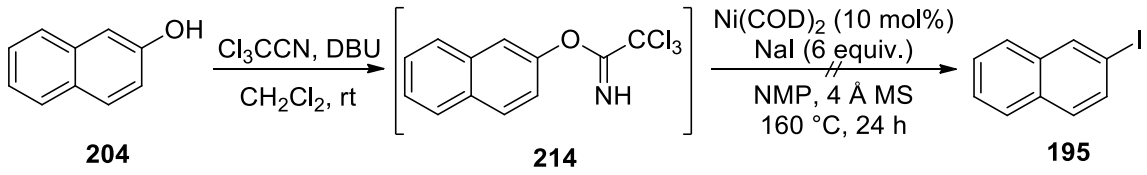
Scheme 102. Attempted iodination reaction *via* a para-nitrobenzoate intermediate.

4.1.5 Trichloroacetimidate leaving group

Trichloroacetimidates are used extensively in our group for Overman rearrangements. This allows the conversion of allylic alcohols to allylic amines by the rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides.[129] Trichloroacetimidates are also commonly employed as leaving groups in the alkylation of alcohols, especially in glycoside synthesis.[130] The metal-catalysed fluorination of allylic and benzylic trichloroacetimidates has also been reported,[131] however no method of halogenation from aryl

trichloroacetimidates is currently in the literature. This functional group was tested as a potential leaving group in the iodination reaction.

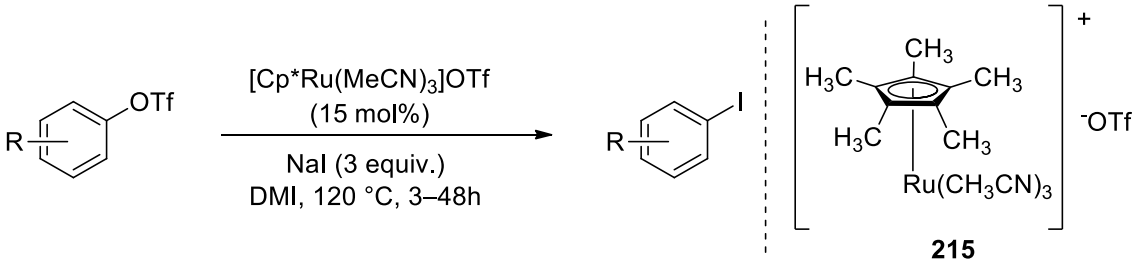
The trichloroacetimidate intermediate of 2-naphthol was synthesised using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a mild base. This was followed by addition of trichloroacetonitrile to afford 2-naphthyl-(2,2,2-trichloroacetimidate) (**214**) as intermediate in the reaction. This would then be used in the nickel-catalysted nucleophilic iodination reaction (Scheme 103). No starting material was observed by TLC after 2 hours. However, filtration through silica during work up resulted in recovery of the 2-naphthol starting material (**204**). Alternative, non-acidic work-ups were investigated, with filtration through neutral alumina and basic alumina both recovering 2-naphthol (**204**). The instability of acetimidates is known and often they are not isolated in reaction, but used straight away. The acetimidate intermediate was gently heated to remove dichloromethane solvent before being used immediately in the nickel-catalysed iodination reaction; however, **204** was again recovered for this reaction, with no iodination observed.



Scheme 103. Acetimidate intermediate attempted in iodination reaction.

4.2 Ruthenium Catalysis

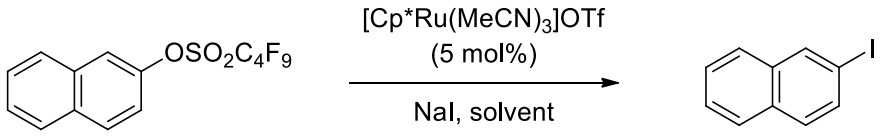
Due to the lack of reactivity in the iodination reaction with nickel catalysts, other catalysts were considered in the reaction. As mentioned previously, the iodination of aryl triflates has been demonstrated by Imazaki *et al* using 3–6 equivalents of sodium iodide and 5–15 mol% of the ruthenium catalyst [Cp*Ru(MeCN)$_3$]OTf (**215**) at 120 °C (Scheme 104).[132] The reaction showed a small scope of substrates (discussed in Introduction, Section 1.4), with no reactivity for electron-rich aryl triflates.



Scheme 104. Ruthenium-catalysed iodination of aryl triflates.

As the nonaflate leaving group had given some success in the nickel-catalysed reaction, it was decided to explore this leaving group in a ruthenium-catalysed reaction also. The use of the ruthenium catalyst [Cp*Ru(MeCN)$_3$]OTf was interesting for the iodination of aryl nonaflate precursors as it was believed that these substrates would be more reactive in the iodination reaction than aryl triflates, which would allow for a milder reaction, as well as a more varied substrate scope. Due to the success with 2-naphthyl nonaflate (**205**) in the Ni(COD)$_2$ catalysed iodination, this substrate was first investigated in the ruthenium-catalysed method. The high reactivity of the nonaflate leaving group would hopefully allow for a reduced catalyst loading, from the high 15 mol% used for the iodination of aryl triflates. The catalyst loading used was 5 mol%, with 1.5 equivalents of sodium iodide at 120 °C. The reaction was first attempted using DMF and NMP as solvents, due to these both being high boiling polar aprotic solvents. The reaction in NMP gave a promising yield of **195** of 47% after 3 hours (Table 18, entry 1), with the reaction in DMF giving a yield of only 10% (Table 18, entry 2). The amount of sodium iodide was increased to 3 equivalents, which showed no improvement in yield in NMP (Table 18, entry 3), however this increased the yield in DMF considerably to give an excellent 92% of **195** after 2 hours (Table 18, entry 4). Attempts to lower the temperature gave an equally impressive yield of 93% at 100 °C after 1 hour in DMF (Table 18, entry 5). Any further reduction in temperature was found to increase the reaction time (Table 18, entry 6). The optimised conditions were found to be a one hour reaction with ruthenium catalyst (5 mol%) and 3 equivalents of sodium iodide, in DMF at 100 °C.

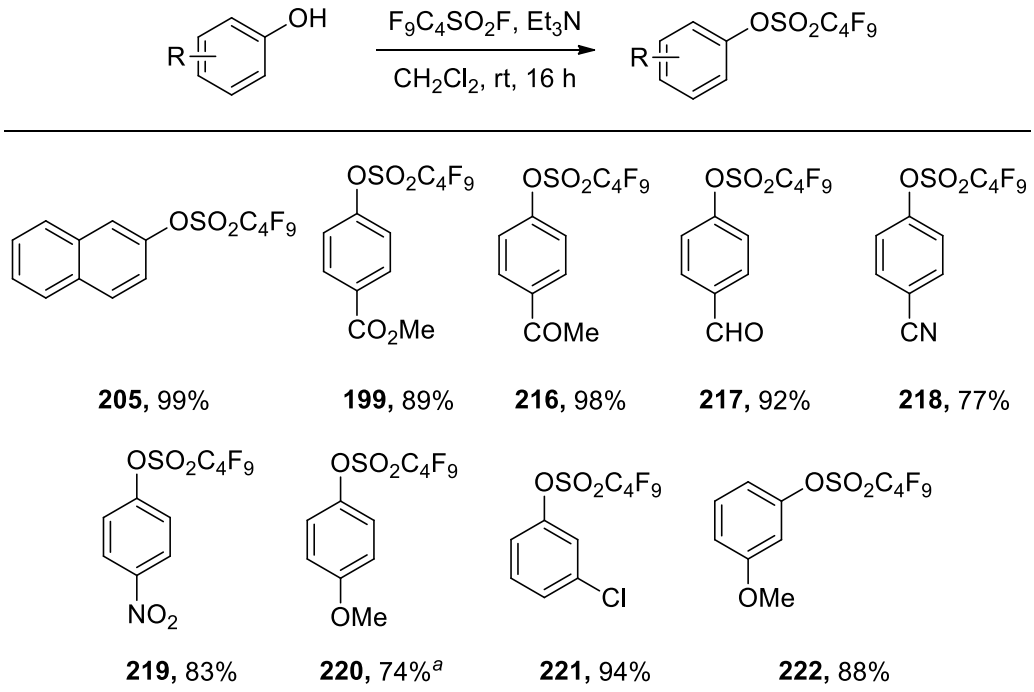
Table 18. Screen of reaction conditions for ruthenium-catalysed iodination.



205 **195**

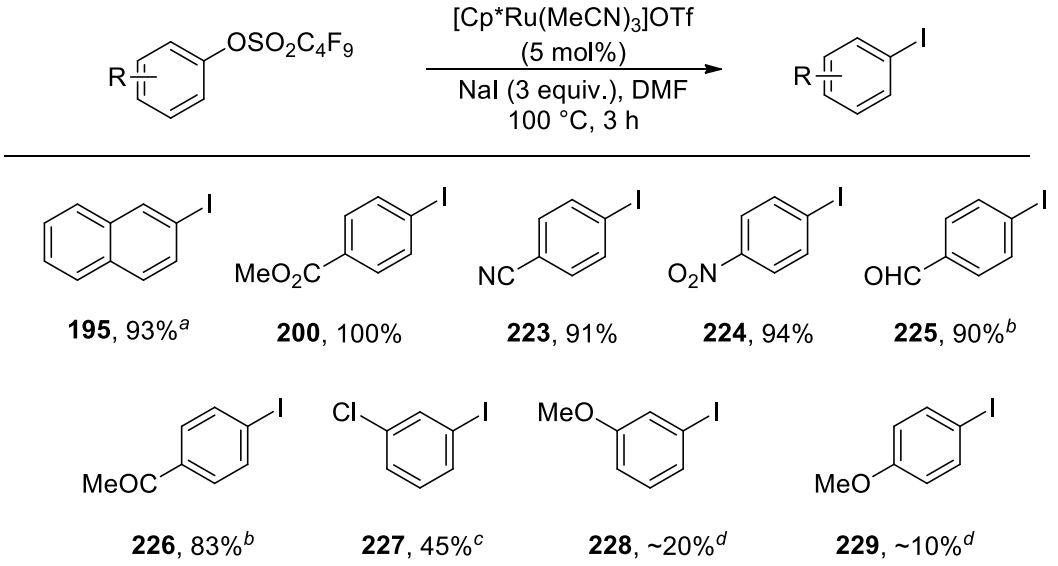
Entry	Solvent	Equiv. NaI	Temperature (°C)	Time (h)	Yield 195 (%)
1	NMP	1.5	120	3	47
2	DMF	1.5	120	3	10
3	NMP	3	120	2	47
4	DMF	3	120	2	92
5	DMF	3	100	1	93
6	DMF	3	80	4	88

With the optimised reaction conditions in place, the next step was to assess the substrate scope of the reaction. Firstly, a number of aryl nonaflates were prepared with a variety of functional groups attached. Reaction of the phenol starting material with nonafluorobutanesulfonyl fluoride and triethylamine proceeded at room temperature to give excellent yields after 16 hours of the nonaflates for both electron-deficient and electron-rich arenes (Scheme 105). The only substrate requiring a longer reaction time was the electron-rich 4-methoxyphenol, which required 48 hours at room temperature to reach completion, giving a 74% yield of 4-methoxyphenyl nonaflate (**220**).



Scheme 105. Synthesis of Nonaflates. [a] Reaction took 48 hours.

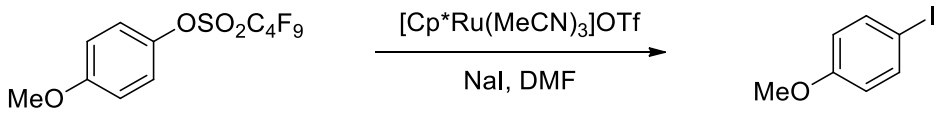
With a variety of nonaflates to hand, these were used with the optimised reaction conditions of ruthenium catalyst (5 mol%) and 3 equivalents of sodium iodide, in DMF at 100 °C. Highly electron-deficient aromatic rings such as methyl 4-iodobenzoate (**200**), 4-iodobenzonitrile (**223**) and 4-iodonitrobenzene (**224**) required a 3 hour reaction to give excellent yields (Scheme 106). 4-Iodobenzaldehyde (**225**) and 4-iodoacetophenone (**226**) required 4 hours in the reaction, but also gave excellent yields of 80–90%. More electron-rich substrates took longer in the reaction, with 1-chloro-3-iodobenzene (**227**) requiring 16 hours, giving a yield of 45%. This reaction was repeated with a temperature of 140 °C, however, this gave no improvement in yield. 3-Iodoanisole (**228**) only gave ~20% conversion to product as detected by ^{1}H NMR spectroscopy after 72 hours. The reaction to give 4-iodoanisole (**229**) also gave a low conversion of ~10% at 100 °C after 72 hours. Therefore the reaction of 4-methoxyphenyl nonaflate (**220**) was investigated further to find conditions which could be applied to more electron-rich substrates.



Scheme 106. Ruthenium-catalysed iodination of aryl nonaflates. [a] Reaction took 1 hour. [b] Reaction took 4 hours. [c] Reaction took 16 hours. [d] Conversion by ^{1}H NMR spectroscopy after 72 hours.

The reaction of 4-methoxyphenyl nonaflate (**220**) was left for a longer reaction time of 40 hours (Table 19, entry 1) which still gave a conversion of ~10% as detected by ^{1}H NMR spectroscopy. Leaving the reaction for an even longer time of 72 hours did not increase the conversion further (Table 19, entry 2). The catalyst loading was increased to 10 mol%, combined with an increase in temperature to 140 °C in an attempt to push the reaction to completion; however this still only showed a 15% conversion to product **229** after 16 hours (Table 19, entry 3). Leaving the iodination for a longer reaction time of 40 hours again did not increase the conversion considerably; however, this gave a conversion of 25%, which allowed for isolation of product **229** in a 20% yield (Table 19, entry 4). Finally, 15 mol% of catalyst was used in the reaction at 140 °C, but the reaction still had not reached completion after 96 hours and **229** was isolated in a 36% yield (Table 19, entry 5). A higher catalyst loading or temperature than this was not desirable, and a shorter reaction time would be needed for the reaction with electron-rich substrates to be practical.

Table 19. Reaction conditions for iodination of 4-methoxyphenyl nonaflate (220).



220 **229**

Entry	Ru-catalyst (mol%)	Equiv. NaI	Temperature (°C)	Time (h)	Conversion to 229 (%)	Yield 229 (%)
1	5	3	100	40	10	n/a
2	5	3	100	72	10	n/a
3	10	3	140	16	15	n/a
4	10	3	140	40	25	20
5	15	6	140	96	40	36

4.3 Conclusions

A nickel-catalysed iodination from non-halogen starting materials was investigated, with a nonaflate leaving group found to give conversion to the iodinated product. 2-Iodonaphthalene (**195**) was synthesised in 33% yield using a nickel(0) catalyst, $Ni(COD)_2$, however, attempts to increase this yield or apply these reaction conditions to other substrates were unsuccessful.

The iodination of aryl nonaflates was also investigated using a ruthenium-catalyst. Using the electron-rich ruthenium catalyst, $[Cp^*Ru(MeCN)_3]OTf$, a number of electron-deficient and electron-neutral aromatic rings were successfully converted to the iodinated products in high yields. The development of the reaction for electron-rich aromatic rings was also studied, with a maximum yield of 36% for 4-iodoanisole (**229**) achieved.

4.4 Future Work

Future work will first focus on developing the ruthenium-catalysed iodination for electron-rich substrates to increase the yield and establish a general method. Alternative ruthenium(II) catalysts containing the strongly electron-donating Cp* ligand will first be investigated as the strongly electron-donating character of this ligand seems to be important in the reactivity of the ruthenium catalyst.

The synthesis of more functionalised targets, including SPECT imaging agents, will then be developed. If the method is successful for the synthesis of SPECT imaging agents using iodine-127, the transformation will then be investigated for the radioiodination of aryl nonaflates, giving a new radioiodination reaction with mild conditions and simple separation of starting material from product.

5.0 Experimental

5.1 General Experimental

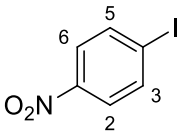
All reagents and starting materials were obtained from commercial sources and used as received unless otherwise stated. Dry solvents (dichloromethane) were purified using a PureSolv 500 MD solvent purification system. All reactions were performed open to air unless otherwise stated. Brine is defined as a saturated aqueous solution of sodium chloride. Room temperature refers to 20–25 °C. Flash column chromatography was carried out using Fisher Matrix silica 60. Macherey-Nagel aluminium-backed plates, pre-coated with silica gel 60 (UV254) were used for thin layer chromatography and were visualised using UV light (254/365 nm) then potassium permanganate solution. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz; ^{13}C: 101 MHz) spectrometer or a Bruker 500 (^{1}H: 500 MHz; ^{13}C: 126 MHz) spectrometer with chemical shift values reported in ppm relative to a residual solvent peak and in the solvent stated. Assignment of ^{1}H NMR signals is based on COSY experiments. Assignment of ^{13}C NMR signals is based on HSQC and/or DEPT experiments. All coupling constants, *J*, are quoted in Hz. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410 spectrometer directly as either a solid or liquid. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Melting points were determined on a Gallenkamp melting point apparatus. Ethyl 7-nitro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (**130**) was supplied by GE Healthcare Ltd.

5.2 One-pot Diazotisation-Iodination Reactions Experimental

General Procedure for Preparation of Polymer-Supported Nitrite[44]

The polymer-supported nitrite reagent was prepared by the addition of Amberlyst® A26 hydroxide form resin (1.0 g, 4.0 mmol) into a solution of $NaNO_2$ (0.55 g, 8.0 mmol) in water (20 mL). The mixture was stirred at room temperature for 0.5 h. The polymer-supported nitrite was filtered and washed with water until the pH of the filtrate became neutral. The content of the polymer-supported nitrite was 3.5 mmol of NO_2/g.[44]

4-Iodonitrobenzene (47)[133]

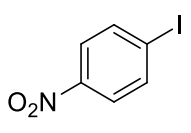


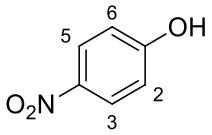
Method A: To a solution of *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol) in acetonitrile (0.5 mL) was added 4-nitroaniline (0.050 g, 0.36 mmol). The solution was cooled in a water bath to 10–15 °C. A solution of sodium nitrite (0.050 g, 0.72 mmol) and sodium iodide (0.080 g, 0.54 mmol) in water (0.2 mL) was added dropwise with vigorous stirring, which resulted in a colour change from yellow to dark red/brown. The reaction mixture was stirred for 0.1 h then warmed to room temperature and stirred for 1 h in total. To the reaction mixture was then added water (10 mL), 1.0 M sodium bicarbonate (until pH = 9–10) and 2.0 M sodium thiosulfate (1 mL). The precipitated 4-iodonitrobenzene (**47**) was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-iodonitrobenzene (**47**) as a pale yellow solid (0.08 g, 86%). Mp 170–172 °C (lit.[133] 169–171 °C); δ_H (400 MHz, $CDCl_3$) 7.91 (2H, d, *J* 8.0 Hz, 3-H and 5-H), 7.94 (2H, d, *J* 8.0 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 102.8 (C), 125.0 (2 × CH), 138.8 (2 × CH), 148.0 (C); *m*/*z* (CI) 250 (MH^+. 60%), 209 (12), 193 (15), 124 (30), 113 (22), 85 (78), 69 (100).

Method B: To a solution of *p*-toluenesulfonic acid monohydrate (0.27 g, 1.1 mmol) in acetonitrile (2 mL) was added 4-nitroaniline (0.050 g, 0.36 mmol). The solution was cooled in a water bath to 10–15 °C. Polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2) was added, followed by sodium iodide (0.11 g, 0.54 mmol) in water (0.2 mL). The reaction mixture was stirred for 0.1 h then warmed to room temperature and stirred for 2 h in total. The mixture was filtered from the resin and the resin was washed with diethyl ether (50 mL). The reaction mixture and diethyl ether washings were combined and washed with water (50 mL). The aqueous layer was then extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified using flash column chromatography

eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-iodonitrobenzene (**47**) as a pale yellow solid (0.080 g, 86%). Spectroscopic data was in agreement with that described above.

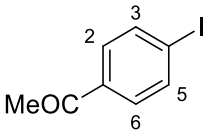
4-Iodonitrobenzene (47)[133] and 4-nitrophenol (48)[134]





The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**), except that all reagents were added at room temperature. The crude material was purified using flash column chromatography, eluting with 20% ethyl acetate in petroleum ether (40—60) to give 4-iodonitrobenzene (**47**) as a pale yellow solid (0.014 g, 15%). Further elution gave 4-nitrophenol (**48**) as a yellow solid (0.030 g, 60%). Spectroscopic data for **47** was in agreement with that described previously. Data for **48**: Mp 114—116 °C (lit.[134] 114—116 °C); δ_H (400 MHz, $CDCl_3$) 4.97 (1H, s, OH), 6.93 (2H, d, *J* 8.6 Hz, 2-H and 6-H), 8.18 (2H, d, *J* 8.6 Hz, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 115.8 (C), 126.4 (2 × CH), 141.8 (2 × CH), 165.2 (C); *m*/*z* (EI) 139 (M^+. 100%), 109 (42), 85 (22), 69 (82).

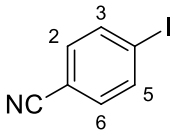
4-Iodoacetophenone (4)[135]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 4-aminoacetophenone (0.050 g, 0.39 mmol), *p*-toluenesulfonic acid monohydrate (0.24 g, 1.1 mmol), polymer-supported nitrite (0.32 g, containing 1.1 mmol of NO_2) and sodium iodide (0.11 g, 0.74 mmol). The crude material was purified using flash column chromatography eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-iodoacetophenone (**4**) as a white solid (0.09 g, 94%). Mp 84–85 °C (lit.[135] 82–84 °C); δ_H (400 MHz, $CDCl_3$) 2.57 (3H, s, $COCH_3$), 7.66 (2H, d, *J* 8.6 Hz, 3-H and 5-H), 7.83 (2H, d, *J* 8.6 Hz, 2-H

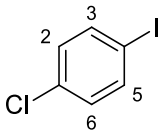
and 6-H); δ_C (101 MHz, $CDCl_3$) 26.6 (CH_3), 101.2 (C), 129.9 (2 × CH), 136.5 (C), 138.1 (2 × CH), 197.5 (C); *m/z* (ESI) 269 (MNa^+. 80%).

4-Iodobenzonitrile (49)[136]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 4-aminobenzonitrile (0.050 g, 0.38 mmol), *p*-toluenesulfonic acid monohydrate (0.24 g, 1.1 mmol), polymer-supported nitrite (0.32 g, containing 1.1 mmol of NO_2) and sodium iodide (0.11 g, 0.74 mmol). The crude material was purified using flash column chromatography eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-iodobenzonitrile (**49**) as a white solid (0.080 g, 68%). Mp 122–124 °C; δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, *J* 8.6 Hz, 3-H and 5-H), 7.84 (2H, d, *J* 8.6 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 100.4 (C), 111.9 (C), 118.3 (C), 133.3 (2 × CH), 138.6 (2 × CH); *m/z* (EI) 229 (M^+. 80%), 102 (100), 84 (95), 69 (31), 49 (38). Spectroscopic data was in agreement with previously published data.[136]

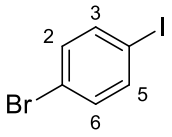
4-Iodochlorobenzene (50)[137]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 4-chloroaniline (0.050 g, 0.41 mmol), *p*-toluenesulfonic acid monohydrate (0.22 g, 1.2 mmol), polymer-supported nitrite (0.34 g, containing 1.2 mmol of NO_2) and sodium iodide (0.12 g, 0.79 mmol). The crude material was purified using flash column chromatography eluting with 5% ethyl acetate in petroleum ether (40–60) to give 4-iodochlorobenzene (**50**) as a white solid (0.058 g, 57%). Mp 55–56 °C (lit.[137] 54–55 °C); δ_H (400 MHz, $CDCl_3$) 7.09 (2H, d, *J* 8.7 Hz, 3-H and 5-H), 7.61 (2H, d, *J* 8.7 Hz, 2-H and 6-H); δ_C (101

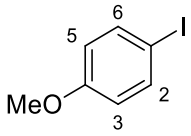
MHz, $CDCl_3$) 91.3 (C), 130.7 (2 × CH), 134.4 (C), 138.9 (2 × CH); *m/z* (EI) 238 (M^+. 52%), 111 (50), 84 (100), 49 (40).

4-Iodobromobenzene (51)[138]



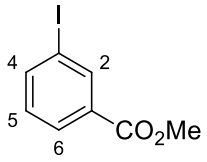
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 4-bromoaniline (0.050 g, 0.28 mmol), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.87 mmol), polymer-supported nitrite (0.25 g, containing 0.87 mmol of NO_2) and sodium iodide (0.090 g, 0.58 mmol). The crude material was purified using flash column chromatography eluting with 5% diethyl ether in petroleum ether (40–60) to give 4-iodobromobenzene (**51**) as a white solid (0.063 g, 77%). Mp 91–92 °C (lit.[138] 90 °C); δ_H (400 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.6 Hz, 3-H and 5-H), 7.54 (2H, d, *J* 8.6 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 92.2 (C), 122.4 (C), 133.6 (2 × CH), 139.2 (2 × CH); *m/z* (EI) 282 (M^+. 48%), 155 (32), 84 (100), 49 (48).

4-Iodoanisole (52)[146]



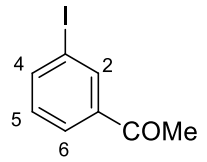
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 4-methoxyaniline (0.050 g, 0.40 mmol), *p*-toluenesulfonic acid monohydrate (0.23 g, 1.2 mmol), polymer-supported nitrite (0.34 g, containing 1.2 mmol of NO_2) and sodium iodide (0.12 g, 0.80 mmol). The crude material was purified using flash column chromatography eluting with 5% ethyl acetate in petroleum ether (40–60) to give 4-iodoanisole (**52**) as a white solid (0.070 g, 71%). Mp 47–48 °C (lit.[146] 49–50 °C); δ_H (400 MHz, $CDCl_3$) 3.78 (1H, s, OCH_3), 6.68 (2H, d, *J* 9.0 Hz, 2-H and 6-H), 7.56 (2H, d, *J* 9.0 Hz, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 55.5 (CH_3), 82.9 (C), 116.5 (2 × CH), 138.4 (2 × CH), 159.6 (C); *m/z* (EI) 234 (M^+. 100%), 219 (22), 191 (11), 92 (14).

Methyl 3-iodobenzoate (53)[139]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using methyl 3-aminobenzoate (0.050 g, 0.33 mmol), *p*-toluenesulfonic acid monohydrate (0.19 g, 0.99 mmol), polymer-supported nitrite (0.28 g, containing 0.99 mmol of NO_2) and sodium iodide (0.10 g, 0.66 mmol). The crude material was purified using flash column chromatography eluting with 20% diethyl ether in petroleum ether (40–60) to give methyl 3-iodobenzoate (**53**) as a pale yellow solid (0.060 g, 71%). Mp 52–53 °C (lit.[139] 54–56 °C); δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, OCH_3), 7.17 (1H, t, *J* 7.9 Hz, 5-H), 7.87 (1H, ddd, *J* 7.9, 1.7, 1.2 Hz, 4-H), 7.99 (1H, ddd, *J* 7.9, 1.7, 1.2 Hz, 6-H), 8.37 (1H, t, *J* 1.7 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 52.5 (CH_3), 93.9 (C), 128.9 (CH), 130.2 (CH), 132.2 (C), 138.6 (CH), 141.9 (CH), 165.7 (C); *m*/*z* (EI) 262 (M^+. 28%), 231 (30), 203 (9), 84 (100), 49 (40).

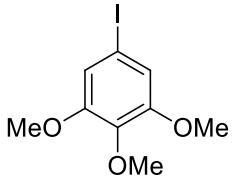
3-Iodoacetophenone (54)[140]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 3-aminoacetophenone (0.050 g, 0.40 mmol), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol), polymer-supported nitrite (0.32 g, containing 1.1 mmol of NO_2) and sodium iodide (0.11 g, 0.74 mmol). The crude material was purified using flash column chromatography eluting with 20% diethyl ether in petroleum ether (40–60) to give 3-iodoacetophenone (**54**) as a colourless oil (0.060 g, 64%). δ_H (500 MHz, $CDCl_3$) 2.58 (3H, s, $COCH_3$), 7.21 (1H, t, *J* 7.9 Hz, 5-H), 7.86–7.93 (2H, m, 4-H and 6-H), 8.28 (1H, t, *J* 1.6 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 26.7 (CH_3), 94.6 (C), 127.6 (CH), 130.5 (CH), 137.5 (CH), 139.0 (C), 142.0 (CH), 196.7 (C); *m*/*z* (EI) 246 (M^+. 78%), 231 (100), 203 (48), 181 (20),

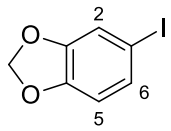
84 (80), 76 (56). Spectroscopic data was in agreement with previously published data.[140]

3,4,5-Trimethoxyiodobenzene (55)[141]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 3,4,5-trimethoxyaniline (0.050 g, 0.29 mmol), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.82 mmol), polymer-supported nitrite (0.23 g, containing 0.82 mmol of NO_2) and sodium iodide (0.080 g, 0.55 mmol). The crude material was purified using flash column chromatography eluting with 20% diethyl ether in petroleum ether (40–60) to give 3,4,5-trimethoxyiodobenzene (**55**) as a yellow solid (0.060 g, 73%). Mp 84–86 °C (lit.[141] 83–85 °C); δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 3.82 (6H, s, 2 × OCH_3), 6.87 (2H, s, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 56.5 (2 × CH_3), 61.0 (CH_3), 86.2 (C), 115.1 (2 × CH), 138.4 (C), 154.1 (2 × C); *m/z* (EI) 294 (M^+. 100%), 279 (58), 251 (19), 236 (18), 124 (21), 109 (12), 84 (70), 49 (25).

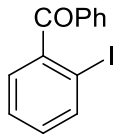
1-Iodo-3,4-methylenedioxybenzene (56)[142]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 3,4-(methylenedioxy)aniline (0.050 g, 0.36 mmol), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol), polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2) and sodium iodide (0.11 g, 0.73 mmol). The crude material was purified using flash column chromatography eluting with 5% ethyl acetate in petroleum ether (40–60) to give 1-iodo-3,4-methylenedioxybenzene (**56**) as a pale yellow oil (0.06 g, 69%). δ_H (400 MHz, $CDCl_3$) 5.96 (2H, s, CH_2), 6.59 (1H, d, *J* 8.1 Hz, 5-H), 7.12 (1H, d, *J* 1.6 Hz, 2-H),

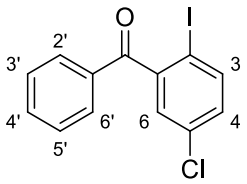
7.14 (1H, dd, *J* 8.1, 1.6 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 82.3 (C), 101.5 (CH_2), 110.6 (CH), 117.8 (CH), 130.7 (CH), 148.0 (C), 148.8 (C); *m/z* (EI) 248 (M^+. 100%), 247 (68), 183 (10), 121 (42), 63 (34). Spectroscopic data was in agreement with previously published data.[142]

2-Iodobenzophenone (57)[143]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 2-aminobenzophenone (0.050 g, 0.25 mmol), *p*-toluenesulfonic acid monohydrate (0.14 g, 0.76 mmol), polymer-supported nitrite (0.22 g, containing 0.76 mmol of NO_2) and sodium iodide (0.080 g, 0.51 mmol). The crude material was purified using flash column chromatography eluting with 5% diethyl ether in petroleum ether (40–60) to give 2-iodobenzophenone (**57**) as an orange solid (0.060 g, 79%). Mp 30–31 °C (lit.[143] 31–32 °C); δ_H (400 MHz, $CDCl_3$) 7.15–7.21 (1H, m, ArH), 7.30 (1H, dd, *J* 7.6, 1.5 Hz, ArH), 7.42–7.49 (3H, m, 3 × ArH), 7.58–7.63 (1H, m, ArH), 7.79–7.83 (2H, m, 2 × ArH), 7.93 (1H, dd, *J* 8.0, 0.8 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 92.3 (C), 127.9 (CH), 128.6 (CH), 128.8 (CH), 130.6 (2 × CH), 131.2 (2 × CH), 133.8 (CH), 135.7 (C), 139.8 (CH), 144.5 (C), 197.3 (C); *m/z* (ESI) 331 (MNa^+. 100%).

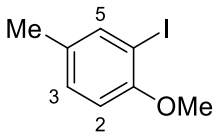
5-Chloro-2-iodobenzophenone (58)[144]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 2-amino-5-chlorobenzophenone (0.050 g, 0.22 mmol), *p*-toluenesulfonic acid monohydrate (0.13 g, 0.66 mmol), polymer-supported nitrite (0.19 g, containing 0.66 mmol of NO_2) and sodium iodide (0.070 g, 0.44 mmol). The crude material was purified using flash column

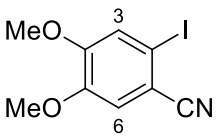
chromatography eluting with 10% diethyl ether in petroleum ether (40–60) to give 5-chloro-2-iodobenzophenone (**58**) as a yellow solid (0.050 g, 66%). Mp 72–74 °C (lit.[144] 80–82 °C); δ_H (400 MHz, $CDCl_3$) 7.18 (1H, dd, *J* 8.4, 2.5 Hz, 4-H), 7.28 (1H, d, *J* 2.5 Hz, 6-H), 7.46–7.52 (2H, m, 2 × ArH), 7.61–7.67 (1H, m, ArH), 7.78–7.82 (2H, m, 2 × ArH), 7.84 (1H, d, *J* 8.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 89.4 (C), 128.6 (CH), 129.0 (2 × CH), 130.6 (2 × CH), 131.4 (CH), 134.2 (CH), 134.8 (C), 135.2 (C), 141.0 (CH), 146.0 (C), 195.9 (C); *m/z* (EI) 342 (M^+. 100%), 265 (20), 215 (20), 152 (14), 105 (59), 77 (26), 51 (11).

2-Iodo-4-methylanisole (59)[145]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 2-methoxy-5-methylaniline (0.050 g, 0.36 mmol), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol), polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2) and sodium iodide (0.11 g, 0.73 mmol). The crude material was purified using flash column chromatography eluting with 20% ethyl acetate in petroleum ether (40–60) to give 2-iodo-4-methylanisole (**59**) as a white solid (0.070 g, 82%). Mp 28–29 °C (lit.[145] 30 °C); δ_H (500 MHz, $CDCl_3$) 2.26 (3H, s, 4-CH_3), 3.85 (3H, s, OCH_3), 6.72 (1H, d, *J* 8.3 Hz, 6-H), 7.10 (1H, dd, *J* 8.3, 1.6 Hz, 5-H), 7.60 (1H, d, *J* 1.6 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 20.1 (CH_3), 56.6 (CH_3), 85.9 (C), 110.9 (CH), 130.1 (CH), 132.2 (C), 140.0 (CH), 156.2 (C); *m/z* (EI) 248 (M^+. 100%), 233 (28), 121 (11), 84 (28), 78 (17).

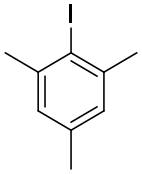
4,5-Dimethoxy-2-iodobenzonitrile (60)[146]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 2-amino-4,5-dimethoxybenzonitrile (0.050 g, 0.28 mmol), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.84 mmol), polymer-

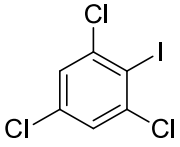
supported nitrite (0.24 g, containing 0.84 mmol of NO_2) and sodium iodide (0.080 g, 0.56 mmol). The crude material was purified using flash column chromatography eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4,5-dimethoxy-2-iodobenzonitrile (**60**) as an orange solid (0.070 g, 86%). Mp 98–99 °C (lit.[146] 103–104 °C); δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 7.02 (1H, s, 3-H), 7.24 (1H, s, 6-H); δ_C (101 MHz, $CDCl_3$) 56.4 (CH_3), 56.6 (CH_3), 88.8 (C), 112.3 (C), 115.9 (CH), 119.9 (C), 121.7 (CH), 149.5 (C), 153.0 (C); *m*/*z* (ESI) 312 (MNa^+. 100%).

2,4,6-Trimethyliodobenzene (61)[147]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 2,4,6-trimethylaniline (0.050 mL, 0.37 mmol), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol), polymer-supported nitrite (0.32 g, containing 1.1 mmol of NO_2) and sodium iodide (0.11 g, 0.74 mmol). The crude material was purified using flash column chromatography eluting with 20% diethyl ether in petroleum ether (40–60) to give 2,4,6-trimethyliodobenzene (**61**) as a yellow solid (0.061 g, 67%). Mp 29–30 °C (lit.[147] 29–30 °C); δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, CH_3), 2.44 (6H, s, 2 × CH_3), 6.90 (2H, s, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 20.8 (CH_3), 29.7 (2 × CH_3), 104.4 (C), 128.1 (2 × CH), 137.5 (C), 141.9 (2 × C); *m*/*z* (EI) 246 (M^+. 100%), 119 (90), 91 (68), 84 (82), 77 (20).

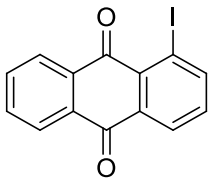
1-Iodo-2,4,6-trichlorobenzene (62)[148]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 1-amino-2,4,6-trichlorobenzene (0.050 g, 0.26 mmol), *p*-toluenesulfonic acid monohydrate (0.15 g, 0.77 mmol), polymer-

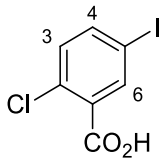
supported nitrite (0.22 g, containing 0.77 mmol of NO_2) and sodium iodide (0.080 g, 0.51 mmol). The crude material was purified using flash column chromatography eluting with 5% diethyl ether in petroleum ether (40–60) to give 1-iodo-2,4,6-trichlorobenzene (**62**) as a white solid (0.060 g, 74%). Mp 53–54 °C (lit.[148] 53 °C); δ_H (400 MHz, $CDCl_3$) 7.37 (2H, s, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 101.7 (C), 127.4 (2 × CH), 135.3 (C), 141.4 (2 × C); *m*/*z* (EI) 308 (M^+. 83%), 181 (30), 143 (12), 84 (100).

1-Iodoanthraquinone (63)[149]



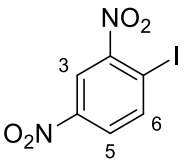
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 1-aminoanthraquinone (0.050 g, 0.22 mmol), *p*-toluenesulfonic acid monohydrate (0.13 g, 0.67 mmol), polymer-supported nitrite (0.19 g, containing 0.67 mmol of NO_2) and sodium iodide (0.070 g, 0.45 mmol). The crude material was purified using flash column chromatography eluting with 10% diethyl ether in petroleum ether (40–60) to give 1-iodoanthraquinone (**63**) as a yellow solid (0.040 g, 54%). Mp 201–202 °C (lit.[149] 204–205 °C); δ_H (400 MHz, $CDCl_3$) 7.40 (1H, t, *J* 7.8 Hz, 3-H), 7.77–7.85 (2H, m, 2 × ArH), 8.25–8.30 (1H, m, ArH), 8.33–8.38 (1H, m, ArH), 8.41 (1H, dd, *J* 7.8, 1.2 Hz, ArH), 8.45 (1H, dd, *J* 7.8, 1.2 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 93.4 (C), 127.0 (CH), 127.9 (CH), 128.5 (CH), 132.5 (C), 132.8 (C), 134.0 (CH), 134.0 (C), 134.2 (CH), 134.7 (CH), 136.0 (C), 148.8 (CH), 181.7 (C), 182.0 (C); *m*/*z* (ESI) 357 (MNa^+. 100%).

2-Chloro-5-iodobenzoic acid (64)[150]



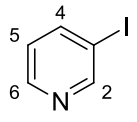
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 5-amino-2-chlorobenzoic acid (0.050 g, 0.29 mmol), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.87 mmol), polymer-supported nitrite (0.25 g, containing 0.87 mmol of NO_2) and sodium iodide (0.090 g, 0.58 mmol). The reaction mixture was stirred at room temperature for 24 h. This gave 2-chloro-5-iodobenzoic acid (**64**) as a white solid (0.070 g, 79%). Mp 155–156 °C (lit.[150] 155.5–156 °C); δ_H (400 MHz, $CDCl_3$) 7.22 (1H, d, *J* 8.4 Hz, 3-H), 7.78 (1H, dd, *J* 8.4, 2.2 Hz, 4-H), 8.32 (1H, d, *J* 2.2 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 90.9 (C), 130.2 (C), 133.2 (CH), 134.9 (C), 141.1 (CH), 142.5 (CH), 168.8 (C); *m*/*z* (EI) 282 (M^+. 100%), 265 (30), 149 (8), 84 (59), 49 (50).

2,4-Dinitro-1-iodobenzene (65)[146]



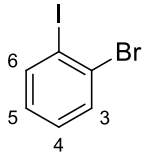
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 1-amino-2,4-dinitrobenzene (0.050 g, 0.27 mmol), *p*-toluenesulfonic acid monohydrate (0.16 g, 0.82 mmol), polymer-supported nitrite (0.23 g, containing 0.82 mmol of NO_2) and sodium iodide (0.080 g, 0.55 mmol). The reaction mixture was stirred at room temperature for 16 h. The crude material was purified using flash column chromatography eluting with 40% ethyl acetate in petroleum ether (40–60) to give 2,4-dinitro-1-iodobenzene (**65**) as a pale yellow solid (0.04 g, 49%). Mp 88–89 °C (lit.[146] 88–89 °C); δ_H (500 MHz, $CDCl_3$) 8.11 (1H, dd, *J* 8.6, 2.5 Hz, 5-H), 8.31 (1H, d, *J* 8.6 Hz, 6-H), 8.68 (1H, d, *J* 2.5 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 94.9 (C), 120.6 (CH), 127.1 (CH), 143.6 (CH), 148.2 (C), 153.4 (C); *m*/*z* (EI) 294 (M^+. 53%), 201 (10), 84 (100), 49 (58).

3-Iodopyridine (66)[151]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 3-aminopyridine (0.030 g, 0.32 mmol), *p*-toluenesulfonic acid monohydrate (0.18 g, 0.96 mmol), polymer-supported nitrite (0.27 g, containing 0.96 mmol of NO_2) and sodium iodide (0.10 g, 0.64 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The crude material was purified using flash column chromatography eluting with 60% ethyl acetate in petroleum ether (40–60) to give 3-iodopyridine (**66**) as a white solid (0.050 g, 74%). Mp 50–51 °C (lit.[151] 52–53 °C); δ_H (400 MHz, $CDCl_3$) 7.11 (1H, dd, *J* 6.4, 4.6 Hz, 5-H), 8.02 (1H, dt, *J* 6.4, 1.4 Hz, 4-H), 8.56 (1H, dd, *J* 4.6, 1.4 Hz, 6-H), 8.84 (1H, d, *J* 1.4, Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 93.8 (C), 125.5 (CH), 144.6 (CH), 148.2 (CH), 155.9 (CH); *m/z* (EI) 205 (M^+. 80%), 139 (44), 84 (78), 44 (100).

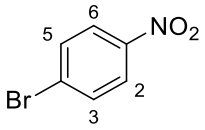
2-Bromo-1-iodobenzene (67)[152]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 2-bromoaniline (0.070 g, 0.43 mmol), *p*-toluenesulfonic acid monohydrate (0.17 g, 0.87 mmol), polymer-supported nitrite (0.25 g, containing 0.87 mmol of NO_2) and sodium iodide (0.090 g, 0.58 mmol). The crude material was purified using flash column chromatography eluting with 10% ethyl acetate in petroleum ether (40–60) to give 2-bromo-1-iodobenzene (**67**) as a brown oil (0.050 g, 40%). δ_H (400 MHz, $CDCl_3$) 7.00 (1H, ddd, *J* 8.0, 7.6, 1.6 Hz, ArH), 7.21 (1H, ddd, *J* 8.0, 7.6, 1.6 Hz, ArH), 7.63 (1H, dd, *J* 8.0, 1.6 Hz, 6-H), 7.86 (1H, dd, *J* 8.0, 1.6 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 101.3 (C), 128.5 (CH), 129.6 (CH), 129.9 (C), 132.9 (CH), 140.5 (CH); *m/z* (EI)

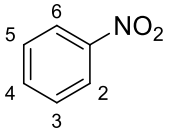
282 (M^+. 100%), 167 (50), 155 (47), 139 (16), 75 (33), 44 (84). Spectroscopic data was in agreement with previously published data.[152]

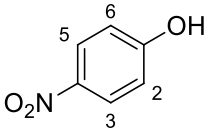
4-Bromo-1-nitrobenzene (76)[153]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 4-nitroaniline (0.050 g, 0.36 mmol), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.1 mmol), polymer-supported nitrite (0.31 g, containing 1.1 mmol of NO_2) and sodium bromide (0.070 g, 0.72 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The crude material was purified using flash column chromatography eluting with 10% ethyl acetate in petroleum ether (40–60) to give 4-bromo-1-nitrobenzene (**76**) as a yellow solid (0.050 g, 54%). Mp 124–125 °C (lit.[153] 125 °C); δ_H (400 MHz, $CDCl_3$) 7.69 (1H, d, *J* 9.1 Hz, 3-H and 5-H), 8.10 (1H, d, *J* 9.1 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 125.1 (2 × CH), 130.1 (C), 132.8 (2 × CH), 147.2 (C); *m/z* (EI) 203 (M^+. 75%), 149 (100), 127 (33), 97 (30), 75 (58), 57 (44), 43 (47).

Nitrobenzene (79)[154] and 4-nitrophenol (48)[134]

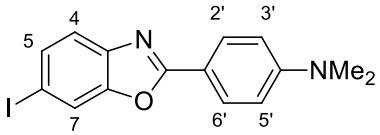




To a solution of *p*-toluenesulfonic acid monohydrate (0.41 g, 2.2 mmol) in acetonitrile (2 mL) was added 4-nitroaniline (0.10 g, 0.72 mmol) at room temperature. The solution was cooled in a water bath to 10—15 °C. This was followed by addition of polymer-supported nitrite (0.62 g, containing 2.2 mmol of NO_2) and water (0.2 mL). The reaction mixture was stirred for 0.25 h, filtered from the polymer-support and the polymer-support was washed with diethyl ether (50 mL). The resulting precipitate was collected by filtration, washing with diethyl ether (50 mL) and dried *in vacuo* to give 4-nitrobenzenediazonium 4-methylbenzenesulfonate (**45**), which was used immediately in the reaction. 4-

Nitrobenzenediazonium 4-methylbenzenesulfonate (0.020 g, 0.062 mmol) was dried under reduced pressure for 2 h. Potassium fluoride (0.0040 g, 0.068 mmol) and 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (0.047 g, 0.12 mmol) were washed with acetonitrile, which was removed under reduced pressure to remove residual water (3 × 5 mL). Acetonitrile (0.5 mL) was added to 4-nitrobenzenediazonium 4-methylbenzenesulfonate, followed by the potassium fluoride and kryptofix® 222 mixture in acetonitrile (0.5 mL). The reaction mixture was heated to 90 °C and stirred for 0.5 h. 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 (10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 30% ethyl acetate in petroleum ether (40—60) to give nitrobenzene (**79**) as a yellow oil (0.002 g, 20%). Further elution gave 4-nitrophenol as a yellow solid (**48**) (0.003 g, 33%). Data for **79**: Spectroscopic data was in agreement with previously published data.[154] δ_H (400 MHz, $CDCl_3$) 7.49—7.58 (2H, m, 3-H and 5-H), 7.66—7.73 (1H, m, 4-H), 8.21 (2H, dd, *J* 8.8, 1.1 Hz, 2-H and 6-H). δ_C (101 MHz, $CDCl_3$) 123.2 (2 × CH), 129.1 (2 × CH), 134.5 (CH), 147.8 (C); *m*/*z* (EI) 123 (M^+. 41%), 93 (42%), 77 (100). Data for **48** was in agreement with that described previously.

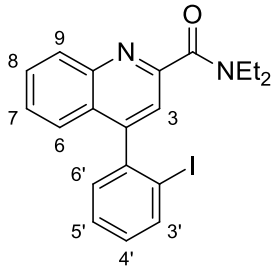
2-(4'-Dimethylaminophenyl)-6-iodobenzoxazole (81)[155]



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) (0.050 g, 0.20 mmol), *p*-toluenesulfonic acid monohydrate (0.11 g, 0.60 mmol), polymer-supported nitrite (0.17 g, containing 0.60 mmol of NO_2) and sodium iodide (0.060 g, 0.40 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The crude material was purified using flash column chromatography eluting with 20% ethyl acetate in petroleum ether (40−60) to give 2-(4'-dimethylaminophenyl)-6-iodobenzoxazole (**81**) as a yellow solid (0.040

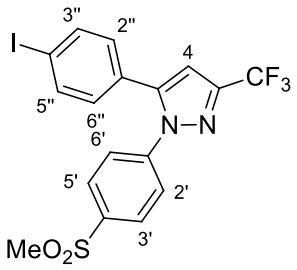
g, 59%). Mp 183–184 °C; δ_H (400 MHz, $CDCl_3$) 3.08 (6H, s, 2 × NCH_3), 6.77 (2H, d, *J* 9.0 Hz, 3'-H and 5'-H), 7.43 (1H, d, *J* 8.4 Hz, 4-H), 7.60 (1H, dd, *J* 8.4, 1.4 Hz, 5-H), 7.86 (1H, d, *J* 1.4 Hz, 7-H), 8.08 (2H, d, *J* 9.0 Hz, 2'-H and 6'-H); δ_C (101 MHz, $CDCl_3$) 40.3 (2 × CH_3), 86.5 (C), 111.9 (2 × CH), 113.8 (C), 119.5 (CH), 120.7 (CH), 129.5 (2 × CH), 133.5 (CH), 142.7 (C), 151.5 (C), 152.7 (C), 164.6 (C); *m*/*z* (ESI) 387 (MNa^+. 100%). Spectroscopic data was in agreement with previously published data.[155]

4-(2-Iodophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (82)[156]



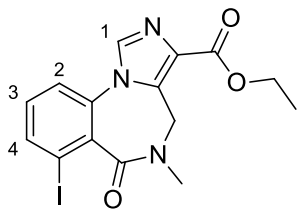
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 4-(2-aminophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (**111**) (0.040 g, 0.12 mmol), *p*-toluenesulfonic acid monohydrate (0.070 g, 0.38 mmol), polymer-supported nitrite (0.11 g, containing 0.38 mmol of NO_2) and sodium iodide (0.038 g, 0.25 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The crude material was purified using flash column chromatography eluting with 40% ethyl acetate in petroleum ether (40–60) to give 4-(2-iodophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (**82**) as a pale yellow solid (0.037 g, 67%). Mp 58–59 °C (lit.[156] 64–66 °C); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.1 Hz, NCH_2CH_3), 1.33 (3H, t, *J* 7.1 Hz, NCH_2CH_3), 3.38–3.60 (2H, m, NCH_2CH_3), 3.63 (2H, q, *J* 7.1 Hz, NCH_2CH_3), 7.18 (1H, td, *J* 7.8, 1.6 Hz, 4'-H), 7.33 (1H, dd, *J* 7.8, 1.6 Hz, 5-H), 7.44–7.55 (4H, m, 3-H, 6-H, 5'-H and 6'-H), 7.75 (1H, ddd, *J* 8.4, 7.8, 1.6 Hz, 7-H), 8.01 (1H, dd, *J* 7.8, 1.6 Hz, 3'-H), 8.19 (1H, d, *J* 8.4 Hz, 8-H); δ_C (126 MHz, $CDCl_3$) 13.1 (CH_3), 14.7 (CH_3), 40.6 (CH_2), 43.6 (CH_2), 98.5 (C), 120.8 (CH), 125.9 (CH), 126.5 (C), 127.6 (CH), 128.3 (CH), 130.1 (CH), 130.1 (CH), 130.2 (CH), 130.3 (CH), 139.5 (CH), 142.6 (C), 147.2 (C), 151.3 (C), 154.5 (C), 168.7 (C); *m*/*z* (EI) 430.0543 (M^+. $C_{20}H_{19}IN_2O$ requires 430.0542), 359 (84%), 331 (91), 294 (23), 203 (100), 176 (26), 149 (26), 72 (78), 69 (31).

1-[4'-(Methylsulfonyl)phenyl]-5-(4''-iodophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (84)



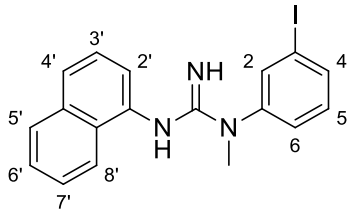
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using 1-[4'-(methylsulfonyl)phenyl]-5-(4''-aminophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (**128**) (0.035 g, 0.090 mmol), *p*-toluenesulfonic acid monohydrate (0.052 g, 0.27 mmol), polymer-supported nitrite (0.077 g, containing 0.27 mmol of NO_2) and sodium iodide (0.027 g, 0.18 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The crude material was purified using flash column chromatography eluting with 20% ethyl acetate in petroleum ether (40–60) to give 1-[4'-(methylsulfonyl)phenyl]-5-(4''-iodophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (**84**) as a white solid (0.027 g, 77%). Mp 178–180 °C; ν_{max}/cm^{-1} (neat) 2929 (CH), 1595, 1466, 1397, 1318, 1296, 1234, 1151, 1128, 1095, 975, 812, 778, 705; δ_H (400 MHz, $CDCl_3$) 3.08 (3H, s, CH_3), 6.79 (1H, s, 4-H), 6.97 (2H, d, *J* 8.5 Hz, 2''-H and 6''-H), 7.53 (2H, d, *J* 8.9 Hz, 2'-H and 6'-H), 7.74 (2H, d, *J* 8.5 Hz, 3''-H and 5''-H), 7.96 (2H, d, *J* 8.9 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 44.6 (CH_3), 96.2 (C), 107.0 (CH), 121.0 (q, *J* 269.0 Hz, C), 125.8 (2 × CH), 128.1 (C), 128.9 (2 × CH), 130.5 (2 × CH), 138.5 (2 × CH), 140.4 (C), 143.2 (C), 144.3 (C), 144.6 (q, *J* 39.4 Hz, C); *m*/*z* (ESI) 514.9489 (MNa^+. $C_{17}H_{12}F_3IN_2NaO_2S$ requires 514.9508).

Ethyl 7-iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (85)



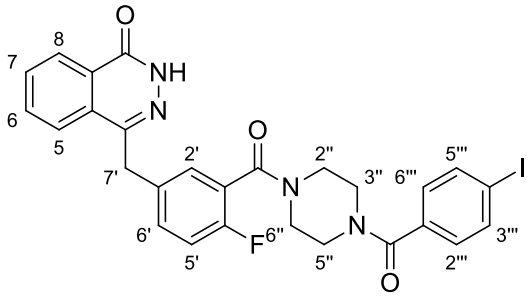
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using ethyl 7-amino-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**131**) (0.020 g, 0.070 mmol), *p*-toluenesulfonic acid monohydrate (0.040 g, 0.21 mmol), polymer-supported nitrite (0.060 g, containing 0.21 mmol of NO_2) and sodium iodide (0.020 g, 0.14 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The crude material was purified using flash column chromatography eluting with 5% methanol in dichloromethane to give ethyl 7-iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**85**) as a white solid (0.020 g, 72%). Mp 232−234 °C; ν_{max}/cm^{-1} (neat) 3091, 2924 (CH), 1694 (C=O), 1647(C=O), 1577, 1486, 1390, 1372, 1348, 1303, 1281, 1240, 1198, 1070, 1050, 938, 799, 772, 705, 664; δ_H (400 MHz, $CDCl_3$) 1.44 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 3.20 (3H, s, NCH_3), 4.33−4.51 (3H, m, $CO_2CH_2CH_3$ and 4-*H*H), 5.14 (1H, d, *J* 15.8 Hz, 4-H*H*), 7.25 (1H, t, *J* 8.0 Hz, 9-H), 7.37 (1H, dd, *J* 8.0, 0.7 Hz, 10-H), 7.89 (1H, s, 1-H), 8.06 (1H, dd, *J* 8.0, 0.7 Hz, 8-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 35.1 (CH_3), 42.7 (CH_2), 61.2 (CH_2), 97.4 (C), 122.4 (CH), 129.4 (C), 132.4 (CH), 132.5 (C), 134.0 (C), 135.1 (CH), 136.0 (C), 141.2 (CH), 163.0 (C), 166.1 (C); *m*/*z* (ESI) 433.9963 (MNa^+. $C_{15}H_{14}IN_3NaO_3$ requires 433.9972).

***N*-(1-Naphthyl)-*N'*-(3-iodophenyl)-*N'*-methylguanidine (86)**



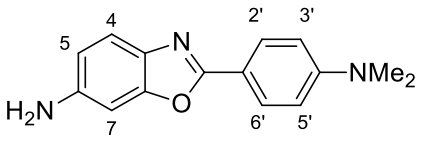
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using *N*-(1-naphthyl)-*N'*-(3-aminophenyl)-*N'*-methylguanidine (**138**) (0.061 g, 0.21 mmol), *p*-toluenesulfonic acid monohydrate (0.12 g, 0.62 mmol), polymer-supported nitrite (0.18 g, containing 0.62 mmol of NO_2) and sodium iodide (0.062 g, 0.41 mmol). The reaction mixture was stirred at room temperature for 16 h. The crude material was purified using flash column chromatography eluting with 60–100% ethyl acetate in petroleum ether (40–60) to give *N*-(1-naphthyl)-*N'*-(3-iodophenyl)-*N'*-methylguanidine (**86**) as a viscous oil (0.049 g, 58%). ν_{max}/cm^{-1} (neat) 3482 (NH), 3385 (NH), 3053, 2924 (CH), 1624, 1557, 1474, 1376, 1266, 1233, 943, 782, 693; δ_H (400 MHz, $CDCl_3$) 3.53 (3H, s, NCH_3), 7.03 (1H, dd, *J* 7.2, 1.1 Hz, 2'-H), 7.13 (1H, t, *J* 8.0 Hz, 5-H), 7.35 (1H, ddd, *J* 8.0, 2.0, 0.9 Hz, 6-H), 7.41 (1H, dd, *J* 8.1, 7.2, Hz, 3'-H), 7.44–7.49 (2H, m, 2 × ArH), 7.52 (1H, br d, *J* 8.1 Hz, 4'-H), 7.58 (1H, ddd, *J* 8.0, 2.0, 0.9 Hz, 4-H), 7.73 (1H, t, *J* 2.0 Hz, 2-H), 7.79–7.85 (1H, m, ArH), 8.09–8.16 (1H, m, ArH); δ_C (101 MHz, $CDCl_3$) 39.2 (CH_3), 94.6 (C), 117.9 (CH), 122.6 (CH), 124.1 (CH), 125.3 (CH), 126.1 (CH), 126.2 (CH), 126.5 (CH), 128.1 (CH), 129.0 (C), 131.1 (CH), 134.9 (C), 135.5 (CH), 135.9 (CH), 145.9 (C), 146.2 (C), 150.5 (C); *m/z* (ESI) 402.0445 (MH^+. $C_{18}H_{17}IN_3$ requires 402.0462).

4-[3'-[4''-(4'''-Nitrobenzoyl)piperazine-1''-carbonyl]-4'-fluorobenzyl]-2*H*-phthalazin-1-one (87)



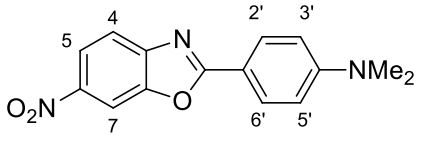
The reaction was carried out according to the previously described general procedure for 4-iodonitrobenzene (**47**) using 4-[3'-[4''-(4'''-aminobenzoyl)piperazine-1''-carbonyl]-4'-fluorobenzyl]-2*H*-phthalazin-1-one (**141**) (30.0 mg, 0.035 mmol), *p*-toluenesulfonic acid monohydrate (20.0 mg, 0.105 mmol), polymer-supported nitrite (30.0 mg, containing 0.105 mmol of NO_2) and sodium iodide (10.5 mg, 0.070 mmol). The reaction mixture was stirred at room temperature for 1 h. Purification by flash column chromatography, using 4% methanol in dichloromethane to give 4-[3'-[4''-(4'''-iodobenzoyl)piperazine-1''-carbonyl]-4'-fluorobenzyl]-2*H*-phthalazin-1-one (**87**) (28.0 mg, 67%) as a white foam. ν_{max}/cm^{-1} (neat) 3198 (NH), 2899 (CH), 1628 (CO), 1587 (C=C), 1427, 1254, 1225, 1001, 747; δH (400 MHz, $CDCl_3$) 3.14–4.02 (8H, m, 4 × NCH_2), 4.29 (2H, s, 7'-H_2), 7.03 (1H, t, *J* 7.8 Hz, 5'-H), 7.14 (2H, d, *J* 8.0 Hz, 3'''-H and 5'''-H), 7.29—7.37 (2H, m, 2'-H and 6'-H), 7.67—7.84 (5H, m, ArH), 8.42—8.51 (1H, m, 8-H), 10.96 (1H, br s, NH); δc (101 MHz, $CDCl_3$) 37.8 (CH_2), 42.2 (2 × CH_2), 47.3 (2 × CH_2), 96.6 (C), 116.3 (d, *J* 21.7 Hz, CH), 123.6 (d, *J* 17.7 Hz, C), 125.1 (CH), 127.3 (CH), 128.4 (C), 128.9 (2 × CH), 129.4 (d, *J* 3.6 Hz, CH), 129.6 (C), 131.8 (CH), 131.9 (d, *J* 8.0 Hz, CH), 133.8 (CH), 134.5 (C), 134.6 (d, *J* 3.7 Hz, C), 138.0 (2 × CH), 145.6 (C), 157.1 (d, *J* 247.1 Hz, C), 160.7 (C), 165.3 (C), 169.8 (C); *m*/*z* (ESI) 619.0597 (MNa^+. $C_{27}H_{22}FIN_4NaO_3$ requires 619.0613).

2-(4'-Dimethylaminophenyl)-6-aminobenzoxazole (88)



2-(4'-Dimethylaminophenyl)-6-nitrobenzoxazole (**91**) (0.12 g, 0.42 mmol) was dissolved in ethanol (10 mL) before addition of tin(II) chloride dihydrate (0.48 g, 2.1 mmol). The solution was stirred under reflux for 16 h. After cooling to room temperature, the reaction was quenched by addition of a saturated aqueous solution of sodium hydrogen carbonate and the product was extracted with ethyl acetate (3 × 5 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 1–5% methanol in dichloromethane to give 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) as an orange solid (0.089 g, 83%). Mp 186–187 °C; ν_{max}/cm^{-1} (neat) 3430 (NH), 3314 (NH), 2916 (CH), 1613 (C=C), 1508, 1489, 1356, 1126, 949, 820; δ_H (500 MHz, $CDCl_3$) 3.05 (6H, s, 2 × NCH_3), 6.65 (1H, dd, *J* 8.4, 2.1 Hz, 5-H), 6.75 (2H, d, *J* 9.0 Hz, 3'-H and 5'-H), 6.84 (1H, d, *J* 2.1 Hz, 7-H), 7.45 (1H, d, *J* 8.4 Hz, 4-H), 8.03 (2H, d, *J* 9.0 Hz, 2'-H and 6'-H); δ_C (126 MHz, $CDCl_3$) 40.3 (2 × CH_3), 96.8 (CH), 111.8 (2 × CH), 112.8 (CH), 115.0 (C), 119.4 (CH), 128.6 (2 × CH), 135.3 (C), 144.1 (C), 151.9 (C), 152.1 (C), 162.6 (C); *m/z* (CI) 254.1289 (MH^+. $C_{15}H_{16}N_3O$ requires 254.1293), 165 (3%), 113 (4), 69 (12).

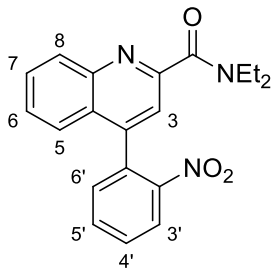
2-(4'-Dimethylaminophenyl)-6-nitrobenzoxazole (91)



4-(Dimethylamino)benzoic acid (0.530 g, 3.25 mmol), 5-nitro-2-aminophenol (0.500 g, 3.25 mmol) and boric acid (0.200 g, 3.25 mmol) in xylene (50 mL) were stirred under Dean-Stark conditions for 72 h. After cooling to room temperature, the reaction mixture was filtered and washed with xylene before concentrating *in vacuo*. Water was added to the residue (20 mL) and the mixture made basic with 1 M sodium hydroxide solution. The aqueous layer was extracted with

dichloromethane (3 × 20 mL) and the organic layers combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 40% ethyl acetate in petroleum ether (40−60) to give 2-(4'-dimethylaminophenyl)-6-nitrobenzoxazole (**91**) as an orange solid (0.485 g, 54%). Mp 215−217 °C; ν_{max}/cm^{-1} (neat) 3422, 3315, 2924 (CH), 1615 (C=C), 1510, 1491, 1357, 822; δ_H (500 MHz, $CDCl_3$) 3.10 (6H, s, 2 × NCH_3), 6.75 (2H, d, *J* 9.1 Hz, 3'-H and 5'-H), 7.69 (1H, d, *J* 8.7 Hz, 4-H), 8.10 (2H, d, *J* 9.1 Hz, 2'-H and 6'-H), 8.26 (1H, dd, *J* 8.7, 2.1 Hz, 5-H), 8.37 (1H, d, *J* 2.1 Hz, 7-H); δ_C (126 MHz, $CDCl_3$) 40.2 (2 × CH_3), 106.7 (CH), 111.7 (2 × CH), 112.5 (C), 118.5 (CH), 120.9 (CH), 130.1 (2 × CH), 144.2 (C), 148.6 (C), 149.9 (C), 153.3 (C), 168.9 (C); *m/z* (EI) 283.0956 (M^+. $C_{15}H_{13}N_3O_3$ requires 283.0957), 253 (31%), 209 (48), 145 (11).

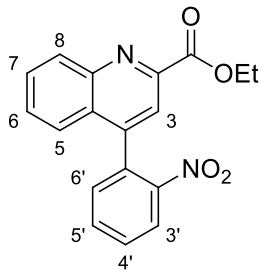
4-(2'-Nitrophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (93)



Ethyl 4-(2'-nitrophenyl)quinoline-2-carboxylate (**94**) (0.380 g, 1.18 mmol) was dissolved in 50% aqueous ethanol (20 mL) before addition of ground sodium hydroxide (0.190 g, 4.72 mmol). The mixture was stirred under reflux for 16 h. After cooling to room temperature, the ethanol was removed *in vacuo* and the water layer acidified (pH 4) with 1 M hydrochloric acid solution. The product was extracted with dichloromethane (3 × 50 mL), washed with water (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 4-(2'-nitrophenyl)quinoline-2-carboxylic acid (**101**) as a brown solid (0.320 g, 92%), which was used without further purification. 4-(2'-Nitrophenyl)quinoline-2-carboxylic acid (**101**) (0.090 g, 0.30 mmol) was dissolved in *N,N'*-dimethylformamide (10 mL), before addition of triethylamine (61 µL, 0.44 mmol) and *N,N,N',N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (0.12 g, 0.32 mmol). The mixture was stirred at room temperature for 1 h and then heated to 50 °C, with the addition of diethylamine (30 µL, 0.44 mmol). The

reaction mixture was stirred at 50 °C for 16 h. Water was added and the mixture stirred for an additional 1 h. After cooling to room temperature, the reaction mixture was diluted in ethyl acetate (20 mL) and washed with a 5% aqueous solution of lithium chloride (3 × 20 mL), followed by brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 60% ethyl acetate in petroleum ether (40–60) to give 4-(2'-nitrophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (**93**) as a colourless oil (0.055 g, 54%). ν_{max}/cm^{-1} (neat) 2974 (CH), 1630 (C=O), 1528, 1346, 1275, 1098, 766; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, NCH_2CH_3), 1.32 (3H, t, *J* 7.2 Hz, NCH_2CH_3), 3.40–3.72 (4H, m, 2 × NCH_2CH_3), 7.42 (1H, dd, *J* 8.4, 1.2 Hz, ArH), 7.47–7.53 (2H, m, 2 × ArH), 7.55 (1H, s, 3-H), 7.66–7.80 (3H, m, 3 × ArH), 8.16–8.24 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 13.1 (CH_3), 14.6 (CH_3), 40.7 (CH_2), 43.7 (CH_2), 119.9 (CH), 124.6 (CH), 124.9 (CH), 126.4 (C), 128.1 (CH), 129.9 (CH), 130.2 (CH), 130.5 (CH), 132.5 (CH), 132.9 (C), 133.5 (CH), 145.9 (C), 146.9 (C), 148.8 (C), 154.4 (C), 168.5 (C); *m*/*z* (ESI) 372.1303 (MNa^+. $C_{20}H_{19}N_3O_3Na$ requires 372.1319).

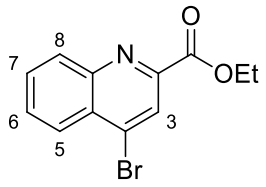
Ethyl 4-(2'-nitrophenyl)quinoline-2-carboxylate (94)[156]



Ethyl 4-bromoquinoline-2-carboxylate (**95**) (0.500 g, 1.79 mmol) was dissolved in *N*,*N'*-dimethylformamide (25 mL) before addition of 2-nitrophenylboronic acid (0.360 g, 2.14 mmol), tetrakis(triphenylphosphine)palladium(0) (0.210 g, 0.180 mmol) and potassium phosphate (0.450 g, 2.14 mmol). The reaction mixture was stirred at 120 °C for 24 h, before addition of 2-nitrophenylboronic acid (0.360 g, 2.14 mmol) and potassium phosphate (0.450 g, 2.14 mmol) and further stirring at 120 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted in ethyl acetate (50 mL) and washed with a 5% aqueous solution of lithium chloride (3 × 50 mL) followed by brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was

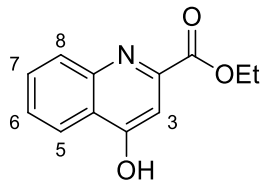
purified using flash column chromatography eluting with 40% ethyl acetate in petroleum ether (40–60) to give ethyl 4-(2'-nitrophenyl)quinoline-2-carboxylate (**94**) as a yellow solid (0.510 g, 88%). Mp 149–150 °C (lit.[156] 156–157 °C); δ_H (500 MHz, $CDCl_3$) 1.49 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.51–4.63 (2H, m, OCH_2CH_3), 7.44–7.48 (2H, m, 2 × ArH), 7.57 (1H, ddd, *J* 8.4, 7.0, 1.6 Hz, ArH), 7.72 (1H, ddd, *J* 8.6, 8.0, 1.6 Hz, ArH), 7.77–7.82 (2H, m, 2 × ArH), 8.07 (1H, s, 3-H), 8.26 (1H, dd, *J* 8.0, 1.0 Hz, ArH), 8.40 (1H, d, *J* 8.6 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 62.6 (CH_2), 120.5 (CH), 124.6 (CH), 125.1 (CH), 127.7 (C), 129.3 (CH), 130.1 (CH), 130.5 (CH), 131.6 (CH), 132.5 (CH), 132.8 (C), 133.6 (CH), 146.5 (C), 147.8 (C), 148.0 (C), 148.7 (C), 165.3 (C); *m/z* (EI) 322 (M^+. 25%), 278 (52), 250 (100), 205 (41), 190 (31), 130 (30), 84 (39).

Ethyl 4-bromoquinoline-2-carboxylate (95)[157]



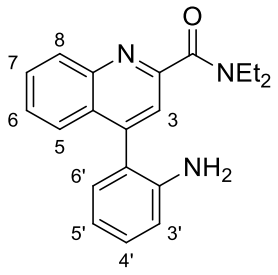
Ethyl 4-hydroxyquinoline-2-carboxylate (**96**) (0.840 g, 3.87 mmol) was dissolved in acetonitrile (50 mL) before addition of phosphorus oxybromide (3.33 g, 11.6 mmol) and potassium carbonate (1.60 g, 11.6 mmol). The mixture was heated under reflux for 2 h. After cooling to room temperature, the solution was concentrated *in vacuo* and water added. The product was extracted with ethyl acetate (3 × 100 mL) and the organic layers dried ($MgSO_4$), filtered and concentrated *in vacuo* to give ethyl 4-bromoquinoline-2-carboxylate (**95**) as a brown solid (1.03 g, 95%). Mp 88–90 °C (lit.[157] 91–92 °C); δ_H (500 MHz, $CDCl_3$) 1.49 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.56 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 7.74 (1H, ddd, *J* 8.4, 6.9, 1.2 Hz, 6-H), 7.83 (1H, ddd, *J* 8.4, 6.9, 1.2 Hz, 7-H), 8.23 (1H, dd, *J* 8.4, 1.2 Hz, 5-H), 8.31 (1H, dd, *J* 8.4, 1.2 Hz, 8-H), 8.46 (1H, s, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 62.7 (CH_2), 125.2 (CH), 126.8 (CH), 129.0 (C), 130.0 (CH), 131.2 (CH), 131.4 (CH), 135.3 (C), 148.1 (C), 148.2 (C), 164.5 (C); *m/z* (CI) 280 (MH^+. 100%), 202 (20), 81 (17), 69 (24).

Ethyl 4-hydroxyquinoline-2-carboxylate (96)[158]



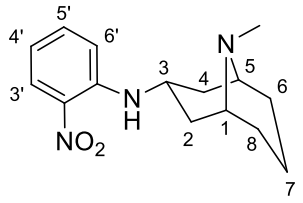
Aniline (1.11 g, 11.9 mmol), diethyl oxaloacetate (2.50 g, 11.9 mmol) and *p*-toluenesulfonic acid (2.26 g, 11.9 mmol) in cyclohexane (50 mL) were stirred vigorously under Dean-Stark conditions for 48 h. After cooling to room temperature, the reaction mixture was filtered and washed with cyclohexane before concentrating *in vacuo* to give the imine as a yellow oil. Neat polyphosphoric acid (~5 g) was added and stirred vigorously at 120 °C for 1 h. After cooling to room temperature, a saturated solution of aqueous sodium hydrogen carbonate (75 mL) was slowly added. Chloroform was added (100 mL) and the two layers separated. The aqueous layer was extracted with chloroform (3 × 100 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 10% methanol in dichloromethane to give ethyl 4-hydroxyquinoline-2-carboxylate (**96**) as a yellow solid (1.24 g, 48%). Mp 214–215 °C (lit.[158] 213 °C); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.48 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 7.00 (1H, s, 3-H), 7.38 (1H, t, *J* 7.6 Hz, ArH), 7.45 (1H, d, *J* 8.2, Hz, ArH), 7.65–7.68 (1H, m, ArH), 8.35 (1H, dd, *J* 8.2, 0.9 Hz, ArH), 8.98 (1H, br s, OH); δ_C (101 MHz, $CDCl_3$) 14.1 (CH_3), 63.4 (CH_2), 111.6 (CH), 118.0 (CH), 124.5 (CH), 126.3 (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%).

4-(2'-Aminophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (111)



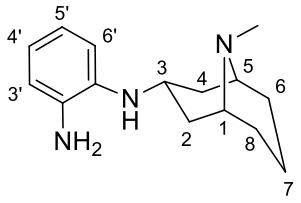
4-(2'-Nitrophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (**93**) (0.050 g, 0.15 mmol) was dissolved in ethanol (2 mL) before addition of tin(II) chloride dihydrate (0.18 g, 0.77 mmol). The solution was stirred under reflux for 16 h. After cooling to room temperature, the reaction was quenched by addition of a saturated aqueous solution of sodium hydrogen carbonate and the product was extracted with ethyl acetate (3 × 5 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 1% methanol in dichloromethane to give 4-(2'-aminophenyl)-*N*,*N*-diethylquinoline-2-carboxyamide (**111**) as a colourless oil (0.045 g, 91%). ν_{max}/cm^{-1} (neat) 3348 (NH), 2973 (CH), 1620 (C=O), 1486, 1451, 1275, 1099, 750; δ_H (500 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, NCH_2CH_3), 1.32 (3H, t, *J* 7.2 Hz, NCH_2CH_3), 3.42−3.67 (6H, m, 2 × NCH_2CH_3 and NH_2), 6.83 (1H, dd, *J* 8.2, 1.2 Hz, ArH), 6.88 (1H, td, *J* 8.2, 1.2 Hz, ArH), 7.14 (1H, dd, *J* 8.2, 1.2 Hz, ArH), 7.28 (1H, td, *J* 8.2, 1.2 Hz, ArH), 7.53 (1H, ddd, *J* 8.2, 7.2, 1.2 Hz, ArH), 7.64 (1H, s, 3-H), 7.71−7.78 (2H, m, 2 × ArH), 8.17 (1H, d, *J* 8.2 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 13.1 (CH_3), 14.6 (CH_3), 40.5 (CH_2), 43.6 (CH_2), 115.9 (CH), 118.6 (CH), 121.4 (CH), 122.7 (C), 126.2 (CH), 126.7 (C), 127.6 (CH), 129.9 (CH), 130.2 (CH), 130.4 (CH), 130.8 (CH), 143.9 (C), 147.3 (C), 147.4 (C), 155.0 (C), 168.8 (C); *m*/*z* (ESI) 320.1743 (MH^+. $C_{20}H_{22}N_3O$ requires 320.1757).

***N*-(2'-Nitrophenyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (116).**



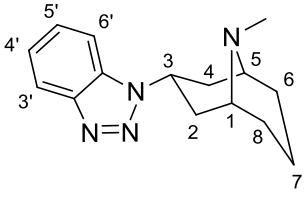
endo-3-Amino-9-methyl-9-azabicyclo[3.3.1]nonane (0.050 g, 0.32 mmol) and sodium *tert*-butoxide (0.13 g, 1.3 mmol) were added to a mixture of 2-bromonitrobenzene (0.13 g, 0.65 mmol), palladium(II) diacetate (0.0020 g, 2 mol%) and (*S*)- 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.0040 g, 2 mol%) in anhydrous toluene (0.6 mL) at room temperature. The reaction mixture was heated to 80 °C and stirred for 48 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL) and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 5% methanol in dichloromethane to give *N*-(2'-nitrophenyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (**116**) as a yellow solid (0.057 g, 64%). Mp 162−164 °C; ν_{max}/cm^{-1} (neat) 3364 (NH), 2922 (CH), 1614 (C=C), 1572, 1505, 1418, 1352, 1267, 1242, 1148, 1067, 1034, 1028, 739; δ_H (500 MHz, $CDCl_3$) 1.05 (2H, br d, *J* 7.0 Hz, 6-*H*H and 8-*H*H), 1.33—1.42 (2H, m, 2- *H*H and 4- *H*H), 1.54 (1H, br d, *J* 4.5 Hz, 7-*H*H), 1.99 (3H, br d, *J* 7.0 Hz 3 × CH, 6-H*H*, 7-H*H* and 8-H*H*), 2.52 (3H, s, NCH_3), 2.57 (2H, td, *J* 11.4, 6.5 Hz, 2-H*H* and 4-H*H*), 3.14 (2H, br d, *J* 11.4 Hz 1-H and 5-H), 4.12—4.24 (1H, m, 3-H), 6.56 (1H, ddd, *J* 8.4, 7.0, 1.3 Hz, 4'-H), 7.00 (1H, d, *J* 8.4 Hz, 6'-H), 7.38 (1H, ddd, *J* 8.4, 7.0, 1.3, 5'-H), 7.98 (1H, d, *J* 7.5 Hz, NH), 8.11 (1H, dd, *J* 8.4, 1.3 Hz, 3'-H); δ_C (126 MHz, $CDCl_3$) 14.1 (CH_2), 23.2 (2 × CH_2), 33.4 (2 × CH_2), 39.6 (CH_3), 43.9 (CH), 51.5 (2 × CH), 114.7 (CH), 115.0 (CH), 127.0 (CH), 131.7 (C), 136.3 (CH), 145.1 (C); *m/z* (ESI) 276.1714 (MH^+. $C_{15}H_{22}N_3O_2$ requires 276.1707).

***N*-(2'-Aminophenyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (117)**



The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using *N*-(2'-nitrophenyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (**116**) (0.17 g, 0.62 mmol) and tin(II) chloride dihydrate (0.70 g, 3.1 mmol) in ethanol (6 mL). The reaction mixture was stirred under reflux for 16 h. The crude material was purified using flash column chromatography eluting with 5% methanol in dichloromethane and 1% ammonium hydroxide to give *N*-(2'-aminophenyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (**117**) as a yellow solid (0.095 g, 63%). Mp 186−188 °C; ν_{max}/cm^{-1} (neat) 3318 (NH), 3223, 2926 (CH), 1622 (C=C), 1597, 1508, 1454, 1275, 1132, 907, 727; δ_H (500 MHz, $CDCl_3$) 1.04 (2H, br d, *J* 12.0 Hz, 6-*H*H and 8-*H*H), 1.24 (2H, ddd, *J* 12.0, 10.7, 3.0 Hz, 2-*H*H and 4-*H*H), 1.51 (1H, br d, *J* 12.0 Hz, 7-*H*H), 1.94—2.09 (3H, m, 6-H*H*, 7-H*H* and 8-H*H*), 2.53 (3H, s, NCH_3), 2.59 (2H, td, *J* 12.0, 6.1 Hz, 2-H*H* and 4-H*H*), 3.11 (2H, br d, *J* 10.7 Hz, 1-H and 5-H), 3.85—3.95 (1H, m, 3-H), 6.64 (1H, td, *J* 7.4, 1.7 Hz, ArH), 6.72 (1H, dd, *J* 7.5, 1.2 Hz, ArH), 6.76—6.84 (2H, m, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 14.4 (CH_2), 24.2 (2 × CH_2), 34.0 (2 × CH_2), 40.1 (CH_3), 44.0 (CH), 51.7 (2 × CH), 113.2 (CH), 117.1 (CH), 118.4 (CH), 121.0 (CH), 134.3 (C), 137.1 (C); *m/z* (ESI) 246.1964 (MH^+. $C_{15}H_{24}N_3$ requires 246.1965).

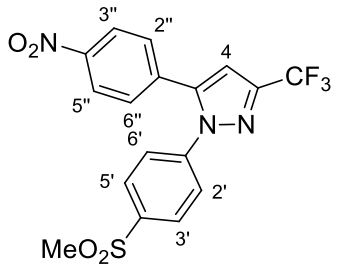
9-Methyl-9-azabicyclo[3.3.1]nonane-3-benzo[1.2.3]triazole (118)



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using *N*-(2'-aminophenyl)-9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (**117**) (0.060 g, 0.24 mmol), *p*-toluenesulfonic

acid monohydrate (0.14 g, 0.73 mmol), polymer-supported nitrite (0.21 g, containing 0.73 mmol of NO_2) and sodium iodide (0.074 g, 0.49 mmol). The reaction mixture was heated to 60 °C and stirred for 16 h. The crude material was purified using flash column chromatography eluting with 10% methanol in dichloromethane and 1% ammonium hydroxide to give 9-methyl-9-azabicyclo[3.3.1]nonane-3-benzo[1.2.3]triazole (**118**) as a white solid (0.024 g, 40%). Mp 78–80 °C; ν_{max}/cm^{-1} (neat) 2922 (CH), 1451, 1310, 1229, 1150, 1061, 1026, 781, 743; δ_H (400 MHz, $CDCl_3$) 1.12 (2H, br d, *J* 13.5 Hz, 6-*H*H and 8-*H*H), 1.64 (1H, br d, *J* 13.5 Hz, 7-*H*H), 2.07 (2H, tt, *J* 13.5, 3.8 Hz, 6-H*H* and 8-H*H*), 2.25 (1H, tt, *J* 13.5, 3.8 Hz, 7-H*H*), 2.35 (2H, td, *J* 13.5, 3.8 Hz, 2-*H*H and 4-*H*H), 2.52—2.63 (5H, m, 2-H*H* and 4-H*H* and NCH_3), 3.24 (2H, br d, *J* 11.0 Hz, 1-H and 5-H), 5.23—5.30 (1H, m, 3-H), 7.35 (1H, ddd, *J* 8.3, 6.9, 1.0 Hz, 4'-H), 7.46 (1H, ddd, *J* 8.3, 6.9, 1.0 Hz, 5'-H), 7.64 (1H, d, *J* 8.3 Hz, 6'-H), 8.05 (1H, d, *J* 8.3 Hz, 3'-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_2), 23.1 (2 × CH_2), 32.9 (2 × CH_2), 39.8 (CH_3), 51.6 (2 × CH), 51.7 (CH), 109.8 (CH), 120.1 (CH), 123.8 (CH), 126.9 (CH), 133.0 (C), 146.1 (C); *m*/*z* (ESI) 257.1752 (MH^+. $C_{15}H_{21}N_4$ requires 257.1761).

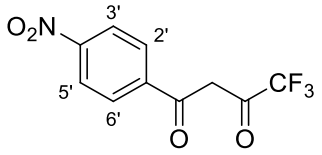
1-[4'-(Methylsulfonyl)phenyl]-5-(4''-nitrophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (121)[159]



To a stirred solution of 1-(4'-nitrophenyl)-3-(trifluoromethyl)butane-1,3-dione (**122**) (0.16 g, 0.61 mmol) in ethanol (5 mL) was added 4-methanesulfonylphenylhydrazine hydrochloride (**123**) (0.15 g, 0.67 mmol). The reaction mixture was stirred under reflux for 120 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the residue diluted with diethyl ether (20 mL), washed with a 5% aqueous solution of hydrochloric acid (2 × 15 mL), followed by brine (15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 60% ethyl acetate in

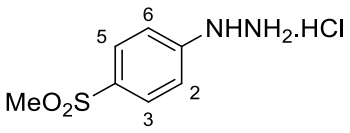
petroleum ether (40–60) to give 1-[4'-(methylsulfonyl)phenyl]-5-(4''-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole (**121**) as a yellow solid (0.067 g, 27%). Mp 201–202 °C (lit.[159] 203–204 °C); δ_H (400 MHz, $CDCl_3$) 3.10 (3H, s, CH_3), 6.92 (1H, s, 4-H), 7.44 (2H, d, *J* 8.9 Hz, 2''-H and 6''-H), 7.53 (2H, d, *J* 8.9 Hz, 2'-H and 6'-H), 8.00 (2H, d, *J* 8.9 Hz, 3'-H and 5'-H), 8.26 (2H, d, *J* 8.9 Hz, 3''-H and 5''-H); δ_C (101 MHz, $CDCl_3$) 44.6 (CH_3), 108.0 (d, *J* 1.9 Hz, CH), 120.8 (q, *J* 269.4 Hz, C), 124.6 (2 × CH), 126.0 (2 × CH), 129.1 (2 × CH), 129.8 (2 × CH), 134.7 (C), 141.0 (C), 142.8 (C), 142.9 (C), 144.9 (q, *J* 39.1 Hz, C), 148.4 (C); *m/z* (ESI) 434 (MNa^+. 100%).

1-(4'-Nitrophenyl)-3-(trifluoromethyl)butane-1,3-dione (122)[160]



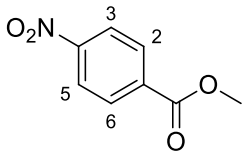
To a stirred solution of methyl trifluoroacetate (1.94 g, 15.2 mmol) in anhydrous toluene (20 mL) was added potassium *tert*-butoxide (2.04 g, 18.2 mmol) followed by 4-nitroacetophenone (1.00 g, 6.06 mmol). The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched with 3 M HCl and acidified to pH 6-7. The mixture was extracted with diethyl ether (3 × 50 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 10% ethyl acetate in petroleum ether (40–60) to give 1-(4'-nitrophenyl)-3-(trifluoromethyl)butane-1,3-dione (**122**) as an orange solid (1.18 g, 75%). Mp 92–94 °C (lit.[160] 99–100 °C); δ_H (400 MHz, $CDCl_3$) 6.62 (1H, s, 2-H), 8.12 (1H, d, *J* 9.1 Hz, 2'-H and 6'-H), 8.36 (1H, d, *J* 9.1 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 93.6 (CH), 116.9 (q, *J* 283.9 Hz, C), 124.3 (2 × CH), 128.7 (2 × CH), 138.2 (C), 150.9 (C), 179.4 (q, *J* 37.0 Hz, C), 182.4 (C); *m/z* (EI) 261 (M^+. 12%), 192 (52), 146 (12), 105 (17), 84 (15), 44 (100).

4-Methanesulfonylphenylhydrazine hydrochloride (123)[161]



4-Chlorophenyl methyl sulfonyl (0.200 g, 1.05 mmol) and hydrazine monohydrate (2.00 mL, 16.0 mmol) were heated in a microwave at 120 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted in ethanol and concentrated *in vacuo*. The white solid was washed with water before stirring with 37% hydrochloric acid (88.0 µL, 1.05 mmol) in ethanol (5 mL) for 0.5 h. The precipitate was collected, washed with ethanol and air dried to give 4-methanesulfonylphenylhydrazine hydrochloride (**123**) as a white solid (0.232 g, 100%). Mp 130–131 °C (lit.[161] 135–136 °C); δ_H (400 MHz, DMSO-d_6) 3.03 (3H, s, CH_3), 6.83 (2H, d, *J* 8.9 Hz, 2-H and 6-H), 7.23 (3H, s, NH_2.HCl), 7.54 (2H, d, *J* 8.9 Hz, 3-H and 5-H), 7.74 (1H, s, NH); δ_C (101 MHz, DMSO-d_6) 44.0 (CH_3), 113.3 (2 × CH), 128.5 (2 × CH), 132.1 (C), 150.0 (C); *m*/*z* (CI) 188 (MH^+. 24%), 173 (67), 157 (100), 79 (24).

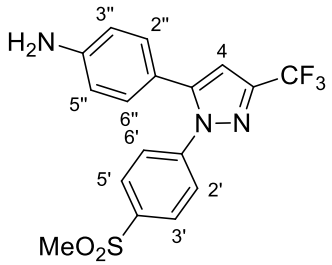
Methyl 4-nitrobenzoate (127)[162]



To a stirred solution of methyl trifluoroacetate (0.093 g, 0.73 mmol) in anhydrous toluene (2 mL) was added potassium *tert*-butoxide (0.20 g, 1.8 mmol) followed by 4-nitroacetophenone (0.10 g, 0.61 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with 3 M HCl and acidified to pH 6—7. The mixture was extracted with diethyl ether (3 × 50 mL). The organic layer was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 60% ethyl acetate in petroleum ether (40–60) to give methyl 4-nitrobenzoate (**127**) as a yellow solid (0.051 g, 46%). Mp 93–95 °C (lit.[162] 93–95 °C); δ_H (500 MHz, $CDCl_3$) 3.98 (2H, s, CH_3), 8.21

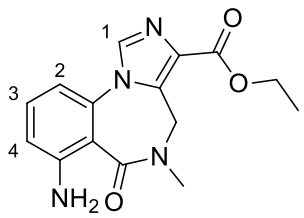
(1H, d, *J* 9.0 Hz, 2-H and 6-H), 8.29 (1H, d, *J* 9.0 Hz, 3-H and 4-H). δ_C (126 MHz, $CDCl_3$) 52.98 (CH_3), 123.70 (CH), 130.87 (CH), 135.65 (C), 150.73 (C), 165.33 (C). *m*/*z* (EI) 181 (M^+. 32%), 164 (28), 150 (100), 120 (44), 84 (15).

1-[4'-(Methylsulfonyl)phenyl]-5-(4''-aminophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (128)



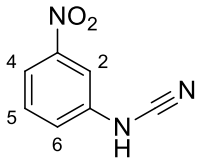
The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using 1-[4'-(methylsulfonyl)phenyl]-5-(4''-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole (**121**) (0.14 g, 0.34 mmol) and tin(II) chloride dihydrate (0.38 g, 1.7 mmol) in ethanol (5 mL). The reaction mixture was stirred under reflux for 16 h. The crude material was purified using flash column chromatography eluting with 60% ethyl acetate in petroleum ether (40–60) to give 1-[4'-(methylsulfonyl)phenyl]-5-(4''-aminophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (**128**) as a white solid (0.11 g, 83%). Mp 165–167 °C; ν_{max}/cm^{-1} (neat) 3489 (NH), 3373 (NH), 1627 (C=C), 1613, 1476, 1449, 1301, 1235, 1153, 1133, 1098, 966, 781; δ_H (400 MHz, $CDCl_3$) 3.06 (3H, s, CH_3), 3.92 (2H, br s, NH_2), 6.62 (2H, d, *J* 8.7 Hz, 3''-H and 5''-H), 6.67 (1H, s, 4-H), 6.98 (2H, d, *J* 8.7 Hz, 2''-H and 6''-H), 7.56 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H), 7.92 (2H, d, *J* 8.8 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 44.6 (CH_3), 105.9 (d, *J* 1.8 Hz, CH), 115.1 (2 × CH), 118.1 (C), 121.2 (q, *J* 269.2 Hz, C), 125.8 (2 × CH), 128.5 (2 × CH), 130.2 (2 × CH), 139.7 (C), 143.8 (C), 144.3 (q, *J* 38.4 Hz, C), 145.8 (C), 147.9 (C); *m*/*z* (ESI) 404.0634 (MNa^+. $C_{17}H_{14}F_3N_3NaO_2S$ requires 404.0651).

Ethyl 7-amino-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (131)



The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using ethyl 7-nitro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (**130**) (0.030 g, 0.090 mmol) and tin(II) chloride dihydrate (0.10 g, 0.45 mmol) in ethanol (1 mL). The reaction mixture was stirred under reflux for 16 h to give ethyl 7-amino-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**131**) as a white solid (0.019 g, 71%). Mp 218–220 °C; ν_{max}/cm^{-1} (neat) 3460 (NH), 3313 (NH), 2926 (CH), 1696 (C=O), 1646 (C=O), 1614, 1582, 1493, 1377, 1317, 1284, 1222, 1195, 1142, 1096, 942, 800, 761, 704; δ_H (400 MHz, $CDCl_3$) 1.43 (3H, t, *J* 7.1 Hz, $CO_2CH_2C\mathit{H}_3$), 3.20 (3H, s, NCH_3), 4.34–4.50 (3H, m, $CO_2C\mathit{H}_2CH_3$ and 4-*H*H), 5.07 (1H, d, *J* 15.5 Hz, 4-H*H*), 5.29 (2H, br s, NH_2), 6.65 (1H, dd, *J* 8.0, 1.0 Hz, 8-H), 6.76 (1H, dd, *J* 8.0, 1.0 Hz, 10-H), 7.27 (1H, t, *J* 8.0 Hz, 9-H), 7.81 (1H, s, 1-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 35.3 (CH_3), 42.4 (CH_2), 61.0 (CH_2), 111.4 (CH), 112.2 (C), 116.6 (CH), 128.4 (C), 132.2 (CH), 133.7 (C), 135.5 (CH), 136.1 (C), 150.0 (C), 163.3 (C), 166.8 (C); *m*/*z* (ESI) 323.1101 (MNa^+. $C_{15}H_{16}N_4NaO_3$ requires 323.1115).

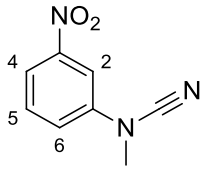
***N*-(3-Nitrophenyl)cyanamide (134)[163]**



Cyanogen bromide (0.12 g, 1.08 mmol) in diethyl ether (5 mL) was added dropwise to a stirred solution of 3-nitroaniline (0.10 g, 0.72 mmol) in diethyl ether (5 mL) at 0 °C. The reaction mixture was heated under reflux for 24 h. After cooling to room temperature, the reaction mixture was filtered and

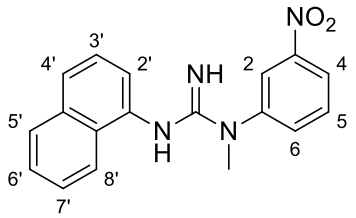
washed with ethyl acetate. The ethyl acetate washings were washed with 10% hydrochloric acid (2 × 10 mL), water (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give (3-nitrophenyl)cyanamide (**134**) as a yellow solid (0.056 g, 46%). Mp 133−135 °C (lit.[163] 133−135 °C); δ_H (400 MHz, CD_3OD) 7.38 (1H, ddd, *J* 8.1, 2.2, 0.8 Hz, 6-H), 7.59 (1H, t, *J* 8.1 Hz, 5-H), 7.81 (1H, t, *J* 2.2 Hz, 2-H), 7.91 (1H, ddd, *J* 8.1, 2.2, 0.8 Hz, 4-H); δ_C (126 MHz, CD_3OD) 110.8 (CH), 112.1 (C), 118.5 (CH), 122.1 (CH), 132.1 (CH), 141.7 (C), 150.6 (C); *m*/*z* (EI) 163 (M^+. 100%), 117 (32), 90 (61), 57 (27).

_N_-Methyl-_N_-(3-nitrophenyl)cyanamide (135)[164]



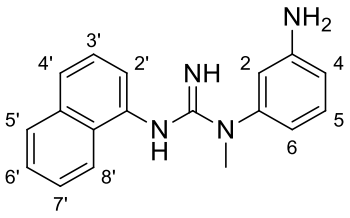
Sodium hydride in 60% mineral oil (0.930 g, 2.33 mmol) was washed with hexane (3 × 10 mL) and dried. This was then added to (3-nitrophenyl)cyanamide (0.190 g, 1.17 mmol) in THF (3 mL) and heated under reflux for 2 h. The reaction mixture was cooled to 0 °C and methyl iodide (180 μL, 2.91 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was then diluted with methanol (5 mL) and water (10 mL) and extracted with chloroform (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 1% methanol in dichloromethane to give *N*-methyl-*N*-(3-nitrophenyl)cyanamide (**135**) as a white solid (0.190 g, 91%). Mp 106−107 °C; δ_H (400 MHz, $CDCl_3$) 3.44 (3H, s), 7.48 (1H, ddd, *J* 8.2, 2.3, 0.9 Hz, 6-H), 7.57 (1H, t, *J* 8.2 Hz, 5-H), 7.86 (1H, t, *J* 2.3 Hz, 2-H), 7.95 (1H, ddd, *J* 8.2, 2.3, 0.9 Hz, 4-H); δ_C (126 MHz, $CDCl_3$) 37.2 (CH_3), 109.4 (CH), 112.7 (C), 118.2 (CH), 121.0 (CH), 130.8 (CH), 142.0 (C), 149.3 (C); *m*/*z* (EI) 177 (M^+. 100%), 152 (67), 131 (74), 104 (61), 90 (26), 77 (60), 63 (25), 50 (18). Spectroscopic data was in agreement with previously published data.[164]

***N*-(1-Naphthyl)-*N'*-(3-nitrophenyl)-*N'*-methylguanidine (137)**



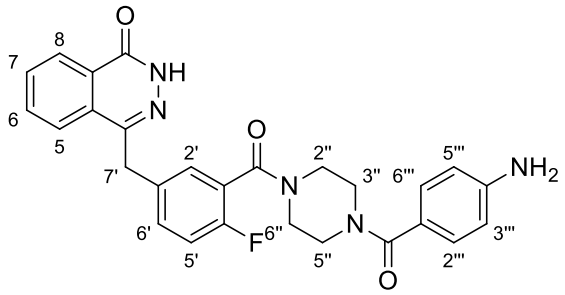
1-Naphthylamine (0.13 g, 0.75 mmol) was dissolved in diethyl ether (1 mL) and converted to its hydrochloride salt by dropwise addition of aqueous hydrochloric acid (1 M) in diethyl ether (1 mL) to give a pink precipitate. This was filtered and dried. This was added to *N*-methyl-*N*-(3-nitrophenyl)cyanamide (**135**) (0.13 g, 0.75 mmol) under argon and the reaction mixture was stirred at 160 °C neat for 3 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (10 mL) and washed with 0.1 M NaOH (10 mL). The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography eluting with 1% methanol and 1% triethylamine in dichloromethane to give *N*-(1-naphthyl)-*N'*-(3-nitrophenyl)-*N'*-methylguanidine (**137**) as a viscous oil (0.20 g, 84%). ν_{max}/cm^{-1} (neat) 3485 (NH), 3386 (NH), 2924 (CH), 1631, 1567, 1522 (NO), 1482, 1379, 1345 (NO), 1234, 960, 854, 783, 771, 732, 684; δ_H (400 MHz, $CDCl_3$) 3.60 (3H, s, NCH_3), 7.02 (1H, dd, *J* 7.2, 1.0 Hz, 2'-H), 7.39–7.58 (5H, m, 5 × ArH), 7.72 (1H, ddd, *J* 8.1, 2.1, 1.0 Hz, 6-H), 7.79–7.86 (1H, m, ArH), 8.03 (1H, ddd, *J* 8.1, 2.1, 1.0 Hz, 4-H), 8.07–8.13 (1H, m, ArH), 8.23 (1H, t, *J* 2.1 Hz, 2-H); δ_C (101 MHz, $CDCl_3$) 39.0 (CH_3), 117.5 (CH), 120.1 (CH), 120.6 (CH), 122.8 (CH), 124.0 (CH), 125.4 (CH), 126.2 (CH), 126.5 (CH), 128.1 (CH), 128.6 (C), 130.2 (CH), 131.9 (CH), 134.9 (C), 145.9 (C), 146.5 (C), 149.1 (C), 150.1 (C); *m/z* (ESI) 321.1333 (MH^+. $C_{18}H_{17}N_4O_2$ requires 321.1346).

***N*-(1-Naphthyl)-*N'*-(3-aminophenyl)-*N'*-methylguanidine (138)**



The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using *N*-(1-naphthyl)-*N'*-(3-nitrophenyl)-*N'*-methylguanidine (**137**) (0.23 g, 0.73 mmol) and tin(II) chloride dihydrate (0.82 g, 3.6 mmol) in ethanol (10 mL). The reaction mixture was stirred under reflux for 16 h to give *N*-(1-naphthyl)-*N'*-(3-aminophenyl)-*N'*-methylguanidine (**138**) as a brown solid (0.12 g, 95%). Mp 96–98 °C; ν_{max}/cm^{-1} (neat) 3322 (NH), 3200 (NH), 3051, 1618, 1599, 1580, 1560, 1491, 1383, 1275, 1227, 970, 781, 750; δ_H (400 MHz, $CDCl_3$) 3.50 (3H, s, NCH_3), 6.53 (1H, ddd, *J* 7.9, 2.2, 0.9 Hz, 4-H), 6.63 (1H, t, *J* 2.2 Hz, 2-H), 6.70 (1H, ddd, *J* 7.9, 2.2, 0.9 Hz, 6-H), 7.05 (1H, dd, *J* 7.4, 1.1 Hz, 2'-H), 7.15 (1H, t, *J* 7.9 Hz, 5-H), 7.40 (1H, dd, *J* 8.4, 7.4 Hz, 3'-H), 7.43–7.49 (2H, m, 2 × ArH), 7.52 (1H, br d, *J* 8.4 Hz, 4'-H), 7.78–7.84 (1H, m, ArH), 8.13–8.19 (1H, m, ArH); δ_C (101 MHz, $CDCl_3$) 39.0 (CH_3), 113.4 (CH), 113.5 (CH), 116.7 (CH), 118.4 (CH), 122.5 (CH), 124.1 (CH), 125.2 (CH), 126.0 (CH), 126.4 (CH), 128.0 (CH), 129.2 (C), 130.6 (CH), 134.9 (C), 145.5 (C), 145.7 (C), 148.0 (C), 151.2 (C); *m/z* (EI) 290.1528 (M^+. $C_{18}H_{18}N_4$ requires 290.1531), 247 (11%), 234 (10), 168 (22), 122 (56), 93 (8).

4-[3'-[4''-(4'''-Aminobenzoyl)piperazine-1''-carbonyl]-4'-fluorobenzyl]-2*H*-phthalazin-1-one (141)



The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using 4-[3'-[4''-(4'''-

nitrobenzoyl)piperazine-1''-carbonyl]-4'-fluorobenzyl]-2*H*-phthalazin-1-one (**140**) (55.0 mg, 0.107 mmol) and tin(II) chloride dihydrate (120 mg, 0.533 mmol) in ethanol (10 mL). The reaction mixture was stirred under reflux for 16 h. The crude material was purified through a short pad of silica, eluting with 2% methanol and 5% triethylamine in dichloromethane to give 4-[3'-[4''-(4'''-aminobenzoyl)piperazine-1''-carbonyl]-4'-fluorobenzyl]-2*H*-phthalazin-1-one (**141**) (45.0 mg, 87%) as a viscous oil. ν_{max}/cm^{-1} (neat) 3347 (NH), 3221 (NH), 3007, 2924 (CH), 2863 (CH), 1605 (CO), 1424, 1256, 1177, 1003, 748, 729; δ_H (400 MHz, $CDCl_3$) 3.32 (2H, br s, NCH_2), 3.52—4.04 (8H, m, 3 × NCH_2, and 4'''-NH_2), 4.28 (2H, s, 7'-H_2), 6.64 (2H, d, *J* 8.4 Hz, 3'''-H and 5'''-H), 7.03 (1H, t, *J* 8.7 Hz, 5'-H), 7.26 (2H, d, *J* 8.4 Hz, 2'''-H and 6'''-H), 7.29—7.36 (2H, m, 2'-H, and 6'-H), 7.68—7.80 (3H, m, 5-H, 6-H, and 7-H), 8.43—8.49 (1H, m, 8-H), 10.59 (1H, s, NH); *δ*c (101 MHz, $CDCl_3$) 37.8 (CH_2), 42.4 (2 × CH_2), 47.3 (2 × CH_2), 114.3 (2 × CH), 116.3 (CH, d, *J* 22.0 Hz), 123.9 (C, d, *J* 17.9 Hz), 124.3 (C), 125.2 (CH), 127.4 (CH), 128.5 (C), 129.4 (CH, d, *J* 3.6 Hz), 129.6 (2 × CH), 129.7 (C), 131.8 (CH), 131.8 (CH), 133.8 (CH), 134.5 (C, d, *J* 3.5 Hz), 145.6 (C), 148.7 (C), 157.1 (C, d, *J* 247.6 Hz), 160.5 (C), 165.3 (C), 171.3 (C); *m*/*z* (ESI) 538.1488 (MNa^+. $C_{27}H_{22}FN_5NaO_5$ requires 538.1497).

5.3 Radioiodination Experimental

General Experimental for Radioiodination of Anilines with Sodium [^{125}I]Iodide

Reductant free sodium [^{125}I]iodide was purchased from Perkin Elmer (product number NEZ033H005MC) with a concentration of 12.95 GBq/mL and specific radioactivity of 643.8 GBq/mg in 0.1 M sodium hydroxide (pH 12—14) aqueous solution. All radiochemical yields were determined by radio-HPLC analysis of the crude product.

Analytical Radio-HPLC Method for Determination of Radioiodide Incorporation

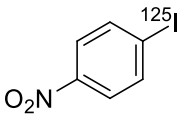
Analytical HPLC was performed with a Dionex Ultimate 3000 HPLC system equipped with a Flowstar LB 513 NaI scintillation detector and a DAD-3000 UV detector using a Synergi 4 µm Hydro-RP 80 Å column (150 × 4.6 mm) with 10 mm guard cartridge, UV 254 nm and flow 1 mL/min. The mobile phase for the

analysis of substrates was water:acetonitrile. Analysis of the reaction mixture (to assess radioiodide incorporation) used a gradient profile of water and acetonitrile, as shown below.

Time (mins)	% MeCN
0—20	10—95
20—24	95
24—25	95—10
25—30	10

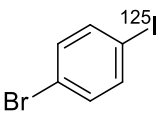
Co-elution with the UV signal from the ^{127}I-compound was used to confirm identity of the ^{125}I-product from each reaction described.

General Method for Radiodination: 4-[^{125}I]Iodonitrobenzene (47)



To a solution of *p*-toluenesulfonic acid monohydrate (2.1 mg, 11.0 μmol) in acetonitrile (0.2 mL) was added 4-nitroaniline (0.50 mg, 3.6 μmol). The solution was cooled in a water bath to 10—15 °C. Polymer-supported nitrite (3.2 mg, containing 11.0 μmol of NO_2) was added and the reaction mixture was stirred for 0.25 h. A 4—6 MBq solution of sodium [^{125}I]iodide in water (0.01 mL) was added and the reaction mixture warmed to 20 °C and stirred for 2 h. The mixture was removed from the resin by syringe and diluted by the addition of water (0.2 mL). Analysis of this solution by analytical radio-HPLC showed a radiochemical yield of 93%.

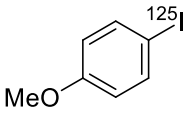
4-[^{125}I]Iodobromobenzene (51)



The reaction was done using 4-bromoaniline (1.0 mg, 5.8 μmol) in acetonitrile (0.2 mL) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-

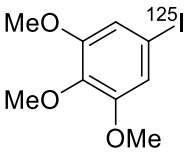
toluenesulfonic acid monohydrate were used. Analysis by radio-HPLC gave a radiochemical yield of 73%.

4-[^{125}I]Iodoanisole (52)



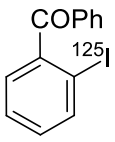
The reaction was done using 4-methoxyaniline (0.50 mg, 4.1 µmol) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used and the reaction was performed at 40 °C. Analysis by radio-HPLC gave a radiochemical yield of 97%.

3,4,5-Trimethoxy[^{125}I]iodobenzene (55)



The reaction was done using 3,4,5-trimethoxyaniline (1.0 mg, 5.5 µmol) in acetonitrile (0.2 mL) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used. Analysis by radio-HPLC gave a radiochemical yield of 94%.

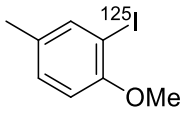
2-[^{125}I]Iodobenzophenone (57)



The reaction was done using 2-aminobenzophenone (0.5 mg, 2.5 µmol) in acetonitrile (0.2 mL) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and

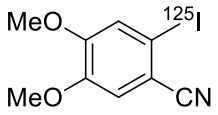
p-toluenesulfonic acid monohydrate were used and the reaction required 4 h. Analysis by radio-HPLC gave a radiochemical yield of 94%.

2-[^{125}I]Iodo-4-methylanisole (59)



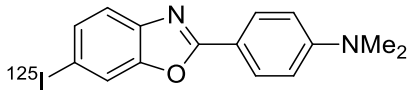
The reaction was performed using 2-methoxy-5-methylaniline (0.50 mg, 3.6 μmol) in acetonitrile (0.2 mL) as described in the general radioiodination procedure except for the following: one equivalent of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used. Analysis by radio-HPLC gave a radiochemical yield of 83%.

4,5-Dimethoxy-2-[^{125}I]iodobenzonitrile (60)



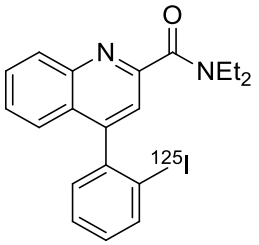
The reaction was performed using 2-amino-4,5-dimethoxybenzonitrile (1.0 mg, 5.6 μmol) in acetonitrile (0.2 mL) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used. Analysis by radio-HPLC gave a radiochemical yield of 61%.

2-(4'-Dimethylaminophenyl)-6-[^{125}I]iodobenzoxazole (81)



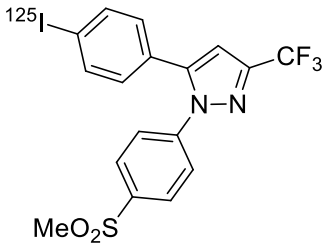
The reaction was performed using 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) (1.0 mg, 4.0 μmol) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used. Analysis by radio-HPLC gave a radiochemical yield of 47%.

4-(2-[^{125}I]Iodophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (82)



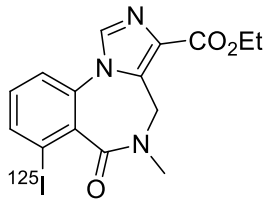
The reaction was performed using 4-(2-aminophenyl)-*N*,*N*-diethylquinoline-2-carboxamide (**111**) (0.50 mg, 1.6 µmol) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used and the reaction was performed at 60 °C. Analysis by radio-HPLC gave a radiochemical yield of 50%.

1-[4'-(Methylsulfonyl)phenyl]-5-(4''-[^{125}I]iodophenyl)-3-(trifluoromethyl)-1*H*pyrazole (84)



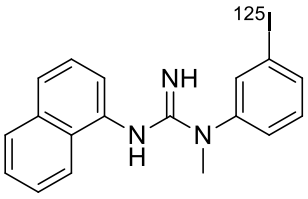
The reaction was performed using 1-[4'-(methylsulfonyl)phenyl]-5-(4''-aminophenyl)-3-(trifluoromethyl)-1*H*-pyrazole (**128**) (1.0 mg, 2.6 µmol) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used. Analysis by radio-HPLC gave a radiochemical yield of 47%.

Ethyl 7-[^{125}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (85)



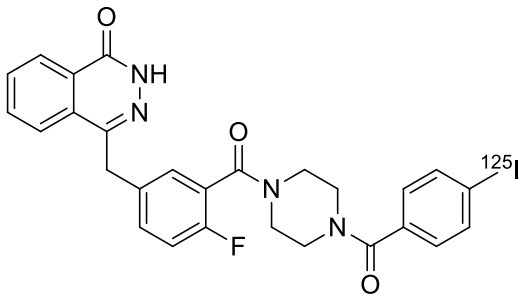
The reaction was performed using ethyl 7-amino-5,6-dihydro-5-methyl-6-oxo-4*H*benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**131**) (0.50 mg, 1.7 µmol) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used and the reaction was performed at 60 °C. Analysis by radio-HPLC gave a radiochemical yield of 94%.

***N*-(1-Naphthyl)-*N'*-(3-[^{125}I]iodophenyl)-*N'*-methylguanidine (86)**



The reaction was performed using *N*-(1-naphthyl)-*N'*-(3-aminophenyl)-*N'*-methylguanidine (**138**) (1.0 mg, 3.4 µmol) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used and the reaction was performed at 60 °C. Analysis by radio-HPLC gave a radiochemical yield of 64%.

4-{3'-[4"-(4'"-[^{125}I]iodobenzoyl)piperazine-1"-carbonyl]-4'-fluorobenzyl}-2*H*-phthalazin-1-one (87)



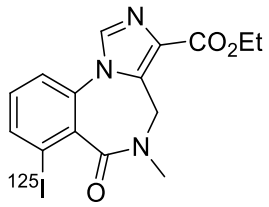
The reaction was performed using 4-{3'-[4"-(4'"-aminobenzoyl)piperazine-1"-carbonyl]-4'-fluorobenzyl}-2*H*-phthalazin-1-one (**141**) (0.50 mg, 1.0 μmol) in acetonitrile (0.2 mL) as described in the general radioiodination procedure except for the following: six equivalents of both polymer-supported nitrite and *p*-toluenesulfonic acid monohydrate were used. Analysis by radio-HPLC gave a radiochemical yield of 59%.

Semi-Preparative Radio-HPLC Method for purification of Ethyl 7-[^{125}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (85)

Semi-preparative HPLC was performed with a Dionex Ultimate 3000 HPLC system equipped with a Knauer Advanced Scientific Instruments Smartline UV Detector 2500 and a photomultiplier tube (PMT) connected to a Lab Logic Flow-Count radiodetector and using a Synergi 4 μm Hydro-RP 80 Å column (150 × 10 mm) with 10 mm guard cartridge, UV 254 nm and flow 3 mL/min. A gradient profile of water and acetonitrile was used, as shown below.

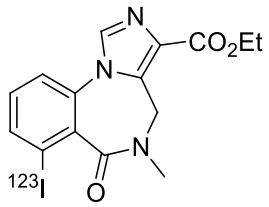
Time (mins)	% MeCN
0—20	10—95
20—24	95
24—25	95—10
25—30	10

Experimental for Iodination with Sodium [^{125}I]Iodide: Synthesis and Purification of Ethyl 7-[^{125}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (85)



To a solution of *p*-toluenesulfonic acid monohydrate (2.1 mg, 11 μmol) in acetonitrile (0.2 mL) was added ethyl 7-amino-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**131**) (0.50 mg, 1.7 μmol). The solution was cooled in a water bath to 10–15 °C. Polymer-supported nitrite (3.2 mg, containing 11.0 μmol of NO_2) was added and the reaction mixture was stirred for 0.25 h. A 4–6 MBq solution of sodium [^{125}I]iodide in water (0.01 mL) was added and the reaction mixture was warmed to 60 °C and stirred for 2 h. The mixture was removed from the resin by syringe and diluted by the addition of water (0.2 mL). The crude product was purified by semi-preparative HPLC and was collected at approximately 12 minutes. The fraction containing ethyl 7-[^{125}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**85**) was concentrated *in vacuo*, then reconstituted in 10% ethanol in 0.9% saline to afford ethyl 7-[^{125}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**85**) in 75 ± 9.9% radioactivity yield, with molar activity of 16.2 ± 1.22 GBq/μmol (n = 2). The radiochemical purity of the final product was determined by analytical HPLC and was >99% (n = 2). The identity of the product was confirmed by comparing the retention time of ethyl 7-[^{125}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate against the retention time of unlabelled ethyl 7-[^{127}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate.

Experimental for Iodination with Sodium [^{123}I]Iodide: Synthesis and Purification of Ethyl 7-[^{123}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (85)



The reaction was performed as described in the procedure for synthesis and purification of ethyl 7-[^{125}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**85**) with sodium [^{125}I]iodide, except no-carrier-added sodium [^{123}I]iodide (30–40 MBq) was used to afford ethyl 7-[^{123}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**85**) in 22 ± 9.2% (n = 4) radioactivity yield with molar activity of >298 ± 42.1 GBq/μmol (n = 4). The amount of [^{123}I]**85** produced fell below the sensitivity threshold of the UV detector for this compound (<6.1 × 10^{-5} μmol), therefore an absolute value for molar activity could not be determined. The radiochemical purity of the final product was determined by analytical HPLC and was >99% (n = 4).

The reaction with carrier-added sodium [^{123}I]iodide (30–40 MBq) gave ethyl 7-[^{123}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**85**) in 52 ± 18% radioactivity yield, with molar activity of >298 ± 42.1 GBq/μmol (n = 3). The molar activity was calculated to be 1278 GBq/μmol with carrier-added sodium [^{123}I]iodide (73 MBq). The radiochemical purity of the final product was determined by analytical HPLC and was >99% (n = 3).

Measurement of Specific Activity of Ethyl 7-[^{123}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (85)

For calculation of the specific activity of ethyl 7-[^{123}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (**85**), a concentration response curve was plotted by injection of 50 μL samples of unlabelled ethyl 7-[^{127}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-

a][1,4]diazepine-3-carboxylate onto the semi-preparative HPLC in concentrations of 1 mg/mL, 0.5 mg/mL, 0.1 mg/mL, 0.05 mg/mL, 0.01 mg/mL, 0.005 mg/mL, 0.001 mg/mL and 0.0005 mg/mL. The UV response (mV/min) of each concentration was plotted against the corresponding moles of unlabelled ethyl 7-[^{127}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate (Figure 20). The crude reaction mixture was injected onto the semi-preparative HPLC system in each reaction, and the resulting UV response (mV/min) of ethyl 7-[^{123}I]iodo-5,6-dihydro-5-methyl-6-oxo-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate product peak measured. The UV response was then used to calculate the number of moles of product. By recording the amount of radioactivity present in the reaction mixture before injection onto the column, integration of the product peak on the radio-HPLC chromatogram would give the radioactivity of the product, allowing specific activity to be calculated after decay correction.

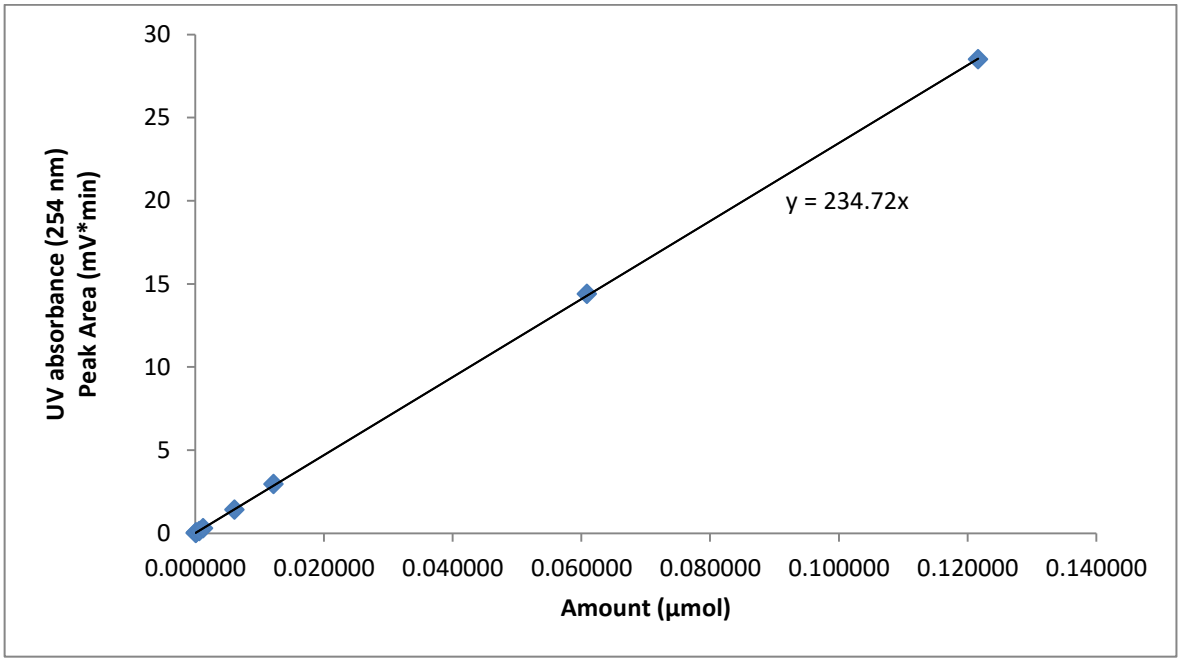
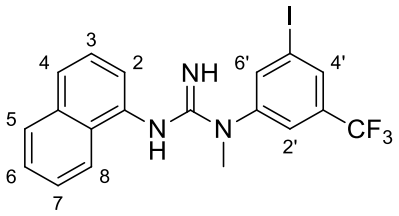


Figure 20. Specific activity UV-HPLC calibration curve for iomazenil.

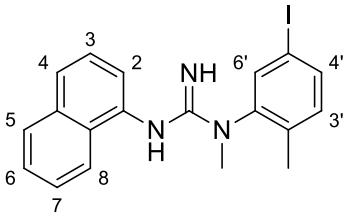
5.4 Synthesis of CNS1261 Analogues Experimental

N-(1-Naphthyl)-*N'*-(3-iodo-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (147)



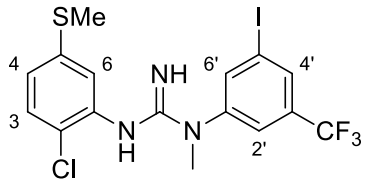
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using *N*-(1-naphthyl)-*N'*-(3-amino-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**187**) (0.060 g, 0.17 mmol), *p*-toluenesulfonic acid monohydrate (0.096 g, 0.25 mmol), polymer-supported nitrite (0.14 g, containing 0.50 mmol of NO_2) and sodium iodide (0.050 g, 0.34 mmol). The reaction mixture was stirred at 60 °C for 24 h. The crude material was purified using flash column chromatography, eluting with 20—60% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(1-naphthyl)-*N'*-(3-iodo-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**147**) as a brown solid (0.034 g, 43%). Mp 142—143 °C; ν_{max}/cm^{-1} (neat) 3426 (NH), 3048 (NH), 2924 (CH), 1636, 1597, 1566, 1435, 1373, 1327, 1273, 1165, 1119, 957, 872, 795, 687, 370, 347; δ_H (400 MHz, $CDCl_3$) 3.57 (3H, s, NCH_3), 4.03 (2H, s, 2 × NH), 7.02 (1H, dd, *J* 7.2, 1.1 Hz, 2-H), 7.42 (1H, dd, *J* 8.1, 7.2 Hz, 3-H), 7.45—7.50 (2H, m, 6-H and 7-H), 7.54 (1H, d, *J* 8.1 Hz, 4-H), 7.60 (1H, br s, 2'-H), 7.78 (1H, br s, 6'-H), 7.80—7.86 (1H, m, 5-H), 7.91 (1H, br s, 4'-H), 8.05—8.13 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 39.0 (CH_3), 94.3 (C), 117.4 (CH), 122.2 (CH, q, *J* 3.6 Hz), 122.7 (C, q, *J* 274.4 Hz), 122.8 (CH), 124.0 (CH), 125.4 (CH), 126.2 (CH), 126.5 (CH), 128.1 (CH), 128.7 (C), 131.1 (CH, q, *J* 3.8 Hz), 133.4 (C, q, *J* 33.0 Hz), 134.9 (C), 138.2 (CH), 145.8 (C), 147.0 (C), 149.8 (C); *m/z* (ESI) 470.0323 (MH^+. $C_{19}H_{16}F_3IN_3$ requires 470.0336).

***N*-(1-Naphthyl)-*N'*-(2-methyl-5-iodophenyl)-*N'*-methylguanidine (148)**



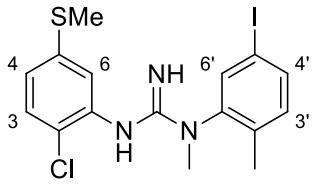
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using *N*-(1-naphthyl)-*N'*-(2-methyl-5-aminophenyl)-*N'*-methylguanidine (**191**) (0.030 g, 0.10 mmol), *p*-toluenesulfonic acid monohydrate (0.056 g, 0.30 mmol), polymer-supported nitrite (0.086 g, containing 0.30 mmol of NO_2) and sodium iodide (0.030 g, 0.20 mmol). The reaction mixture was stirred at 60 °C for 16 h. The crude material was purified using flash column chromatography, eluting with 20—60% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(1-naphthyl)-*N'*-(2-methyl-5-iodophenyl)-*N'*-methylguanidine (**148**) as a brown solid (0.024 g, 59%). Mp 126—128 °C; ν_{max}/cm^{-1} (neat) 3487 (NH), 2924 (CH), 1620, 1558, 1522, 1481, 1443, 1381, 1265, 1096, 941, 864, 779, 748, 571, 455, 424, 393, 332; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, 2'-CH_3), 3.43 (3H, s, NCH_3), 3.83 (1H, s, NH), 6.99—7.05 (2H, m, 2-H and 3'-H), 7.40 (1H, dd, *J* 8.1, 7.3 Hz, 3-H), 7.43—7.49 (2H, m, 6-H and 7-H), 7.51 (1H, d, *J* 8.1 Hz, 4-H), 7.55 (1H, dd, *J* 8.1, 1.2 Hz, 4'-H), 7.66 (1H, br s, 6'-H), 7.78—7.84 (1H, m, 5-H), 8.10—8.21 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 17.4 (CH_3), 37.9 (CH_3), 90.9 (C), 118.1 (C), 122.4 (C), 124.1 (CH), 125.2 (CH), 126.0 (CH), 126.5 (CH), 128.0 (CH), 129.3 (CH), 133.3 (CH), 134.9 (C), 137.1 (CH), 137.1 (CH) 137.2 (C), 137.8 (CH), 144.2 (C), 150.6 (C); *m/z* (EI) 415.0557 (M^+. $C_{19}H_{18}IN_3$ requires 415.0545), 400 (49%), 247 (42), 169 (17), 143 (26).

***N*-(2-Chloro-5-(methylthio)phenyl)-*N'*-(5-iodo-3-(trifluoromethyl)phenyl)-*N'*-methylguanidine (150)**



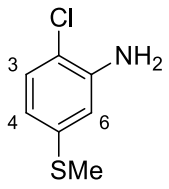
The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(3-amino-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**186**) (0.030 g, 0.077 mmol), *p*-toluenesulfonic acid monohydrate (0.044 g, 0.23 mmol), polymer-supported nitrite (0.066 g, containing 0.23 mmol of NO_2) and sodium iodide (0.023 g, 0.15 mmol). The reaction mixture was stirred at room temperature for 16 h. The crude material was purified using flash column chromatography, eluting with 60—100% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(1-naphthyl)-*N'*-(3-iodophenyl)-*N'*-methylguanidine (**150**) as a brown solid (0.020 g, 52%). Mp 74—76 °C; ν_{max}/cm^{-1} (neat) 3495 (NH), 3464 (NH), 2918 (CH), 2355, 2330, 1638, 1589, 1560, 1443, 1375, 1331, 1292, 1171, 1128, 1094, 972, 891, 872, 799, 689; δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, SCH_3), 3.43 (3H, s, NCH_3), 4.02 (2H, s, 2 × NH), 6.85 (1H, dd, *J* 8.3, 2.3 Hz, 4-H), 6.88 (1H, d, *J* 2.3 Hz, 6-H), 7.29 (1H, d, *J* 8.3 Hz, 3-H), 7.56 (1H, br s, 6'-H), 7.77 (1H, br s, 2'-H), 7.88 (1H, br s, 4'-H); δ_C (101 MHz, $CDCl_3$) 16.1 (CH_3), 39.0 (CH_3), 94.3 (C), 122.0 (CH), 122.3 (CH), 122.3 (q, *J* 3.7 Hz, CH), 122.6 (q, *J* 274.4 Hz, C), 124.2 (C), 130.3 (CH), 131.4 (q, *J* 3.7 Hz, CH), 133.4 (q, *J* 33.2 Hz, C), 138.2 (CH), 138.3 (C), 138.3 (C), 146.6 (C), 150.4 (C); *m/z* (ESI) 499.9656 (MH^+. $C_{16}H_{15}{}^{35}ClF_3IN_3S$ requires 499.9666).

_N_-(2-Chloro-5-(methylthio)phenyl)-_N'_-(2-methyl-5-iodophenyl)-_N'_-methylguanidine (151)



The reaction was carried out according to the previously described method B for 4-iodonitrobenzene (**47**) using *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(2-methyl-5-aminophenyl)-*N'*-methylguanidine (**190**) (0.055 g, 0.16 mmol), *p*-toluenesulfonic acid monohydrate (0.094 g, 0.49 mmol), polymer-supported nitrite (0.14 g, containing 0.49 mmol of NO_2) and sodium iodide (0.049 g, 0.33 mmol). The reaction mixture was stirred at 60 °C for 16 h. The crude material was purified using flash column chromatography, eluting with 20—60% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(2-methyl-5-iodophenyl)-*N'*-methylguanidine (**151**) as a viscous oil (0.056 g, 77%). ν_{max}/cm^{-1} (neat) 3478 (NH), 3377 (NH), 2916 (CH), 1627, 1580, 1560, 1481, 1400, 1375, 1094, 1038, 962, 885, 739, 702, 581; δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, 2'-CH_3), 2.46 (3H, s, SCH_3), 3.30 (3H, s, NCH_3), 3.73 (2H, s, 2 × NH), 6.82 (1H, dd, *J* 8.3, 2.3 Hz, 4-H), 6.90 (1H, d, *J* 2.3 Hz, 6-H), 7.03 (1H, d, *J* 8.1 Hz, 3'-H), 7.27 (3H, d, *J* 8.3 Hz, 3-H), 7.57 (1H, dd, *J* 8.1, 1.8 Hz, 4'-H), 7.62 (1H, br s, 6'-H); δ_C (101 MHz, $CDCl_3$) 16.1 (CH_3), 17.3 (CH_3), 37.7 (CH_3), 90.9 (C), 121.6 (CH), 123.0 (CH), 124.9 (C), 129.2 (C), 130.2 (CH), 133.1 (C), 133.3 (CH), 137.3 (CH), 137.8 (CH), 137.9 (C), 143.9 (C), 150.6 (C); *m/z* (ESI) 445.9938 (MH^+. $C_{16}H_{18}{}^{35}ClIN_3S$ requires 445.9949).

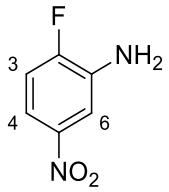
2-Chloro-5-(methylthio)aniline (159)[165]



To a stirred solution of 2-chloro-5-(methylthio)benzoic acid (0.50 g, 2.5 mmol) in *tert*-butanol (5 mL) at room temperature was added triethylamine (0.55 mL, 3.9

mmol), followed by diphenylphosphoryl azide dropwise (0.58 mL, 2.7 mmol). The reaction mixture was heated under reflux for 6 h, cooled to room temperature and concentrated *in vacuo*. The crude residue was diluted in tetrahydrofuran (2.5 mL) and hydrochloric acid (10% w/v; 2.5 mL) and heated under reflux. After 16 h, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was cooled to 0 °C and basified to pH ~ 12 with sodium hydroxide (20% w/v). The mixture was extracted with ethyl acetate (3 × 15 mL), and the combined organic extracts were washed with water (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 10% ethyl acetate in petroleum ether (40—60) to give 2-chloro-5-(methylthio)aniline (**159**) (0.29 g, 68%) as an off-white solid. Mp 180—182 °C (lit.[165] 180—181 °C); δ_H (400 MHz, $CDCl_3$) 2.44 (3H, s, SCH_3), 4.04 (2H, br s, NH_2), 6.59 (1H, dd, *J* 8.3, 2.2 Hz, 4-H), 6.65 (1H, d, *J* 2.2 Hz, 6-H), 7.14 (1H, d, *J* 8.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 16.2 (CH_3), 113.8 (CH), 116.4 (C), 117.5 (CH), 129.7 (CH), 138.1 (C), 143.2 (C); *m*/*z* (EI) 173 (M^+. 100%), 160 (67), 140 (47), 128 (84), 77 (91).

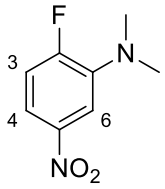
2-Fluoro-5-nitroaniline (166)[166]

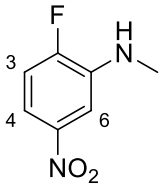


Reduced iron powder (0.075 g, 1.3 mmol, 25 mol%) and palladum(II) chloride (0.019 g, 0.11 mmol, 2.0 mol%) were added to a flask with acetic acid (10 mL) and ethanol (10 mL). 1-Fluoro-2,4-dinitrobenzene (1.0 g, 5.4 mmol) was added with stirring, before the solvent was degassed with hydrogen gas and hydrogen was bubbled into the reaction mixture *via* a balloon. The reaction was complete after 2 h, as followed by TLC. The reaction mixture was filtered through celite, washing with diethyl ether. The organic mixture was washed with water and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 20—40% ethyl acetate in petroleum ether (40—60) to give 2-fluoro-5-nitroaniline (**166**) as a yellow solid (0.48 g, 58%). Mp 99—100 °C (lit.[166] 99—101 °C); δ_H (400 MHz,

$CDCl_3$) 4.04 (2H, s, NH_2), 7.09 (1H, dd, *J* 10.1, 8.9 Hz, 3-H), 7.60 (1H, ddd, *J* 8.9, 4.1, 2.7 Hz, 4-H), 7.66 (1H, dd, *J* 7.6, 2.7 Hz, 6-H); δ_C (101 MHz, $CDCl_3$) 111.6 (d, *J* 5.9 Hz, CH), 114.2 (d, *J* 8.3 Hz, CH), 115.7 (d, *J* 21.4 Hz, CH), 135.7 (d, *J* 14.5 Hz, C), 144.9 (d, *J* 1.4 Hz, C), 154.8 (d, *J* 250.1 Hz, C); *m*/*z* (EI) 156 (M^+. 100%), 110 (46), 83 (39).

_N_,_N_-Dimethyl-2-fluoro-5-nitroaniline (171)[167] and _N_-methyl-2-fluoro-5-nitroaniline (170)[168]

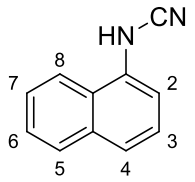


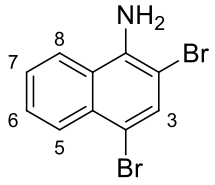


2-Fluoro-5-nitroaniline (**166**) (0.26 g, 1.7 mmol), trimethyl orthoformate (0.35 mL, 3.3 mmol) and 1 drop of sulfuric acid were slowly heated to 120 °C, allowing methanol to be distilled from the reaction. The reaction mixture was then stirred at 120 °C for 2 h, heated to 170 °C for 0.5 h, before cooling to 100 °C. Hydrochloric acid (10% w/v, 1.3 mL) was added dropwise and the mixture was heated under reflux for 16 h. The reaction mixture was cooled to room temperature, made alkaline with 1 M sodium hydroxide (10 mL), extracted with ethyl acetate (3 × 10 mL) and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 10% ethyl acetate in petroleum ether (40—60) to give *N,N*-dimethyl-2-fluoro-5-nitroaniline (**171**) as a yellow oil (0.025 g, 8%). Further elution gave *N*-methyl-2-fluoro-5-nitroaniline (**170**) as a yellow solid (0.28 g, 64%). Data for **171**: Spectroscopic data was in agreement with previously published data.[167] δ_H (400 MHz, $CDCl_3$) 2.96 (6H, d, *J* 5.2 Hz, 2 × NCH_3), 7.06 (1H, dd, *J* 10.8, 8.7 Hz, 3-H), 7.66 (1H, dd, *J* 7.6, 2.8 Hz, 6-H), 7.69 (1H, ddd, *J* 8.8, 4.0, 2.8 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 42.3 (2 × CH_3), 112.8 (d, *J* 6.2 Hz, CH), 115.8 (d, *J* 8.8 Hz, CH), 116.4 (d, *J* 22.2 Hz, CH), 141.0 (d, *J* 12.4 Hz, C), 144.6 (C), 157.8 (d, *J* 256.0 Hz, C); *m*/*z* (EI) 184 (M^+. 82%), 136 (58), 124 (42), 84 (100), 77 (22). Data for **170**: Mp 90—91 °C (lit.[168] 95—97 °C); δ_H (400 MHz, $CDCl_3$) 2.96 (3H, d, *J* 5.2 Hz, NCH_3), 4.25 (1H, s, NH), 7.04 (1H, dd, *J* 10.8, 8.7 Hz, 3-H), 7.50 (1H, dd, *J* 7.6, 2.8 Hz, 6-H), 7.54 (1H, ddd, *J* 8.8, 4.0, 2.8 Hz,

4-H); δ_C (101 MHz, $CDCl_3$) 30.1 (CH_3), 106.2 (d, *J* 6.0 Hz, CH), 112.3 (d, *J* 8.4 Hz, CH), 114.4 (d, *J* 21.2 Hz, CH), 138.5 (d, *J* 13.2 Hz, C), 145.4 (C), 154.8 (d, *J* 250.2 Hz, C); *m*/*z* (EI) 170 (M^+. 27%), 151 (16), 136 (8), 124 (12), 84 (100), 77 (33), 51 (33).

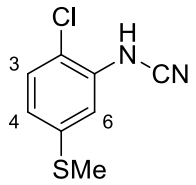
1-Naphthylcyanamide (174)[169] and 2,4-dibromo-1-naphthylamine (175)[170]





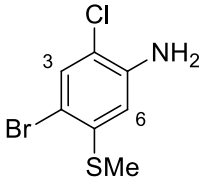
Cyanogen bromide (0.068 g, 0.64 mmol) in diethyl ether (1 mL) was added dropwise to a stirred solution of 1-naphthylamine (0.061 g, 0.43 mmol) in diethyl ether (1 mL) at 0 °C. The reaction mixture was heated under reflux and stirred for 24 h. After cooling to room temperature, the reaction mixture was diluted in diethyl ether (10 mL) and this was washed with water (10mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 10—20% ethyl acetate in petroleum ether (40—60) to give 1-naphthylcyanamide (**174**) as a clear, glassy solid (0.045 g, 63%). Further elution gave 2,4-dibromo-1-naphthylamine (**175**) as a brown solid (0.018 g, 14%). Data for **174**: Mp 128—130 °C (lit.[169] 124—126 °C); δ_H (400 MHz, DMSO-d_6) 7.24 (1H, d, *J* 7.9 Hz, 2-H), 7.51 (1H, t, *J* 7.9 Hz, 3-H), 7.54—7.63 (2H, m, 2 × ArH), 7.65 (1H, d, *J* 7.9 Hz, 4-H), 7.96 (1H, dd, *J* 7.9, 2.6 Hz, ArH), 8.08 (1H, m, dd, *J* 7.9, 2.6 Hz, ArH), 10.22 (1H, s, NH); δ_C (101 MHz, DMSO-d_6) 111.1 (CH), 112.7 (C), 121.0 (CH), 123.1 (CH), 123.2 (C), 126.0 (CH), 126.1 (CH), 126.7 (CH), 128.4 (CH), 133.9 (C), 134.4 (C); *m*/*z* (ESI) 191 (MNa^+. 100%). Data for **175**: Mp 119—120 °C (lit.[170] 121—123 °C); δ_H (400 MHz, $CDCl_3$) 4.62 (2H, s, NH_2), 7.50 (1H, ddd, *J* 8.3, 6.9, 1.2 Hz, 7-H), 7.58 (1H, ddd, *J* 8.3, 6.9, 1.2 Hz, 6-H), 7.75 (1H, d, *J* 8.3 Hz, 8-H), 7.78 (1H, s, 3-H), 8.15 (1H, dd, *J* 8.3, 1.2 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 103.5 (C), 111.0 (C), 121.4 (CH), 124.5 (C), 126.6 (CH), 127.5 (CH), 128.1 (CH), 131.4 (C), 132.7 (CH), 139.7 (C); *m*/*z* (EI) 301 (M^+. 100%), 140 (34).

***N*-(2-Chloro-5-(methylthio)phenyl)cyanamide (176)**



Cyanogen bromide (0.25 g, 2.3 mmol) in water (2 mL) was added dropwise to a stirred solution of 2-chloro-5-(methylthio)aniline (**159**) (0.10 g, 0.58 mmol) in water (2 mL) at room temperature. The reaction mixture was heated to 40 °C and stirred for 16 h. After cooling to room temperature, the reaction mixture was diluted in water (10 mL), extracted with ethyl acetate (3 × 10 mL) and the organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 10—20% ethyl acetate in petroleum ether (40—60) to give *N*-(2-chloro-5-(methylthio)phenyl)cyanamide (**176**) as a white solid (0.065 g, 57%). Mp 191—193 °C; ν_{max}/cm^{-1} (neat) 3173 (NH), 2918 (CH), 2259, 1611, 1574, 1400, 1103, 1038, 851, 804; δ_H (500 MHz, $CDCl_3$) 2.49 (3H, s, SCH_3), 6.38 (1H, s, NH), 6.90 (1H, dd, *J* 8.5, 2.0 Hz, 4-H), 7.12 (1H, d, *J* 2.0 Hz, 6-H), 7.24 (1H, d, *J* 8.5 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 15.7 (CH_3), 109.5 (C), 113.1 (CH), 116.5 (C), 122.2 (CH), 129.8 (CH), 134.4 (C), 140.4 (C); *m/z* (EI) 198.0020 (M^+. $C_8H_7{}^{35}ClN_2S$ requires 198.0018), 84 (33%), 77 (31), 66 (32).

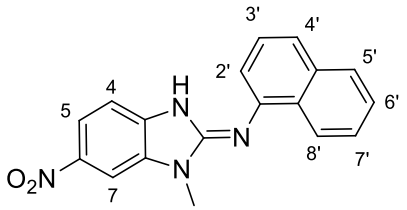
4-Bromo-2-chloro-5-(methylthio)aniline (177)



Cyanogen bromide (0.25 g, 2.3 mmol) in acetonitrile (2 mL) was added dropwise to a stirred solution of 2-chloro-5-(methylthio)aniline (**159**) (0.10 g, 0.58 mmol) in acetonitrile (2 mL) at 0 °C. The reaction mixture was heated under reflux and stirred for 40 h. After cooling to room temperature, the reaction mixture was diluted in ethyl acetate (10 mL) and this was washed with water (10mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL) and the organic

layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 10—20% ethyl acetate in petroleum ether (40—60) to give 4-bromo-2-chloro-5-(methylthio)aniline (**177**) as a white solid (0.019 g, 45%). Mp 204—205 °C; ν_{max}/cm^{-1} (neat) 3212 (NH), 3173 (NH), 2918 (CH), 2249, 1554, 1442, 1103, 1035, 804; δ_H (400 MHz, $CDCl_3$) 2.42 (3H, s, SCH_3), 4.08 (2H, s, NH_2), 6.52 (1H, s, 6-H), 7.38 (1H, s, 3-H); δ_C (126 MHz, $CDCl_3$) 16.2 (CH_3), 109.2 (C), 112.4 (CH), 116.3 (C), 132.5 (CH), 139.0 (C), 142.8 (C); *m/z* (EI) 250.9169 (M^+. $C_7H_7{}^{79}Br^{35}ClNS$ requires 250.9171), 157 (50), 128 (21).

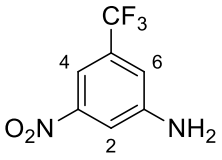
1-Methyl-2-(1-naphthylimino)-6-nitrobenzimidazole (179)



N-Methyl-2-Fluoro-5-nitroaniline (**170**) (0.091 g, 0.53 mmol) was dissolved in diethyl ether (1 mL) and converted to its hydrochloride salt by dropwise addition of aqueous hydrochloric acid (1 M) in diethyl ether (1 mL). This was concentrated *in vacuo* to give a white solid. 1-Naphthylcyanamide (**174**) (0.090 g, 0.53 mmol) was added under argon and the reaction mixture was stirred at 160 °C neat for 3 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (5 mL) and purified using flash column chromatography, eluting with 0—1% methanol and 1% triethylamine in dichloromethane to give 1-methyl-2-(1-naphthylimino)-6-nitrobenzimidazole (**179**) as a yellow solid (0.12 g, 68%). Mp 141—142 °C; ν_{max}/cm^{-1} (neat) 3342 (NH), 2926 (CH), 1643, 1572, 1540, 1326, 1395, 1284, 1182, 1137, 972, 749, 686, 409; δ_H (500 MHz, $CDCl_3$) 3.59 (3H, s, NCH_3), 6.38 (1H, d, *J* 8.4 Hz, 4-H), 7.48—7.51 (2H, m, 2 × ArH), 7.55 (1H, dd, *J* 7.3, 1.1 Hz, ArH), 7.59 (1H, ddd, *J* 8.4, 5.5, 2.5 Hz, ArH), 7.65 (1H, dd, *J* 8.4, 7.3 Hz, ArH), 7.82 (1H, d, *J* 2.1 Hz, 7-H), 7.85 (1H, dd, *J* 8.4, 2.1 Hz, 5-H), 8.01 (1H, d, *J* 8.4 Hz, ArH), 8.07 (1H, d, *J* 8.4 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 28.6 (CH_3), 101.9 (CH), 106.2 (CH), 118.3 (CH), 122.4 (CH), 126.1 (CH), 127.3 (CH), 127.4 (CH), 128.0 (CH), 129.0 (CH), 129.6

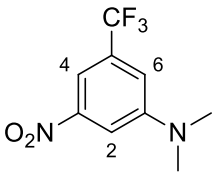
(C), 130.0 (C), 130.8 (CH), 133.0 (C), 135.1 (C), 138.0 (C), 142.8 (C), 155.4 (C); *m*/*z* (ESI) 319.1184 (MH^+. $C_{18}H_{15}N_4O_2$ requires 319.1190).

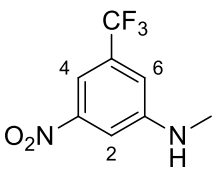
3-Nitro-5-(trifluoromethyl)aniline (181)[171]



3,5-Dinitrobenzotrifluoride (1.0 g, 4.2 mmol) was dissolved in a mixture of 1,4-dioxane (20 mL) and methanol (20 mL) and heated under reflux. Concentrated hydrochloric acid (2.7 mL) was added, followed by iron powder (0.95 g, 17 mmol) in small portions to avoid violent effervescence. The reaction mixture was heated under reflux for 1 h, cooled to room temperature and filtered through celite, washing with dichloromethane. The organic layer was concentrated *in vacuo* and dissolved in dichloromethane (50 mL). The organic mixture was washed with water (2 × 50 mL), followed by brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 10—20% ethyl acetate in petroleum ether (40—60) to give 3-nitro-5-(trifluoromethyl)aniline (**181**) as a yellow solid (0.56 g, 64%). Mp 80—82 °C (lit.[171] 80—82 °C); δ_H (400 MHz, $CDCl_3$) 4.24 (2H, s, NH_2), 7.16 (1H, br s, 6-H), 7.64 (1H, t, *J* 2.0 Hz, 2-H), 7.81 (1H, br s, 4-H); δ_C (101 MHz, $CDCl_3$) 109.9 (CH, q, *J* 4.0 Hz), 111.8 (CH), 116.5 (CH, q, *J* 3.6 Hz), 123.1 (C, q, *J* 272.9 Hz), 133.1 (C, q, *J* 33.7 Hz), 148.2 (C), 149.6 (C); *m*/*z* (EI) 206 (M^+. 65%), 176 (52), 160 (53), 69 (49), 55 (100).

***N*,*N*-dimethyl-3-nitro-5-(trifluoromethyl)aniline (183) and *N*-Methyl-3-nitro-5-(trifluoromethyl)aniline (182)**

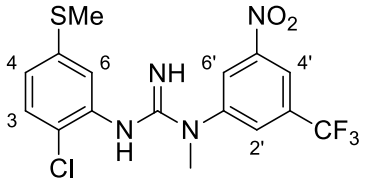




The reaction was carried out according to the previously described procedure for *N*-methyl-2-fluoro-5-nitroaniline (**170**) using 3-nitro-5-(trifluoromethyl)aniline

(**181**) (1.9 g, 9.2 mmol), trimethyl orthoformate (1.5 mL, 14 mmol), concentrated sulfuric acid (2 drops) and 10% aqueous hydrochloric acid (2 mL). The crude material was purified using flash column chromatography, eluting with 10—20% ethyl acetate in petroleum ether (40—60) to give *N,N*-dimethyl-3-nitro-5-(trifluoromethyl)aniline (**183**) as an orange solid (0.42 g, 20%). Further elution gave *N*-methyl-3-nitro-5-(trifluoromethyl)aniline (**182**) as a yellow solid (0.95 g, 47%). Data for **183**: Mp 64—65 °C; ν_{max}/cm^{-1} (neat) 3113 (CH), 2926 (CH), 1626, 1582, 1541 (NO), 1503, 1479, 1377, 1344, 1302, 1273, 1155, 1112, 1098, 1065, 1003, 895, 856, 764, 745, 692; δ_H (400 MHz, $CDCl_3$) 3.10 (6H, s, 2 × NCH_3), 7.11 (1H, br s, 6-H), 7.62 (1H, t, *J* 2.2 Hz, 2-H), 7.74 (1H, br s, 4-H); δ_C (101 MHz, $CDCl_3$) 40.32 (2 × CH_3), 107.03 (q, *J* 4.0 Hz, CH), 108.69 (d, *J* 0.7 Hz, CH), 113.15 (q, *J* 3.7 Hz, CH), 123.34 (q, *J* 272.9 Hz, C), 132.57 (q, *J* 33.2 Hz, C), 149.49 (C), 150.88 (C); *m/z* (EI) 234.0610 (M^+. $C_9H_9F_3N_2O_2$ requires 234.0616), 151 (82%), 121 (23), 105 (51), 84 (28), 77 (100), 51(68). Data for **182**: Mp 71—72 °C; ν_{max}/cm^{-1} (neat) 3404 (NH), 3100 (CH), 2949, 2918, 1634, 1555, 1368, 1339, 1271, 1161, 1125, 1103, 1078, 864, 685; δ_H (500 MHz, $CDCl_3$) 2.95 (3H, d, *J* 5.2 Hz, NCH_3), 4.35 (1H, s, NH), 7.05 (1H, br s, 6-H), 7.53 (1H, t, *J* 2.1 Hz, 2-H), 7.74 (1H, br s, 4-H); δ_C (126 MHz, $CDCl_3$) 30.6 (CH_3), 108.4 (CH, q, *J* 3.8 Hz), 108.9 (CH, s), 114.1 (CH, q, *J* 3.7 Hz), 123.3 (C, q, *J* 273.0 Hz), 132.8 (C, q, *J* 33.3 Hz), 149.7 (C), 150.4 (C); *m/z* (EI) 220.0450 (M^+. $C_8H_7F_3N_2O_2$ requires 220.0460), 190 (26%), 174 (36), 153 (18).

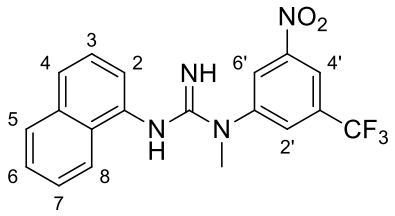
_N_-(2-Chloro-5-(methylthio)phenyl)-_N'_-(5-nitro-3-(trifluoromethyl)phenyl)-_N'_-methylguanidine (184)



N-Methyl-3-nitro-5-(trifluoromethyl)aniline **182** (0.12 g, 0.51 mmol) was dissolved in diethyl ether (1 mL) and converted to its hydrochloride salt by dropwise addition of hydrochloric acid (1 M) in diethyl ether (1 mL). This was concentrated *in vacuo* to give a white solid. *N*-(2-Chloro-5-methylthio)cyanamide (**176**) (0.10 g, 0.51 mmol) was added under argon and the reaction mixture was

stirred at 160 °C neat for 3 h. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (5 mL) and purified using flash column chromatography, eluting with 0—1% methanol and 1% triethylamine in dichloromethane to give *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(3-nitro-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**184**) as a yellow solid (0.14 g, 64%). Mp 122—123 °C; ν_{max}/cm^{-1} (neat) 3394 (NH), 2947 (CH), 1636, 1551, 1427, 1327, 1265, 1157, 1103, 1072, 980, 864, 772, 687; δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, SCH_3), 3.50 (3H, s, NCH_3), 4.13 (2H, s, 2 × NH), 6.81—6.90 (2H, m, 6-H and 4-H), 7.28 (1H, d, *J* 8.1 Hz, 3-H), 7.96 (1H, s, 2'-H), 8.18 (1H, s, 6'-H), 8.39 (1H, s, 4'-H); δ_C (101 MHz, $CDCl_3$) 15.9 (CH_3), 38.4 (CH_3), 115.8 (q, *J* 3.8 Hz, CH), 121.6 (CH), 121.9 (CH), 122.1 (CH), 122.7 (q, *J* 273.2 Hz, C), 123.5 (C), 126.6 (q, *J* 3.3 Hz, CH).130.3 (CH), 132.7 (q, *J* 34.1 Hz, C), 138.3 (C), 145.9 (C), 147.2 (C), 148.9 (C), 150.5 (C); *m/z* (ESI) 419.0532 (MH^+. $C_{16}H_{15}{}^{35}ClF_3N_4O_2S$ requires 419.0551).

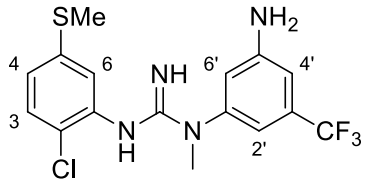
_N_-(1-Naphthyl)-_N'_-(5-nitro-3-(trifluoromethyl)phenyl)-_N'_-methylguanidine (185)



N-Methyl-3-nitro-5-(trifluoromethyl)aniline (**182**) (0.17 g, 0.75 mmol) was dissolved in diethyl ether (1 mL) and converted to its hydrochloride salt by dropwise addition of aqueous hydrochloric acid (1 M) in diethyl ether (1 mL). This was concentrated *in vacuo* to give a white solid. 1-Naphthylcyanamide (**174**) (0.14 g, 0.82 mmol) was added under argon and the reaction mixture was stirred in anhydrous toluene (3 mL) at 130 °C for 16 h. After cooling to room temperature, the reaction mixture was diluted in dichloromethane (5 mL) and purified using flash column chromatography, eluting with 0–1% methanol and 1% triethylamine in dichloromethane to give *N*-(1-naphthyl)-*N'*-(3-nitro-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**185**) as a yellow solid (0.19 g, 67%). Mp 117—119 °C; ν_{max}/cm^{-1} (neat) 3379 (NH), 2924 (CH), 1643, 1574, 1543, 1366, 1335, 1288, 1173, 1134, 972, 779, 748, 694, 409; δ_H (400 MHz, $CDCl_3$) 3.59

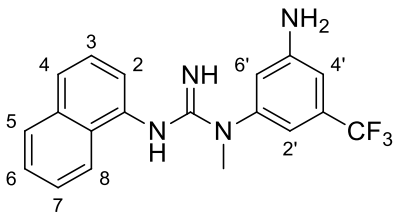
(3H, s, NCH_3), 4.20 (2H, s, 2 × NH), 6.99 (1H, d, *J* 7.1 Hz, 8-H), 7.42 (1H, t, *J* 8.0 Hz, 3-H), 7.45—7.50 (2H, m, 6-H and 7-H), 7.55 (1H, d, *J* 8.0 Hz, 4-H), 7.82 (1H, d, *J* 7.1 Hz, 5-H), 7.93 (1H, br s, 2'-H), 8.01 (1H, d, *J* 8.0 Hz, 2-H), 8.18 (1H, br s, 6'-H), 8.37 (1H, br s, 4'-H); δ_C (126 MHz, $CDCl_3$) 38.6 (CH_3), 115.6 (CH), 117.2 (CH), 121.7 (CH), 122.8 (q, *J* 273.7 Hz, C), 123.2 (CH), 123.7 (CH), 125.6 (CH), 126.3 (CH), 126.3 (CH), 126.4 (CH), 128.2 (CH), 128.3 (C), 132.8 (q, *J* 34.2 Hz, C), 134.8 (C), 145.1 (C), 147.6 (C), 149.0 (C), 150.0, (C); *m/z* (ESI) 389.1207 (MH^+. $C_{19}H_{16}F_3N_4O_2$ requires 389.1220).

_N_-(2-Chloro-5-(methylthio)phenyl)-_N'_-(5-amino-3-(trifluoromethyl)phenyl)-_N'_-methylguanidine (186)



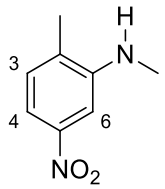
The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(3-nitro-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**184**) (0.10 g, 0.24 mmol) and tin(II) chloride dihydrate (0.28 g, 1.2 mmol) in ethanol (10 mL). The reaction mixture was stirred under reflux for 16 h. The crude material was purified using flash column chromatography, eluting with 1—5% methanol and 1% triethylamine in dichloromethane to give *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(3-amino-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**186**) as a cream solid (0.072 g, 76%). Mp 62—64 °C; ν_{max}/cm^{-1} (neat) 3476 (NH), 3368, 3192, 2922 (CH), 1624, 1584, 1560, 1460, 1400, 1371, 1298, 1165, 1123, 1096, 1007, 889, 706; δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, SCH_3), 3.40 (3H, s, NCH_3), 3.98 (3H, s, NH and NH_2), 6.75—6.79 (2H, m, 4'-H and 6'-H), 6.83 (1H, dd, *J* 8.4, 2.3 Hz, 4-H), 6.90 (1H, d, *J* 2.3 Hz, 6-H), 6.93 (1H, s, 2'-H), 7.28 (1H, d, *J* 8.4 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 16.1 (CH_3), 38.9 (CH_3), 109.5 (q, *J* 3.8 Hz, CH), 113.1 (q, *J* 3.8 Hz, CH), 115.9 (CH), 121.6 (CH), 122.5 (CH), 123.8 (q, *J* 272.8 Hz, C), 124.5 (C), 130.2 (CH), 133.1 (q, *J* 32.3 Hz, C), 138.0 (C), 146.3 (C), 147.3 (C), 148.2 (C), 150.7 (C); *m/z* (ESI) 389.0799 (MH^+. $C_{16}H_{17}{}^{35}ClF_3N_4S$ requires 389.0809).

***N*-(1-Naphthyl)-*N'*-(3-amino-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (187)**



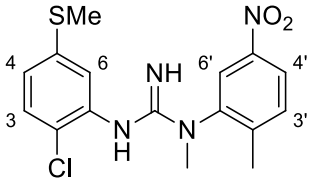
The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using *N*-(1-naphthyl)-*N'*-(3-nitro-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**185**) (0.16 g, 0.41 mmol) and tin(II) chloride dihydrate (0.47 g, 2.1 mmol) in ethanol (5 mL). The reaction mixture was stirred under reflux for 16 h. The crude material was purified using flash column chromatography, eluting with 40—60% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(1-naphthyl)-*N'*-(3-amino-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**187**) as a brown solid (0.15 g, 100%). Mp 123—124 °C; ν_{max}/cm^{-1} (neat) 3383 (NH), 3214, 1624, 1567, 1580, 1566, 1384, 1296, 1265, 1165, 1123, 999, 781, 708; δ_H (500 MHz, $CDCl_3$) 3.52 (3H, s, NCH_3), 3.97 (3H, s, NH_2 and NH), 6.74 (1H, br s, 6'-H), 6.78 (1H, t, *J* 1.8 Hz, 4'-H), 6.97 (1H, br s, 2'-H), 7.03 (1H, dd, *J* 7.3, 1.0 Hz, 2-H), 7.41 (1H, dd, *J* 8.2, 7.3 Hz, 3-H), 7.45—7.48 (2H, m, 6-H and 7-H), 7.52 (1H, d, *J* 8.2 Hz, 4-H), 7.78—7.84 (1H, m, 5-H), 8.11—8.17 (1H, m, 8-H); δ_C (126 MHz, $CDCl_3$) 38.8 (CH_3), 109.3 (q, *J* 3.7 Hz, CH), 113.0 (q, *J* 3.7 Hz, CH), 115.8 (CH), 117.7 (CH), 122.4 (CH), 123.8 (q, *J* 272.6 Hz, C), 124.1 (CH), 125.2 (CH), 126.1 (CH), 126.5 (CH), 128.1 (CH), 129.0 (C), 133.0 (q, *J* 32.3 Hz, C), 134.9 (C), 146.4 (C), 146.6 (C), 148.2 (C), 150.4 (C); *m/z* (EI) 358.1409 (M^+. $C_{19}H_{17}F_3N_4$ requires 358.1405), 190 (70%), 168 (28%), 143 (11), 127 (17).

***N*-Methyl-2-methyl-5-nitroaniline (189)**



The reaction was carried out according to the previously described procedure for *N*-methyl-3-nitro-5-(trifluoromethyl)aniline (**182**) using 2-methyl-5-nitroaniline (0.50 g, 3.3 mmol), trimethyl orthoformate (0.54 mL, 4.9 mmol), concentrated sulfuric acid (2 drops) and 10% aqueous hydrochloric acid (2 mL). The crude material was purified using flash column chromatography, eluting with 20% ethyl acetate in petroleum ether (40—60) to give *N*-methyl-2-methyl-5-nitroaniline (**189**) as an orange solid (0.45 g, 83%). Mp 97—99 °C; ν_{max}/cm^{-1} (neat) 3426 (NH), 2369, 2183, 1620, 1520 (NO), 1504, 1342 (NO), 1281, 1157, 1096, 849, 802, 733; δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, CH_3), 2.97 (3H, d, *J* 5.0 Hz, NCH_3), 3.83 (1H, s, NH), 7.14 (1H, d, *J* 8.1 Hz, 3-H), 7.38 (1H, s, 6-H), 7.52 (1H, d, *J* 8.1 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 17.7 (CH_3), 30.7 (CH_3), 103.2 (CH), 111.9 (CH), 129.3 (C), 130.0 (CH), 147.9 (C), 148.1 (C); *m*/*z* (EI) 166.0738 (M^+. $C_8H_{10}N_2O_2$ requires 166.0742), 151 (87%), 105 (49), 84 (100), 77 (88), 51 (42).

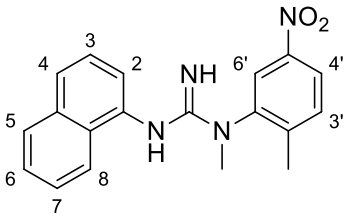
***N*-(2-Chloro-5-(methylthio)phenyl)-*N'*-(2-methyl-5-nitrophenyl)-*N'*-methylguanidine (190)**



The reaction was carried out according to the previously described procedure for *N*-(1-naphthyl)-*N'*-(3-nitro-5-(trifluoromethyl)phenyl)-*N'*-methylguanidine (**185**) using *N*-methyl-2-methyl-5-nitroaniline (**189**) (0.082 g, 0.50 mmol), *N*-(2-chloro-5-methylthio)cyanamide (**176**) (0.11 g, 0.54 mmol) and anhydrous toluene (3 mL). The reaction mixture was stirred at 130 °C for 24 h. The crude material was purified using flash column chromatography, eluting with 20—60% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(2-chloro-5-

(methylthio)phenyl)-*N*′-(2-methyl-5-nitrophenyl)-*N*′-methylguanidine (**190**) as a brown solid (0.14 g, 78%). Mp 117—119 °C; ν_{max}/cm^{-1} (neat) 3480 (NH), 3387 (NH), 2924 (CH), 1628, 1558, 1520, 1443, 1373, 1342, 1273, 1126, 1096, 1034, 903, 856, 802, 733, 586, 455; δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, 2'-CH_3), 2.48 (3H, s, SCH_3), 3.35 (3H, s, NCH_3), 3.74 (2H, s, 2 × NH), 6.83 (1H, dd, *J* 8.3, 2.1 Hz, 4-H), 6.89 (1H, d, *J* 2.1 Hz, 6-H), 7.27 (1H, d, *J* 8.3 Hz, 3-H), 7.47 (1H, d, *J* 8.3 Hz, 3'-H), 8.10 (1H, dd, *J* 8.3, 2.1 Hz, 4'-H), 8.18 (1H, d, *J* 2.1 Hz, 6'-H); δ_C (101 MHz, $CDCl_3$) 16.1 (CH_3), 18.1 (CH_3), 37.8 (CH_3), 121.6 (CH), 122.6 (CH), 122.9 (CH), 124.3 (CH), 124.5 (C), 130.2 (CH), 132.4 (CH), 138.0 (C), 143.7 (C), 145.8 (C), 147.2 (C), 147.3 (C), 150.2 (C); *m*/*z* (ESI) 365.0827 (MH^+. $C_{16}H_{18}{}^{35}ClN_4O_2S$ requires 365.0834).

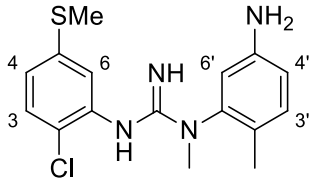
_N_-(1-Naphthyl)-_N_′-(2-methyl-5-nitrophenyl)-_N_′-methylguanidine (191)



The reaction was carried out according to the previously described procedure for *N*-(1-naphthyl)-*N*′-(3-nitro-5-(trifluoromethyl)phenyl)-*N*′-methylguanidine (**185**) using *N*-methyl-2-methyl-5-nitroaniline (**189**) (0.060 g, 0.36 mmol), 1-naphthylcyanamide (**174**) (0.055 g, 0.33 mmol) and anhydrous toluene (3 mL). The reaction mixture was stirred at 130 °C for 16 h. The crude material was purified using flash column chromatography, eluting with 1% methanol and 1% triethylamine in dichloromethane to give *N*-(1-naphthyl)-*N*′-(2-methyl-5-nitrophenyl)-*N*′-methylguanidine (**191**) as an orange solid (0.11 g, 100%). Mp 121—123 °C; ν_{max}/cm^{-1} (neat) 3485 (NH), 3379 (NH), 3048, 2926 (CH), 1632, 1582, 1566, 1518, 1489, 1445, 1383, 1346, 1265, 1234, 1125, 962, 810, 797, 781, 758, 735; δ_H (500 MHz, $CDCl_3$) 2.51 (3H, s, 2'-CH_3), 3.46 (3H, s, NCH_3), 3.81 (2H, s, 2 × NH), 7.00 (1H, dd, *J* 7.2, 1.0 Hz, 2-H), 7.40 (1H, dd, *J* 8.2, 7.2 Hz, 3-H), 7.43—7.49 (3H, m, 6-H, 7-H and 3'-H), 7.51 (1H, d, *J* 8.2 Hz, 4-H), 7.79—7.83 (1H, m, 5-H), 8.08 (1H, dd, *J* 8.2, 2.4 Hz, 4'-H), 8.12—8.16 (1H, m, 8-H), 8.21 (1H, d, *J* 2.4 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 18.2 (CH_3), 37.9 (CH_3), 117.7 (CH), 122.5 (CH), 122.7 (CH), 124.0 (CH), 124.2 (CH), 125.3 (CH), 126.1 (CH), 126.5

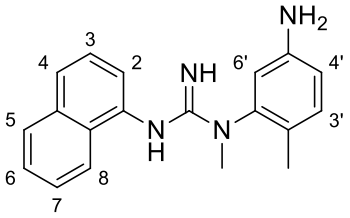
(CH), 128.1 (CH), 129.1 (C), 132.3 (CH), 134.9 (C), 144.1 (C), 145.7 (C), 146.2 (C), 147.3 (C), 150.0 (C); *m/z* (EI) 334.1428 (M^+. $C_{19}H_{18}N_4O_2$ requires 334.1430), 319 (9%), 169 (10), 86 (64), 84 (100), 51 (36).

_N_-(2-Chloro-5-(methylthio)phenyl)-_N'_-(2-methyl-5-aminophenyl)-_N'_-methylguanidine (192)



The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(2-methyl-5-nitrophenyl)-*N'*-methylguanidine (**151**) (0.10 g, 0.27 mmol) and tin(II) chloride dihydrate (0.31 g, 1.4 mmol) in ethanol (5 mL). The reaction mixture was stirred under reflux for 16 h. The crude material was purified using flash column chromatography, eluting with 20—60% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(2-chloro-5-(methylthio)phenyl)-*N'*-(2-methyl-5-aminophenyl)-*N'*-methylguanidine (**192**) as a brown solid (0.061 g, 66%). Mp 95—97 °C; ν_{max}/cm^{-1} (neat) 3464 (NH), 3287 (NH), 2916 (CH), 1597, 1558, 1504, 1435, 1373, 1288, 1134, 1096, 1072, 1042, 995, 826, 802, 702, 594, 471, 447; δ_H (400 MHz, $CDCl_3$) 2.19 (3H, s, 2'-CH_3), 2.44 (3H, s, SCH_3), 3.27 (3H, s, NCH_3), 3.64 (1H, s, NH), 6.57 (1H, dd, *J* 8.1, 2.3 Hz, 4'-H), 6.59 (1H, d, *J* 2.3 Hz, 6'-H), 6.79 (1H, dd, *J* 8.1, 2.3 Hz, 4-H), 6.91 (1H, d, *J* 2.3 Hz, 6-H), 7.03 (1H, d, *J* 8.1 Hz, 3'-H), 7.25 (1H, d, *J* 8.1 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 16.0 (CH_3), 16.5 (CH_3), 37.3 (CH_3), 115.1 (CH), 115.2 (CH), 121.1 (CH), 123.0 (CH), 124.9 (C), 126.4 (C), 130.1 (CH), 132.2 (CH), 137.6 (C), 142.8 (C), 145.8 (C), 147.9 (C), 151.0 (C); *m/z* (ESI) 335.1078 (MH^+. $C_{16}H_{20}{}^{35}ClN_4S$ requires 335.1092).

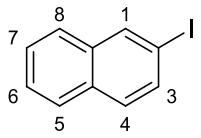
***N*-(1-Naphthyl)-*N'*-(2-methyl-5-aminophenyl)-*N'*-methylguanidine (193)**



The reaction was carried out according to the previously described procedure for 2-(4'-dimethylaminophenyl)-6-aminobenzoxazole (**88**) using *N*-(1-naphthyl)-*N'*-(2-methyl-5-nitrophenyl)-*N'*-methylguanidine (**148**) (0.10 g, 0.30 mmol) and tin(II) chloride dihydrate (0.34 g, 1.5 mmol) in ethanol (2 mL). The reaction mixture was stirred under reflux for 16 h. The crude material was purified using flash column chromatography, eluting with 60% ethyl acetate and 5% triethylamine in petroleum ether (40—60) to give *N*-(1-naphthyl)-*N'*-(2-methyl-5-aminophenyl)-*N'*-methylguanidine (**193**) as a brown solid (0.080 g, 88%). Mp 110—112 °C; ν_{max}/cm^{-1} (neat) 3478, 3381 (NH), 3206 (NH), 2926 (CH), 2361, 1613, 1580, 1564, 1505, 1449, 1387, 1288, 1080, 806, 781; δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, 2'-CH_3), 3.41 (3H, s, NCH_3), 3.75 (4H, s, NH_2 and 2 × NH), 6.53 (1H, dd, *J* 8.1, 2.4 Hz, 4'-H), 6.60 (1H, d, *J* 2.4 Hz, 6'-H), 7.00—7.07 (2H, m, 2-H and 3'-H), 7.40 (1H, t, *J* 8.1 Hz, 3-H), 7.43—7.48 (2H, m, 6-H and 7-H), 7.50 (1H, d, *J* 8.1 Hz, 4-H), 7.79—7.84 (1H, m, 5-H), 8.18—8.27 (1H, m, 8-H); δ_C (101 MHz, $CDCl_3$) 16.6 (CH_3), 37.4 (CH_3), 115.1 (CH), 115.2 (CH), 118.1 (CH), 121.9 (CH), 124.3 (CH), 125.0 (CH), 125.9 (CH), 126.3 (C), 126.5 (CH), 127.9 (CH), 129.4 (C), 132.2 (CH), 134.9 (C), 143.2 (C), 145.9 (C), 146.9 (C), 150.9 (C); *m/z* (EI) 304.1680 (M^+. $C_{19}H_{20}N_4$ requires 304.1688), 289 (93%), 162 (19), 136 (20), 127 (27), 121 (28).

5.5 Metal-Catalysed Iodination Experimental

2-Iodonaphthalene (195)[173]

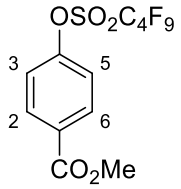


Method A: 2-naphthyl nonafluorobutanesulfonate (**205**) (0.10 g, 0.23 mmol), sodium iodide (0.21 g, 1.4 mmol), bis(1,5-cyclooctadiene)nickel(0) (0.0065 g, 0.023 mmol, 10 mol%), *N*-methylpyrrolidinone (0.50 mL) and 4 Å molecular sieves were placed in a sealed tube and heated to 180 °C for 24 h. The reaction was then allowed to cool and ethyl acetate (5 mL) and water (5 mL) were added. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 1–10% diethyl ether in petroleum ether (40–60) to give 2-iodonaphthalene (**195**) as a white solid (0.019 g, 33%). Mp 50—52 °C (lit.[173] 53—55 °C); δ_H (400 MHz, $CDCl_3$) 7.47–7.52 (2H, m, ArH), 7.58 (1H, d, *J* 8.7 Hz, 4-H), 7.70–7.74 (2H, m, ArH), 7.79–7.82 (1H, m, ArH), 8.25 (1H, br d, *J* 1.2 Hz, 1-H); δ_C (101 MHz, $CDCl_3$) 91.7 (C), 126.7 (CH), 126.9 (CH), 127.0 (CH), 128.0 (CH), 129.7 (CH), 132.3 (C), 134.6 (CH), 135.2 (C), 136.8 (CH); *m/z* (EI) 254 (M^+. 100%), 127 (93), 126 (21), 77 (13).

Method B: A stirrer bar and sodium iodide (0.052 g, 0.18 mmol) were dried overnight in a microwave tube. 2-naphthyl nonafluorobutanesulfonate (**205**) (0.050 g,0.12 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.0030 g, 0.0059 mmol, 5 mol%) and *N*,*N*'-dimethylformamide (0.50 mL) were added to the dried tube under a stream of argon before the tube was sealed. The resulting mixture was stirred at 100 °C and the reaction was complete after 1 h, as followed by TLC. The reaction mixture was then allowed to cool and ethyl acetate (5 mL) and water (5 mL) were added. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified through a short pad of silica, eluting

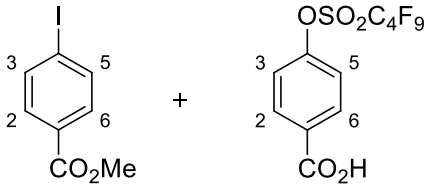
with petroleum ether (40–60) to give 2-iodonaphthalene (**195**) as a white solid (0.028 g, 93%). Spectroscopic data was in agreement with that described above.

Methyl 4-nonafluorobutanesulfonyloxybenzoate (199)[172]



Triethylamine (1.1 mL, 8.2 mmol) was added to a solution of methyl 4-hydroxybenzoate (0.50 g, 3.3 mmol) in dichloromethane (10 mL) with stirring at 0 °C. Perfluoro-1-butanesulfonyl fluoride (1.5 g, 4.9 mmol) was added and the reaction mixture was warmed to room temperature. The reaction mixture was stirred for 16 h. The mixture was washed with water (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 5% diethyl ether in petroleum ether (40–60) to give methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) as a colourless oil (1.2 g, 89%). Spectroscopic data was in agreement with previously published data.[172] δ_H (400 MHz, $CDCl_3$) 3.94 (3H, s, OCH_3), 7.36 (2H, d, *J* 8.9 Hz, 3-H and 5-H), 8.14 (2H, d, *J* 8.9 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 52.7 (CH_3), 121.6 (2 × CH), 130.5 (2 × CH), 132.0 (C), 152.9 (C), 165.6 (C); *m/z* (EI) 434 (M^+. 70%), 403 (40), 339 (100), 151 (38), 123 (42).

Methyl 4-iodobenzoate (200)[173] **and 4-nonafluorobutanesulfonyloxybenzoic acid (201)**[174]

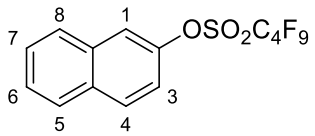


Method A: The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method A) using methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) (0.10 g, 0.23 mmol), sodium iodide (0.22 g, 1.4 mmol), bis(1,5-cyclooctadiene)nickel(0) (0.0066 g, 0.024 mmol, 10

mol%), *N*-methylpyrrolidinone (0.50 mL). The reaction mixture was stirred at 180 °C for 24 h. The crude material was purified using flash column chromatography, eluting with 1–10% diethyl ether in petroleum ether (40–60) to give methyl 4-iodobenzoate (**200**) (0.0050 g, 8%), followed by elution with 50–60% diethyl ether in petroleum ether (40–60) to give 4-nonafluorobutanesulfonyloxybenzoic acid (**201**) as a white solid (0.047 g, 51%). Data for **200**: Mp 114–116 °C (lit.[173] 119–120 °C); δ_H (400 MHz, $CDCl_3$) 3.91 (3H, s, CH_3), 7.74 (2H, d, *J* 8.7 Hz, 3-H and 5-H), 7.80 (2H, d, *J* 8.7 Hz, 2-H and 6-H); δ_C (101 MHz, $CDCl_3$) 52.4 (CH_3), 100.9 (C), 129.8 (2 × CH), 131.2 (2 × CH), 137.9 (C), 166.8 (C); *m*/*z* (EI) 262 (M^+. 93%), 231 (100), 203 (38), 76 (67). Data for **201**: Mp 172—174 °C (lit.[174] 180 °C); δ_H (400 MHz, DMSO-d_6) 7.49 (2H, d, *J* 8.9 Hz, 3-H and 5-H), 8.19 (2H, d, *J* 8.9 Hz, 2-H and 6-H); δ_C (101 MHz, DMSO-d_6) 121.8 (2 × CH), 131.4 (C), 131.9 (2 × CH), 152.0 (C), 165.9 (C); *m*/*z* (ESI) 419 ($M-H^+$. 80%), 299 (100), 283 (40).

Method B: The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method B) using methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) (0.058 g, 0.13 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.0034 g, 0.0062 mmol, 5 mol%), sodium iodide (0.060 g, 0.40 mmol) and *N*,*N*'-dimethylformamide (0.50 mL). The reaction mixture was stirred for 3 h. The crude material was purified through a short pad of silica, eluting with 10% diethyl ether in petroleum ether (40–60) to give methyl 4-iodobenzoate (**200**) as a white solid (0.035 g, 100%).

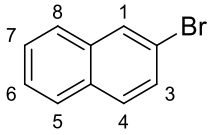
2-Naphthyl nonafluorobutanesulfonate (205)[175]



The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**), using 2-naphthol (1.0 g, 7.1 mmol), triethyamine (2.4 mL, 17 mmol) and perfluoro-1-butanesulfonyl fluoride (1.9 mL, 10 mmol). The reaction mixture was stirred for 36 h. The crude material was purified using flash column chromatography, eluting with 5%

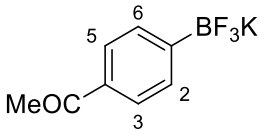
diethyl ether in petroleum ether (40–60) to give 2-naphthyl nonafluorobutanesulfonate (**205**) as a colourless oil (3.0 g, 99%). Spectroscopic data was in agreement with previously published data.[175] δ_H (400 MHz, $CDCl_3$) 7.39 (1H, dd, *J* 9.0, 2.5 Hz, 3-H), 7.54–7.63 (2H, m, ArH), 7.77 (1H, d, *J* 2.5 Hz, 1-H), 7.84–7.98 (3H, m, 3 × ArH); δ_C (101 MHz, $CDCl_3$) 119.4 (CH), 119.8 (CH), 127.4 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 130.8 (CH), 132.5 (C), 133.5 (C), 147.5 (C); *m*/*z* (ESI) 424.9882 ($M-H^+$. requires 424.9899).

2-Bromonaphthalene (207)[176]



The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method A) using 2-naphthyl nonafluorobutanesulfonate (**205**) (0.10 g, 0.23 mmol), sodium bromide (0.14 g, 1.4 mmol), bis(1,5-cyclooctadiene)nickel(0) (0.0065 g, 0.023 mmol, 10 mol%) and *N*-methylpyrrolidinone (0.50 mL). The reaction mixture was stirred at 180 °C for 22 h. The crude material was purified using flash column chromatography, eluting with 1–10% diethyl ether in petroleum ether (40–60) to give 2-bromonaphthalene (**207**) as a white solid (0.0056 g, 11%). Mp 55–56 °C (lit.[176] 55 °C); δ_H (500 MHz, $CDCl_3$) 7.48—7.53 (2H, m, ArH), 7.55 (1H, dd, *J* 8.8, 2.0 Hz, 3-H), 7.72 (1H, d, *J* 8.8 Hz, 4-H), 7.75—7.76 (1H, m, ArH), 7.80—7.82 (1H, m, ArH), 8.01 (1H, br d, *J* 1.7 Hz, 1-H); δ_C (126 MHz, $CDCl_3$) 120.0 (C), 126.5 (CH), 127.1 (CH), 127.2 (CH), 128.0 (CH), 129.4 (CH), 129.7 (CH), 130.1 (CH), 132.0 (C), 134.7 (C); *m*/*z* (EI) 206 (M^+. 80%), 127 (100), 126 (29), 84 (72), 69 (35).

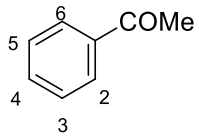
Potassium (4-acetylphenyl)trifluoroborate (210)[177]



A solution of potassium fluoride (0.35 g, 6.1 mmol) in water (0.60 mL) was added to a suspension of 4-(acetyl)phenylboronic acid (0.25 g, 1.5 mmol) in acetonitrile

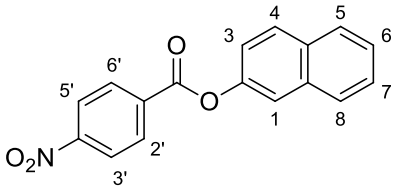
(10 mL), and the mixture was stirred until complete dissolution (1 min). L-(+)-Tartaric acid (0.47 g, 3.1 mmol) in tetrahydrofuran (2.5 mL) was added dropwise to the biphasic solution with stirring, during which a white precipitate formed. The reaction mixture was filtered, washed with acetonitrile (30 mL), and the filtrate was concentrated *in vacuo* to give potassium (4-acetylphenyl)trifluoroborate (**210**) as a white solid (0.28 g, 81%). Mp > 250 °C (lit.[177] > 250 °C); δ_H (400 MHz, DMSO-d_6) 2.49 (3H, s, CH_3), 7.60 (2H, d, *J* 7.9 Hz, 2-H and 6-H), 7.74 (2H, d, *J* 7.9 Hz, 3-H and 5-H); δ_C (126 MHz, (DMSO-d_6) 26.5 (CH_3), 126.3 (2 × CH), 131.4 (2 × CH), 134.3 (C), 155.7 (C), 198.2 (C); *m*/*z* (ESI) 187 ($M-K^+$. 100%)

Acetophenone (211)[178]



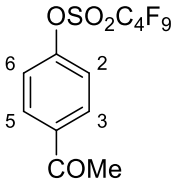
The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195**) (method A) using potassium (4-acetylphenyl)trifluoroborate (**210**) (0.057 g, 0.25 mmol), sodium iodide (0.23 g, 1.5 mmol), bis(1,5-cyclooctadiene)nickel(0) (0.0069 g, 0.025 mmol, 10 mol%) and *N*-methylpyrrolidinone (0.50 mL). The crude material was purified using flash column chromatography, eluting with 1–10% diethyl ether in petroleum ether (40–60) to give acetophenone (**211**) as a viscous oil (0.012 g, 41%). Spectroscopic data was in agreement with previously published data.[178] δ_H (500 MHz, $CDCl_3$) 2.61 (3H, s, CH_3), 7.47 (2H, t, *J* 7.4 Hz, 3-H and 5-H), 7.57 (1H, t, *J* 7.4 Hz, 4-H), 7.96 (2H, m, 2-H and 6-H); δ_C (126 MHz, ($CDCl_3$) 26.8 (CH_3), 128.5 (2 × CH), 128.7 (2 × CH), 133.3 (CH), 137.3 (C), 198.3 (C); *m*/*z* (EI) 120 (M^+. 100%), 84 (80), 76 (34).

2-Naphthyl 4-nitrobenzoate (213)



4-Nitrobenzoyl chloride (0.49 g, 2.7 mmol) in dichloromethane (10 mL) was added to a solution of triethylamine (0.40 mL, 2.9 mmol) and naphthol (0.35 g, 2.4 mmol) in dichloromethane (10 mL) at 0 °C with stirring. The reaction was allowed to warm to room temperature and was stirred for 2 h, during which the solution turned bright yellow. The reaction mixture was then washed with water (50 mL) and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified using flash column chromatography, eluting with 5% ethyl acetate in petroleum ether (40–60) to give 2-naphthyl 4-nitrobenzoate (**213**) as a yellow solid (0.78 g, 87%). Mp 162–164 °C; ν_{max}/cm^{-1} (neat) 1739 (C=O), 1519, 1347, 1323, 1273, 1262; δ_H (500 MHz, $CDCl_3$) 7.37 (1H, dd, *J* 8.9, 2.3 Hz, 3-H), 7.50–7.56 (2H, m, ArH), 7.72 (1H, d, *J* 2.3 Hz, 1-H), 7.84–7.86 (1H, m, ArH), 7.89–7.91 (1H, m, ArH), 7.94 (1H, d, *J* 8.9 Hz, 4-H), 8.39 (2H, d, *J* 9.0 Hz, 2'-H and 6'-H), 8.44 (2H, d, *J* 9.0 Hz, 3'-H and 5'-H); δ_C (101 MHz, $CDCl_3$) 118.8 (CH), 120.9 (CH), 124.0 (2 × CH), 126.3 (CH), 127.0 (CH), 127.9 (CH), 128.1 (CH), 129.9 (CH), 131.5 (2 × CH), 131.9 (C), 133.9 (C), 135.2 (C), 148.3 (C), 151.2 (C), 163.7 (C); *m/z* (ESI) 292.0610 ($M-H^+$. requires 292.0615).

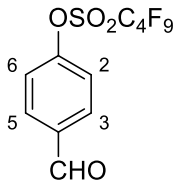
4-Acetylphenyl nonafluorobutanesulfonate (216)[172]



The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) using 4-hydroxyacetophenone (0.50 g, 3.7 mmol), triethyamine (1.3 mL, 9.2 mmol) and

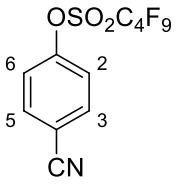
perfluoro-1-butanesulfonyl fluoride (0.99 mL, 5.5 mmol). The reaction mixture was stirred for 16 h. The crude material was purified using flash column chromatography, eluting with 30% diethyl ether in petroleum ether (40–60) to give 4-acetylphenyl nonafluorobutanesulfonate (**216**) as a white solid (1.5 g, 98%). Mp 38–40 °C (lit.[172] 38–40 °C); δ_H (500 MHz, $CDCl_3$) 2.63 (3H, s, CH_3), 7.39 (2H, d, *J* 8.9 Hz, 2-H and 6-H), 8.06 (2H, d, *J* 8.9 Hz, 3-H and 5-H); δ_C (126 MHz, $CDCl_3$) 26.8 (CH_3), 121.8 (2 × CH), 130.7 (2 × CH), 137.0 (C), 152.9 (C), 196.3 (C); *m*/*z* (EI) 418.1 (M^+. 30%), 403 (100), 339 (38), 107 (38).

4-Formylphenyl nonafluorobutanesulfonate (217)[179]



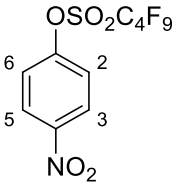
The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) using 4-hydroxybenzaldehyde (0.49 g, 3.7 mmol), triethyamine (1.4 mL, 10 mmol) and perfluoro-1-butanesulfonyl fluoride (1.1 mL, 6.1 mmol). The reaction mixture was stirred for 20 h. The crude material was purified using flash column chromatography, eluting with 30% diethyl ether in petroleum ether (40–60) to give 4-formylphenyl nonafluorobutanesulfonate (**217**) as a viscous oil (1.5 g, 92%). Spectroscopic data was in agreement with previously published data.[179] δ_H (500 MHz, $CDCl_3$) 7.48 (2H, d, *J* 8.7 Hz, 2-H and 6-H), 8.01 (2H, d, *J* 8.7 Hz, 3-H and 5-H), 10.05 (1H, s CHO); δ_C (101 MHz, $CDCl_3$) 122.4 (2 × CH), 131.9 (2 × CH), 136.1 (C), 153.7 (C), 190.3 (C); *m*/*z* (EI) 404 (M^+. 40%), 339 (100), 93 (25), 121 (15), 65 (43).

4-Cyanophenyl nonafluorobutanesulfonate (218)[172]



The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) using 4-cyanophenol (0.20 g, 1.7 mmol), triethyamine (0.59 mL, 4.2 mmol) and perfluoro-1-butanesulfonyl fluoride (0.46 mL, 2.5 mmol). The reaction mixture was stirred for 16 h. The crude material was purified using flash column chromatography, eluting with 20% diethyl ether in petroleum ether (40–60) to give 4-cyanophenyl nonafluorobutanesulfonate (**218**) as a white solid (0.52 g, 77%). Mp 109–110 °C (lit.[172] 111–112 °C); δ_H (500 MHz, $CDCl_3$) 7.44 (2H, d, *J* 9.0 Hz, 2-H and 6-H), 7.79 (2H, d, *J* 9.0 Hz, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 113.0 (C), 117.2 (C), 122.8 (2 × CH), 134.6 (2 × CH), 152.4 (C); *m*/*z* (EI) 401 (M^+. 38%), 118 (47), 102 (100), 90 (71), 77 (41), 69 (99).

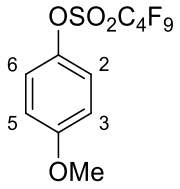
4-Nitrophenyl nonafluorobutanesulfonate (219)[179]



The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) using 4-nitrophenol (0.055 g, 0.40 mmol), triethyamine (0.14 mL, 0.99 mmol) and perfluoro-1-butanesulfonyl fluoride (0.11 mL, 0.59 mmol). The reaction mixture was stirred for 16 h. The crude material was purified through a short pad of silica, eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-nitrophenyl nonafluorobutanesulfonate (**219**) as a yellow solid (0.14 g, 83%). Mp 67–68 °C (lit.[179] 67.8–69.6 °C); δ_H (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 9.2 Hz, 2-H and 6-H), 8.36 (2H, d, *J* 9.2 Hz, 3-H and 5-H); δ_C (101 MHz, $CDCl_3$) 122.7 (2 × CH), 126.1 (2

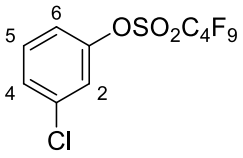
× CH), 147.3 (C), 153.5 (C); *m/z* (EI) 421 (M^+. 30%), 131 (40) 77 (99), 69 (100), 51 (61).

4-Methoxyphenyl nonafluorobutanesulfonate (220)[172]



The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) using 4-methoxyphenol (0.10 g, 0.81 mmol), triethyamine (0.28 mL, 2.0 mmol) and perfluoro-1-butanesulfonyl fluoride (0.22 mL, 1.2 mmol). The reaction mixture was stirred for 48 h. The crude material was purified using flash column chromatography, eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-methoxyphenyl nonafluorobutanesulfonate (**220**) as a colourless oil (0.25 g, 74%). Spectroscopic data was in agreement with previously published data.[172] δ_H (500 MHz, $CDCl_3$) 3.82 (3H, s, CH_3), 6.92 (2H, d, *J* 9.2 Hz, 3-H and 5-H), 7.21 (2H, d, *J* 9.2 Hz, 2-H and 6-H); δ_C (126 MHz, $CDCl_3$) 55.8 (CH_3), 115.2 (2 × CH), 122.5 (2 × CH), 143.4 (C), 159.2 (C); *m/z* (EI) 406 (M^+. 12%), 123 (100), 95 (14), 69 (11), 52 (5).

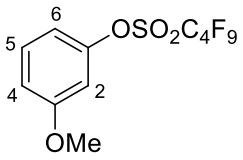
3-Chlorophenyl nonafluorobutanesulfonate (221)[180]



The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) using 3-chlorophenol (0.11 g, 0.85 mmol), triethyamine (0.30 mL, 2.1 mmol) and perfluoro-1-butanesulfonyl fluoride (0.23 mL, 1.3 mmol). The reaction mixture was stirred for 16 h. The crude material was purified through a short pad of silica, eluting with 20% ethyl acetate in petroleum ether (40–60) to give 3-chlorophenyl nonafluorobutanesulfonate (**221**) as a colourless oil (0.30 g, 94%). Spectroscopic

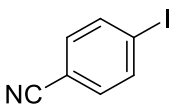
data was in agreement with previously published data.[180] δ_H (500 MHz, $CDCl_3$) 7.18–7.24 (1H, m), 7.30–7.33 (1H, m), 7.38–7.43 (2H, m); δ_C (126 MHz, $CDCl_3$) 119.9 (CH), 122.2 (CH), 129.0 (CH), 131.1 (CH), 135.8 (C), 149.9 (C); *m/z* (EI) 410 (M^+. 58%), 127 (59), 111 (100), 99 (93), 69 (84).

3-Methoxyphenyl nonafluorobutanesulfonate (222)



The reaction was carried out according to the previously described procedure for methyl 4-nonafluorobutanesulfonyloxybenzoate (**199**) using 3-methoxyphenol (0.51 g, 4.1 mmol), triethyamine (1.4 mL, 10 mmol) and perfluoro-1-butanesulfonyl fluoride (1.1 mL, 6.0 mmol). The reaction mixture was stirred for 16 h. The crude material was purified using flash column chromatography, eluting with 5% diethyl ether in petroleum ether (40–60) to give 3-methoxyphenyl nonafluorobutanesulfonate (**222**) as a colourless oil (1.5 g, 88%). ν_{max}/cm^{-1} (neat) 2962 (CH), 1612, 1491, 1423, 1236, 1225, 1200, 1142, 1107; δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, CH_3), 6.81 (1H, t, *J* 2.3 Hz, 2-H), 6.88 (1H, dd, *J* 8.3, 2.3 Hz, 4-H), 6.90 (1H, dd, *J* 8.3, 2.3 Hz, 6-H), 7.34 (1H, t, *J* 8.3 Hz, 5-H); δ_C (101 MHz, $CDCl_3$) 55.8 (CH_3), 107.7 (CH), 113.4 (CH), 114.2 (CH), 130.7 (CH), 150.6 (C), 161.0 (C); *m/z* (EI) 405.9921 (M^+. $C_{11}H_7F_9O_4S$ requires 405.9922), 342 (24%), 219 (12), 131 (15), 95 (100), 84 (100), 49 (62).

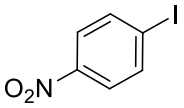
4-Iodobenzonitrile (223)



The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method B) using 4-cyanophenyl nonafluorobutanesulfonate (**218**) (0.055 g, 0.14 mmol), sodium iodide (0.062 g, 0.41 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.0035 g, 0.0069 mmol, 5 mol%) and *N,N'*-

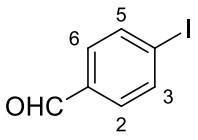
dimethylformamide (0.50 mL). The reaction mixture was stirred for 3 h. The crude material was purified through a short pad of silica, eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-iodobenzonitrile (**223**) as a white solid (0.039 g, 91%). Spectroscopic data was in agreement with that described previously.

4-Iodonitrobenzene (224)



The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method B) using 4-nitrophenyl nonafluorobutanesulfonate (**219**) (0.052 g, 0.12 mmol), sodium iodide (0.056 g, 0.37 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.0030 g, 0.0062 mmol, 5 mol%) and *N*,*N*'-dimethylformamide (0.50 mL). The reaction mixture was stirred for 3 h. The crude material was purified using flash column chromatography, eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-iodonitrobenzene (**224**) as a pale yellow solid (0.029 g, 94%). Spectroscopic data was in agreement with that described previously.

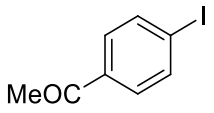
4-Iodobenzaldehyde (225)[181]



The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method B) using 4-formylphenyl nonafluorobutanesulfonate (**217**) (0.052 g, 0.13 mmol), sodium iodide (0.058 g, 0.39 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.0033 g, 0.0064 mmol, 5 mol%) and *N*,*N*'-dimethylformamide (0.50 mL). The reaction mixture was stirred for 4 h. The crude material was purified through a short pad of silica, eluting with 20% ethyl

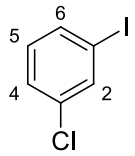
acetate in petroleum ether (40–60) to give 4-iodobenzaldehyde (**225**) as a white solid (0.027 g, 90%). Mp 75—76 °C (lit.[181] 77—78 °C); δ_H (400 MHz, $CDCl_3$) 7.59 (2H, d, *J* 8.0 Hz, 3-H and 5-H), 7.92 (2H, d, *J* 8.0 Hz, 2-H and 6-H), 9.96 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 102.9 (C), 131.0 (2 × CH), 135.8 (C), 138.6 (2 × CH), 191.5 (CHO); *m*/*z* (EI) 232 (M^+. 29%), 231 (51), 203 (21), 76 (56), 65 (43), 51 (27).

4-Iodoacetophenone (226)



The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method B) using 4-acetylphenyl nonafluorobutanesulfonate (**216**) (0.041 g, 0.10 mmol), sodium iodide (0.044 g, 0.29 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.0030 g, 0.0062 mmol, 5 mol%) and *N*,*N*'-dimethylformamide (0.50 mL). The reaction mixture was stirred for 4 h. The crude material was purified using flash column chromatography, eluting with 20% ethyl acetate in petroleum ether (40–60) to give 4-iodoacetophenone (**226**) as a white solid (0.020 g, 83%). Spectroscopic data was in agreement with that described previously.

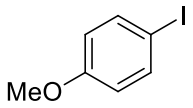
1-Chloro-3-iodobenzene (227)[173]



The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method B) using 3-chlorophenyl nonafluorobutanesulfonate (**221**) (0.054 g, 0.13 mmol), sodium iodide (0.059 g, 0.39 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.0033 g, 0.0064 mmol, 5 mol%) and *N*,*N*'-dimethylformamide (0.50 mL). The crude material was purified through a short pad of silica, eluting with 1% ethyl acetate in petroleum ether (40–60) to give 1-

chloro-3-iodobenzene (**227**) as a clear oil (0.014 g, 45%). Spectroscopic data was in agreement with previously published data.[173] δ_H (400 MHz, $CDCl_3$) 7.03 (1H, t, *J* 8.0 Hz, 5-H), 7.32 (1H, ddd, *J* 8.0, 1.7, 1.0 Hz, 4-H), 7.59 (1H, ddd, *J* 8.0, 1.7, 1.0 Hz, 6-H), 7.72 (1H, t, *J* 1.7 Hz, 2-H). δ_C (101 MHz, $CDCl_3$) 94.2 (C), 128.1 (CH), 131.1 (CH), 135.1 (C), 135.8 (CH), 137.2 (CH); *m/z* (EI) 238 (M^+. 62%), 113 (21), 76 (56), 69 (46), 51 (32).

4-Iodoanisole (229)



The reaction was carried out according to the previously described procedure for 2-iodonaphthalene (**195)** (method B) using 4-methoxyphenyl nonafluorobutanesulfonate (**220**) (0.052 g, 0.13 mmol), sodium iodide (0.12 g, 0.77 mmol), tris(acetonitrile)pentamethylcyclopentadienylruthenium(II) trifluoromethanesulfonate (0.010 g, 0.019 mmol, 15 mol%) and *N*,*N*'-dimethylformamide (0.50 mL). The reaction mixture was stirred for 96 h. The crude material was purified using flash column chromatography, eluting with 20% ethyl acetate in petroleum ether (40—60) to give 4-iodoanisole (**229**) as a white solid (0.011 g, 36%). Spectroscopic data was in agreement with that described previously.

6.0 References

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