N-, *O*-Arylation Using Diaryliodonium Salts in Continuous Flow

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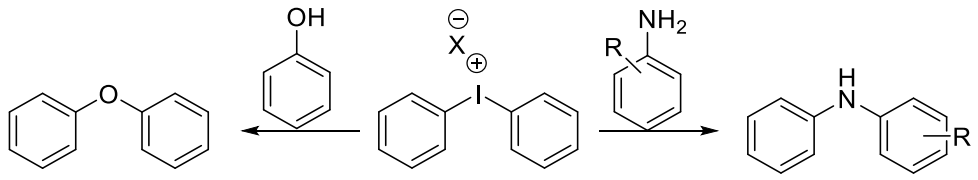
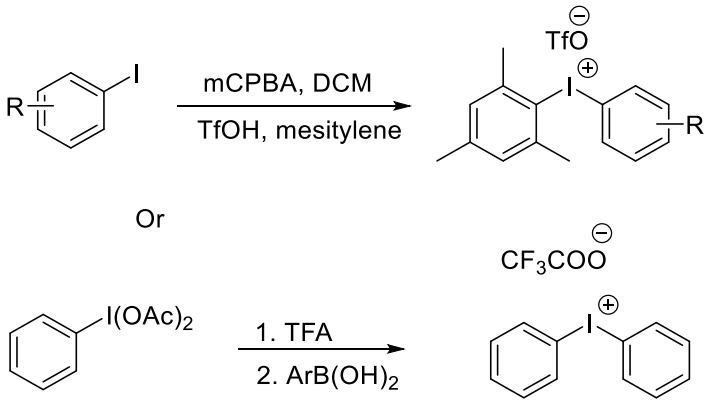
Abstract

The work presented herein describes a novel and practical methodology for the synthesis of diarylamines and diarylethers using diaryliodonium salts and the selectivity between *N*-, and *O*-nucleophiles using continuous flow chemistry protocols with the FlowSyn™ automated reaction system (Scheme 1).[1]



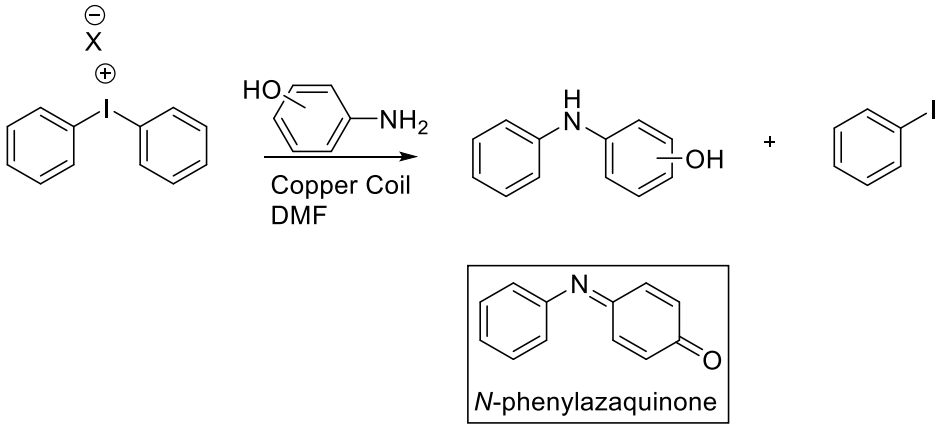
Scheme 1: *N*-, *O*-Arylation using diaryliodonium salts

The translation from batch conditions successfully reduced the time for the reaction (24 h to 80 min) and a further refinement of using a copper coil as both reactor and catalyst generated the desired products under even milder conditions (130 °C to RT).



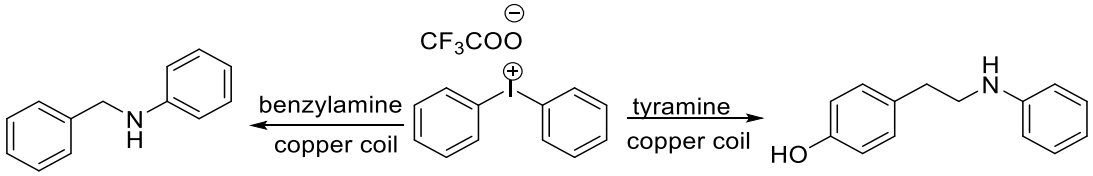
Scheme 2: Diaryliodonium salt synthesis

The diaryliodonium salts were easily synthesised from commercial, inexpensive, starting materials and purified by recrystallization (Scheme 2).[2, 3] The stability of these salts allowed us to investigate a range of diaryliodonium salts to determine which aromatic ring reacted with the nucleophile, their solubility and that of the aniline/phenol in DMF allowed us to use flow chemistry as the reaction mixture was homogeneous.



Scheme 3: Selectivity of *N*-, *O*-arylation using diaryliodonium salts

The methodology was extended to also investigate the arylation of *O*-nucleophiles under the same reaction conditions using the FlowSyn™ (Scheme 1) however the selectivity between the two types of nucleophiles was unknown and a range of hydroxyanilines were used to explore this (Scheme 3). The method gave high yields of the arylated product with a notable preference for *N*-arylation over *O*-arylation, although some *N*, *O*-diarylation was observed. Of particular interest was the production of *N*-phenylazaquinone 82% when 4-hydroxyaniline was used with two equivalents of diphenyliodonium trifluoroacetate indicating a two-step process was present, the first equivalent resulting in *N*-arylation and the second oxidising the product.[4, 5]



Scheme 4: Arylation of aliphatic amines

The methodology has also proven to be valuable for the arylation of aliphatic amines for instance those examples shown in Scheme 4, however the yield of the desired product was lower than that obtained for the aromatic amines. This project has indicated that aromatic amines are more suitable substrates for arylation with diaryliodonium salts and in the case where both *N*- and *O*-nucleophiles are present the nitrogen was always selectively arylated over the oxygen nucleophile.

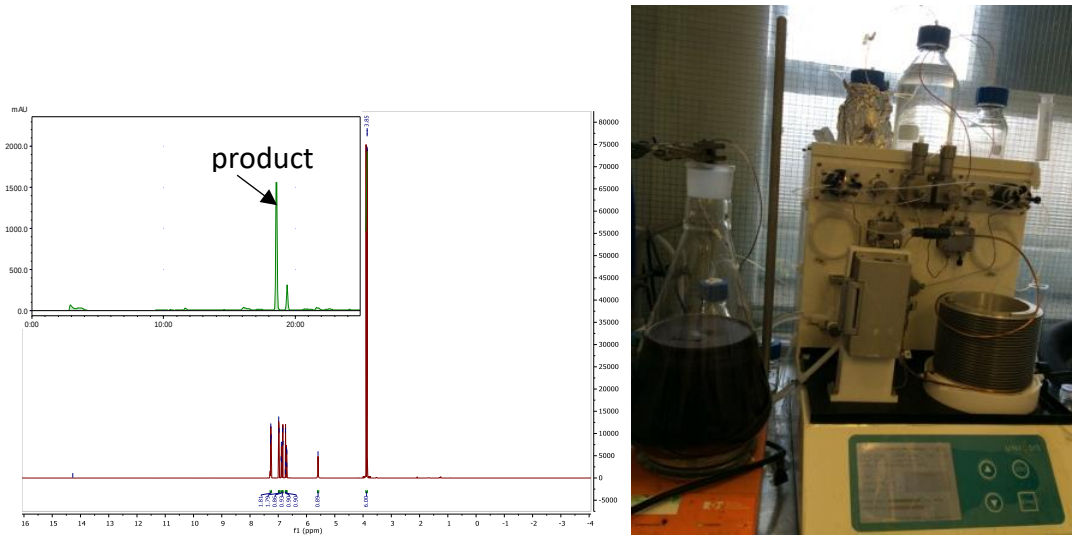


Figure 1: HPLC chromatogram of crude 3, 4-dimethoxydiphenylamine, ^{1}H NMR of pure product (left), FlowSyn™ (right).

The translation of the reaction methodology to flow chemistry protocols has also allowed us to scale up the production, for example 3, 4-dimethoxydiphenylamine was prepared in a high yield (80%) at room temperature using diphenyliodonium trifluoroacetate (13.79 g, 35 mmol) and 3,4-dimethoxyaniline (5.36 g, 35 mmol). Simple washing of the precipitated product with ether gave the pure material (Fig. 1).

1. www.uniqsis.com.
2. M. A. Carroll and R. A. Wood, *Tetrahedron*, 2007, **63**, 11349-11354.
3. M. Bielawski, M. Zhu and B. Olofsson, *Adv. Synth. Catal*, 2007, **349**, 2610-2618.
4. A. Varvoglis, *Tetrahedron*, 1997, **53**, 1179-1255.
5. T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, K. Morimoto, H. Fujioka and Y. Kita, *Tetrahedron*, 2009, **65**, 10797-10815.

Abbreviations

AcOH	Acetic acid
Ac_2O	Acetic acid
ACPI	Atmospheric pressure chemical ionization
aq.	Aqueous
Ar	Aryl
ASAP	Atmospheric solids analysis probe
BINAP	(2,2′-Bis(diphenylphosphino)1,1′-binaphthyl)
Boc	Tert-butyloxycarbonyl
Bu_4NBr	Tetrabutylammonium bromide
$CDCl_3$	Deuterated chloroform
CD_3CN	Deuterated acetonitrile
COX-2	Cyclooxygenase
CTRF	Copper tube flow reactor
$Cu(acac)_2$	Copper acetylacetonate
CyDA	Rac-trans-1,2-cyclohexanediamine
d	Doublet
DAB	3,3′-Diaminobenzidine
DBU	1, 8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethan
dd	Double doublet
ddd	Double doublet of doublets
Dioxane	1, 4-Dioxane
DMEDA	*N*,*N*-Dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMAP	4-(Dimethylamino)pyridine
DMSO	Dimethylsulfoxide

d_6-DMSO	Deuterated dimethylsulfoxide
DTBP	Di-tert-butyl peroxide
EDG	Electron-donating group
EDTA	Ethylene diaminetetraacetic acid
EI	Electron impact ionization
Equiv.	Equivalent
EtOH	Ethanol
Et_3N	Triethylamine
EWG	Electron-withdrawing group
g	Gram
H	Hours
HBDs	Hydrogen bond donors
Het	Heteroaromatic
HPLC	High-performance liquid chromatography
Hz	Hertz
IR	Infra red
J	Coupling constant
L	Ligand (generic)
M	Molar
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
MeO	Methoxy
Mes	Mesitylene/mesityl
*m*CPBA	*meta*-Chloroperoxybenzoic acid
$[M+H]^+$	Molecular ion peak + a proton
min	Minutes
mL	Millilitre
mmol	Millimole

MS	Mass spectrometry
MsO	Methane sulfonate
Mp	Melting point
MW	Microwave
m/z	Mass/charge ratio
NaAsc	Sodium ascorbate
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
NP	Nano particles
NSI	Nano-electrospray ionization
Nu	Nucleophile
OAc	Acetate
OTf	Trifluoromethane sulfonate (triflate)
OTs	*para*-Tolylsulfonate (tosylate)
PEEK	Polyetheretherketone
Ph	Phenyl
Phen	1-10-phenanthroline
PFA	Polyfluoroacetate
psi	Pressure unit
PTFE	Polytetrafluoroethylene
R_f	Retardation factor
R_t	Retention time
RT	Room temperature
S	Singlet
SET	Single electron transfer
$SnBu_3$	Tributyltin
S_NAr	Nucleophilic aromatic substitution
t	Triplet
tt	Triple triplet

TBAA	tert-Butyl acetoacetate
TBAF	Tetra-n-butylammonium fluoride
TBDMS	tert-Butyldimethylsilyl ether
TBME	tert-Butyl methyl ether
t-BuOK	Potassium tert-butoxide
t-BuONa	Sodium tert-butoxide
t-BuONO	tert-Butyl nitrite
Temp.	Temperature
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TFA	Trifluoroacetic acid/trifluoroacetate
TFE	Trifluoroethanol
TfOH	Triflic acid
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
p-xylene	1,4-Dimethylbenzene
UV	Ultra violet
Vioxx	Rofecoxib

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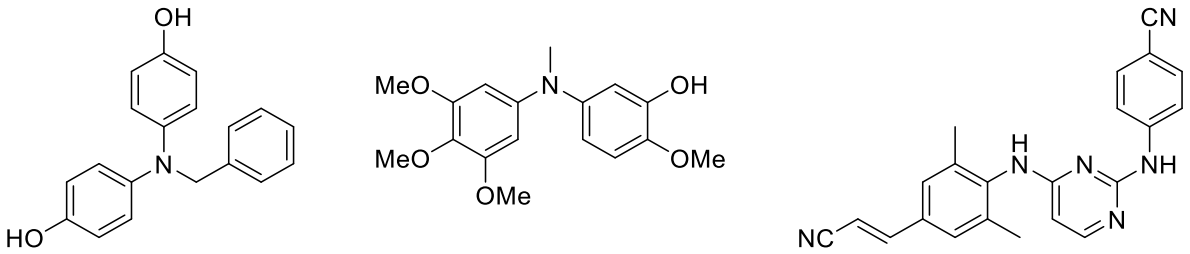
1 Introduction

1.1 Arylation of nitrogen



Azaisoerianin **Estrogen Receptor Ligands** **Rilpivirine**

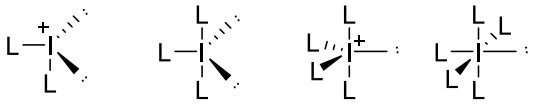
1 **2** **3**

Figure 1: Examples of biological active arylamines

Diarylamines are useful compounds due to their wide range of biological activity for example Figure 1,[6-8] the functionality is also found in natural products and as a structural component in material science. They have been synthesized using Ullmann-type conditions[9] which involve the reaction of amines with aryl halides in the present of copper and/or palladium but the reaction conditions may be harsh, provide low yields and may also require large (for example stoichiometric) amounts of catalyst. Copper and palladium catalysts have also been used in the arylation of nitrogen in a method reported by Buchwald and Hartwig.[9-11] They have also been synthesised under metal-free conditions as well as Friedel-Crafts or S_NAr-type mechanisms and Chan-Lam-type *N*-arylations.[12] The arylation of nitrogen nucleophiles has been reported under both metal-free[2] and metal catalysed conditions[13-15] using diaryliodonium salts and it is this methodology that the research group continues to pursue.

1.2 Iodine

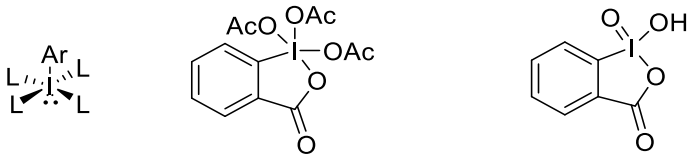
Iodine was discovered by the industrial chemist Bernard Courtois and it was separated from the ash of seaweed for the first time in 1811.[16] It has a large size, is polarisable and is of limited electronegativity, therefore it has the ability to make polycoordinate, multivalent compounds. The dissociation bond energy between carbon and iodine is 55 Kcal/mol therefore it is a weak bond which is also helpful for taking part in organic reactions.[16, 17] Hypervalent iodine reagents such as (dichloroiodo)benzene were first reported by Willgerodt in 1886 and he published a book on these materials in 1914. The chemistry of hypervalent iodine has gained much interest within the chemistry community and some further compounds were published in 1960. Hypervalent molecules are described as elements of groups 15 – 18 which have more than eight electrons in the valence shell, and thus form a 3-centre-4-electron (3c-4e) system which is known as hypervalent bond.[18]



8-I-2 **4** | 10-I-3 **5** | 10-I-4 **6** | 12-I-5 **7**

Figure 2: Structures of hypervalent iodine compounds.[16]

There are different types of hypervalent iodine compounds and they are classified according to the oxidation state of the iodine such as monovalent iodine (I), iodine (III) which are known as λ3-iodanes, the most common species among hypervalent iodine compounds and iodine (v) species known as λ5-iodanes. Polyvalent iodine is distinguished by the number of electrons surrounding the iodine centre, the number of ligands and their resultant chemistry.[16, 18, 19] Figure 2 shows the structure of two λ3-iodanes (**4, 5**) a λ4-iodane (**6**) and a λ5-iodane (**7**).



8 **9** **10**

Figure 3: Structure of iodine (v) λ5-compounds

λ5-Aryliodanes ($ArIL_4$) which have a dodecet structure typically adopt a square based pyramidal geometry, where it has orthogonal hypervalent 3c-4e bonds with an aryl group in apical position and four heteroatom ligands in the basal positions. The bonds between iodine and the ligands are as follows; a covalent bond to the Ar group, and two orthogonal hypervalent 3c-4e bonds which provide the links to the remaining four ligands[18]. For example the Dess-Martin periodinane (**9**), which is used in the selective oxidation of alcohols to aldehydes, and (**10**) IBX (2-iodoxybenzoic acid) which is used as an oxidising agent for a wide range of functional groups adopt this structure.[19, 20]

1.3 Iodine (III) compounds

1.3.1 Structure and bonding

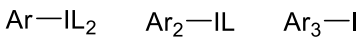


Figure 4: Iodine (III) aryliodanes

λ3-Aryliodanes are classified into three types (Figure 4), the first type of which is $ArIL_2$ which has one carbon – the aromatic group – and two heteroatom ligands, where the two heteroatom ligands sit in the pseudoaxial positions with the two remaining equatorial positions occupied by the lone pairs of electrons. They are mild oxidising agents typically used in the oxidation of alcohols, alkenes and α-hydroxyl carbonyl compounds where one heteroatom ligand undergoes exchange with the substrate and the second heteroatom ligand undergoes a subsequent elimination reaction as the iodine containing fragment is a good leaving group.[18] The C-I bond length in this class of hypervalent iodine species is the sum of the covalent radii of iodine and carbon (2.00 to 2.10 Å). The length of the iodine to heteroatom bonds in these 10-I-3 structures is longer than the covalent C-I bond but shorter

than an ionic bond, for instance in $PhICl_2$ the I-Cl bond lengths are 2.45 Å and in $PhI(OAc)_2$ the I-O bond lengths are 2.15–2.16 Å, which is longer than the combination of the I and O covalent radii which is 1.99 Å.[16]

In the λ3-aryliodanes ($ArIL_2$), the iodine (III) keeps its T-shaped geometry as indicated by X-ray structural analysis as the iodine and two heteroatom ligand share a hypervalent bond. It adopts a decet trigonal bipyramidal geometry, with the aryl group and the two lone pairs of electrons in the pseudoequatorial positions and the two heteroatom ligands in the pseudoaxial position. The λ3-iodanes use a 5p orbital in the linear L-I-L bond, this 3c-4e bond is formed from the bonding and non-bonding orbitals as shown in Figure 5. It has a node at the central iodine atom and there is therefore a partial positive charge on the central iodine and corresponding partial negative charges on the two heteroatom ligands.[21] [18, 22]

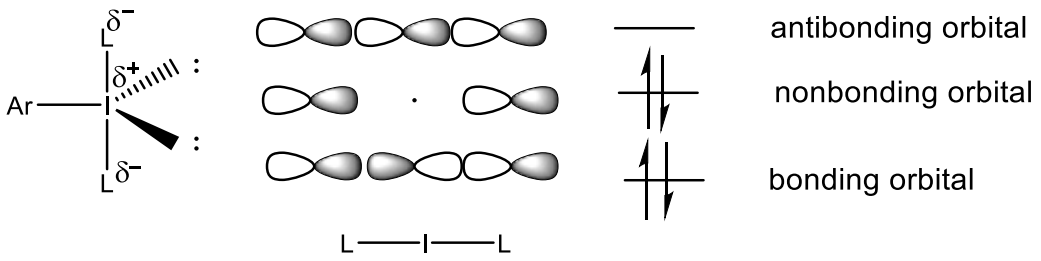


Figure 5: From left to right: structure of $ArIL_2$, the associated molecular orbitals and electron occupancy.[18]

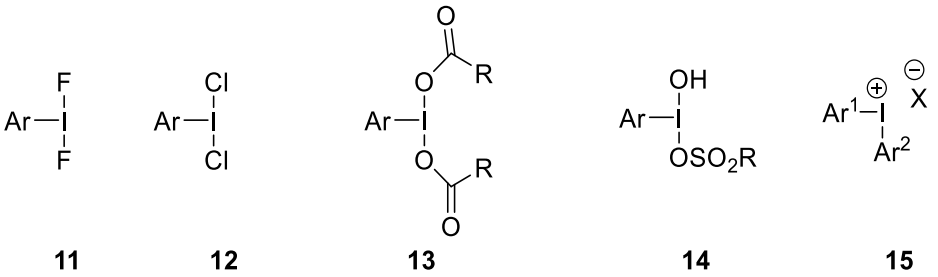
In the hypervalent iodine structure the 3c-4e bonds are not only weaker than the Ar-I bond but are also longer.

The second type of λ3-aryliodanes, Ar_2IL, has two carbon based ligands and one heteroatom ligand derived ligand.[18] They are commonly known as a diaryliodonium salts, it is indicated that the structure is similar to type 1, has trigonal bipyramidal geometry and the bond angle Ar-I-Ar is about 90° and the covalent bond length is 2.3 to 2.7 Å between the iodine atom and heteroatom ligand L.[23]

As a consequence of this bonding, and subsequent reactivity this class of species is the most common within the range of possible hypervalent iodine species. Due to its highly electron-

deficient nature and the presence of a very good leaving group, they have found use as arylating agents with many different types of nucleophiles. They are used in organic synthesis for carbon-carbon bond formation and as an alternative to toxic heavy metal-based oxidants. These species are also used in the copper and palladium catalysed cross-coupling reactions and often perform better than aryl halides.[22]

Finally Ar_3I has three carbon based ligands, the chemistry of these species has been considered less than the other types because they are less stable thermally and therefore more difficult to use.[16, 18]



11 **12** **13** **14** **15**

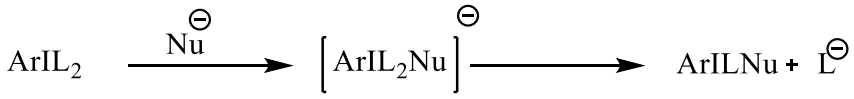
Figure 6: Structures of some iodine (III) compounds.[21]

The examples in Figure 6 shows some of the iodine (III) compounds, compound **11** is a fluorinating reagent and **12** is a chlorinating.agent. The compounds **13**, **14** are oxidising reagents and **15** is used commonly as an arylating reagent.

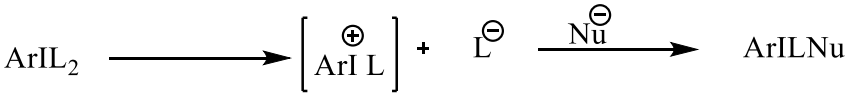
1.3.2 Iodanes: Reactivity

1.3.2.1 Ligand exchange

The heteroatom ligands of λ3-aryliodanes facilitate the reaction between iodine (III) and nucleophiles by ligand exchange with the nucleophile. The iodine centre behaves as an electrophile because of the node in the non-bonding orbitals making up the hypervalent bond. The two major possible mechanistic pathways for this reaction are an associative and a dissociative process.[18]



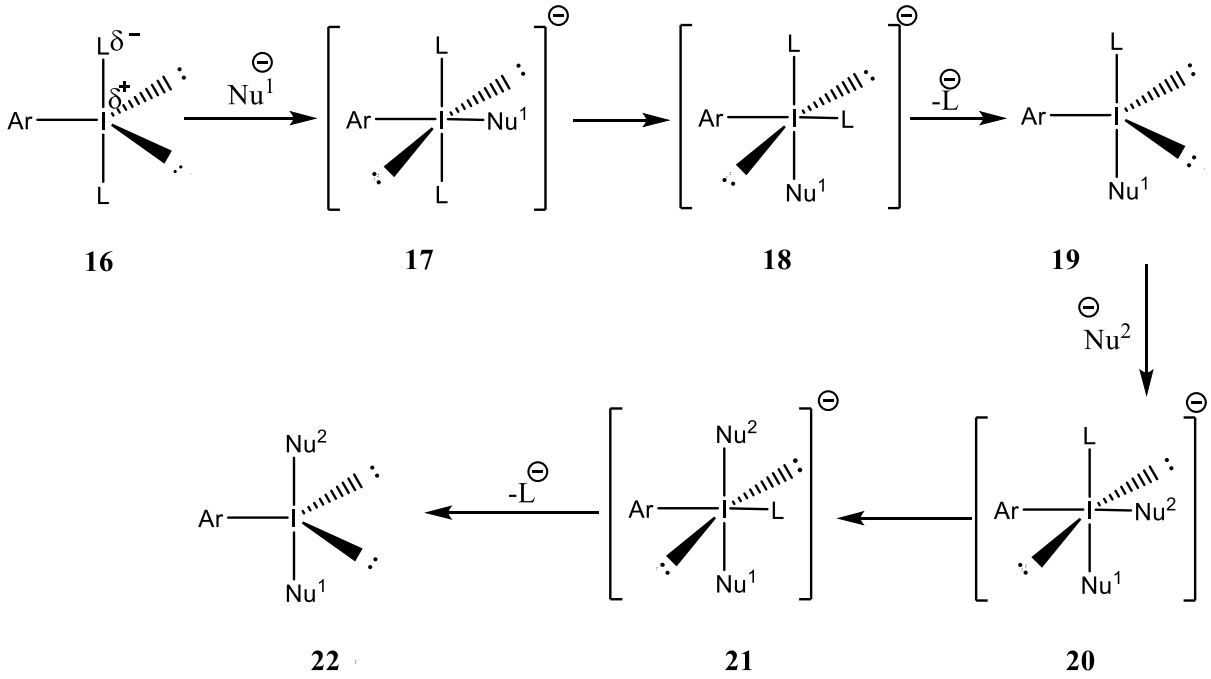
associative pathway



dissociative pathway

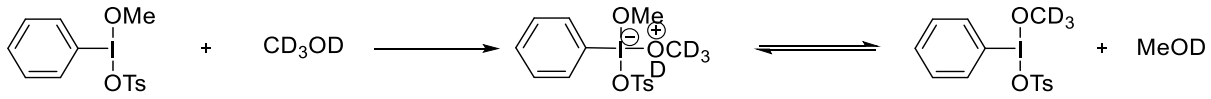
Scheme 1: Nucleophilic substitution of $ArIL_2$

In the associative pathway the nucleophile reacts with the λ3-aryliodanes leading to an intermediate (12-I-4) having the resultant groups in a square planar arrangement which allows the relationship between the heteroatom ligands to change from trans (**17**) to cis (**18**). One of the original heteroatom ligands (L) then leaves forming the λ3-aryliodanes ArILNu (**19**).



Scheme 2: Reaction of $ArIL_2$ with a nucleophile, Nu.[18]

If an excess of the nucleophile is available the second heteroatom ligand (L) will also exchange through this addition–elimination reaction forming $ArI(Nu)_2$ (**22**) (Scheme 2).



23

Scheme 3: Ligand exchange of 23 in CD_3OD

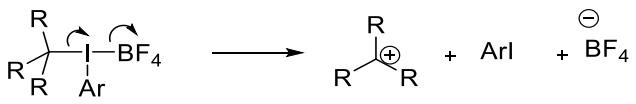
An example of this ligand exchange with an oxygen nucleophile is seen by 360 MHz NMR when (methoxy(tosyloxy)iodo)benzene (**23**) is dissolved in deuterated methanol 2.28 (s, 3H, tosyloxy), 3.92 (s, 3H, OMe), 8.2 (m, 9H, aromatic)[24] when the tetracoordinated intermediate species is observed (Scheme 3).[18]

1.3.2.2 Reductive elimination

The hypervalent λ3-iodanes have the potential to spontaneously generate monovalent iodide without the presence of additional reagents, via a reductive elimination process. The leaving group – aryliodanyl – is known as a hyper/supernucleofuge as it is ~10^6 times better as a leaving group than triflate. For example Table 2 shows the leaving group ability for some hypernucleofuges.[18]

Table 1. Leaving group ability

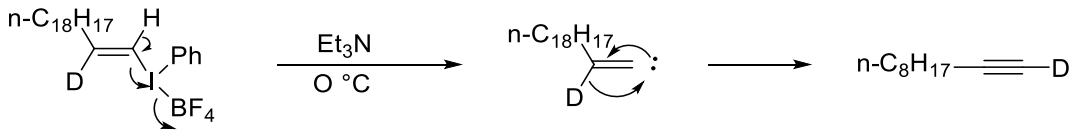
Nucleofuge	K_{rel}	Nucleofuge	K_{rel}
AcO	1.4×10^{-6}	I	9.1×10
F	9.0×10^{-6}	MsO	3.0×10^{4}
Me_2S^+	5.3×10^{-2}	TsO	3.7×10^{4}
Cl	1.0	TfO	1.4×10^{8}
F_3CCO_2	2.5	4-$MeC_6H_4(BF_4)I$	6.2×10^{13}
NO_3	7.2	$C_6H_5(BF_4)I$	1.2×10^{14}
Br	1.4×10	4-$ClC_6H_4(BF_4)I$	2.9×10^{13}



Scheme 4: Reductive elimination

The example shown in Scheme 4 also demonstrates that entropy favours this process where a λ3-aryliodane is used as the leaving group as two species are generated rather than the usual one. Electron-withdrawing substituents on the aromatic ring also enhance this reaction pathway.[18]

1.3.2.3 Reductive α-elimination

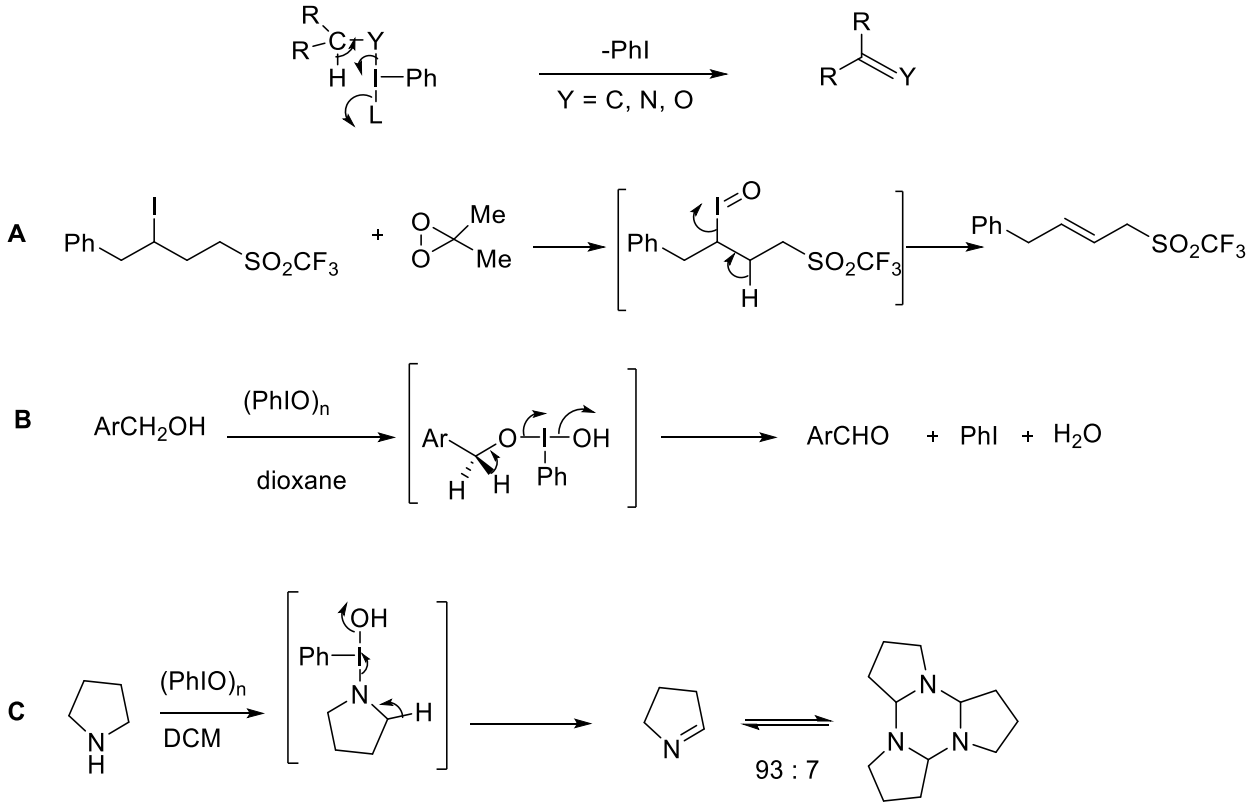


Scheme 5: Reductive α-elimination in alkenyl-λ3-iodanes

Carbenes are formed from α-elimination on a single carbon atom and proceed via abstraction of an α-hydrogen followed by reductive elimination, an example is in the reaction of

alkenyliodonium salts which decompose to form carbene which then undergoes a rearrangement to give an alkyne (Scheme 5).[18]

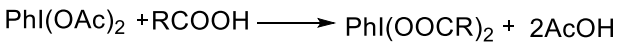
1.3.2.4 Reductive β-elimination



Scheme 6: Reductive β elimination on (A) carbon, (B) oxygen and (C) nitrogen.

Reductive β-elimination in species with a C-I bond results in the formation of carbon-carbon double bonds however in the presence of I-O and I-N bonds the reductive β-elimination generates carbonyl and imine functionality effectively resulting in an oxidation reaction (Scheme 6).[18, 25, 26]

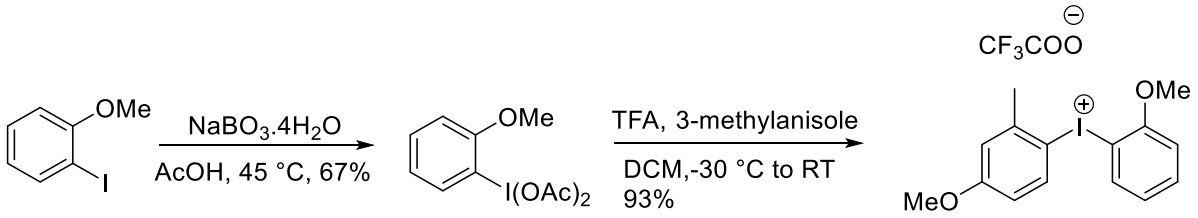
1.3.3 Diacetoxyiodoarene compounds



24

Scheme 7: Ligand exchange between diacetoxyiodobenzne (24) and carboxylic acid[18]

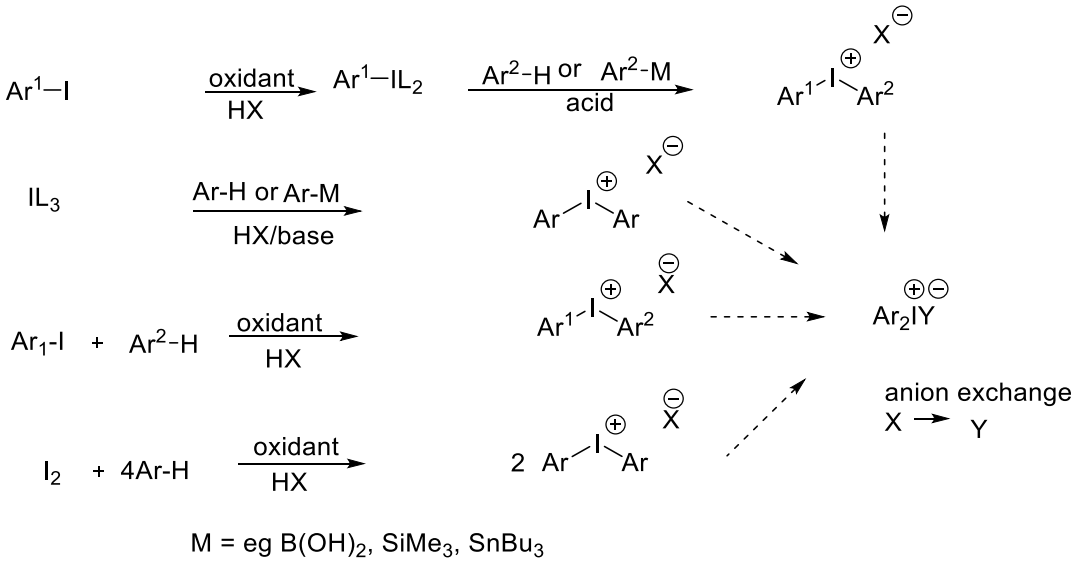
The diacetoxyiodoarenes are important compounds in organic synthesis and used not only as oxidising agents but also for the preparation diaryliodonium salts and hence the arylation of nucleophiles. They are prepared by oxidation of the corresponding iodoarene, with H_2O_2/AcOH/Ac_2O being the first recorded reagents for this transformation. Other oxidising agents can be used, for instance $NaBO_3 \cdot 4H_2O$ in AcOH.[18, 27] The phenyl derivative is diacetoxyiodobenzene and is commercially available and inexpensive, the acetate ligands can be exchanged in situ for other groups, such as trifluoroacetate, which may make the iodine more electrophilic and hence the reagent more reactive.[21, 28] In addition it is a much safer source of iodine (III) than iodosybenzene which is insoluble in organic solvents and has also demonstrated explosive properties.[21, 29]



Scheme 8: Ligand exchange in the preparation of diaryliodonium salt

As stated the acetate group can also be exchanged with trifluoroacetate, which enhances the positive charge on iodine, and has found use in the preparation of diaryliodonium trifluoroacetates (e.g. Scheme 8).[17]

1.4 Synthesis of diaryliodonium salts



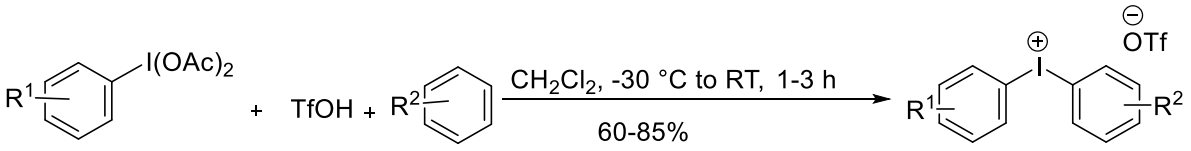
Scheme 9: Synthesis of diaryliodonium salt using different strategies

There are many different methods for the preparation of diaryliodonium salts, early methods used iodosylarene and iodooxyarene. Diaryliodonium salts were prepared for the first time by Hartmann and Meyer in 1894 iodosylarene and sulfuric acid but this strategy was low yielding and involved long reaction times.[22 30] Other methods, it involves two or three steps, for example oxidation of the aryliodide to iodine (III) in the form of $ArIL_2$ and then ligand exchange replacing one of the labile ligands (L) with an arene. Diaryliodonium salts can also be obtained direct from arenes or iodoarenes which also involves an oxidation and ligand exchange step as shown in Scheme 9.[22, 31]

Symmetrical diaryliodonium salts are readily prepared by the methods described above as they avoid chemoselectivity issues whereas the selective preparation of unsymmetrical diaryliodonium salts present complications as control of the reaction needed.

To control the regioselectivity of the diaryiodonium salt formation iododestannylation and iododesilylation are commonly used. For example a diacetoxyiodoarene or iodosylbenzene are reacted with tributylphenylstannane or trimethylsilylbenzene in the presence of boron trifluoride etherate. Perfluoroaryliodonium salts may be prepared by electrophilic arylation of C_6F_5I with a pentafluorophenylxenonium hexafluoroarsenates described by Frohn and co-workers. The most common method using iodosylbenzene or diacetoxyiodobenzene for the preparation of unsymmetrical diaryliodonium triflates uses arenes with triflic acid (Scheme

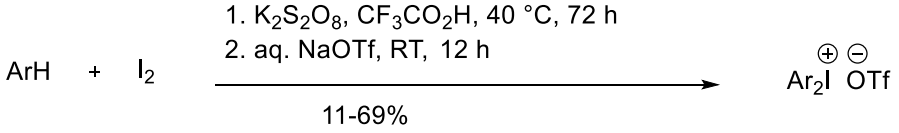
10) but this method is limited because some arenes are sensitive to strong acid and may also result in the formation of regioisomeric by-products. However this aspect may be improved by using an arylboronic acids as the substrate[23, 32] as electron-rich substrates such as methoxyarenes also suffer from complications when using TfOH leading to polymeric quinone derived materials.



R^1= 2-Me, 3-Me, 3,5-Me_2, 2,4,6-Me_3
R^2= 4-Me, 4-OMe, 4-Butyl

Scheme 10: Synthesis of unsymmetrical diaryliodonium triflates

An example of one-pot oxidation and arylation was used for preparing symmetrical diaryliodonium salts, introduced by Kitammura and Hossain. This used aromatic substrates, iodine and an oxidant such as $K_2S_2O_8$ in TFA (Scheme 11).[23]



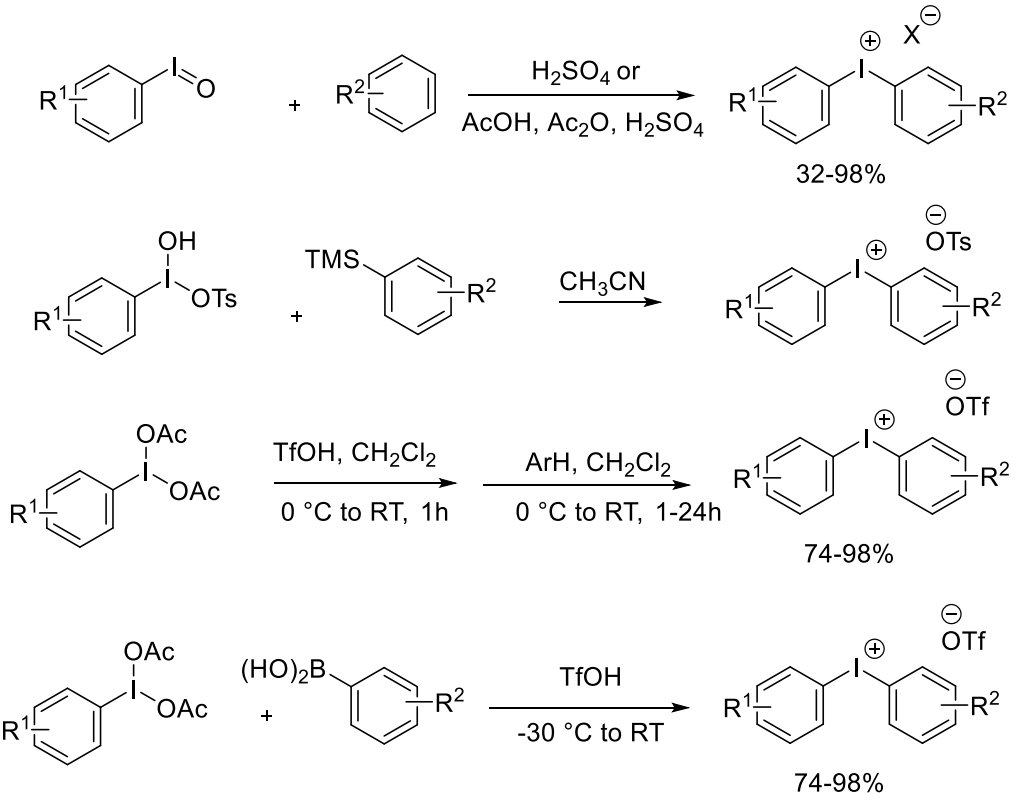
Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-MeC_6H_4, 4-$Bu^tC_6H_4$

Scheme 11: Synthesis of diaryliodonium salts in one pot oxidation

The one-pot synthesis has been improved by Olofsson and co-workers for preparing both symmetrical and unsymmetrical diaryliodonium salts, where both electron-rich and electron-deficient arenes are reacted with aryl iodides in the presence of an oxidant such as *m*CPBA, and triflic acid.[22, 33]

The reactivity and yield depends on the electronic properties of an arene, sulfuric acid is good for electron-deficient substrates whereas trifluoroacetic acid is needed for electron-rich arenes and heteroarenes.[7] Koser and co-workers improved the regioselective control of the

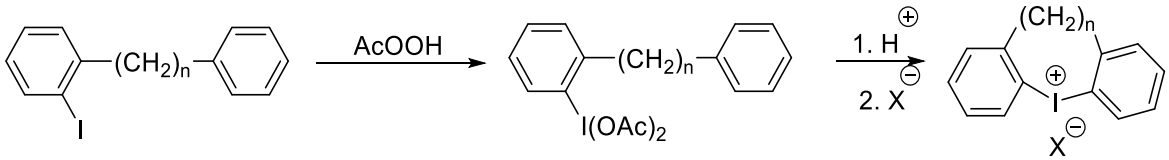
reaction by using the less reactive Koser's reagent (hydroxy(tosyloxy)iodobenzene) with arylsilanes under neutral conditions. Thiophene reacts directly with Koser's reagents and does not need activating groups such as trimethylsilyl[22] allowing the formation of 2-thienyliodonium salts directly.



Scheme 12: Synthesis of diaryliodonium salts using different iodine (III) reagents

The triflic acid is useful in organic solvents for the preparation of simple diaryliodonium salts as it is forms triflate salts directly and does not need an anion exchange step and they are generally easy to isolate. Beringer and co-workers published a large number of diaryliodonium salts in 1950 and used both iodosylarenes and iodoxyarenes with a range of acids as shown in Scheme 12.[22, 34-39]

Aryl stannanes are also used in the preparation diaryliodonium salts as they are more reactive than the corresponding arylsilane, they also react with Koser's reagent directly to give diaryliodonium tosylates.[22]



X= HSO_4, 1/2$(SO)_4$, Cl, Br

n = 0, 99%
n = 1, 95%
n = 2, 60%
n = 3. 70%

Scheme 13: Preparation of cyclic diaryliodonium salts

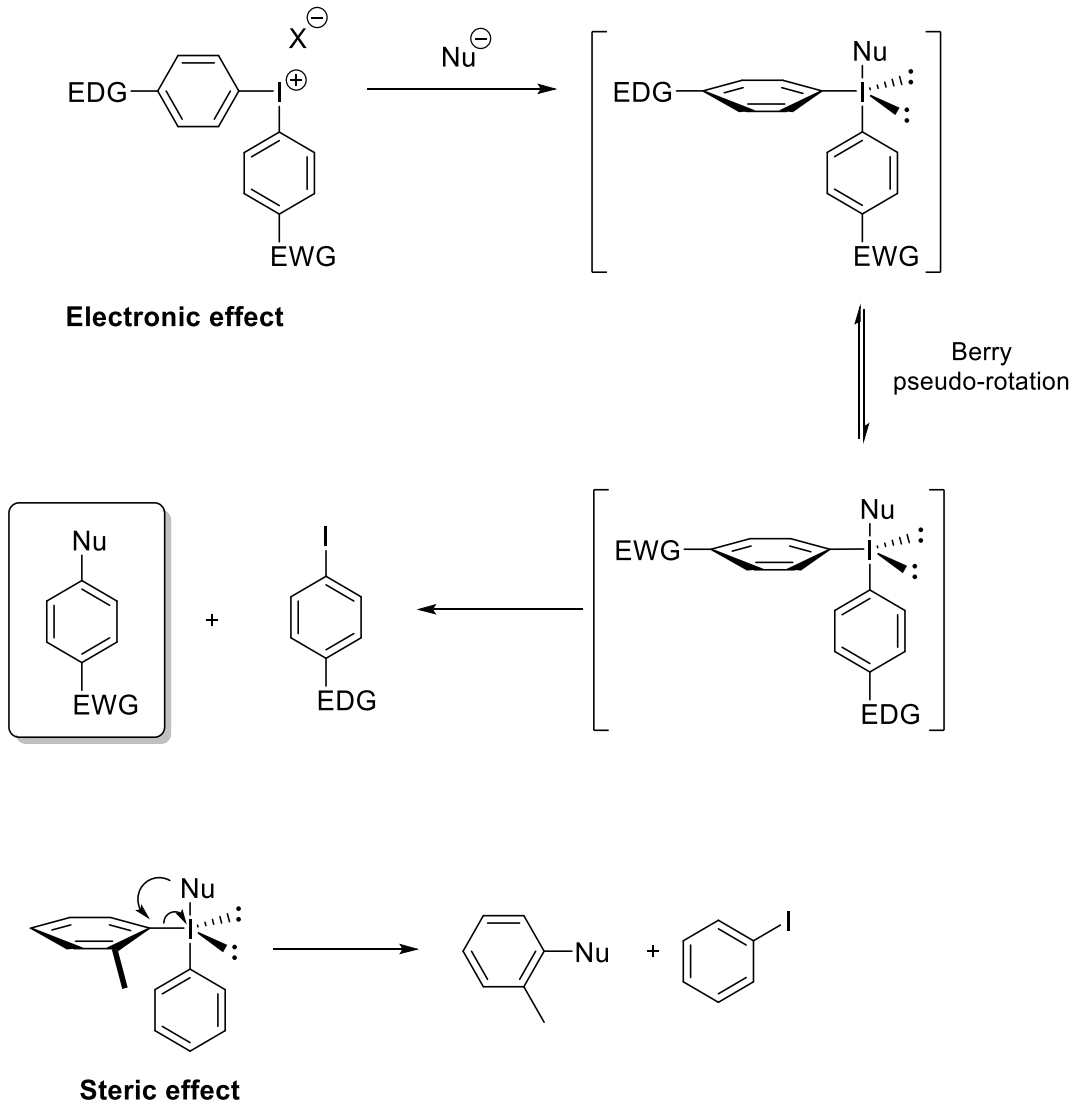
Synthesis of cyclic diaryliodonium salts can be achieved using a one-pot synthesis (via a ring closing process) which includes two steps, in the first step the iodoarene is oxidised to the diacetoxyiodoarene and in the presence of strong acid subsequently converted to a cyclic diaryliodonium salt (Scheme 13). This may also be achieved in the presence of potassium persulfate and sulfuric acid.[40 41]

1.4.1 An overview of diaryliodonium salt reactivity

Diaryliodonium salts are typically non-explosive, non-toxic and stable crystalline solids and can be used for arylating a wide variety of both organic and inorganic nucleophiles. They are also used instead of toxic, and often expensive, heavy metal containing reagents/intermediates such as those based on Hg, Pb and Pd, and also act as successful partners in a range of metal catalysed reactions such as the Suzuki, the Stille and the Heck reaction.

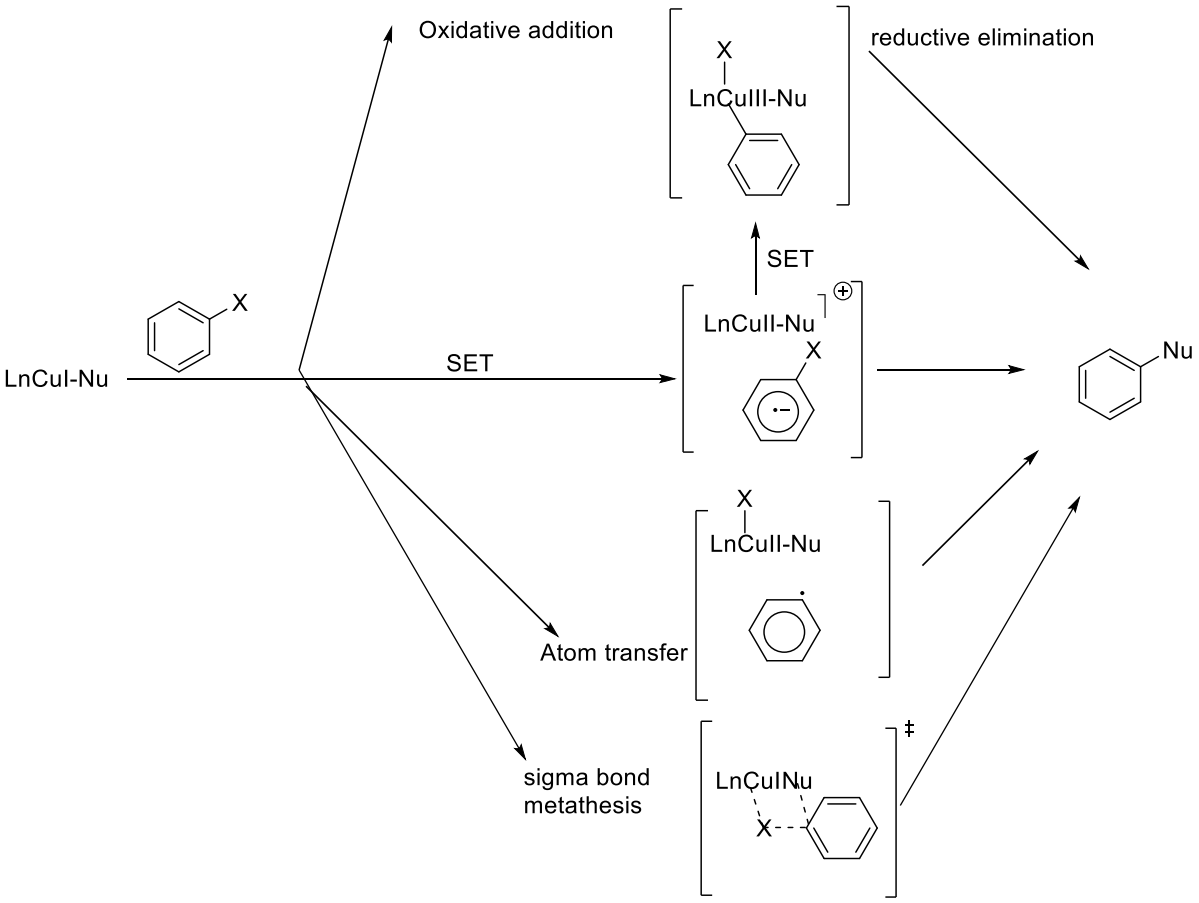
The mechanism of the reaction of diaryliodonium salts with nucleophiles may be via a polar (two electron process) or radical mechanism. Under metal-free conditions the diaryliodonium salt initially forms a T-shaped intermediate where the nucleophile replaces the counter-ion, and the following step involves the nucleophile and the adjacent aryl group (the one in the equatorial position) which proceeds via a ligand coupling/ reductive elimination process. However in unsymmetrical diaryliodonium salts, there are two possible T-shaped intermediates (Scheme 14),[42] however it has been shown that the most electron-deficient

group reacts with the nucleophile. This can be achieved as Berry pseudorotation may occur allowing interchange between the two possible intermediates and hence the two possible different transition states. The most favourable transition state is when the positive charge on the iodine is stabilised the most by the most electron-rich aromatic ring adopting the pseudoaxial position. If the *ortho*-position of the aromatic substituent bears bulky substituents, such as methyl groups, this ring then prefers to adopt the least hindered pseudoequatorial position, as a result the nucleophile reacts with this aromatic group and this is called the *ortho*-effect. This offers the possibility of controlling the selectivity of the reaction by both the relative electronic nature of the two aromatic rings and/or their relative size close to the iodine centre. [30]



Scheme 14: Proposed mechanism of nucleophile with diaryiodonium salt (electronic control and steric control).

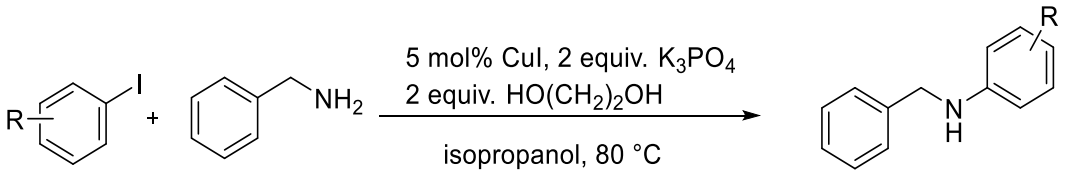
1.5 Arylation of nitrogen nucleophiles using arylhalide



Scheme 15: Proposed mechanism of the copper catalysed arylation using aryl halide

The Ullmann reaction is a nucleophilic substitution reaction between an aryl halide and nucleophile in the present of a copper catalyst and was discovered by Ullmann and Goldberg in the early 1900.[43] These reactions usually required harsh conditions, for instance high temperature, long reaction times and large amounts of catalyst. The proposed mechanism generates various organo copper intermediates (via single electron transfer SET, atom transfer from the arylhalide or sigma bond metathesis) from the arylhalides and the nucleophile through an oxidative addition process which then undergoes reductive elimination to give the product (Scheme 15).[44-48]

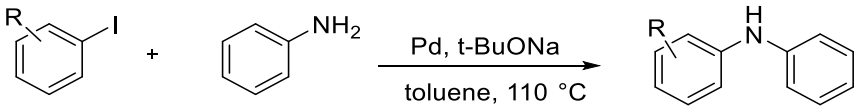
1.5.1 Arylation of alkylamines



Scheme 16: Arylation of benzylamine

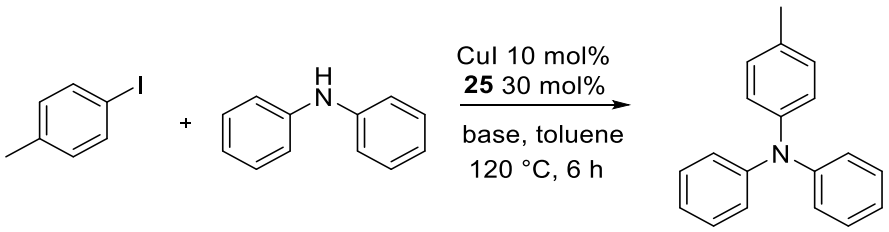
Another study used iodobenzene for the arylation of benzylamine in the presence of copper iodide (as it is stable to air and an inexpensive source of Cu^{I}) and a solvent such as isopropanol which is less toxic than the DMF traditionally used (Scheme 16). 3- and 4-Substituted iodobenzenes gave good yields of the desired product but 2-substituted substrates were less successful as they required high amounts of the copper catalyst.[49]

1.5.2 Arylation of arylamines



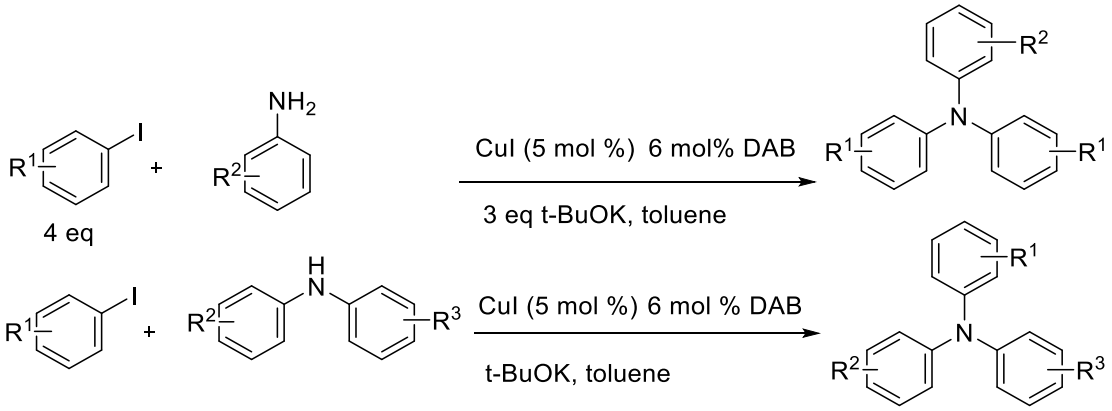
Scheme 17: Arylation of aniline using aryl halide

Aniline may be arylated with arylhalides using palladium catalysis in the Buchwald-Hartwig reaction. The aryl halide with either electron-donating groups or electron-withdrawing groups gave the desired product in good yield, however the presence of *ortho*-substituents resulted in a much decreased yield, probably due to the increased steric hindrance in the transition state.[50]



Scheme 18: Arylation of *N*-phenylaniline using copper complex 25

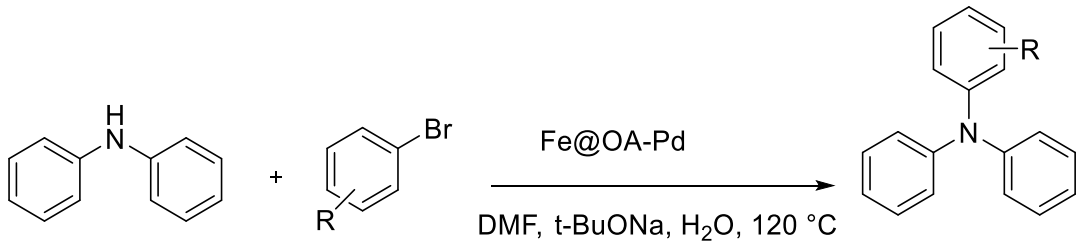
It has been reported that the copper complex **25** $[K_3(phen)_8][Cu(NPh_2)_2]_3$ (Scheme18), also catalyses the arylation of *N*-phenylaniline. The complex was formed from the reaction of copper iodide-phen-t-BuOK and $[Na(phen)_3][Cu(NPh_2)_2]$copper complex **26** from iodide-phen-t-BuONa. The best results were obtained from using complex **25** rather than complex **26.**[51] It was observed that a SET mechanism was in operation with complex **25** as the addition of TEMPO resulted in a decreased yield whilst the yield was only slightly deceased in presence of TEMPO when using complex **26** suggesting alternative mechanisms are operating for the two catalysts and that it is two-electron process with complex **26.**[51, 52]



Scheme19: Synthesis of triarylamines using arylhalide, DAB ligand

Other triarylamine compounds have also been synthesised using this copper catalysed reaction as they are useful building blocks for organic materials with electronic, photo-electronic and magnetic properties. It has been reported that triarylamines may be prepared in the presence of a ligand such as *N,N*-bis(2,6-diisopropylphenyl)-1,4-diaza-1,3-butadiene (DAB: prepared from the condensation of glyoxal with primary amines). This complex is stable to moisture and air making it easy to use however it was reported that iodoarenes with electron-donating groups result in a lower yield while diarylamines having increase steric

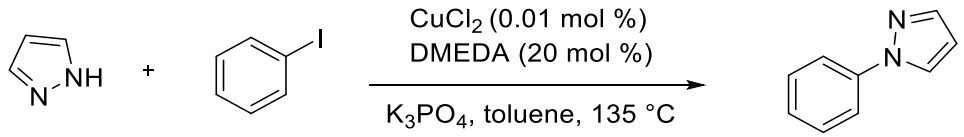
hindrance also led to a reduced yield. This method was also used for the arylation of primary arylamines such as aniline however four equivalent of aryl iodides was used to prevent the formation of a mixture of diarylamine and triarylamine (Scheme 19). [53]



Scheme 20: Synthesis of arylamines using Fe/Pd catalysis

Another report observed arylation of diphenylamine using arylbromides in the presence of palladium supported on magnetic nanoparticles covered by oleic acid (Fe@OA-Pd), the base t-BuONa was also required (Scheme 20). The arylation was successful however arylbromides with electron-withdrawing groups resulted in a lower yield of the product because of the competing dehalogenation reaction, the *ortho*-effect was also observed limiting the yield for sterically demanding substrates.[54]

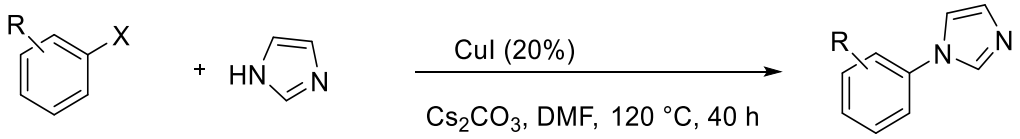
1.5.3 Arylation of heteroaromatics



Scheme 21: Arylation of pyrazole with iodobenzene

Heteroaromatic compounds for instance, pyrazoles have been arylated using arylhalides in the presence of copper and DMEDA[55-57] (Scheme 21), as an alternative method to the classical Ullmann reaction although which requires high load of catalyst, high temperature and is limited to certain substrates. The diamine-ligated Cu(I) catalyst used in the reaction catalyses the coupling of arylhalides and amides and proceeds through a three-centered-oxidative addition and reductive elimination mechanism.[58] It has been reported that the strength of

the halogen bond in the aryl halide and the ligand-copper-nucleophile complex have an influence on the coupling reaction.[59] Only trace amounts of the copper was needed compared to the DMEDA which was used in combination with a polar solvent. It was demonstrated that the reaction did not work at room temperature and without large quantities of ligand.

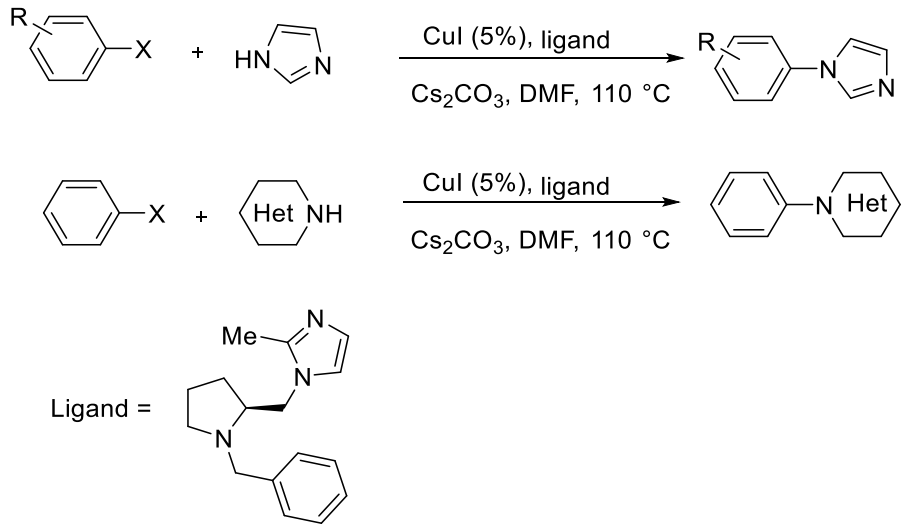


X = Cl, Br

X	**R**	**%**
Br	4-Me	80
Br	2-OMe	57
Br	4-OH	85
Br	H	91
Br	4-NH_2	79
Cl	4-NO_2	95
Cl	4-CN	90

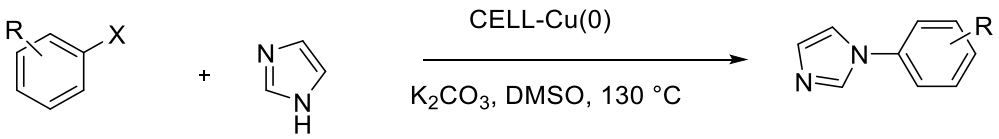
Scheme 22: Coupling between imidazole and aryl halide or heteroaryl

Another study reported the arylation of imidazole using copper iodide in the presence of Cs_2CO_3 and the solvent DMF (Scheme 22). It has been found that both DMF and/or imidazole could have acted as the ligand for the copper however both were successful with various functional groups, with the products obtained in good yield. The substrates with *ortho*-substituents also gave the desired product. Other heteroaromatics for instance indazoles, triazoles and benzimidazole were also arylated under these reaction conditions.[60]



Scheme 23: *N*-Arylation of imidazole and heteroaromatic with arylhalide

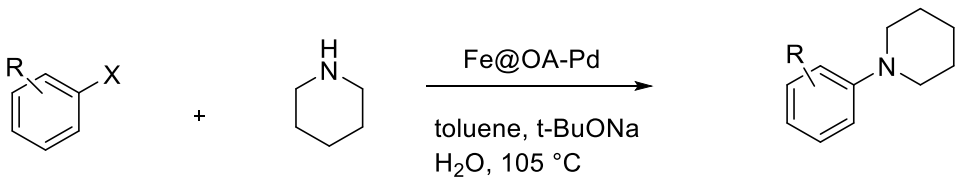
N-Arylation of imidazole has also been achieved with copper catalysis (Scheme 23) but this time in the presence of a ligand for instance (*S*)-1-((1-benzylpyrrolidin-2-yl)methyl)-2-methyl-1-H-imidazole. This method was applicable to aryl halide with different functional group for example esters as it prevents hydrolysis to benzoic acids at high temperature and conversion of nitriles to amides, this method also selectively arylated the nitrogen of imidazole. The use of 2-bromophenol, 4-bromophenol and 3-bromoaniline avoids the need of protecting groups, also mono arylation has been achieved when 1-4-dibromobenzene was used and a high yield of product obtained. The optimized conditions were successfully applied to other heteraromatic compounds for instance pyrroles, pyrazoles, indazole and triazole and gave the desired product in high yield.[61]



X	R	%
I	H	95
I	4-OMe	89
I	2-OMe	40
Br	4-COMe	70
Br	H	70
Cl	4-NO_2	95
Cl	4-COMe	50
Cl	H	20

Scheme 24: Arylation of imidazole with substituent aryl halide

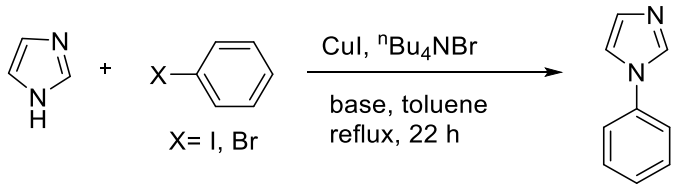
The arylation of imidazole has also been carried out using cellulose supported copper as cellulose stabilises the metal nanoparticles in the presence of base and DMSO as the solvent. A range of arylhalides were used with *ortho*-substituted substrates giving low yields possibly due to increased steric hindrance, as expected arylchlorides also gave lower yields than bromides and iodides, however imidazole with 4-nitrochlorobenzene gave a good yield of product probably due to the presence of the strong electron-withdrawing group over coming the less labile C-Cl bond (Scheme 24).[62]



X	R	%
Br	4-CN	0
Br	4-NO_2	41
Cl	4-CN	42
Cl	4-NO_2	63
Cl	4-NH_2	76

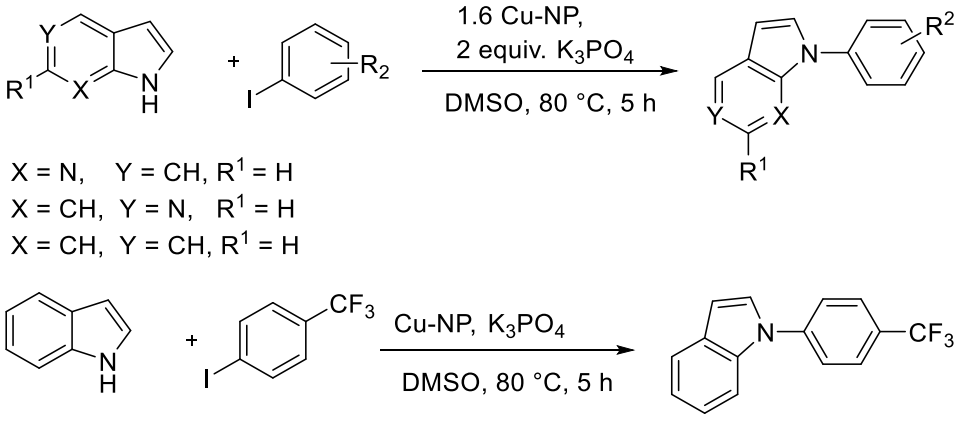
Scheme 25: Coupling of piperidine and aryl halides

Another study reported arylation of piperidine using arylbromides and arylchlorides in the presence of a palladium catalyst, which was supported on magnetic nanoparticles, to improve the activity of the palladium and potentially to aid recovery of the catalyst, this system has been recently used in the arylation of other amines as described in Section 1.5.2 (Scheme 20), this time the reaction was carried out using piperidine in the presence of toluene solvent. It was noted the base t-BuONa reduced the reaction time significantly.[54, 63, 64] The arylation of aniline however gave a low yield of the product and also generated triphenylamine as a by-product whereas using piperdine gave high yields. The reaction was unsuccessful in the presence of some electron-withdrawing groups, for instance with 4-bromobenzonitrile the reaction did not happen at all probably due to the dehalogenation reaction, whereas 4-chlorobenzonitrile gave 42% of the desired product (Scheme 25). The reaction was selective for instance 4-chloroaniline (76 %) of the desired product and also sterically hindered arylhalide for instance 1-chloronaphthalene gave a high yield of the desired product (90%).[54]



Scheme 26: Arylation of imidazole with aryl halides

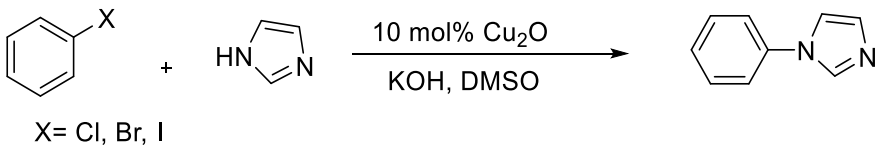
Arylation of imidazole was also observed using aryl halides in the presence of copper iodide in association with Bu_4NBr as a phase transfer catalyst (Scheme 26), the presence of the phase transfer catalyst was important as without it the reaction did not work very well. The reactivity of the arylhalides was examined with I>Br>Cl>F being found, the coupling process was successful and the electronic nature of aryliodide did not affect the yield. 2-Methyliodobenzene gave a low yield (63%) of the product indicating steric hindrance was important, arylation of hindered 2-acetylpyrrole also resulted in a low yield (50%).[65]



Scheme 27: Cu-NP catalysed reaction of aryl iodides with pyrrole, indole and azaindole

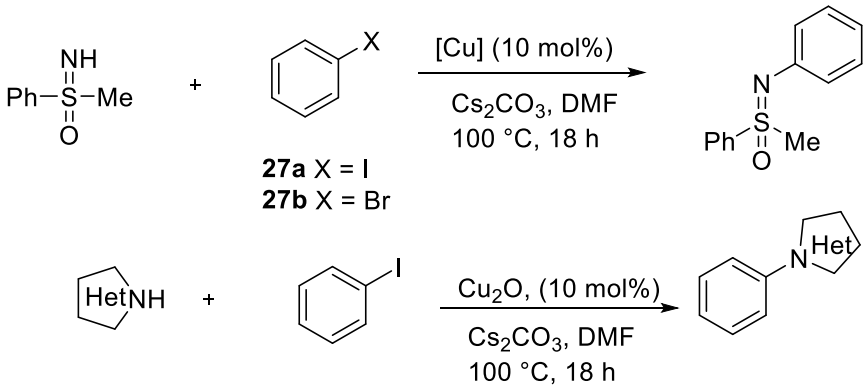
These product heteroaromatic compounds *N*-arylindoles, *N*-arylpyrroles and *N*-arylimidazole have been shown to have useful biological activity[66] and many methods have been used for their synthesis. *N*-arylindoles and *N*-arylpyrroles have been synthesised in the presence of copper nanoparticles and aryl halide (Scheme 27) as these metal nanoparticles provide a great surface to volume ratio limiting the amount required.[67] The reaction also required a base and the solvent DMSO was found to be the best, however increasing the time resulted in a drop in yield from 82% to 68% due to an increase in side reactions. Aryliodides bearing different electron-withdrawing groups at all the positions gave good yields however

substituents in the 2-position gave lower yields than when the substituent was in the corresponding 4-position, probably due to steric hindrance.[68]



Scheme 28: Arylation of imidazole with aryl halides

The arylation of heterocycles using aryl halides was also reported in the presence of Cu_2O (Scheme 28), the advantages of using Cu_2O is that it costs less than CuI, is not soluble in DMSO, meaning that the copper catalyst can be then used again as the recovery process is a simple filtration.[69, 70] As expected, and evident from previous methods, the aryliodide was more reactive than the arylbromide which in turn was more reactive than the arylchloride. Reactions gave high yields with aryl subsistents at the *ortho*-, *para*- and *meta*-positions, 3-amino imidazole was selectively arylated on the nitrogen of imidazole, however ethyl 4-iodobenzoate gave a low yield even in the presence of molecular sieves and due to hydrolysis of ester (base was KOH) whereas a change to Cs_2CO_3 as the base gave a good yield of the product. These reaction conditions were applied to benzimidazole, pyrrole, indole and pyrazole which were all found to give good yields of the desired products.[70]



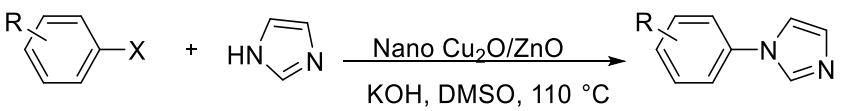
Scheme 29: Arylation of sulfoximine and *N*-heteroaromatic with aryl halide

Table 2

Entry	Arylhalide	Cu source	Yield %[a]
1	**27a**	Cu	32
2	**27a**	CuI	26
3	**27a**[b]	CuI	56
4	**27a**	CuO	8
5	**27a**	Cu_2O	95
6	**27a**[c]	Cu_2O	76
7	**27a**	CuBr	76
8	**27a**	$Cu(acac)_2$	77
9	**27b**[d]	Cu_2O	89

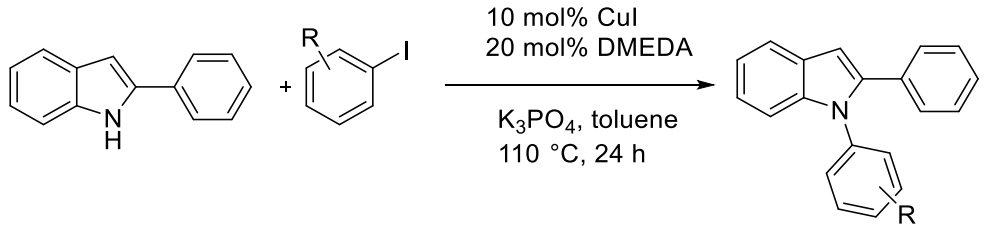
[a] yield after flash chromatography. [b] 20% CuI. [c] 5 mol% Cu_2O. [d] Temp. 110 °C

Using Cu_2O as a catalyst has also been reported under ligand free conditions (Scheme 29). The reaction was also observed using different sources of copper, the *N*-arylation of methylphenylsulfoximine was used as a screening test for the copper source and Cu_2O was found to be the best (Table 2), it is of note that no formation of biaryl by-products or reduction of the iodobenzene was observed. Cu_2O has also been used for the arylation of imidazole, pyrazole, pyrrole, triazole, indole and benzimidazole. The optimized conditions were applied to pyrazole successfully with various aryl halides (Scheme 29). The presence of *ortho* substituents on the aryl halide did not affect the product yield, however for instance benzylaniline did not work under the reaction condition.[71 72]



Scheme 30: *N*-Arylation of imidazole using Cu_2O/ZnO catalysis

N-Arylation of imidazole using Cu_2O/ZnO nano flake particles under ligand free conditions has also been investigated (Scheme 30). The system was stable to air and the optimized conditions were applicable for both electron-donating and electron-withdrawing groups at the 2-,3- and 4-positions of the arylhalide. The reaction was also compatible with sterically hindered arylhalides. The reaction was also selective, for instance 1-bromo-4-chlorobenzene, 1-bromo-4-fluorobenzene resulted only in 1-(4-chlorophenyl)-1H-imidazole and 1-(4-fluorophenyl)-1H-imidazole respectively. The aryl chloride was less reactive than either the aryl bromide or the aryl iodide.[73]

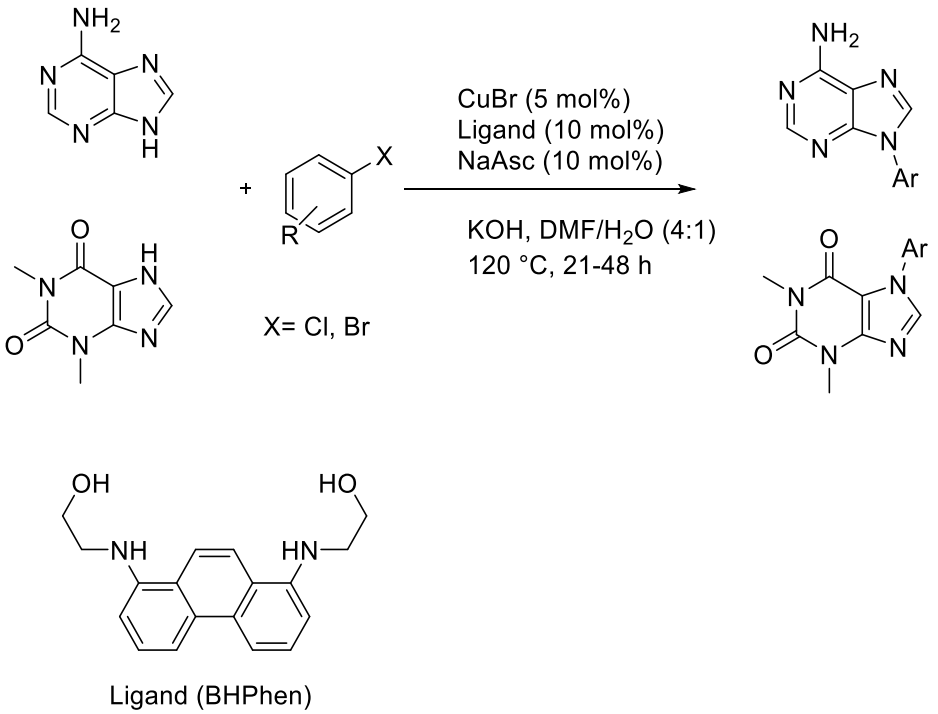


R	**%**
H	91
4-Me	90
2-Me	0
4-Cl	74
2-Cl	0
3-OMe	87
2-OMe	<5
3,4-$(OMe)_2$	86
4-n-Bu	94

Scheme 31: Synthesis of *N*-arylated 2-phenylindoles

N-Arylation of 2-arylindoles has been achieved using an aryl halide, copper iodide and a suitable ligand. The *N*-arylation of heterocycles in the presence of copper and a ligand had

already been reported – first copper catalysed of indoles in the presence diamine ligand was reported by Buchwald in 2002,[74] with other ligands also having been used in the arylation processes for instance L-proline,[75] benzotriazole,[76] 8-hydroxyquinalidine[77] and tetrazole-1-acetic acid.[78] *N*-Arylation of 2-arylindole was based on using the DMEDA ligand and CuI which is stable to moisture when in association with a base. The arylation was successful with arylhalides bearing different substituent at the 4- and 3- positions, however a substituent in the 2-position resulted in trace amounts or no arylation product at all (Scheme 31).[79]

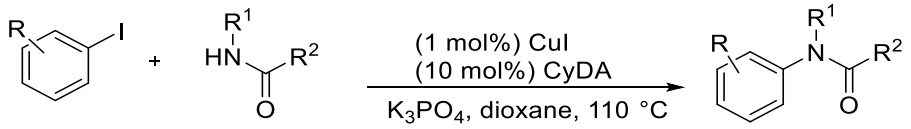


Scheme 32: Coupling of adenine and aryl halides

Arylation of N^9-aryl purines has been reported using aryl halides as purine-based compounds are important building blocks in medicinal chemistry, for instance as antiviral, antibacterial and anticancer compounds[80, 81] and have been used for the treatment of HSV, HIV, and hepatitis infections. The arylation of purine was achieved in the presence of 4,7-bis(2-hydroxyethylamino)-1,10-phenanthroline (BHPhen), sodium ascorbate (NaAsc) and a copper catalyst (Scheme 32),[82, 83] The direct coupling between purine and aryl halides with a variety substituents, for example electron-donating and electron-withdrawing groups, were successful except for those with substituents in the 2-position. The reaction was selective for the adenine and 2,6-diaminopurine N^9 position as the N^7 position is blocked by the 6-amino

group whereas theophylline is selective for N^7 position due to steric hindrance at the N^9 position by N^3–methyl substituent.[82]

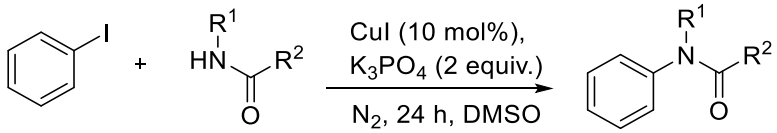
1.5.4 *N*-Arylation of amides



R	R^1	R^2	%
4-NH_2	Phenyl	Me	81
2-OMe	H	Me	94
2-NO_2	H	Phenyl	69

Scheme 33: *N*-Arylation of amides

N-Arylation of amides uses the Goldberg reaction which is carried out in the presence of a copper catalyst as an alternative to palladium due to the high cost and sensitivity to electron-rich or 2-substituted aryl halides. It can also be used for arylation of azoles under the following conditions:- CuI (1 mol%), a diamine ligand, aryl iodide, and K_3PO_4 or Cs_2CO_3 as the base (Scheme 33). It was reported that the use of strong bases will retard the catalytic process as the amides produced bind to the copper and retard the catalytic process. The process is chemoselective for primary amides and can be done at room temperature, aryl bromide can also be used with a higher loading of catalyst (10 mol%).[11, 84, 85]

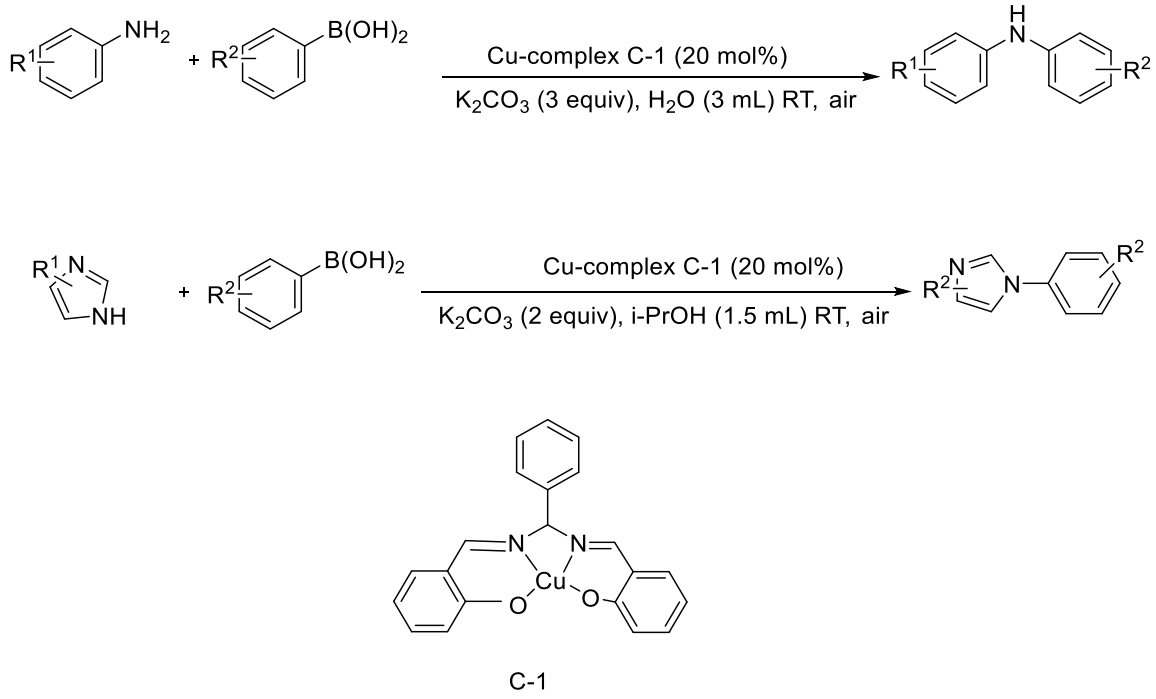


R^1	R^2	%
H	Phenyl	97
Me	Me	66
Ethyl	Me	23
Phenyl	Phenyl	5

Scheme 34: Coupling of amide and iodobenzene under ligand free condition

N-Arylation of amides has also been reported under similar conditions, however the presence of aprotic solvent in this case is important for the reaction as it increase the solubility of the base and also works as a ligand as it is donating electron. The optimized reaction conditions were suitable for both primary aromatic amides and aliphatic amides as the reaction was sensitive to steric hindrance of secondary amides and gave low yields and in acyclic secondary amide cross-coupling reaction was observed for instance *N*-methylacetamide and *N*-ethylacetamide gave 66% , 23% respectively of the desired product (Scheme 34).[86]

1.6 Arylation of nitrogen nucleophiles using arylboronic acids



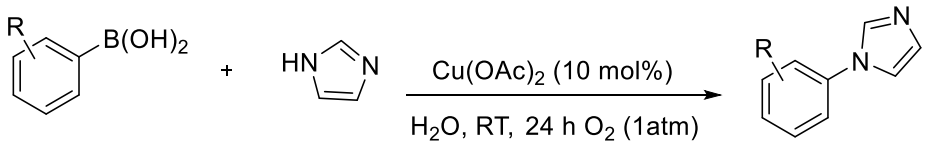
C-1

Scheme 35: Synthesis of arylamine and hetroaromatic amine using Chan-Lam strategy.

The arylation of nitrogen nucleophiles discovered by Chan and Lam uses arylboronic acids under cross-coupling reaction conditions, arylboronic acids have been commonly employed in organic synthesis due to their stability, structural diversity, low toxicity and wide availability.[87] However the reaction required long reaction times and used large amounts of arylboronic acid, some reactions were carried out in the presence of additional reagents for instance TEMPO, molecular oxygen and pyridine-*N*-oxide to determine a possible mechanism for the process.[88] The arylation of aniline and imidazole was observed under these conditions using water as the solvent as the arylboronic acid is very stable in water. The arylboronic acid may have electron-rich groups and/or electron-deficient groups with both giving the final product in high yield, however only electron-donating groups in the 3-position gave good yields of product and electron-deficient groups in the 4-position only produced the desired product in moderate yields. The reaction was selective in the case of two nucleophiles being present, for instance with 3-hydroxyaniline reaction only occurred at nitrogen and did not take place at OH. The optimized conditions were achieved using imidazole in isopropanol as

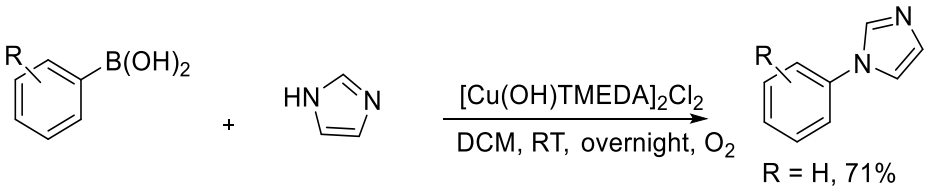
the solvent (Scheme 35) and in the case of imidazole the reaction did need longer reaction times as the substrate is no longer a primary amine.[89]

1.6.1 Arylation of heteroaromatic compounds



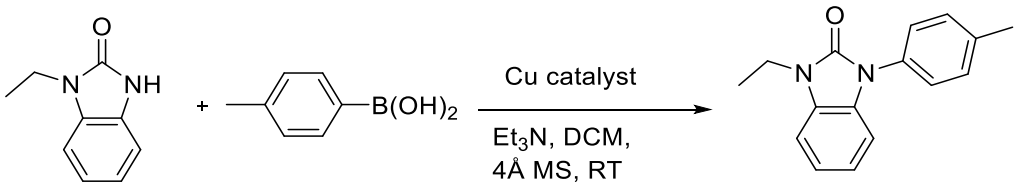
Scheme 36: Arylation of imidazole using arylboronic acids

It was observed in the arylation of imidazole using arylboronic acids that in water and in the presence of copper supported by appropriate an amphiphilic surfactant prevented oxidation of the arylboronic acid to phenol.[90, 91] It was reported that using different surfactants, including the fluorous surfactant (F-PEG) which has been used commonly in organic synthesis[92, 93] was also possible. The conditions were applicable for a whole range of different functional groups, for instance alkoxycarbonyl, cyano groups and halogens, by using appropriate surfactant (Scheme 36).[94] However water is not as commonly used as a solvent as not all polar organic molecules dissolve in water. Water has also not been used as the solvent in the arylation of nitrogen with arylboronic acids as the arylboronic acid readily oxidised to phenol. The use of a surfactant allows microhydrophobic regions to be formed – micelles – and it is in these that the reaction takes place. The Chan-Lam conditions have been successfully used with different surfactants for example F-PEG (50), Brij 30, and TritonX-100 with a range of substituted arylboronic acids. Not all functionality on the arylboronic acid did work, for instance 3-aminophenylboronic acid gave low yield of the product. In addition to imidazole, benzimidazole and phenylimidazole were also arylated under the conditions used.[94]



Scheme 37: Arylation of imidazole with arylboronic acid

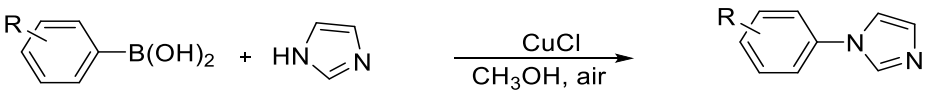
Arylation of imidazole has been done via nucleophilic aromatic substitution using several methods including a combination of an aryl halide and imidazole, however it requires an aryl halide with electron-withdrawing groups. A method was described by Chan-Lam using an aryl boronic acid, imidazole, copper acetate and triethylamine or pyridine under ambient conditions. Arylation of imidazole was reported under catalytic conditions using $[Cu(OH)TMEDA]_2Cl_2$ in dry DCM under ambient oxygen levels as dioxygen can regenerate the $[Cu(OH)TMEDA]_2Cl_2$ (Scheme 37). Arylboronic acids with different substituents were used, methyl groups gave good yield when in the 2- and 4-positions, however the methoxy group gave lower yields when in these two positions. Using 4-phenylimidazole and 2-tolylboronic acid was not as selective and gave a mixture of two *N*-arylated products.[95]



Scheme 38: Arylation of a benzimidazolinone with 4-tolylboronic acid

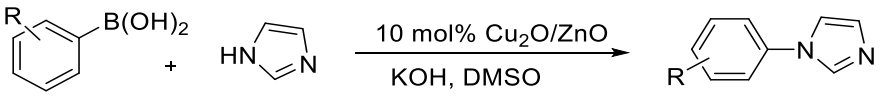
The method described above was not suitable for aniline, amines and phenol, the presence of oxygen in the reaction oxidized the Cu(II) to Cu(III) where the resultant complex which can then undergo the reductive-elimination,[96] therefore it has been observed that the use of an oxidizing agent, for instance pyridine *N*-oxide (PNO) and TEMPO facilitated the Cu (II) to Cu (III) conversion more than oxygen and not the oxidation of the arylboronic acid to phenol.[96] Three catalytic systems were used 1) $Cu(OAc)_2$/TEMPO, 2) $Cu(OAc)_2$/PNO and 3) $Cu(OAc)_2/O_2$ for the arylation of benzimidazolinone (Scheme 38) and it was found that the first two catalytic systems gave higher yields. Catalytic $[Cu(OH)TMEDA]_2Cl_2/O_2$ did not work as had

been previously reported. The conditions were also successfully applied to the aniline, pyridine, sulfonamide and benzimidazole etc.[97]



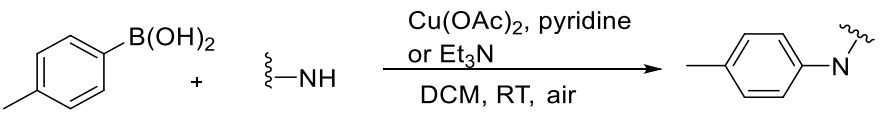
Scheme 39: Arylation of imidazole with arylboronic acid

It has been reported that the arylation of imidazole under simple copper catalysed conditions without the addition of ligand and base was also successful. The CuCl had to be used in the presence of a protic solvent such as methanol or a water/methanol mixture and proved that protic solvents are important for the cross-coupling reaction when using arylboronic acids, heating was also required as room temperature did not work (Scheme 39). The conditions were also used for different type of arylboronic acids and produced high yields of product, however hindered arylboronic acids needed longer reaction times for instance 2-tolylboronic acid.[98]



Scheme 40: Arylation of imidazole with arylboronic acid

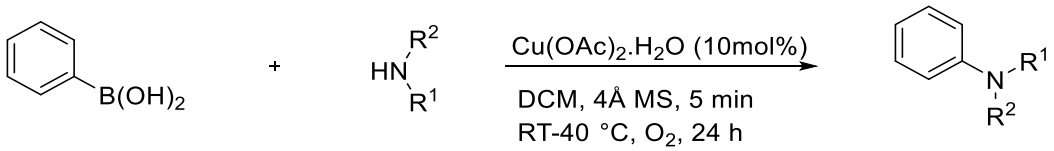
Arylation of imidazole using arylboronic acids in the presence of catalyst Cu_2O/ZnO nano flake has also been reported, the advantages of using Cu_2O is that it costs less than CuI,[70] it is not soluble in DMSO and can therefore be readily used again (Scheme 40). It gave the desired product in high yield with both electron-withdrawing groups and electron-donating groups on the arylboronic acid.[99]



Scheme 41: Arylation of hetroaromatic with 4-tolyboronic acid

Arylation of different heteroaromatics has been demonstrated in the presence of copper acetate, a tertiary amine such as triethylamine or pyridine at room temperature (Scheme 41). The yield was high in the case of strong nucleophiles such as pyrazole, imidazole and indazole whereas for the less nucleophilic ones, for example triazoles and tetrazole, the reaction yield was low.[100]

1.6.2 Arylation of aniline and aliphatic amines



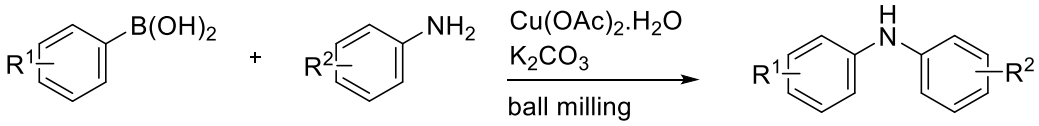
R^1	R^2	Temp.	%
Butyl	H	RT	92
4-Bromophenyl	H	40	53
t-Butyl	H	40	39
Cyclohexane	H	40	85

Scheme 42: Coupling of aliphatic amines and aniline with arylboronic acid

As described in section 1.6.1 Scheme 37, the method by Collman using $[Cu(OH)TMEDA]_2Cl_2$ catalyst has so far been limited to the arylation of imidazole derivatives.[95, 101] Lam had observed arylation, using arylboronic acids, in the presence of molecular oxygen, TEMPO, and pyridine-*N*-oxide as in situ oxidants to regenerate the copper catalyst, however the oxidant can result in the oxidation of some arylboronic acids giving phenols as unwanted by-products. It has been reported that the arylation of the aliphatic amines (e.g. n-butylamine), with arylboronic acid also proceeds under the original Chan-Lam conditions, however a second side reaction was noted – copper promoted *N*-dialkylation as the first arylation product went on to react with a second equivalent of arylboronic acid. Diarylation results from the presence of the bis (μ-oxo) copper complex[102] which can be avoided by using a lower amount of copper and also diluting the reaction. The use of tertiary alkylamines did not result in the arylation

product at room temperature, however the reaction conditions were successful for different types of alkyl and arylamines with different functional group (Scheme 42), however aniline gave only a low/average yield of the product. Arylboronic acids with different substituents were also used and the 2-substituted derivatives did give reasonable yields of the product but the presence of very sterically hindered groups, for instance 2, 6-dimethylphenylboronic acid gave a very low yield of the desired product when 1,4-dioxa-8-azaspiro[4.5]decane was used as a nucleophile but in the case of 2-methylphenylboronic acid gave good yield of the desired product.[103]

1.6.3 Arylation of anilines

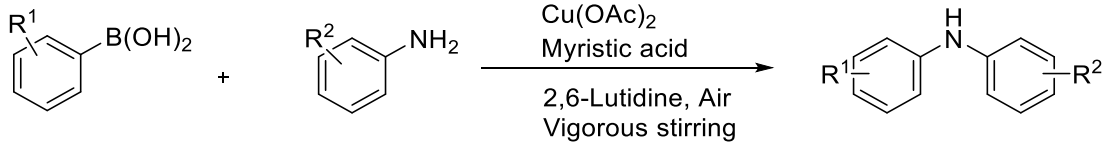


R^1	R^2	%
H	H	86
H	4-Me	79
4-OMe	H	77
4-Cl	4-OMe	58
H	2-Br	55
H	4-Cl	50

Scheme 43: Coupling of aniline with arylboronic acid

It was reported that arylation of amines under solvent -free conditions using high speed ball milling (HSBM) reduces the hazards from the reaction (Scheme 43), lowers the reaction time and also stimulates some solid-state reactions.[104] The reaction was performed with an arylboronic acid, copper catalyst, a base, for instance K_2CO_3, and a grinding auxiliary such as KF-Al_2O_3. It was found Cu(II) worked better than Cu(I). Different aromatic amines were used with different substituents, electron-rich and electron-deficient groups at the 2- and 4-positions, and it was found that electron-withdrawing groups gave lower yields than electron-rich groups, in particular the 2-bromo group gave the desired product at a low yield. The scope

of the reaction was also investigated for alkylamines, however aliphatic secondary amines such as diethylamine did not undergo cross-coupling with the arylboronic acid whereas phenylethyl-2-amine gave a good yield of the desired product (70%).[105]

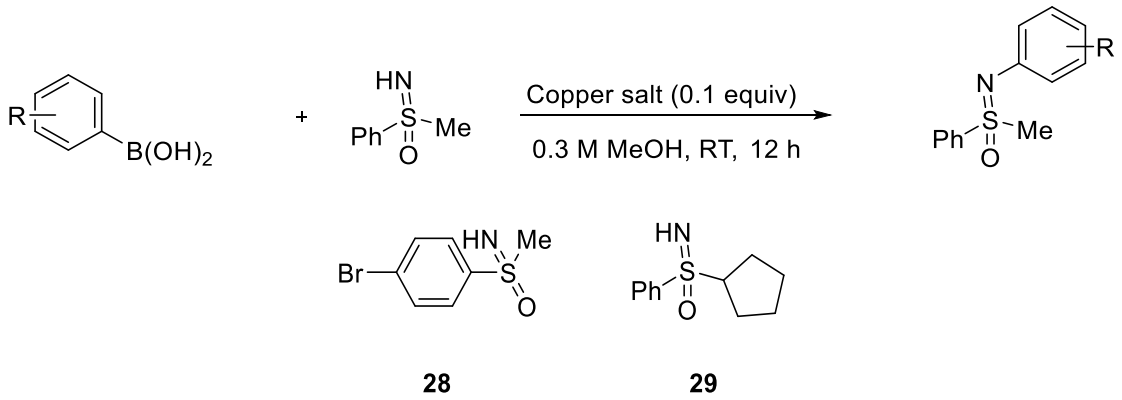


R^1	R^2	%
4-Me	H	91
4-Me	4-OMe	82
4-Me	2-t-Butyl	79
4-Cl	H	10 (GC)

Scheme 44: Coupling of anilines with arylboronic acid

The arylation of nitrogen nucleophiles under Ullmann conditions using an aryl halide often required high temperatures[106] and a transmetallating agent, for instance aryllead triacetate[107] and arylbismuth[108] have both been used. Chan and Lam conditions using arylboronic acid required stoichiometric quantities of copper acetate therefore catalytic conditions were developed, (20 mol% of Cu) for the cross-coupling reaction, for example between 4-tolylboronic acid with aniline which was carried out under an air atmosphere and at ambient temperature (Scheme 44). The reaction was improved further by the addition of myristic acid. Many functional groups are tolerated on the aniline component, for example electron-rich, electron-deficient and sterically hindered groups all gave desired product in high yield, however arylboronic acids with electron deficient groups, for instance chloride gave low yields. and also sterically demanding group gave low yields.[109] The conditions were also applied to primary alkylamines and secondary amines and both types of substrate were found to give reasonable yields of the arylated product.

1.6.4 Arylation of sulfoximine

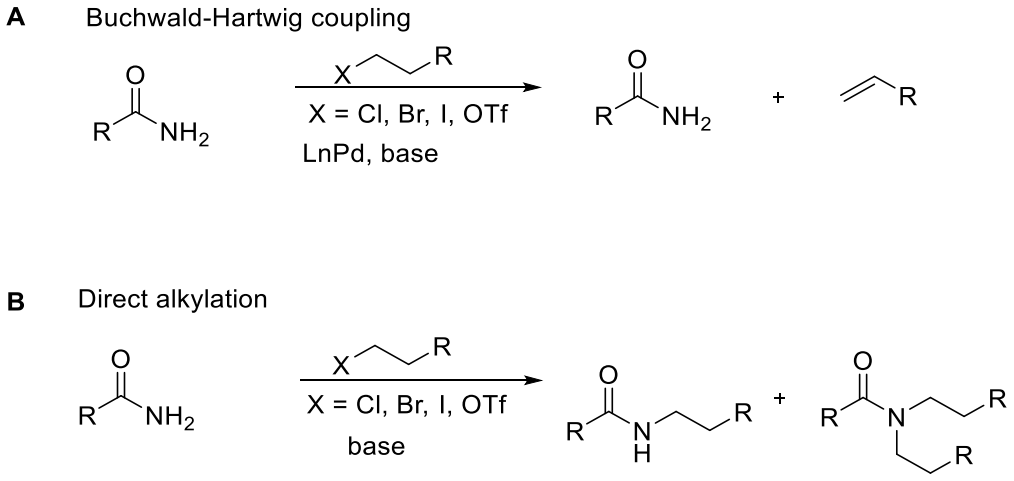


28 **29**

Scheme 45: Coupling of sulfoximine with arylboronic acid

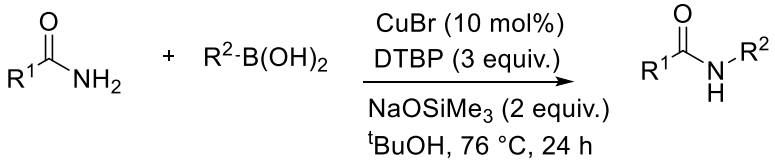
The arylation of sulfoximines has also been reported using arylboronic acid under copper catalysed conditions, with 10 mol% of copper (II) found to be more effective than copper (I) under the anhydrous conditions used, the reaction was completed with two equivalent of arylboronic acid as using less affected the product yield. The reaction was also carried out with different substituent on the arylboronic acid and any in the 2-position reduced the yield.[110] The compound **28** was also arylated and the reaction was selective for *N*-arylation over carbon arylation (Suzuki coupling reaction),[111] increasing the steric hindrance of the aliphatic substituent at the alpha-carbon of the sulfoximine compound, e.g. **29**, did not affect the reaction and gave the desired product as expected (Scheme 45).[110]

1.6.5 Arylation of primary amides to synthesise secondary amides



Scheme 46: General methods towards monoalkylation

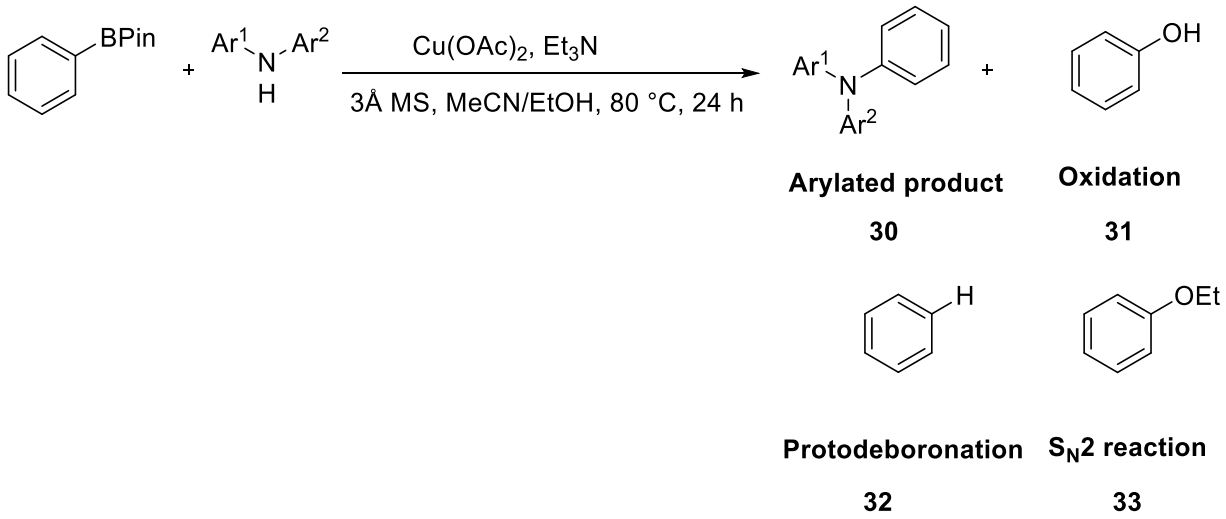
Secondary amides are useful compounds as their functionality is found in the backbones of all natural peptides and proteins and also many therapeutic molecules and synthetic intermediates.[112] The methods to form such amides from alkyhalides/alkylboronic acids is limited due to the lower reactivity of the primary amide compared to the amine, intermediate alkylmetal complexes tend to undergo β-hydride elimination instead of reaction with the amide (Scheme 46: Eq. **A**).[113] Traditional methods has been used in the alkylation of aniline stoichiometric amount of copper, alkylboronic acid about 4 equivalent[114] and also prepared from acylation of primary amide with an alky halide but over alkylation was observed (Scheme 46: Eq. **B**).[115]



Scheme 47: Synthesis of secondary amide

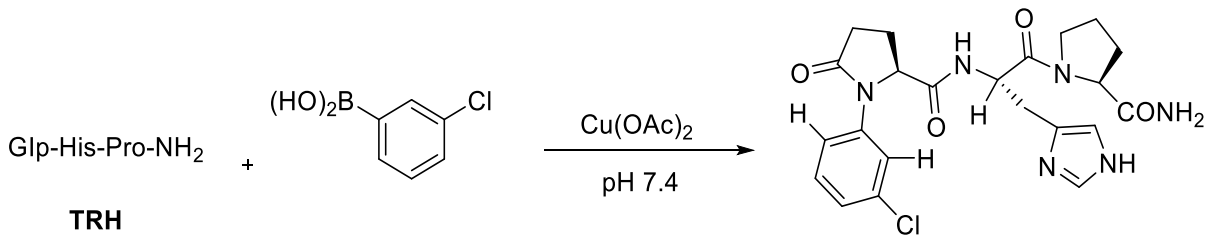
It has reported that the alkylation of primary amine using Chan-Lam conditions proceeded in the presence of a base (e.g. $NaOSiMe_3$). As the yield was higher with this base, it was suggested that a weak base might slow deprotonation of the amide therefore it prevented

degradation of the copper catalyst. [116, 117] Oxidants other than DTBP were unsuccessful, for instance diacetoxyiodobenzene, benzoquinone, hydrogen peroxide and *m*CPBA, CuBr was also preferred as it gave a good yield, higher than when using copper acetate (Scheme 47). The reaction also tolerated different functional groups on the amide for example alkyl group, aromatic ethers and tertiary amides, amides with fluoro and chloro substitunets were also arylated whereas amides with strongly electron-withdrawing groups were not arylated. Substrates with aromatic and aliphatic esters were not arylated, whereas boronic acids were used with many different functional groups, for instance arenes, ethers, and alkenes and also sterically hindered groups such as in neopentylboronic acid whereas other tertiary boronic acids were not successful. Secondary boronic acids, for example isopropylboronic acid were successful but additional quantities of reagent and catalyst was necessary to affect the reaction yet still giving a lower yield than with primary boronic acids.[117]



Scheme 48: Arylation of secondary amine using pinacol aryboronate

Arylation of secondary amines has also been reported under Chan-Evans-Lam reaction conditions using a copper catalyst in the presence of MeCN, molecular sieves were used to remove water therefore the by-products being formed from the pinacol arylboronate ester starting material by protodeboronation **32** and/or phenol **31** resulting from oxidation were decreased. The addition of ethanol led to produce ether by-product due to alcoholic nature, however mixture of Et_3N/EtOH decrease the ether **33** by-products observed during reaction optimization such as those shown in Scheme 48.[118]

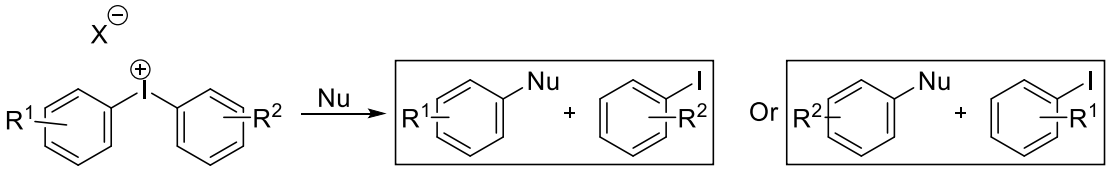


Scheme 49: Copper catalyst coupling of *N*-H bonds of TRH tripeptide with arylboronic acid

Polypeptides are often found in drug development, biomaterial design, and biological structures,[119, 120] however selective *N*-arylation of the back bones of polypeptides is limited. Therefore selective modification has been observed for the N-H bonds through neighbouring TRH residue by using copper acetate and arylboronic acid (Scheme 49), arylboronic acids with different substituents were also used however the yield was low for these derivatives.[121-123]

1.7 Arylation of nitrogen nucleophiles using diaryliodonium salt

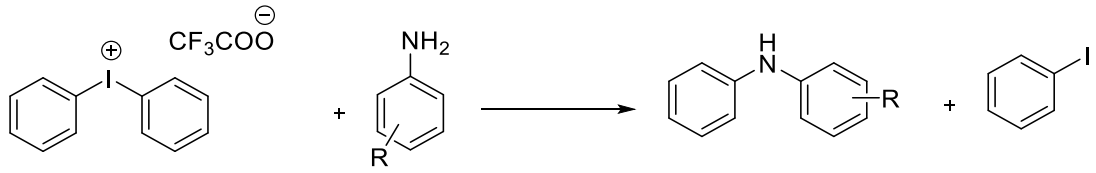
The use of diaryliodonium salts both symmetrical and unsymmetrical has been used as arylating agent widely under metal-free and metal conditions. The transfer of aryliodonium is related to the electronic and steric effect and the reactivity of these is influenced by the functional group and the nature of nucleophile.[124]



Scheme 50: Arylation of nucleophile using aryliodonium salt as arylating agent

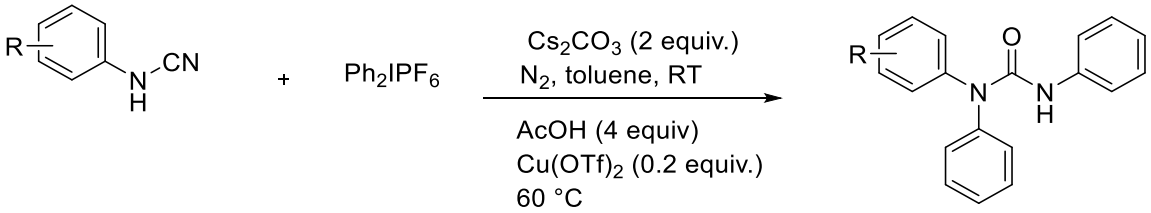
Metal-free arylation of aniline using diaryliodonium salts has been reported, in this study, it appeared increasing reaction time had a positive effect on the yield and the best temperature was 130 °C. Also the effect of the counter ion was also studied; in general and subject to the stability of the diaryliodonium salt the less nucleophilic counter ion was preferred, for example trifluoroacetate, however tetrafluoroborate did not give a high yield of the product. The use of unsymmetrical diaryliodonium salts will generally result in the nucleophilic

substitution occurring on the sterically demanding aromatic ring (the *ortho*-effect) or the electron-deficient ring (Scheme 51).[2]



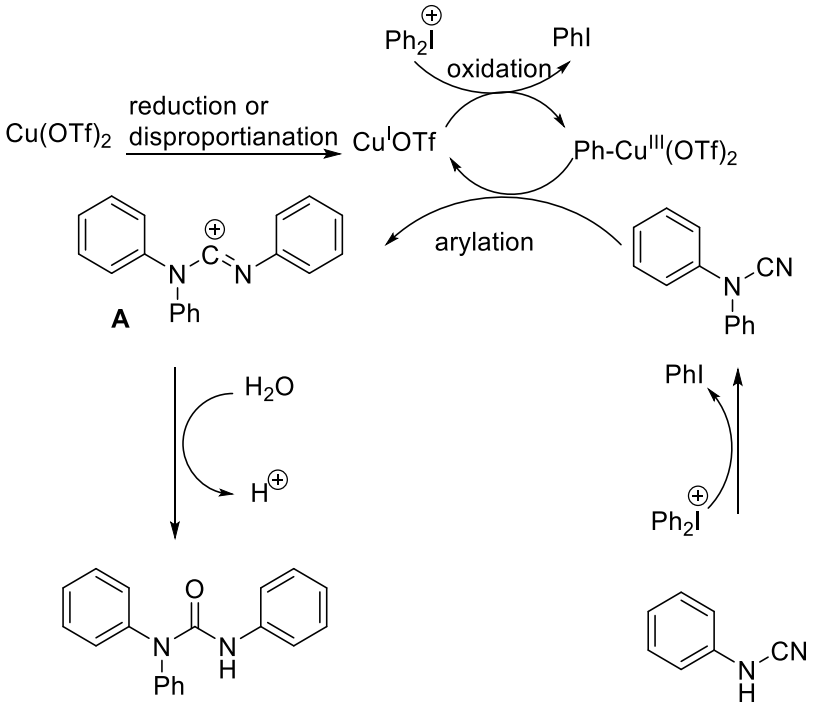
Scheme 51: Synthesis of diarylamines using diaryliodonium salts

1.7.1 Synthesis of *N*-Arylurea



Scheme 52: Synthesis of *N*-arylurea

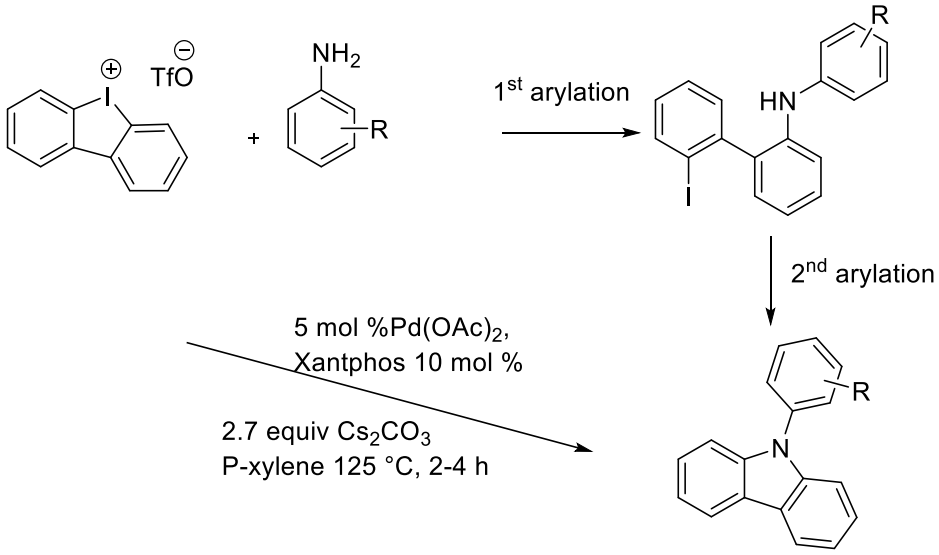
A method towards the synthesis of triarylurea derivatives has also been reported as these have shown activity as inhibitors of HIV protease.[125] Phosgene and the derivatives of phosgene which are typically used in the preparation of these materials[126, 127] produce toxic waste[128] therefore diaryliodonium salts have been developed as an efficient and practical way for the formation of triarylureas, (from *N*-arylcyanamide with diaryliodonium salts, Scheme 52). The *N*-arylcyanamide tolerated a range of substituents, both electron-donating groups and electron-withdrawing groups did not affect the reaction and only slight decreases in yield was observed with sterically demanding groups. Unsymmetrical diaryliodonium salts were also used with both electron-donating and electron-withdrawing groups, the product was obtained in a good yield however in this case the increased steric hinderance affected the yield and also the chemoselectivity of the process.[129] The proposed mechanism was elucidated based on these results (Scheme 53).[130, 131]



Scheme 53: Proposed mechanism for the synthesis of *N*-arylureas

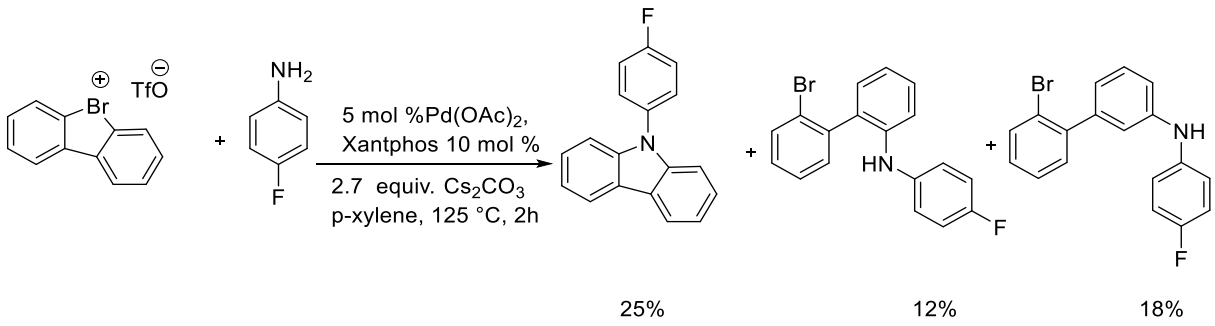
The $Cu(OTf)_2$ was initially reduced to Cu(I)OTf, oxidative addition of the diaryliodonium salt to the Cu(I)OTf results in a Ph-Cu(III) species, transfer of the aryl group generates intermediate **A**, addition of water results the product.[129]

1.7.2 Synthesis of *N*-arylated carbazoles



Scheme 54: Proposed mechanism between cyclic diaryliodonium salt and aniline

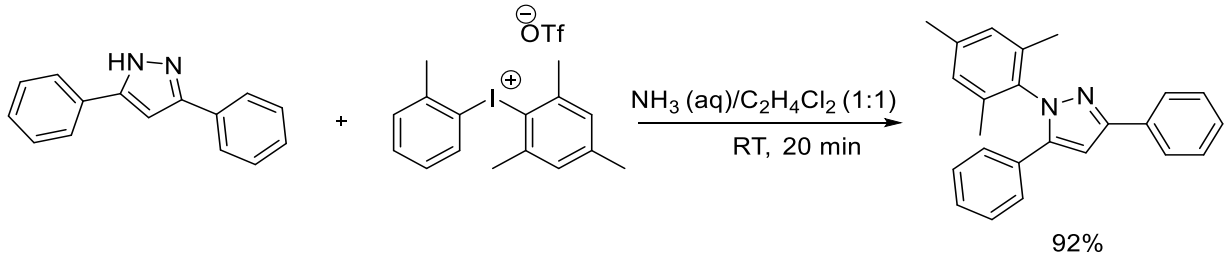
Carbazoles are useful compounds in pharmaceuticals and the ring system is also present in alkaloids[132] and it has been synthesised successfully by the reaction of a cyclic diaryliodonium salt with anilines as shown in Scheme 54.[133] It has been synthesised through ring-opening of the cyclic diaryliodonium salt followed by ring closing where the introduced nitrogen from the aniline acts as an intramolecular nucleophile.



Scheme 55: *N*-Arylation of 4-fluoroaniline using cyclic diaryliodonium salt

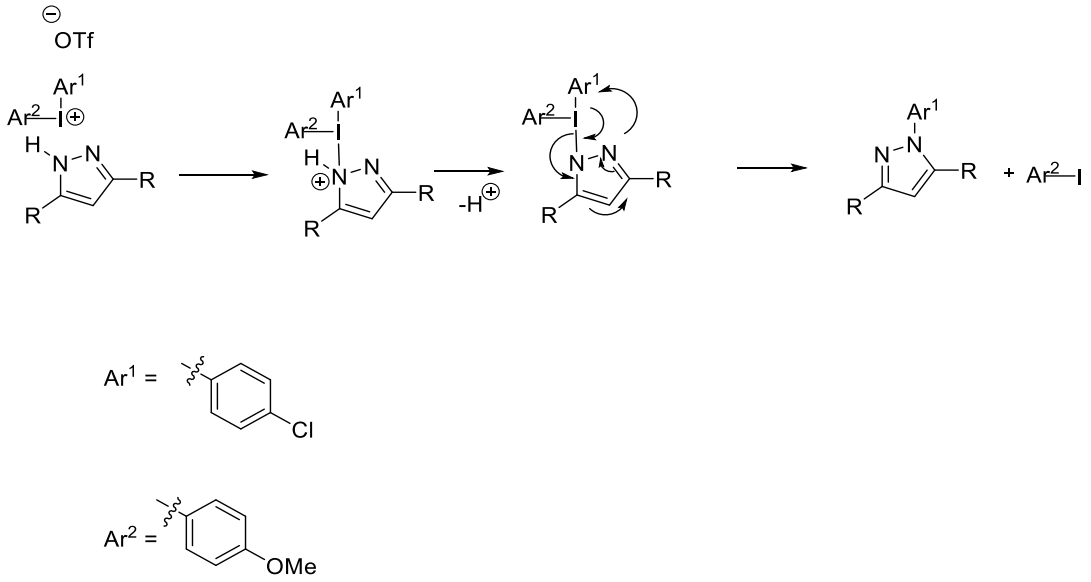
The method shown in Scheme 54 was less successful when cyclic diarylbromonium salts were used as it resulted in by-products as the key intermediate is less reactive then its iodo counterpart reducing the chance of nucleophilic attack at the 6-position. The second by-product, the meta-derivative, was suggested to be because of a benzyne intermediate resulting from the reaction of diaryliodonium salt with a base, aniline in this case promoting the β-elimination path-way (Scheme 55).[133]

1.7.3 Arylation of pyrazoles



Scheme 56: Arylation of pyrazoles

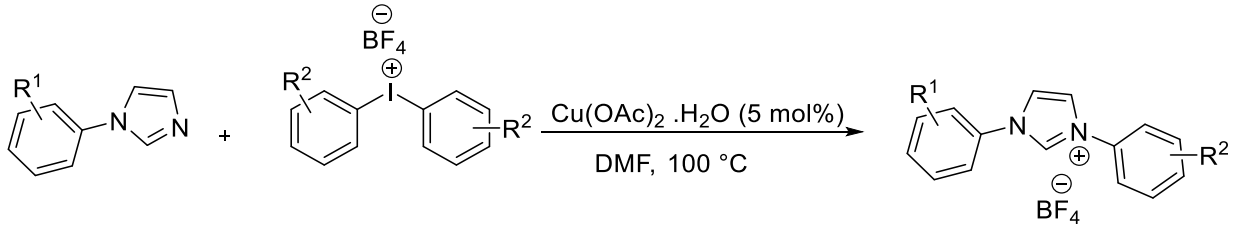
Diaryliodonium salts have also been used for the formation of *N*-arylated pyrazoles which are useful building blocks and also have agrochemistry and pharmaceutical applications.[134] The arylation of pyrazole was reported with diaryliodonium salts under metal-free conditions (Scheme 56)[135] and the selectivity of the reaction is as would be expected in that the sterically hindered and/or electron-deficient aromatic is transferred.



Scheme 57: Proposed mechanism of arylation of pyrazole with diaryliodonium salt

As it was initiated that the 2,3 rearrangement (transfer of Ar^1 group) more favourable than the 1,2 rearrangement (transfer of Ar^2 group) and also neighbouring effect of the pyrazole nitrogen will be more nucleophilic as a consequence of diaryliodonium salt and results in an intermediate T-shaped *N*-iodo species which undergoes reductive elimination via [2,2] rearrangement which is more favourable than [1,2] (Scheme 57).[135]

1.7.4 Arylation of *N*-substituent imidazole

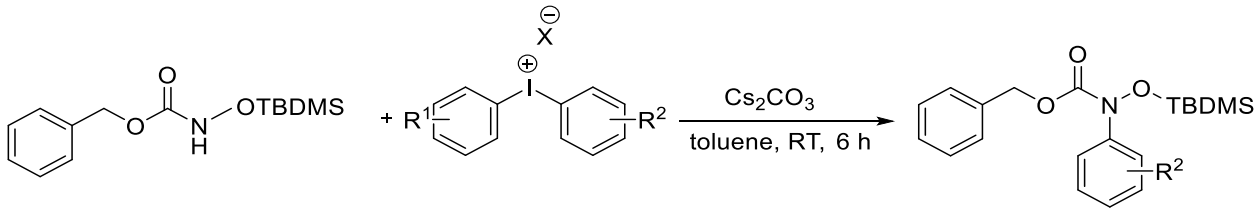


R[1]	**R[2]**	**%**
2-Me	H	91
4-Br	H	95
3-OMe	3-OMe	83
4-OH	H	64

Scheme 58: Synthesis of unsymmetrical diarylimidazolium salts

As has already been highlighted diaryliodonium salts have been used for the *N*-arylation of imidazole, *N*-substituted imidazoles may also undergo arylation in the presence of a copper catalyst, it was noted that the counter ion of the diaryliodonium salt affected the yield and the reaction was most successful with non-nucleophilic anions. High yields were obtained with electron-rich diaryliodonium salts in combination with electron-deficient imidazoles. The reaction is useful as it is also tolerant of many functional groups on the imidazole moiety for example acetyl, formyl, ester and hydroxyl groups do not affect the yield but the reaction was affected by high steric hindrance on the imidazole such as an *N*-(2,6-diisopropylphenyl)imidazole, which gave a yield of only 56%. In addition the reaction does not need strong acid or base and is therefore carried out under mild conditions (Scheme 58).[136]

1.7.5 Arylation of *N*-hydroxylamines

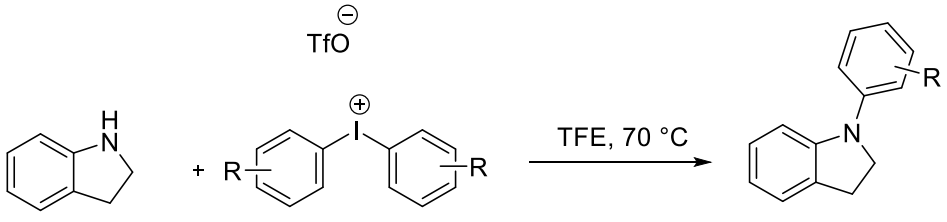


R^1	R^2	X	%
H	Mes	TfO^-	86
4-OMe	4-OMe	TfO^-	61
3-NO_2	3-NO_2	Br^-	45
4-OMe	4-NO_2	TsO^-	58
4-Me	4-Me	TfO^-	90

Scheme 59: Arylation of *N*-hydroxylamines

The arylation of *N*-hydroxylamines with diaryliodonium salts was observed and the process was successful with range of unsymmetrical diaryliodonium salts under metal-free conditions. The hydroxyl group was protected as its t-butyldimethylsilyl/TBDMS ether (Scheme 59) and it was found that in the case of sterically hindered diaryliodonium salts the reaction was selective with, the hindered group being transferred, for instance mesityl. Electronic selectivity was also achieved with the most electron-deficient group being transferred, for instance the 4-nitrophenyl group. Both electron-donating groups and electron-deficient groups (e.g. methoxy and chloro groups in the examples reported Scheme 59) are tolerated in the reaction. The type of counter ion did not affect the reaction, however of those investigated triflate afforded higher yields.[137]

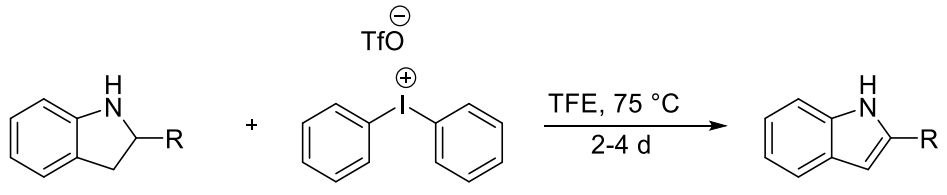
1.7.6 Arylation of indoline



R	%
4-OMe	0
4-Me	41
4-Br	65
4-CF_3	62

Scheme 60: Arylation of indoline with diaryliodonium salts

Indoline is an important functionality in both alkaloid natural products and also in pharmaceuticals,[138, 139] it has been *N*-arylated under metal-free conditions using diaryliodonium salts in an acidic fluorinated solvent (e.g. TFE), as it was found that the use of aprotic solvents, for instance DMSO, did not give good yields. Diaryliodonium salts with electron-donating groups gave lower yields than those with electron-deficient groups, for instance those with the 4-methoxyphenyl group did not give the arylation product whereas those with electron-deficient groups, for instance 4-bromophenyl and 4-trifluoromethylphenyl, gave the desired product (Scheme 60).[140]

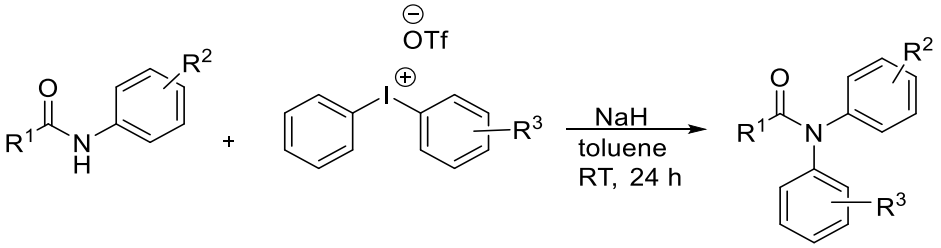


R = Ph
R = COOMe

Scheme 61: Arylation 2-substituent indoline with diaryliodonium triflate

The counter ion of the diaryliodonium salt also influenced the outcome of the reaction, tosylate gave a lower yield while trifluoroacetate and tetrafluoroborate gave a similar result to the triflate counter ion. These reactions using *N*-heteroaromatic substrates, for instance 1H-indazole, result in a very low yield of the *N*-arylated product whereas for 1H-benzotriazole the reaction was selective for *N*-2 position[141], some indolines were also oxidised and gave indoles (Scheme 61).[140]

1.7.7 Arylation of secondary amides

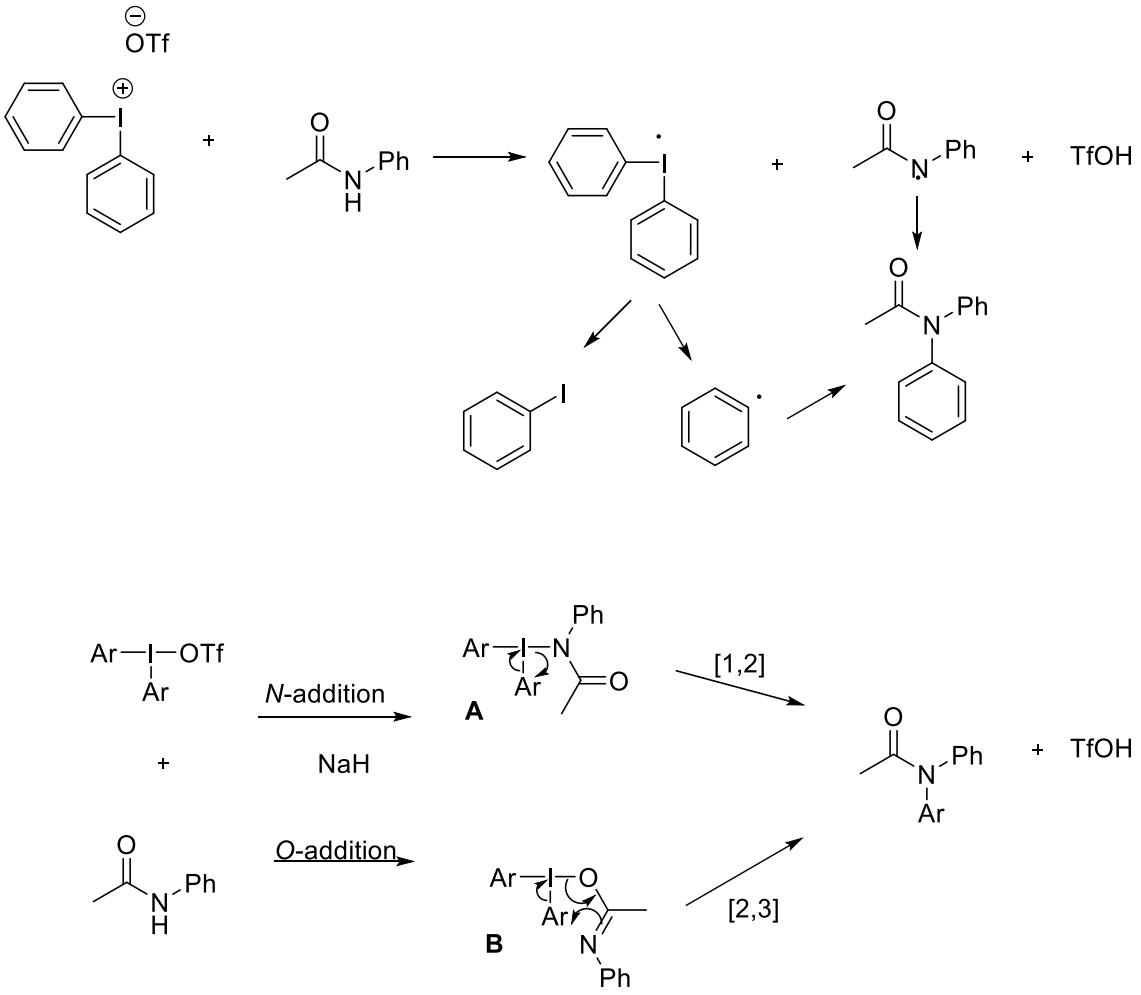


R^1	R^2	R^3	%
Me	H	H	83
Ethyl	4-NO_2	H	77
Me	4-Br	H	40
Me	H	4-NO_2	99

Scheme 62: Secondary amide coupling with diaryliodonium salt

Aryl amides are important compounds for the synthesis of peptodomimetics, polymers and inflammatory compounds,[142] as a result many methods have been introduced for their preparation. Metal-free *N*-arylation and the metal-catalysed related process, for instance using Pd-catalysis or Cu-catalysis, have been used for the synthesis of tertiary amide.[143] This report has described the metal-free *N*-arylation of secondary amides using diaryliodonium salts in combination with a base, for instance NaH. The arylation of acetanilide with diaryliodonium salts bearing different counter ions such as trifluoroacetate, tosylate and tetrafluoroborate all result in similar yields. From the optimization process arylamides with electron-donating groups gave better yields and in those examples of diaryliodonium salts bearing *ortho*-substituents, it was the hindered group that was transferred, and where there

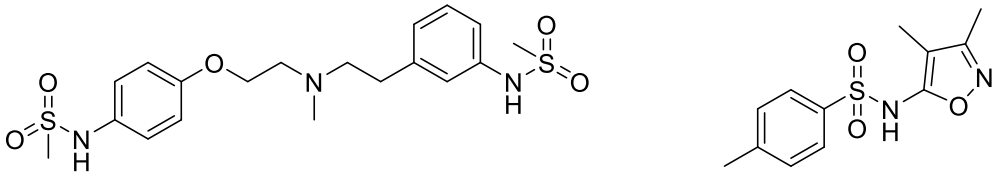
was an electronic difference between the two arenes it was the more electron-deficient arene that was transferred.[144]



Scheme 63: Proposed SET mechanisim and [1,2], [2,3] rearrangement mechanism of arylation of secondary amide with diaryliodonium salt

The mechanism could happen by a SET mechanism, in which a single electron transfers from nucleophile to the diaryliodonium cation which then reduced to intermediate 9-I-2, the intermediate decomposes to radical benzene and iodobenzene. The radical benzene reacts with radical nucleophile or absorb hydrogen from solvent to form benzene (Scheme 66)[5, 40]or via a two possible T-shaped intermediates rearrangements **A** and **B**, it is [1,2]-rearrangement or [2,3]-rearrangement as shown in the (Scheme 63).[144]

1.7.8 Arylation of sulfonamide

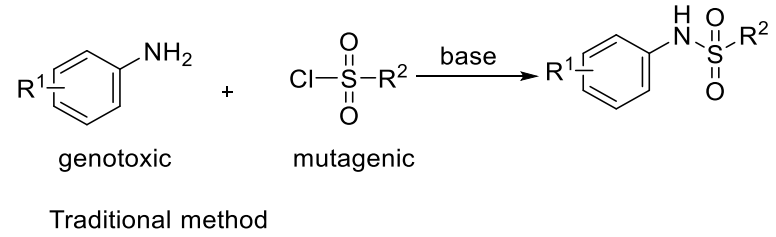


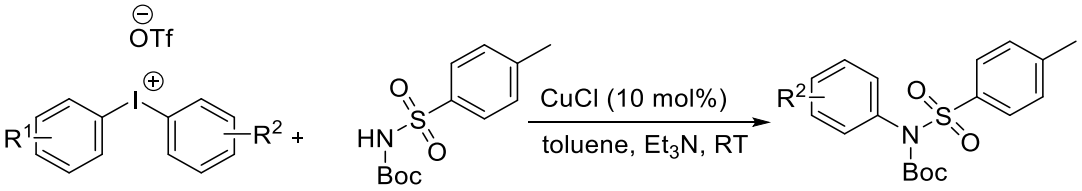
Dofetillide **Pediazole**

34 **35**

Figure 7: *N*-Arylsulfonamides compounds

N-Arylsulfonamides are a popular functionality found in anti-cancer drugs, anti-HIV, antibacterial and anti-convulsant compounds, for instance Dofetillide and Pediazole (Figure 7).[145, 146] A method has been described for their synthesis using diaryliodonium salts as a safer method as alternatives use mutagenic or genotoxic species such as aniline and sulfonyl chlorides (Scheme 64).[147]

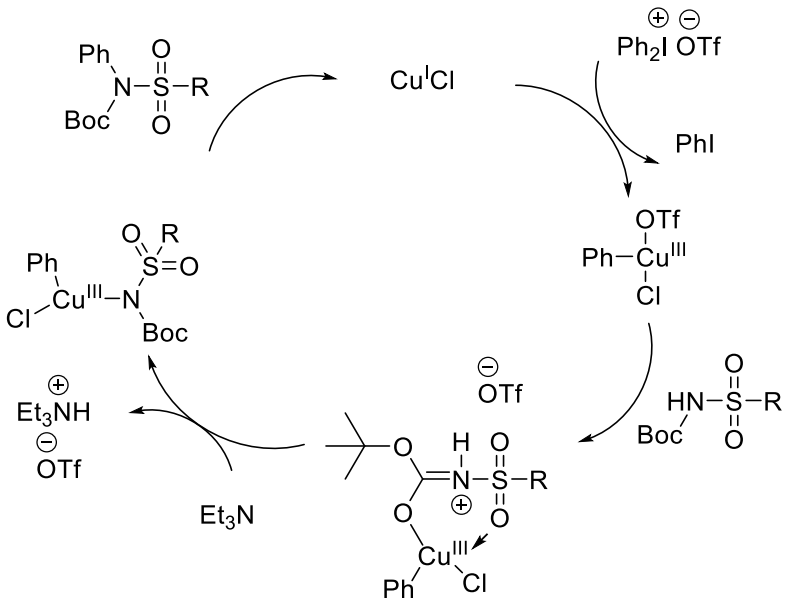




R^1	R^2	%
H	4-Me	97
H	4-CF_3	87
4-Mes	4-Mes	0
H	4-OMe	96

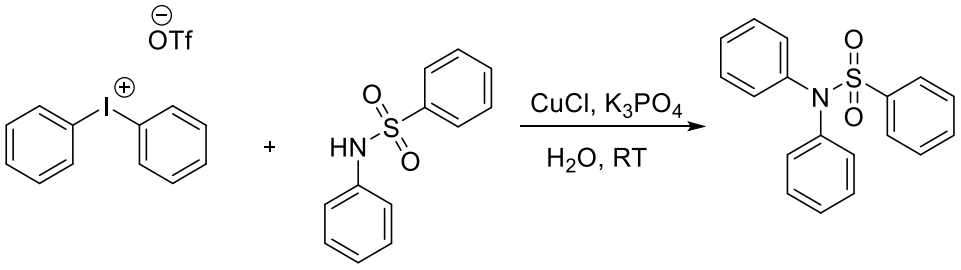
Scheme 64: Arylation of tert-butyl-*N*-sulfonycarbamates using diaryliodonium salt

In this study t-butyl-*N*-tosylcarbamate was reacted with diaryliodonium triflates in the presence of a Cu(I) catalyst. A range of substituent of t-butyl-*N*-sulfonylcarbamates were used and gave the desired product in a good yield, also unsymmetrical diaryliodonium triflates were used and the chemoselectivity was observed for example when using mesityl derived diaryliodonium triflates and the other aryl group was selectively transferred, the symmetrical dimesityliodonium triflate did not give the desired product as both groups are too hindered for the reaction to take place.[148]



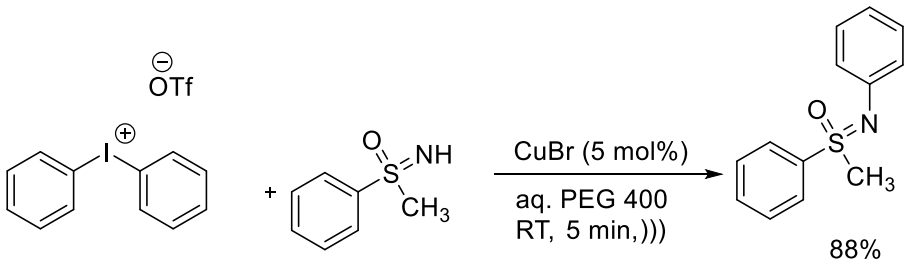
Scheme 65: Proposed mechanism of tert-butyl-*N*-sulfonylcarbamates and diphenliodonium triflate

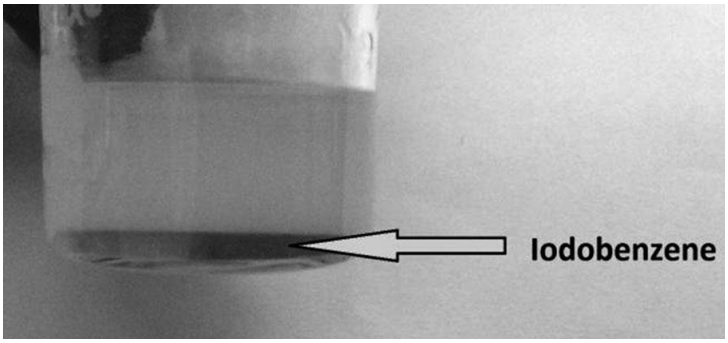
In the proposed mechanism[149, 150] for arylation tert-buty-*N*-sulfonycarbamates with diaryliodoniumtriflate under copper-catalysed conditions, the Cu(I) is oxidised to Cu(III) by reaction with the diaryliodonium salt resulting in an aryl copper species, nucleophilic addition of the sulphonamide with coordination of the copper with the oxygen lone pair of the Boc group leads to removal of the acidic proton by the base, then rearrangement to the Cu(III) complex and reductive elimination gives the product regenerating the copper catalyst (Scheme 65).[148]



Scheme 66: Synthesis of *N*-arylsulfonamide using a diphenyliodonium triflate

In other research an *N*-arylsulfonamide was also observed using diaryliodonium salts in the presence of the base K_3PO_4 rather than Et_3N as used here (Scheme 66).[151] When diaryliodonium triflates were used in the reaction a good yield of the product was obtained however when tosylate or the bromide salts were used lower but still acceptable yields were observed. Unsymmetrical diaryliodonium salts bearing halo substituents resulted in a good yield except for the 4-fluoro derivative due to its low solubility whereas diaryliodonium salts with weakly electron-donating group such as 4-t-butyl gave only moderate yields. Unsymmetrical diaryliodonium salts led to transfer of the less hindered group as this is a copper catalysed mechanism. The *N*-arylsulfonamide tolerated both electron-withdrawing groups and electron-donating groups and gave the product in a good yield except the combination of *N*-cyclohexylsulfonamide and 4-methoxyphenylsulfonamide which gave a very low yield of the product.[151]

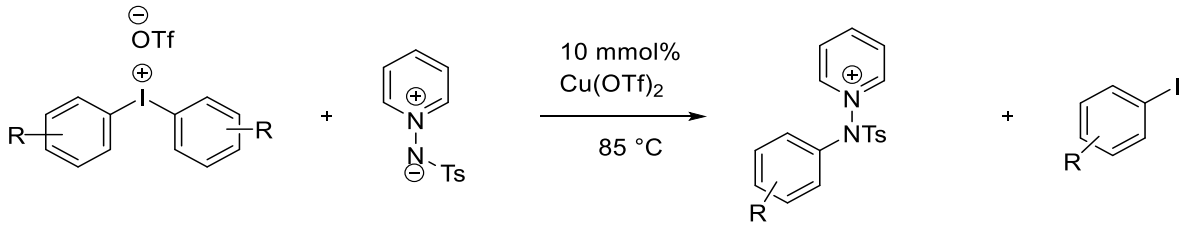




Scheme 67: *N*-Arylation of sulfoximine with diaryliodonium salt using ultra sonication

In further research, arylation of *N*-sulfoximine was performed using ultrasonication, ultrasound in organic reaction may activate the reaction by acoustic cavitation,[152] where micro regions of high temperatures and high pressures in the liquid result in a decrease in reaction time.[152] The reaction was demonstrated by using a diaryliodonium salt, CuBr, aqueous PEG-400 and *N*-arylsulfonamides, and the reaction was finished in 5 min. Another advantage of this process modification is that the iodobenzene was readily separated from the reaction mixture at end of the reaction as a layer of iodobenzene was formed at the bottom of the beaker which could then be recycled by conversion into further quantities of the diaryliodonium salt (see Scheme 67).[153]

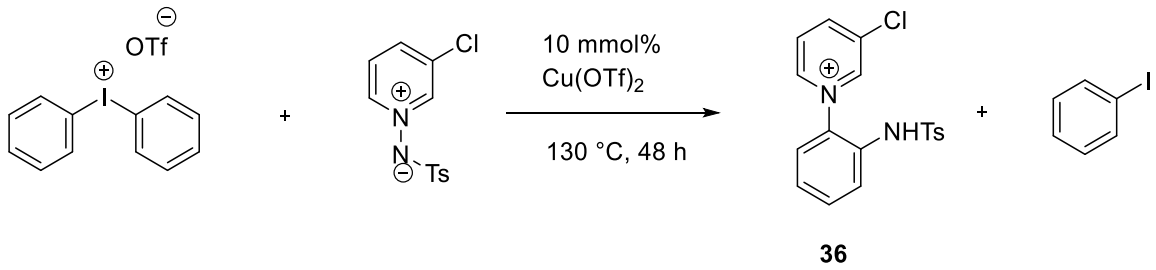
1.7.9 Arylation of pyridinium sulfonamidates



R	%
4-Br	0
4-CF_3	0
4-Cl	63
4-Me	77

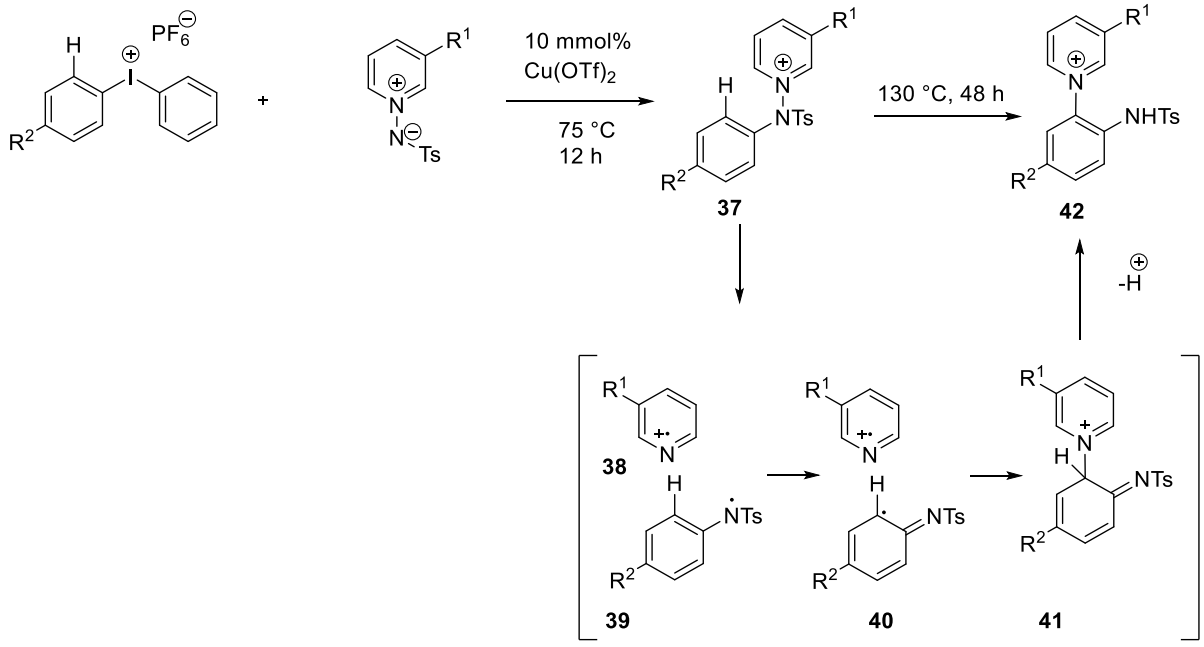
Scheme 68: Arylation of pyridinium sulfonamidates

Another report also demonstrated arylation of *N*-pyridinium sulfonamidates under copper catalysed conditions, for diaryliodonium salts with electron-donating groups the reaction worked well when electron-withdrawing groups were present, for instance bromo and trifluoromethyl groups the arylated product was not produced. The chemoselectivity for this reaction when unsymmetrical diaryliodonium salts were used was as expected in that the less hindered group was coupled to the nitrogen of pyridinium sulfonamidate (Scheme 68).[154]



Scheme 69: Arylation of pyridinium sulfonamidates

The pyridinium sulfonamidates with electron-donating substitutes worked well with diaryliodonium salts which also had electron-donating groups however in the case of electron-withdrawing groups on the diaryliodonium salt these did not give the arylated product (Scheme 69). The pyridinium sulfonamidates with halogens substituents were also reactive and gave the re-arrangement product.[154]

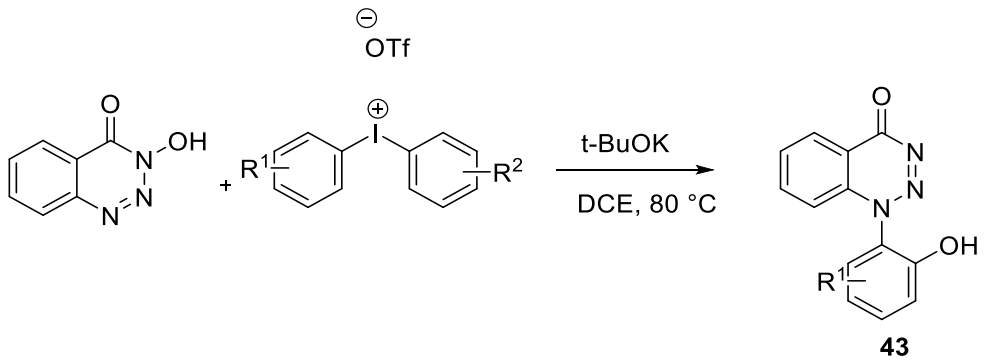


Scheme 70: Proposed mechanism of *N*-arylation of pyridinium sulfonamidates

This rearrangement follows the homolytic-cleavage of the C-N bond which gives radical pair: the tosylate aniline **39** and the pyridinium radical **38** and recombination of the two radical furnished the rearrangement product **42**. The electronic effect of the substituent on the

phenyl ring effects this radical rearrangement for instance electron deficient group such as CF_3 did not afford the rearrangement product (Scheme 70).[154-156]

1.7.10 Synthesis of *N*-aryl benzo[1,2,3]triazin-4(1H)-one derivatives



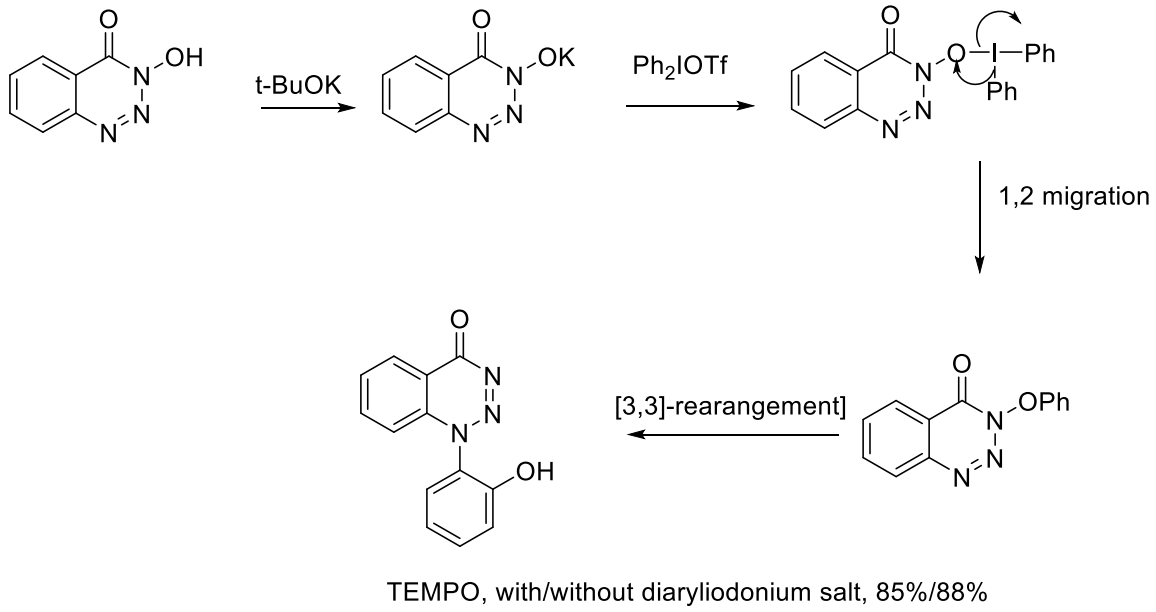
43

Entry	R^1	R^2	%
1	3,5-Me_2	3,5-Me_2	5
2	4-Br	4-MeO	63
3	4-iPr	4-MeO	78
4	4-Cl	4-Cl	85
5	3-NO_2	3-NO_2	59
6	2-Me	2-Me	42

Scheme 71: Arylation of *N*-hydroxybenzole [1,2,3]-triazin-4-(3H)-one using diaryliodonium salt

The benzo[1,2,3]triazin-4-one derivatives **43** are important compounds in pharmaceutical sector and typically synthesised by a [3,3]-rearrangement through a one-pot reaction initially involving *N*-*O*-arylation followed by a [3,3]-rearrangement. [157, 158] The [3,3]-rearrangement process has gained much attention in organic chemistry[159] as it allows accesses to some compounds which are difficult to synthesise by other methods for instance Claisen rearrangement.[157] The diaryliodonum salt was used for this purpose, in the presence of base with no additional catalyst required, the diaryliodonium salt may be used with both electron-donating and electron-withdrawing substituents, the presence of 2- and 3-substituents giving

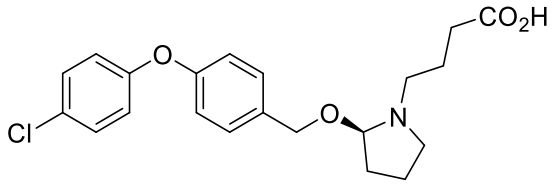
a lower yield (entries 5,6 Scheme 71) might have subject to steric hindrance and electronic effect respectively. The more electron-deficient aromatic ring was transferred under these metal-free conditions which is expected and opposite to the metal catalysed process. The reaction was also dramatically affected by steric hindrance with these salts giving only 5% of the product (Entry 1, Scheme 71).[160]



Scheme 72: Proposed mechanism of arylation of *N*-hydroxybenzole [1,2,3]-triazin-4-(3H)-one and diaryliodonium salt

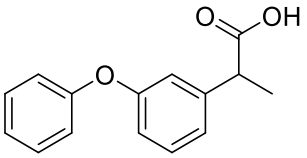
The radical trap TEMPO was added under optimized condition and proved that the *N*-*O* bond cleavage did not proceed via a radical mechanism as when the reaction was heated at 50 ˚C the *O*-arylation intermediate was still obtained and increasing the temperature to 80 ˚C the *N*-arylation product was obtained,[160] the proposed mechanism is shown in Scheme 72.[160-162]

1.8 Arylation of oxygen



Leukotriene A4 hydrolase inhibitor of leukotriene synthesis

44



Fenoprofen

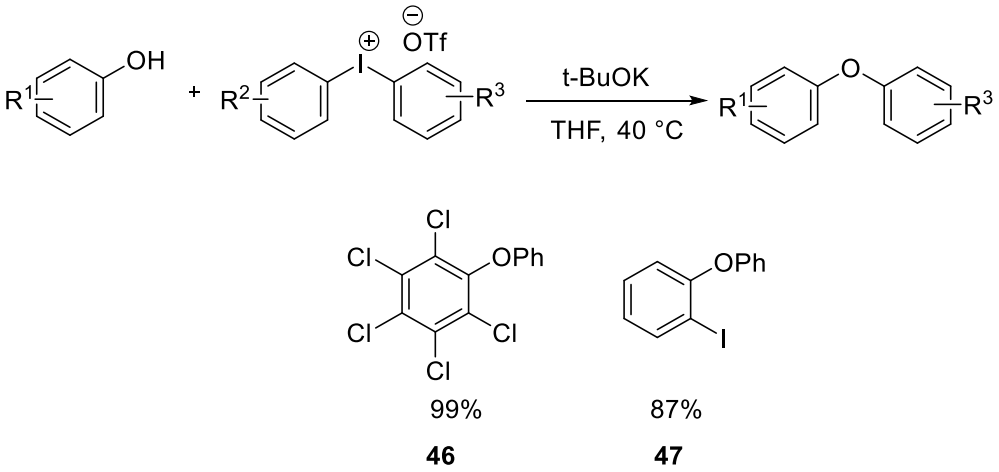
45

Figure 8: Bioactive compounds containing diarylether

The diarylether is a widespread functionality in pharmaceutically active compounds and in the fine chemicals and polymer industry. Diarylethers are also found in many natural products for instance vancomycin, glycopeptide antibiotics and also as anti-HIV agents for example chloropeptin, and also in compound **44** and compound **45** (Figure 8).[163-166]

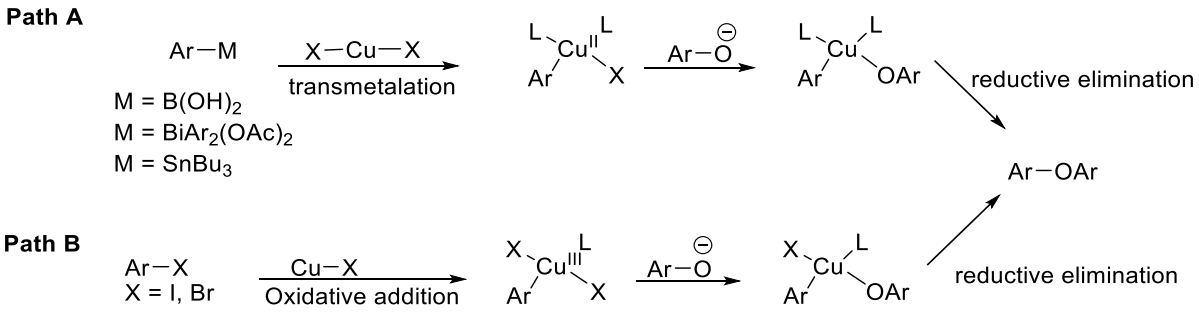
The early method for the preparation of diarylethers is the Ullmann coupling reaction which involves the reaction of phenol with aryl halides[167] but it requires high temperatures and uses aryl compounds that are sensitive to oxidation, for example phenol. Diarylethers have also been synthesised from phenol and arylboronic acids[168] in the presence of a copper-catalyst at room temperature but it requires an excess of copper.[169, 170] Another method using a palladium catalysed cross-coupling reaction is carried out at high temperature, uses expensive reagents and non-commercial ligands increasing the cost still further.[163] As a result there remains much scope to improve the formation of these materials.

1.8.1 Arylation of phenol



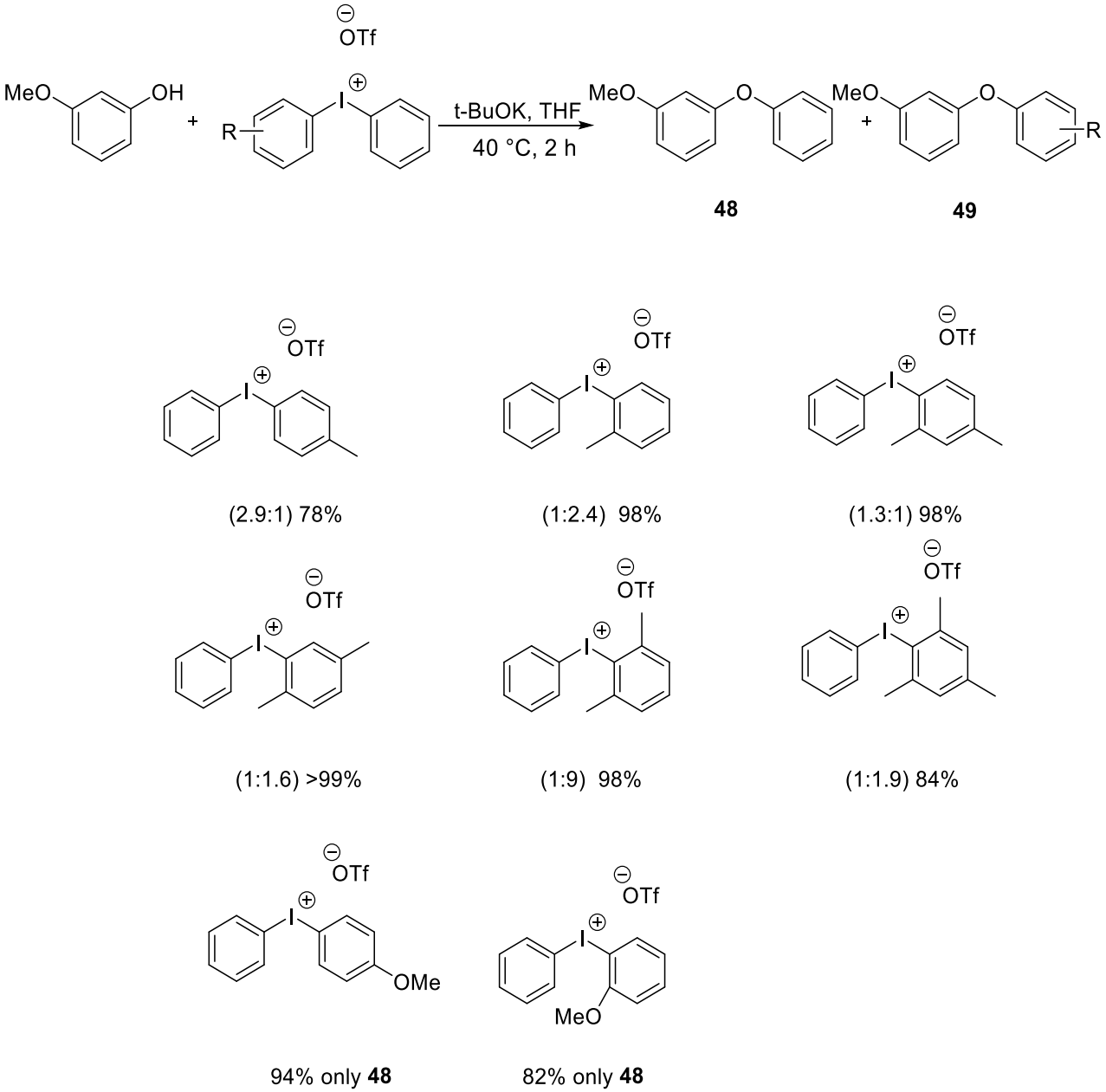
Scheme 73: Arylation of phenol using diaryliodonium salt

In a similar manner to the preparation of diarylamines, diarylethers have been synthesised using diaryliodonium salts[171-173] under both metal-catalysed conditions and metal-free conditions, the choice of counter-ion and polarity of solvent also effect the outcome of the reaction. The metal-free synthesis of diarylethers has been reported using diaryliodonium salts which allowed the synthesis of a wide range of diarylethers having electron-donating and electron-withdrawing groups, phenols bearing electron-withdrawing groups achieved lower yields than those with electron-donating groups, halo substituted phenols gave high yields of products such as **46** and **47**, it was reported that these products are difficult to obtain by conventional metal-catalyst processes (Scheme 73). The iodobenzene by-product can be recovered and used with an oxidant to reform a diaryliodonium salt increasing the efficiency of the process. The arylation of phenol with unsymmetrical salts such as 4-tolyphenyliodonium salt led to a mixture but the chemoselectivity for 4-methoxypheny(phenyl)iodonium salt was good suggesting some electronic control in the process.[163]



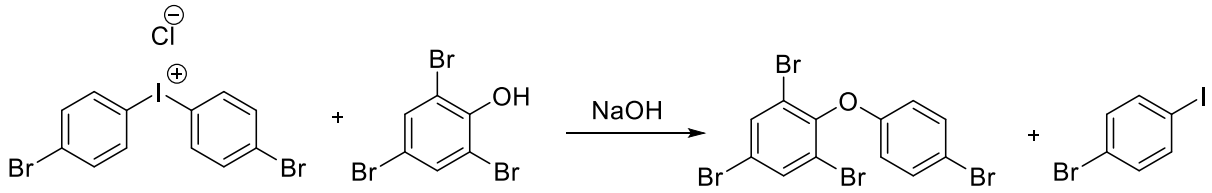
Scheme 74: Proposed catalytic cycle [96]

The mechanism of the copper-catalysed process is unclear and there are different options regarding the catalytic cycle, however they all involve transmetallation/ oxidative addition, followed by reductive elimination although the order of the steps unknown.[11] It was also reported that catalytic cycle for copper(I) starts with oxidative addition to the aryl halide and results in a copper (III) intermediate and finally reductive elimination to give the product. The transmetalation step, transferring the ligands from the metal to the arylhalide results in a copper (II) intermediate and finally reductive elimination to give the product (Scheme 74).[174]



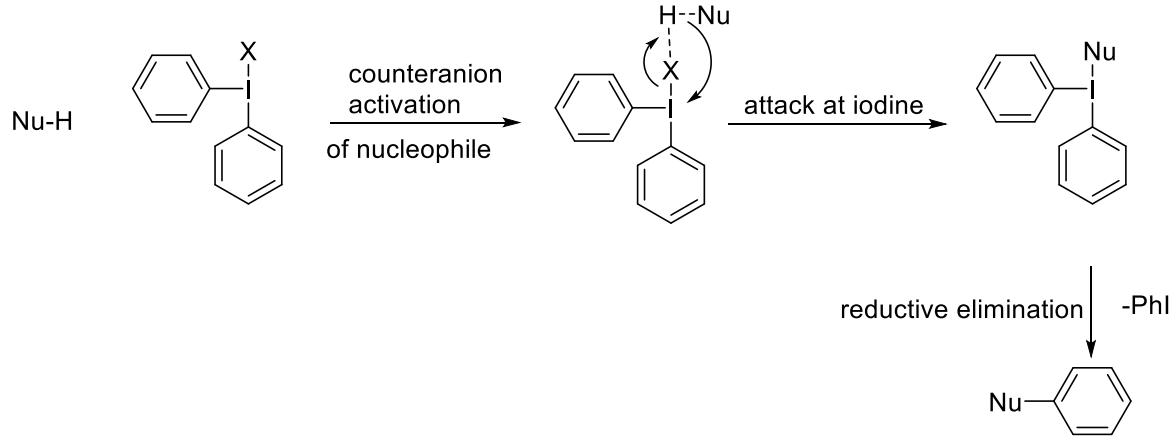
Scheme 75: Coupling of 3-methoxy phenol with diaryliodonium triflate

The chemoselectivity when using unsymmetrical diaryliodonium salts in the arylation of phenol was also studied, as described earlier it is the more electron-deficient group that will be transferred under metal-free conditions.[2, 175, 176] The diaryliodonium trifluoroacetate with a 4-methyl group gave an unselective reaction gave a mixture of 2.9 compound **48** (78 %) to 1 of compound **49** which is not surprising as the two aromatic groups are similar. The 4-methyl is affected by electronic and steric factor whereas the 4-methoxyphenyl derivative gave selective reaction (Scheme 75), the *ortho*-effect was also observed (Scheme 75).[162]



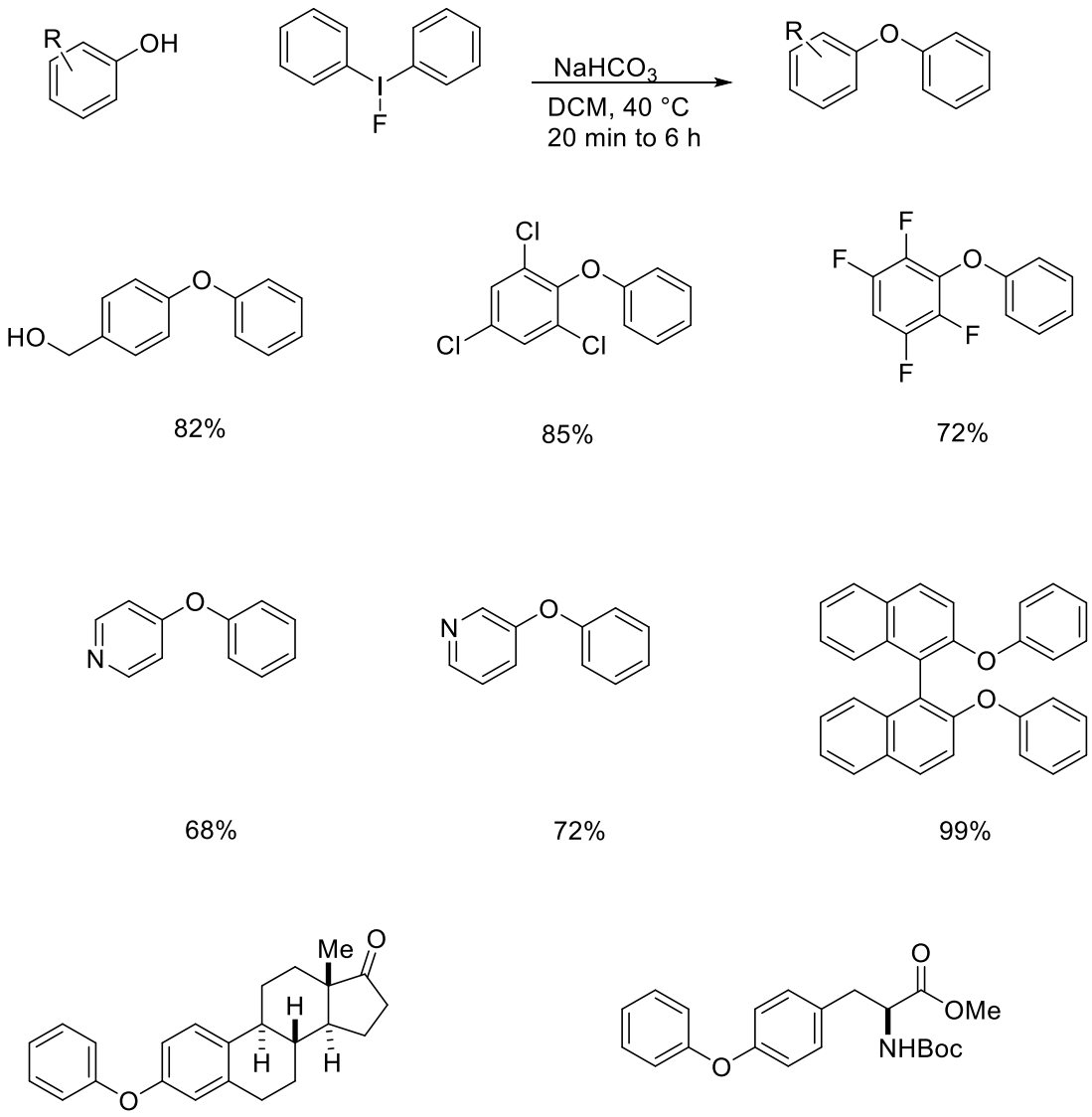
Scheme 76: Synthesis of polybrominated diphenylether

Polybrominated diphenylethers have been synthesised from brominated diaryliodonium salts and brominated phenols (e.g. Scheme 76),[177] these brominated ethers have found many applications in industry for example as flame-retardants in electronics, plastics, textiles and finishing foam.[178, 179]



Scheme 77: Arylation of phenol using diaryliodonium fluorides

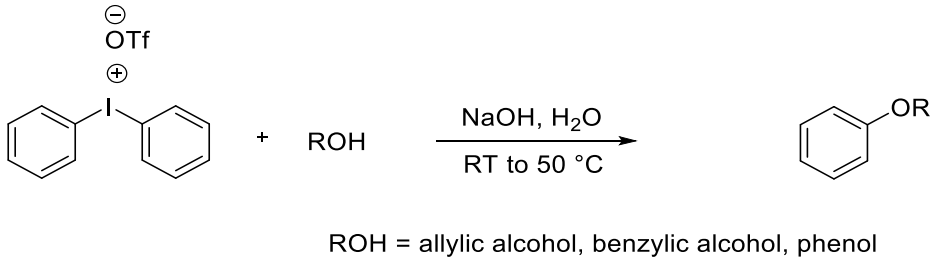
As described earlier, and in some cases the counter-ion of diaryliodonium salts has an effect on the reaction outcome, the counter-ion may not act as just a leaving group alone. In the case of diaryliodonium salt with fluoride counter-ion the fluoride could act as a base and stimulate the nucleophilic activity[180] of an additional species through formation of a F-H bond which facilitates attack on the iodine (III) centre (Scheme 77).



Scheme 78: Synthesis of substituted diarylethers

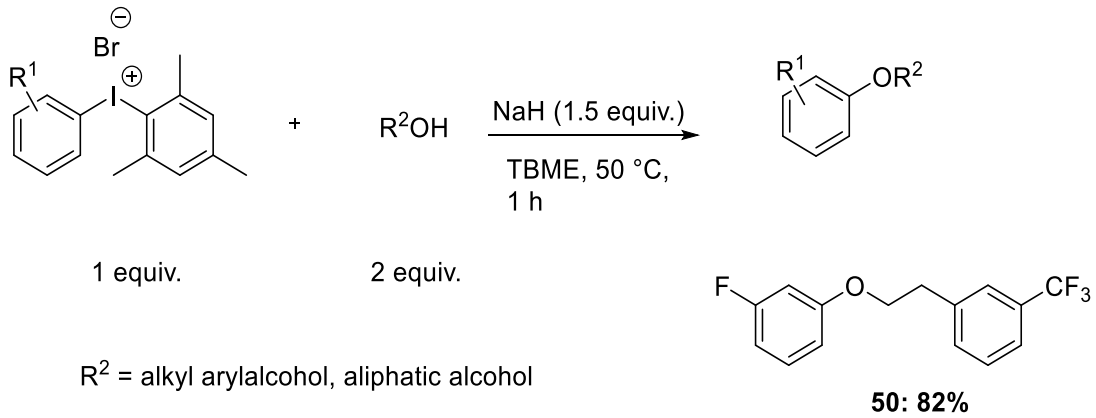
Using this approach the phenols were arylated with diphenyliodonium fluoride, phenols with electron-deficient groups and electron-donating groups are both tolerated and gave the desired product in a good yield. Also sterically hindered species with *ortho* substituents were used and the product was still obtained in excellent yield (Scheme 78).[181] The diaryliodonium triflate did not work under these conditions whereas addition of TBAF to the diaryliodonium triflate did result in arylation of the phenol. When unsymmetrical diaryliodonium triflates were used the selectivity observed was that the more electron-deficient aryl was transferred. It was also observed that arylation of L-tyrosine under optimised condition[182] using diaryliodonium fluorides was possible,[181] this is useful as these material have demonstrated applications in the pharmaceutical industry, as dietary supplements and food additives.[181]

1.8.2 Synthesis of alkylarylethers



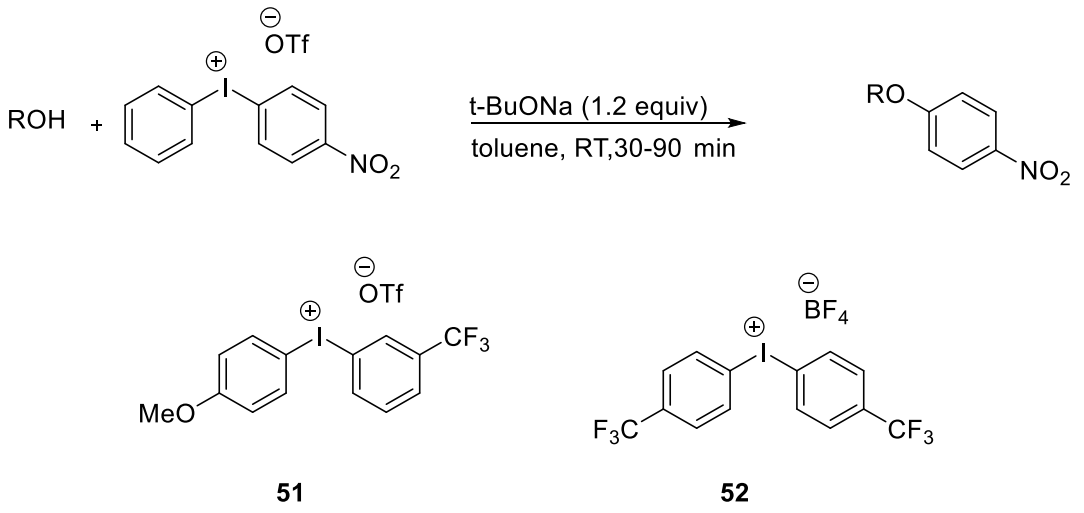
Scheme 79: Synthesis of alkylarylethers

In the addition to the formation of diarylethers the general arylation of alcohols using diaryliodonium salts has been reported at room temperature, whereas most of methods such as the Williamson ether synthesis,[183] S_NAr reactions[184-189] and the use of Mitsunobu type reagents[190] usually require high temperatures, toxic reagents and/or have restricted range of substrates[191]. Diaryliodonium salts are less toxic than some metal catalysts and therefore they are a suitable reagents for the arylation of allylic alcohols, however allylic alcohols are readily oxidised to aldehydes, ketones and carboxylic acids with powerful oxidants such as hypervalent iodine species so this needs to be considered. This reaction was carried out in the presence of a base and water at room temperature to also prevent arylation of the base. The observed chemoselectivity was that *ortho*-substituted diaryliodonium salts were less selective while those with electron-withdrawing groups gave a good yields of the product. This method was not suitable for the arylation of normal aliphatic alcohols as their pKa is too high.[192]



Scheme 80: Synthesis of alkyl-aryl ethers

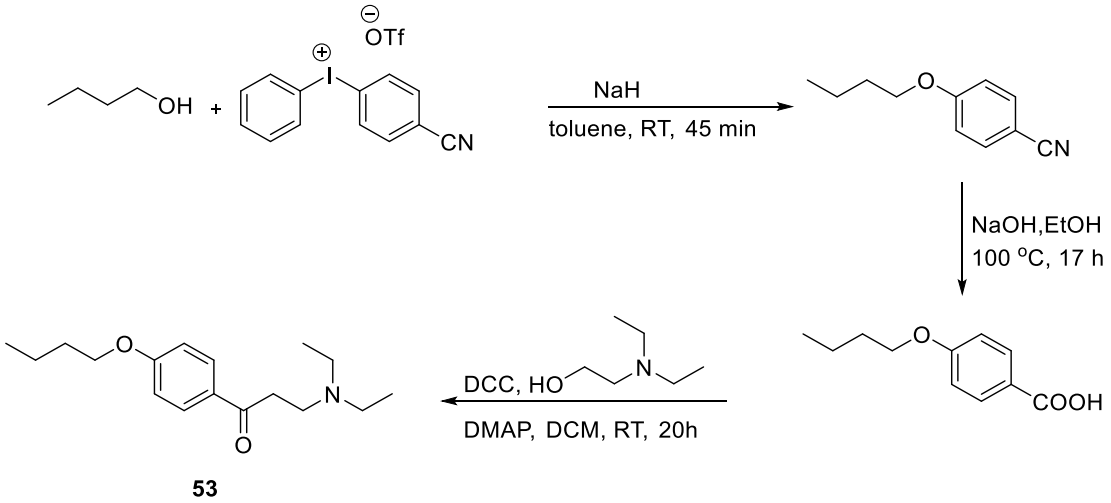
The arylation of secondary alcohols remains a challenge since oxidation was observed and resulted in ketone by-products. When unsymmetrical diaryliodonium salts were used to arylate alkyl alcohols under metal-free conditions, with NaH as the base, and TBME as a solvent (Scheme 80)[191] the usual chemoselectvity was observed and the less electron-rich aryl group was transferred forming the alkylaryl ether. The alkylaryl ether with a fluorinated group was observed under these conditions for instance compound **50** which is difficult to obtain under other methods, for example in S_NAr reaction as the fluoride is good leaving group.[191]



Scheme 81: Arylation of aliphatic alcohol with diaryliodonium salts

It has also been shown that the arylation of aliphatic alcohols in toluene is possible as some of the aliphatic alcohols do not react as desired in the presence of water under metal-free conditions[163, 193] or at room temperature and without an excess of reagent.[193] Diphenyliodonium triflate was used for arylation of a number of different aliphatic alcohols, however the benzyl ether and cinnamyl ether were not produced in high yield. When 4-nitrodiphenyliodonium triflate was used for formation of a range of alkylaryl ethers, the usual chemoselectivity was observed and the 4-nitropheyl group was coupled to the alcohol. When diaryliodonium salt **51** was used the same pattern was followed and the 3-trifluoromethylphenyl was coupled to the alcohol whereas diaryliodonium salt **52 (**Scheme 81) with two electron-withdrawing groups present successfully arylated 1-pentanol and

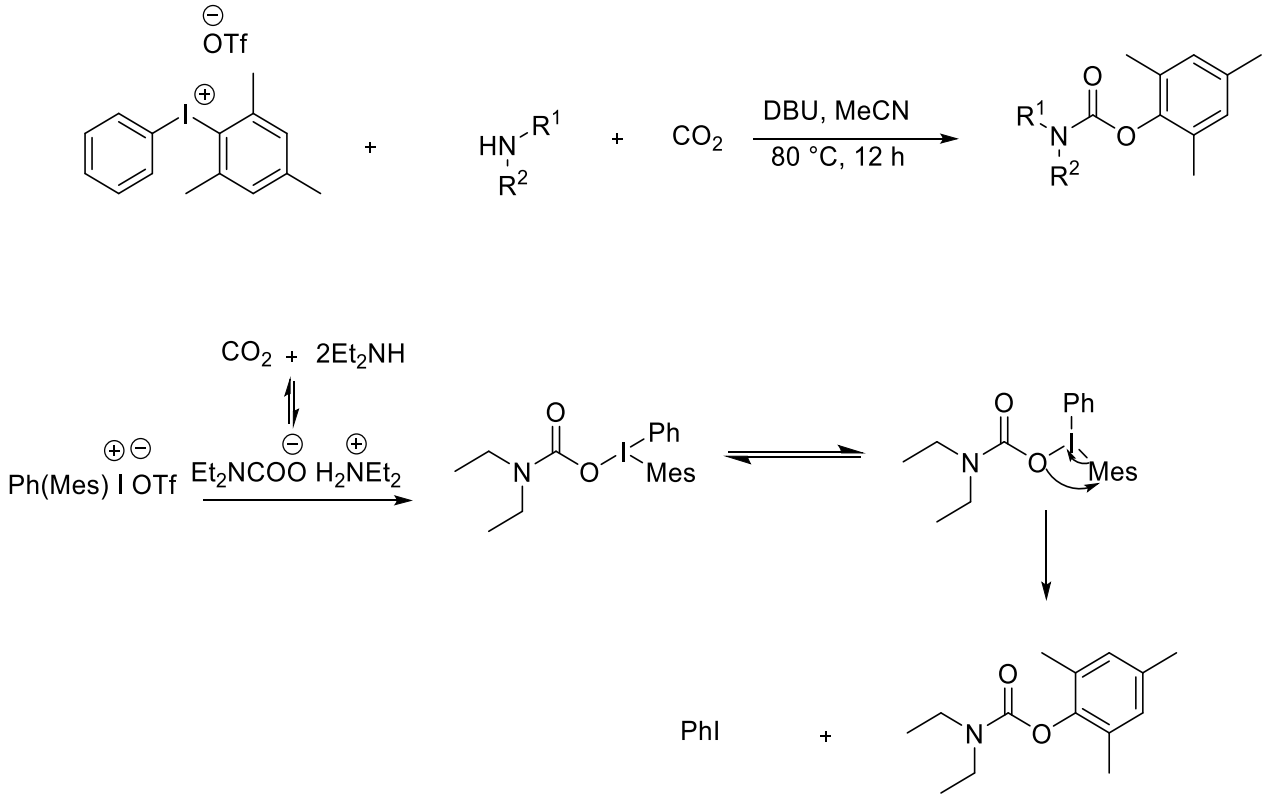
geraniol and was also used to synthesise fluoxetine. Whereas the diaryliodonium salt with only electron-donating groups and those with *ortho*-substituents did not work.[193]



Scheme 82: Synthesis of Butoxycaine (53)

The synthesis of **53** was also achieved using a diaryliodonium salt triflate under these conditions (Scheme 82).[193, 194]

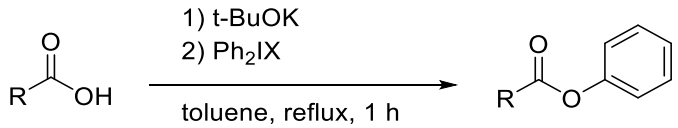
1.8.3 Synthesis of *O*-aryl carbamates



Scheme 83: Synthesis of *O*-aryl carbamates and the proposed mechanism for the reaction

It has been reported that the synthesis of *O*-aryl carbamates maybe achieved from the reaction of an amine, CO_2 and diaryliodonium salts.[195] The carbamate functionality is found in natural products,[196] agricultural chemicals[197] and pharmaceuticals,[198] for instance the anti-Alzheimer's drug, rivastigmine. The dimesityliodonium salt was used with two equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and diethylamine under 4 MPa of CO_2 (Scheme 83). The effect of the anion was also studied and the triflate was best among tetrafluoroborate, bromide and tosylate. Unsymmetrical diaryliodonium salts were used and the chemoselectivity observed was that the more electron-deficient group and the most hindered group was transferred. A proposed mechanism for this reaction has been reported (Scheme 83).[195]

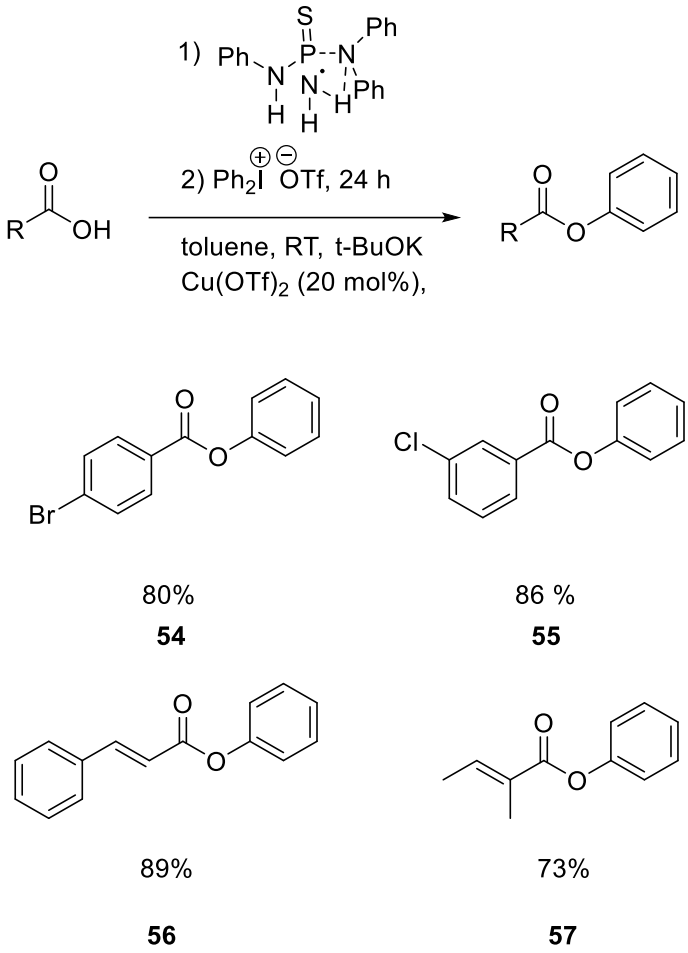
1.8.4 Arylation of carboxylic acids



Scheme 84: Arylation of carboxylic acids using diaryliodonium salts

Aryl esters are also important building blocks in pharmaceuticals, agrochemicals and polymers, they also occur in natural compounds and are widely used in organic synthesis. The reaction conditions required by the early methods were long reaction times, stoichiometric amounts of reagents and also the use of protic solvents and reflux temperatures. The Chan-Lam reaction, copper catalysed carbonylation using aryl halides and phenol addresses some of these limitations.[199]

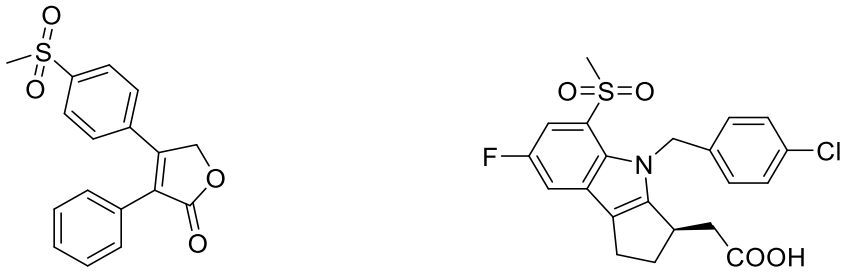
Arylation of carboxylic acids with diaryliodonium salts in the presence of sodium carboxylates was reported in 1950s. Early methods used stoichiometric amounts of sodium benzoate in the presence of protic solvents, examples where enolizable carbonyl groups were present were not suitable substrates under these conditions thereby restricting the utility of the process. Diaryliodonium salts with different anions can also be used but the bromide anion resulted in the by-product bromobenzene being formed from intramolecular coupling of the bromide anions and phenyl ring of the diaryliodonium salt. As is often seen in diaryliodonium salts the electron-deficient aromatic group is coupled to the nucleophile – carboxylic acid in this case, whilst in the presence of a metal catalyst and one arene being sterically demanding, such as mesityl, the opposite chemoselectivity is observed, enabling an electron-rich to couple to the carboxylic acid. Carboxylic acids bearing strong electron-withdrawing groups such as nitro gave the product in low yields as it had a detrimental effect on the nucleophilicity of carboxylic acid. Bulky *ortho*-substituent diaryliodonium salts and carboxylic acids gave good yields of the product.[163, 199]



Scheme 85: Arylation of carboxylic acids with diaryliodonium salt

Arylation of carboxylic acids was reported in the presence of hydrogen bond donors (HBD) for example thiophosphoramides in the presence of copper catalyst, which stimulates ion pairs by making three hydrogen bonds with anions,[200] the reaction also required a non-polar solvent to favour the hydrogen bond formation. The HBDs also worked with non-coordinating anions, for instance when using diaryliodonium tetrafluoroborates, the lack of these HBDs meant the reaction did not work. The reaction was also affected by the type of catalyst used, in the case of $Cu(BF_4)_2$ this resulted in a decreased yield as the HBD failed to coordinate the tetrafluoroborate anion which did not therefore activate the catalyst. The optimised conditions worked successfully for the electron-deficient substituted substrates such instance compound **54** and compound **55** (Scheme 85), it should be noted that the yields of these two products are higher than under metal-free reaction conditions. The system is also active for the arylation of aliphatic acids and α ,β-unsaturated acids for example compounds **56** and **57** (Scheme 85).[201]

1.8.5 Arylation of sulfonic acids

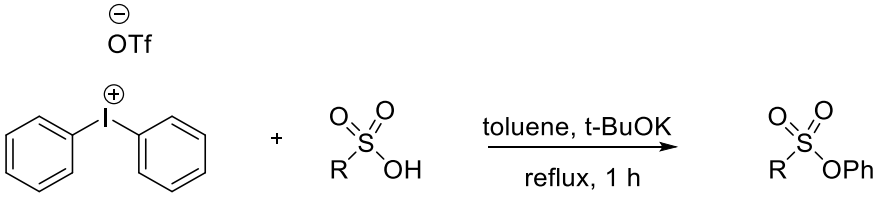


Vioxx **58**

Laropiprant **59**

Figure 9: Anti-inflammatory drugs COX-2 containing arylsulfones

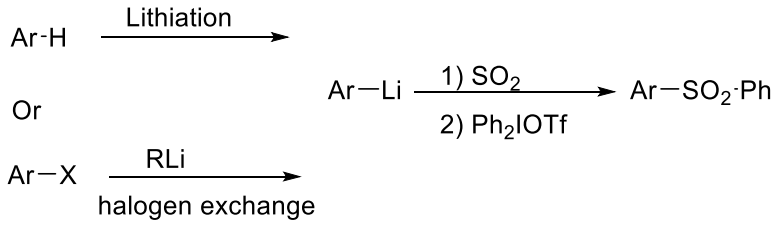
Drugs such as the COX-2 inhibitor Vioxx **58** and prostaglandin D2 antagonist Laropiprant **59** contain arylsulfones in their structure (Figure 9), diarylsulfones have also been shown to have antitumor activity and hamper the HIV-1 reverse transcriptase therefore arylsulfones are useful compounds in medicinal chemistry.[202] Different methods have been used to synthesise diarylsulfones, both in the presence of metal catalysts and using metal-free synthetic routes. The method above which described the synthesis of an aryl ester may also be used to synthesise aryl sulfonate esters, however in lower yields using diaryliodonium triflate as the attack on iodine by the less nucleophilic sulfonate anion is the rate determining step in the reaction (Scheme 86).[163]



Scheme 86: Arylation of sulfonic acids using diaryliodonium salts

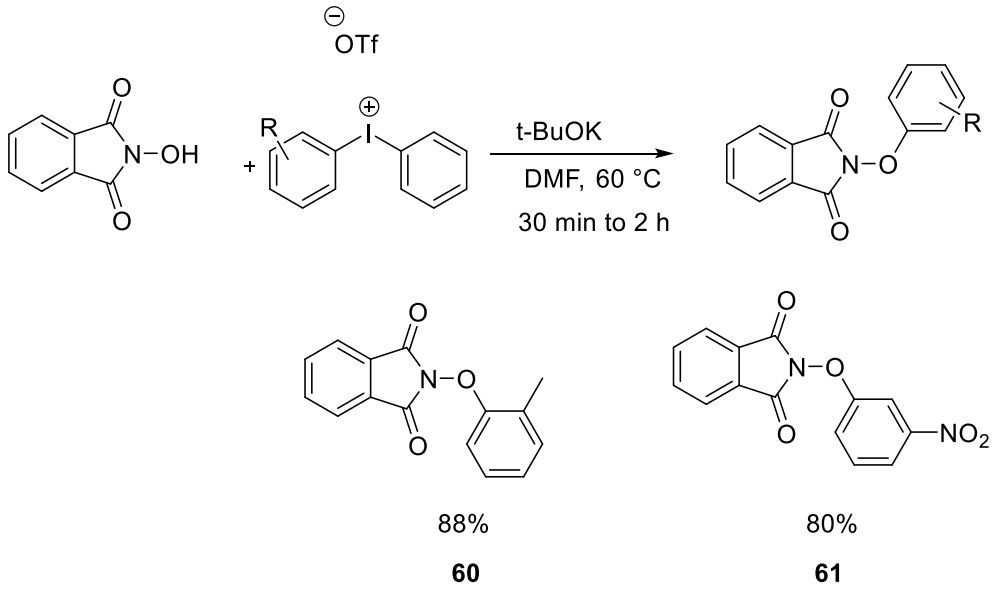
The synthesis of diarylsulfones may also be achieved from lithium sulfinates which are easily prepared in situ via lithiation of a haloarene in the presence of sulfur dioxide. The reaction is sensitive to the choice of counter-ion with a more nucleophilic counter ion, such as Cl^- and

TsO^- resulting in lower yield. Like many reactions the process was selective when unsymmetrical diaryliodonium salts were used.[202]



Scheme 87: Formation of diarylsulfonates

1.8.6 Synthesis of aryl *N*-aryloxyimides and aryloxamines



Scheme 88: Synthesis of aryl *N*-aryloxyimide using diaryliodonium salts

As discussed in Section 1.8.1 the arylation of oxygen, aryloxamines also have been synthesised under metal-catalysed conditions, however it was observed that the arylation of *N*-hydroxysuccinimide (NHS) using diaryliodonium salts and a base proceeded under metal-free conditions.[3, 33, 203-206] For unsymmetrical diaryliodonium salts was used, the usual chemoselectivity was observed with the 2-methyl-substituted arene or the more electron-deficient group 3-NO_2 was transferred (e.g. **60** and **61** in Scheme 88).[207]

1.9 Summary

As discussed above the arylation of *N*-nucleophiles has been achieved using a variety of different methods, for instance the palladium-catalysed Buchwald-Hartwig type reaction, copper mediated Ullmann type and Chan-Lam reactions either with aryl halides or arylboronic acids as the source of the aromatic ring, however the conditions often required a strong base, high temperatures, and also limited the functionality of the substrate and the yields were low in the presence of electron-withdrawing groups.

As iodine (III) compounds are very electrophilic at the iodine because of the node in the non-bonding orbital they are therefore very reactive towards nucleophiles. The diaryliodonium salts were used widely for the arylation of nucleophiles, as discussed for example nitrogen and oxygen, diaryliodonium salts have also been used in the arylation of sulfur,[208] carbon[209] and fluorine[17] which have not been discussed in this review. The reaction conditions depend on both the nature of nucleophile and the counter-ion of the diaryliodonium salt, the latter also has an effect on the stability of the diaryliodonium salt itself. The counter-ion triflate was used in most cases as simple diaryliodonium salts are readily prepared although poly-functional derivatives are much more difficult. It is the exploration of this area and the actual reaction conditions that forms the basis of this thesis particularly as our research group[2, 210, 211] and others have reported that these parameters can greatly influence the outcome of such reactions.

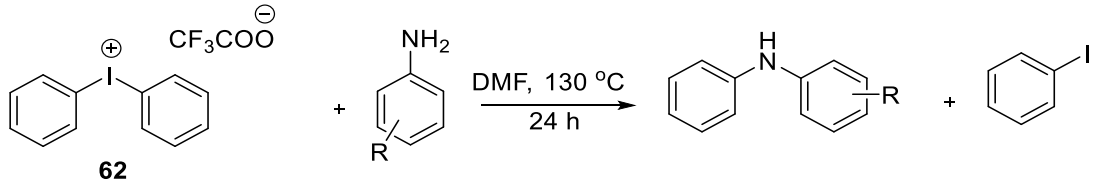
Despite many studies using diaryliodonium salt in the arylation of nucleophiles finding an efficient general method which provides shorter reaction times and also has the potential to scale up the production of the target material remains of interest as it is this that will see diaryliodonium salts adopted as routine arylating agents in a commercial setting.

In addition there has not been any reports on the arylation of oxygen nucleophiles using diaryliodonium salts in the absence of base and extremely limited studies on functional group selectivity given the ultimate application is the efficient preparation of diverse polyfunctional molecules (for example selectivity between *N*- and *O*-nucleophiles).

2 Results and Discussion

2.1 Aims

As discussed in Chapter 1, palladium and copper are used widely in organic synthesis to catalyse *N*-arylation reactions which it is also possible to make under metal-free conditions, this range of methodology is a result of the importance of this functionality as it has been used in numerous products such as pharmaceuticals. The arylation of both aliphatic and aromatic amines has been reported using a Buchwald-Hartwig type reaction[212, 213] and also with or without the presence of a phosphine ligand, such as the chelating phosphine BINAP.[214, 215] However, as mentioned in Chapter 1, these methods often require high temperatures, long reaction times, stoichiometric amounts or an excess of reagents (e.g. base and ligands). Yet these methods have become standard procedures for the arylation of nitrogen, oxygen and carbon centres.



62

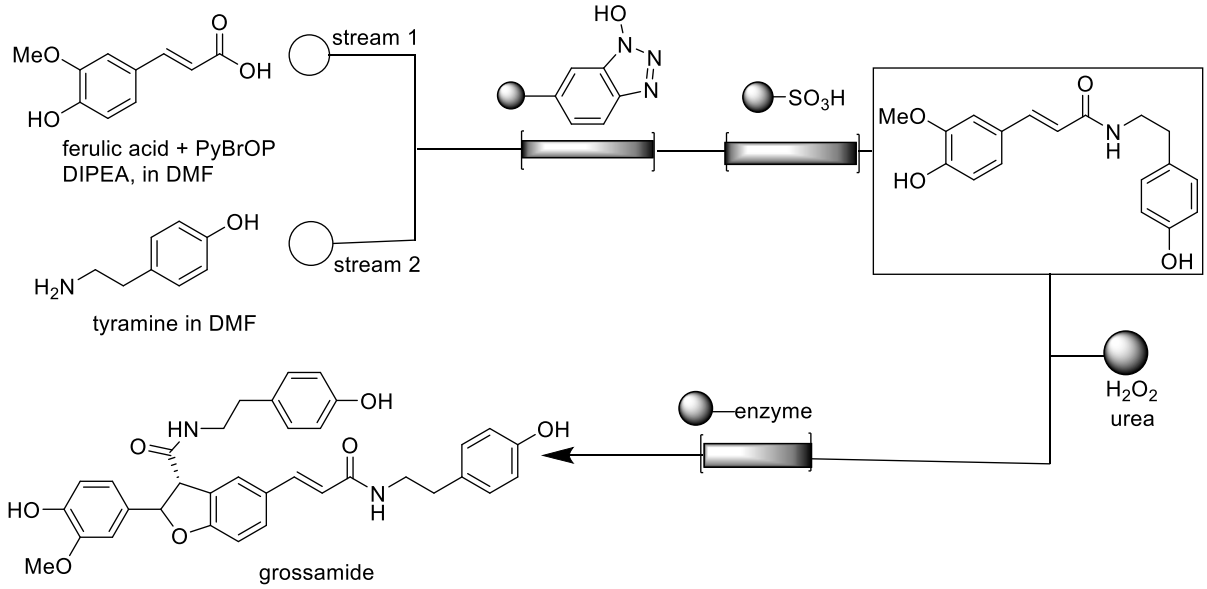
Scheme 89: Synthesis of diarylamines

Most recently diaryliodonium salts were used in the arylation of aromatic amines as they are non-toxic, stable and easy to prepare and are also extremely electrophilic and therefore have been used widely in the arylation of a range of nucleophiles.[16, 18, 19, 22, 23, 28, 29]

The *N*-arylation of aniline has been reported under metal-free conditions by our group[2] which required 24 h at 130 °C so there was an opportunity to reduce this time and/or the temperature required by the translation of the method to a flow chemistry protocol.

A wide range of methods have been used to synthesise arylamines as mentioned in Chapter 1, however to date no publication highlighted the use of diaryliodonium salts to synthesise these materials under continuous reaction conditions. Only two studies have reported the synthesis of arylamines in the flow chemistry[216, 217] and these employed the reaction of an arylhalide and arylboronic acid, therefore finding a reliable method towards the synthesis of

arylamines and assess its potential for the production of large quantities would be beneficial to industry. It also highlighted the opportunity to develop a generic 'flow chemistry' route towards the synthesis of this functionality as an alternative to the conventional batch reaction.



Scheme 90: Synthesis of grossamide using flow chemistry

Transfer of the chemistry from batch conditions to flow chemistry offers the opportunity to improve safety, efficiency, reproducibility and product purity. It also allows the products to be made in useful quantities, for example for biological evaluation, without further optimization due to the increase in scale. The flow system also allows multi-step reactions to be done and avoids large scale use of hazardous substances at a particular point in the process. It also has the potential for improving the yields and solid reagents can also be easily used in flow processes simplifying the purification of the product, the recycling/regeneration of reagents and the handling of waste.[218] For instance the increased range of process parameters means that safer methods may be used for the reaction optimization, quenching of a reaction and eventually scale-up, for instance grossamide has been synthesized using a continuous flow process giving the final product in a high yield (Scheme 90) therefore with this feature automated computer control, LC-MS optimization and UV monitoring, flow chemistry has provided synthesis of a complex molecule.[219]

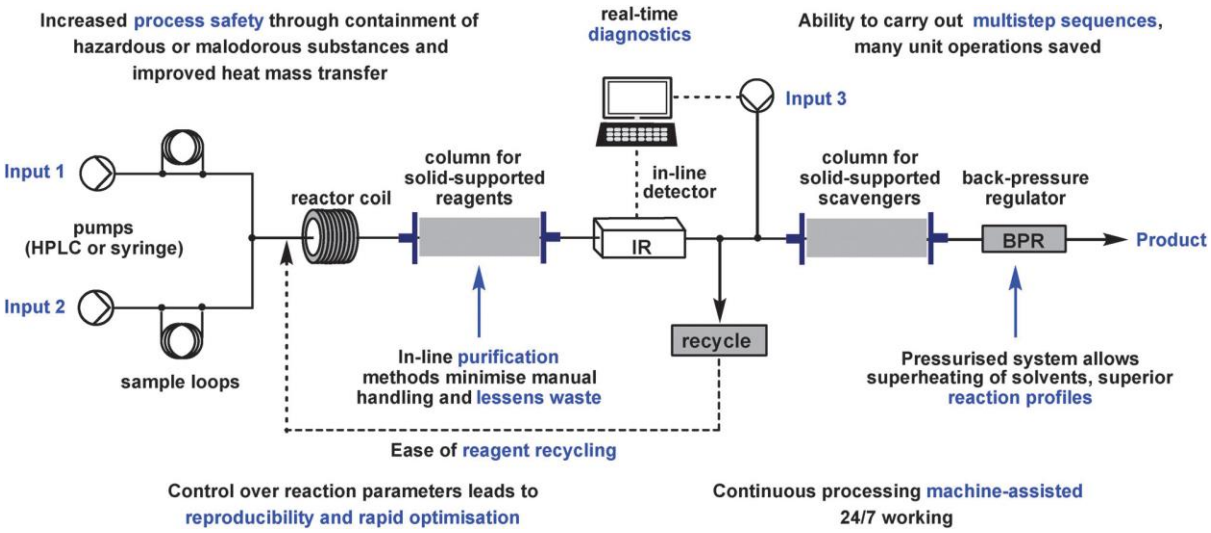
2.2 Flow chemistry

Figure 10: Flow chemistry systems[219]

Flow chemistry systems (for examples see Fig. 10), using both micro and mesoscale methods have been widely used for the organic and inorganic synthesis, compared to some batch reactions they allowed easy scale-up, product separation and demonstrated increased tolerance of multiple functional groups. Flow chemistry systems started with inexpensive syringe or HPLC pumps connected to a reactor, for example a coil which may be made from steel, glass, PEEK, PTFE and PFA (polyfluoroacetate) polymer, copper, palladium alloys and stainless steel or a micro or meso-fluidic reactor chip. The system has safety advantages as the reaction process takes place in sealed system which also limits the amounts of hazardous substance under the reaction conditions at any one time. The system may also have input pumps and/or reagent sample loops which are controlled through the computer software or manually. The use of small diameter tubing and reactors provides excellent heat transfer,

efficient mixing of reagents and hence improves reproducibility, this automation coupled with reduced reaction times and the scale of the reaction allows for rapid reaction optimization.[219]

The technology allows for multiple flow paths to be incorporated, either with additional reagents, reactors under different conditions or to allow in-line purification, such as by using bespoke in-line cartridges or packed omnifit tubes containing solid-supported reagents and/or scavenging resins, with a further advantage being limiting the amount of solvent used in the whole process.[219-221]



Scheme 91: Flow reactor configuration and its components[219]

Use of back pressure regulator allows super heating of the solvent enabling reactions to be conducted at temperatures above the usual boiling point of the solvent which is often a limiting factor in process design. The flow pathway, and variation in the combination of reactors/cartridges etc. provides a flexible system, different configurations may also offer additional criteria to optimize a process in comparison to the relevant batch reaction. Scheme 91 shows an example configuration of a flow reactor with the pumps and injection loops which can be controlled through the computer software, and an IR detector[222] within the system which monitors the reaction in real time allowing in situ refinement of the reaction conditions.[219]

Flow chemistry has been used for the synthesis of natural products using a range of chemistries such as Sonogashira C-C coupling, ring closing synthesis of heterocycles, Ullmann couplings, 1,3-dipolar cycloadditions and C-N bond formations.[223]

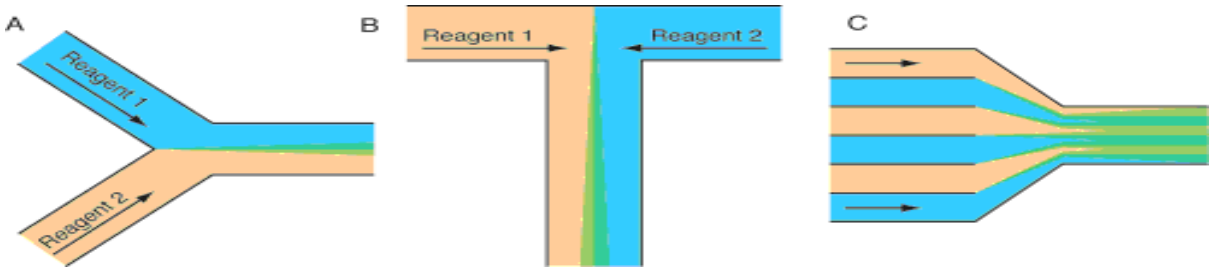
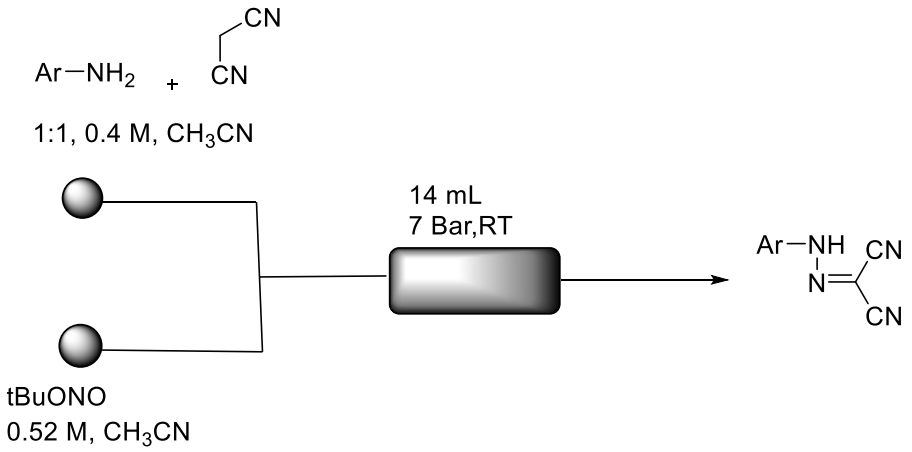


Figure 11: T-shape mixture of the flow chemistry[224]

To summarize the advantages of flow chemistry are:-

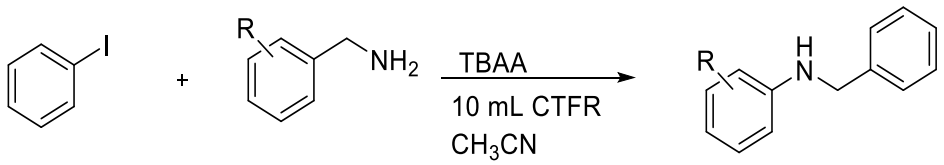
- Industrial and academic applications
- Micro, meso and very large scale processes possible
- Excellent mixing, heat and mass transfer (e.g. Figure 11, A: Y-mixer, B:T-mixer)
- Increase production without additional optimization (e.g. Figure 11, C multi-channel process)
- Wider range of reaction parameters compared to traditional batch methods
- Multi-step reactions possible
- Enhanced safety as it limits the amount of hazardous substances under the reaction conditions at any one time
- The flow chemistry also include the automation of the system allowing 24/7 working
- it also reduces the amount of solvent used and continuous processes provide an alternative method to the batch reaction.[217, 219]



Scheme 92: Synthesis of 2-arylhydrazonomalonitriles using flow chemistry

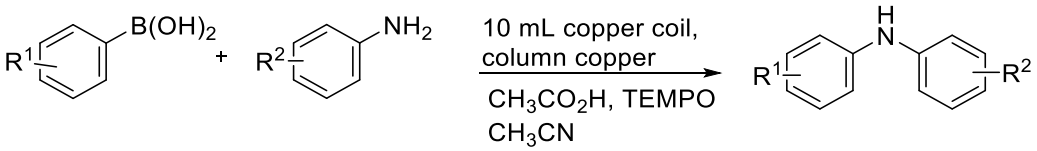
Synthesis of 2-arylhydrazonomalonitriles using flow chemistry is shown in Scheme 92[225] and is carried using the oxidant tBuONO which is a stable, non-explosive reagent and therefore is more reliable than the traditional sodium nitrite. In addition the diazonium product is potentially explosive reagent and presents safety concerns under large scale batch conditions, therefore the translation to a flow chemistry protocol also enables a safer process.[225-227]

2.3 Synthesis of arylamine using Vapourtec R4 system



Scheme 93: Synthesis of arylamine using Vapourtec R4 system

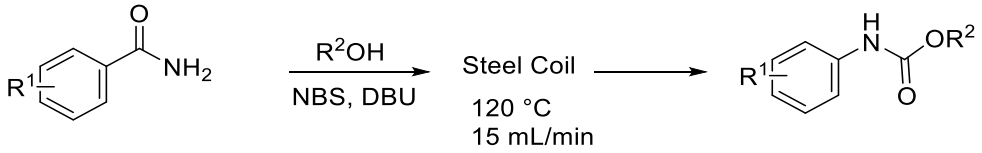
Synthesis of arylamines using the Vapourtec R4 system has been reported based on the Ullmann condensation reaction but without the need for a ligand, the reaction was performed in the presence of arylhalide in a copper tube flow reactor (CTFR) with inner diameter is 1.0 mm which was wound around a mesh support and inserted into a glass jacket, the reaction was heated at 150 °C but can also be heated to 250 °C by using a metal rather than glass jacket , the copper tube acted as both the reactor and as a source of fresh copper catalyst and gave good yields of the desired products.[216]



R^1	R^2	%
H	H	71
H	4-Cl	68
4-Me	H	71
4-Me	2-OMe	45
4-Cl	H	39
H	2-OMe	66

Scheme 94: Synthesis of arylamine

The synthesis of diarylamines has also been reported using flow chemistry (Vapourtec R4 reactor) in the presence of arylboronic acid, acetic acid, TEMPO and copper (as a 10 mL copper tube reactor or copper powder packed in a column). However the yield observed was low in the case of 4-chlorophenylboronic acid and 4-methoxyphenylboronic acid, however the desired product was obtained in a good yield in the case of phenylboronic acid, the yield was improved to 75% with the addition of TEMPO along with acetic acid. It was suggested the use of oxygen as an oxidant in the *N*-arylation using arylboronic acids could improve the yield.[217, 228]



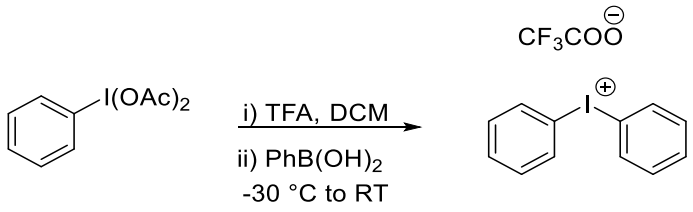
R^1	R^2	%
4-OMe	Me	80
2-OMe	Me	62
4-Me	Me	80

Scheme 95: The Hofmann rearrangement of arylamide using Advion NanoTek™

The Hofmann rearrangement was performed using a continuous flow process using a primary amide, 1, 8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base and alcohol as the solvent in the Advion NanoTek™ microreactor platform. A series of primary aromatic amides was used generating a range of carbamates (Scheme 95).[229]

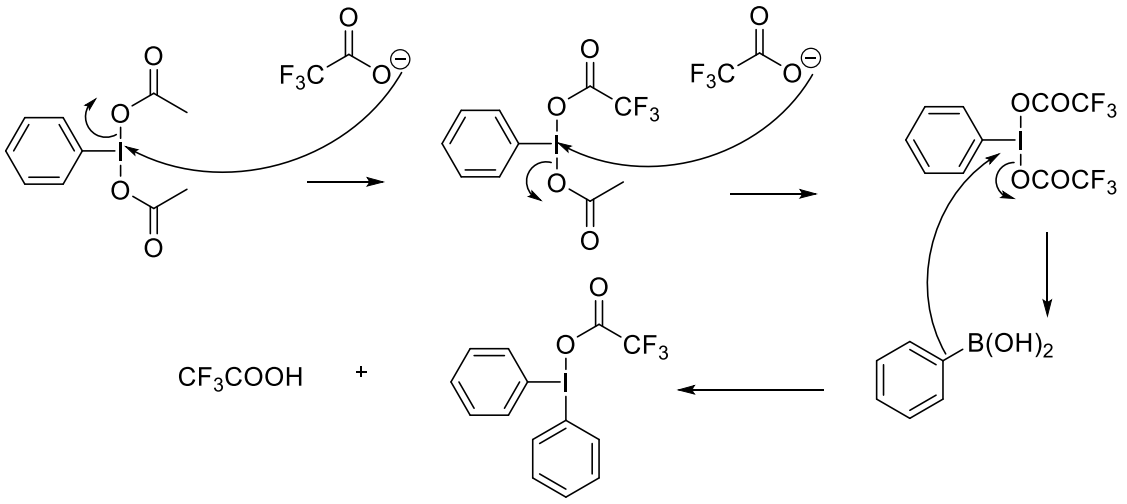
2.4 Diarylamines from diaryliodonium salts - Results

2.4.1 Synthesis of diaryliodonium salts



Scheme 96: Synthesis of diphenyliodonium trifluoroacetate (62)[2]

The project started with the synthesis of a symmetrical diaryliodonium salt following the literature procedure[2] (Scheme 96) and using this diaryliodonium salt for the arylation of a nitrogen nucleophile, in the form of aniline. Diaryliodonium salts are generally air and moisture stable, can be prepared from inexpensive starting materials, are reactive in their own right and are also suitable for use in reactors with or without metal a catalyst.[7] The good solubility of diaryliodonium salts in many organic solvents is another feature which allowed them to be used with a flow chemistry protocol.



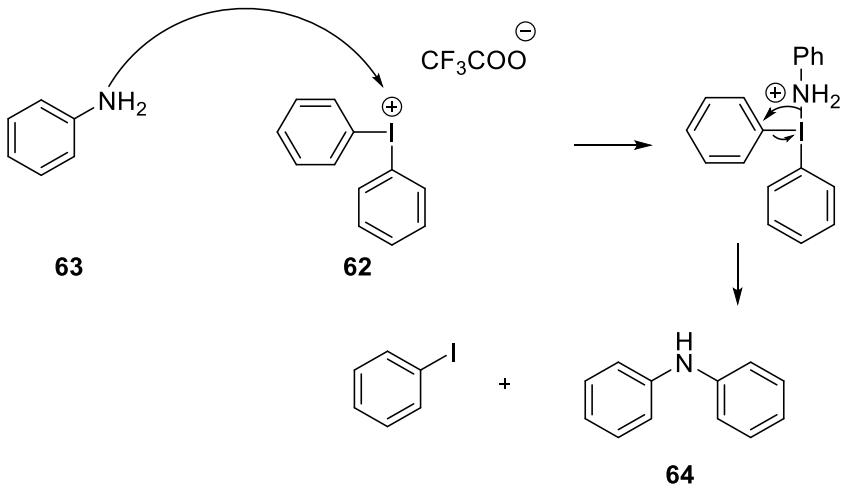
62

Scheme 97: Proposed mechanism of formation of 62

The diphenyiodonium trifluoroacetate was successfully synthesised in a good yield (74%) and the purity of the product was confirmed by ^{1}H NMR, ^{13}C NMR, mp, mass spectrum and elemental analysis. The mechanism involves multiple exchanges of the groups on iodine (acetate to trifluoroacetate to phenyl) giving the diphenyliodonium salt, there is no chemoselectivity issue in this case as it is symmetrical salt. Trifluoroacetic acid was added as it generates a very good leaving group compared to more stable acetate thus facilitating the reaction. It should be noted that trifluoroacetate salts are generally more stable than the corresponding triflates, particularly for polyfunctional and/or electron-rich arene derivatives, making this the initial counter ion of choice (Scheme 97).

2.4.2 Arylation of aniline

Diphenylamine was successfully synthesised by the reaction of diphenyliodonium trifluoroacetate with aniline, substituted anilines were also successfully used as substrates, and as a symmetrical diaryliodonium salt was used there was no chemoselectivity issues observed.



Scheme 98: Proposed mechanism of formation of (64)

The accepted mechanism involves addition of the nucleophile ($PhNH_2$) to the hypervalent iodine centre followed by reductive elimination of iodobenzene and thus transfer of nucleophile to the phenyl ring forming diphenylamine (Scheme 98).

Table 3: Synthesis of diarylamine under the batch condition

Entry	R	Isolated yield, %
1	H	61
2	4-F	55
3	4-Cl	47
4	2,4,6-Me_3	57

Diphenyliodonium trifluoroacetate (5 mmol), $ArNH_2$ (5 mmol), DMF (50 mL), 130 °C , 24 h

Method A

The synthesis of diarylamine was initially carried out under the reported batch conditions using diphenyliodonium trifluoroacetate and aniline. The metal-free arylation proceeded as

expected, the yield was good using reaction conditions of 130 °C and a reaction time of 24 h.[2] The diphenylamine and a range of substituted of diphenylamines were successfully synthesised (Table 3).The reaction gave the products in moderate yields, for instance diphenylamine was obtained in 61%, whilst 4-fluoro and 4-chloroaniline gave 55% and 47% respectively due to the electron-withdrawing group resulting in a less nucleophilic aniline, however the use of a sterically hindered aniline such as 2,4,6-trimethyaniline gave a 57% yield of the desired product as the diaryliodonium salt structure tolerates large groups in proximity to the iodine due to the T-shaped geometry.

Method B

In this method a catalyst was used to make the reaction faster. Copper catalysts have been used widely in the arylation of aromatic amines, such as in the Ullmann reaction, and a wide range of other reactions mentioned in Chapter 1. Two types of copper (I) catalyst were investigated, copper bromide, CuBr and copper chloride, CuCl to find out if the copper source had an effect on the reaction. Copper chloride has been used in the formation of C-P bonds[230] and has also been used in the carboarylation of alkynes in the presence of diaryliodonium salts. The catalytic copper cycle is via oxidative addition and transmetallation as mentioned in Section 1.5.[231]

Table 4: Reaction profiling data for copper catalysed arylation of aniline under batch conditions.

Entry	Catalyst (mol%)	64 Yield/% RT	64 Yield/% 130 °C	Time (h)
1	CuCl (1)	83[a]	83[a]	24
2	CuCl (10)	79[a]	83[a]	24
3	CuBr (1)	80[b]	85[c]	24
4	CuBr (10)	75[b]	84[a]	7

Diphenyliodonium trifluoroacetate (5 mmol), aniline (5 mmol), DMF (50 mL), RTand 130 °C

[a] by HPLC; [b] by ^{1}H NMR; [c] isolated.

The copper catalyst was used with the initial reactions carried out using batch conditions and the product was obtained in a good yield (85%, Table 4; entry 3) in the presence of CuBr and also (Table 4; entry 1) in the presence of CuCl, 83%. The results for both types of copper catalyst were similar as indicated by ^{1}H NMR and HPLC analysis of the resultant reaction mixtures.

To further investigate the effect of the copper catalyst, the reaction was carried out with different amounts and analysed by HPLC. This study also highlighted the formation of biphenyl (for its origin see Scheme 99), when a 10 mol% loading of the catalyst was used whereas formation of this by-product was not observed with a loading of only 1 mol% of the catalyst, however the yields were similar in all of the reactions. The reaction was also performed at room temperature rather than 130 °C and continued to give high yields of the desired product (Table 4), demonstrating the advantages of adding copper.

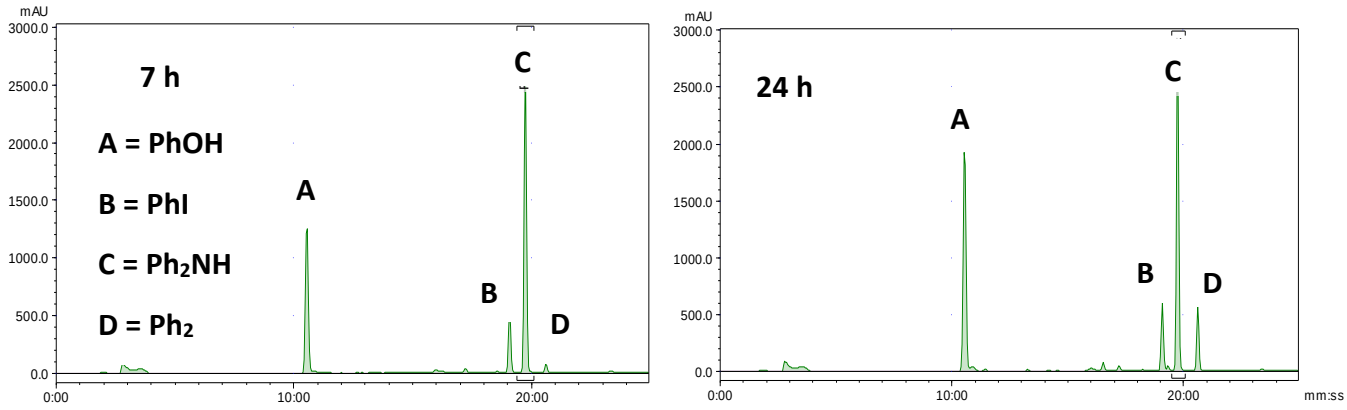


Figure 12: HPLC Chromatogram of diphenylamine synthesis at 130 °C 7 h (left) and 24 h (right) under batch reacton conditions, diphenyliodonium trifluoroacetate (5 mmol), aniline (5 mmol), DMF (50 mL).

The reaction was also performed over a shorter time period (7 h), with 10 mol% of CuBr at 130 °C, the diphenylamine was again obtained in high yield (84%) with reduced formation of the by-product biphenyl (Fig. 12), however in this case phenol was also formed as a by-product in the reaction. The amount of by-products, for example biphenyl and phenol increased with increasing reaction time as evident from the HPLC chromatograms of the crude reaction (Fig. 12).

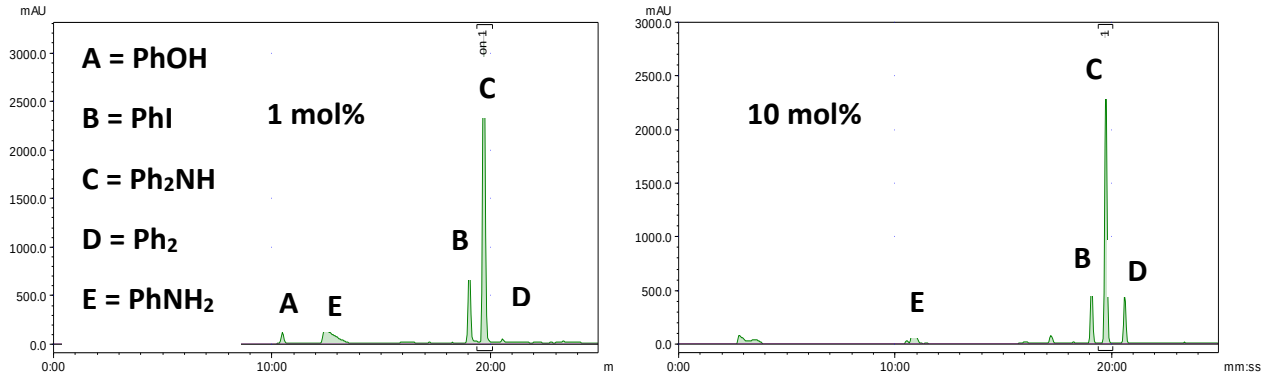


Figure 13: Chromatogram of anline batch reaction at RT, CuCl 1 mol% (left) and 10 mol% (right), diphenyliodonium salt (5 mmol), aniline (5 mmol), DMF (50 mL).

The amount of the by-product phenol generated was reduced when the reaction was performed at room temperature. The phenol may arise from the addition of water, as a competing nucleophile, to the diphenyliodonium salt but also from hydrolysis of phenyltrifluoroacetae which results from the counter-ion adding as a nucleophile, the latter being an intramolecular process. Biphenyl was detected but in a very small amount with 1 mol% of the catalyst (Figure 13).

These results suggested that the reaction benfits from a shorter time and a lower temperature as these conditions gave an improved yield of the desired product coupled with a reduced formation of by-products facilitating purification. The reaction also proceeded best when less of the copper catalyst was used.

2.4.3 Transfer to flow chemistry

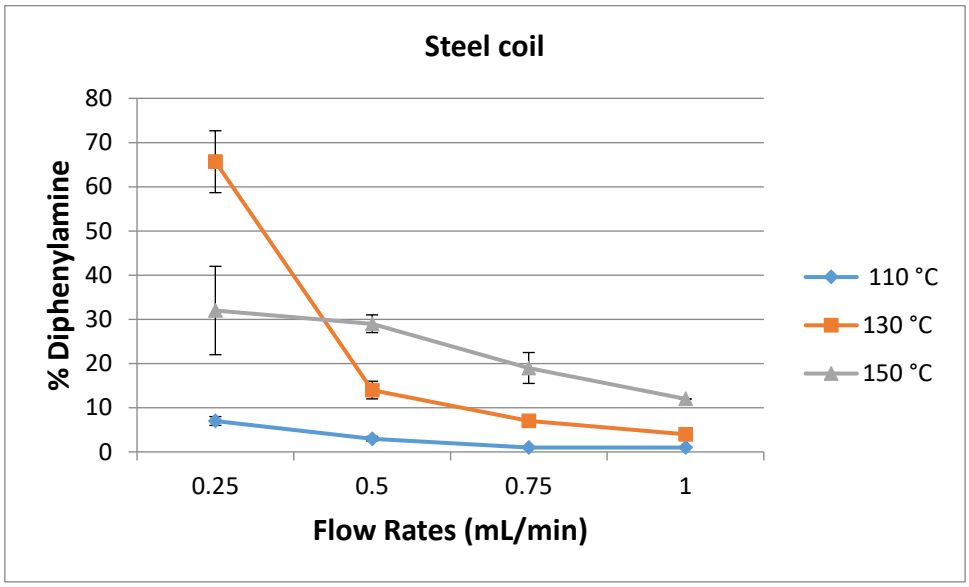


Figure 14: Optimisation of diphenylamine synthesis (n = 3), diphenyliodonium trifluoroacetate (5 mmol), aniline (5 mmol), DMF (50 mL).

The next step was to transfer the arylation of aniline to flow chemistry in this case using the Uniqsis FlowSyn™ platform (see section 4, Figure 44).[1] The reaction was investigated at different flow rates and temperatures using a reactor coil starting with a steel coil (20 mL). The results from using flow chemistry were initially analysed by ^{1}H NMR but the reaction outcome was not clear due to overlapping signals and therefore the reaction was repeated and analysed by HPLC as it gave a clearer understanding of the results. Commercial diphenylamine was used as a standard to establish the appropriate calibration curve. The reaction was performed at three different temperatures and the results are shown in Figure 14.

The results indicated that longer reaction times (slower flow rates) gave higher yields, with a flow rate of 0.25 mL/min giving about a 65% yield of the desired product at 130 °C. The faster flow rate resulted in a low recovery of the diphenyliodonium salt as the reaction is incomplete at faster flow rate and the decomposition reaction becomes more important therefore the reaction of aniline with diphenyliodonium salt is the slower process.

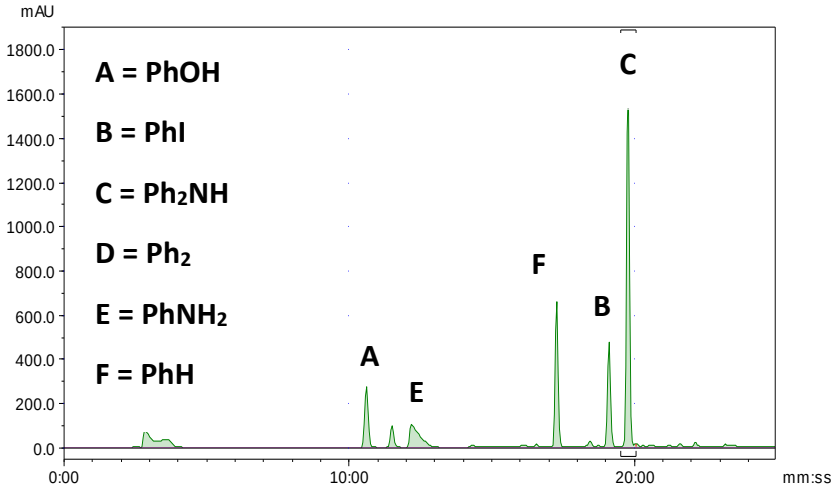
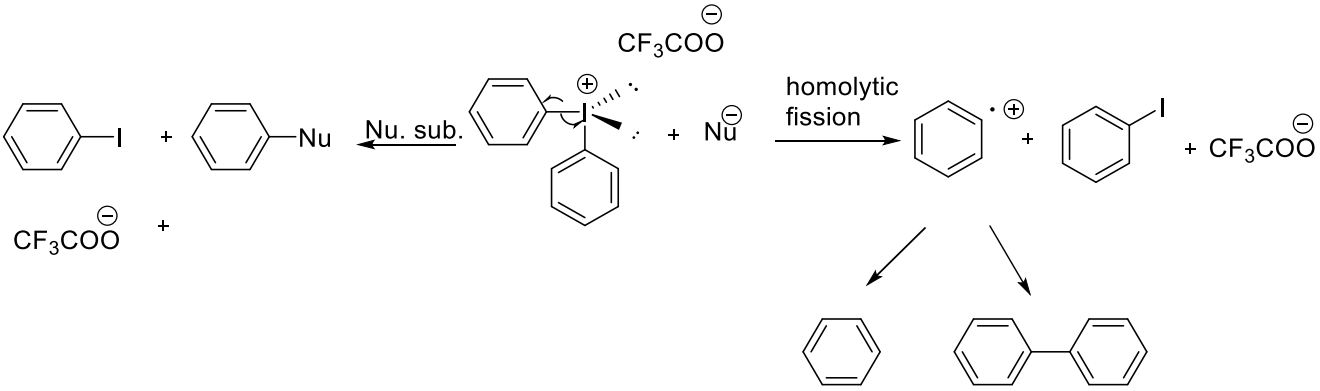


Figure 15: Chromatogram of diphenylamine synthesis, diphenyliodonium trifluoroacetate (5 mmol), aniline (5 mmol), DMF (50 mL), flow rate 0.25 mL/min, 130 °C.

The chromatogram shown in Figure 15 is for the reaction flow rate 0.25 mL/min at 130 °C, and a residence time of 80 min using a steel coil, one of the major by-products of this process is benzene.



Scheme 99: Proposed mechanism of arylation of nucleophile using diaryliodonium salt[40]

The presence of benzene suggested the formation of the aromatic radical as an alternative reaction pathway rather than the desired nucleophilic substitution mechanism leading to the arylation of aniline (Scheme 99). However good yield (65%) of the target diphenylamine was also achieved under these conditions.

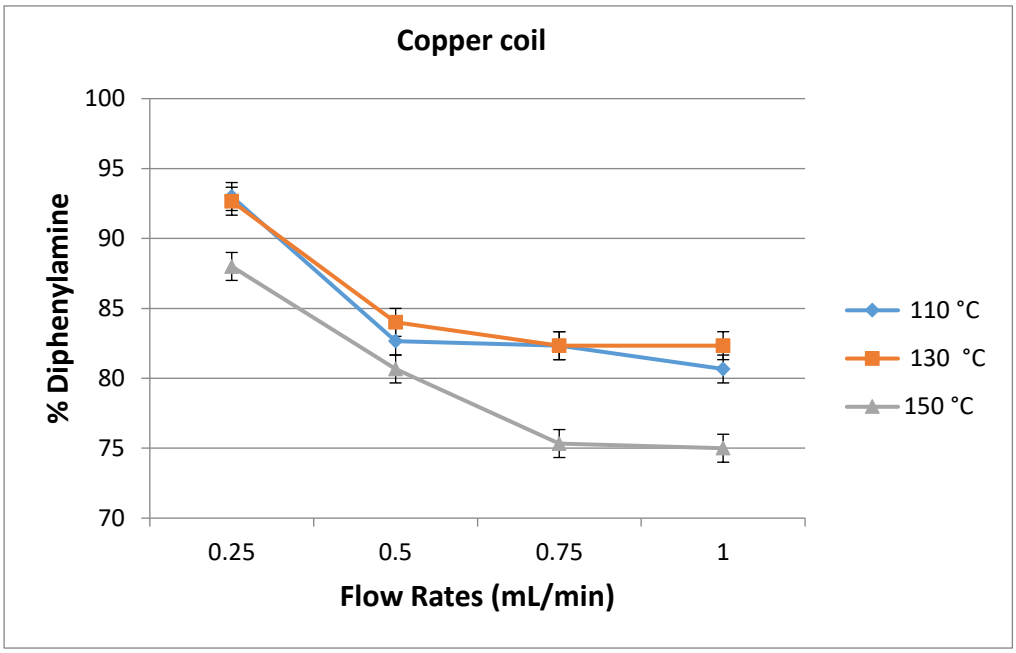


Figure 16: Optimisation of diphenylamine synthesis (n = 3), diphenyliodonium trifluoroacetate (5 mmol), aniline (5 mmol), DMF (50 mL).

As the batch reaction using the copper catalyst gave a higher yield than using metal-free conditions the reaction of diphenyliodonium trifluoroacetate with aniline was also performed using a copper coil reactor. The results also indicated that a flow rate 0.25 mL/min gave an excellent yield of the desired product (93%) however in this case the other flow rates also gave good yields of the product, but it should be noted that as the flow rate increased and/or the temperature increased the yield dropped(see Figure 16). As before the faster flow rate was leading to formation of the by-product biphenyl (Figure 17)

A = PhOH

B = PhI

C = Ph_2NH

D = Ph_2

E = $PhNH_2$

F = PhH

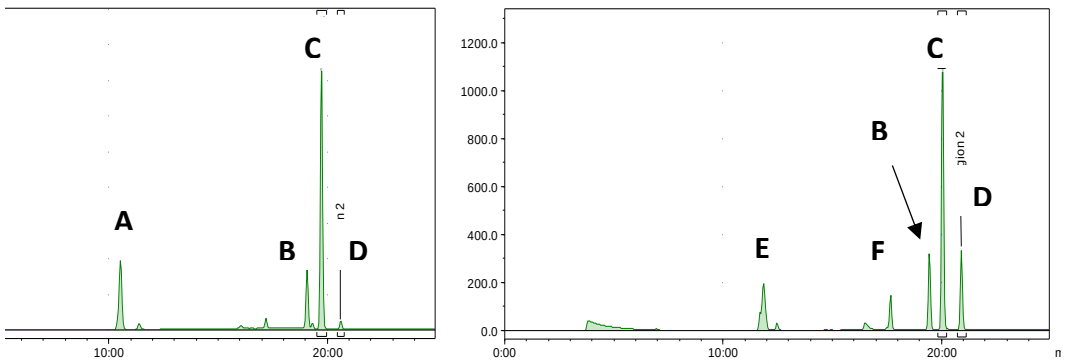


Figure 17: HPLC chromatogram of aniline reaction at flow rate 0.25 mL/min (left), flow rate 1 mL/min (right), diphenyliodonium trifluoroacetate (5 mmol), aniline (5 mmol), DMF (50 mL), 130 °C.

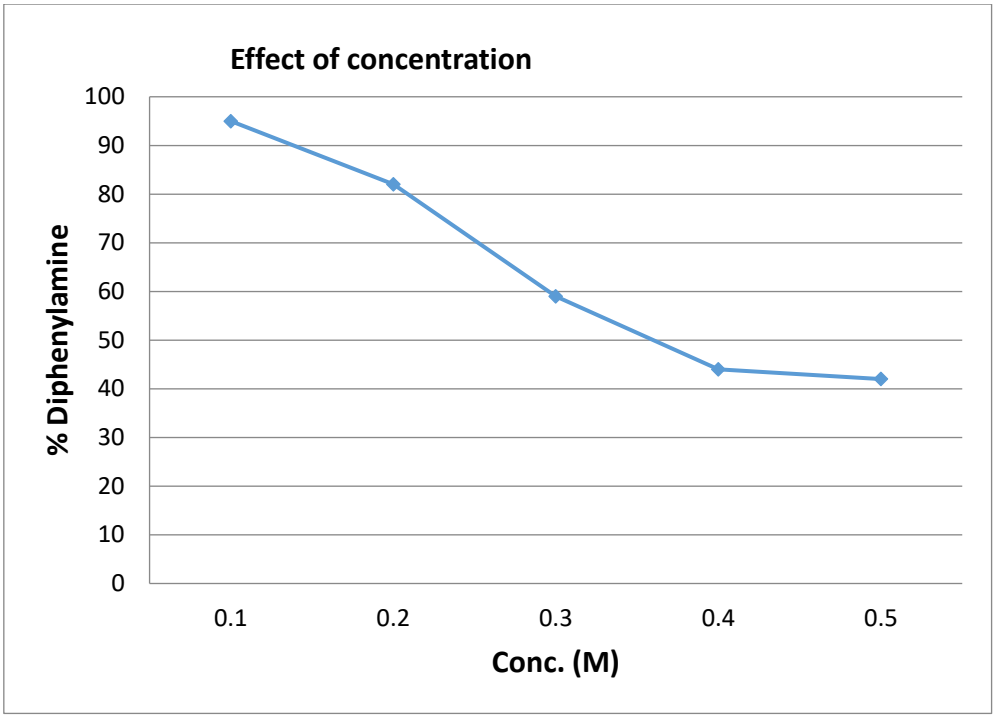


Figure 18: Effect of concentration on diphenylamine synthesis, flow rate 0.25 mL/min, 130 °C (n =1)

From these optimization reactions, the copper coil was found to give an excellent yield of diphenylamine. In order to improve the process still further the effect of concentration was therefore studied at the best conditions of 0.25 mL/min and 130 °C, it was found a concentration of 0.1 M of starting material diaryliodonium trifluoroacetae and aniline gave the highest yield, it was evident that as the concentration increased more starting material was left in the crude reaction mixture according to the HPLC analysis (Figure 18).

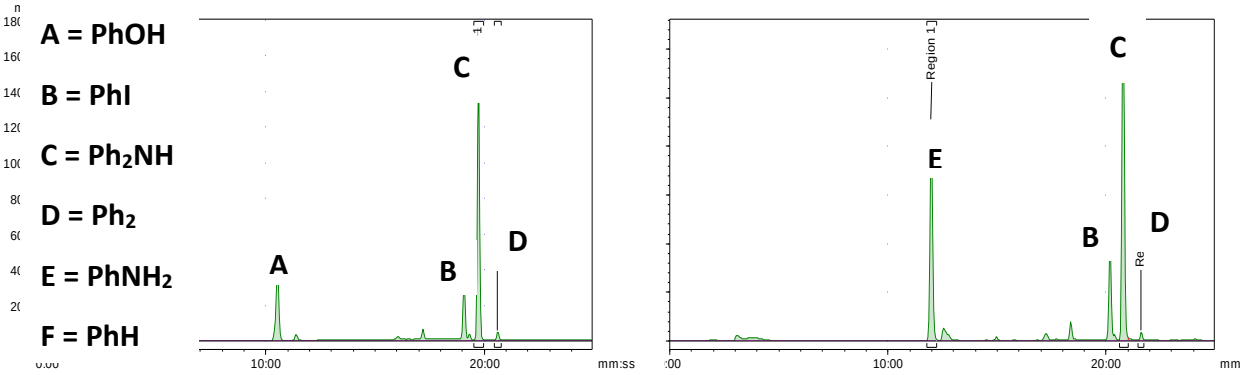


Figure 19: HPLC chromatogram of aniline reaction at 0.1 M (left), 0.4 M (right) at 130 °C, flow rate 0.25 mL/min, 130 °C.

For instance the HPLC chromatogram for the reaction mixture obtained using a concentration of 0.4 M, more of the staring material aniline (at retention time 13 min) was left in the reaction mixture (Figure 19) and as such the lower concentration was preferred.

2.4.4 Substrate control

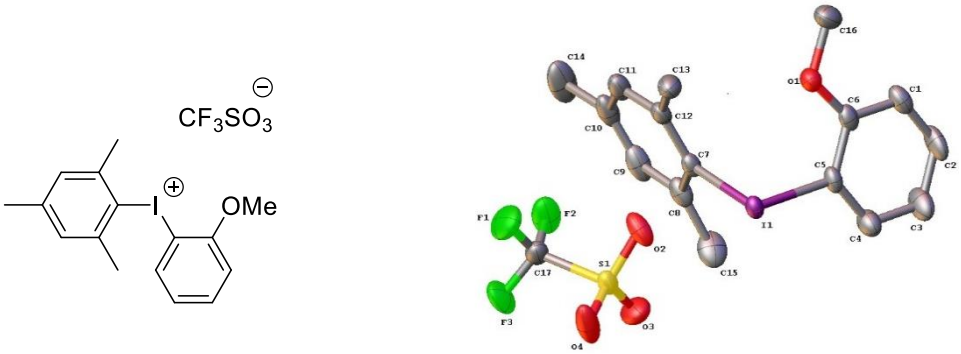


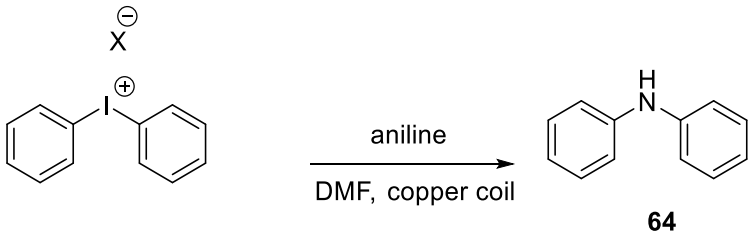
Figure 20: X-ray crystal structure of 2-methoxyphenyl(mesityl) triflate

Diaryliodonium salts, Ar_2IX, adopt a trigonal bipyramidal geometry[23] and it is the relative orientation of the two aromatic rings, in the transition state, which is critical in the arylation process (to note that the relative arrangement in the transition state may not always be the same as in the ground state as determined by X-ray crystallography). Preferential reaction occurs between the nucleophile/counter-ion (X) and the aromatic ring in the syn-position (pseudo-equatorial). Figure 20 shows the crystal structure of 2-

methoxyphenyl(mesityl)iodonium triflate, the 2-methoxylphenyl group is in the pseudo-axial position and the mesityl group in the pseudo-equatorial position.

2.4.5 Effect of counter ion

Table 5: Synthesis of diphenylamine using a diphenyliodonium salt with different counter ions



64

X	**64** (%) 130 °C (n = 3)	**64** (%) RT (n = 3)
TfO	90 ± 3 (**64a**)	51 ± 4(**64a**)
TsO	88 ± 5 (**64b**)	1 ± 1(**64b**)
TFA	92 ± 4 (**64c**)	94 ± 2(**64c**)

Diphenyliodonium salt (5 mmol), aniline (5 mmol), DMF (50 mL), flow rate 0.25 mL/min, 130 °C and RT.

The counter ion of the diaryliodonium salt may also influence the out-come of the reaction[232] and therefore a range of counter-ions were investigated at the optimised reaction conditions. Diphenyliodonium tosylate was prepared, and the diphenyliodonium triflate was commercially available, and as before the reaction was then performed at 130 °C and room temperature. The diphenyliodonium trifluoroacetate gave excellent yields of the product at both temperatures whereas diphenyliodonium triflate and diphenyliodonium tosylate gave diphenylamine in an excellent yield at 130 °C whereas at room temperature diphenyliodonium tosylate gave only a low yield of the product (about 2%). The diphenyliodonium triflate gave moderate yield at room temperature (51%) of diphenylamine, however it should be noted that with the reaction using diphenyliodonium tosylate the back pressure regulator became blocked probably due to the formation of tosic acid (Table 5) which may have influenced the

outcome or maybe due to the addition of counter ion to the iodonium rather than aniline. The effect of the counter-ion in the batch reactions has also been reported, indicating the trifluoroacetate was the best choice for both the fluoridation of diaryliodonium salts[17] and the reactions alkynyiodonium salts.[211]

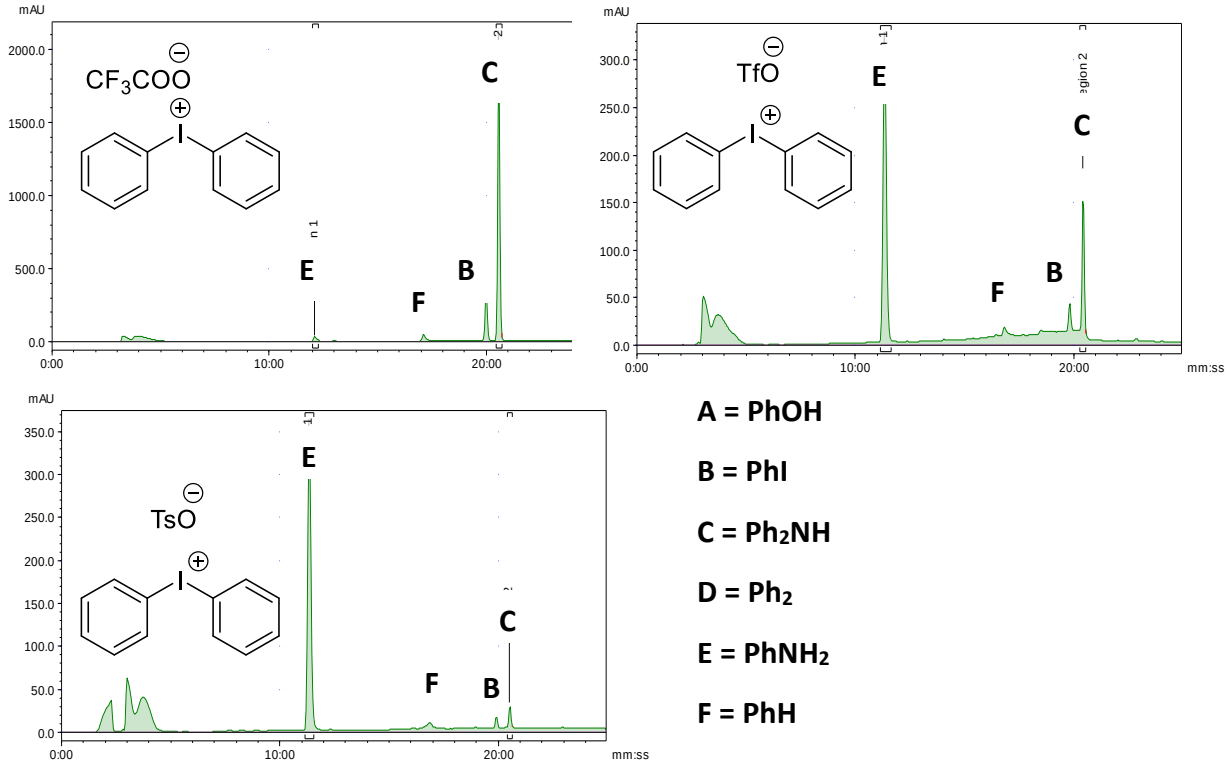


Figure 21: HPLC chromatogram of aniline and diphenyliodonium salts, diphenyliodonium salt (5 mmol), aniline (5 mmol), DMF (50 mL), flow rate 0.25 mL/min, RT.

The HPLC chromatogram of the reaction of diphenyliodonium trifluoroacetate with aniline at room temperature is very clean with traces of side-products evident therefore this substrate was able to perform the reaction at room temperature. The HPLC chromatogram for the reaction of the diphenyliodonium salt with the other counter-ions, triflate and tosylate shows a small peak for diphenylamine with the major peak present being unreacted aniline which would be expected given the lower yield of the product (Figure 21) suggesting that the nucleophilic addition step is more difficult in these cases, it may be due to the addition of counter ion to the iodonium rather than aniline or the diphenyl iodonium salt decompose before the addition of aniline to iodobenzene and triflic acid or tosic acid as it is not stable such as the counter ion trifluoroacetate.

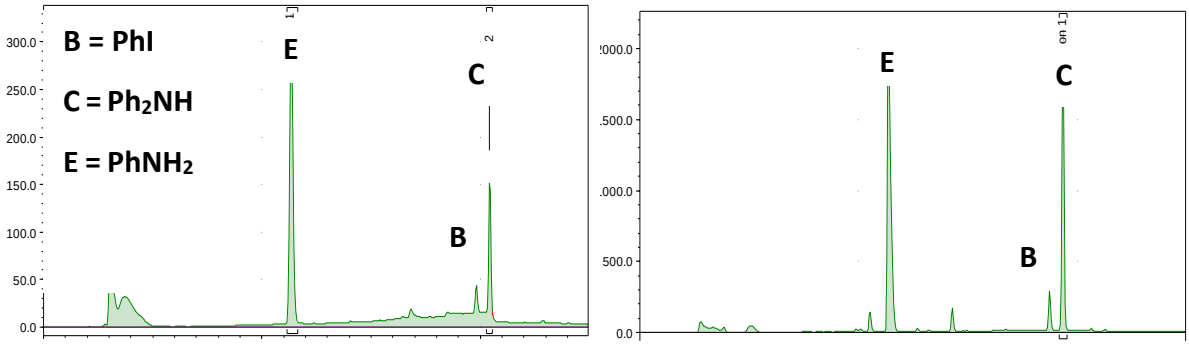
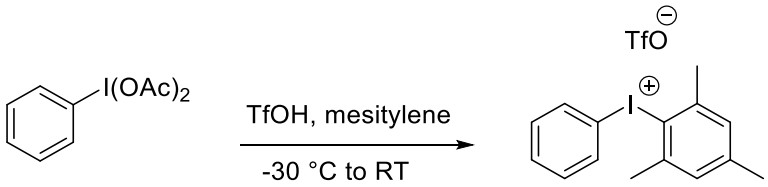


Figure 22: HPLC chromatogram of the reaction of aniline (5mmol) with diphenyliodonium triflate (5 mmol), anline (5 mmol) DMF (50 mL)at RT, flow rate 0.25 mL/min (left), under batch conditions (right), 24 h RT.

The reaction of diphenyliodonium triflate was also investigated under batch conditions at room temperature, and the reaction gave a similar yield (49%) to the reaction performed using the FlowSyn™ as shown in the HPLC chromatogram (Figure 22). Some starting material, aniline, is left which may be because the diphenyliodonium triflate decomposes at room temperature as it is less stable than diphenyliodonium trifluoroacetate as the starting material aniline has not reacted as it shown in Figure 22.

2.4.6 Synthesis of mesityl aryliodonium salts

Method A:

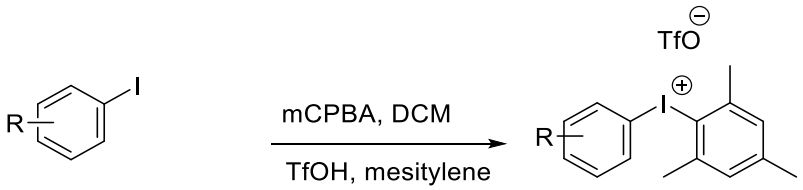


Scheme 100: Synthesis of mesityl(phenyl)iodonium triflate

The phenyl(mesityl)iodonium triflate was synthesised[2] to study the effect of steric factors on the reactions of aniline with diaryliodonium salts as the mesitylene group should provide high selectivity for controlling the reaction and only transferring the smaller group in the case of the copper catalysed process. The preparation was carried out by the reaction of iodobenzene biacetate and mesitylene in the presence of triflic acid, it gave a yield of 51% of the desired product (Scheme 100).

Method B

Table 6: Synthesis of mesityl(phenyl)iodonium triflate



Entry	R	Product %
1	H	76
2	4-Me	67
3	2-Me	81
4	4-OMe	2[a]
5	2-OMe	76
6	4-Cl	73
7	2-Cl	82

Aryliodide (7.77 mmol), mesitylene (7.77 mmol), *mCPBA* (7.77 mmol), TfOH (15.54 mmol), DCM (70 mL)

[a]Yield by crude ^{1}H NMR

An alternative procedure[3, 233, 234] is a one-pot synthesis using iodobenzene, mesitylene and an oxidant, such as *m*CPBA, the resultant product was recrystallized directly using ether and no further purification was necessary, this approach giving a higher yield than Method A at about 76% (Table 6).

Substituted phenyl(mesityl)iodonium triflates were also synthesised successfully using this method. *Ortho*- and *para*-electron-rich for instance 2-, or 4-methyl and electron-deficient substituents were used, all gave good yields of the desired product, surprisingly the presence of an electron-deficient group at the *ortho*-position also gave a good yield of the product, for instance 2-chloroiodobenzene gave the diaryliodonium salt in 82% yield.

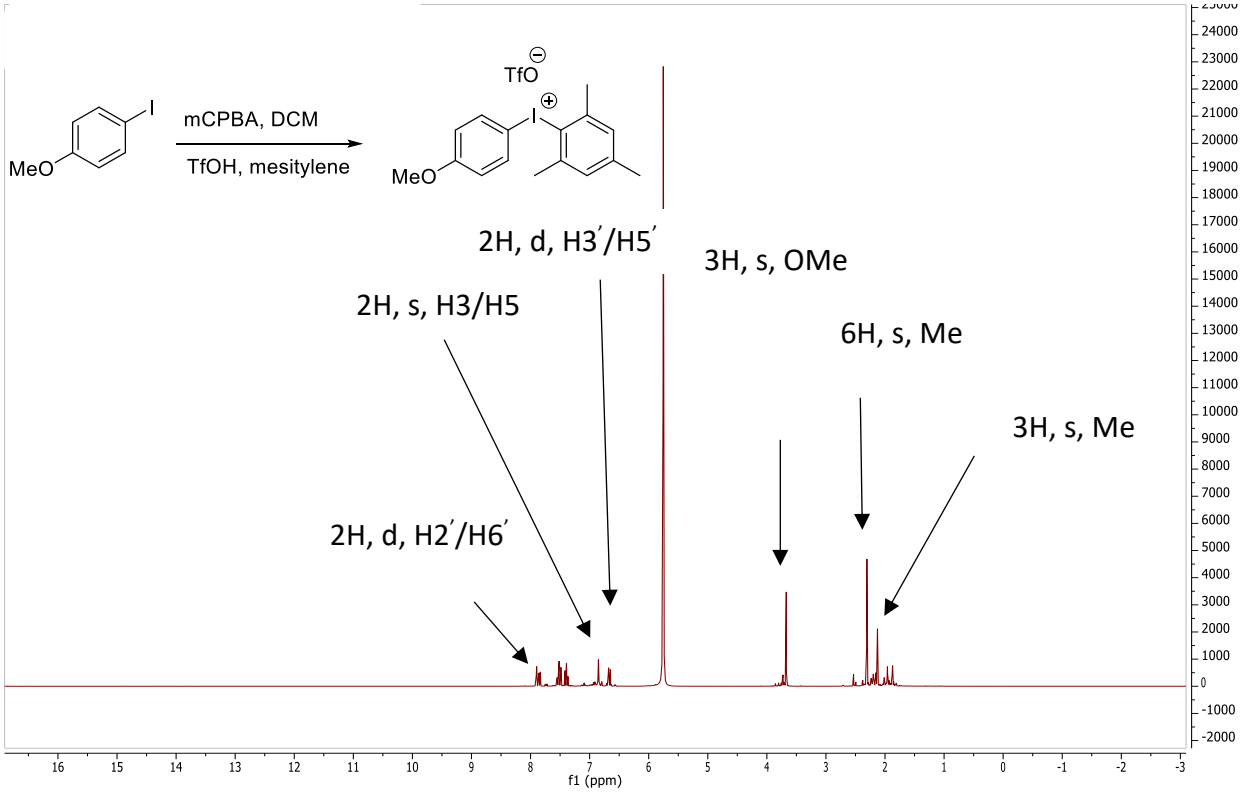
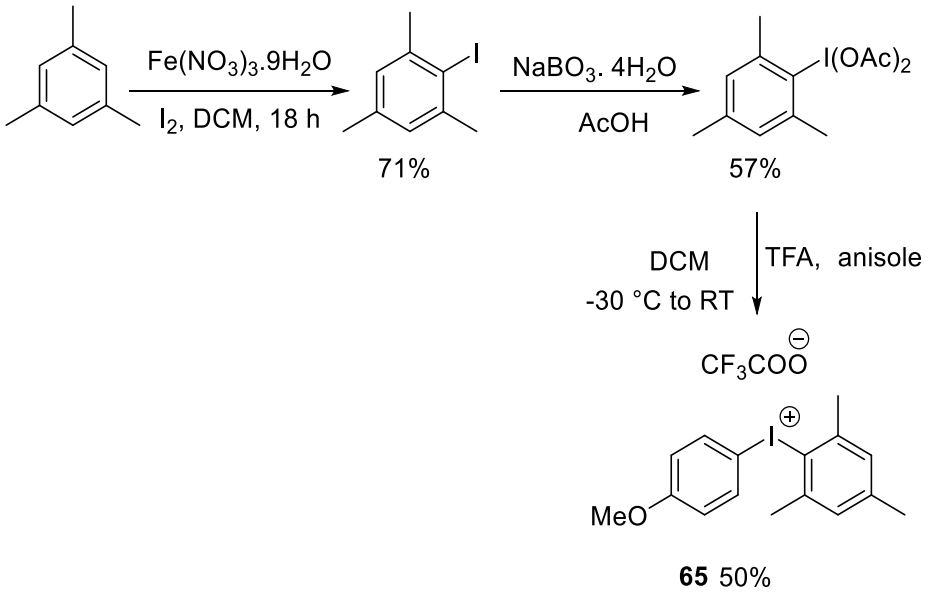


Figure 23: ^{1}H NMR of the crude reaction of synthesis 4-methoxyphenyl(mesityl)iodonium triflate

It is noted that when using anisole (entry 4, Table 6) only 2% product, even though the reaction was run at -75 °C, the reaction mixture turned black highlighting the lack of the stability of electron-rich diaryliodonium triflates under the reaction conditions or may be due to the 4-methoxy iodine (III) species generated in situ is less stable regenerating iodine and 4-methoxybenzene, the ^{1}H NMR analysis of the crude reaction confirmed about 2% of the desired product was present but it was not possible to isolate the desired product (Figure 23). Therefore an attempt to synthesis 4-methoxyphenyl(mesityl)iodonium triflate was made using method A which also proved unsuitable.

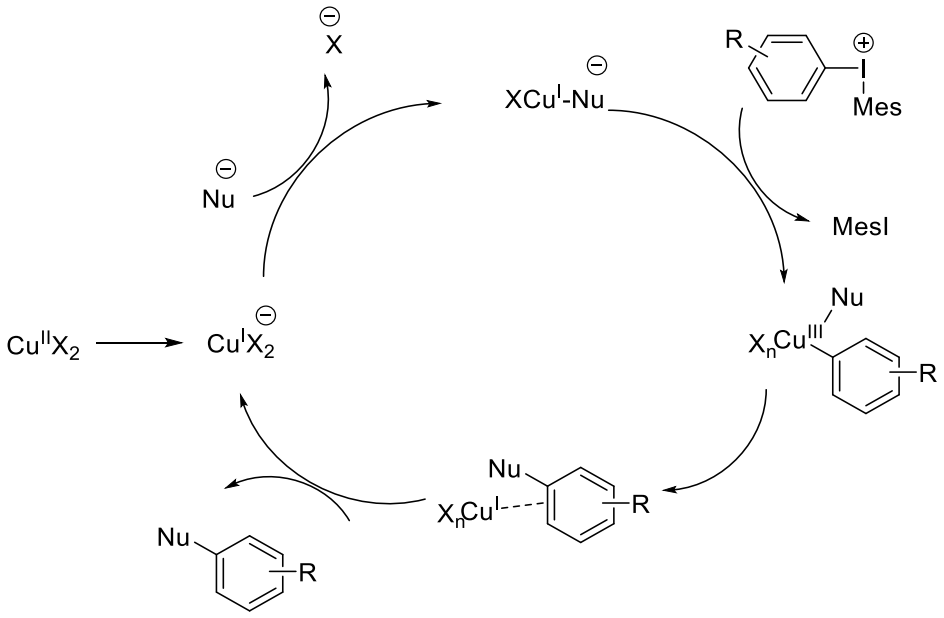
2.4.7 Synthesis of 4-methoxyphenyl(mesityl)iodonium trifluoroacetate (65)



Scheme 101: Synthesis of 65

As the synthesis of 4-methoxyphenyl(mesityl)iodonium triflate **65** was not successful using the above methods it was decided to prepare the trifluoroacetate derivative as they have been shown to be much more stable than the corresponding triflate. Using iodomesitylene diacetate which prepared from iodomesitylene (formed by iodination of mesitylene) acetic acid and sodium perborate, as show in Scheme 101, the reaction was successful and gave a yield of 50% of the desired product demonstrating the increased stability of the trifluoroacetate salts.

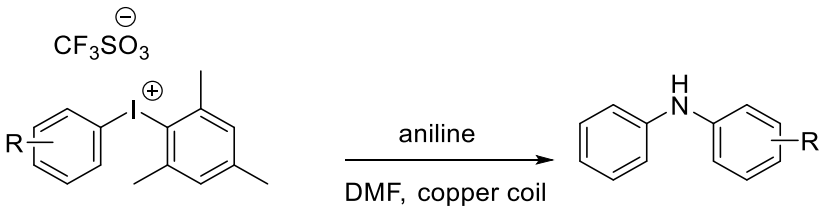
2.4.8 Diphenylamine synthesis using mesityl(aryl)iodonium salt using the FlowSyn™



Scheme 102: Proposed mechanism of copper catalysis using mesityl(phenyl)iodonium salts[235]

Diphenylamine has been synthesised from mesityl(phenyl)iodonium triflates and aniline using the FlowSyn™ at the optimized conditions of 0.25 mL/min at both 130 °C and room temperature. Arylation of the mesityl group has not been included in the process as this is copper catalysed mechanism which has been shown to be selective for the least hindered ring (Scheme 102).[138, 235, 236]

Table 7: Synthesis of diphenylamine using mesitylene aryliodonium triflate



Entry	R	RT (%)	130 °C (%)[a,b]
1	H	84	72 (67)
2	4-Me	4	86 (75)
3	2-Me	38	75 (64)
4	2-OMe	4	86 (73)
5	4-Cl	4	75 (65)
6	2-Cl	2	67 (56)

Diaryliodonium triflate (5 mmol), aniline (5 mmol), DMF (50 mL), 0.25 mL/min, in flow

[a]Yields by HPLC, [b] isolated yield in parenthesis

The reaction was also carried out with the substituents of phenyl(mesityl)iodonium triflates, with the less hindered group is transferred to the aniline, the reaction at room temperature gave low yields of the product but higher yields were obtained at 130 °C. As discussed earlier the diphenyliodonium triflate also gave a low yield at room temperature, those reagents with more electron-rich groups gave slightly higher yields than those with substrates bearing electron-deficient groups (Table 7).

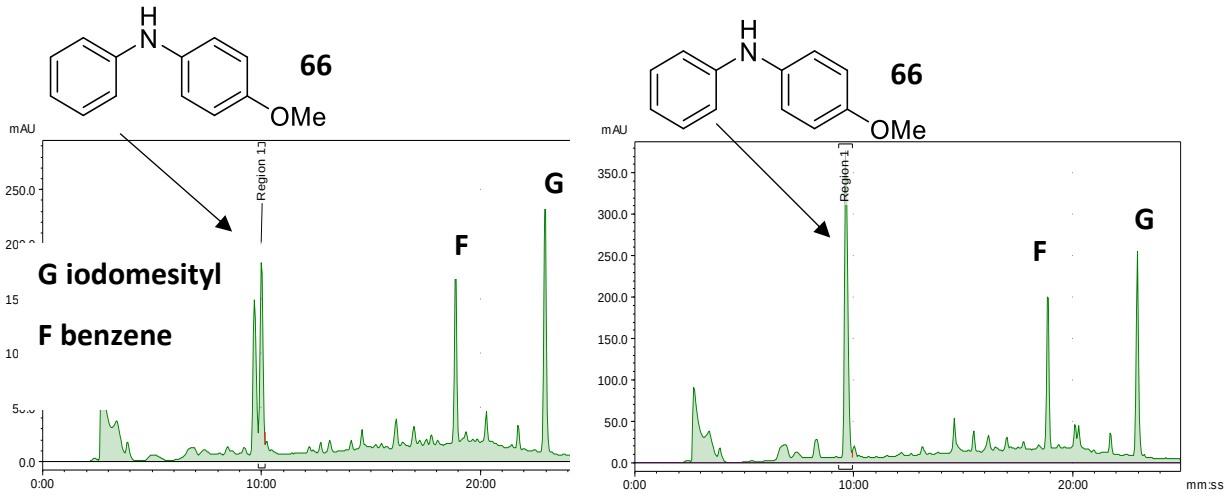
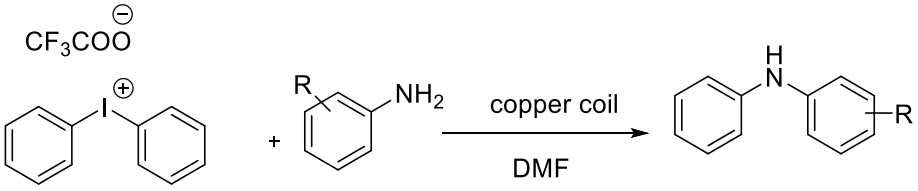


Figure 24: Chromatogram of formation of 4-methoxydiphenylamine at RT (left) and 130 °C (right), 4-methoxyphenyl(mesityl)iodonium trifluoroacetate (5 mmol), aniline (5 mmol), DMF (50 ml), flow rate 0.25 mL/min.

Synthesis of 4-methoxydiphenylamine **66** from 4-methoxyphenyl(mesityl)iodonium trifluoroacetate **65** and aniline has given only a 23% yield of the desired product as there is more formation of by-products at both room temperature and 130 °C, probably due to the lower stability of the electron-rich intermediates. The reaction gave a low yield of the product at room temperature due to the lack stability and therefore the faster decomposition pathway is preferred (Figure 24).

2.4.9 Synthesis of analogues of diphenylamine using the FlowSyn™

Table 8: synthesis of analogues of diphenylamine



Entry	R	Yield at RT (%)[a,b]	Yield at 130 °C (%)
1	H	72 (67)	84
2	4-F	96 (83)	80
3	4-Cl	81 (72)	70
4	4-Br	78 (73)	67
5	4-NO_2	73 (64)	65
6	4-OMe	88 (78)	81
7	3,5-$(OMe)_2$	92 (83)	78
8	3,4-$(OMe)_2$	86 (79)	79
9	2,4,6-Me_3	95 (81)	87
10	2-t-Bu	89 (81)	78
11	1-naphthaleneamine	77 (66)	70

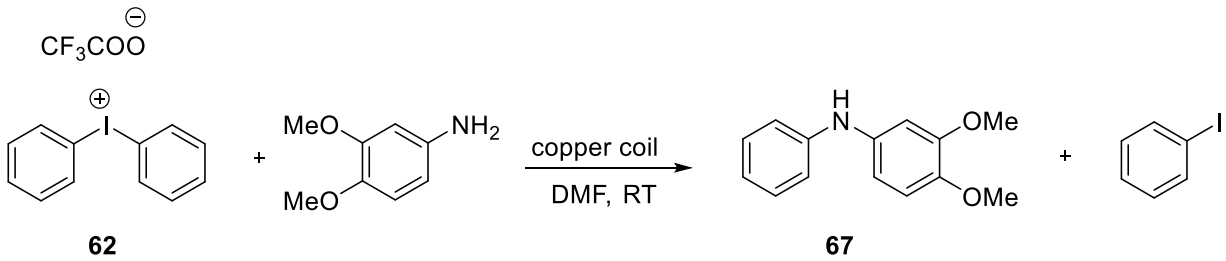
Diaryliodonium trifluoroacetate (5 mmol), $ArNH_2$ (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

[a] Yields by HPLC, [b] isolated yield in parenthesis

Synthesis of a range of diphenylamines was successfully carried out using the FlowSyn™ under the optimised condition of 0.25 mL/min at both temperature 130 °C and room temperature. A series of anilines was investigated with electron-deficient, electron-rich and bulky substituents and all were successful (Table 8). The reaction gave excellent yields of the desired product and there was no significant difference between any of the substituents at either temperature. As this process used a symmetrical diaryliodonium salt no chemoselectivity was

observed. As shown in Table 8, for instance 4-fluoroaniline (entry 2) gave the product in a 83% yield, 4-chloroaniline (entry 3) gave 72% and the presence of a very electron-deficient group, for example 4-nitroaniline (entry 5), still gave the product in a moderate yield of 64%. The electron-rich derivatives (entries 6, 7, 8) gave excellent yields of the products. The hindered and bulky aniline (entry 9 and 10) gave 81% and 66% respectively of the desired product with the 2-t-Bu (entry 10) giving the desired product in 81% yield.

2.4.10 Scale up of 3,4-dimethoxydiphenylamine (67)



62 67

Scheme 103: Synthesis of 3, 4-methoxydiphenylamine (67)

We have shown that diaryliodonium salts are suitable arylating agents for a range of substrates, including anilines, but this process required extended reaction times (24 h) limiting its application. The processes we have developed allows the production of these materials at room temperature using a copper coil as both catalyst and reactor thereby allowing the

formation a range of diarylamines under more practical conditions. One of the benefits of flow chemistry is the potential to scale-up the process without any additional optimization of the reaction conditions and we have demonstrated this through the production of larger amounts of 3,4-dimethoxydiphenylamine (Table , entry 8) simply by running the system for longer.

This was achieved by using diphenyliodonium trifluoroacetate (13.79 g, 35 mmol) dissolved in dimethylformamide (175 mL) and 3,4-dimethoxyaniline (5.36 g, 35 mmol) also dissolved in dimethylformamide (175 mL). The FlowSyn™ was fitted with a 20 mL copper reactor coil and the two reagent solutions were passed through a T-mixer, the copper coil and then a fixed back pressure regulator (100 psi) at room temperature. The outflow of the reactor was directed into an Erlenmeyer flask (5.0 L) containing water (2.5 L) that was continually stirred using a magnetic stirrer.

Table 9

	Mass Recovered	**Yield**	**^{1}H NMR purity**
Run 1	6.21 g	80%	>98%
Run 2	6.11 g	78%	>98%
Run 3	6.23 g	81%	>98%

Diphenyliodonium trifluoroacetate (35 mmol), 3,4-dimethoxyaniline (35 mmol), DMF (350 mL), 0.25 mL/min, RT

Once the reagent solutions had passed into the reactor the inlet valves were switched to just solvent and pumped for 15 min (30 mL) to allow all of the reaction mixture to pass through the reactor, the contents of the Erlenmeyer flask (reaction mixture and water) was filtered and the precipitate washed with water (500 mL) and then with petrol (500 mL). The precipitate was then dissolved in ether (1500 mL) and concentrated under reduced pressure to give the product as a dark brown solid which on a single crystallisation (diethylether–petrol) provided the pure product. The reaction gave high yields of the product (see Table 9).[237]

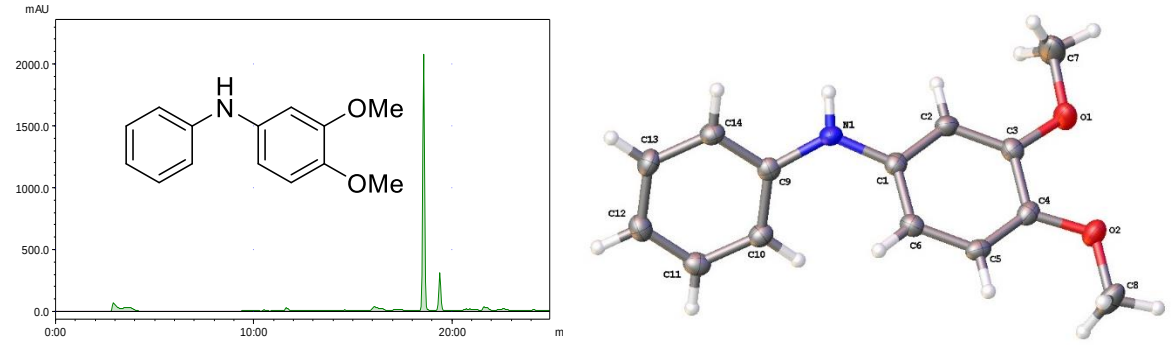


Figure 25: HPLC chromatogram of crude 3,4-dimethoxydiphenylamine 67 (left) and x-ray crystal structure of the product(right), diphenyliodonium trifluoroacetate (35 mmol), 3,4-dimethoxydiphenylamine (35 mmol), DMF (350 mL), 0.25 mL/min, RT

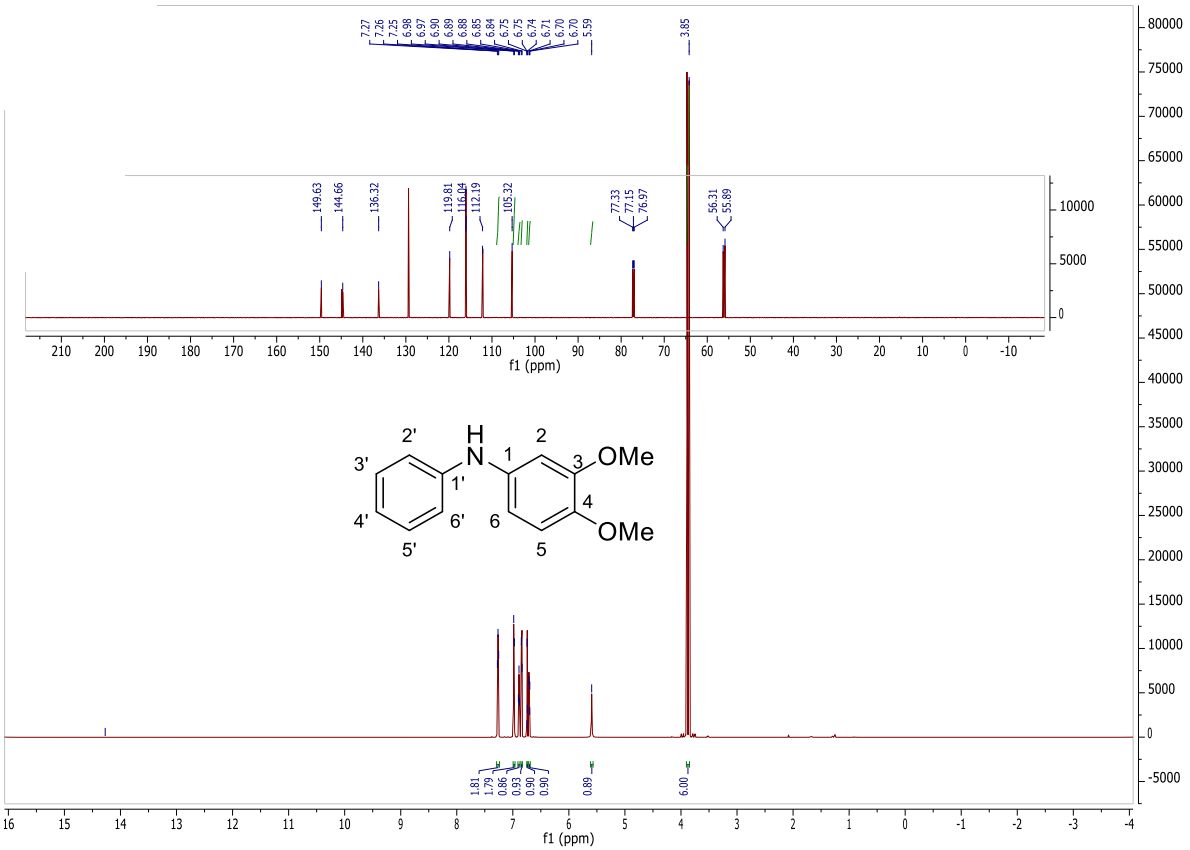


Figure 26: ^{1}H NMR and ^{13}C NMR of 3,4-dimethoxydiphenylamine after washing with ether

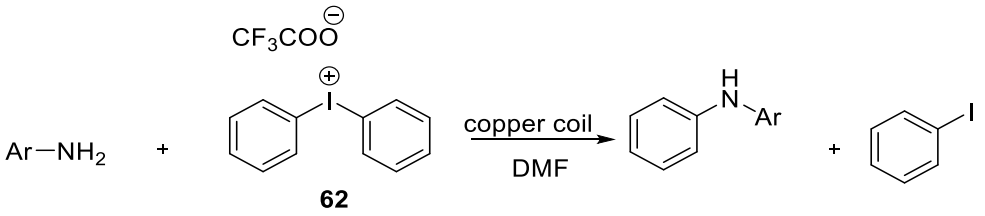
The reaction was run three times and gave a consistent high yield of the desired product, the purity and identity of the material was proven by the analytical data (NMR and HPLC) and

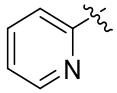
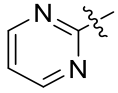
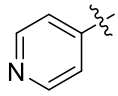
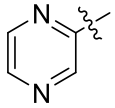
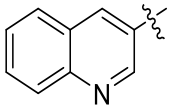
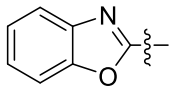
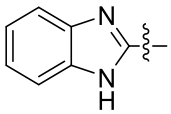
determination of the crystal structure (Figures 25 and 26). For assignment of the NMR data see Section 4.19).

2.4.11 Synthesis of diarylamines using heteroaromatic amines

As the optimized conditions were successfully applied to aniline and its derivatives at room temperature and 130 °C we then decided to investigate some of the heteroaromatic amines in order to determine the range of the process.

Table 10: Synthesis of heteroaromatic amines



Entry	Ar	Isolated yield at 130 °C, %
1		43
2		69
3		75
4		69
5		61
6		43
7		9[a]

Diphenyliodonium trifluoroacetate (5 mmol), $HetNH_2$ (5 mmol), DMF (50 mL), 0.25 mL/min, 130 °C, [a] Yield by HPLC

As shown in Table 10, both aminopyridines were successful with the 2-aminopyridine (entry 1) giving a lower yield than 4-aminopyridine (entry 3) at 43% and 75% respectively, probably due to the increased steric hindrance due to the *ortho*-substituent. However 2-

aminopyrimidine (entry 2) gave 69% of the desired product, as did 2-aminopyrazine. (entry 4) 3-Aminoquinoline (entry 5) gave 61% whereas the 2-aminobenzoxazole (entry 6) gave 43% of the product indicating that the process was compatible with a range of heteroaromatic amines.

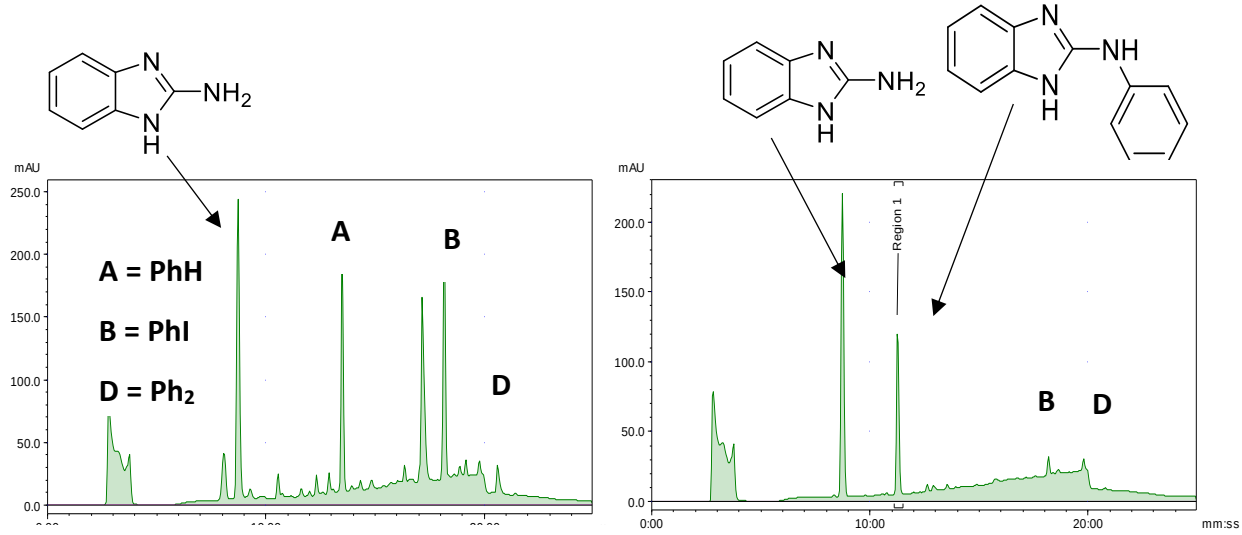


Figure 27: HPLC chromatogram of reaction 2-aminobenzimidazole at RT (left) and 130 °C (right), diphenyliodonium trifluoroacetate (5 mmol), 2-aminobenzimidazole (5 mmol), DMF (50 mL), 0.25 mL/min.

The 2-aminobenzimidazole gave 9% of the desired product when analysed by HPLC however no product could be isolated. There is also the possibility of alternative *N*-arylation sites however the primary amine would be expected to be preferred.

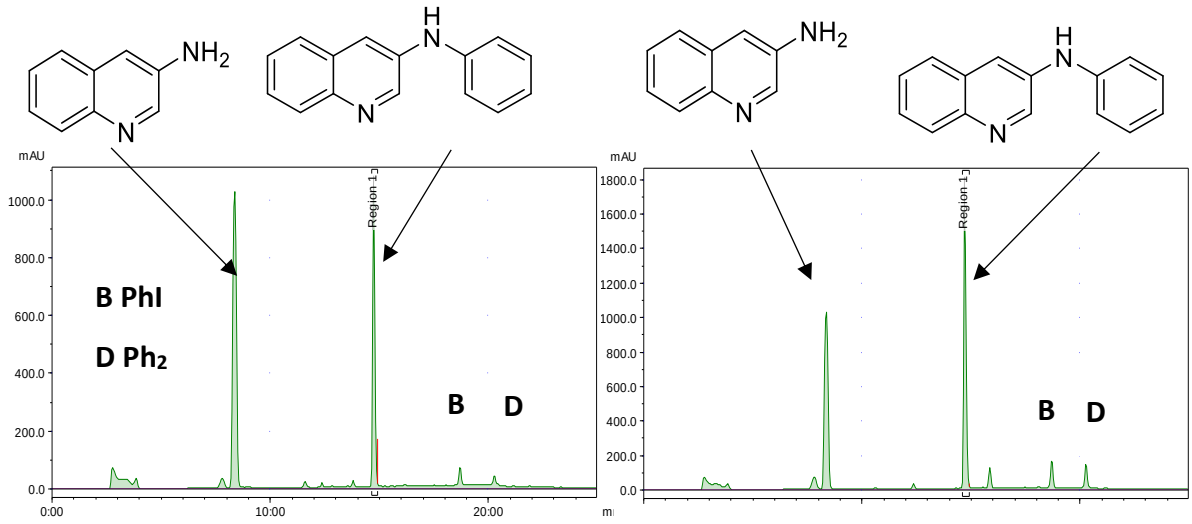
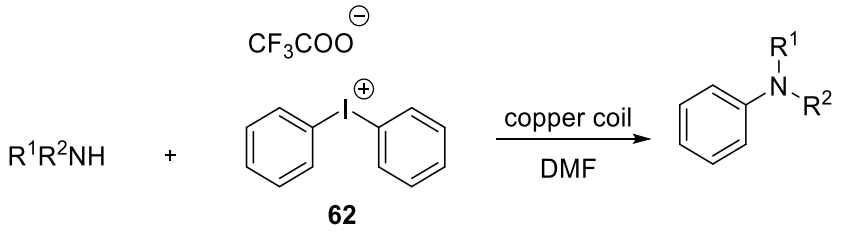


Figure 28: Chromatogram of reaction 3-aminoquinoline at RT (left) and 130 °C (right), diphenyliodonium trifluoroacetate (5 mmol), 3-aminoquinoline (5 mmol), DMF (50 mL), 0.25 mL/min.

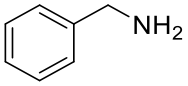
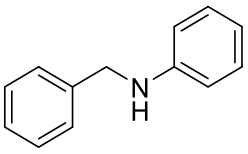
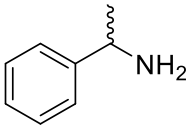
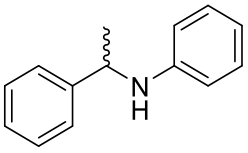
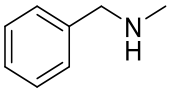
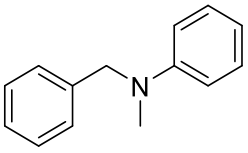
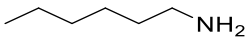
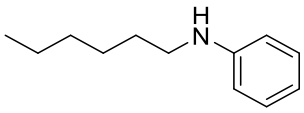
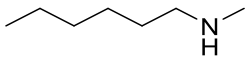
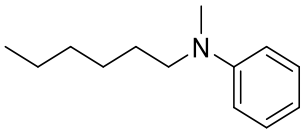
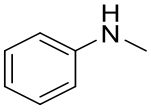
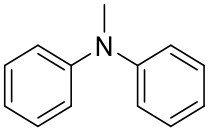
The reaction was also performed at room temperature but the yield was slightly lower than 130 °C, for instance the reaction of 3-aminoquinoline gave 56% at room temperature and 61% of the desired product at 130 °C as there was more starting material left in the reaction mixture at room temperature (Figure 28).

2.4.12 Synthesis of *N*-benzylaniline, *N*-alkylaniline and diphenylamine using arylhalide

Table 11: Synthesis of *N*-benzylaniline, *N*-alkylamine and diphenylamine using diphenyliodonium trifluoroacetate



62

Entry	R^1R^2NH	Product	130 °C (%)[a,b]
1			79 (74)
2			96 (83)
3			87 (74)
4			85 (72)
5			82 (67)
6			55 (52)

Diphenyliodonium trifluoroacetate (5 mmol), $ArNH_2$ (5 mmol), DMF (50 mL),flow rate 0.25 mL/min, 130 °C, [a] Yields by HPLC, [b]Isolated yield in parenthesis

As mentioned in Section 2.3, the synthesis of *N*-arylamines has been reported using a copper coil as both reactor and catalyst and an aryl halide,[223] with tetra-n-butylammonium acetate (TBAA) present as a base, therefore we carried out the synthesis of *N*-phenylbenzylamine using diphenyliodonium trifluoroacetate and the copper coil flow reactor. The reaction was successful at 130 °C and gave a high yield of the desired product (Table 11, entry 1), however when using *N*-methylaniline a low yield was obtained compared to aniline suggesting that primary aromatic amines are much more reactive than secondary derivatives. *N*-methylhexylamine gave 67% yield of the product (entry 5) whereas the primary amine, hexylamine, gave 72% of the desired product (entry 4) probably due to an increase in steric hindrance however, unlike the aromatic amines, there is little difference in the case of aliphatic amines.

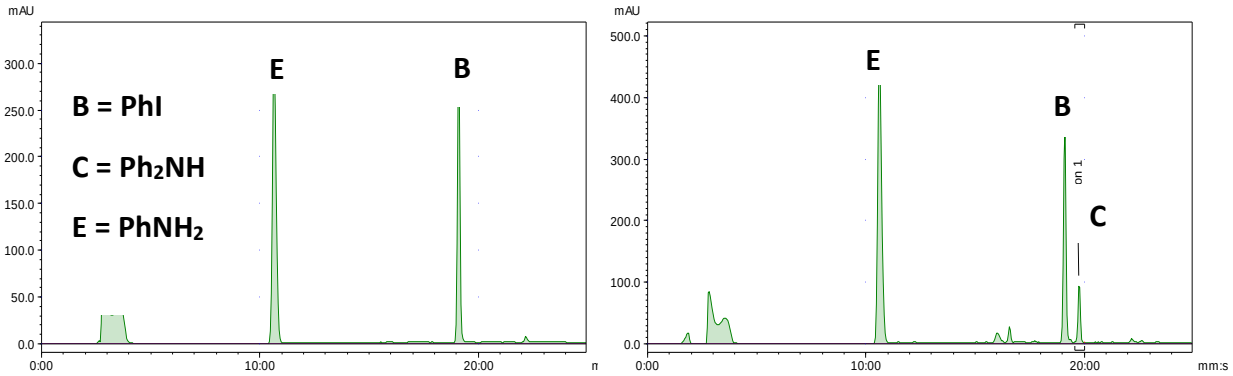
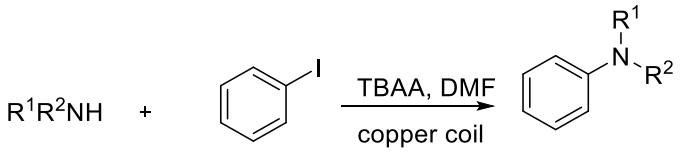
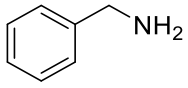
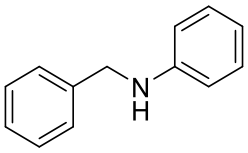
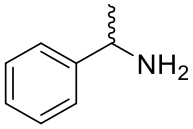
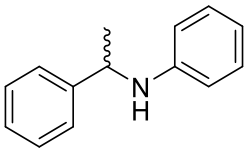
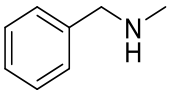
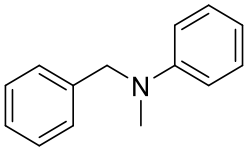
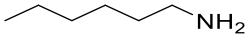
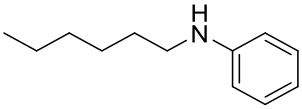
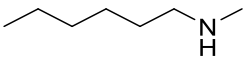
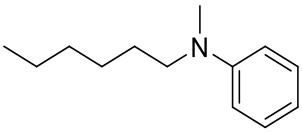
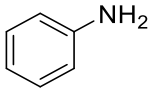
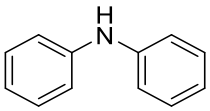
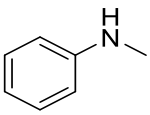
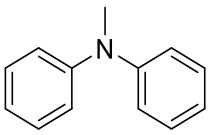


Figure 29: HPLC chromatogram of reaction aniline and iodobenzene at 130 °C (left) and 230 °C (right), diphenyliodonium trifluoroacetate (5 mmol), ainline (5 mmol), DMF (50 mL), flow rate 0.25 mL/min

We also examined the direct reaction of aniline with iodobenzene under these conditions as PhI may be acting as the arylating agent rather than the diphenyliodonium salt however the results indicate that the reaction did not occur at 130 °C but was possible at 230 °C which gave about 7% of diphenylamine by HPLC analysis. These results confirm that the diaryliodonium salt is indeed the arylating agent supporting the mechanistic rationale (increased electrophilic character of the hypervalent iodine reagent facilitating the addition of the nucleophile and enhanced leaving group ability of iodobenzene compared to iodide).

Table 12: Synthesis of *N*-benzylaniline, *N*-alkylamine and diphenylamine using arylhalide



Entry	R^1R^2NH	Product	Yield by HPLC 130 °C (%)
1			57
2			7
3			2
4			66
5			1
6			8
7			0

Iodobenzene (5 mmol), R^1R^2NH (5 mmol), TBAA (5.5 mmol), DMF (50 mL), flow rate 0.25 mL/min, 130 °C

As the reaction was attempted using just iodobenzene and without any additive, the reaction was also carried out using added base (e.g. TBAA) following the literature conditions to determine if this had an influence on the outcome. The reaction gave a moderate yield of some products, albeit lower than using diphenyliodonium trifluoroacetate on its own at 130 °C, while the TBAA containing reaction at room temperature gave no product at all. As shown in Table 12, benzylamine (entry 1) gave a moderate yield of the product 57% whereas entries 2, 3, 5 gave very low yields again suggesting that the diaryliodonium salt is the critical reagent, particularly giving the outcome of the reactions carried out at room temperature. The less reactive aromatic amines (entries 6 and 7) are less nucleophilic and more sensitive to the reactivity of the arylating agent and as a result only trace amounts of product was formed with aniline and no product at all with *N*-methylaniline.

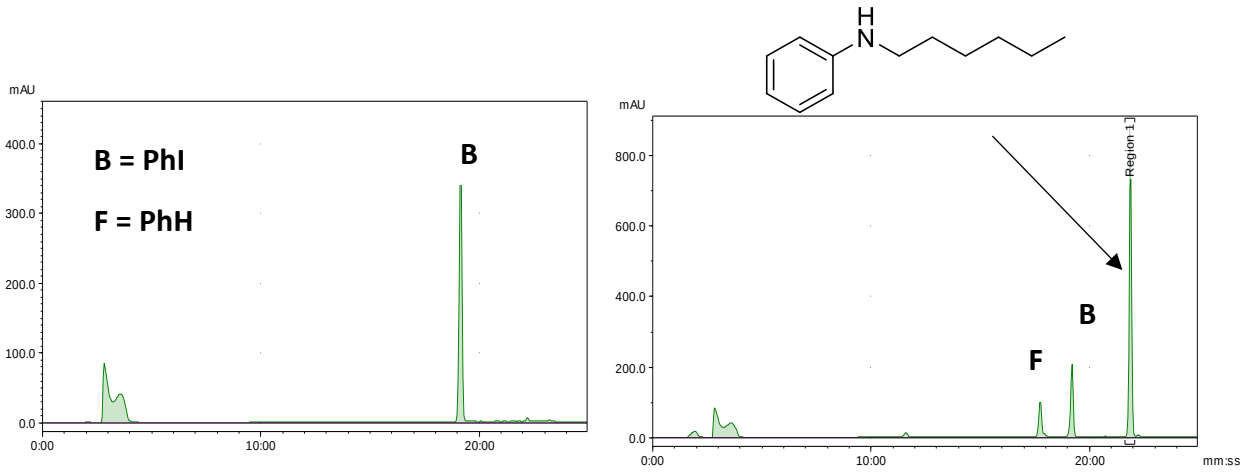


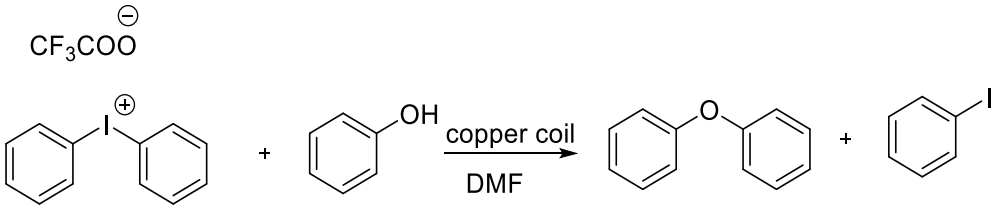
Figure 30: HPLC chromatogram of reaction hexylamine and iodobenzene at RT (left) and 130 °C (right) diphenyliodonium trifluoroacetate (5 mmol), hexaylamine (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

All the reactions did not work at room temperature for instance the HPLC chromatogram from the reaction with hexylamine shows no formation of product, it only shows the peak for the starting material iodobenzene and as hexylamine is not UV active, it does not show in the chromatogram (Figure 30).

2.4.13 Synthesis of diarylamines: Summary

In summary, we have developed the first practical method for the synthesis of diarylamines using diaryliodonium salts. Unlike the literature methods for the synthesis of diarylamines, our method does not use a base or any additive thereby simplifying the process. The reactions were also largely carried out at room temperature and thus do not require heating, in addition the reaction time was improved from 24 h to 80 min.

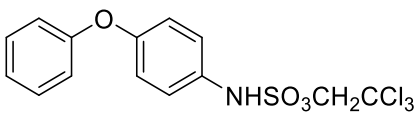
2.5 Synthesis of diarylethers



62 **68**

Scheme 104: Synthesis of diarylether

The next step in the development of this methodology was to transition from *N* to *O*-nucleophiles as a range of diarylamines were successfully synthesised. The synthesis of diarylethers was also investigated in the similar manner to the diphenylamine using the FlowSyn™ in combination with the copper coil reactor, as discussed earlier in the section (1.8.1), the functionality is widespread in pharmaceuticals, for example in the anti-cancer agents which act as sulfatase-2 inhibitors **69** (Figure 31).[238]



Sulfatase-2 inhibitor

69

Figure 31: Biological compound contain arylether

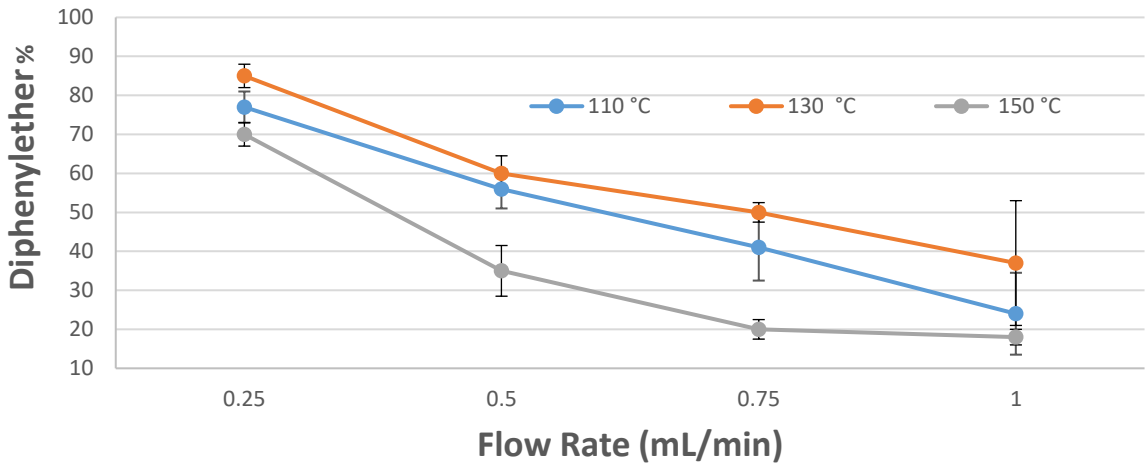
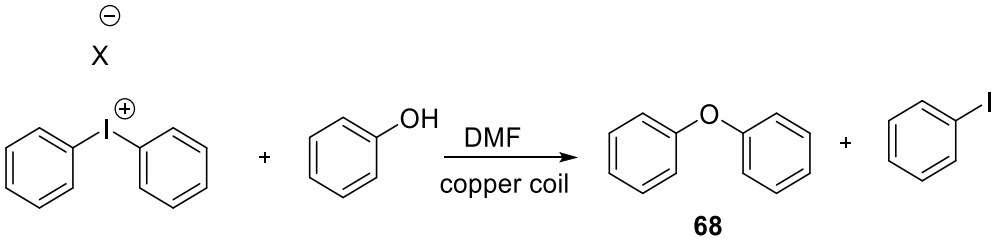


Figure 32: Optimization of the production of 68 (n = 3) diphenyliodonium trifluoroacetate (5 mmol), phenol (5 mmol), DMF (50 mL).

From the data shown in Figure 32, the best conditions are 0.25 mL/min and 130 °C, the same for the preparation diarylamines as it gave the highest yield of the product. As the flow rate increased the yield of diarylether decreased, increasing temperature also led to a decrease in the yield of the product probably through facilitating the thermal decomposition pathway. The Olofsson group have used diaryliodonium triflates in the formation of diarylethers therefore we examined the effect of counter ion on the reaction given the advantages demonstrated for the trifluoroacetate counter-ion in the formation of diarylamines.

2.5.1 Effect of counter ion

Table 13: Synthesis of diphenylether using diphenyliodonium salts



68

X	68 (%) RT (n = 3)	68 (%) 130 °C (n = 3)
TfO	19 ± 4	42 ± 3
TsO	7 ± 1	23 ± 5
TFA	62 ± 2	85 ± 4

Diphenyliodonium salt (5 mmol), phenol (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

As shown in Table 13, the reaction of diphenyliodonium salts with three different counter ions were run at the conditions defined earlier (flow rate 0.25 mL/min) and at temperatures of 130 °C and room temperature. From the results for the reactions at 130 °C the counter ion trifluoroacetate gave highest yield 85% with the triflate, tosylate giving diphenylether at 42% and 23% respectively. The reaction was also run at room temperature and these conditions gave a much lower yield than those carried out with 130 °C with only the diphenyliodonium trifluoroacetate giving a practical yield of 62 % yield. The counter-ions, triflate and tosylate gave only very low yields of the product at room temperature which is the same trend observed for the *N*-nucleophiles further demonstrating the importance of the trifluoroacetate counter-ion under these mild reaction conditions.

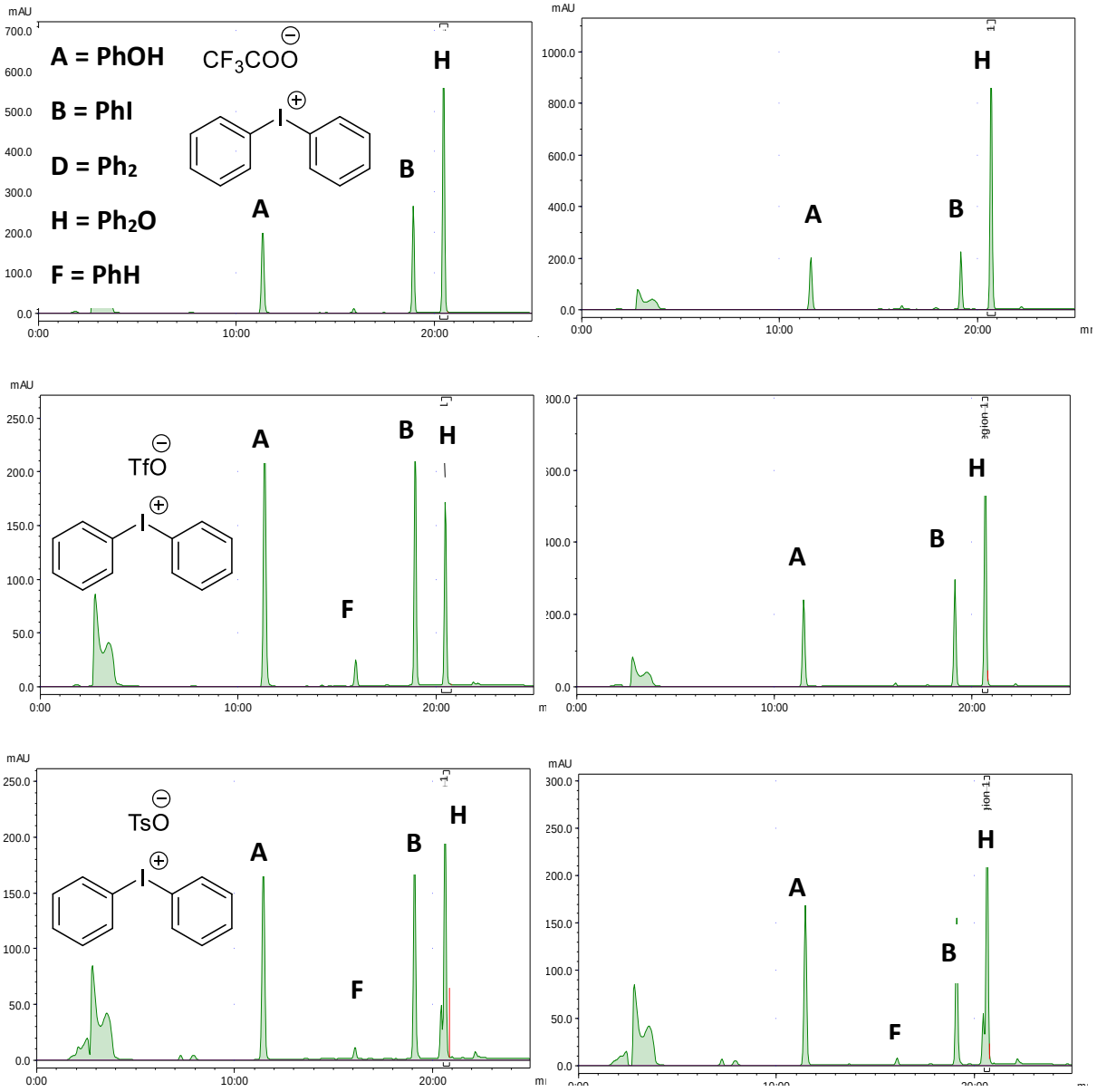
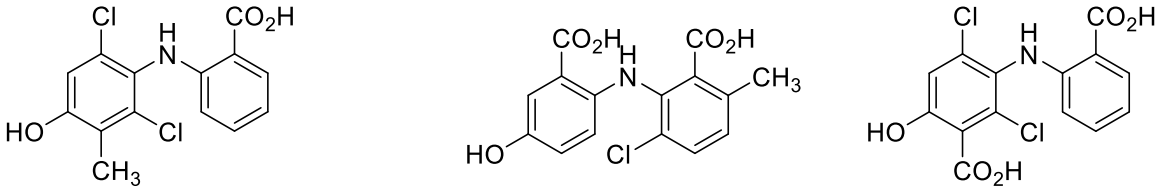


Figure 33: HPLC chromatogram of reaction diphenyliodonium salts and phenol at RT (left) and 130 °C (right) diphenyliodonium salt (5 mmol), phenol (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

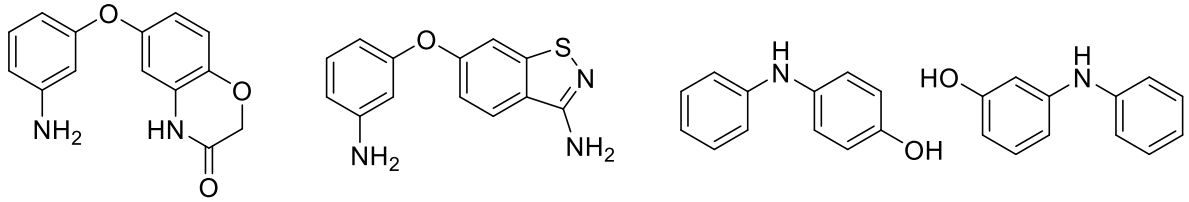
The HPLC chromatogram of the reactions of diphenyliodonium triflate at 130 °C, and at room temperature, show more of starting material, phenol, remains in the reaction (Figure 33). When phenol was mixed with iodobenzene, rather than the diphenyliodonium salt, at the optimized reaction conditions (flow rate 0.25 mL/min and 130 °C) no product was observed by the HPLC analysis. In a similar fashion to the *N*-arylation reactions it was possible that

phenol would react directly with iodobenzene and this result demonstrates that this is not the case.

2.5.2 Selectivity of *N*, *O*-nucleophile



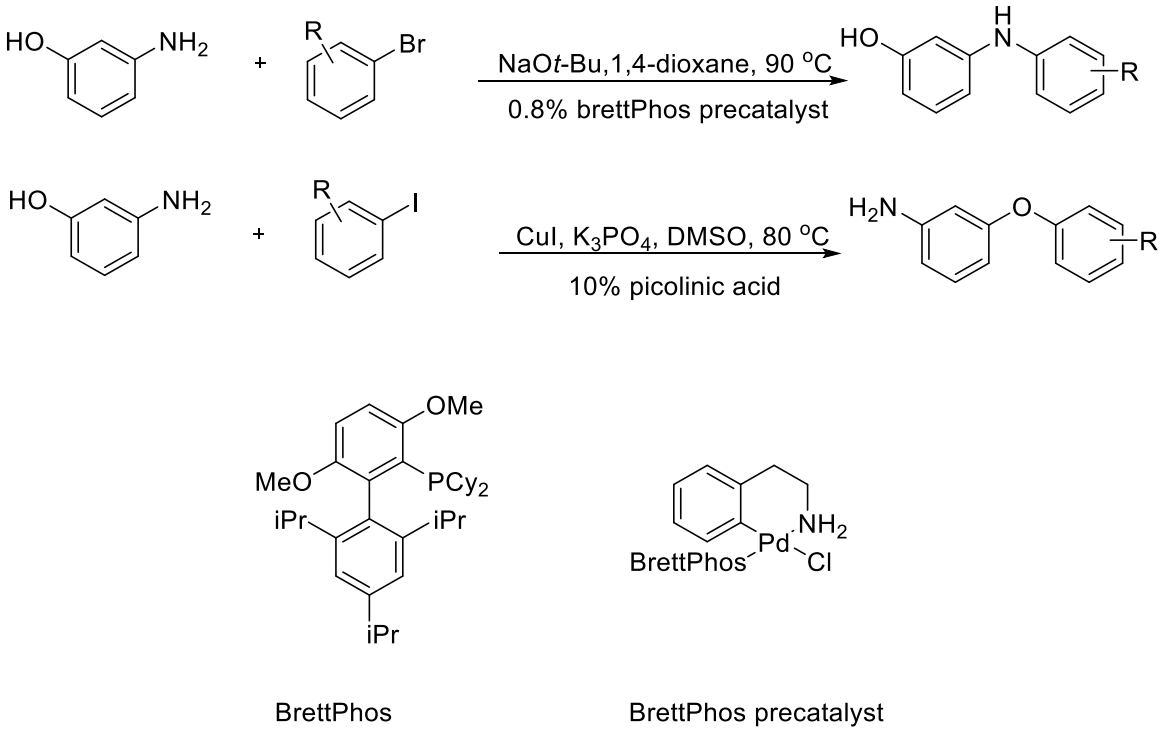
Human urinary metabolites of meclomen, used for neurodegenerative disorder treatment



angiogenesis treatment | theraputic agent (endothelial disorder) | scald protection | oxidative hair-dyeing agent

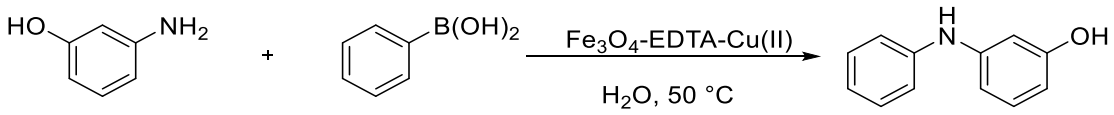
Figure 33: *N*- and *O*-arylated aminophenol derivatives[239]

As we have successfully synthesised both diarylamines and diarylethers using diaryliodonium salts in a continuous process we decided to study the *N*,*O*-selectivity of this process under these conditions, as a number of potential targets for this methodology have both type of nucleophile present (for example see over Figure 33)[239] yet the reaction and hence di functional substrates remain unstudied using Flow chemistry however recent study has highlighted the regioselectivity of synthesis *N*-arylquinolones and *O*-quinolines under metal-free batch conditions.[240]



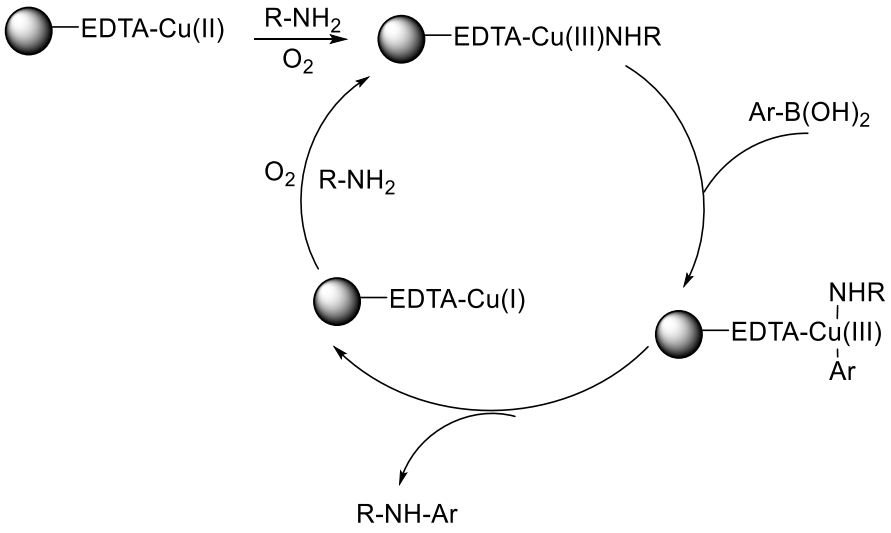
Scheme 105: Arylation of 3-aminophenol[239]

The synthesis of 3-hydroxydiphenylamine and 3-aminodiphenylether has been reported using a palladium catalyst, arylhalide, base and ligand. The selectivity was related to the type of ligand, catalyst and the base as shown in Scheme 105.[239] The selective *O*-arylation has also been reported for 2-aminophenol but was not possible under the optimized condition and the *N,N*-diarylated product was also observed. The conditions were also applied to 4-aminophenol and selective *N*- and *O*-arylated products were prepared but this was very dependent on the reaction conditions similar to that observed for the 3-aminophenol reaction described above.



Scheme 106: Arylation of 3-aminophenol

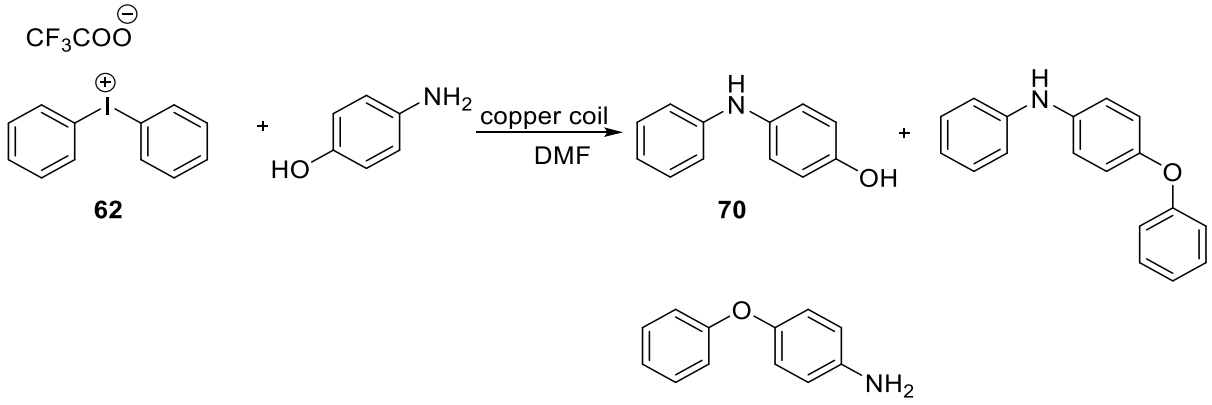
It has also been reported that the reaction of 3-hydroxyaniline with phenylboronic acid in the presence of Fe_3O_4-EDTA-Cu(II) nanoparticles was *N*-selective (Scheme 106).[241]

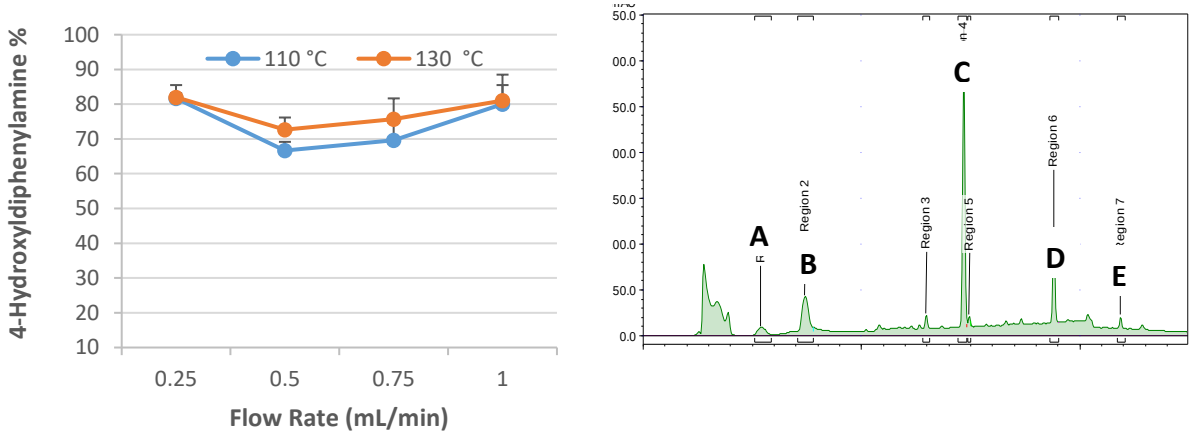


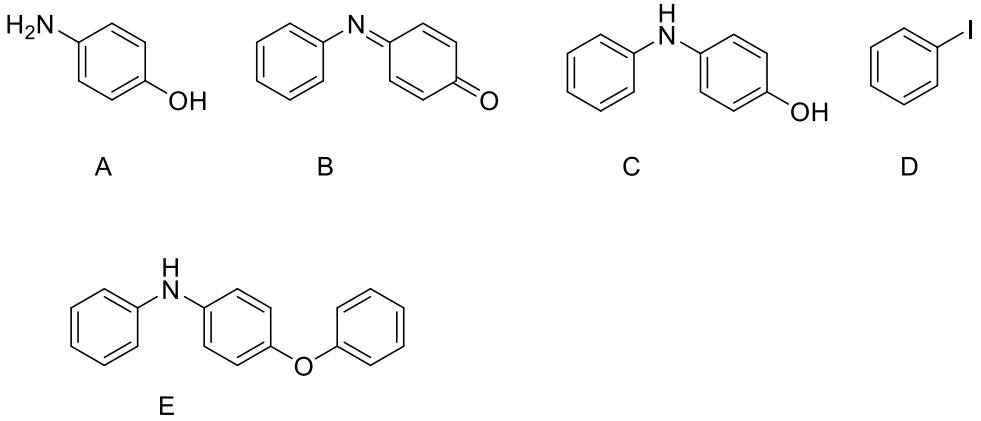
Scheme 107: Proposed mechanism of *N*-arylation using Fe_3O_4-EDTA-Cu(II)[241]

The proposed mechanism is copper catalysed (the copper being attached to the nanoparticle via EDTA coordination),the initial copper (II) species is oxidised by O_2 to copper (III) with coordination of the amine, this is then followed by the trans metalation with the arylboronic acid and subsequent reductive elimination to give the product (Scheme 107).[109, 241]

2.5.3 Arylation of 4-aminophenol







Scheme 108: Effect of flow rate on 4-hydroxyldiphenylamine (70) production (n = 3) (left) HPLC chromatogram of reaction of 4-aminophenol at 130 °C (right), diphenyliodonium trifluoroacetate (5 mmol), 4-aminophenol (5 mmol), DMF (50 mL).

N-, *O*-selectivity of the nucleophile using diphenyliodonium trifluoroacetate, under the continuous process with a copper coil reactor, was investigated with 4-aminophenol and the result indicates *N*-selectivity as shown in Scheme 108, all flow rates gave the product in high yield and the best conditions were 0.25 mL/min at 130 °C – the same as for the individual processes. Trace amounts of the product resulting from *N*, *O*-diarylation were also observed (Scheme 108) although none of just the *O*-arylated product suggesting that *N*-arylation is the much more facile process.

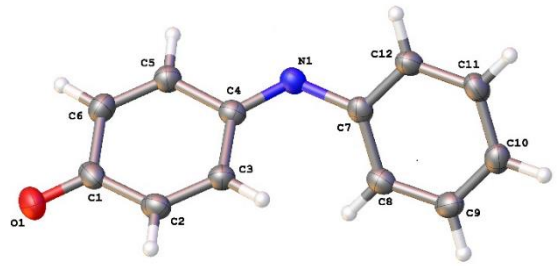
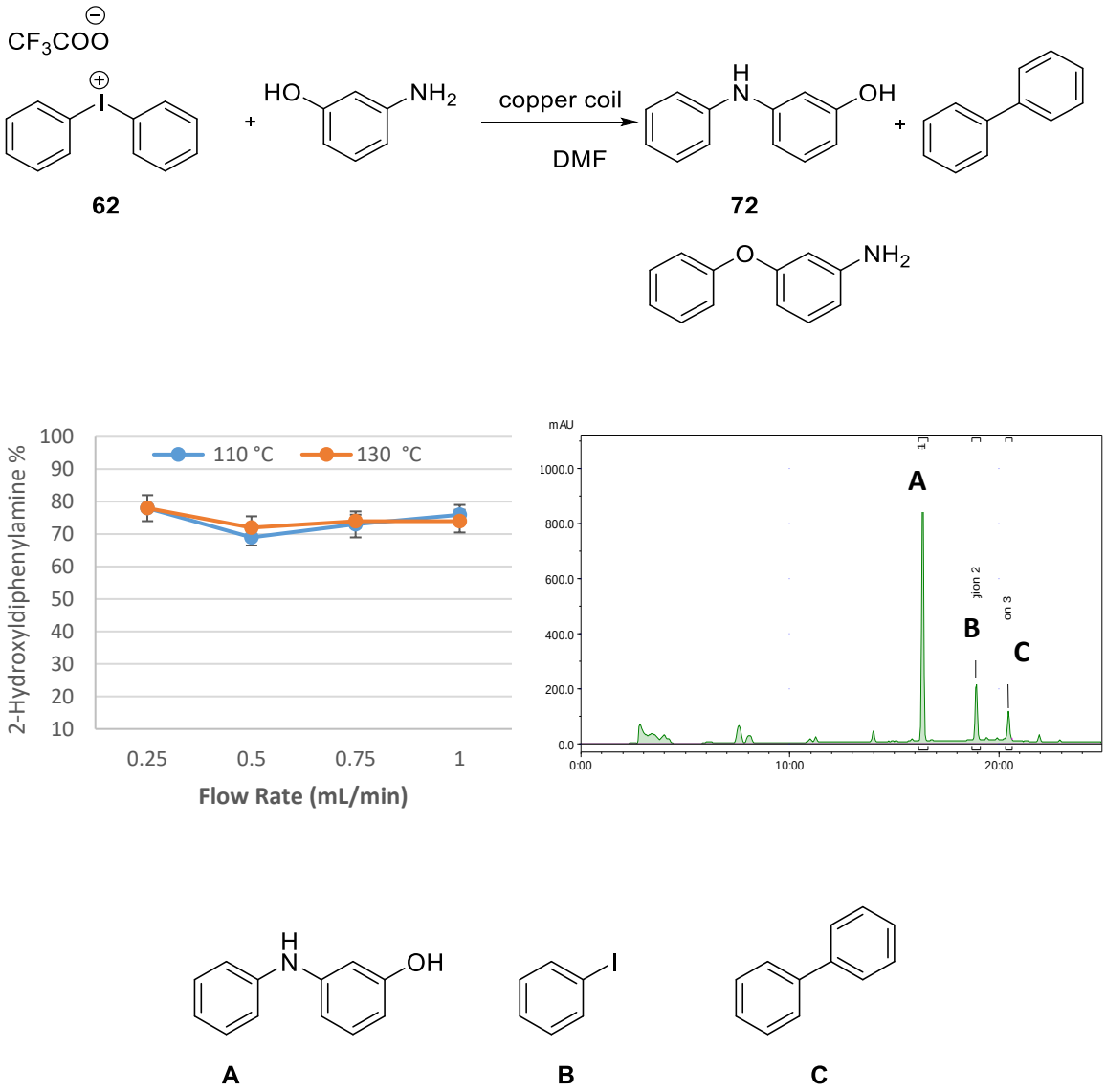


Figure 35: X-ray crystal structure of *N*-phenylazaquinone 71 (left)

Hypervalent iodine reagents are also used as oxidising agents[4] such as the Dess-Martin periodane and the aryliodine (III) dicarboxylates, they have found many applications due to their tolerance of a wide range of functional groups. Therefore it was no surprise that a trace amount of *N*-phenylazaquinone **71** was detected using 1 equivalent of diphenyliodonium trifluoroacetate which would result from oxidation of the 4-hydroxydiphenylamine, this material was isolated and x-ray crystal structure analysis confirmed the structure.

2.5.4 Arylation of 3-aminophenol

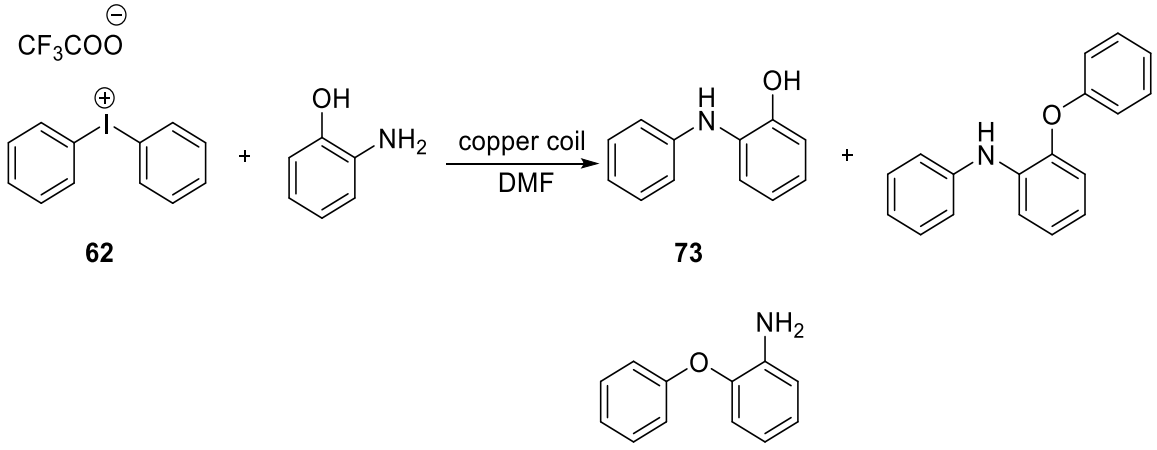


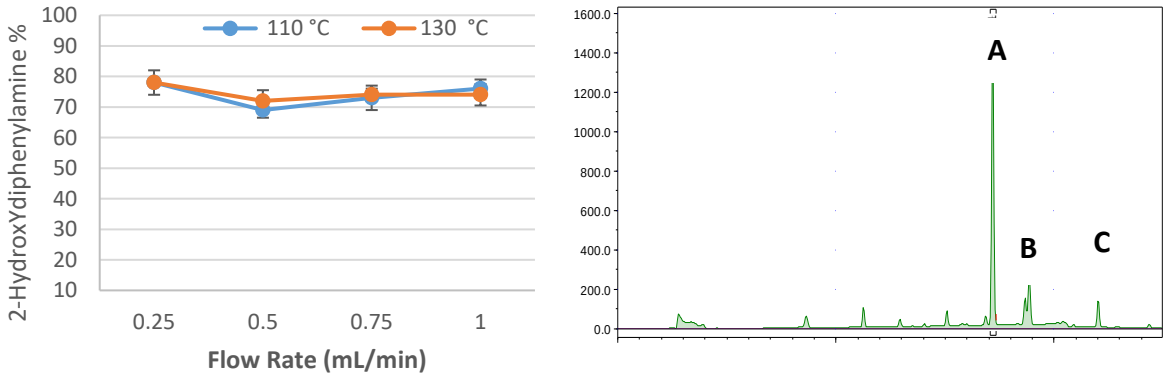
Scheme 109: Optimization of 3-hydroxyldiphenylamine 72 (n = 3), HPLC chromatogram for 3-aminophenol reaction) diphenyliodonium trifluoroacetate (5 mmol), 3-aminophenol (5 mmol), DMF (50 mL).

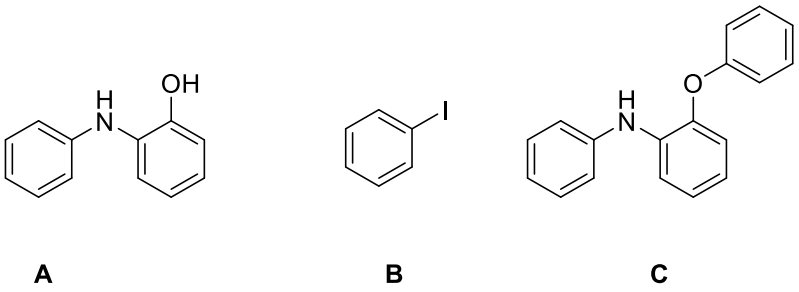
The amine of 3-aminophenol was also selectively arylated (Scheme 109), and gave similar results to those seen when 4-aminophenol was used as the substrate, as before the best conditions were 0.25 mL/min at 130 °C. The *N*, *O*-diarylation product was not observed in this

case but the formation of biphenyl was deticted on the HPLC, probably formed from phenyl radicals resulting from the degradation of the diphenyliodonium trifluoroacetate.

2.5.5 Arylation of 2-aminophenol



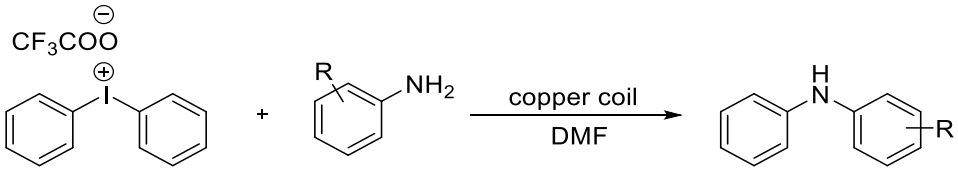




Scheme 110: Optimization of 2-hydroxyldiphenylamine 73 production (n = 3) (left) HPLC chromatogram for 2-aminophenol reaction (right),),diphenyliodonium trifluoroacetate (5 mmol), 2-aminophenol (5 mmol), DMF (50 mL).

The arylation of 2-aminophenol was also successfully carried out and gave the desired product in high yield, this time the optimisation was carried out at different elevated temperatures (110 °C and 130 °C) and a range of flow rates and gave similar results to those observed with 3- and 4-aminophenol (Scheme 110), trace amounts of the *N*, *O*-diarylated product were also present in this case.

Table 14: Arylation of substituent of aminophenol in Flow™



Entry	R	70, 72, 73 (%) RT (n = 3)	70, 72, 73 (%) 130 °C (n = 3)
1	4-OH (**70**)	78	82
2	3-OH (**72**)	89	82
3	2-OH (**73**)	85	78

Diphenyliodonium trifluoroacetate (5 mmol), Ar(NH_2) (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

The reaction was also performed at room temperature using the FlowSyn™ (see Table 14) and the products were obtained in a high yield at flow rate 0.25 mL/min.

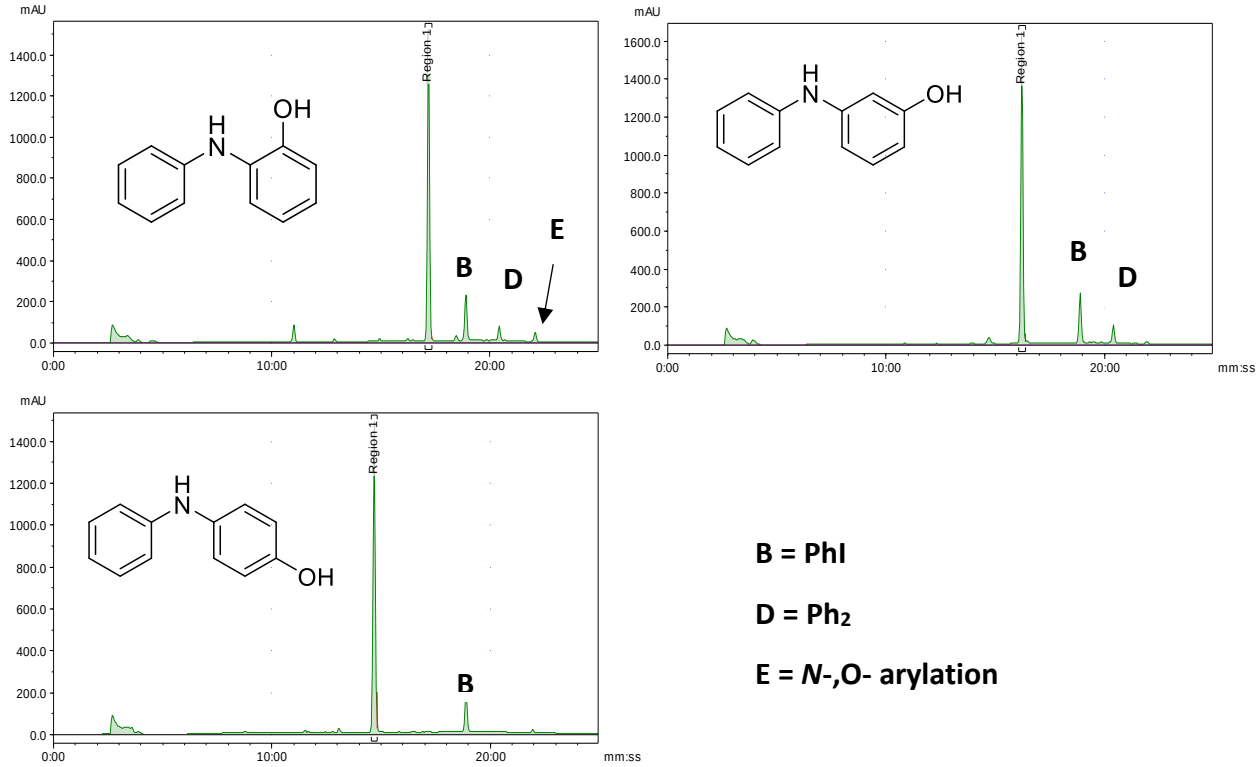
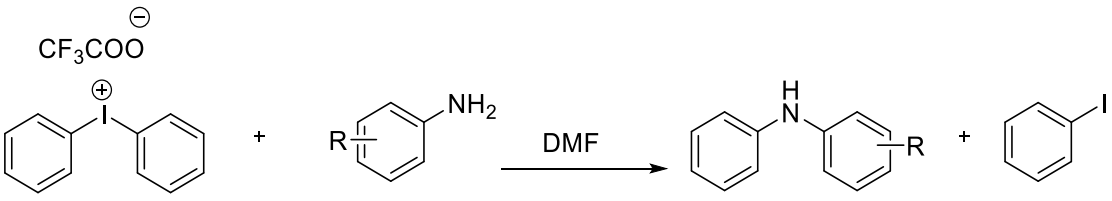


Figure 36: HPLC chromatogram 2-aminophenol, 3-aminophenol and 4-aminophenol reaction, diphenyliodonium trifluoroacetate (5 mmol), Ar(NH_2) (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

The HPLC chromatogram shows the major peak is for the desired product at a flow rate of 0.25 mL/min carried out at room temperature, for instance the reaction of 4-aminophenol did not now give the oxidised by-product *N*-phenylazaquinone and the *N*, *O*-diarylation by-product was also not detected. In the 3-aminophenol reaction a very small peak for the biphenyl by-product was detected and in the case of 2-aminophenol a very small peak for the *N*, *O*-diarylation by-product was observed (Figure 36) suggesting that the lower reaction temperature dramatically reduced the incidence of side reactions.

Table 15: Arylation of 2-, 3- and 4-aminophenol with diaryliodonium trifluoroacetate (62)



Entry	R	No copper/130°C	CuBr(1 mol%)/% 130 °C
1	4-OH (**70**)	93	74
2	3-OH (**72**)	87	74
3	2-OH (**73**)	58	59

Diphenyliodonium trifluoroacetate (5 mmol), Ar(NH_2) (5 mmol), DMF (50 mL), 24 h

The reactions of 2-, 3- and 4-aminophenol were also carried out under batch condition at 130 °C both with copper catalysis and without added copper, the reactions for 3- or 4-aminophenol gave higher yields without copper whereas 2-aminophenol gave a lower yield of the desired product may due to steric hindered (Table 15)

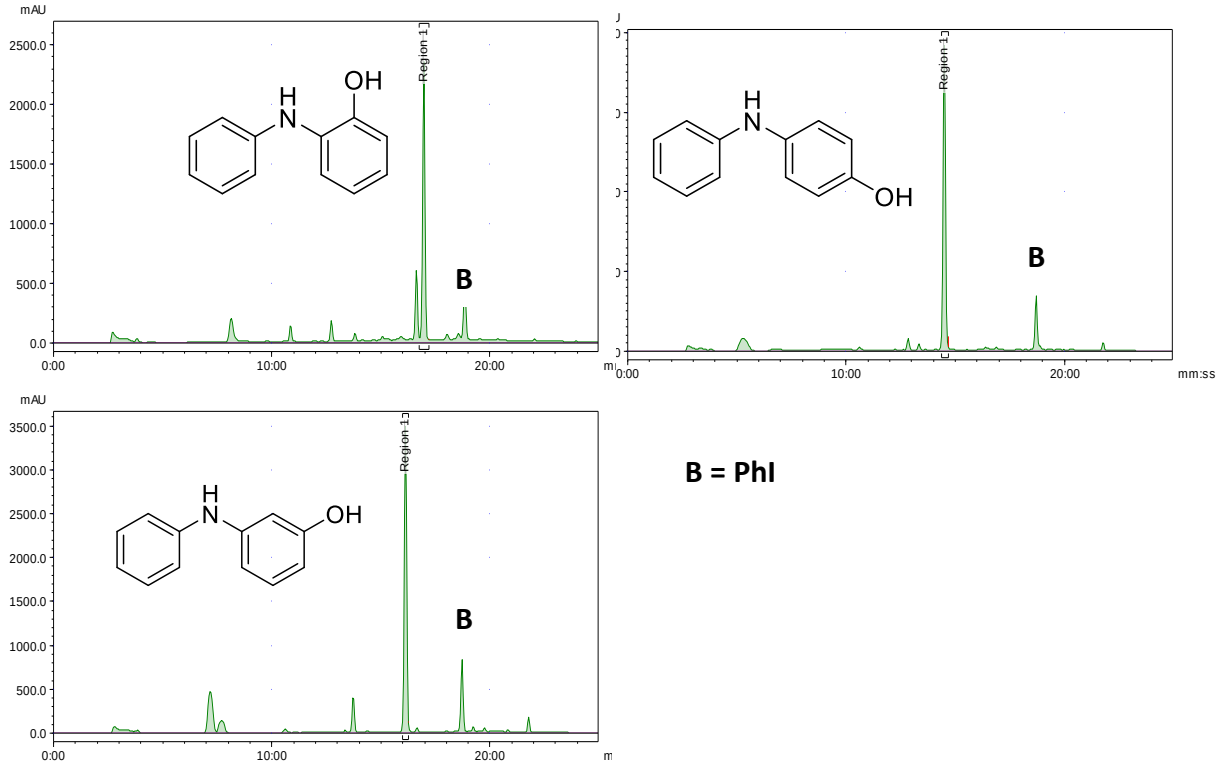


Figure 37: HPLC chromatogram 2-aminophenol/ no copper, 4-aminophenol/no copper and 3-aminophenol/no copper, diphenyliodonium trifluoroacetate (5 mmol), Ar(NH_2) (5 mmol), DMF (50 mL), 24 h

The HPLC chromatograms for the reactions of 2- and 3-aminophenol respectively (Figure 37) show traces of the unknown by-product at retention time 8, 11, 13, 14, 16.5 min from the degradation of diphenyliodonium trifluoroacetate whereas the 4-aminophenol shows the peak of trace starting material 4-aminophenol.

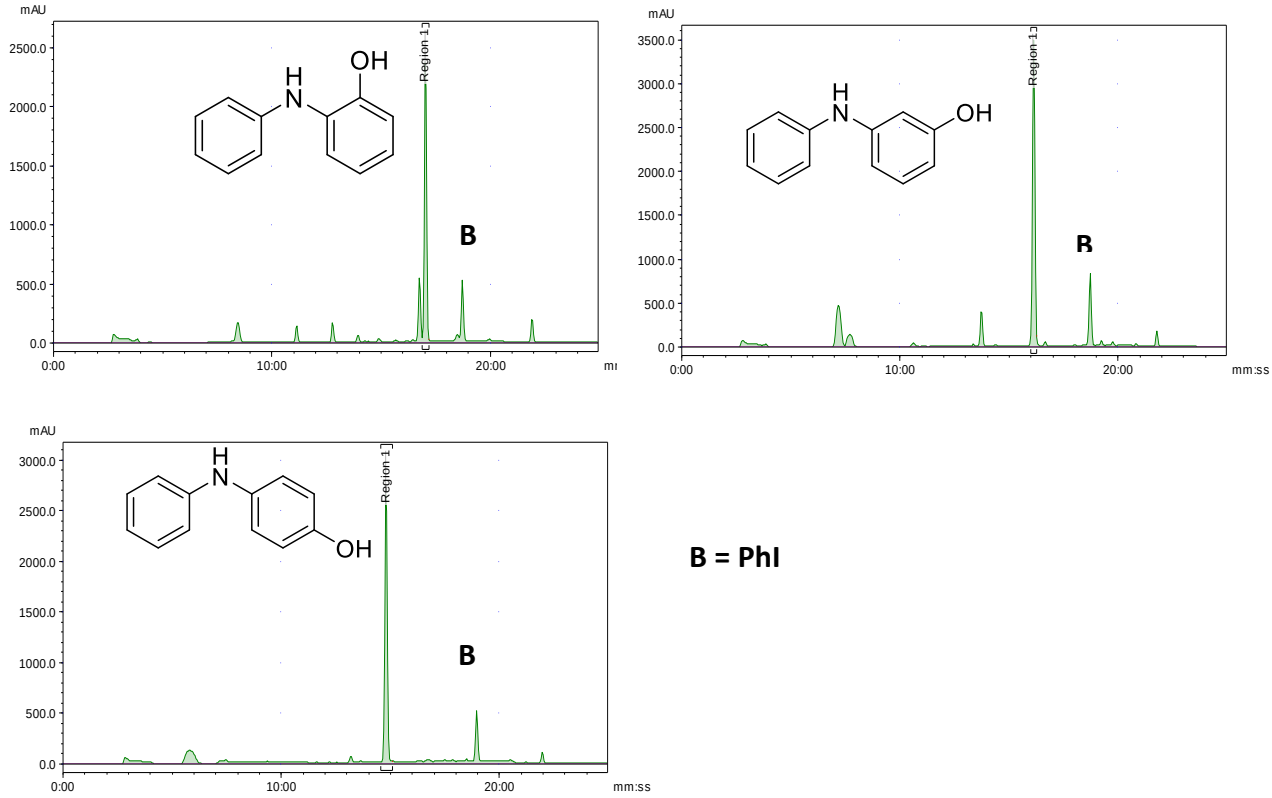
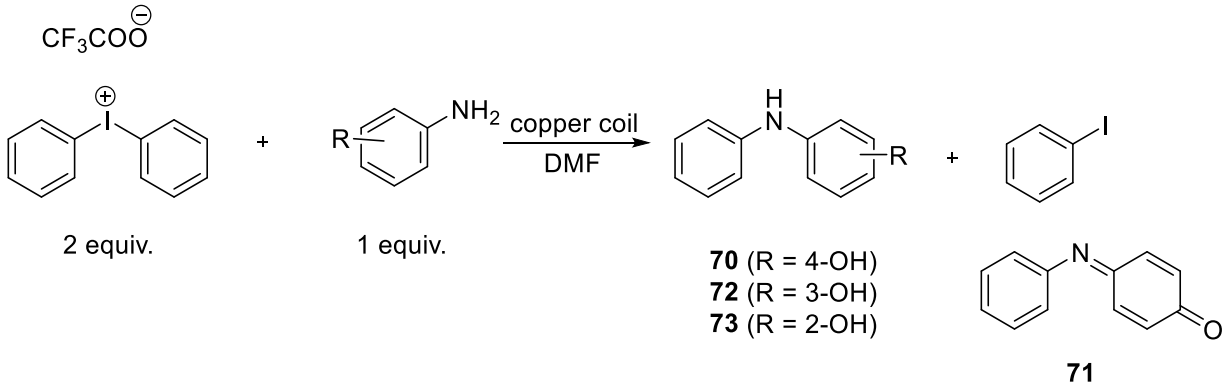


Figure 38: HPLC chromatogram 2-aminophenol/ copper, 3-aminophenol/ copper and 4-aminophenol/ copper diphenyliodonium trifluoroacetate (5 mmol), Ar(NH_2) (5 mmol), DMF (50 mL), CuBr (1% mol), 24 h

The HPLC chromatograms for the batch reactions of 2-, 3-and 4-aminophenol with diphenyliodonium trifluoroacetate at 130 °C in the presence of copper catalyst for 24 hours are shown in Figure 38. It is interesting to note that the 2-aminophenol reaction gave similar results in both cases; the presence and absence of the copper catalyst.

Table 16: **Arylation of 2-, 3- and 4-aminophenol with 2 equivalent diphenyliodonium trifluoroacetate**



Entry	R	70, 72, 73 (%) RT (n = 3)	70, 72, 73 (%) 130 °C (n = 3)	71 (%) 130 °C (n = 3)
1	4-OH	53 (**70**)	0	82
2	3-OH	59 (**72**)	64	0
3	2-OH	46 (**73**)	33	0

Diphenyliodonium trifluoroacetate (5 mmol), Ar(NH_2) (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

In an alternative process to favour the generation of *N*-phenylazaquinones the reactions of 2-, 3-and 4-aminophenol were carried out with 2 equivalents diphenyliodonium trifluoroacetate at 130 °C and a flow rate of 0.25 mL/min using the Flowsyn ™as the addition of extra hypervalent iodine reagent to the reaction would facilitate the oxidation of the initial *N*-arylation product. The results are shown in (Table 16).

It was pleasing to see that this process modification with 4-aminophenol gave about 82% of *N*-phenylazaquinone **71** at 130 °C (Table 16, entry 1) supporting the premise that the diphenyliodonium salt was also acting as an oxidising agent. It is also of note that the oxidation only takes place at the higher reaction temperature with none of the azaquinone detected at room temperature. Given the diversity of functionality and reactions possible with azaquinones it is surprising that this compound class remains unexplored as a building block in synthetic chemistry – this potential new application will continue to be investigated

by the research group. The 2-amino phenol gave a low yield of the *N*-arylation product at both temperatures and also 3-amino phenol gave a moderate yield of the *N*-arylation product at both temperatures (Table 16).

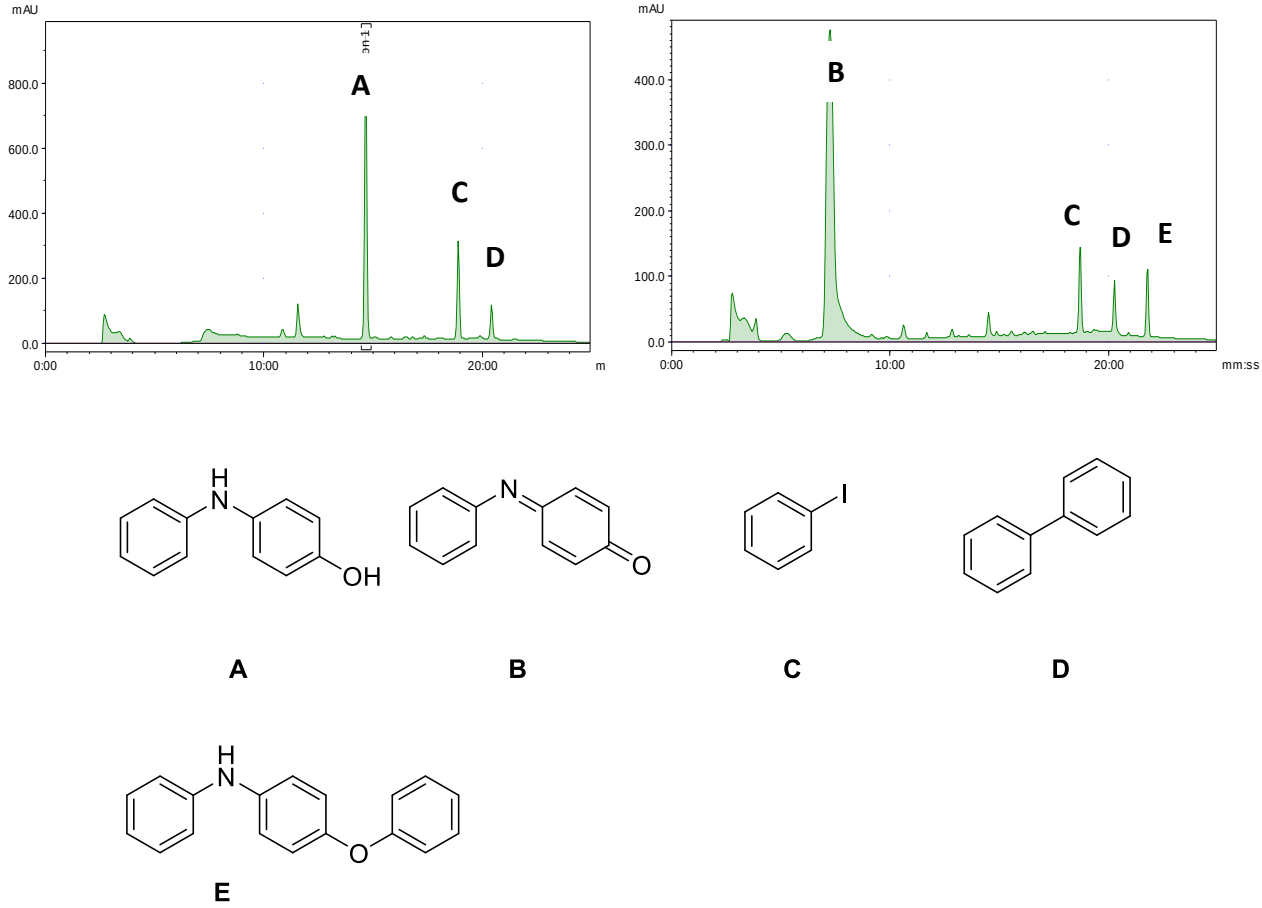


Figure 39: HPLC chromatogram of the 4-aminophenol reaction at room temperature (left) and 130 °C (right), diphenyliodonium trifluoroacetate (5 mmol), 4-aminophenol (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

From Figure 39, the HPLC chromatogram of the 4-amino phenol reacted with two equivalents of diphenyliodonium trifluoroacetate, the major peak is now *N*-phenylazaquinone, with the *N*, *O*-diarylation by-product also being obtained, however at room temperature only a trace of the *N*-phenylazaquinone was observed despite the extra hypervalent iodine reagent. The reaction did give the by-product biphenyl resulting from the degradation of diphenyliodonium trifluoroactate.

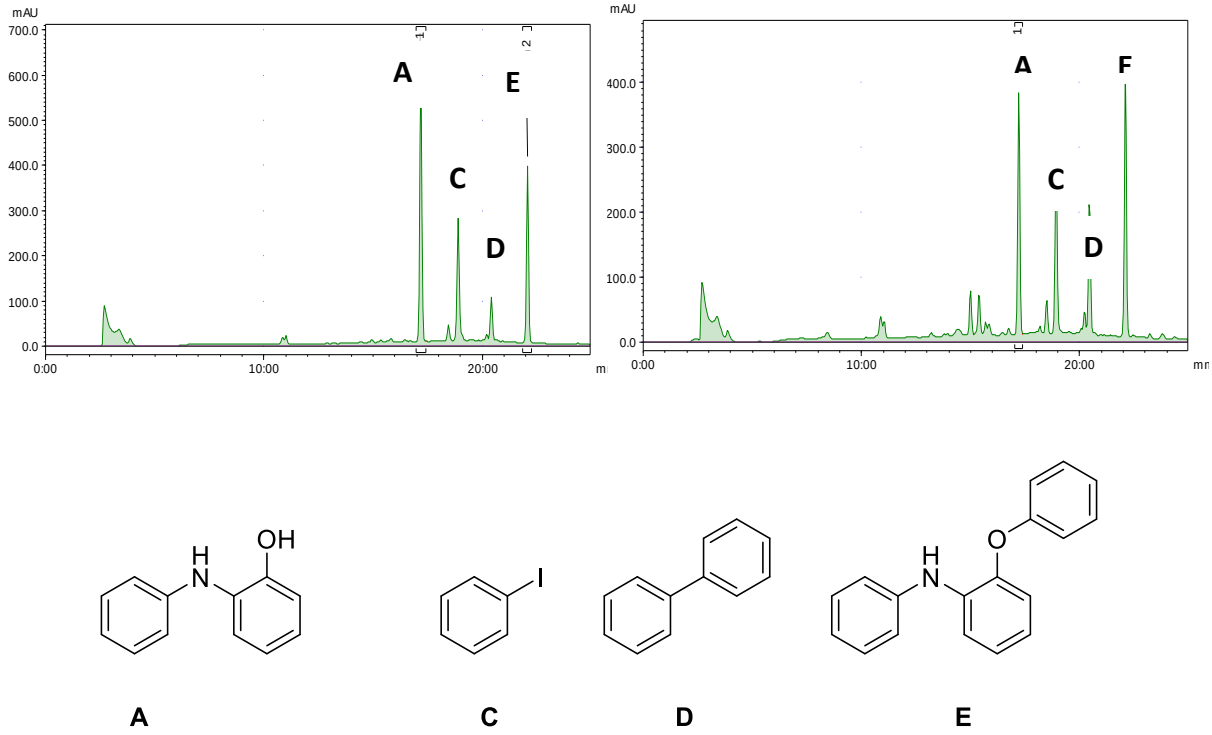


Figure 40: HPLC chromatogram of the 2-aminophenol reaction at room temperature (left) and 130 °C (right) diphenyliodonium trifluoroacetate (5 mmol), Ar(NH_2) (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

The HPLC chromatogram for the 2-aminophenol reacted with two equivalents of diphenyliodonium trifluoroacetate, an increase in the by-products, for instance the *N*, *O*-diarylation product and biphenyl, results in a decreasing yield of the *N*-arylated product probably due to the increased steric hindrance associated with the *ortho*-substituents (Figure 40).

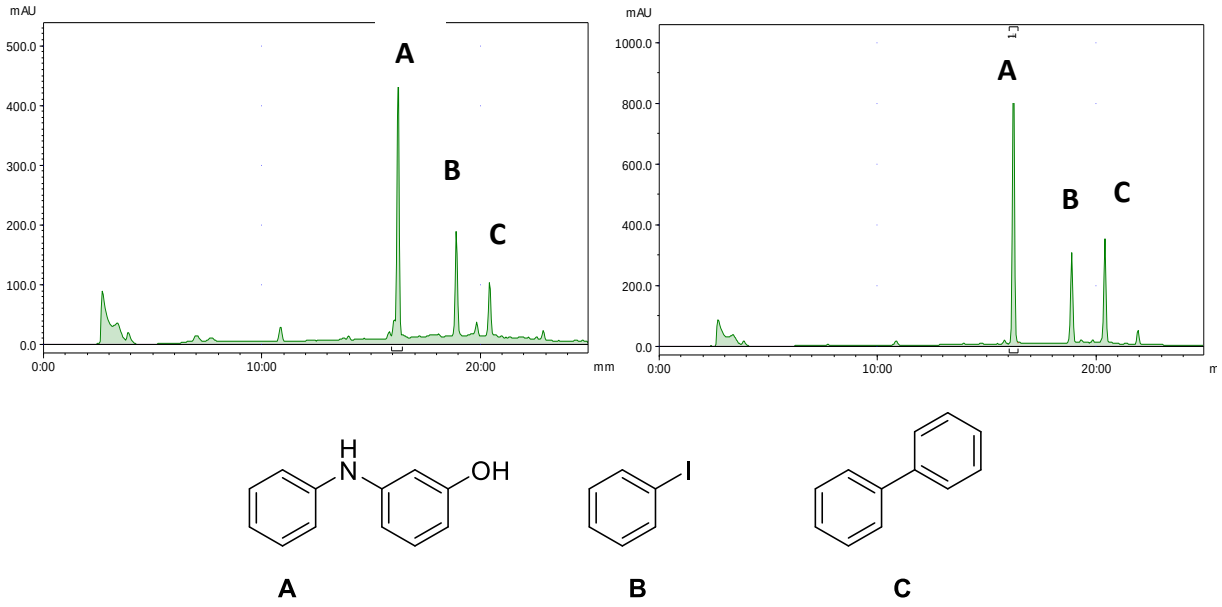
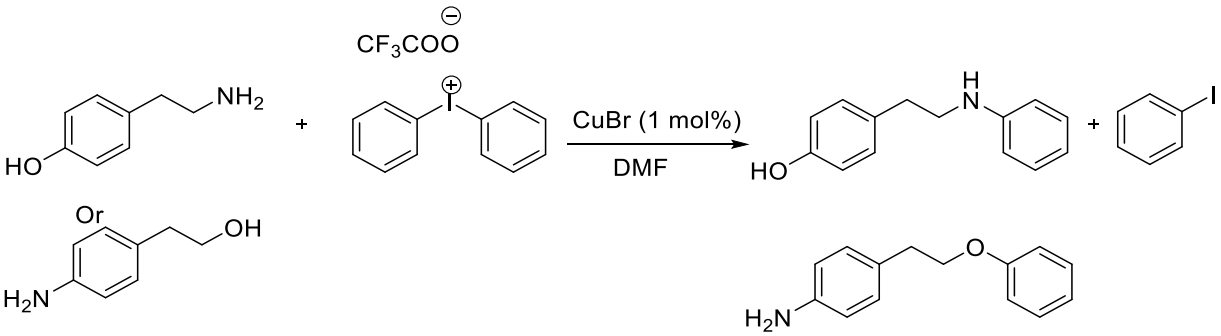


Figure 41: HPLC chromatogram of the 3-aminopheNol reaction at room temperature (left) and 130 °C (right), diphenyliodonium trifluoroacetate (5 mmol), 3-aminophenol (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

When 3-aminophenol was reacted with two equivalents of diphenyliodonium trifluoroacetate a moderate yield of the *N*-arylation product at both temperatures (room temperature and 130 °C) was obtained probably due to lower steric hindrance than is present in the 2-hydroxy derivatives but reduced nucleophilicity compared to the 4-hydroxy derivative (Figure 41).

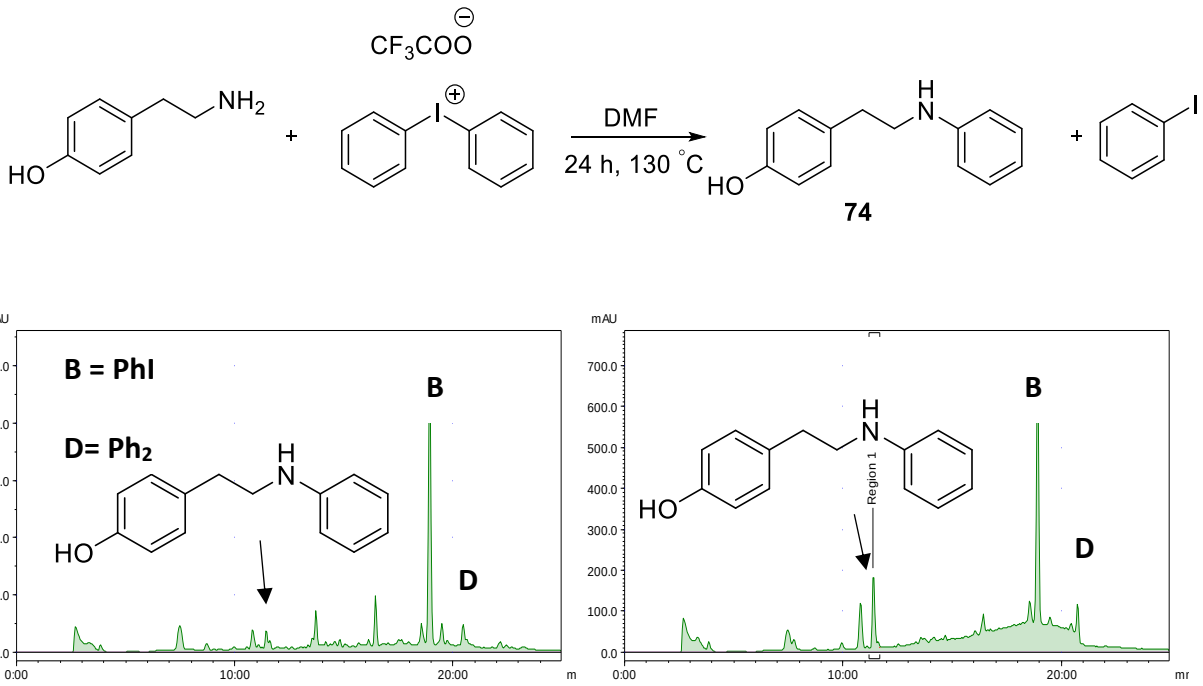
2.5.6 *N*, *O*-Selectivity of (aliphatic amine)



Scheme 111:

As diphenyliodonium trifluoroacetate successfully selectively arylated the amine group of 2-, 3- and 4-aminophenol, we decided to investigate whether this would also be the case for

aliphatic amines. Therefore to determine this selectivity between *N*- and *O*-nucleophiles studies using tyramine and 4-aminophenethyl alcohol were carried out. Tyramine which has an aliphatic amine nitrogen and an aromatic oxygen was reacted with diphenyliodonium trifluoroacetate under batch conditions at 130 °C for 24 hours (38%) of the desired product, the reaction did not give the desired product under metal-free conditions however under metal catalysed conditions the reaction gave the *N*-arylation product only **74**, as shown in the Scheme 112 .



Scheme 112: *N*-arylation of tyramine under batch condition HPLC chromatogram for tyramine reaction/ copper free (left) and copper (right), diphenyliodonium trifluoroacetate (5 mmol), tyramine (5 mmol), DMF (50 mL), 130 °C. 24h.

The reaction was then transferred to the FlowSyn™ using the copper coil reactor at a flow rate of 0.25 mL/min, at 130 °C, the reaction gave 43% of the *N*-arylated products, however the reaction at room temperature only gave these desired products in trace amounts. Unfortunately attempts to isolate these materials using column chromatography were not successful for the room temperature reaction (Figure 42).

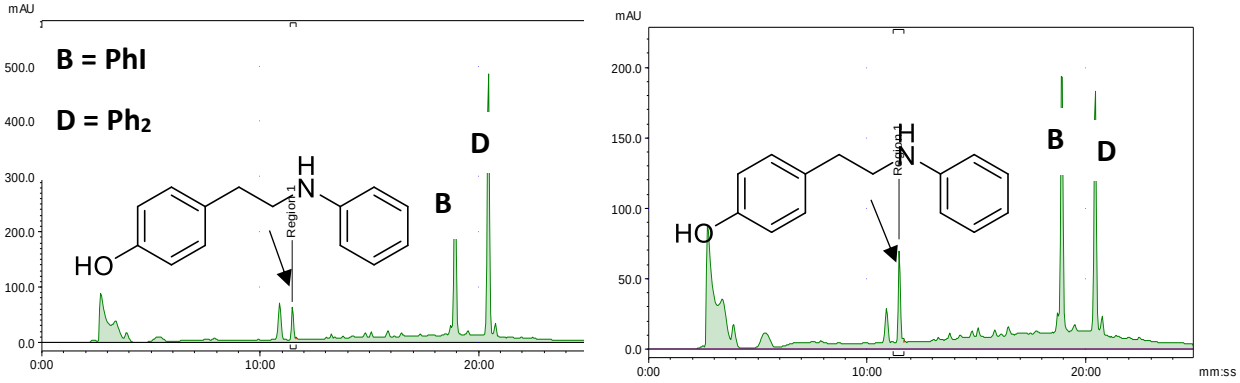
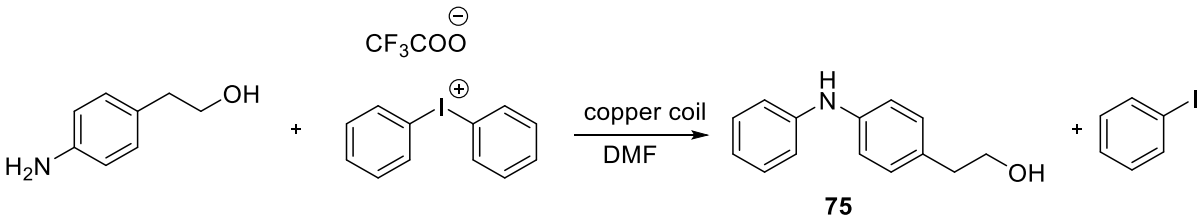


Figure 42: HPLC chromatogram for the reaction of tyramine using Flow™ at RT (left) and 130 °C (right), diphenyliodonium trifluoroacetate (5 mmol), tyramine (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

Using 4-aminophenethyl alcohol with diphenyliodonium trifluoroacetate was also carried out under the same conditions, the reaction was carried out three time at both temperatures with 130 °C giving 79% of only the *N*-arylated product **75** (Figure 43), whereas the reaction at room temperature gave about 91%. As is shown in Figure 43 the reaction at room temperature is also much cleaner than the reaction at 130 °C, although the high temperature makes the reaction faster it also results in more degradation of the hypervalent iodine starting material resulting in the generation of more by-products.



75

Scheme 113: *N*-Arylation reaction of 4-aminophenethyl alcohol 75.

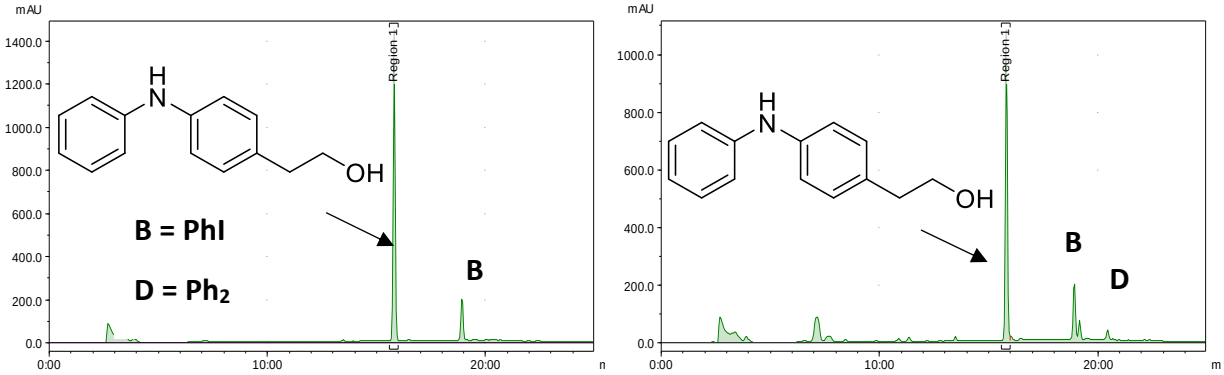


Figure 43: HPLC chromatogram for the reaction of 4-aminophenethyl alcohol at RT (left) and 130 °C (right) diphenyliodonium trifluoroacetate (5 mmol), 4-aminophenethyl alcohol (5 mmol), DMF (50 mL), flow rate 0.25 mL/min.

From the results obtained the reaction of 4-aminophenethyl alcohol gave more of the *N*-arylated product than tyramine and also the 4-aminophenethyl alcohol worked better at room temperature as the aromatic amine is more reactive than the aliphatic nitrogen therefore reaction of 4-aminophenethyl alcohol gave higher yield than the reaction of tyramine just as aniline and its derivatives gave higher yield of the desired than the reaction of for instance *N*-hexylamine. These results suggest that there is a preference for *N*-arylation over *O*-arylation irrespective of whether the amino group is aromatic or aliphatic in nature. The reaction using 4-aminophenethyl alcohol gave more biphenyl (from the degradation of the diphenyliodonium trifluoroacetate) as a by-product than the corresponding tyramine reaction, suggesting the *N*-arylation of the aliphatic amine was more difficult than *N*-arylation of aniline.

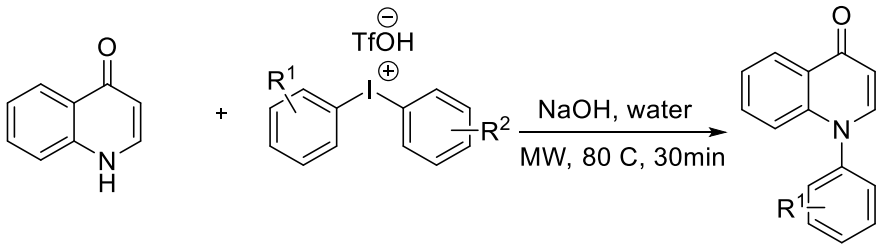
2.5.7 *N*-, *O*-selectivity: Summary

- *N*, *O*-Arylation was carried out using diphenyliodonium trifluoroacetate and a copper coil reactor on the FlowSyn™ flow chemistry platform, the reaction was found to selective for nitrogen nucleophiles over oxygen nucleophiles irrespective of whether they were aromatic or aliphatic.
- Anilines were more reactive than the aliphatic amines giving a high yield of the desired product, from the results it conclude the order of reactivity.

$$\boxed{ArNH_2 > HetNH_2 > RNH_2 > ArOH > ROH}$$

- Reaction conditions were also identified to allow selective formation of *N*-phenyl azaquinone by using 2-equivalents of the diaryliodonium salt utilising both its property as an arylating agent and an oxidising agent.

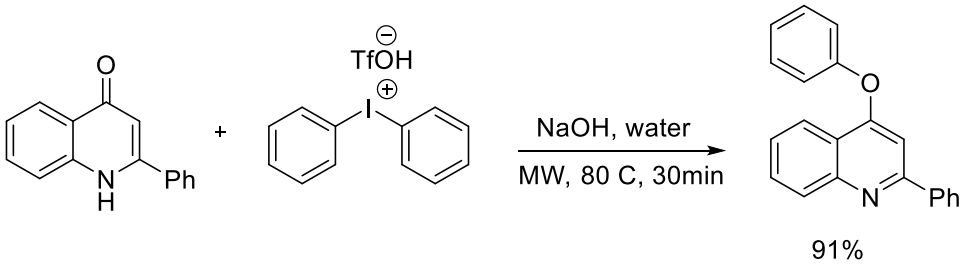
Recently the nitrogen oxygen selectivity has been carried out using diaryliodonium salt.[242] *N*-arylation of 4-methylquinolin-2(1H)one under mild condition using microwave heating, the diaryliodonium salt was used with different groups, electron-donating groups and electron-defcient groups and gave the desired product in a moderate yield (Scheme 114). It has suggested that the oxgen may be rendered less reactive through hydrogen bonding with water and therefore the arylation is selective for the nitrogen.



R^1	R^1	%
H	H	91
4-Cl	4-Cl	88
3-Br	Mes	75
4-Me	Mes	67

Scheme 114: *N*-Arylation of quinolin-4(1H)one

The selectivity for oxygen was observed when the presence of two carbon substituents effectively hindered the nitrogen resulting in the oxygen being successfully arylated (Scheme115).



Scheme 115: *O*Arylation of quinolin-4(1H)one

3 Conclusions and Future Work

3.1 Conclusion

It can be concluded from the work presented here, that one of the best methods for the synthesis of diarylamines is the Ullmann type coupling using diaryliodonium salts under flow chemistry conditions using a copper coil reactor due to its simplicity, no added extra reagents are needed such as a base or the ligands necessary for a traditional homogeneous catalyst, and the desired product is obtained in a high yield. The reaction may also be carried out faster and at a lower temperature (e.g. RT) compared to conventional methods, these parameters coupled with the observation that the reaction is not sensitive to air makes for a simple yet practical process.

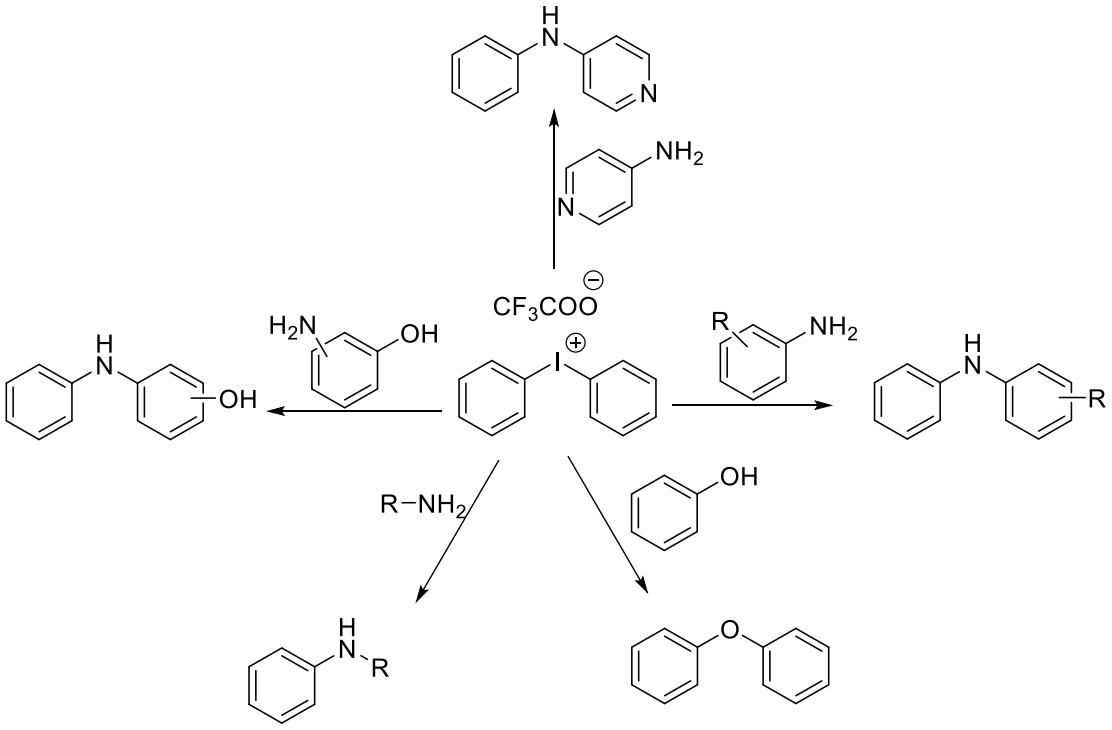
The trifluoroacetate derivative of diaryliodonium salts has proven to be the best electrophilic arylating reagent for the preparation of arylamines and arylethers compared to the more usual arylhalide and arylboronic acids. The synthesis of diaryliodonium trifluoroacetates was achieved using a simple method using inexpensive starting material and stirring the reaction at room temperature where the product can be crystalized directly with no further purification required. The route also enabled the synthesis of unsymmetrical diaryliodonium salts such as those with electron-rich groups, for instance the 4-methoxy group, as it was not practical to synthesise electron-rich diaryliodonium triflates due to their lack of stability. Another practical advantage is that the diaryliodonium trifluoroacetates enable the reaction to be performed at room temperature giving the product in excellent yield whilst the more typical diaryliodonium triflate only gave a moderate yield of the desired product at this temperature.

Further advantages of the flow chemistry protocol is that the reaction time decreased from 24 h to 80 min, and by the use of mild reaction conditions it also improved the safety of the process. Flow chemistry methods have also been demonstrated to have a high degree of reproducibility and associated product purity, for example in the synthesis of 3,4-dimethoxydiphenylamine no further purification was required and the process was straight forward to scale up. The translation to flow chemistry also reduced the amount of solvents used as no additional purification was required which would be particularly useful for industrial applications. Although not the optimized conditions in this particular case the flow

chemistry protocol also allowed the reaction to be carried out at 230 °C, which would be difficult to do under batch conditions, giving a wider range of reaction parameters to be investigated as part of the development of any new method. Determination of the *N*, *O*-selectivity has also been carried out with diaryliodonium trifluoroacetates using the FlowSyn™ which has never been established previously. The nitrogen nucleophile proved to be more reactive than the oxygen nucleophile as the reaction selectively allowed *N*-arylation. It also found that in the case of phenyl(mesityl)iodonium salts, the mesityl group was not coupled to the nucleophile and it was possible to couple the more electron-rich group when using the copper catalyzed mechanism.

The copper coil reactor played an important role in the arylation of both anilines and phenol and a key feature for this process is that, it is easy to use, and a separate catalyst does not need to be prepared. It is also more economic than the copper powder as the coil reactor can be used for many reactions and at a maximum temperature higher than used in batch reaction e.g. upto 250 °C, thereby increasing throughput.

It can also be concluded from the results that aromatic amines are more likely to be arylated than aliphatic amines, the analogues of aniline gave the product in excellent yield whether they had electron-withdrawing groups, electron-donating groups or sterically demanding groups such as 2-tert-butyl present. The use of tyramine and 4-aminophenethyl alcohol as substrates reinforced this selectivity.



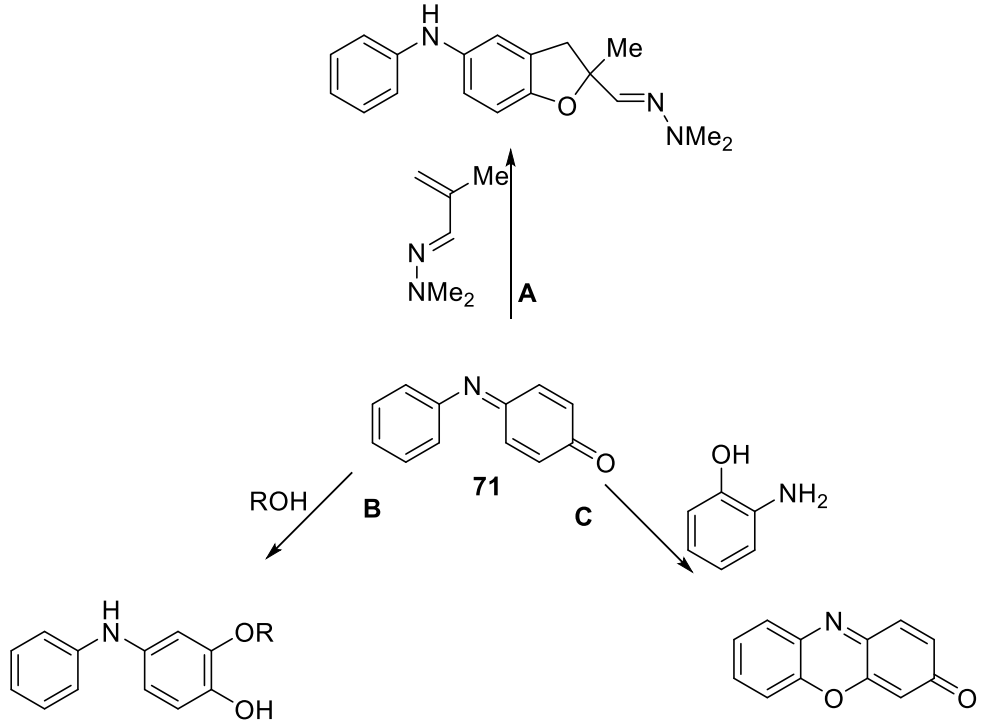
Scheme 116: Arylation of nitrogen and oxygen nucleophiles using diphenyliodonium trifluoroacetate

3.2 Future Work

A large fraction of the research reported herein has been directed towards the development of robust and practical methodology for the arylation nitrogen and oxygen nucleophile using diaryliodonium salt, further extension of experiments towards the unsymmetrical diaryliodonium trifluoroacetate and aryl(mesityl)iodonium trifluoroacetates, these huge potential in this methodology remains for the arylation of arylamine.

Further to these initial experiments, it would be useful to extend the range of anilines, and in particular *N*-heteroaromatic compounds to provide a better understanding of the scope of the reaction. Application of the methodology to the five membered rings, for instance imidazole, would be useful due to their extensive use in pharmaceuticals, to date they have been arylated with arylhalides or arylboronic acids (as described in Chapter 1) but the advantages of using diaryliodonium salts remains to be exploited.

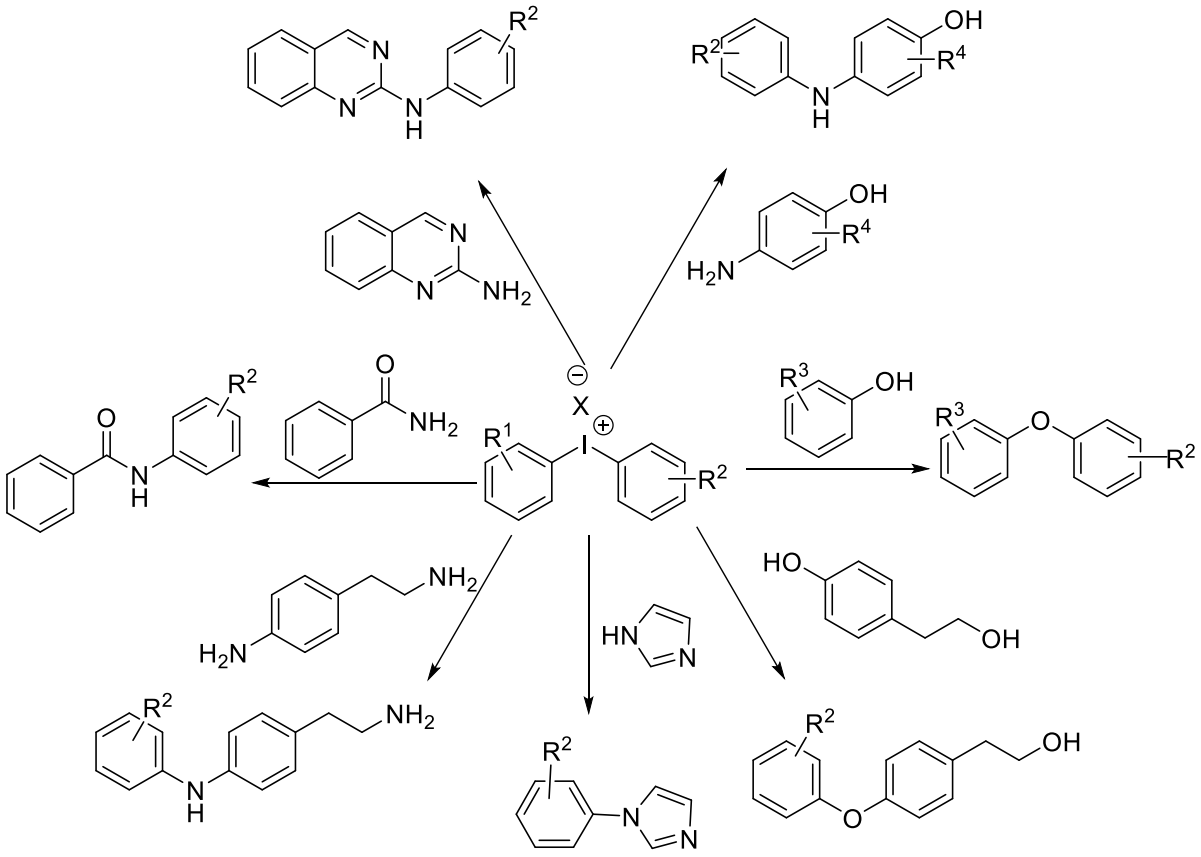
Although the selectivity of between *N*- and, *O*-arylation for 2-, 3- and 4-aminophenol has been investigated here, as has comparison between aromatic and aliphatic functionality, there remains many combinations/variations left to explore. The realization of multi-step reactions is also possible using the FlowSyn™ or any automated reaction platform (as mentioned in Section 2.2) to extend the utility of the methodology still further, for example the reaction using two equivalents of diaryliodonium salt with 1- equivalent of 4-aminophenol gave 82% of *N*-phenylazaquinone (from arylation and oxidation), which could then be used further to rapidly generate polyfunctional molecules in a single process without isolation of any of the intermediates. For instance selective nucleophilic addition to the various electrophilic centres of the azaquinone system (all six carbon atoms in the azaquinone ring are different).



Scheme 117: Possible reactions of *N*-phenylazaquinone (71) with nucleophiles

The formation of *N*-phenylazaquinone suggested that further reactions of this material with a range of nucleophiles were now possible, this methodology combined with the benefits of flow chemistry offers the exciting prospect of multi-step reactions during this single automated process. For instance cycloaddition reactions, nucleophilic additions to the different α, β-conjugated systems and oxidative cyclization (Scheme 117: **A**, **B**, and **C** respectively).[243-245]

N-Arylation of benzamides with diaryliodonium salts should also be considered as this is another critical functionality although this may possibly require the presence of a base (see Section 1.7.7).



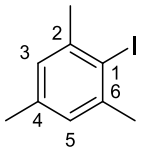
Scheme 118: Arylation of different nitrogen and oxygen nucleophiles using unsymmetrical iodonium salts

4 Experimental

Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under a positive pressure of nitrogen. Anhydrous solvents were prepared in accordance with standard protocols. Infrared spectra were recorded on Varian Scimitar Series 800 FT-IR spectrometer with internal calibration. ^{1}H, ^{13}C and ^{19}F–NMR were recorded on Bruker Advance 300 MHz and 500 MHz spectrometers, Jeol 400 and 700 spectrometers with residual protic solvent as an internal reference. Mass spectra were recorded at the EPSRC mass spectrometry service, Swansea. Elemental analyses were recorded at London Metropolitan University. Melting points were recorded on a Gallenkamp MF-370 melting point apparatus and are uncorrected. Automated flash chromatography was performed using a Varian Intelliflash 971-FP discovery scale flash purification system. The Uniqsis FlowSyn^{TM} system was used to carry out continuous flow reactions, and an Agilent 1200 HPLC system provided with a UV absorbance detector (λ^{max} 254 nm) was used for HPLC analysis. TLC Silica gel 60 $F_{254,}$ 25 Aluminium backed were used to measure the R_f values for the compounds which were purified by Flash chromatography. Diphenyliodonium triflate is commercially available.

Caution: Some hypervalent iodine compounds are potentially explosive and should be used taking the appropriate precautions.[246-248]

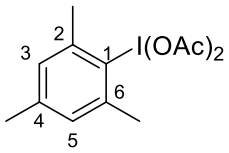
4.1 Iodo mesitylene (76)[249]



Iron nitrate nonahydrate (8.01 g, 19.83 mmol) and silica gel (8.01 g, 19.83 mmol) were combined and ground together to give a fine powder which was added to a solution of iodine (5.57 g, 21.96 mmol) in DCM (500 mL). After stirring the mixture for 5 minutes mesitylene (4.74 g, 39.47 mmol) was added and the whole mixture then stirred overnight. The reaction mixture was filtered and aqueous sodium thiosulfate (2 M, 300 mL, 600 mmol) was added to the filtrate and the mixture stirred until a colourless solution was observed. The organic layer

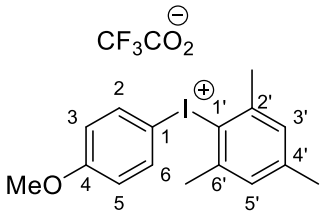
was washed with brine (200 mL) and extracted with DCM (3 × 200 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo to give the product as a colourless crystalline solid (6.90 g, 28 mmol, 71%); mp 27–29 °C (from DCM) (lit.,[250] mp 30 °C from ethanol); IR ν_{max}/cm^{-1} (neat) 2978, 2929, 2409, 2196, 1843, 1645, 1368, 1266, 1011, 925; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 6.94 (2H, s, H3/H5), 2.49 (6H, s, 2-Me/6-Me), 2.29 (3H, s, 4-Me); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 147.8 (C2/C6), 137.3 (C4), 128.0 (C3/C5), 104.3 (C1), 29.5 (2-Me/6-Me), 20.7 (4-Me); m/z (EI) 245 ($[M+H]^+$, 100%) 117 (50), 115 (30), 103 (35), 91 (15), 65 (3), 63 (5). Found $[M+H]^+$ 245.9906. $C_9H_{11}I$ requires 245.9914. Anal. Calcd. for $C_9H_{11}I$: C, 43.93; H, 4.51. Found: C, 43.71; H, 4.62.

4.2 Mesityl iodobenzenebisacetate (77)[17, 251]



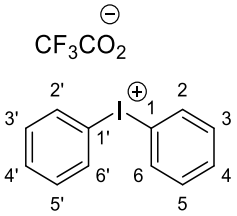
Iodomesitylene **76** (5.51 g, 16 mmol) was dissolved in acetic acid (160 mL) and sodium perborate tetrahydrate (24.62 g, 160 mmol) added portion-wise at 45°C over 1 hour. The solution was stirred at this temperature for a further 3.5 hour. The reaction mixture was allowed to attain room temperature when cold water (500 mL) was added. The crude product was washed with water (500 mL) and extracted with DCM (3 × 500 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed in vacuo and the crude product crystallised from DCM–ether to give the product as a white crystalline solid (3.34 g, 9 mmol, 57%); mp 160–162 °C (from DCM–ether) (lit.,[251] mp 160–163 °C from hexane); IR ν_{max}/cm^{-1} (neat) 2930, 2286, 1645, 1455, 1368, 1264, 1011, 925, 665; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.28 (2H, s, H3/H5), 2.73 (6H, s, 2-Me/6-Me), 2.38 (3H, s, 4-Me), 1.99 (6H, s, OAc); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 176.4 (CO), 143.2 (C4), 141.3 (C2/C6), 129.6 (C1), 129.0 (C3/C5), 26.7 (2-Me/6-Me), 21.2 (4-Me), 20.33 (OAc). Anal. Calcd. for $C_{13}H_{17}IO_4$: C, 42.88; H, 4.71. Found: C, 42.77; H, 4.59

4.3 4-Methoxyphenyl(mesityl)iodonium trifluoroacetate (65)



Trifluoroacetic acid (0.92 mL, 12 mmol) was added slowly, at −30 °C to a solution of iodomesitylenebisacetate **77** (2.24 g, 6 mmol) in dichloromethane (100 mL) and the mixture stirred for half an hour which was then allowed to attain room temperature for 1 h. After one hour, anisole (0.65 mL, 6 mmol) was then added to the recooled mixture (−30 °C). The reaction mixture was allowed to attain room temperature again and stirred overnight. The solvent was removed in vacuo and the crude product crystallised from DCM–ether to give the product as a white crystalline solid (1.4 g, 3.0 mmol, 50%); mp 190–192 °C (from DCM–ether); IR ν_{max}/ cm^{-1} (neat) 2842, 1658, 1572, 1487, 1297, 1253, 1179, 1127, 829; ^{1}H–NMR (300 MHz, CD_3CN) δ 7.82 (2H, d, H2/H6, J 9 Hz), 7.16 (2H, s, H3′/H5′), 6.99 (2H, d, H3/H5, J 9 Hz), 3.81 (3H, s, OMe), 2.33 (6H, s, 2-Me/6-Me), 1.95 (3H, s, 4-Me); ^{13}C–NMR (75 MHz, CD_3CN) δ 162.9 (C4), 161.4 (q, C=O, J 37 Hz), 144.3 (C4′), 142.3 (C2′/C6′), 136.8 (C2/C6), 130.3 (C3′/C5′), 124.3 (q, CF_3, J 192 Hz), 56.1 (4-OMe), 26.7 (2-Me/6-Me), 20.6 (4-Me); ^{19}F–NMR (282 MHz, CD_3CN) δ −79.32; m/z (NSI) 353 ([M−TFA], 100%), 226 (15). Found $[M-TFA]^+$ 353.0397. $C_{16}H_{18}I$ requires 353.0397. Anal. Calcd. for $C_{18}H_{18}F_3IO_3$ requires C, 46.37; H, 3.89. Found: C, 46.19; H, 3.82.

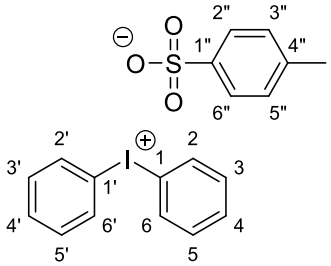
4.4 Diphenyliodonium trifluoroacetae (62)[2]



Trifluoroacetic acid (0.77 mL, 10 mmol) was added slowly, at −30 °C, to a solution of diacetoxyiodobenzene (1.61 g, 5 mmol) in dichloromethane (50 mL) and the mixture stirred for half an hour which was then allowed to attain room temperature for 1 h. After one hour, benzeneboronic acid (0.61 g, 5 mmol) was then added to the recooled mixture (−30 °C). The reaction mixture was allowed to attain room temperature and stirred overnight. The solvent

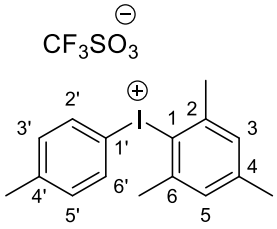
was removed in vacuo and the crude product crystallised from DCM–ether to give the product as a white crystalline solid (1.45 g, 3.7 mmol, 74%); mp 190–192 °C (from DCM–ether) (lit.,[2] mp 186–190 °C from acetone–ether); IR ν_{max} /cm^{-1} (neat) 3059, 1648, 1477, 1444, 1411, 1178, 1126; ^{1}H–NMR (300 MHz, d_6-DMSO) δ 8.26 (4H, d, H2/H2′/H6/H6′, J 8 Hz), 7.64 (2H, t , H4/H4′, J 8 Hz), 7.51 (4H, m, H3/H3′/H5/H5′); ^{13}C–NMR (75 MHz, d_6-DMSO) δ 159.3 (q, C=O, J 96 Hz), 135.6 (C2/C2′/C6/C6′), 132.2 (C4/C4′), 132.0 (C3/C3′/C5/C5′), 123.6 (q, CF_3, J 184 Hz); ^{19}F–NMR (282 MHz, d_6-DMSO) δ −73.42; m/z (NSI) 281 ([M−TFA]$^+$, 100%), 154 (45). Found: [M−TFA]$^+$, 280.9815. $C_{12}H_{10}I$ requires 280.9822. Anal. Calcd. for $C_{14}H_{10}F_3IO_2$ requires C, 42.66; H, 2.56. Found: C, 42.52; H, 2.57.

4.5 Diphenyliodonium tosylate (78)



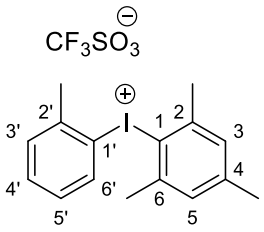
Tributylphenyl stannane (1.6 mL, 5 mmol) was added slowly to a solution of Koser's reagent (1.96 g, 5 mmol) in DCM (50 mL). The reaction mixture was heated for 3 h at 35 °C and it was left to stir over night at RT. The solvent was removed in vacuo and the crude product was crystallised from DCM–ether–petrol to give the product as a white solid (1.32 g, 2.92 mmol, 58%); mp 188–192 °C (from DCM–ether) (lit.,[252] mp 179–180 °C from DCM–hexane); IR ν_{max} /cm^{-1} (neat) 3078, 1660, 1598, 1441, 1208, 1166, 118, 1008, 989, 734; ^{1}H–NMR (300 MHz, CD_3CN) δ 8.08 (4H, m, H2/H2′/H6/H6′), 7.71 (2H, m, H4/H4′), 7.52 (6H, m, H3/H3′/H3″ /H5/H5′/H5″), 7.15 (2H, d, H2″/H6″, J 6.5 Hz), 2.35 (3H, s, Me); ^{13}C–NMR (75 MHz, DMSO-d_6) δ 146.15 (C1″), 138.1 (C4″), 135.7 (C2/C2′/C6/C6′), 132.4, 132.2 (C4/C4′), 128.5 (C3/ C3′/C5/C5′), 126.0 (C3″/C5″), 117.1 (C1/C1′), 21.3 (Me); m/z (NSI) 281 ([M−TsO]$^+$, 100%), 154 (100). Found: [M−TsO]$^+$, 280.9825. $C_{12}H_{10}I$ requires 280.9822. Anal. Calcd. for $C_{19}H_{17}IO_3S$ requires C, 50.45; H, 3.79; Found: C, 50.38; H, 3.74.

4.6 4-Methylphenyl(mesityl)iodonium triflate (79)[3]



A round bottom flask was charged with *mCPBA* (2.4 g, 7.77 mmol), it was dried under vacuum for 3 h and then dissolved in dry DCM (70 mL). To this solution 4-iodotoluene (1.54 g, 7.77 mmol) was added along with mesitylene (1.1 mL, 7.77 mmol) under nitrogen. The resulting solution was cooled to 0 °C and trifluoromethane sulfonic acid (1.4 mL, 15.54 mmol) was added drop-wise over a period of 10-15 min. The reaction mixture was stirred for 6 h. The solvent was removed in vacuo and the crude product was crystallised from DCM–ether to give the product as a white crystalline solid (2.30 g, 4.73 mmol, 67%); mp 178–180 °C (from DCM–ether) (lit.,[253] mp 183–184 °C); IR ν_{max}/cm^{-1} (neat) 3060, 2360, 1582, 1248, 1222, 1158, 1026, 984; ^{1}H–NMR (300 MHz, CD_3CN) δ 7.79 (2H, d, H2′/H6′, J 8 Hz), 7.35 (2H, d, H3′/H5′, J 8 Hz), 7.23 (2H, s, H3/H5), 2.63 (6H, s, 2-Me/6-Me), 2.40 (3H, s, 4-Me), 2.36 (3H, s, 4′-Me); ^{13}C–NMR (300 MHz, CD_3CN) δ 145.3 (C4′), 144.3 (C4), 143.0, 134.9, 133.6 (C2/C6), 130.8 (C3′/C5′), 123.6 (q, CF_3, J 158 Hz), 121.4 (C1′), 117.9 (C3/C5), 119.3 (C1), 26.8 (2-Me/6-Me), 20.9 (4-Me), 20.7 (4′-Me); ^{19}F–NMR (282 MHz, CD_3CN) δ −79.17; m/z (NSI) 338 $(M-TfO)^+$, 100%), 210 (15), 195 (66), 180 (10). Found: $[M-TfO]^+$ 337.0449. $C_{16}H_{18}I$ requires 337.0448. Anal. Calcd. for $C_{17}H_{18}F_3IO_3S$ requires C, 41.99; H, 3.73. Found: C, 42.07; H, 3.73.

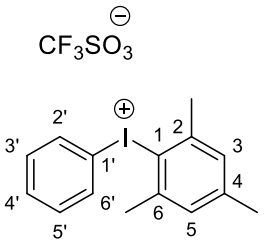
4.7 2-Methylphenyl(mesityl)iodonium triflate (80)[3]



The product prepared according to procedure **79** (Section 4.6). White crystalline solid (2.80 g, 5.76 mmol, 81%); mp 160–162 °C (from DCM–ether) (lit.,[3] mp 164–166 °C from DCM–ether); IR ν_{max}/cm^{-1} (neat) 3054, 2919, 2361, 1467, 1387, 1246, 1165, 1028, 1027, 1001,855; ^{1}H–NMR

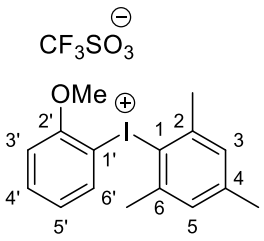
(300 MHz, CD_3CN) δ 7.74 (1H, d, H6′, J 9 Hz), 7.61 (2H, m, H4′/H5′), 7.27 (1H, d, H3′, J 3 Hz), 7.25 (2H, s, H3/H5), 2.60 (9H, d, 2-Me/2′-Me/6-Me, J 4 Hz), 2.37 (3H, s, 4-Me); ^{13}C–NMR (75 MHz, CD_3CN) δ 145.4 (C4), 143.2 (C2/C6), 141.6 (C2′), 135.9 (C4′), 133.5 (C5′), 133.0 (C3′), 131.1, 130.4 (C6′), 123.7 (q, CF_3, J 176 Hz), 120.3 (C1′), 117.9 (C3/C5), 117.0 (C1), 26.7 (2-Me/6-Me), 24.9 (4-Me), 20.6 (2′-Me); ^{19}F–NMR (282 MHz, CD_3CN) δ −79.23; m/z (NSI) 338 ([M−TfO]$^+$, 100%), 244 (7), 216 (22), 210 (21), 195 (66), 180 (11). Found: [M−TfO]$^+$ 337.0448. $C_{16}H_{18}I$ requires 337.0448. Anal. Calcd. for $C_{17}H_{18}F_3IO_3S$ requires C, 41.99; H, 3.73. Found: C, 41.96; H, 3.69.

4.8 Phenyl(mesityl)iodonium triflate (81)[3]



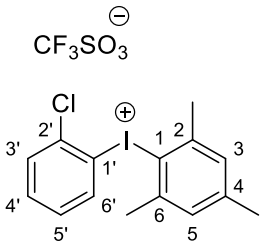
The product prepared according to procedure for **79** (Section 4.6). White crystalline solid (2.70 g, 5.38 mmol, 76%); mp 144–146 °C (from DCM–ether) (lit.,[254] mp 137–138 °C); IR ν_{max}/cm^{-1} (neat) 2983, 2844, 2361, 1654, 1590, 1478, 1436, 1382, 1277, 1237, 1157, 1023, 986; ^{1}H–NMR (300 MHz, CD_3CN) δ 7.87 (2H, d, H2′/H6′, J 9 Hz), 7.69 (1H, t, H4′, J 9 Hz), 7.53 (2H, m, H3′/H5′), 7.25 (2H, s, H3/H5), 2.63 (6H, s, 2-Me/6-Me), 2.37 (3H, s, 4-Me); ^{13}C–NMR (75 MHz, CD_3CN) δ 145.5 (C4), 143.2 (C4′), 134.8 (C2/C6), 133.0 (C2′/C6′), 130.9 (C3′/C5′), 123.7 (q, CF_3 196 Hz), 121.1 (C1), 119.4 (C3/C5), 112.5 (C1′), 26.8 (2-Me/6-Me), 20.7 (4-Me); ^{19}F–NMR (181 MHz, CD_3CN) δ −79.25; m/z (NSI) 324 ([M−TfO]$^+$, 100%), 196 ((19), 181 (6), 166 (5). Found: [M−TfO]$^+$, 323.0291. $C_{16}H_{18}I$ requires 323.0291. Anal. Calcd. for $C_{17}H_{18}F_3IO_4S$ requires C, 40.65; H, 3.61. Found: C, 40.71; H, 3.68.

4.9 2-Methoxyphenyl(mesityl)iodonium triflate (82)[3]



The product prepared according to procedure for **79** (Section 4.6). White crystalline solid (2.70g, 5.38 mmol, 76%); mp 126–128 °C (from DCM–ether); IR ν_{max}/cm^{-1} (neat) 2983, 2844, 2361, 1654, 1590, 1478, 1436, 1382, 1277, 1237, 1157, 1023, 986; ^{1}H–NMR (300 MHz, CD_3CN) δ 7.70 (2H, m, H3′/H5′), 7.25 (1H, d, H6′, J 2 Hz), 7.24 (2H, s, H3/H5), 7.09 (1H, q, H4′, J 7 Hz), 3.95 (3H, s, 2-OMe), 2.62 (6H, s, 2-Me/6-Me), 2.37 (3H, 4-Me); ^{13}C–NMR (75 MHz, CD_3CN) δ 145.3 (C2′), 144.3 (C4), 143.0 (C6′), 134.9 (C2/C6), 133.6 , 130.6, 130.8, 123.6, (q, CF_3, J 195 Hz), 121.4 (C1′), 108.8 (C1), 26.8 (2-Me/6-Me), 20.9 (2-OMe), 20.7 (4-Me); ^{19}F–NMR (282 MHz, CD_3CN) δ −79.23; m/z (NSI) 354 ([M−TfO]$^+$ 100%), 226 (11), 211 (34), 195 (20), 183 (7). Found: [M−TfO]$^+$, 353.0397. $C_{16}H_{18}I$ requires 353.0397. Anal. Calcd. for $C_{17}H_{18}F_3IO_4S$ requires C, 40.65; H, 3.61. Found: C, 40.71; H, 3.68.

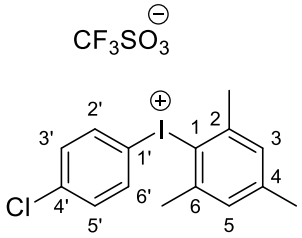
4.10 2-Chlorophenyl(mesityl)iodonium triflate (83)[3]



The product prepared according to procedure for **79** (Section 4.6). White crystalline solid (2.7 g, 5.19 mmol, 73%); mp 168–170 °C (from DCM–ether) (lit.,[255] mp 179–181 °C); IR ν_{max}/cm^{-1} (neat) 3064, 2985, 1590, 1450, 1218, 1278, 1241, 1162, 1026, 1002, 942,633; ^{1}H–NMR (300 MHz, CD_3CN) δ 7.77 (1H, dd, H6′, J 2, 6 Hz), 7.72 (2H, m, H3′/H5′), 7.41 (1H, m, H4′), 7.28 (2H, s, H3/H5), 2.62 (6H, s, 2-Me/6-Me), 2.39 (3H, s, 4-Me); ^{13}C–NMR (75 MHz, CD_3CN) δ 145.8 (C4), 143.6 (C2/C6), 136.3 (C4′), 136.3 (C3′/C5′), 131.8 (C2′/C6′), 131.2 (C3/C5), 123.6 (CF_3, q, J 181 Hz), 121.0 (C1′), 119.4, 113.7 (C1), 26.8 (2-Me/4-Me), 20.7 (4-Me); ^{19}F–NMR (282 MHz,

CD_3CN) δ −79.18; m/z (NSI) 358 ([^{37}Cl] M^+, 32%), 356 ([^{35}Cl] M^+, 100%), 230 (11). Found: $[M-TfO]^+$ 356.9895 $C_{15}H_{16}{}^{35}ClI$ requires 356.9901. Anal. Calcd. for $C_{16}H_{15}ClF_3IO_3S$ requires C, 37.93; H, 2.98. Found: C, 38.03; H, 3.05.

4.11 4-Chlorophenyl(mesityl)iodonium triflate (84)[3]



The product prepared according to procedure for **79** (Section 4.6). White crystalline solid (3.01 g, 5.78 mmol, 82%); mp 176–178 °C (from DCM–ether) (lit.,[253] mp 177–178 °C); IR ν_{max}/cm^{-1} (neat) 3063, 2975, 1748, 1473, 1245, 1222, 1162, 1088, 1024, 1000, 806, 631; ^{1}H–NMR (300 MHz, CD_3CN) δ 7.86 (2H, m, H2′/H6′), 7.54 (2H, m, H3′/H5′), 7.24 (2H, s, H3/H5), 2.62 (6H, s, 2-Me/6-Me), 2.36 (3H, s, 4-Me); ^{13}C–NMR (75 MHz, CD_3CN) δ 145.5 (C4), 143.2 (C2/C6), 139.1 (C4′), 136.4 (C3′/C5′), 132.9 (C2′/C6′), 130.9 (C3/C5), 127.8 (q, CF_3, J 172), 121.5 (C1′), 109.7 (C1), 26.8 (2-Me/6-Me), 20.7 (4-Me); ^{19}F–NMR (282 MHz, CD_3CN) δ −79.18; m/z (NSI) 358 ([^{37}Cl] M^+, 32%), 356 ([^{35}Cl] M^+, 100%), 230 (18). Found: M^+ 356.9900 $C_{15}H_{15}{}^{35}ClI$ requires $[M-TfO]^+$ 356.9901. Anal. Calcd for $C_{16}H_{15}ClF_3IO_3S$ requires C, 37.93; H, 2.97. Found C, 38.02; H, 3.01.

4.12 General Procedure using the FlowSyn™

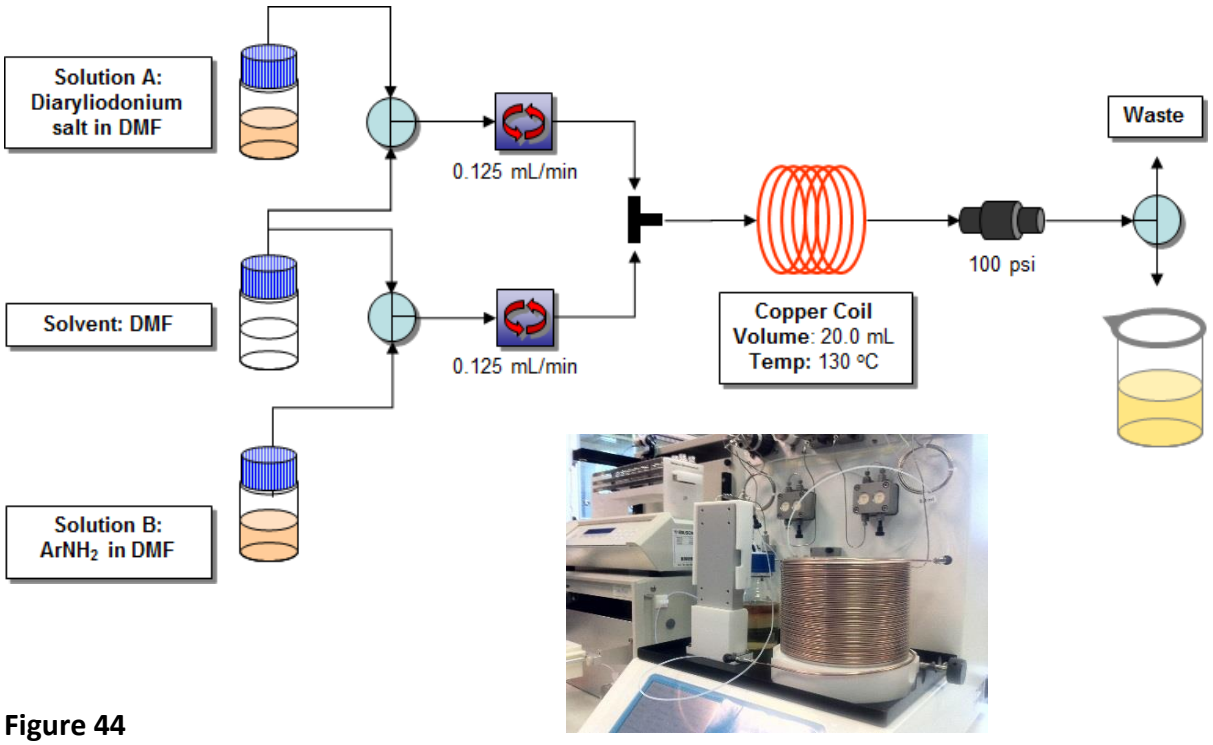


Figure 44

A series of experiments was carried out under manual control using the Uniqsis FlowSyn™ at different temperatures RT, 110 °C, 130 °C, and 150 °C. The FlowSyn™ was furnished with a 20 mL Uniqsis copper coil tube reactor (Figure 44) and the inlets were both set to the solvent and the outlet to the waste. The lines for both solvents and reagents were primed with solvent e.g. DMF, for 10 minutes, between runs and at the end of experiments for 10 minutes and finally with isopropanol for 10 minutes. The flow reactor was allowed to equilibrate (20 min) to the required temperature each time.

Series A (*N*-Arylation of aniline)

Sample bottle A was filled with a stock solution of diaryliodonium salt (5 mmol) in DMF (25 mL) and sample bottle B filled with $ArNH_2$ (5 mmol) also in DMF (25 mL). The solutions were pumped, through a T-mixer, by pump A and pump B respectively with DMF as the following solvent at 0.25 mL/min. The reaction solution was then passed through the copper coil reactor (20 mL) and the outflow through a 100 psi back pressure regulator. The crude product was collected in a measuring cylinder, which was cooled to 0 °C for the reactions at 110 °C, 130 °C, and 150 °C and the resultant mixture analysed by HPLC. The product was isolated by the addition of water, extraction with ether and then purification by flash chromatography.

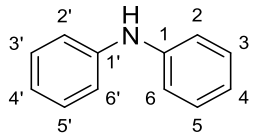
Series B (*N* & *O*-selectivity)

Sample bottle A was filled with a stock solution of diaryliodonium trifluoroacetate (5 mmol) in DMF (25 mL) and sample bottle B filled with the nucleophile (5 mmol e.g. ArOH) also in DMF (25 mL). The solutions were pumped, through a T-mixer, by pump A and pump B respectively with DMF as the following solvent at 0.25 mL/min. The reaction solution was then passed through the copper coil reactor (20 mL) and the outflow through a 100 psi back pressure regulator. The crude product was collected in a measuring cylinder, which was cooled to 0 °C for the reactions at 110 °C, and 130 °C and the resultant mixture analysed by HPLC. The product was isolated by the addition of water, extraction with ether and then purification by flash chromatography.

Table 1: System configuration and manual setup

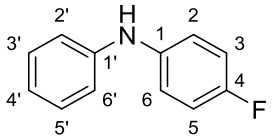
System Configuration			
RH reactor:		**LH reactor:**	
Type	Coil	Type	No
Material	Copper	Material	
Volume	20 mL	Volume	
Max Tem	150 °C	Max Temp	
System Dead Volume	0.0 mL	Heat Exchanger	Yes
Minimum Pressure	-15 psi	Pump Start Delay	5 s
Maximum Pressure	500 psi	Pressure Unit	psi
Pressure Threshold	Off	Equil. Flow Rate	0.5 mL/min
Wash Flow Rate	5.0 mL/min		
Manual Setup			
Inlet A	Reagent	Pump A	0.125 mL/min
Inlet B	Reagent	Pump B	0.125 mL/min
Outlet	Collect	Total flow rate	0.25 mL/min
Loop A	Load	Coil temperature	RT,110, 130,150
Loop B	Load	Column temp	RT

4.13 Diphenylamine (64)



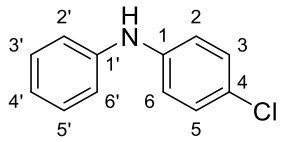
Using aniline gave the product as a white crystalline solid (0.16 g, 0.95 mmol, 85%); mp 50–52 °C (from ether–petrol) (lit.,[2] mp 51–53 °C); R_f = 0.33 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat), 3383, 3042, 1584, 1484, 1307, 1172, 1023; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.84 (4H, m, H3/H3′/H5/H5′), 7.59 (4H, d, H2/H2′/H6/H6′, J 9 Hz), 7.42 (2H, t, H4/H4′, J 9 Hz,), 5.87 (1H, s, br, N-H); ^{13}C–NMR (100 MHz, $CDCl_3$) δ 154.0 (C1/C1′), 137.0 (C3/C3′/C5/C5′), 126.3 (C4/C4′), 122.6 (C2/C2′/C6/C6′); m/z (NSI) 170 ($[M+H]^+$, 100%). Found: $[M+H]^+$, 170.0963 $C_{12}H_{12}N$ requires 170.0964.

4.14 4-Fluorodiphenylamine (85)



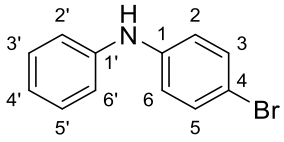
Using 4-fluoroaniline gave the product as a white crystalline solid (0.17 g, 0.91 mmol, 83%); mp 33–35 °C (from ether–petrol) (lit.,[2] mp 36–38 °C from petrol); R_f = 0.34 (15: 85 ether/petrol); IR ν_{max}/cm^{-1} (neat), 3382, 3052, 1595, 1505, 1321, 1216, 1447, 1320, 1217, 1098; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.19 (2H, t, H3′/H5′, J 8 Hz), 6.99 (6H, m, H2/H2′/H3/H5/H6/H6′), 6.84 (1H, t, H4′, J 7 Hz), 5.47 (1H, s, br, N-H); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 159.7 (C4, d, J 160 Hz), 143.5 (C1′), 138.9 (C1), 129.4 (C3′/C5′), 120.6 (C2/C6), 120.5 (C2′/C6′), 116.8 (C3/C5), 115.8 (C4′); ^{19}F–NMR (282 MHz, $CDCl_3$) δ 121.89; m/z (NSI) 188 ($[M+H]^+$, 100%), 149 (4). Found: $[M+H]^+$, 188.0870. $C_{12}H_{11}FN$ requires 188.0870. Anal. Calcd for $C_{12}H_{10}FN$ C, 76.99; H, 5.38; N, 7.48. Found: C, 76.93; H, 5.47; N, 7.47.

4.15 4-Chlorodiphenylamine (86)



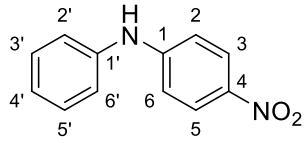
Using 4-chloroaniline gave the product as a white crystalline solid (0.16 g, 0.79 mmol, 71%); mp 60–62 °C (from ether–petrol) (lit.,[256] mp 64–66 °C from hexane); R_f = 0.52 (1.5:8.5 ether/petrol); IR ν_{max}/cm^{-1}(neat) 3403, 1586, 1483, 1444, 1307, 1307, 1238, 1171, 1089; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.15 (4H, m, H3/H3′/H5/H5′), 6.99 (5H, m, H2/H2′/H4′/H6/H6′), 5.61 (1H, s, br, N-H); ^{13}C–NMR (100 MHz, $CDCl_3$) δ 153.4 (C1′), 152.1 (C1), 137.0 (C3/C5), 136.4 (C3′/C5′), 131.9 (C4), 127.1(C4′), 123.6 (C2/C6), 122.7 (C2′/C6′); m/z (APCI) 206 ([^{37}Cl]M^+, 32%), 204 ([^{35}Cl]M^+, 100%), 202 (3), 123 (14), 117 (44), 111 (60), 109 (44),103 (19). Found: $[M+H]^+$, 204.0577. $C_{12}H_{11}{}^{35}ClN$ requires 204.0575. Anal. Calcd for $C_{12}H_{10}ClN$; C, 70.77; H, 4.95; N, 6.88. Found: C, 70.69; H, 5.04; N, 6.91.

4.16 4-Bromodiphenylamine (87)



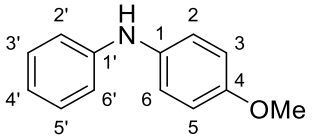
Using 4-bromoaniline gave the product as a white crystalline solid (0.19 g, 0.77 mmol, 70%); mp 84–88 °C (from ether–petrol) (lit.,[10] mp 87–89 °C from petrol); R_f = 0.42 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3400, 2536, 1580, 1481, 1309, 1239, 1071, 1001, 802, 747, 690; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.27 (4H, m, H3/H5/H3′/H5′), 6.96 (2H, dd, H2′/H6′, J 1, 7Hz), 6.88 (1H, t, H4′, J 7 Hz), 6.86 (2H, m, H2/H6), 5.57 (1H, s, NH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 142. 4 (d, C1/C1′, J 3 Hz) 132.2 (C3/C5), 129.5 (C3′/C5′), 121.7 (C4′), 119.0 (C2′/C6′), 118.3 (C2/C6), 112.6 (C4); m/z (NSI) 250 ([^{81}Br] $[M+H]^+$, 99%), 248 ([^{79}Br] $[M+H]^+$, 100%), 186 (13), 149 (26), 136 (5). Found: $M+H^+$, 248.0071 $C_{12}H_{11}{}^{79}BrN$; requires $M+H^+$, 248.0069; Anal. Calcd for $C_{12}H_{10}BrN$; C, 58.09; H, 4.06; N, 5.65. Found: C, 57.91; H, 3.93; N, 5.74.

4.17 4-Nitrodiphenylamine (88)



Using 4-nitroaniline gave the product as a yellow crystalline solid (0.15, 0.70 mmol, 64%); mp 131–134 °C (from ether–petrol) (lit.,[10] mp 135–136 °C); R_f = 0.34 (2:8 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3337, 1661, 1494, 1295, 1186, 1111, 1001, 829; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 8.05 (2H, d, H3/H5, J 9Hz), 7.35 (2H, m, H3′/H5′), 7.16 (3H, m, H2′/H4′/H6′), 6.88 (2H, d, H2/H6, J 9Hz), 6.18 (1H, s, NH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 150.1 (C1), 140.0 (C1′), 139.5 (C4), 129.8 (C3′/C5′), 126.3 (C3/C5), 124.7 (C2/C6), 117.2 (C4′) 113.7 (C2′/C6′); m/z (APCI) 215 ([M+H]$^+$, 100%), 123 (16), 117 (12), 111 (50), 107 (5), 102 (35). Found [M+H]$^+$ 215.0818. $C_{12}H_{11}N_2O_2$ requires 215.0815.

4.18 4-Methoxydiphenylamine (66)



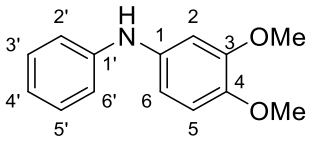
Method A

Using diphenyliodonium trifluoroacetate **62** and 4-methoxy aniline gave the product as a white crystalline solid (0.18 g, 0.90 mmol, 82%); mp 102–104 °C (from ether–petrol) (lit.,[10] mp 101–102 °C), R_f = 0.34 (1.5:8.5 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3387, 3009, 2960, 2538, 1867, 1595, 1500, 1402, 1297, 1236, 1177, 1297, 1236, 1024, 749; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, t, H3′/H5′, J 8Hz), 7.11 (2H, d, H3/H5, J 8 Hz), 6.95 (2H, d, H2/H6, J 9 Hz), 6.92 (3H, m, H2′/H4′/H6′), 5.53 (1H, s, NH), 3.84 (3H, s, OMe); ^{13}C–NMR (100 MHz, CD_3CN) δ 155.3 (C4), 145.2 (C1′), 135.7 (C1), 129.3 (C3′/C5′), 122.2 (C2/C6), 119.6 (C4′), 115.6 (C2′/C6′), 114.7 (C3/C5), 55.6 (OMe); m/z (NSI) 200 ([M+H]$^+$, 100%), 199 (6), 186 (8), 169 (2), 149 ((4). Found: [M+H]$^+$, 200.1065 $C_{13}H_{14}NO$ requires, 200.1070. Anal. Calcd for $C_{13}H_{13}NO$; C, 78.22; H, 6.58; N, 7.03. Found C, 78.29; H, 6.46; N, 6.98.

Method B

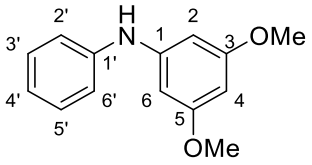
Using 4-Methoxyphenyl(mesityl)iodonium trifluoroacetate **65** and aniline gave the product as white crystalline solid (0.05 g, 0.25 mmol, 23%).

4.19 3,4-Dimethoxydiphenylamine (67)



Using 3,4-dimethoxy aniline gave the product as a white crystalline solid (0.22 g, 0.95 mmol, 87%); mp 98–100 °C (from ether–petrol) (lit.,[2] mp 96–98 °C); R_f = 0.31 (1.5:8.5 ether/petrol), IR ν_{max}/cm^{-1} (neat): 3380, 2957, 2928, 1592, 1500, 1458, 1308, 1230, 1165, 1024; ^{1}H–NMR ($CDCl_3$, 700 MHz) δ 7.27 (2H, t, H3′/H5′, J 7 Hz), 6.98 (2H, d, H2′/H6′, J 7 Hz), 6.90 (1H, t, H4′, J 7 Hz), 6.85 (1H, d, H5 or H6, J 8 Hz), 6.75 (1H, d, H2, J 2 Hz), 6.70 (1H, dd, H6 or H5, J 2, 8 Hz), 5.39 (1H, s,br, NH) 3.89 (3H, s, 4-OMe) 3.85 (3H, s, 3-OMe);^{13}C–NMR (175MHz, $CDCl_3$) δ 149.6 (C1′), 144.9 (C3), 144.7 (C4), 136.3 (C1), 129.4 (C3′/C5′), 119.8 (C4′), 116.0 (C2′/C6′), 112.1 (C5/C6), 105.3 (C2), 56.3 (3-OMe), 55.9 (4-OMe); m/z: (NSI) 252 ([M+Na]$^+$, 100%), 230 (36). Found: [M+H]$^+$ 230.1175. $C_{14}H_{16}NO_2$ requires 230.1176. Anal. Calcd. For $C_{14}H_{15}NO_2$; C, 73.34; H, 6.59; N, 6.11. Found: C, 73.40; H, 6.59; N, 6.13.

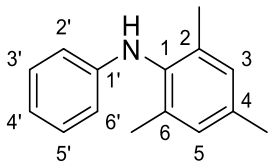
4.20 3,5-Dimethoxydiphenylamine (89)



Using 3,5-dimethoxyaniline gave the product as a white crystalline Solid (0.20 g, 0.87 mmol , 79%); mp 100–102 °C (from ether–petrol) (lit.,[257] mp 72–73 °C); R_f = 0.31 (1.5:8.5 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3352, 3047, 2943, 1590, 1536, 1482, 1290, 1251, 1203, 1146, 1053, 928, 810; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, t, H3′/H5′, J 8 Hz), 7.13 (2H, d, H2′/H6′, J 8 Hz), 7.00 (1H, t, H4′, J 8 Hz), 6.27 (2H, s, H2/H6), 6.10 (1H, s, H4), 5.74 (1H, s, NH), 3.79 (6H,

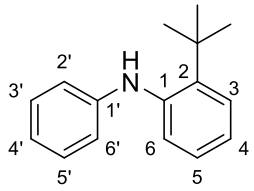
s, 3-OMe/5-OMe); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 161. 6 (C3/C5), 142.3 (C1), 142.5 (C1′), 129.4 (C3′/C5′), 121.5 (C4′), 118.8 (C2′/C6′), 95.8 (C2/C6), 93.0 (C4), 55.3 (3-OMe/5-OMe); m/z (NSI) 230 ([M+H]$^+$, 100%), 229 (6), 220 (8), 198 (5), 187 (14), 172 (24), 149 (6). Found: [M+H]$^+$, 230.1177. $C_{14}H_{16}NO_2$ requires 230.1176. Anal. Calcd. for $C_{14}H_{15}NO_2$; C, 73.34; H, 6.59; N, 6.11. Found: C, 73.27; H, 6.95; N, 6.19.

4.21 2,4,6-Trimethyldiphenylamine (90)



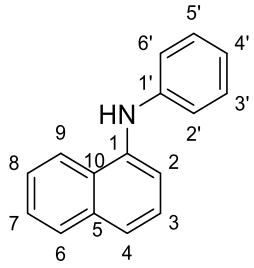
Using 2,4,6-trimethylaniline gave the product as a white crystalline solid (0.19 g, 0.90 mmol, 81%); mp 52–54 °C (from ether–petrol) (lit.,[10] mp 54–56 °C); R_f = 0.4 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat), 3390, 2964, 1599, 1496, 1376, 1312, 1254, 1069; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.18 (2H, t, H3′/H5′, J 7 Hz), 6.97 (2H, s, H3/H5), 6.96 (1H, t, H4′, J 8 Hz), 6.51 (2H, d, H2′/H6′, J 8 Hz), 5.12 (1H, s, br, N-H), 1.76 (3H, s, 4-Me), 1.59 (6H, s, 2-Me/6-Me); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 158.5 (C1′), 145.3 (C2/C6), 144.6 (C1), 144.4 (C4′),136.7(C3′/C5′),122.8 (C3/C5), 166.7 (C2′/C6′), 21.9 (4-Me), 18.6 (2-Me/6-Me); m/z (NSI) 212 ([M+H]$^+$, 100%), 211 (42), 197 (6), 180 (2), 149 (4). Found: [M+H]$^+$, 212.1434. $C_{15}H_{18}N$ requires 212.1434. Anal. Calcd. for $C_{15}H_{17}N$; C, 85.26; H, 8.11; N, 6.63. Found: C, 85.15; H, 8.24; N, 6.72.

4.22 2-tert-Butyldiphenylamine (91)



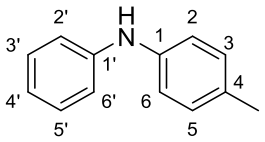
Using 2-tert-butylaniline gave the product as a white crystalline solid (0.20 g, 0.89 mmol, 80%); mp 65–68 °C (from ether–petrol) (lit.,[10] mp 64–65 °C); R_f = 0.42 (5:95 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3440, 2965, 1594, 1504, 1441, 1308, 1259, 1177, 744; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.36 (1H, dd, H3, J 2, 6 Hz), 7.22 (4H, m, H2′/H3′/H5′/H6′), 7.02 (1H, m, H4′), 6.77 (3H, m, H4/H5/H6) 5.33 (1H, s, NH), 1.36 (9H, s, 3 × Me); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 145.9 (C1′), 143.4 (C2), 141.2 (C1), 129.3 (C3′/C5′), 127.1 (C5), 126.9, 125.9, 123.9, 119.2, 115.9 (C2′/C6′), 34.9 (C-Me_3). 30.6 (3 × Me); m/z (NSI) 226 ([M+H]$^+$, 100%), 220 (3), 210 (5), 194 (7), 149 (4). Found: 226.1591. $C_{16}H_{20}N$ requires 226.1590. Anal. Calcd. for $C_{16}H_{19}N$; C, 85.28; H, 8.50; N, 6.22. Found: C, 85.34; H, 8.53; N, 6.2

4.23 *N*-Phenylnaphthalen-1-amine (92)



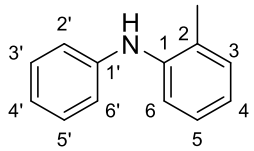
Using 1-naphthylamine gave the product as a white solid (0.16 g, 0.73 mmol, 67%); mp 51–54 °C (from ether–petrol) (lit.,[258] mp 54–56 °C); R_f = 0.42 (5:95 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3407, 3053, 2411, 1574, 1523, 1492, 1306, 1270, 1095, 734; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, m, H8), 7.80 (1H, m, H9), 7.48 (1H, m, H4), 7.42 (2H, m, H2/H3), 7.32 (2H, m, H3′/H5′), 7.21 (2H, m, H6/H7), 6.93 (2H, m, H2′/H6′), 6.84 (1H, tt, H4′, J 1, 6 Hz), 5.46 (1H, s, NH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 144.8 (C1′), 138.8 (C1), 134.7 (C5), 129.4 (C3′/C5′), 128.6 (C10), 127.8, 126.2 (d, C7/C9, J 8 Hz), 125.7 (C4′), 123.0, 121.8, 120.5 (C4), 117.4 (C2′/C6′), 115.9 (C2); m/z (NSI) 220 ([M+H]$^+$, 100%), 219 (2), 186 (4), 149 (3). Found: [M+H]$^+$, 220.1122. $C_{16}H_{14}N$ requires [M+H]$^+$ 220.1121. Anal. Calcd. for $C_{16}H_{13}N$; C, 87.64; H, 5.98; N, 6.39. Found: C, 87.55; H, 6.08; N, 6.48.

4.24 4-Methyldiphenylamine (93)



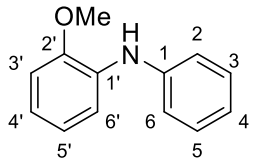
Using 4-methylphenyl(mesityl)iodonium triflate gave the product as a white crystalline solid (0.15 g, 0.82 mmol, 75%); mp 78–80 °C (from ether–petrol) (lit.,[259] mp 86–89 °C); R_f = 0.40 (1:9 ether/petrol); IR, ν_{max}/cm^{-1} (neat) 3395, 3015, 2918, 2360, 1594, 1499, 1307, 1241, 1078, 807, 745; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.13 (2H, t, H3′/H5′, J 8 Hz), 6.99 (2H, d, H2′/H6′, J 8 Hz), 6.91 (4H, d, H2/H3/H5/H6, J 7 Hz), 6.80 (1H, t, H4′, J 8 Hz), 5.49 (1H, s, NH), 2.21 (3H, s, Me); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 148.3 (C1), 142.8 (C1′), 133.0 (C4), 129.3 (C3/C5), 121.2, 120.8 (C4′), 119.9, 118.6 (C2/C6), 114.7, 110.6, 55.6 (Me); m/z (NSI) 184 ($[M+H]^+$, 100%), 183 (2), 180 (2), 169 (6), 156 (2), 149 (20), 129 (2). Found: $[M+H]^+$, 184.1120. $C_{13}H_{14}N$ requires 184.1121. Anal. Calcd for $C_{13}H_{13}N$; C, 85.21; H, 7.15; N, 7.64. Found: C, 85.19; H, 7.21; N, 7.69.

4.25 2-Methyldiphenylamine (94)



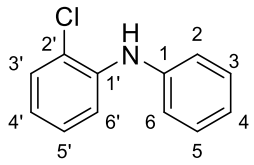
Using 2-methylphenyl(mesityl)iodonium triflate gave the product as a white crystalline solid (0.13 g, 0.71 mmol, 64 %); mp 38–40 °C (from ether–petrol) (lit.,[259] mp 39–40 °C); R_f = 0.40 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3403, 1930, 1493, 1386, 1315, 1258, 1175, 114, 1042, 742; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.20 (4H, m, H2′/H3′/H5′/H6′), 7.07 (1H, t, H4′, J 6 Hz), 6.90 (4H, m, H3/H4/H5/H6), 5.30 (1H, s, NH), 2.18 (3H, s, Me); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 143.9 (C1′), 141.2, (C1), 131.0 (C2), 129.3 (C3′/C5′), 128.3 (C3), 126.8 (C5), 122.0 (C4), 120.5 (C6), 118.7 (C4′), 117.5 (C2′/C6′), 18.0 (Me); m/z (NSI) 184 ($[M+H]^+$, 100%) 169 (8), 149 (4). Found: $[M+H]^+$, 184.1120 $C_{13}H_{14}N$ requires 184.1121.

4.26 2-Methoxydiphenylamine (95)



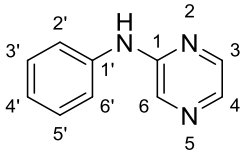
Using 2-methoxyphenyl(mesityl)iodonium triflate gave the product as a white crystalline solid (0.16 g, 0.80 mmol, 73%); mp 29–30 °C (from ether–petrol) (lit.,[260] mp 31–32 °C); R_f = 0.33 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3407, 3047, 2834, 1590, 1513, 1463, 1232, 1115, 1026, 738; ^{1}H–NMR (400 MHz, $CDCl_3$) δ (3H, m, H3′/H4′/H5′), 7.08 (2H, m, H2/H6), 6.86 (1H, t, H6′, J 8 Hz), 6.82 (3H, m, H3/H4/H5), 6.06 (1H, s, NH), 3.79 (3H, s, OMe); ^{13}C–NMR (100 MHz, $CDCl_3$) δ 148.3 (C2′), 142.7 (C1), 133.0 (C1′), 129.3 (C3/C5), 121.2, 120.8, 119.9, 118.6 (C2/C6), 114.7 (C3′), 110.5 (C6′), 55.6 (OMe); m/z (NSI) 200 ([M+H]$^+$, 100%), 185 (74) 180 (4) 168 (52), 156 (7). Found: [M+H]$^+$, 200.1068 $C_{13}H_{14}$ NO requires 200.1070. Anal. Calcd. for $C_{13}H_{13}NO$; C, 78.36; H, 6.58; N, 7.03. Found: C, 78.38; H, 6.49; N, 7.04.

4.27 2-Chlorodiphenylamine (96)



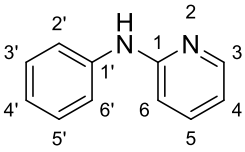
Using 2-chlorophenyl(mesityl)iodonium triflate gave the product as a white crystalline solid (0.13 g, mmol, 0.64, 58%); mp 98–99 °C (from ether–petrol) (lit.,[261] mp 101–102 °C); R_f = 0.34 (1.5:8.5 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3405, 3041, 2401, 1931, 1591, 1497, 1314, 1219. 1035, 741; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.40 (4H, m, H2/H3/H5/H6), 7.20 (3H, m, H3′/H5′/H6′), 7.09 (1H, m, H4), 6.86 (1H, ddd, H4′, J 2, 2, 7 Hz); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 141.5 (C1′)140.3 (C1), 129.7 (C3′), 129.4 (C3/C5), 127.4 (C5′), 122.7 (C2′), 121.5 (C6′), 120.3, 120.2 (C2/C6), 115.7 (C4); m/z (NSI) 206 ([^{37}Cl]M$^+$, 32%), 204 ([^{35}Cl]M$^+$, 100%), 202 (2). Found [M+H]$^+$ 204.0574. $C_{12}H_{11}{}^{35}ClN$ requires 204.0575.

4. 28 *N*-Phenyl2-aminopyrazine (97)



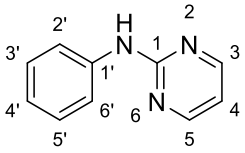
Using 2-aminopyrazine gave the product as a white crystalline solid (0.13 g, 0.76 mmol, 69%); mp 133–135 °C (from ether–petrol) (lit.,[262] mp 130–132 °C); R_f = 0.25 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3277, 3211, 3100, 3053, 2923, 1584, 1520, 1444, 1327, 1197; 1H–NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, s, H6), 8.04 (1H, m, H3), 7.91 (1H, d, H4, J 3 Hz), 7.38 (4H, m, H2′/H3′/H5′/H6′) 7.06 (1H, m, H4′), 6.72 (1H, s, N-H); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 152.3 (C1), 142.0 (C3), 139.2 (C1′), 134.9 (C4), 132.9 (C6), 129.4 (C3′/C5′), 123.6 (C4′), 120.3 (C2′/C6′); m/z (NSI) 172 ([M+H]$^+$, 100%), 149 (2). Found [M+H]$^+$ 172.0866. $C_{10}H_{10}N_3$ requires 172.0869. Anal. Calcd. for $C_{10}H_9N_3$ requires C, 70.16; H, 5.30; N, 24.50. Found: C, 70.25; H, 5.35; N, 24.53.

4.29 *N*-Phenyl-2-aminopyridine (98)



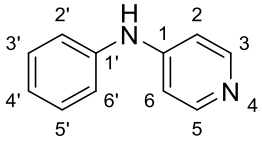
Using 2-aminopyridine gave the product as a white crystalline solid (0.08 g, 0.47 mmol, 43%); mp 141–143 °C (from ether–petrol) (lit.,[118] mp 140–141°C); R_f = 0.22 (3:7 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3226, 3178, 3098, 3011, 254, 2855, 1589, 1443, 1327, 1160; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, d, H3, J 6 Hz), 7.44 (1H, m, H4′), 7.26 (3H, m, H2′/H5/H6′) 7.00 (1H, m, H6), 6.82 (1H, t, H4, J 8 Hz), 6.68 (2H, m, H3′/H5′); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 156.0 (C1), 148.4 (C3), 140.5 (C1′), 137.7 (C5), 129.3 (C3′/C5′), 122.8 (C4′), 120.4 (C2′/C6′), 115.0 (C4), 108.2 (C6); m/z (NSI) 171 ([M+H]$^+$, 100%). Found [M+H]$^+$ 171.0913. $C_{11}H_{11}N_2$ requires 171.0917. Anal. Calcd. for $C_{11}H_{10}N_2$ requires C, 77.62; H, 5.92; N, 16.46. Found: C, 77.67; H, 5.99; N, 16.32

4.30 *N*-Phenyl-2-aminopyrimidine (99)



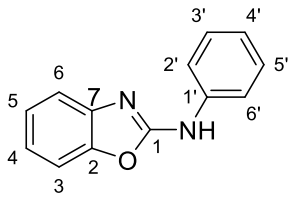
Using 2-aminopyrimidine gave the product as a white crystalline solid (0.13 g, 0.76 mmol, 69%); mp 104–106 °C (from ether–petrol) (lit.,[262] mp 106–108 °C); R_f = 0.23 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3339, 3268, 2926, 2358, 2166, 1980, 1594, 1498, 1460, 1416, 1285, 1156, 1034, 891; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 8.36 (2H, d, H3/H5, J 4 Hz), 7.56 (2H, d, H2′/H6′ J 7 Hz), 7.30 (2H, t, H3′/H5′, J 8 Hz), 7.07 (1H, s, NH), 7.01 (1H, t, H4′, J 7 Hz), 6.67 (1H, t, H4, J 5 Hz); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 158.0 (C3/C5), (139.3 (C1), 136.4 (C1′), 129.0 (C3′/C5′), 122.7 (C4′), 119.5 (C2′/C6′), 112.6 (C4); m/z (NSI) 172 ($[M+H]^+$, 100%), 171 (5). Found $[M+H]^+$ 172.0867. $C_{10}H_{10}N_3$ requires 172.0869. Anal. Calcd. for $C_{10}H_9N_3$requires C, 70.16; H, 5.30; N, 24.54. Found: C, 69.99; H, 5.25; N, 24.42.

4.31 *N*-Phenyl-4-aminopyridine (100)



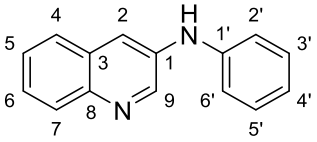
Using 4-aminopyridine gave the product as a white crystalline solid (0.14 g, 0.82 mmol, 75%); mp 174–176 °C (from ether–petrol) (lit.,[263] mp 175 °C from water); R_f = 0.23 (4:6 ether/petrol). IR ν_{max}/cm^{-1} (neat): 3344, 2925, 1602, 1446, 1221, 1015, 836; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.13 (2H, m, H3′/H5′), 7.04 (2H, d, H3/H5, J 9 Hz), 6.73 (2H, d, H2′/H6′, J 9 Hz), 6.66 (1H, t, H4′, J 7 Hz), 6.56 (2H, m, H2/H6), 4.55 (1H, s, NH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 148.0 (C1), 131.5 (C1′), 129.9 (C3/C5), 129.3 (C3′/C5′), 117.5 (C4′), 115.4 (C2′/C6′), 113.0 (C2/C6).

4.32 *N*-Phenyl-2-aminobenzoxazole (101)



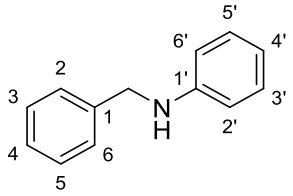
Using 2-aminooxazole gave the product as a white crystalline solid (0.10 g, 0.47 mmol, 43%); mp 173–175 °C (from ether–petrol) (lit.,[264] mp 176–179 °C); R_f = 0.26 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3564, 3390, 2925, 1981, 1599, 1498, 1446, 1243, 1057, 1031, 802; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, m, H4/H5), 7.45 (1H, d, H2′, J 7 Hz), 7.36 (3H, m, H3/H6/H6′), 7.17 (1H, m, H4′), 7.09 (2H, m, H3′/H5′); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 147.8 (C1), 146.3 (C2), 142.4 (C7), 137.7 (C1′), 129.4 (C3′/C5′), 124.3 (C5), 123.4 (C4′), 122.0 (C4), 118.3 (C2′/C6′), 117.3 (C6), 109.1 (C3); m/z (ASAP) 211 ([M+H]$^+$, 100%), 179 (28), 169 (45), 161 (37), 137 (46), 135 (8), 120 (4), 90 (5). Found [M+H]$^+$ 211.0871. $C_{13}H_{11}N_2O$ requires 211.0869.

4.33 *N*-Phenyl-3-aminoquinoline (102)



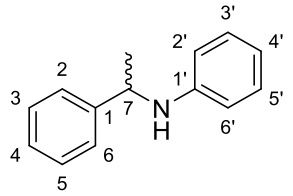
Using 3-aminoquinoline gave the product as a white crystalline solid (0.15 g, 0.68 mmol, 61%); mp 124–126 °C (from ether–petrol) (lit.,[265] mp 116 °C); R_f = 0.33 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3273, 3194, 3032, 2927, 1595, 1494, 1307, 734; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 8.73 (1H, d, H2, J 3 Hz), 8.04 (1H, d, H6, J 8 Hz), 7.76 (1H, d, H9, J 4 Hz), 7.68 (1H, dd, H7, J 2, 8 Hz), 7.55 (2H, m, H3′/H5′), 7.41 (2H, m, H2′/H6′), 7.23 (2H, m, H4/H5), 7.10 (1H, m, H4′), 5.96 (1H, s, NH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 145.0 (C2), 143.6 (C1′), 141.8 (C1), 137.0 (C3), 129.7 (C3′/C5′), 129.0 (C5), 128.8 (C4), 127.2 (C9), 126.6 (C6), 126.5 (C7), 122.4 (C8), 118.6 (C2′/C6′), 117.0 (C4′); m/z (NSI) 221 ([M+H]$^+$, 100%) 219 (4), 206 (5). Found [M+H]$^+$ 221.1071. $C_{10}H_{10}N_2$ requires 221.1073. Anal. Calcd. for $C_{10}H_9N_2$ requires C, 81.79; H, 5.49; N, 12.72. Found: C, 81.78; H, 5.40; N, 12.65.

4.34 *N*-Benzylaniline (103)



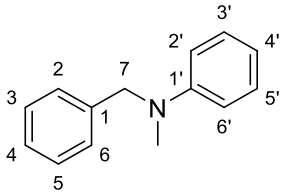
Using benzylamine gave the product as a white crystalline solid (0.15 g, 0.82 mmol, 74%); mp 38–40 °C (lit.,[266] mp 39–40 °C); R_f = 0.36 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3419, 2849, 1601, 1505, 1452, 1324, 1266, 1180, 1028, 747, 691; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.31 (5H, m, H2/H3/H4/H5/H6), 7.13 (2H, t, H3′/H5′, J 8 Hz), 6.66 (1H, t, H4′, J 8 Hz), 6.58 (2H, d, H2′/H6′ J 8 Hz), 4.25 (2H, s, CH_2), 3.94 (1H, s, N-H); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 148.1 (C1′), 139.4 (C1), 129.3 (C3′/C5′), 128.7 (C3/C5), 127.5 (C2/C6), 127.3 (C4), 117.6 (C4′), 112.9 (C2′/C6′), 48.4 (CH_2); m/z (NSI) 184 ([M+H]$^+$, 100%) 181 (2), 163 (2), 149 (4). Found [M+H]$^+$ 184.1119. $C_{13}H_{14}N$ require 184.1121. Anal. Calcd for $C_{13}H_{13}N$ requires C, 85.21; H, 7.15; N, 7.64. Found: C, 85.14; H, 7.23; N, 7.61.

4.35 (±)-*α*-Methylbenzylaniline (104)



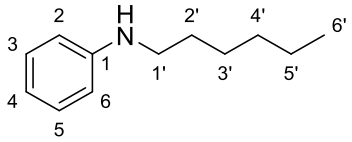
Using (±)-*α* -methylbenzylamine gave the product as a white crystalline solid (0.18 g, 0.91 mmol, 83%); mp 50–52 °C (from ether–petrol) (lit.,[267] mp 39–41°C); R_f = 0.41 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3411, 2964, 2867, 2410, 1600, 1503, 1316, 1257, 747, 691; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.30 (4H, m, H2/H3/H5/H6), 7.16 (1H, ttt, H4, J 2, 5, 7 Hz), 7.03 (2H, m, H3′/H5′), 6.58 (1H, t, H4′, J 7 Hz), 6.44 (2H, d, H2′/H6′, J 8 Hz), 4.43 (1H, q, CH, J 7 Hz), 3.93 (1H, s, NH), 1.43 (3H, d, Me, J 7 Hz); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 147.3 (C1′), 145.3 (C1), 129.2 (C3′/C5′), 128.7 (C3/C5), 126.9 (C2/C6), 125.9 (C4), 117.3 (C4′), 113.3 (C2′/C6′), 53.5 (CH), 25.1 (Me); m/z (NSI) 198 ([M+H]$^+$, 100%), 193 (2), 178 (2), 163 (3), 149 (6). Found [M+H]$^+$ 198.1277. $C_{14}H_{16}N$ requires 198.1277. Anal. Calcd. for $C_{14}H_{15}N$ requires C, 85.24; H, 7.66; N, 7.10. Found C, 85.17; H, 7.74; N, 7.09.

4.36 *N*-Methylbenzylaniline (105)



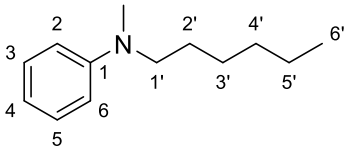
Using *N*-methylbenzylamine gave the product as a white crystalline solid (0.16 g, 0.81 mmol, 74%); mp 37–39 °C (lit.,[268] mp 38 °C); R_f = 0.40 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3062, 3026, 2870, 2818, 1598, 1505, 1451, 1353, 1250, 1116, 1028, 747, 727, 690; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.23 (2H, m, H3/H5), 7.14 (5H, m, H2/H2′/H4/H6/H6′), 6.67, (3H, m, H3′/H4′/H5′), 4.42, (2H, s, CH_2), 2.90 (3H, s, Me); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 149.9 (C1), 139.2 (C1′), 129.3 (C3′/C5′), 128.7 (C3/C5), 126.7 (C2/C6), 126.9 (C4), 116.7 (C4′), 112.5 (C2′/C6′), 56.7 (CH_2), 38.6 (Me); m/z (NSI) 198 ([M+H]$^+$, 100%). Found [M+H]$^+$ 198.1275. $C_{14}H_{16}N$ requires 198.1277. Anal. Calcd. for $C_{14}H_{15}N$ requires C, 85.24; H, 7.66; N, 7.10. Found: H, 85.17; H, 7.81; N, 7.17.

4.37 *N*-Hexyl aniline (106)



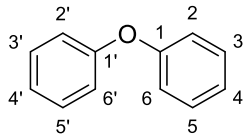
Using *N*-hexylamine gave the product as a white solid (0.14 g, 0.79 mmol, 72%); mp 170–172 °C (from ether–petrol); R_f = 0.42 (0.5:9.5 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3416, 2926, 2856, 1912, 1602, 1506, 1476, 1320, 1256, 1179, 746, 691; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.13 (2H, m, H3/H5), 6.63 (1H, ttt, H4, J 1, 6, 7 Hz), 6.52 (2H, m, H2/H6), 3.49 (1H, s, NH), 3.03 (2H, t, H1′, J 7 Hz), 1.57 (2H, q, H2′, J 7 Hz), 1.29 (6H, H3′/H4′/H5′), 0.85 (3H, t, H6, J 7 Hz); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 148.6 (C1), 129.3 (C3/C5), 117.1 (C4′), 112.7 (C2/C6), 44.1 (C1′), 31.7 (C2′), 29.6 (C3′), 26.9 (C4′), 22.7 (C5′), 14.1 (C6′); m/z (NSI) 178 ([M+H]$^+$, 100%). Found [M+H]$^+$ 178.1586. $C_{12}H_{20}N$ requires 178.1590. Anal. Calcd. for $C_{12}H_{19}N$ requires C, 81.30; H, 10.80; N, 7.90. Found: H, 81.42; C, 10.91; N, 7.81.

4.38 *N*-Methyl-*N*-hexylaniline (107)



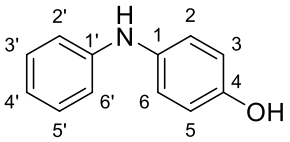
Using *N*-methylhexylamine gave the product as a white solid (0.14 g, 0.78 mmol, 67%); mp 97–98 °C (from ether–petrol); R_f = 0.47 (0.5:9.5 ether/petrol); IR ν_{max}/cm^{-1} (neat) 2925, 1599, 1506, 1466, 1367, 1192, 1091, 990, 858; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.16 (2H, m, H3/H5), 6.62 (3H, m, H2/H4/H6), 3.23 (2H, t, H1′, J 8 Hz), 2.83 (3H, s, Me), 1.53 (2H, m, H2′), 1.29 (6H, m, H3′/H4′/H5′), 0.84 (3H, m, H6′); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 149.4 (C1), 129.2 (C3/C5), 115.8 (C4), 112.1 (C2/C6), 52.9 (C1′), 38.3 (Me), 31.8 (C3′), 26.9 (d, C2′/C4′, J 18 Hz), 22.7 (C5′), 14.1 (C6′); m/z (NSI) 192 ($[M+H]^+$, 100%) 191 (10). Found $[M+H]^+$ 192.1742. $C_{13}H_{22}N$ requires 192.1747. Anal. Calcd. for $C_{13}H_{21}N$ requires C, 81.61; H, 11.06; N, 7.32. Found: C, 81.54; H, 11.17; N, 7.26.

4.39 Diphenylether (68)



Using phenol gave the product as a white crystalline solid (0.13 g, 0.76 mmol, 69%); mp 26–27 °C (from ether–petrol) (lit.,[269] mp 28 °C); R_f = 0.35 (1:9 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3059 3038, 2939, 2284, 1583, 1485, 1233, 1163, 1022; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.29 (4H, m, H3/H3′/H5/H5′), 7.05(2H, ttt, H4/H4′ J 2, 7, 7 Hz), 6.95 (4H, m, H2/H2′/H6/H6′); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 157.3 (C1/C1′), 129.8 (C3/C3′/C5/5′), 123.3 (C4/C4′), 119.0 (C2/C2′/C6/C6′).

4.40 4-Hydroxydiphenylamine (70)

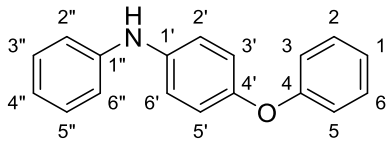


Using 4-hydroxyaniline gave the product as a white crystalline solid (0.15 g, 0.81 mmol, 74%); mp 72–74 °C (from ether–petrol) (lit.,[239] mp 70 °C); R_f = 0.25 (4:6 ether/petrol); IR ν_{max}/cm^{-1}

(neat) 3407, 3371, 3279, 3038, 2468, 1835, 1595, 1450, 1103, 815; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 7.16 (2H, m, H3′/H5′), 6.95 (2H, m, H2/H6), 6.83 (2H, m, H3/H5), 6.78 (1H, ttt, H4′, J 1, 2, 6 Hz), 6.72 (2H, m, H2′/H6′), 5.37 (1H, s, NH), 4.86 (1H, s, OH); ^{13}C–NMR (100 MHz, $CDCl_3$) δ 151.1 (C4), 145.2 (C1′), 135.8 (C1), 129.3 (C3′/C5′), 122.5 (C2/C6), 119.7 (C4′), 116.1 (C2′/C6′), 115.7 (C3/C5); m/z (NSI) 186 ([M+H]$^+$, 100%) 184 (5). Found [M+H]$^+$ 186.0913. $C_{12}H_{12}NO$ requires 186.0913. Anal. Calcd. for $C_{12}H_{11}NO$ requires C, 77.81; H, 5.99; N, 7.56. Found: C, 77.69; H, 5.90; N, 7.42.

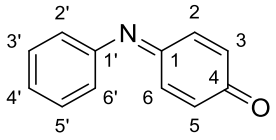
The by-products below were also produced during this reaction.

4-Phenoxy-*N*-phenylaniline (108)



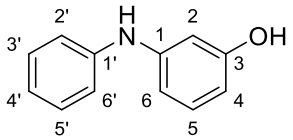
Obtained as a by-product as an off white solid (0.01 g, 0.04 mmol, 3%); mp 96–97 °C (from ether–petrol) (lit.,[270] mp 95–98 °C); R_f = 0.34 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3346, 3046, 2958, 2926, 1948, 1592, 1494, 1457, 1280, 1103, 888; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.28 (4H, m, H2/H2′/H6/H6′), 7.03 (3H, m, H3″/H4″/H5″), 6.96 (6H, m, H2″/H3/H3′/H5/H5′/H6″), 6.85 (1H, m, H1), 5.52 (1H, s, NH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 158.2 (C4), 151.2 (C4′), 143.9 (C1″), 138.8 (C1′), 129.7 (C3″/C5″), 129.4 (C2/C6), 122.6 (C4″), 120.5 (C2′/C6′), 120.4 (C2″/C6″), 117.9 (C3/C5), 116.9 (C3′/C5′); m/z (NSI) 262 [(M+H]$^+$, 100%) 239 (10), 226 (5), 199 (5), 185 (30), 169 (10), 149 (12). Found [M+H]$^+$ 262.1229. $C_{18}H_{16}NO$ requires 262.1226; Anal. Calcd. for $C_{18}H_{15}N$ requires C, 82.73; H, 5.79; N, 5.42. Found: C, 82.66; H, 5.80; N, 5.42.

***N*-Phenylazaquinone (71)**



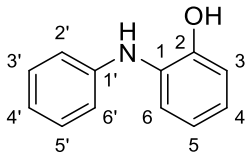
Obtained as a by-product an orange crystalline solid (0.01 g, 0.05 mmol, 5%); mp 130–132 °C (from ether–petrol) (lit.,[243] mp 132–133 °C; R_f = 0.33 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3049, 1643, 1612, 1576, 1476, 1446, 1319, 1163, 1096, 951; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.37 (2H, m, H3′/H5′), 7.26 (1H, dd, H4′, J 3, 7 Hz), 7.20 (2H, m, H2′/H6′), 7.04 (1H, dd, H2, J 3, 7 Hz), 6.84 (1H, m, H6), 6.65 (1H, dd, H3, J 3, 7 Hz), 6.49 (1H, dd, H5, J 3, 7 Hz); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 187.6 (C4), 157.4 (C1), 149.4 (C1′), 141.9 (C2), 135.5 (C6), 132.3 (C4′), 129.1 (C3/C5), 128.2 (C5′), 126.2 (C3′) 120.6 (C2′/C6′); m/z (ESI) 184 [(M+H]$^+$, 100%) Found [M+H]$^+$ 184.0756. $C_{12}H_{10}NO$ requires 184.0757.

4.41 3-Hydroxydiphenylamine (72)



Using 3-Hydroxyaniline gave the product as a white crystalline solid (0.16 g, 0.85 mmol, 78%); mp 78–80 °C (from ether–petrol) (lit.,[239] mp 81°C); R_f = 0.33 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3379, 3327, 3044, 1595, 1494, 1460, 1337, 1244, 1160, 1024, 969; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.33 (2H, m, H3′/H5′), 7.16 (3H, m, H2′/H4′/H6′), 7.00 (1H, t, H6, J 7 Hz), 6.65 (2H, m, H2/H4), 6.42 (1H, dd, H5, J 6, 2 Hz), 5.71 (1H, s, NH), 4.63 (1H, s, OH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 156.5 (C3), 145.0 (C1), 142.5 (C1′), 130.4 (C5), 129.4 (C3′/C5′), 121.5 (C4′), 118.7 (C2′/C6′), 110.0 (C6), 107.6 (C4), 103.9 (C2); m/z (NSI) 186 ([M+H]$^+$, 100%) 185 (5). Found [M+H]$^+$ 186.0912. $C_{12}H_{12}NO$ requires 186.0913. Anal. Calcd. for $C_{12}H_{11}NO$ requires C, 77.81; H, 5.99; N, 7.56. Found: C, 77.90; H, 6.04; N, 7.47.

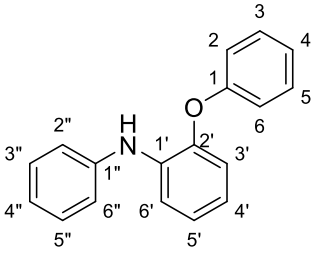
4.42 2-Hydroxydiphenylamine (73)



Using 2-hydroxyaniline gave the product as a white crystalline solid (0.14 g, 0.76 mmol, 69%); mp 65–67 °C (from ether–petrol) (lit.,[239] mp 57 °C); R_f = 0.45 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3383.4, 3337, 2361, 1593, 1492, 1456, 1282, 1102, 747; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.16 (3H, m, H3′/H4′/H5′), 7.03 (1H, t, H2′, J 8 Hz), 6.91 (1H, d, H6′ J 7 Hz), 6.82 (2H, m, H3/H5), 6.70 (2H, d, H4/H6, J 8 Hz), 5.70 (1H, s, OH), 5.15 (1H, s, NH); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 151.1 (C2), 145.5 (C1′), 129.5 (C3′/C5′), 129.1 (C1), 126.2 (C5), 124.8 (C3), 121.1 (C4), 120.4, 115.9, 115.4 (C2/C6); m/z (NSI) 186 ($[M+H]^+$, 100%). Found $[M+H]^+$ 186.0912. $C_{12}H_{12}N$ requires 186.0913. Anal. Calcd for $C_{12}H_{11}NO$ requires C, 77.81; H, 5.99; N, 7.56. Found: C, 77.69; H, 5.88; N, 7.48.

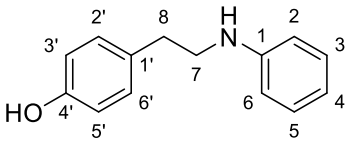
The by-product below was isolated from this reaction.

2-Phenoxy-*N*-phenylanline (109)



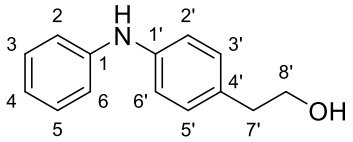
Obtained as by-product as an off white solid (0.03 g, 0.14 mmol, 13%); mp 93–94 °C (from ether–petrol); R_f = 0.56 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat) 3346, 3047, 1912, 1708, 1592, 1494, 1457, 1281, 1102, 888; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.33 (2H, m, H3/C5), 7.26 (4H, m, H2/H3/H5/H6), 7.08 (2H, m, H2″/H6″), 7.01 (4H, H4/H4″/H5′/H6′), 6.89 (2H, m, H3′/H4′); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 157.2 (C1), 144.9 (C2′), 142.2 (C1″), 135.6 (C1′), 129.8 (C3″/C5″), 129.3 (C3/C5), 124.3 (C4″), 123.1 (C4), 121.7 (C4′), 120.1 (C3′), 119.6 (C5′), 119.1 (C2″/C6″), 117.8 (C2/C6), 115.8 (C6′). Anal. Calcd. for $C_{18}H_{15}NO$ requires C, 82.73; H, 5.79; N, 5.36. Found: C, 82.60; H, 5.70; N, 5.35.

4.43 4-(2-Phenylaminoethyl) phenol (74)



Using tyramine gave the product as a white crystalline solid (0.10 g, 0.47 mmol, 43%); mp 46–48 °C (from ether–petrol) (lit.,[241] mp 50–51°C); R_f = 0.28 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3391, 3343, 3050, 2925, 2857, 2577, 1889, 1738, 1600, 1490, 1220, 1056; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.14 (2H, m, H3/H5), 7.04 (2H, m, H2′/H6′), 6.66 (2H, m, H3′/H5′), (1H, ttt, H4, J 1, 6, 1 Hz), 6.56 (2H, m, H2/H6), 4.62 (1H, s, NH), 3.61 (1H, s, OH), 3.31 (2H, t, H7, J 7 Hz), 2.80 (2H, t, H8, J 7 Hz); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 154.1 (C4′), 148.0 (C1), 131.4 (C1′), 129.9 (C2′/C6′), 129.3 (C3/C5), 117.5 (C4), 115.4 (C3′/C5′), 113.1 (C2/C6), 45.2 (C7), 34.6 (C8); m/z (NSI) 214 ([M+H]$^+$, 100%) 199 (10) 167 (8), 149 (20). Found [M+H]$^+$ 214.1227. $C_{14}H_{16}NO$ requires 214.1226. Anal. Calcd. for $C_{14}H_{15}NO$ requires C, 78.84; H, 7.09; N, 6.57. Found: C, 78.90; H, 7.02; N, 6.68.

4.44 2-(4-(Phenylamino)phenyl)ethanol (75)



Using 4-Aminophenethanol gave the product as a white crystalline solid (0.8 g, 0.84 mmol, 80%); mp 74–76 °C (from ether–petrol); R_f = 0.25 (4:6 ether/petrol); IR ν_{max}/cm^{-1} (neat): 3564, 3391, 2926, 1594, 1513, 1311, 1052, 1019; ^{1}H–NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, m, H3′/H5′), 7.18 (2H, m, H2/H6), 7.09 (4H, m, H3/H5/H2′/H6′), 6.97 (1H, ttt, H4, J 1, 6, 1 Hz), 5.69 (1H, s, NH), 3.90 (2H, t, H7, J 7 Hz), 2.87 (2H, t, H8, J 7 Hz); ^{13}C–NMR (75 MHz, $CDCl_3$) δ 143.4 (C1), 141.5 (C1′), 131.0 (C4), 129.9 (C3′/C5′), 129.4 (C3/C5), 120.8 (C4′), 118.4 (C2/C6), 117.4 (C2′/C6′), 63.8 (C7), 38.5 (C8); m/z (NSI) 214 ([M+H]$^+$, 100%), 196 (5)), 180(2), 149 (6). Found [M+H]$^+$ 214.1226. $C_{14}H_{16}NO$ requires 214.1226. Anal. Calcd. for $C_{14}H_{15}NO$ requires C, 78.84; H,7.09; N, 6.57. Found: C, 79.01; H, 7.03; N, 6.68.

4.45 HPLC Method

The HPLC methods were carried out by using an Agilent 1200 HPLC system provided with a UV absorbance detector (λ^{max} 254 nm). The fluorophase PFP, part number 82705-154630, particle size 5 µm, 150 mm × 4.6 mm column was used to separate the compounds of reaction mixture, it was eluted at 1 mL/min using water/acetonitrile and the mobile phase configuration started at 10% acetonitrile which increased linearly to 75% acetonitrile over 20 min with a pre-run of 5 min.

For example the HPLC chromatogram for the starting material and product standard at a concentration of 0.1 M.

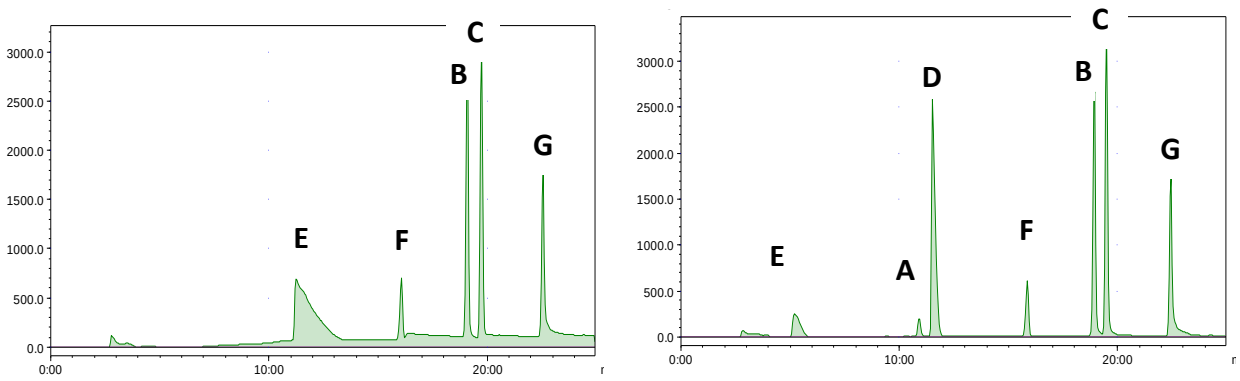


Figure 45: HPLC chromatogram water/MeCN (left), water:1% TFA/MeCN (right): A = PhOH, B = PhI, C = Ph_2NH, D = Ph_2ITAF, E = $PhNH_2$, F = PhH, G = Ph_3N

The standard commercial diphenylamine, diphenylether and 4-hydroxydiphenylamine were used to determine the calibration curve.

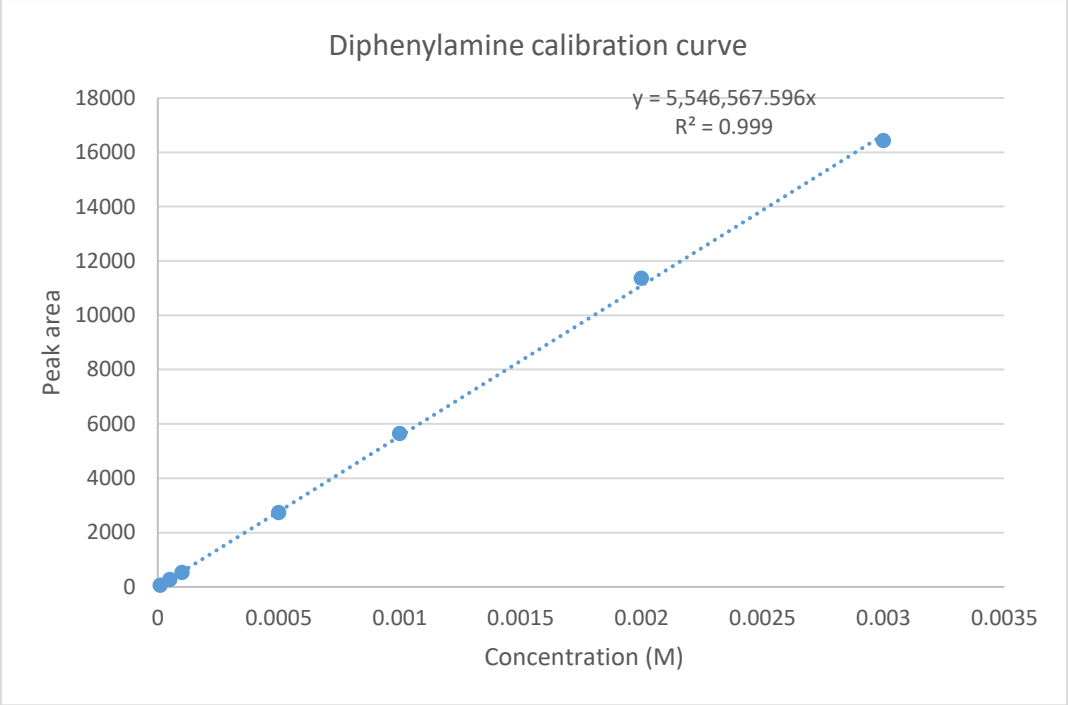


Figure 46: Calibration curve, diphenylamine 64

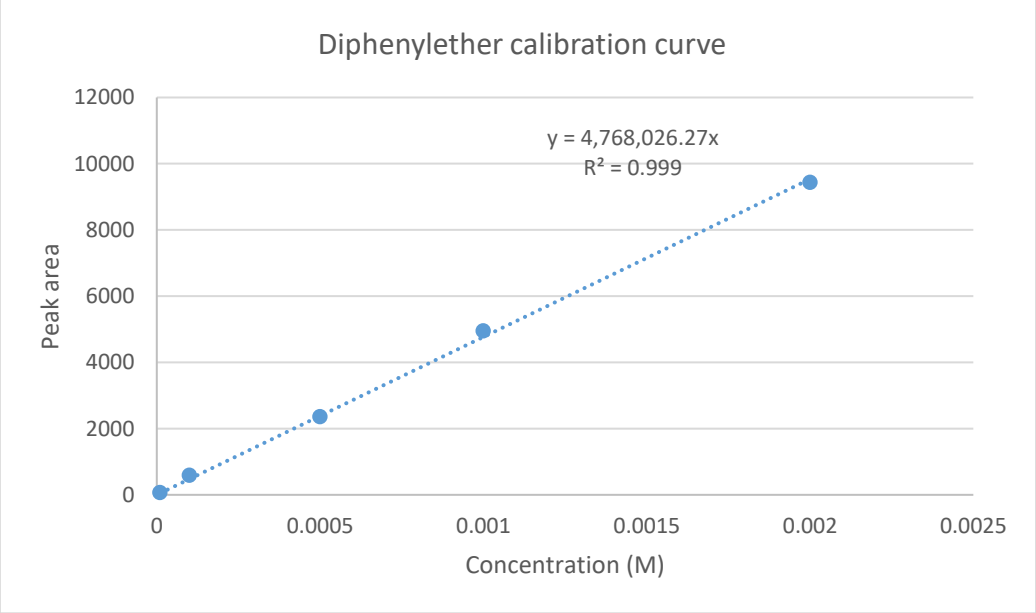


Figure 47: Calibration curve diphenylether 68

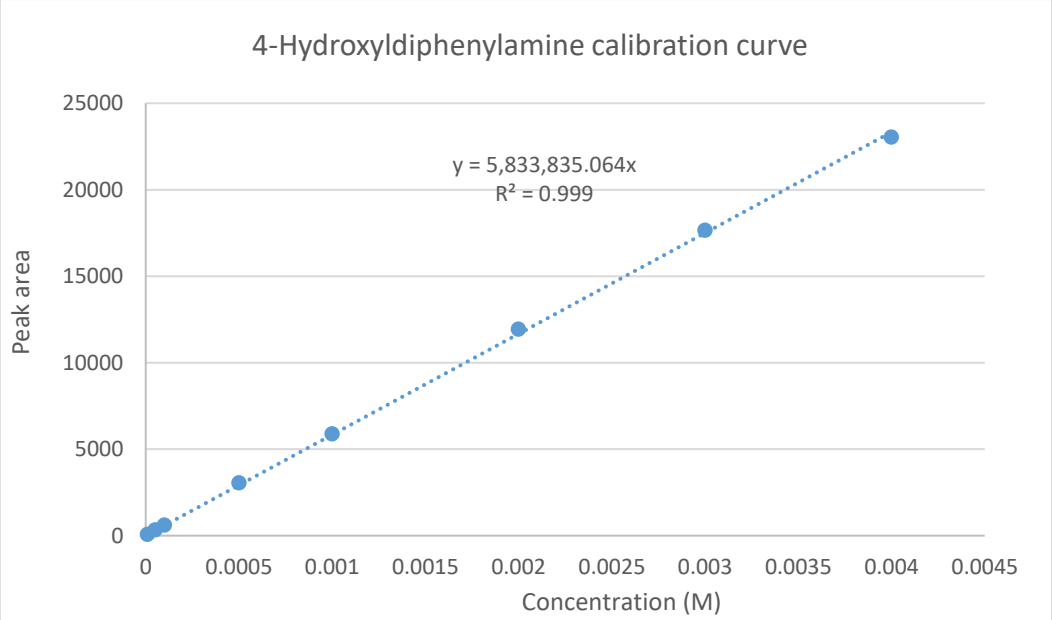


Figure 48: Calibration curve 4-Hydroxydiphenylamine 70

Table 17: HPLC Retention time (R_t), water/MeCN , (90/10)

Compound	Rt/ min	Compound	Rt/min
Aniline (**63**)	13.0	Diphenylamine (**64**)	20.0
4-Fluoroaniline (**110**)	13.2	4-Fluorodiphenylamine (**85**)	21.0
4-Chloroaniline (**111**)	16.1	4-Chlorodiphenylamine (**86**)	22.0
4-Methoxyaniline (**112**)	13.3	4-Methoxydiphenylamine (**66**)	21.4
1-Naphthylamine (**113**)	18.1	*N*-Phenylnaphthalen-1-amine(**92**)	22.3
4-Nitroaniline (**114**)	9.2	4-Nitrodiphenylamine (**88**)	20.5
4-Bromoanline (**115**)	18.1	4-Bromodiphenylamine (**87**)	22.5
3,5-Dimethoxyaniline (**116**)	13.1	3,5-Dimethoxydiphenylamine (**89**)	20.1
3,4-Dimethoxyaniline (**117**)	10.5	3,4-Dimethoxydiphenylamine (**67**)	18.3
2-tert-Butylaniline (**118**)	18.2	2-tert-Butyldiphenylamine (**91**)	22.3
2,4,6-Trimethylaniline (**119**)	18.1	2,4,6-Trimethyldiphenylamine (**90**)	22.0
Phenol (**120**)	11.5	Diphenylether (**68**)	20.4

Benzylamine (**121**)	14.0	*N*-Benzylaniline (**103**)	19.5
(±)-*α*-Methylbenzylamine (**122**)	15.0	(±)-α-Methylbenzylaniline(**104)**	20.20
N-Methylaniline (**123**)	15.0	*N*-Methyldiphenylamine (**143**)	21.1
Hexylamine (**124**)	Not UV active	*N*-Hexylaniline (**106**)	22.0
N-Methylbenzylamine (**125**)	14.0	*N*-Benzylmethylaniline (**105**)	21.3
N-Methylhexylamine (**126**)	Not UV active	*N*-Methylhexylaniline (**107**)	23.3
2-Methoxydiphenylamine (**95**)	20.3	4-Methyldiphenylamine (**93**)	21.0
2-Chlorodiphenylamine (**96**)	21.3		

Table 18: HPLC Retention time (R.T), water:1% TFA/MeCN , (90/10)

Compound	**R_t/min**	**Compound**	**R_t/min**
3-Aminophenol (**127**)	4.5	3-Hydroxydiphenylamine (**72**)	16.2
4-Aminophenol (**128**)	5.9	4-Hydroxydiphenylamine (**70**)	14.2
2-Aminophenol (**129**)	5.0	2-Hydroxydiphenylamine (**73**)	17.1
Tyramine (**130**)	5.9	4-(2-Phenylaminoethyl) phenol (**74**)	11.4
4-Aminophenethanol (**131**)	4.5	2-(4-(Phenylamino)phenyl)ethanol (**75**)	15.5

3-Aminoquinoline (**132**)	9.0	*N*-Phenyl-3-aminoquinoline (102)	15.1
4-Aminopyridine (**133**)	4.0	*N*-Phenyl-4-aminopyridine (**100**)	11.4
2-Aminopyridine (**134**)	4.4	*N*-Phenyl-2-aminopyridine (**98**)	10.4
2-Aminopyrimidine (**135**)	4.1	*N*-Phenyl-2-aminopyrimidine (**99**)	11.0
2-Aminopyrazine (**136**)	4.0	*N*-Phenyl-2-aminopyrazine (**97**)	11.2
2-Aminobenzoxazole (**144**)	9.0	*N*-Phenyl-2-aminobenzoxazole (**101**)	17.8
2-Aminobenzimidazole (**137**)	9.0	*N*-Phenyl-2-aminobenzimidazole (**138**)	11.3
Diphenyliodonium trifluoroacetate (**62**)	12.0	Diphenyliodonium triflate ((**139**)	11.9
Phenyl(mesityl)iodonium triflate (**81**)	16.0	Diphenyliodonium tosylate (**78**)	12.0
2-Methylphenyl(mesityl)iodonium triflate (**80**)	17.0	4-Methylphenyl(mesityl)iodonium triflate (**79**)	16.0
2-Chlorophenyl(mesityl)iodonium triflate (**83**)	16.9	4-Chlorophenyl(mesityl)iodonium triflate (**84**)	17.5
2-Methoxyphenyl(mesityl)iodonium triflate (**82**)	17.0	Triphenylamine (**141**)	23.0

Iodobenzene (**140**)	16.1	Biphenyl (**142**)	20.6
N-Phenylazaquinone (**71**)	7.5	4-Phenoxy-*N*-phenylaniline (**108**)	22.0

5 References

1. www.uniqsis.com).
2. M. A. Carroll and R. A. Wood, *Tetrahedron*, 2007, **63**, 11349-11354.
3. M. Bielawski, M. Zhu and B. Olofsson, *Adv. Synth. Catal.*, 2007, **349**, 2610-2618.
4. A. Varvoglis, *Tetrahedron*, 1997, **53**, 1179-1255.
5. T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, K. Morimoto, H. Fujioka and Y. Kita, *Tetrahedron*, 2009, **65**, 10797-10815.
6. M. A. Soussi, O. Provot, G. Bernadat, J. Bignon, J. Wdzieczak-Bakala, D. Desravines, J. Dubois, J.-D. Brion, S. Messaoudi and M. Alami, *Eur. J. Med. Chem.*, 2014, **78**, 178-189.
7. K. Ohta, Y. Chiba, A. Kaise and Y. Endo, *Bioorg. Med. Chem.*, 2015, **23**, 861-867.
8. L.-Q. Sun, L. Zhu, K. Qian, B. Qin, L. Huang, C. H. Chen, K.-H. Lee and L. Xie, *J. Med. Chem.*, 2012, **55**, 7219-7229.
9. A. J. Burke and C. S. Marques, *Catalytic Arylation Methods*, Wiley-VCH, Weinhem, 2014.
10. Z. Liu and R. C. Larok, *J. Org. Chem.*, 2006, **71**, 3198-3209.
11. I. P. Beletskay and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337-2364.
12. S. G. Modha and M. E. Greaney, *J. Am. Chem. Soc.*, 2015, **137**, 1416-1419.
13. Y. Yang, J. Han, X. Wu, S. Xu and L. Wang, *Tetrahedron Lett.*, 2015, **56**, 3809-3812.
14. H.-Y. Niu, C. Xia, G.-R. Qu, Q. Zhang, Y. Jiang, R.-Z. Mao, D. Y. Li and H.-M. Guo, *Org. Biomol. Chem.*, 2011, **9**, 5039-5042.
15. S. Pankajakshan, Z. G. Chng, R. Ganguly and T. P. Loh, *Chem. Commun.*, 2015, **51**, 5929-5931.
16. P. J. Stang, *Chem. Rev.*, 1996, **96**, 1123-1178.
17. M. A. Carroll, J. Nairne, G. Smith and D. A. Widdowson, *J. Fluorine Chem.*, 2007, **128**, 127-132.
18. T. Wirth, Y. Kita, G.F.Koser, M. Ochiai, H. Tohma, A. Varvoglis, T. Wirth and V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Springer, Lodon, 2002.
19. V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2002, **102**, 2523-2584.
20. L. F. Silva and J. B. Olofsson, *Nat. Prod. Rep.*, 2011, **28**, 1722-1754.
21. V. V. Zhdankin, *ARKIVOC*, 2009, **i**, 1-62.
22. E. A. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48**, 9052-9070.
23. M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, *ARKIVOC*, 2011, **i**, 370-409.
24. G. F. Koser and R. H. Wettach, *J. Org. Chem.*, 1980, **45**, 4988-4989.
25. H. J. Reich and S. L. Peake, *J. Am. Chem. Soc.*, 1978, **100**, 4888-4889.
26. M. Ochiai, M. Inenaga, Y. Nagao, R. M. Moriarty, R. K. Vaid and M. P. Duncan, *Tetrahedron Lett.*, 1988, **29**, 6917-6920.
27. P. J. Stang, M. Boehsar, H. Wingert and T. Kitamura, *J. Am. Chem. Soc.*, 1988, **110**, 3272-3278.
28. P. J. Stang, *J. Org. Chem.*, 2003, **68**, 2997-3008.
29. V. V. Zhdakin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299-5358.
30. M. S, Yusubov, D. Yu, Svitich, M. S, Larkina and V. V. Zhdankin, *ARKIVOC*, 2013, **i**, 364-395.
31. M. Bielawki, M. Zhu and B. Olofsson, *Adv. Synth. Catal.*, 2007, **349**, 2610-2618.
32. M. A. Carroll, V. W. Pike and D. Widdowson, *Tetrahedron Lett.*, 2000, **41**, 5393-5396.
33. M. Bielawski, D. Aili and B. Olofsson, *J. Org. Chem.* , 2008, **73**, 4602-4607.

34. F. M. Beringer, M. Drexler, E. M. Gindler and C. C. Lumpkin, *J. Am. Chem. Soc.*, 1953, **75**, 2705-2708.
35. C. S. Carman and G. F. Koser, *J. Org. Chem.*, 1983, **48**, 2534-2539.
36. T. Kitamura, R. Furnki, K. Nagata, H. Taniguchi and P. J. Stang, *J. Org. Chem.*, 1992, **57**, 6810-6814.
37. M. A. Carroll, V. W. Pike and D. A. Widdowson, *Tetrahedron Lett.*, 2000, **41**, 5393-5396.
38. F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner and E. Sommer, *J. Am. Chem. Soc.*, 1959, **81**, 342-351.
39. G. F. Koser, R. H. Wettach and C. S. Smith, *J. Org. Chem.*, 1980, **45**, 1543-1544.
40. V. V. Grushin, *Chem. Soc. Rev.*, 2000, **29**, 315-324.
41. N. Jalalian and B. Olofsson, *Tetrahedron*, 2010, **66**, 5793-5800.
42. J. Malmgren, S. Santoro, N. Jalalian, F. Himo and B. Olofosson, *Chem. Eur. J.* , 2013, **19**, 10334-10342.
43. C. Sambiagio, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev.*, 2014, **43**, 3525-3550.
44. G. O. Jones, P. Liu, K. N. Houk and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 6205-6213.
45. C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.*, 1957, **79**, 2942-2948.
46. G. M. Whitesides and P. E. Kendall, *J. Org. Chem.*, 1972, **37**, 3718-3725.
47. C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, 1973, **95**, 7783-7785.
48. T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, 1976, **98**, 748-753.
49. F. Y. Kwong, A. Klapars and S. L. Buckwald, *Org. Lett.*, 2002, **4**, 581-584.
50. S. Paradhan, A. Bhattacharyya and R. P. John, *Tetrahedron Lett.*, 2016, **57**, 1532-1536.
51. C.-K. Tseng, C.-R. Lee, M.-C. Tseng, C.-C. Han and S.-G. Shyu, *Dalton Trans.*, 2014, **DOI: 10.1039/c4dt00051j**.
52. K.-T. Wong, S.-Y. Ku and F.-W. Yen, *Tetrahedron Lett.*, 2007, **48**, 5051-5054.
53. Y.-H. Liu, C. Chena and L.-M. Yang, *Tetrahedron Lett.*, 2006, **47**, 9275-9278.
54. E. Rafiee, A. Ataei and M. Joshaghani, *Tetrahedron Lett.*, 2016, **57**, 219-222.
55. P.-F. Larsson, A. Correa, M. Carril, P.-O. Norrby and C. Bolm, *Angew. Chem. Int. Ed.*, 2009, **48**, 5691-5693.
56. P.-F. Larsson, C. Bolm and P.-O. Norrby, *Chem. Eur. J.*, 2010, **16**, 13613-13616.
57. P.-F. Larsson, C.-J. Wallentin and P.-O. Norrby, *ChemCatChem*, 2014, **6**, 1277-1282.
58. S.-L. Zhang, L. L. Y. Fu and Q.-X. Guo, *Organometallics*, 2007, **26**, 4546-4554.
59. G. Lefevre, G. France, C. Adamo, A. Jutand and I. Ciofini, *Organometallics*, 2012, **31**, 914-920.
60. L. Zhu, P. Guo, G. Li and J. Lan, *J. Org. Chem*, 2007, **72**, 8535-8538.
61. L. C. L. Zhu, Y. Zhang, R. Xie and J. You, *J. Org. Chem.*, 2007, **72**, 2737-2743.
62. K. R. Reddy, N. S. Kumar, B. Sreedhar and M. L. Kantam, *J. Mol. Cata.*, 2006, **252**, 136-141.
63. E. Rafiee, A. Ataei, S. Nadri, M. Joshaghani and S. Eavani, *Inorg. Chim. Acta*, 2014, **409**, 302-309.
64. K. Mori, N. Yoshioka, T. Takeuchi and H. Yamashita, *Green Chem.*, 2009, **11**, 1337-1342.
65. J. W. Chang, X. Xu and P. W. Chan, *Tetrahedron Lett.*, 2007, **48**.
66. P. N. Craig, *In Comprehensive Medicinal Chemistry*, New York, 1991.
67. D. Astruc, *Nanoparticles and catalysis*, Wiley-VCH, Weinheim, 2008.
68. G. Pai and A. P. Chattopadhyay, *Tetrahedron Lett.*, 2014, **55**, 941-944.
69. L. Rout, S. Jammi and T. Punniyamurty, *Org. Lett.*, 2007, **9**, 3397-3399.

70. Y.-Z. Huang, H. Miao, Q.-H. Zhang and C.-C. J. Xu, *Catal. Lett.*, 2008, **122**.
71. A. Correa and C. Bolm, *Adv. Synth. Catal.*, 2007, **349**, 2673-2676.
72. Z.-L. Xu, H.-X. Li, Z.-G. Ren, W.-Y. Du, W.-C. Xu and J.-P. Lang, *Tetrahedron*, 2011, **67**, 5282-5288.
73. M. H.-Sarvari and F. Moeini, *RSC. Adv.*, 2014, **4**, 7321-7329.
74. A. Kalpars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727-7729.
75. X. Diao, Y. Wang, Y. Jiang and D. Ma, *J. Org. Chem.*, 2009, **74**, 7974-7977.
76. A. K. Verma, J. Singh and R. C. Larock, *Tetrahedron*, 2009, **65**, 8434-8439.
77. X. Yang, H. Xing and Y. Zhang, *Chin. J. Chem.*, 2012, **30**, 875-880.
78. F. Wu, P. Liu, X. Ma, J. Xie and B. Dai, *Chin. Chem. Lett.*, 2013, **24**, 893-896.
79. W. Liu, L.-Y. Han, R.-L. Liu, L.-G. Xu and Y.-L. Bi, *Chin. Chem.Lett.*, 2014, **25**, 1240-1243.
80. M. F. Welsch, S. A. Synderand and B. R. Stockwell, *Curr. Opin. Chem. Biol*, 2010, **14**, 347-361.
81. M. Legraverend and D. S. Grierson, *Bioorg. Med. Chem.,*, 2006, **14**, 3987-4006.
82. A. F. Larsen and T. Ulven, *Chem. Commun.*, 2014, **50**, 4997-4999.
83. L. Aguado, H. J. Thibuat, E.-M. Priego, M.-L. Jimeno, M.-J. Camarasa, J. Neyts and M.-J. Perez-Perez, *J. Med. Chem.*, 2009, **53**, 316-324.
84. A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727-7729.
85. A. Klapars, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 7421-7428.
86. I. Güell and X. Ribas, *Eur. J. Org. Chem.*, 2014, **2014**, 3188–3195.
87. D. G. Hall, *Boronic acid*, Wiley-VCH, Weinheim, 2005.
88. P. Y. S. Lam, G. Vincent, D. Bonne and C. G. Clark, *Tetrahedron Lett.*, 2003, **44**, 4927-4931.
89. A. Gogoi, G. Sarmah, A. Dewan and U. Bora, *Tetrahedron Lett.*, 2014, **55**, 31-35.
90. P. Y. S. Lam, G. Vincent, C. G. Clark and A. P. Combs, *Tetrahedron Lett.*, 2003, **44**, 1691-1694.
91. K. Inamoto, K. Nozawa, M. Yonemoto and Y. Kondo, *Chem. Commun.*, 2011, **47**, 11775-11777.
92. K. Nishimoto, S. Kim, Y. Kitano, M. Tada and K. Chiba, *Org. Lett.*, 2006, **8**, 5545-5547.
93. W.-B. Yi and C. J. Cai, *J. Fluorine Chem.*, 2009, **130**, 1054-1058.
94. K. Inamoto, K. Nozawa, J. Kadokawa and Y. Kondo, *Tetrahedron*, 2012, **68**, 7794-7798.
95. J. P. Collman and M. Zhong, *Org. Lett.*, 2000, **2**, 1233-1236.
96. D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937-2940.
97. P. Y. S. Lam, G. Vincent, C. G. Clark, S. Deudon and P. K. Jadhav, *Tetrahedron Lett.*, 2001, **42**, 3415-3418.
98. J.-B. Lan, L. Chen, X.-Q. Yu, J.-S. You and R.-G. Xie, *Chem. Commun.*, 2004, 188-189.
99. M. Hosseini and F.Moeini, *RSC. Adv.*, 2014, **4**, 7321-7329.
100. D. M. T. Chan, K. L. Monaco, R.-P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933-2936.
101. J. P. Collman, M. Zhong, L. Zeng and S. Costanzo, *J. Org. Chem.*, 2001, **66**, 1528-1531.
102. M. Samiran, J. A. Halfen, E. C. Wilkinson, X. W. G. Pan, V. G. Young, C. J. Cramer, L. Que and W. B. Tolman, *J. Am. Chem. Soc.*, 1996, **118**, 11555-11574.
103. T. D. Quach and R. A. Batey, *Org. Lett.* , 2003, **23**, 4397-4400.
104. A. Stolle, T. Szuppa, S. E. S. Leonhard and B. Ondruschka, *Chem. Soc. Rev.*, 2011, **40**, 2317-2329.

105. X. Zhu, Q. Zhang and W. Su, *RSC. Adv.*, 2014, **4**, 22775-22778.
106. A. Kiyomori, J.-F. Marcoux and S. L. Buchwald, *Tetrahedron Lett.*, 1999, **40**, 2657-2660.
107. G. I. Elliott and J. P. Konopelski, *Org. Lett.* , 2000, **2**, 3055-3057.
108. R. J. Sorenson, *J. Org. Chem.*, 2000, **65**, 7747-7749.
109. J. C. Antilla and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 2077-2079.
110. C. Moessener and C. Bolm, *Org. Lett.*, 2005, **7**, 2667-2669.
111. G. Y. Cho, H. Okamura and C. Bolm, *J. Org. Chem.*, 2005, **70**, 2346-2349.
112. C. Sinning, B. Watzer, L. D. Petrocells, V. D. Marzo and P. Imming, *Chem. Med. Chem.* , 2008, **3**, 1956-1964.
113. R. Jana, T. P. Pathak and M. s. Sigman, *Chem. Rev.*, 2013, **111**, 1417-1492.
114. L. Naya, M. Larrosa, R. Rodrguez and J. Cruces, *Tetrahedron Lett.*, 2012, **53**, 769-772.
115. J. Qiao and P. Lam, *Synth.*, 2011, 829-856.
116. S. Sueki and Y. Kuninobu, *Org. Lett.*, 2013, **15**, 1544-1547.
117. S. A. Rossi, K. W. Shimkin, Q. Xu, L. M. Mori-Quroz and D. A. Watson, *Org. Lett.*, 2013, **15**, 2314-2317.
118. J. C. Vantourout, R. P. Law, A. Isidro-Llobet, S. J. Atkinson and A. J. B. Watson, *J. Org. Chem.*, 2016, **81**, 3942-3950.
119. S. N and M. Francis, *Nat. Chem. Biol.*, 2011, **15**, 876-884.
120. E. M. Seletten and C. R. Bertozzi, *Angew. Chem. Int. Ed.*, 2009, **48**, 6974-6998.
121. J. Ohata, M. B. Minus, M. E. Abernathy and Z. T. Ball, *J. Am. Chem. Soc.*, 2016, **138**, 7472-7475.
122. Y. Jin, M. A. Lewis, N. H. Gokhale, E. C. Long and J. A. Cowan, *J. Am. Chem. Soc.*, 2007, **129**, 8353-8361.
123. Y.-A. Choi, J. O. Keem, C. Y. Kim, H. R. Yoon, W. D. Heo, B. H. Chung and Y. Jung, *Chem. Sci.*, 2015, **6**, 1301-1307.
124. D. R. Stuart, *Chem. Eur. J.*, 2017, **23**, 15852-15863.
125. P. Y. S. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, L. T. B. Y. Ru, J. L. Meek, M. J. Otto, M. M. Rayner and Y. N. Wong, *Science*, 1994, **260**, 380-384.
126. M. Dudic, P. Lhotak, I. Stibor, K. Lang and P. Proskova, *Org. Lett.*, 2003, **5**, 149-152.
127. S. Ozaki, *Chem. Rev.*, 1972, **72**, 457-496.
128. M. T. Goulet and J. Boger, *Tetrahedron Lett.*, 1990, **31**, 4845-4848.
129. P. Li, G. Cheng, H. Zhang, X. Xu, Jingyuan and X. Cui, *J. Am. Chem. Soc.*, 2014, **79**, 8156-8162.
130. Bo. Chen, X.-L. Hou, Y.-X. Li and Y.-D. Wu, *J. Am. Chem. Soc.*, 2011, **133**, 7668-7671.
131. R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong and M. Gaunt, *J. Am. Chem. Soc.*, 2012, **134**, 10773-10776.
132. H.-K. Knolker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303-4428.
133. S. Riedmuller and B. J. Nachtsheim, *Beilstein J. Org. Chem.*, 2013, **9**, 1202-1209.
134. J. Elguero, A. M. S. Silva and A. C. Tome, Wiley-VCH, Weinheim, 2011.
135. Z. Gonda and Z. Novak, *Chem. Eur. J.*, 2015, **21**, 16801-16806.
136. T. Lv, Z. Wang, J. You, J. Lan and G. Gao, *J. Org. Chem.*, 2013, **78**, 5723-5730.
137. Y. Yang, J. Han, X. Wu, S. Mao, X. Qian and L. Wang, *Eur. J. Org. Chem.*, 2014, 6854-6857.
138. S. Zhu and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2012, **134**, 10815-10818.
139. R. J. Mathvink, A. M. Barrita, M. R. Candelore, M. A. Cascieri, D. Liping, C. D. Strader, M. J. Wyvratt, M. H. Fisher and A. E. Weber, *Beilstein J. Org. Chem.*, 1999, **9**, 1869-1874.

140. S. Riedmullar and B. J. Nachtsheim, *Synlett*, 2015, **26**, 651-655.
141. Y. Liu, W. Yan, Y. Chen, J. L. Petersen and X. Shi, *Org. Lett.*, 2008, **10**, 5389-5392.
142. Z.-T. Li, J.-L. Hou and C. Li, *Acc. Chem. Res.*, 2008, **41**, 1343-1353.
143. E. Racine, F. Monnier, J.-P. Vors and M. Taillefer, *Org. Lett.* , 2011, **13**, 2818-2821.
144. F. Tinnis, E. Stridfeld, H. Lundberg, H. Adolfsson and B. Olofsson, *Org. Lett.*, 2015, **17**, 2688-2691.
145. A. Sozzafava, T. Owa, A. Mastroorenzo and C. T. Supuran, *Curr. Med. Chem.*, 2003, **10**, 925-935.
146. D. A. Smith and A. Scozzafavs, *Curr. Opin. Drug Discov. Dev.*, 2008, **11**, 72-79.
147. D. J. Snodin, *Org. Process Res. Dev.*, 2010, **14**, 960-976.
148. S.-Y. Moon, M. Koh, K. Rathwell, S.-H. Jung and W.-S. Kim, *Tetrahedron*, 2015, **71**, 1566-1573.
149. A. Casitas and X. Ribas, *Chem. Sci.*, 2013, **4**, 2301-2318.
150. M. Fananas-Mastral and B. L. Feringa, *J. Am. Chem. Soc.*, 2014, **136**, 9894-9897.
151. X. Geng, S. Mao, L. Chen, J. Yu, J. Han, J. Hua and L. Wang, *Tetrahedron Lett.*, 2014, **55**, 3856-3859.
152. K. S. Suslick, *Science*, 1990, **247**, 1439-1445.
153. B. Vaddula, J. Leazer and R. S. Varma, *Adv. Synth. Catal.*, 2012, **354**, 986-990.
154. Y. Wang, M. Li, L. Wen, P. Jing, X. Su and C. Chen, *Org. Biomol. Chem.*, 2015, **13**, 751-763.
155. S. F. Nelsen and R. T. Landis, *J. Am. Chem. Soc.*, 1973, **95**, 8707-8713.
156. J. A. Blake, D. A. Pratt, J. C. W. S. Lin, P. Mulder and K. U. Ingold, *J. Org. Chem.*, 2004, **69**, 3112-3120.
157. H. Wu, W. Zi, G. Li, H. Lu and F. D. Toste, *Angew. Chem. Int. Ed.*, 2015, **54**, 8529-8532.
158. A. A. Tabolin and S. L. Ioffe, *Chem. Rev.*, 2014, **114**, 5426-5476.
159. Y. Zhu, L. Sun, P. Lu and Y. Wang, *ACS Catal.*, 2014, **4**, 1911-1925.
160. W.-M. Shi, X.-P. Ma, C.-X. Pan, G.-F. Su and D.-L. Mo, *J. Org. Chem.*, 2015, **80**, 11175-11183.
161. P.-O. Norrby, T. B. Peterson, M. Bielawski and B. Oloffson, *Chem. Eur. J.*, 2010, **16**, 8251-8254.
162. J. Malmgren, S. Santoro, N. Jalalian, F. Himo and B. Olofssen, *Chem. Eur. J.*, 2013, **19**, 10334-10342.
163. N. Jalalian, T. B. Petersen and B. Olofsson, *Chem. Eur. J.*, 2012, **18**, 14140-14149.
164. J. W. W. Chang, S. Chee, S. Maka, P. Buranaprasertsuk, W. Chavasiri and P. W. H. Chan, *Tetrahedron Lett.*, 2008, **49**, 2018-2022.
165. A. S. Hampton, L. Mikulski, W. Palmer-Brown, C. D. Murphy and G. Sandford, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 2255-2258.
166. P. Petiot, J. Dansereau, M. Hebert, I. Khene, T. Ahmed, S. Samaali, M. Leroy, F. Pinsommeault, C. Y. Legault and A. Gagnon, *Org. Biomol. Chem.*, 2015, **13**, 1322-1327.
167. I. Guell and X. Ribas, *Eur. J. Org. Chem.*, 2014, **2014**, 3188-3195.
168. S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400-5449.
169. K. C. Nicolaou, C. N. C. Boddy, S. Natarajan, T.-Y. Yue, H. Liu and S. Brase, *J. Am. Chem. Soc.*, 1997, **119**, 3421-3422.
170. C. Sambiagio, R. H. Munday, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Eur. J.*, 2014, **20**, 17606-17615.
171. N. Hamaguchi, M. Kuriyama and O. Onomura, *Tetrahedron* 2016, **27**, 177-181.
172. N. Jalalian, T. B. P. etersen and B. Olofsson, *Chem. Eur. J.* , 2012, **18**, 14140-14149.

173. E. Stridfeldt, E. Lindstedt, M. Reitti, J. Blid, P.-O. Norrby and B. Olofsson, *Chem. Eur. J.*, 2017, **23**, 13249-13258.
174. G. O. Jones, P. Liu, K. N. Houk and S. L. Buchwald, *J. Am. Com. Soc.*, 2010, **132**, 6205-6213.
175. C. H. Oh, J. S. Kim and H. H. Jung, *J. Org. Chem*, 1999, **64**, 1338-1340.
176. N. Jalalian, E. E. Ishikawa, L. F. Silva and B. Olofsson, *Org. Lett.* , 2011, **13**, 1552-1555.
177. H. Liu, M. Bernhardsen and A. Fiksdahl, *Tetrahedron*, 2006, **62**, 3564-3572.
178. P. O. Darnerud, *Environ. Int.*, 2003, **29**, 841-853.
179. M. A. Siddiqi, R. H. Laessig and K. D. Reed, *Clin. Med. Res.*, 2003, **1**, 281-290.
180. M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, *ARKIVOC*, 2011, **i**, 370.
181. L. Chan and A. M. a. M. J. G. A. McNallQ. Y. Toh, *Chem. Sci.*, 2015, **6**, 1277-1281.
182. C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer and M. J. Gaunt, *Angew. Chem. Int. Ed.*, 2011, **50**, 458-462.
183. B. Jursic, *Tetrahedron*, 1988, **44**, 6677-6680.
184. D. Lednicer, John Wiley, New York, 2009.
185. M. A. Khalilzadeh, A. Hosseini and A. Pilevar, *Eur. J. Org. Chem.*, 2011, **2011**, 1587-1592.
186. S. B. Hofling, A. L. Bartuschat and M. R. Heinrich, *Angew. Chem.* , 2010, **122**, 9963-9966.
187. S. B. Hofling, A. L. Bartuschat and M. R. Heinrich, *Angew. Chem. Int. Ed.*, 2010, **49**, 9769-9772.
188. Q. W. F. Li, Z.Ding and F. Tao, *Org. Lett.*, 2003, **5**, 2169-2171.
189. J.-K. Lee, M. J. Fuchter, R. M. Williamson, G. A. Leeke, E. J. Bush, I. F. McConvey, S. Subern, J. H. Ryan and A. B. Holmes, *Chem. Commun.*, 2008, 4780-4782.
190. R. G. Gentles, D. Wodka, D. C. Park and A. Vasudevan, *J. Comb. Chem.*, 2002, **4**, 442-456.
191. K. S. Sundalam and D. R. Stuart, *J. Org. Chem.*, 2015, **80**, 6456-6466.
192. E. Lindsted, R. Ghosh and B. Olofsson, *Org. Lett.*, 2013, **15**, 6070-6073.
193. R. Ghosh, E. Lindstedt, N. Jalalian and B. Olofsson, *Chem. Open*, 2014, **3**, 54-57.
194. S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 11592-11598.
195. W. Xiong, Y. P. C. Qi, T. Guo, M. Zhang and H. Jaing, *Chem. Eur. J.* , 2015, **21**, 14314-14318.
196. V. R. Espejo, X.-B. Li and J. D. Rainer, *J. Am. Chem. Soc.*, 2010, **132**, 8282-8284.
197. M. Takino, K. Yamaguchi and T. Nakahara, *J. Agric. Food Chem.*, 2004, **52**, 727-735.
198. K. G. A and M. Brindisi, *J. Med. Chem.*, 2015, **58**, 2895-2940.
199. T. B. Petersen, R. Khan and B. Olofsson, *Org. Lett.*, 2011, **13**, 3462-3465.
200. A. Borovika, P.-I. Tan, S. Klapman and P. Nagorry, *Angew. Chem. Int. Ed.*, 2013, **52**, 13424-13428.
201. B. Bhattarai, J.-H. Tay and P. Nagorny, *Chem. Commun.*, 2015, **51**, 5398-5401.
202. N. Umierski and G. Manolikakes, *Org. Lett.*, 2013, **15**, 4972-4975.
203. M. Bielawski, J. Malmgre, L. M. Pardo and Y. Wikmark, *Chem. Open*, 2014, **3**, 19-22.
204. M. Zhu, N. Jalalin and B. Olofsson, *Synlett*, 2008, 592-596.
205. M. Bielawksi, D. Ali and B. Olofsson, *J. Org. Chem.*, 2008, **73**, 592-596.
206. M. Bielawski and B. Olofsson, *Chem. Commun.*, 2007, 2521-2523.
207. R. Ghosh and B. Olofsson, *Org. Lett.* , 2014, **16**, 1830-1832.
208. B. Y. Bhong, A. V. Shelke and N. N. Karade, *Tetrahedron Lett.*, 2013, **54**, 739-743.

209. J. Wen, R.-Y. Zhang, S.-Y. Chen, J. Zhang and X.-Q. Yu, *J. Org. Chem.*, 2012, **77**, 766-771.
210. L. I. Dixon, M. A. Carroll, T. J. Greson, G. J. Ellames, R. W. Harrington and W. Clegg, *Org. Biomol. Chem.*, 2013, **11**, 5877-5884.
211. L. I. Dixon, M. A. Carroll, T. J. Greson, G. J. Ellames, R. W. Harrington and W. Clegg, *Eur. J. Org. Chem.*, 2013, 2334-2345.
212. A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131-209.
213. A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1995, **34**, 1348-1350.
214. C. Fischer and B. Koenig, *Beilstein J. Org. Chem*, 2011, **7**, 59-74.
215. J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1144-1157.
216. Y. Zhang, T. F. Jamison, S. Patel and N. Mainolfi, *Org. Lett.*, 2011, **13**, 280-283.
217. J. Bao and G. K. Tranmer, *Tetrahedron Lett.*, 2016, **57**, 654-657.
218. C. J. Smith, C. D. Smith, N. Nikbin, S. V. Ley and I. R. Baxendale, *Org. Biomol. Chem.*, 2011, **9**, 1927–1937.
219. J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8849-8869.
220. S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer and S. J. Taylor, *J. Chem. Soc., Perkin Trans*, 2000, **1**, 3815-4195.
221. B. J. Deadman, C. Battilocchio, E. Sliwinski and S. V. Ley, *Green Chem.*, 2013, **15**, 2050-2055.
222. Z. Qian, I. R. Baxendale and S. V. Ley, *Chem. Eur. J.*, 2010, **16**, 12342-12348.
223. Z. Zhang, T. F. Jamison, S. Patel and N. Mainolfi, *Org. Lett.*, 2011, **13**, 280-283.
224. www.thalesnano.com, (accessed 15/11/2017, 2017).
225. J. Jacq and P. Pasau, *Chem. Eur. J.*, 2014, **20**, 12223-12233.
226. B. A.-Omer, D. A. Barrow and T. Wirth, *Tetrahedron Lett.*, 2009, **50**, 3352-3355.
227. M. A. Nielsen, M. K. Nielsen and T. Pittelkow, *Org. Process Res. Dev.*, 2004, **8**, 1059-1064.
228. B. K. Singh, C. V. Stevens, D. R. J. Acke, V. S. Parmar and E. V. V. d. Eycken, *Tetrahedron Lett.*, 2009, **50**, 15-18.
229. A. Palmieri, S. V. Ley, K. Hammond, A. Polyzos and I. R. Baxendale, *Tetrahedron Lett.*, 2009, **50**, 3287-3289.
230. J. Xu, P. Zhang, Y. C. Y. Gao, G. T. G. Tang and Y. Zhao, *J. Org. Chem.* , 2013, **78**.
231. A. J. Walkinshaw, W. Xu, M. G. Suero and M. J. Gaunt, *J. Am. Chem. Soc.*, 2013, **135**, 12532−12535.
232. T. L. Ross, J. Ermert, C. Hocke and H. H. Coenen, *J. Am. Chem. Soc.*, 2007, **129**, 8018-8025.
233. M. Bielawksi and B. Olofsson, *Chem. Commun.*, 2007, 2521-2523.
234. M. Bielawksi, J. Malmgren, L. M. Pardo, Y. W.ikmark and B. Olofsson, *Chem. Open*, 2014, **3**, 19-22.
235. N. Ichiishi, A. J. Canty, B. F. Yates and M. S. Sanford, *Org. Lett.*, 2013, **15**, 5134-5137.
236. N. R. Deprez and M. S. Sanford, *Inorg. Chem.*, 2007, **46**, 1924-1935.
237. S. M. Omar and M. A. Carroll, Application Note 30: Copper catalysed N-arylation).
238. T. Reuillon, S. F. Alhasan, G. S. Beale, A. Bertoli, A. Brennan, C. Cano, H. L. Reeves, D. R. Newell, B. T. Golding, D. C. Miller and R. J. Griffin, *Chem. Sci.*, 2016, **7**, 7821-2826.
239. D. Maiti and S. L. Buchwald, *J. Am. Chem. Soc*, 2009, **131**, 17423-17429.
240. M. K. Mehra, M. P. Tantak, V. Arun, I. Kumar and D. Kumar, *Org. Biomol. Chem.*, 2017, **15**, 4956-4961.

241. R. Mostafalu, B. Kaboudin, F. Kazemi and T. Yokomatsu, *RSC. Adv.*, 2014, **4**, 49273-49279.
242. M. K. Mehra, M. P. Tantak, I. K. V. Arun and D. Kumar, *Org. Biomol. Chem.*, 2017, **15**, 4956-4961.
243. F. Baragona, T. Lomberget, C. Duchamp, N. Henriques, E. L. Piccolo, P. Diana, A. Montalbano and R. Barret, *Tetrahedron*, 2011, **67**, 8731-8739.
244. P. R. Weider, L. S. Hegedus, H. Asada and S. V. D'Andreq, *J. Org. Chem.*, 1985, **50**, 4276-4281.
245. Z. W. Z. Lai and J. Sun, *Org. Lett.*, 2015, **17**, 6058-6061.
246. D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277-7287.
247. H. Tohma, S. Takizawa, T. Maegawa and Y. Kita, *Angew. Chem.*, 2000, **112**, 1362-1364.
248. P. J. Stang, *Chem. Eng. News*, 1989, **67**, 4.
249. T. D. Tilve, V. M. Alexander and B. M. Khadilkar, *Tetrahedron Lett.* , 2002, **43**, 9457-9459.
250. F. Brown, J. M. A. D. Bruyne and P. Gross, *J. Am. Chem. Soc.*, 1934, **56**, 1291-1293.
251. M. A. Carroll, J. Nairne, G. Smith and D. A. Widdowson, *Eur. J. Org. Chem.*, 2004, 894-898.
252. T. Dohi, M. Ito, K. Morimoto, Y. Minamitsuji, N. Takenaga and Y. Kita, *Chem. Commun.*, 2007, 4152–4154.
253. Z. Gonda and Z. Novak, *Chem. Eur. J.*, 2015, 16801-16806.
254. A. Bigot, A. E. Williamson and M. J. Gaunt, *J. Am. Chem. Soc.*, 2011, **133**, 13778-13781.
255. Y. Yang, H. Jianwei, W. Xunshen, M. Song, Y. Jianjun and W. Limin, *Synlett*, 2014, **25**, 1419-1424.
256. S. L. MacNeil, B. J. Wilson and V. Snieckus, *Org. Lett.*, 2006, **8**, 1133-1136.
257. B. Liegault, D. Lee, M. P. Huestis, D. R. Stuart and K. Fagnou, *J. Org. Chem.*, 2008, **73**, 5022-5028.
258. T.-P. Liu, Q. Cheng, W.-J. Song, L.-Z. Cai and X.-C. Tao, *Synlett*, 2012, **23**, 2333-2336.
259. W.-B. Sun, P.-Z. Zhang, T. Jiang, C.-K. Li, L.-T. An, A. Shoberu and J.-P. Zou, *Tetrahedron*, 2016, **72**, 6477-6483.
260. l. Ilies, T. Matsubara and E. Nakamura, *Org. Lett.*, 2012, **14**, 5570-5573.
261. S. Liu, S. Zhu, Y. Wu, J. Gao, P. Qian, Y. Hu, L. Shi, S. Chen, S. Zhang and Y. Zhang, *J. Org. Chem.*, 2015, 3048-3052.
262. G. Qian, B. Liu, Q. Tan, S. Zhang and B. Xu, *Eur. J. Org. Chem.*, 2014, **2014**, 4837-4843.
263. E. Koenigs and H. Greiner, *Chem. Ber.*, 1931, **64**, 1045-1047.
264. C. L. Cioffi, J. J. Lansing and H. Yuksel, *J. Org. Chem.*, 2010, **75**, 7942-7945.
265. T. Dhanabal, R. Sangeetha and P. S. Mohan, *Tetrahedron*, 2006, **62**, 6258-6263.
266. D.-W. Tan, H.-X. Li, D. J. Young and J.-P. Lang, *Tetrahedron*, 2016, **72**, 4169-4176.
267. S. A. Bentley, S. G. Davies, J. A. Lee, P. M. Roberts and J. E. Thomson, *Org. Lett.*, 2011, **13**, 2544-2547.
268. G. Verardo, A. G. Giumanini and P. Strazzolini, *Synth. Commun.*, 1994, **24**, 609-627.
269. N. Xia and M. Taillefer, *Chem. Eur. J.*, 2008, **14**, 6037-6039.
270. B. R. Kim, S.-D. Cho, E. J. Kim, I.-H. Lee, G. H. Sung, J.-J. Kim, S.-G. Lee and Y.-J. Yoon, *Tetrahedron*, 2012, **68**, 287-293.

6 Appendices

6.1 X-ray crystal structure of phenyl(mesityl)iodonium triflate (81)

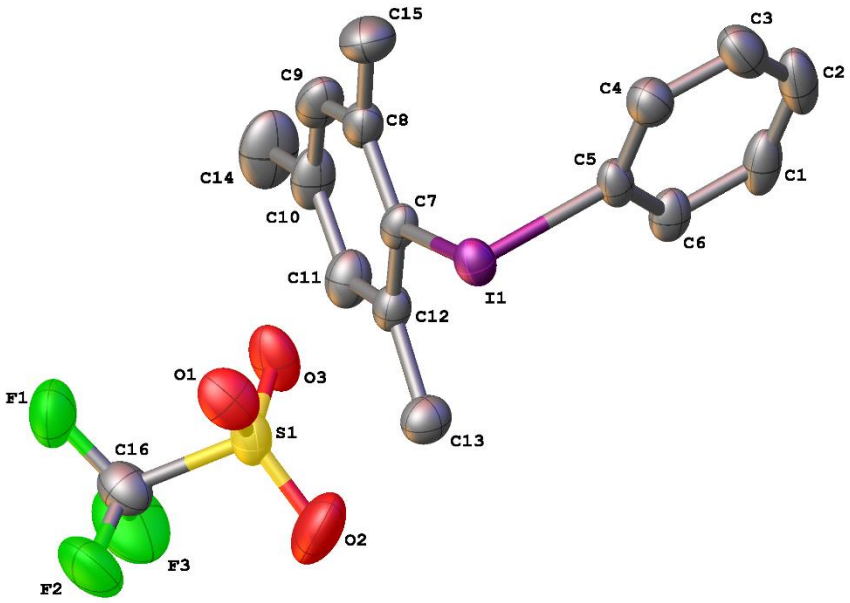


Table 1 Crystal data and structure refinement for mac150013_fa.

Identification code	mac150013_fa
Empirical formula	$C_{36}H_{42}F_6I_2O_7S_2$
Formula weight	1018.61
Temperature/K	180.0(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.7684(3)
b/Å	10.4450(4)
c/Å	11.9460(5)
α/°	92.881(3)
β/°	102.190(3)
γ/°	102.030(3)
Volume/Å^3	1040.84(7)
Z	1
ρ_{calc}g/cm^3	1.625
μ/mm^{-1}	1.681
F(000)	506.0
Crystal size/mm^3	0.29 × 0.27 × 0.07
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.196 to 57.374
Index ranges	$-11 \leq h \leq 11$, $-13 \leq k \leq 13$, $-15 \leq l \leq 14$
Reflections collected	16698
Independent reflections	4719 [R_{int} = 0.0555, R_{sigma} = 0.0639]
Data/restraints/parameters	4719/24/252
Goodness-of-fit on F^2	1.067
Final R indexes [I>=2σ (I)]	R_1 = 0.0434, wR_2 = 0.0718
Final R indexes [all data]	R_1 = 0.0684, wR_2 = 0.0823
Largest diff. peak/hole / e Å^{-3}	0.72/-0.48

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150013_fa. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
I1	3110.8(3)	5528.9(3)	1455.6(2)	34.71(10)
S1	5595.3(12)	2971.8(11)	1162.0(9)	42.0(3)
F1	7356(3)	2119(3)	2864(2)	68.0(8)
F2	6789(4)	873(3)	1293(3)	82.9(9)
F3	5029(4)	911(3)	2283(3)	98.8(12)
O1	7037(4)	3699(3)	921(3)	56.3(8)
O2	4429(4)	2304(4)	172(3)	87.3(12)
O3	4985(4)	3638(3)	1987(3)	57.5(9)
O4	0	10000	5000	118(2)
C1	-927(5)	7354(5)	1184(3)	50.6(12)
C2	-294(6)	8650(6)	1086(4)	59.3(14)
C3	1296(6)	9060(5)	1089(4)	55.7(13)
C4	2290(5)	8186(4)	1197(4)	44.7(10)
C5	1628(5)	6892(4)	1300(3)	34.9(9)
C6	33(5)	6448(4)	1293(3)	39.2(10)
C7	2660(4)	4980(4)	3055(3)	31.0(9)
C8	3385(5)	5850(4)	4025(3)	40.4(10)
C9	2972(5)	5485(5)	5050(4)	49.5(12)
C10	1907(5)	4326(5)	5094(3)	47.9(12)
C11	1254(5)	3486(5)	4100(4)	45.2(11)
C12	1607(4)	3765(4)	3042(3)	33.6(9)
C13	898(5)	2796(4)	1998(3)	43(1)
C14	1445(7)	3993(6)	6220(4)	74.7(17)
C15	4561(6)	7118(5)	4027(4)	58.2(13)
C16	6215(6)	1640(5)	1940(4)	50.6(12)
C17	-822(15)	10390(13)	5767(12)	99(3)
C18	-2448(18)	10400(20)	5309(18)	108(4)
C19	1600(14)	10191(13)	5291(12)	99(3)
C20	2320(20)	10080(20)	4278(17)	108(4)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for mac150013_fa. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	40.01(16)	38.73(16)	31.55(16)	6.63(11)	12.76(11)	17.10(12)
S1	43.2(6)	53.5(7)	36.3(6)	8.5(5)	9.4(5)	24.8(5)
F1	72.7(18)	80(2)	55.6(18)	17.1(16)	1.7(15)	35.9(16)
F2	110(2)	60.2(19)	90(2)	-0.8(18)	22(2)	48.4(19)
F3	87(2)	68(2)	148(3)	43(2)	46(2)	4.3(18)
O1	71(2)	56(2)	54(2)	18.0(17)	33.8(17)	17.8(17)
O2	69(2)	124(4)	60(2)	-11(2)	-18.4(19)	40(2)
O3	70(2)	73(2)	50.6(19)	15.4(17)	28.1(17)	44.7(18)
O4	95(4)	125(6)	142(6)	-7(5)	50(4)	25(4)
C1	49(3)	88(4)	27(2)	13(2)	8(2)	39(3)
C2	79(4)	81(4)	36(3)	15(3)	12(2)	57(3)
C3	83(4)	48(3)	43(3)	7(2)	12(3)	33(3)
C4	52(3)	45(3)	38(3)	4(2)	7(2)	17(2)
C5	44(2)	43(2)	24(2)	7.0(18)	7.5(17)	24(2)
C6	42(2)	55(3)	25(2)	8.0(19)	8.6(18)	20(2)
C7	29.8(19)	43(2)	23(2)	1.6(18)	5.7(16)	15.5(18)
C8	45(2)	46(3)	32(2)	-1(2)	1.8(19)	22(2)
C9	57(3)	65(3)	28(2)	-7(2)	3(2)	28(3)
C10	52(3)	78(4)	25(2)	12(2)	15(2)	33(3)
C11	43(2)	61(3)	36(3)	12(2)	12(2)	17(2)
C12	34(2)	43(2)	27(2)	4.4(18)	5.6(17)	15.9(19)
C13	47(2)	43(3)	36(2)	5(2)	8(2)	6(2)
C14	85(4)	120(5)	36(3)	20(3)	26(3)	44(4)
C15	64(3)	45(3)	55(3)	-5(2)	-3(2)	7(2)
C16	50(3)	42(3)	63(3)	9(2)	19(3)	11(2)
C17	103(5)	70(6)	131(7)	25(5)	41(5)	22(5)
C18	111(5)	104(13)	130(10)	26(6)	42(6)	52(6)
C19	103(5)	70(6)	131(7)	25(5)	41(5)	22(5)
C20	111(5)	104(13)	130(10)	26(6)	42(6)	52(6)

Table 4 Bond Lengths for mac150013_fa.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
I1	C5	2.109(4)	C3	C4	1.381(6)
I1	C7	2.114(3)	C4	C5	1.377(6)
S1	O1	1.426(3)	C5	C6	1.377(5)
S1	O2	1.428(4)	C7	C8	1.384(5)
S1	O3	1.432(3)	C7	C12	1.402(5)
S1	C16	1.824(5)	C8	C9	1.397(6)
F1	C16	1.319(5)	C8	C15	1.499(6)
F2	C16	1.328(5)	C9	C10	1.377(6)
F3	C16	1.307(5)	C10	C11	1.381(6)
O4	C17	1.374(12)	C10	C14	1.521(6)
O4	C19	1.341(12)	C11	C12	1.394(5)
C1	C2	1.372(7)	C12	C13	1.500(6)
C1	C6	1.385(6)	C17	C18	1.418(16)
C2	C3	1.370(7)	C19	C20	1.488(16)

Table 5 Bond Angles for mac150013_fa.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C5	I1	C7	94.24(14)	C7	C8	C9	116.1(4)
O1	S1	O2	114.6(2)	C7	C8	C15	124.1(4)
O1	S1	O3	114.7(2)	C9	C8	C15	119.8(4)
O1	S1	C16	103.97(19)	C10	C9	C8	122.0(4)
O2	S1	O3	115.4(2)	C9	C10	C11	119.1(4)
O2	S1	C16	103.7(2)	C9	C10	C14	120.1(5)
O3	S1	C16	102.1(2)	C11	C10	C14	120.8(5)
C19	O4	C17	120.5(8)	C10	C11	C12	122.9(4)
C2	C1	C6	120.6(4)	C7	C12	C13	124.6(3)
C3	C2	C1	120.2(4)	C11	C12	C7	114.9(4)
C2	C3	C4	120.9(5)	C11	C12	C13	120.5(4)
C5	C4	C3	117.8(4)	F1	C16	S1	110.4(3)
C4	C5	I1	118.7(3)	F1	C16	F2	107.5(4)
C4	C5	C6	122.7(4)	F2	C16	S1	111.3(3)
C6	C5	I1	118.5(3)	F3	C16	S1	111.7(3)
C5	C6	C1	117.8(4)	F3	C16	F1	107.4(4)
C8	C7	I1	118.1(3)	F3	C16	F2	108.5(4)
C8	C7	C12	125.0(3)	O4	C17	C18	116.1(13)
C12	C7	I1	116.9(3)	O4	C19	C20	112.8(12)

Table 6 Torsion Angles for mac150013_fa.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
I1	C5	C6	C1	-179.6(3)	C3	C4	C5	C6	0.3(6)
I1	C7	C8	C9	175.9(3)	C4	C5	C6	C1	-0.4(6)
I1	C7	C8	C15	-4.4(5)	C6	C1	C2	C3	0.4(7)
I1	C7	C12	C11	-175.5(3)	C7	C8	C9	C10	0.1(6)
I1	C7	C12	C13	5.3(5)	C8	C7	C12	C11	2.7(5)
O1	S1	C16	F1	57.2(4)	C8	C7	C12	C13	-176.5(4)
O1	S1	C16	F2	-62.0(4)	C8	C9	C10	C11	1.4(6)
O1	S1	C16	F3	176.6(4)	C8	C9	C10	C14	-177.8(4)
O2	S1	C16	F1	177.4(3)	C9	C10	C11	C12	-0.9(6)
O2	S1	C16	F2	58.1(4)	C10	C11	C12	C7	-1.0(6)
O2	S1	C16	F3	-63.3(4)	C10	C11	C12	C13	178.2(4)
O3	S1	C16	F1	-62.4(3)	C12	C7	C8	C9	-2.3(6)
O3	S1	C16	F2	178.4(3)	C12	C7	C8	C15	177.3(4)
O3	S1	C16	F3	57.0(4)	C14	C10	C11	C12	178.3(4)
C1	C2	C3	C4	-0.5(7)	C15	C8	C9	C10	-179.5(4)
C2	C1	C6	C5	0.0(6)	C17	O4	C19	C20	-163.2(12)
C2	C3	C4	C5	0.2(6)	C19	O4	C17	C18	167.3(12)
C3	C4	C5	I1	179.6(3)					

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mac150013_fa.

Atom	*x*	*y*	*z*	U(eq)
H1	-2032	7076	1176	61
H2	-961	9264	1017	71
H3	1720	9958	1014	67
H4	3394	8467	1201	54
H6	-396	5549	1360	47
H9	3439	6054	5738	59
H11	532	2682	4139	54
H13A	139	3156	1448	65
H13B	338	1971	2225	65
H13C	1753	2628	1639	65
H14A	2199	4574	6859	112
H14B	1479	3076	6334	112
H14C	360	4114	6193	112
H15A	5414	6949	3667	87
H15B	5025	7507	4822	87
H15C	4012	7728	3595	87
H17A	-257	11287	6121	118
H17B	-780	9799	6390	118
H18A	-2529	11288	5114	162
H18B	-3076	10142	5881	162
H18C	-2861	9781	4614	162
H19A	1893	9536	5818	118
H19B	2055	11076	5710	118
H20A	3461	10100	4541	162
H20B	2186	10815	3817	162
H20C	1781	9248	3807	162

Table 8 Atomic Occupancy for mac150013_fa.

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
C17	0.5	H17A	0.5	H17B	0.5
C18	0.5	H18A	0.5	H18B	0.5
H18C	0.5	C19	0.5	H19A	0.5
H19B	0.5	C20	0.5	H20A	0.5
H20B	0.5	H20C	0.5		

6.2 X-ray crystal structure of 2-methylPhenyl(mesityl)iodonium triflate (80)

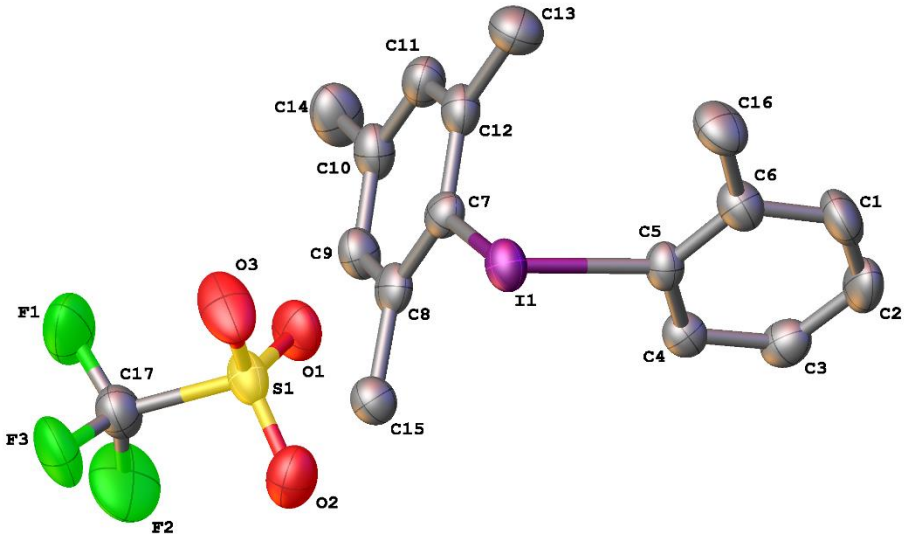


Table 1 Crystal data and structure refinement for mac150011_fa.

Identification code	mac150011_fa
Empirical formula	$C_{17}H_{18}F_3IO_3S$
Formula weight	486.27
Temperature/K	180.0(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.6352(4)
b/Å	11.0670(7)
c/Å	11.3887(6)
α/°	115.965(6)
β/°	100.808(4)
γ/°	98.135(4)
Volume/Å^3	929.83(10)
Z	2
ρ_{calc}g/cm^3	1.737
μ/mm^{-1}	1.876
F(000)	480.0
Crystal size/mm^3	0.31 × 0.19 × 0.12
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.488 to 57.502
Index ranges	$-10 \leq h \leq 11$, $-14 \leq k \leq 14$, $-14 \leq l \leq 15$
Reflections collected	15226
Independent reflections	4259 [R_{int} = 0.0560, R_{sigma} = 0.0678]
Data/restraints/parameters	4259/0/230
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0441, wR_2 = 0.0678
Final R indexes [all data]	R_1 = 0.0752, wR_2 = 0.0790
Largest diff. peak/hole / e Å^{-3}	0.96/-0.53

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150011_fa. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
I1	3276.0(3)	7300.4(3)	1439.2(3)	37.53(11)
S1	6588.3(12)	5229.7(12)	2220.2(11)	39.2(3)
F1	7827(4)	6051(3)	4796(3)	87.6(10)
F2	5845(4)	4241(4)	3794(4)	91.7(11)
F3	8190(4)	4107(3)	3489(3)	70.7(8)
O1	5551(3)	6146(3)	2630(3)	54.0(8)
O2	5772(4)	3879(3)	1093(3)	57.5(9)
O3	8115(4)	5835(4)	2150(4)	70.8(11)
C1	-125(6)	8212(5)	-1220(5)	51.3(12)
C2	-1598(6)	7616(5)	-1176(5)	49.9(12)
C3	-1694(5)	6989(4)	-383(4)	42.1(11)
C4	-272(5)	6931(4)	356(4)	34.3(9)
C5	1207(5)	7528(4)	287(4)	33.6(9)
C6	1345(5)	8190(4)	-481(4)	41.7(11)
C7	2784(4)	8394(4)	3335(4)	34.0(9)
C8	2155(4)	7628(4)	3915(4)	36.4(10)
C9	1765(5)	8380(4)	5124(4)	39.2(10)
C10	1992(5)	9801(5)	5724(4)	42.5(11)
C11	2650(5)	10505(5)	5109(4)	44.0(11)
C12	3062(5)	9837(5)	3904(4)	39.5(10)
C13	3733(6)	10665(5)	3277(5)	50.4(12)
C14	1564(6)	10603(5)	7034(5)	57.3(13)
C15	1904(5)	6076(4)	3318(4)	38.6(10)
C16	2941(5)	8882(5)	-547(5)	52.0(12)
C17	7126(6)	4892(5)	3648(5)	48.0(12)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for mac150011_fa. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	33.59(16)	49.02(19)	39.59(17)	25.94(14)	13.63(12)	17.77(12)
S1	31.4(6)	55.5(7)	47.3(7)	35.3(6)	14.7(5)	17.6(5)
F1	122(3)	75(2)	47.1(19)	22.1(17)	-6.2(18)	32(2)
F2	89(2)	131(3)	97(3)	86(2)	46(2)	17(2)
F3	87(2)	80(2)	72(2)	54.4(18)	19.6(16)	44.6(18)
O1	47.6(18)	58(2)	62(2)	30.3(18)	12.9(16)	29.5(16)
O2	57(2)	64(2)	46(2)	22.0(18)	9.6(16)	20.7(17)
O3	37.4(18)	110(3)	108(3)	85(3)	29.9(19)	20.0(19)
C1	57(3)	57(3)	58(3)	43(3)	12(2)	22(2)
C2	44(3)	50(3)	50(3)	24(2)	-3(2)	18(2)
C3	34(2)	40(3)	45(3)	14(2)	11(2)	10.4(19)
C4	37(2)	36(2)	34(2)	17.3(19)	13.4(19)	12.1(18)
C5	32(2)	41(2)	32(2)	18(2)	9.0(18)	15.5(18)
C6	43(3)	46(3)	45(3)	27(2)	16(2)	17(2)
C7	28(2)	37(2)	34(2)	15(2)	4.7(17)	10.1(17)
C8	25(2)	48(3)	38(2)	23(2)	4.8(18)	13.2(19)
C9	45(3)	46(3)	35(2)	24(2)	13(2)	17(2)
C10	41(3)	54(3)	38(3)	25(2)	10(2)	21(2)
C11	47(3)	42(3)	36(3)	16(2)	3(2)	13(2)
C12	33(2)	50(3)	38(3)	25(2)	5.0(19)	12(2)
C13	54(3)	45(3)	56(3)	29(2)	15(2)	9(2)
C14	78(4)	61(3)	40(3)	24(3)	23(3)	32(3)
C15	40(2)	41(3)	40(2)	22(2)	14(2)	12.6(19)
C16	52(3)	59(3)	65(3)	43(3)	23(2)	14(2)
C17	56(3)	50(3)	44(3)	27(3)	12(2)	18(2)

Table 4 Bond Lengths for mac150011_fa.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
I1	C5	2.125(4)	C4	C5	1.384(5)
I1	C7	2.123(4)	C5	C6	1.374(6)
S1	O1	1.431(3)	C6	C16	1.511(6)
S1	O2	1.436(3)	C7	C8	1.395(6)
S1	O3	1.425(3)	C7	C12	1.399(6)
S1	C17	1.816(5)	C8	C9	1.397(5)
F1	C17	1.318(5)	C8	C15	1.509(5)
F2	C17	1.311(5)	C9	C10	1.378(6)
F3	C17	1.335(5)	C10	C11	1.387(6)
C1	C2	1.368(6)	C10	C14	1.514(6)
C1	C6	1.396(6)	C11	C12	1.388(6)
C2	C3	1.365(6)	C12	C13	1.504(6)
C3	C4	1.379(5)			

Table 5 Bond Angles for mac150011_fa.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C7	I1	C5	94.73(14)	C12	C7	I1	117.8(3)
O1	S1	O2	114.47(18)	C7	C8	C9	116.3(4)
O1	S1	C17	102.5(2)	C7	C8	C15	123.7(4)
O2	S1	C17	103.6(2)	C9	C8	C15	120.0(4)
O3	S1	O1	115.3(2)	C10	C9	C8	122.4(4)
O3	S1	O2	114.6(2)	C9	C10	C11	118.5(4)
O3	S1	C17	104.0(2)	C9	C10	C14	121.8(4)
C2	C1	C6	122.0(4)	C11	C10	C14	119.7(4)
C3	C2	C1	121.2(4)	C10	C11	C12	122.8(4)
C2	C3	C4	118.8(4)	C7	C12	C13	124.1(4)
C3	C4	C5	119.1(4)	C11	C12	C7	116.0(4)
C4	C5	I1	114.4(3)	C11	C12	C13	119.9(4)
C6	C5	I1	122.1(3)	F1	C17	S1	111.5(3)
C6	C5	C4	123.5(4)	F1	C17	F3	106.3(4)
C1	C6	C16	119.9(4)	F2	C17	S1	111.6(3)
C5	C6	C1	115.4(4)	F2	C17	F1	108.3(4)
C5	C6	C16	124.7(4)	F2	C17	F3	107.5(4)
C8	C7	I1	118.2(3)	F3	C17	S1	111.4(3)
C8	C7	C12	124.0(4)				

Table 6 Torsion Angles for mac150011_fa.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
I1	C5	C6	C1	177.7(3)	C2	C3	C4	C5	1.0(6)
I1	C5	C6	C16	-3.1(6)	C3	C4	C5	I1	-178.4(3)
I1	C7	C8	C9	-176.6(3)	C3	C4	C5	C6	0.3(6)
I1	C7	C8	C15	4.1(5)	C4	C5	C6	C1	-0.8(6)
I1	C7	C12	C11	177.0(3)	C4	C5	C6	C16	178.4(4)
I1	C7	C12	C13	-1.9(5)	C6	C1	C2	C3	1.1(7)
O1	S1	C17	F1	-57.6(4)	C7	C8	C9	C10	-0.4(6)
O1	S1	C17	F2	63.7(4)	C8	C7	C12	C11	-0.9(6)
O1	S1	C17	F3	-176.1(3)	C8	C7	C12	C13	-179.7(4)
O2	S1	C17	F1	-176.9(3)	C8	C9	C10	C11	-0.8(6)
O2	S1	C17	F2	-55.7(4)	C8	C9	C10	C14	-180.0(4)
O2	S1	C17	F3	64.5(4)	C9	C10	C11	C12	1.2(6)
O3	S1	C17	F1	62.9(4)	C10	C11	C12	C7	-0.4(6)
O3	S1	C17	F2	-175.8(3)	C10	C11	C12	C13	178.5(4)
O3	S1	C17	F3	-55.6(4)	C12	C7	C8	C9	1.2(5)
C1	C2	C3	C4	-1.6(7)	C12	C7	C8	C15	-178.1(4)
C2	C1	C6	C5	0.1(7)	C14	C10	C11	C12	-179.6(4)
C2	C1	C6	C16	-179.1(4)	C15	C8	C9	C10	179.0(4)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mac150011_fa.

Atom	*x*	*y*	*z*	U(eq)
H1	-103	8654	-1770	62
H2	-2572	7639	-1706	60
H3	-2723	6599	-341	50
H4	-306	6488	904	41
H9	1327	7895	5548	47
H11	2827	11487	5531	53
H13A	4737	10430	3074	76
H13B	3969	11659	3915	76
H13C	2929	10446	2435	76
H14A	2503	10872	7811	86
H14B	637	10017	7079	86
H14C	1275	11438	7061	86
H15A	1155	5614	2398	58
H15B	1440	5763	3890	58
H15C	2952	5843	3278	58
H16A	3239	9875	109	78
H16B	2824	8765	-1467	78
H16C	3795	8456	-328	78

6.3 4-Chlorophenyl(mesityl)iodonium triflate (84)

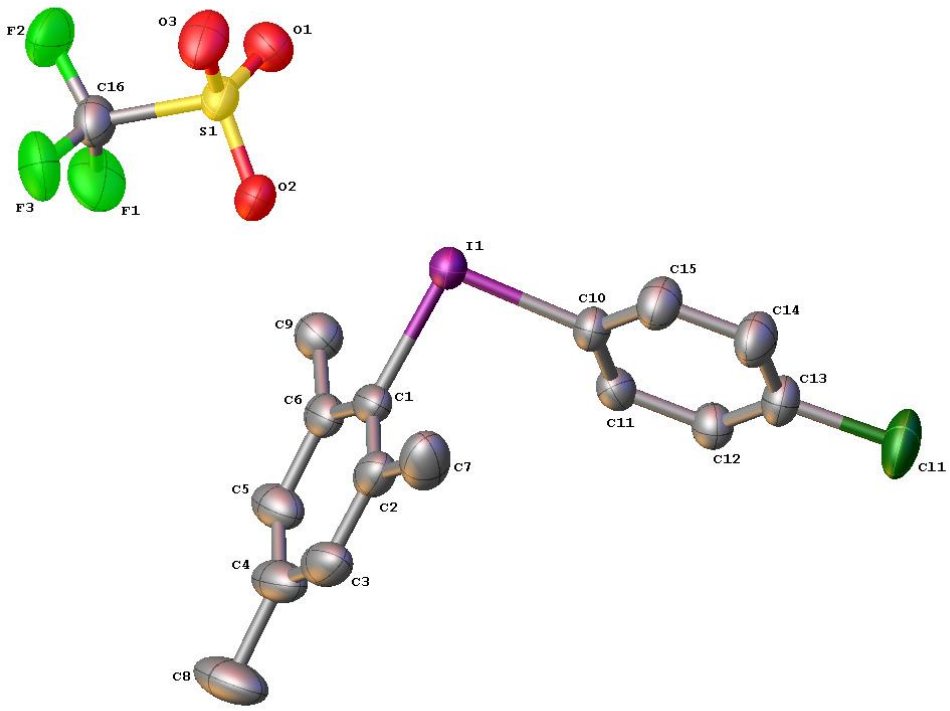


Table 1 Crystal data and structure refinement for mac150006_fa.

Identification code	mac150006_fa
Empirical formula	$C_{36}H_{40}Cl_2F_6I_2O_7S_2$
Formula weight	1087.50
Temperature/K	150.0(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.5843(4)
b/Å	11.5417(5)
c/Å	11.8946(5)
α/°	101.572(4)
β/°	105.069(4)
γ/°	100.878(4)
Volume/Å^3	1078.08(9)
Z	1
ρ_{calc}g/cm^3	1.675
μ/mm^{-1}	14.118
F(000)	538.0
Crystal size/mm^3	0.25 × 0.15 × 0.07
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.98 to 133.798
Index ranges	$-10 \leq h \leq 10$, $-13 \leq k \leq 13$, $-14 \leq l \leq 14$
Reflections collected	15495
Independent reflections	3807 [R_{int} = 0.0439, R_{sigma} = 0.0347]
Data/restraints/parameters	3807/209/261
Goodness-of-fit on F^2	1.015
Final R indexes [I>=2σ (I)]	R_1 = 0.0304, wR_2 = 0.0711
Final R indexes [all data]	R_1 = 0.0404, wR_2 = 0.0767
Largest diff. peak/hole / e Å^{-3}	1.08/-0.58

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150006_fa. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
I1	6590.4(3)	4319.8(2)	8250.1(2)	42.77(10)
Cl1	11173.1(16)	369.9(11)	8508.6(14)	70.6(4)
S1	4062.6(12)	6596.5(8)	9015.7(9)	39.1(2)
F1	5531(4)	8645(3)	8688(3)	73.3(8)
F2	3561(4)	8789(2)	9459(3)	73.7(8)
F3	2992(4)	7914(3)	7580(3)	71.7(8)
O1	5177(4)	6913(3)	10220(3)	54.4(7)
O2	4673(4)	5998(3)	8103(3)	52.0(7)
O3	2361(4)	6078(3)	8902(3)	59.9(8)
O4	10000	0	5000	110(2)
C1	10680(5)	2583(4)	8410(4)	42.7(9)
C2	9954(5)	1401(4)	8394(4)	46.1(9)
C3	8295(6)	1036(4)	8330(5)	53.6(11)
C4	7317(6)	1868(4)	8258(4)	50.4(10)
C5	8051(5)	3042(3)	8271(4)	39.7(8)
C6	9702(5)	3417(3)	8349(3)	40.4(8)
C7	7294(5)	5012(4)	6884(4)	40.8(8)
C8	6695(6)	4252(4)	5718(4)	48.8(10)
C9	7238(6)	4730(5)	4854(4)	59.6(12)
C10	8281(6)	5875(6)	5132(4)	61.5(12)
C11	8789(6)	6593(5)	6306(4)	55.4(11)
C12	8321(5)	6189(4)	7224(4)	42.9(9)
C13	8903(6)	7020(4)	8483(4)	49.2(10)
C14	8848(8)	6326(7)	4159(5)	89(2)
C15	5555(7)	2994(5)	5352(5)	65.9(13)
C16	4038(6)	8068(4)	8669(4)	49.2(10)
C17	11496(17)	433(14)	5117(18)	107(3)
C18	12697(19)	-284(15)	5350(30)	127(5)
C19	8655(18)	445(14)	4768(17)	107(3)
C20	7055(17)	-295(15)	4430(30)	127(5)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for mac150006_fa. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	52.82(17)	44.73(14)	47.92(16)	22.85(11)	25.84(12)	26.94(11)
Cl1	67.0(7)	51.5(6)	109.6(10)	33.5(6)	29.5(7)	37.2(6)
S1	38.4(5)	37.2(4)	54.5(6)	21.0(4)	23.2(5)	17.5(4)
F1	62.8(17)	61.1(16)	109(2)	44.3(16)	38.0(17)	5.9(13)
F2	102(2)	47.1(14)	97(2)	27.8(14)	52.4(19)	39.1(15)
F3	78.2(19)	66.5(16)	80.0(19)	40.3(15)	13.5(16)	33.9(15)
O1	58.6(18)	62.9(18)	52.2(17)	25.8(14)	21.6(15)	22.5(15)
O2	64.5(19)	56.9(17)	55.8(17)	25.9(14)	30.2(15)	37.3(15)
O3	43.1(16)	49.0(16)	100(3)	30.1(17)	34.7(17)	12.3(13)
O4	115(5)	112(5)	139(6)	57(5)	56(5)	60(4)
C1	43(2)	46(2)	46(2)	18.9(17)	15.6(19)	17.6(17)
C2	49(2)	44(2)	54(2)	19.0(18)	17(2)	24.3(18)
C3	57(3)	39(2)	76(3)	22(2)	27(2)	19.7(19)
C4	47(2)	43(2)	69(3)	19(2)	23(2)	16.6(18)
C5	44(2)	40.1(18)	44(2)	17.3(16)	17.8(18)	21.2(16)
C6	51(2)	38.0(18)	41(2)	17.7(16)	19.0(18)	16.6(17)
C7	44(2)	54(2)	40(2)	22.3(16)	20.6(17)	27.8(17)
C8	56(3)	60(2)	41(2)	16.0(18)	16.8(19)	34(2)
C9	63(3)	90(3)	41(2)	24(2)	21(2)	41(2)
C10	53(3)	104(3)	50(2)	38(2)	27(2)	38(2)
C11	45(2)	83(3)	53(2)	36(2)	22(2)	23(2)
C12	38(2)	58(2)	47(2)	24.9(18)	17.7(18)	26.2(18)
C13	49(2)	54(2)	49(2)	18.6(19)	18(2)	16(2)
C14	76(4)	151(6)	66(3)	58(4)	40(3)	32(4)
C15	87(4)	59(3)	51(3)	10(2)	14(3)	32(3)
C16	51(2)	42(2)	67(3)	26.4(19)	26(2)	17.6(18)
C17	101(5)	92(6)	152(9)	52(6)	53(6)	41(5)
C18	109(6)	81(9)	215(14)	46(11)	69(7)	51(6)
C19	101(5)	92(6)	152(9)	52(6)	53(6)	41(5)
C20	109(6)	81(9)	215(14)	46(11)	69(7)	51(6)

Table 4 Bond Lengths for mac150006_fa.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
I1	C5	2.108(4)	C3	C4	1.391(6)
I1	C7	2.119(4)	C4	C5	1.377(6)
Cl1	C2	1.730(4)	C5	C6	1.375(6)
S1	O1	1.431(3)	C7	C8	1.389(6)
S1	O2	1.436(3)	C7	C12	1.389(6)
S1	O3	1.430(3)	C8	C9	1.399(7)
S1	C16	1.829(4)	C8	C15	1.498(7)
F1	C16	1.320(5)	C9	C10	1.371(8)
F2	C16	1.326(5)	C10	C11	1.382(7)
F3	C16	1.327(5)	C10	C14	1.512(7)
O4	C17	1.247(13)	C11	C12	1.391(6)
O4	C19	1.337(12)	C12	C13	1.505(6)
C1	C2	1.383(6)	C17	C18	1.445(19)
C1	C6	1.392(5)	C19	C20	1.38(2)
C2	C3	1.384(6)			

Table 5 Bond Angles for mac150006_fa.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C5	I1	C7	95.67(14)	C12	C7	I1	117.5(3)
O1	S1	O2	114.92(19)	C7	C8	C9	115.5(4)
O1	S1	C16	104.2(2)	C7	C8	C15	124.7(4)
O2	S1	C16	101.95(19)	C9	C8	C15	119.8(4)
O3	S1	O1	114.3(2)	C10	C9	C8	122.6(5)
O3	S1	O2	115.3(2)	C9	C10	C11	118.7(4)
O3	S1	C16	103.82(19)	C9	C10	C14	119.9(5)
C17	O4	C19	132.8(9)	C11	C10	C14	121.4(6)
C2	C1	C6	118.6(4)	C10	C11	C12	122.6(5)
C1	C2	Cl1	118.9(3)	C7	C12	C11	115.5(4)
C1	C2	C3	121.7(4)	C7	C12	C13	124.4(4)
C3	C2	Cl1	119.3(3)	C11	C12	C13	120.1(4)
C2	C3	C4	119.5(4)	F1	C16	S1	111.2(3)
C5	C4	C3	118.3(4)	F1	C16	F2	108.0(4)
C4	C5	I1	118.0(3)	F1	C16	F3	107.7(4)
C6	C5	I1	119.3(3)	F2	C16	S1	111.2(3)
C6	C5	C4	122.6(4)	F2	C16	F3	107.8(4)
C5	C6	C1	119.3(4)	F3	C16	S1	110.8(3)
C8	C7	I1	117.5(3)	O4	C17	C18	120.7(13)
C8	C7	C12	125.0(4)	O4	C19	C20	122.1(13)

Table 6 Torsion Angles for mac150006_fa.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
I1	C5	C6	C1	177.5(3)	C3	C4	C5	C6	0.2(7)
I1	C7	C8	C9	-177.8(3)	C4	C5	C6	C1	0.5(6)
I1	C7	C8	C15	1.7(6)	C6	C1	C2	Cl1	-178.3(3)
I1	C7	C12	C11	178.2(3)	C6	C1	C2	C3	-0.6(7)
I1	C7	C12	C13	-2.7(5)	C7	C8	C9	C10	-0.5(6)
Cl1	C2	C3	C4	179.0(4)	C8	C7	C12	C11	-1.6(6)
O1	S1	C16	F1	62.7(4)	C8	C7	C12	C13	177.4(4)
O1	S1	C16	F2	-57.7(4)	C8	C9	C10	C11	-1.3(7)
O1	S1	C16	F3	-177.7(3)	C8	C9	C10	C14	178.8(5)
O2	S1	C16	F1	-57.2(4)	C9	C10	C11	C12	1.7(7)
O2	S1	C16	F2	-177.6(3)	C10	C11	C12	C7	-0.3(6)
O2	S1	C16	F3	62.5(3)	C10	C11	C12	C13	-179.4(4)
O3	S1	C16	F1	-177.4(3)	C12	C7	C8	C9	2.0(6)
O3	S1	C16	F2	62.3(4)	C12	C7	C8	C15	-178.5(4)
O3	S1	C16	F3	-57.7(4)	C14	C10	C11	C12	-178.4(5)
C1	C2	C3	C4	1.3(7)	C15	C8	C9	C10	180.0(4)
C2	C1	C6	C5	-0.2(6)	C17	O4	C19	C20	166(2)
C2	C3	C4	C5	-1.0(7)	C19	O4	C17	C18	-178.7(19)
C3	C4	C5	I1	-176.9(3)					

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mac150006_fa.

Atom	*x*	*y*	*z*	U(eq)
H1	11823	2821	8461	51
H3	7828	223	8337	64
H4	6171	1633	8201	60
H6	10171	4235	8361	48
H9	6870	4243	4044	72
H11	9487	7394	6493	66
H13A	7937	7086	8762	74
H13B	9499	7832	8482	74
H13C	9652	6682	9025	74
H14A	9092	5657	3638	134
H14B	9855	7002	4534	134
H14C	7963	6612	3675	134
H15A	6137	2455	5738	99
H15B	5219	2675	4473	99
H15C	4562	3030	5606	99
H17A	11897	1191	5784	128
H17B	11534	680	4372	128
H18A	12831	-686	4582	190
H18B	12302	-905	5732	190
H18C	13772	252	5881	190
H19A	8713	865	4126	128
H19B	8783	1086	5502	128
H20A	6897	-643	5086	190
H20B	6884	-957	3710	190
H20C	6248	191	4236	190

Table 8 Atomic Occupancy for mac150006_fa.

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
C17	0.5	H17A	0.5	H17B	0.5
C18	0.5	H18A	0.5	H18B	0.5
H18C	0.5	C19	0.5	H19A	0.5
H19B	0.5	C20	0.5	H20A	0.5
H20B	0.5	H20C	0.5		

6.4 X-ray of crystal structure of 2-chlorophenyl(mesityl)iodonium triflate (83)

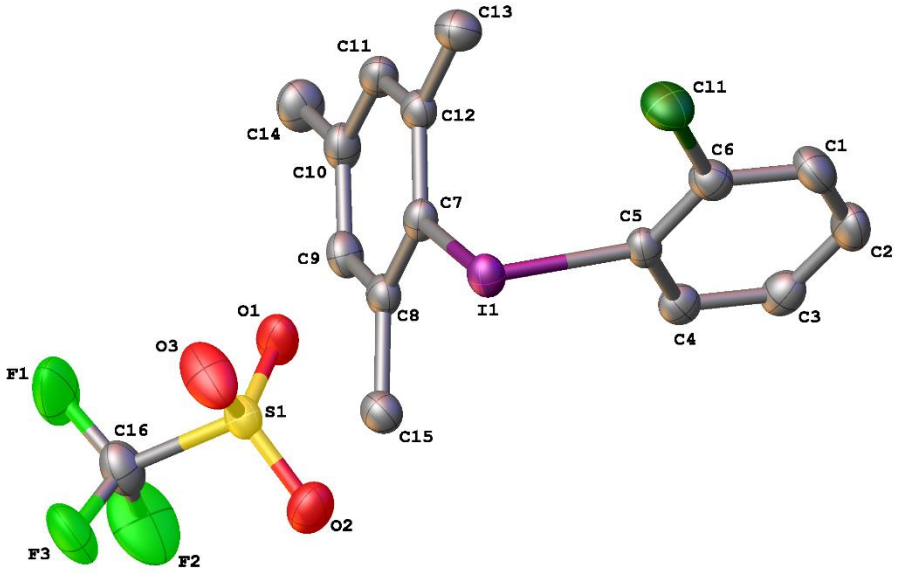


Table 1 Crystal data and structure refinement for mac150012_fa.

Identification code	mac150012_fa
Empirical formula	$C_{16}H_{15}ClF_3IO_3S$
Formula weight	506.69
Temperature/K	150.0(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.4163(2)
b/Å	10.9826(3)
c/Å	11.3719(3)
α/°	114.968(3)
β/°	99.049(2)
γ/°	94.766(2)
Volume/Å^3	927.83(5)
Z	2
ρ_{calc}g/cm^3	1.814
μ/mm^{-1}	2.023
F(000)	496.0
Crystal size/mm^3	0.32 × 0.18 × 0.11
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.92 to 58.802
Index ranges	$-11 \leq h \leq 11$, $-14 \leq k \leq 14$, $-15 \leq l \leq 15$
Reflections collected	29814
Independent reflections	4457 [R_{int} = 0.0428, R_{sigma} = 0.0332]
Data/restraints/parameters	4457/0/229
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0291, wR_2 = 0.0503
Final R indexes [all data]	R_1 = 0.0408, wR_2 = 0.0546
Largest diff. peak/hole / e Å^{-3}	0.65/-0.43

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150012_fa. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
I1	3374.5(2)	7187.0(2)	1312.1(2)	27.85(6)
Cl1	3188.8(9)	8885.8(8)	-649.9(8)	44.16(18)
S1	6660.9(8)	5359.1(7)	2267.3(6)	28.15(14)
F1	7967(3)	6053(2)	4743.2(19)	84.2(8)
F2	5873(3)	4472(3)	3925(2)	87.6(8)
F3	8156(3)	4034(2)	3426.9(19)	59.8(5)
O1	5799(2)	6484(2)	2785(2)	43.6(5)
O2	5673(3)	4137(2)	1243(2)	45.3(5)
O3	8199(3)	5683(3)	2006(3)	58.5(7)
C1	-100(4)	8279(3)	-1223(3)	41.8(7)
C2	-1578(4)	7730(3)	-1124(3)	41.9(7)
C3	-1641(3)	7082(3)	-322(3)	35.4(6)
C4	-213(3)	6961(3)	374(2)	29.2(6)
C5	1274(3)	7501(3)	266(2)	26.3(5)
C6	1346(3)	8169(3)	-523(3)	32.5(6)
C7	2834(3)	8284(3)	3202(2)	26.0(5)
C8	2220(3)	7544(3)	3825(2)	27.7(6)
C9	1823(3)	8314(3)	5042(3)	31.1(6)
C10	2034(3)	9727(3)	5616(3)	32.9(6)
C11	2667(3)	10398(3)	4956(3)	32.1(6)
C12	3092(3)	9708(3)	3736(2)	28.2(6)
C13	3761(4)	10496(3)	3066(3)	37.5(7)
C14	1583(4)	10525(3)	6930(3)	41.8(7)
C15	2006(3)	6023(3)	3281(3)	32.8(6)
C16	7187(4)	4963(3)	3667(3)	43.3(7)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for mac150012_fa. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	28.45(10)	30.32(10)	25.12(9)	10.88(7)	7.12(7)	11.66(7)
Cl1	44.9(4)	47.5(4)	51.5(4)	31.2(4)	15.8(3)	5.1(3)
S1	25.6(3)	34.3(4)	29.4(3)	17.1(3)	8.0(3)	9.9(3)
F1	127(2)	67.1(15)	35.8(11)	10.5(11)	-18.4(12)	34.7(14)
F2	85.7(16)	139(2)	92.8(18)	88.0(18)	53.2(14)	34.5(16)
F3	79.4(14)	62.1(13)	55.2(12)	38.4(10)	12.7(10)	35.4(11)
O1	43.9(12)	38.2(12)	39.2(11)	9.2(10)	-0.9(9)	19.1(9)
O2	47.8(12)	41.2(12)	35.3(11)	8.5(10)	1.5(9)	8.4(10)
O3	36.6(12)	87.7(19)	83.3(18)	62.3(16)	25.3(12)	17.5(12)
C1	50.6(19)	40.7(17)	41.8(17)	26.3(15)	4.7(14)	13.2(14)
C2	39.7(17)	38.4(17)	42.3(17)	15.7(14)	-3.2(13)	13.9(14)
C3	30.2(15)	33.0(15)	35.8(15)	8.6(13)	6.3(12)	6.6(12)
C4	34.3(14)	27.2(14)	24.5(13)	8.6(11)	8.4(11)	7.8(11)
C5	29.7(13)	26.2(13)	21.7(12)	8.9(11)	4.1(10)	9.8(11)
C6	36.9(15)	29.5(14)	32.2(14)	13.5(12)	9.1(12)	8.9(12)
C7	25.3(13)	28.3(14)	21.3(12)	7.5(11)	3.7(10)	9.7(11)
C8	25.6(13)	29.6(14)	26.5(13)	11.9(11)	1.6(10)	7.4(11)
C9	33.0(14)	39.4(16)	25.1(13)	17.8(12)	5.8(11)	8.7(12)
C10	34.3(15)	36.7(16)	24.9(13)	11.3(12)	2.8(11)	11.8(12)
C11	35.6(15)	25.8(14)	28.5(14)	7.0(12)	1.2(12)	10.4(12)
C12	27.6(13)	28.0(14)	27.0(13)	10.9(11)	2.2(11)	8.0(11)
C13	42.9(17)	30.2(15)	38.6(16)	15.1(13)	7.0(13)	6.3(13)
C14	50.9(18)	44.0(18)	28.4(15)	11.9(13)	11.5(13)	14.8(14)
C15	34.4(15)	31.9(15)	33.9(15)	16.0(13)	6.2(12)	8.0(12)
C16	51.1(19)	52(2)	35.4(16)	24.7(15)	12.6(14)	19.8(16)

Table 4 Bond Lengths for mac150012_fa.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
I1	C5	2.109(2)	C3	C4	1.381(4)
I1	C7	2.119(2)	C4	C5	1.385(4)
Cl1	C6	1.735(3)	C5	C6	1.383(4)
S1	O1	1.4383(19)	C7	C8	1.399(4)
S1	O2	1.428(2)	C7	C12	1.401(4)
S1	O3	1.423(2)	C8	C9	1.395(4)
S1	C16	1.821(3)	C8	C15	1.500(4)
F1	C16	1.320(4)	C9	C10	1.388(4)
F2	C16	1.317(4)	C10	C11	1.385(4)
F3	C16	1.324(3)	C10	C14	1.508(4)
C1	C2	1.379(4)	C11	C12	1.393(4)
C1	C6	1.389(4)	C12	C13	1.503(4)
C2	C3	1.378(4)			

Table 5 Bond Angles for mac150012_fa.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C5	I1	C7	94.41(9)	C12	C7	I1	117.46(18)
O1	S1	C16	102.69(13)	C7	C8	C15	124.4(2)
O2	S1	O1	114.50(12)	C9	C8	C7	115.8(2)
O2	S1	C16	104.30(14)	C9	C8	C15	119.8(2)
O3	S1	O1	115.24(14)	C10	C9	C8	122.6(3)
O3	S1	O2	114.22(15)	C9	C10	C14	121.1(3)
O3	S1	C16	103.81(14)	C11	C10	C9	118.7(2)
C2	C1	C6	120.1(3)	C11	C10	C14	120.2(3)
C3	C2	C1	120.6(3)	C10	C11	C12	122.4(2)
C2	C3	C4	119.9(3)	C7	C12	C13	124.1(2)
C3	C4	C5	119.6(3)	C11	C12	C7	116.1(2)
C4	C5	I1	116.29(18)	C11	C12	C13	119.8(2)
C6	C5	I1	122.82(19)	F1	C16	S1	111.2(2)
C6	C5	C4	120.9(2)	F1	C16	F3	107.0(3)
C1	C6	Cl1	119.2(2)	F2	C16	S1	111.1(2)
C5	C6	Cl1	121.8(2)	F2	C16	F1	108.8(3)
C5	C6	C1	119.0(3)	F2	C16	F3	107.0(3)
C8	C7	I1	118.22(18)	F3	C16	S1	111.6(2)
C8	C7	C12	124.3(2)				

Table 6 Torsion Angles for mac150012_fa.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
I1	C5	C6	Cl1	-3.3(3)	C2	C3	C4	C5	0.4(4)
I1	C5	C6	C1	177.2(2)	C3	C4	C5	I1	−177.66(19)
I1	C7	C8	C9	−177.50(17)	C3	C4	C5	C6	0.5(4)
I1	C7	C8	C15	3.7(3)	C4	C5	C6	Cl1	178.6(2)
I1	C7	C12	C11	177.61(17)	C4	C5	C6	C1	-0.8(4)
I1	C7	C12	C13	-1.4(3)	C6	C1	C2	C3	0.7(4)
O1	S1	C16	F1	-53.7(3)	C7	C8	C9	C10	-0.6(4)
O1	S1	C16	F2	67.6(3)	C8	C7	C12	C11	-1.3(4)
O1	S1	C16	F3	-173.0(2)	C8	C7	C12	C13	179.7(2)
O2	S1	C16	F1	-173.5(2)	C8	C9	C10	C11	-0.2(4)
O2	S1	C16	F2	-52.1(3)	C8	C9	C10	C14	179.7(2)
O2	S1	C16	F3	67.2(3)	C9	C10	C11	C12	0.3(4)
O3	S1	C16	F1	66.6(3)	C10	C11	C12	C7	0.4(4)
O3	S1	C16	F2	-172.0(2)	C10	C11	C12	C13	179.5(2)
O3	S1	C16	F3	-52.7(3)	C12	C7	C8	C9	1.4(4)
C1	C2	C3	C4	-1.1(4)	C12	C7	C8	C15	-177.4(2)
C2	C1	C6	Cl1	-179.3(2)	C14	C10	C11	C12	-179.6(2)
C2	C1	C6	C5	0.2(4)	C15	C8	C9	C10	178.2(2)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mac150012_fa.

Atom	*x*	*y*	*z*	U(eq)
H1	-71	8723	-1760	50
H2	-2542	7798	-1603	50
H3	-2644	6728	-249	42
H4	-248	6519	912	35
H9	1401	7864	5486	37
H11	2813	11344	5342	39
H13A	4786	10242	2868	56
H13B	3917	11454	3644	56
H13C	3005	10297	2257	56
H14A	2314	10443	7621	63
H14B	484	10174	6896	63
H14C	1663	11467	7110	63
H15A	1289	5614	2420	49
H15B	1545	5745	3867	49
H15C	3048	5735	3207	49

6.5 X-ray crystal structure of 2-methoxyphenyl(mesityl)iodonium triflate (82)

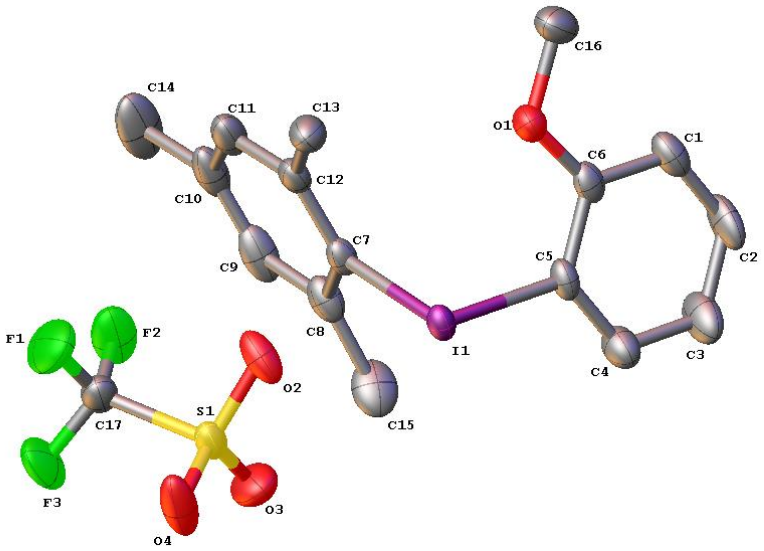


Table 1 Crystal data and structure refinement for mac150005.

Identification code	mac150005
Empirical formula	$C_{38}H_{46}F_6I_2O_9S_2$
Formula weight	1078.67
Temperature/K	150.0(2)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	14.31878(17)
b/Å	10.45390(9)
c/Å	15.38049(16)
α/°	90
β/°	109.5753(12)
γ/°	90
Volume/Å^3	2169.19(4)
Z	2
ρ_{calc}g/cm^3	1.651
μ/mm^{-1}	12.955
F(000)	1076.0
Crystal size/mm^3	0.22 × 0.15 × 0.12
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.304 to 133.768
Index ranges	$-16 \leq h \leq 17$, $-9 \leq k \leq 12$, $-17 \leq l \leq 18$
Reflections collected	15924
Independent reflections	3845 [R_{int} = 0.0318, R_{sigma} = 0.0242]
Data/restraints/parameters	3845/38/271
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0227, wR_2 = 0.0538
Final R indexes [all data]	R_1 = 0.0264, wR_2 = 0.0556
Largest diff. peak/hole / e Å^{-3}	0.47/-0.53

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150005. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
I1	5664.0(2)	5859.8(2)	6802.1(2)	23.02(6)
S1	4031.7(5)	3222.0(7)	5478.0(4)	32.65(16)
F1	3990(2)	950.9(19)	6161.9(18)	74.8(7)
F2	3608.5(18)	2468(2)	6918.3(13)	63.9(6)
F3	2581.9(16)	1839(3)	5626.8(15)	69.6(7)
O1	7392.2(15)	6329.4(19)	8606.1(14)	36.1(5)
O2	5058.0(16)	3317(2)	6033.7(16)	43.3(5)
O3	3474(2)	4371(2)	5488.9(19)	59.7(7)
O4	3820(2)	2647(3)	4586.7(15)	65.2(9)
O5	5000	10000	10000	88.8(15)
C1	7349(2)	8634(3)	8807(2)	36.7(7)
C2	6896(2)	9774(3)	8453(3)	46.2(8)
C3	6114(3)	9828(3)	7632(3)	49.5(9)
C4	5754(2)	8706(3)	7156(2)	38.6(7)
C5	6195(2)	7563(3)	7515.5(19)	27.1(6)
C6	7007(2)	7499(3)	8336.7(19)	28.2(6)
C7	5106(2)	5050(3)	7786.7(17)	25.8(6)
C8	4226(2)	5545(3)	7844(2)	34.1(7)
C9	3877(3)	4976(4)	8496(2)	45.6(8)
C10	4368(3)	3972(4)	9052(2)	46.4(8)
C11	5225(3)	3513(3)	8947(2)	42.0(8)
C12	5621(2)	4028(3)	8310.4(19)	31.2(6)
C13	6536(2)	3444(3)	8206(2)	38.6(7)
C14	3948(4)	3388(5)	9743(3)	71.1(14)
C15	3657(3)	6609(3)	7244(3)	49.3(9)
C16	8277(3)	6239(4)	9396(2)	46.7(8)
C17	3527(2)	2066(3)	6081(2)	39.0(7)
C19	5936(7)	10229(12)	10500(6)	81(2)
C20	6230(9)	10076(12)	11511(7)	70(2)
C21	4629(7)	9823(12)	9136(6)	81(2)
C22	3619(8)	9382(11)	8761(8)	70(2)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150005. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
I1	25.52(10)	23.29(10)	21.94(9)	-5.26(6)	10.19(7)	-7.18(6)
S1	37.1(4)	37.9(4)	21.7(3)	-1.4(3)	8.2(3)	-16.5(3)
F1	103(2)	29.6(11)	75.1(16)	8.2(10)	7.6(15)	-1.5(11)
F2	90.9(17)	74.8(15)	33.5(10)	-7.6(10)	30.7(11)	-37.3(13)
F3	46.2(12)	99.1(18)	56.2(12)	8.2(12)	7.4(10)	-44.3(12)
O1	34.4(12)	33.0(11)	34.2(11)	1.3(9)	2.7(9)	-9.6(9)
O2	30.0(11)	48.6(13)	53.2(13)	-24.3(11)	16.5(10)	-13(1)
O3	62.3(17)	36.9(13)	63.1(16)	14.1(12)	-1.2(14)	3.3(12)
O4	92(2)	79.0(19)	30.5(12)	-18.8(12)	28.9(13)	-58.3(17)
O5	52(3)	123(4)	82(3)	-36(3)	11(2)	12(3)
C1	31.1(16)	44.0(18)	35.6(15)	-14.1(14)	12.0(13)	-13.0(13)
C2	37.3(18)	33.9(18)	65(2)	-26.3(16)	14.3(17)	-11.7(14)
C3	41.4(19)	27.7(16)	72(2)	-13.8(16)	9.1(18)	-0.9(14)
C4	32.5(16)	32.2(16)	45.9(18)	-6.7(14)	6.3(14)	-2.5(13)
C5	28.7(14)	25.5(14)	30.1(14)	-9.9(11)	13.7(12)	-10.3(11)
C6	26.8(14)	32.8(15)	29.2(14)	-6.1(12)	14.9(12)	-10.7(12)
C7	26.3(13)	32.1(14)	21.4(12)	-5.9(11)	11.2(11)	-11.1(11)
C8	32.0(15)	37.3(16)	36.9(15)	-16.8(13)	16.6(13)	-9.9(12)
C9	45.2(19)	59(2)	44.6(18)	-25.4(16)	30.9(16)	-23.2(16)
C10	53(2)	63(2)	27.4(15)	-16.1(14)	19.0(15)	-34.1(16)
C11	45.1(18)	52.2(19)	26.0(14)	-1.2(14)	8.4(13)	-23.8(15)
C12	31.2(15)	35.5(15)	23.0(13)	-2.9(11)	3.8(12)	-13.3(12)
C13	31.4(17)	36.1(17)	42.2(17)	7.7(14)	3.9(14)	-4.7(13)
C14	87(3)	98(3)	45(2)	-18(2)	43(2)	-51(3)
C15	35.8(19)	45.6(19)	75(2)	-8.6(18)	29.1(18)	3.3(15)
C16	35.2(18)	58(2)	37.5(17)	8.5(16)	0.4(14)	-10.8(16)
C17	45.4(19)	41.8(18)	25.5(14)	3.8(13)	6.1(13)	-14.2(15)
C19	65(5)	108(6)	64(5)	-2(4)	13(3)	-12(4)
C20	59(4)	79(7)	65(6)	-4(4)	12(4)	-6(5)
C21	65(5)	108(6)	64(5)	-2(4)	13(3)	-12(4)
C22	59(4)	79(7)	65(6)	-4(4)	12(4)	-6(5)

Table 4 Bond Lengths for mac150005.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
I1	C5	2.096(3)	C2	C3	1.380(5)
I1	C7	2.112(2)	C3	C4	1.388(5)
S1	O2	1.435(2)	C4	C5	1.378(4)
S1	O3	1.446(3)	C5	C6	1.403(4)
S1	O4	1.433(2)	C7	C8	1.392(4)
S1	C17	1.814(3)	C7	C12	1.391(4)
F1	C17	1.326(4)	C8	C9	1.395(4)
F2	C17	1.322(4)	C8	C15	1.500(5)
F3	C17	1.321(4)	C9	C10	1.387(6)
O1	C6	1.348(4)	C10	C11	1.375(5)
O1	C16	1.435(4)	C10	C14	1.515(4)
O5	C19	1.324(9)	C11	C12	1.394(4)
O5	C21	1.269(9)	C12	C13	1.504(4)
C1	C2	1.378(5)	C19	C20	1.477(11)
C1	C6	1.391(4)	C21	C22	1.442(12)

Table 5 Bond Angles for mac150005.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C5	I1	C7	97.08(10)	C12	C7	C8	124.3(3)
O2	S1	O3	113.25(14)	C7	C8	C9	115.9(3)
O2	S1	C17	104.19(15)	C7	C8	C15	123.6(3)
O3	S1	C17	103.41(17)	C9	C8	C15	120.5(3)
O4	S1	O2	116.40(16)	C10	C9	C8	122.4(3)
O4	S1	O3	114.79(18)	C9	C10	C14	119.9(4)
O4	S1	C17	102.55(14)	C11	C10	C9	118.7(3)
C6	O1	C16	118.3(2)	C11	C10	C14	121.4(4)
C21	O5	C19	128.4(6)	C10	C11	C12	122.4(3)
C2	C1	C6	119.7(3)	C7	C12	C11	116.3(3)
C1	C2	C3	121.8(3)	C7	C12	C13	124.2(3)
C2	C3	C4	119.5(3)	C11	C12	C13	119.5(3)
C5	C4	C3	118.8(3)	F1	C17	S1	111.2(2)
C4	C5	I1	119.3(2)	F2	C17	S1	111.5(2)
C4	C5	C6	122.3(3)	F2	C17	F1	108.1(3)
C6	C5	I1	118.5(2)	F3	C17	S1	111.2(2)
O1	C6	C1	125.3(3)	F3	C17	F1	106.4(3)
O1	C6	C5	116.8(2)	F3	C17	F2	108.2(3)
C1	C6	C5	117.9(3)	O5	C19	C20	117.9(9)
C8	C7	I1	117.7(2)	O5	C21	C22	118.5(9)
C12	C7	I1	117.9(2)				

Table 6 Torsion Angles for mac150005.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
I1	C5	C6	O1	0.3(3)	C3	C4	C5	C6	-1.2(5)
I1	C5	C6	C1	-179.6(2)	C4	C5	C6	O1	-178.3(3)
I1	C7	C8	C9	179.4(2)	C4	C5	C6	C1	1.8(4)
I1	C7	C8	C15	0.3(4)	C6	C1	C2	C3	-1.0(5)
I1	C7	C12	C11	-179.5(2)	C7	C8	C9	C10	-0.4(4)
I1	C7	C12	C13	-1.4(4)	C8	C7	C12	C11	-2.0(4)
O2	S1	C17	F1	-59.2(2)	C8	C7	C12	C13	176.0(3)
O2	S1	C17	F2	61.5(3)	C8	C9	C10	C11	-0.8(5)
O2	S1	C17	F3	-177.6(2)	C8	C9	C10	C14	-179.6(3)
O3	S1	C17	F1	-177.8(2)	C9	C10	C11	C12	0.7(5)
O3	S1	C17	F2	-57.1(3)	C10	C11	C12	C7	0.7(4)
O3	S1	C17	F3	63.8(3)	C10	C11	C12	C13	-177.5(3)
O4	S1	C17	F1	62.6(3)	C12	C7	C8	C9	1.9(4)
O4	S1	C17	F2	-176.7(3)	C12	C7	C8	C15	-177.2(3)
O4	S1	C17	F3	-55.8(3)	C14	C10	C11	C12	179.5(3)
C1	C2	C3	C4	1.7(6)	C15	C8	C9	C10	178.7(3)
C2	C1	C6	O1	179.4(3)	C16	O1	C6	C1	-5.7(4)
C2	C1	C6	C5	-0.7(4)	C16	O1	C6	C5	174.4(3)
C2	C3	C4	C5	-0.6(5)	C19	O5	C21	C22	169.9(10)
C3	C4	C5	I1	-179.7(3)	C21	O5	C19	C20	-164.7(10)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mac150005.

Atom	*x*	*y*	*z*	U(eq)
H1	7893	8625	9369	44
H2	7128	10543	8784	55
H3	5825	10627	7394	59
H4	5212	8725	6592	46
H9	3281	5287	8562	55
H11	5558	2819	9323	50
H13A	6360	2990	7615	58
H13B	6829	2840	8712	58
H13C	7016	4119	8222	58
H14A	3415	2791	9426	107
H14B	3684	4067	10035	107
H14C	4474	2928	10217	107
H15A	4064	7385	7362	74
H15B	3049	6772	7384	74
H15C	3486	6366	6594	74
H16A	8802	6753	9292	70
H16B	8490	5343	9493	70
H16C	8145	6558	9942	70
H19A	6092	11117	10372	97
H19B	6358	9655	10277	97
H20A	5822	10634	11749	105
H20B	6930	10309	11796	105
H20C	6135	9184	11658	105
H21A	5053	9198	8959	97
H21B	4675	10641	8828	97
H22A	3601	8452	8829	105
H22B	3348	9607	8105	105
H22C	3221	9788	9093	105

Table 8 Atomic Occupancy for mac150005.

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
C19	0.5	H19A	0.5	H19B	0.5
C20	0.5	H20A	0.5	H20B	0.5
H20C	0.5	C21	0.5	H21A	0.5
H21B	0.5	C22	0.5	H22A	0.5
H22B	0.5	H22C	0.5		

6.6 X-ray crystal structure of 3,4-dimethoxydiphenylamine (67)

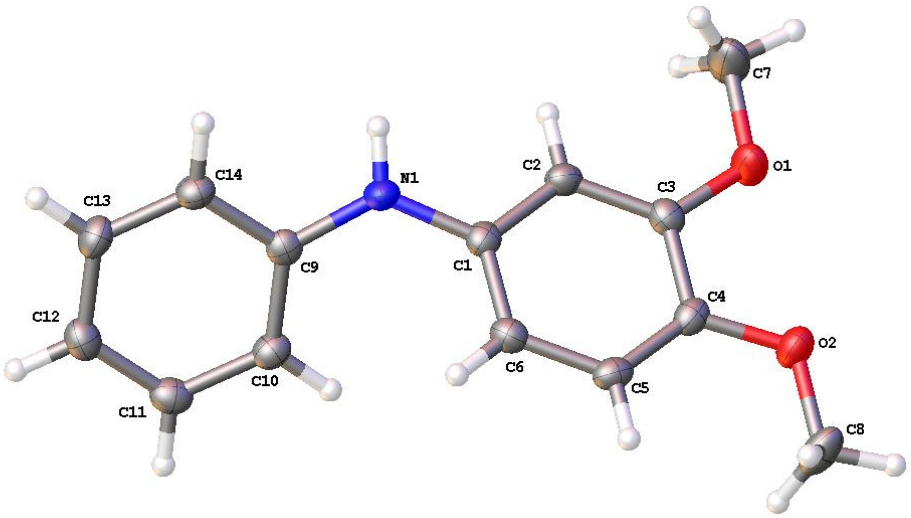


Table 1 Crystal data and structure refinement for mac150002_fa.

Identification code	mac150002_fa
Empirical formula	$C_{14}H_{15}NO_2$
Formula weight	229.27
Temperature/K	150.00(10)
Crystal system	orthorhombic
Space group	Pbca
a/Å	9.1183(3)
b/Å	7.2016(3)
c/Å	35.4587(12)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2328.42(14)
Z	8
ρ_{calc}g/cm^3	1.308
μ/mm^{-1}	0.088
F(000)	976.0
Crystal size/mm^3	0.44 × 0.11 × 0.05
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.894 to 55.652
Index ranges	$-11 \leq h \leq 12$, $-8 \leq k \leq 9$, $-42 \leq l \leq 45$
Reflections collected	17480
Independent reflections	2538 [R_{int} = 0.0618, R_{sigma} = 0.0382]
Data/restraints/parameters	2538/0/159
Goodness-of-fit on F^2	1.097
Final R indexes [I>=2σ (I)]	R_1 = 0.0488, wR_2 = 0.0927
Final R indexes [all data]	R_1 = 0.0699, wR_2 = 0.1005
Largest diff. peak/hole / e Å^{-3}	0.19/-0.17

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150002_fa. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	6093.0(14)	6705.0(16)	4703.9(3)	34.4(3)
O2	4575.5(13)	9236.9(15)	4372.5(3)	32.2(3)
N1	6264.9(16)	2905.2(18)	3582.0(4)	26.0(3)
C1	5783.1(16)	4528(2)	3763.3(4)	21.7(3)
C2	6163.4(17)	4762(2)	4143.9(4)	22.9(3)
C3	5763.0(17)	6351(2)	4336.5(4)	23.9(4)
C4	4950.8(17)	7746(2)	4152.6(4)	22.8(3)
C5	4601.9(17)	7523(2)	3777.4(4)	23.4(3)
C6	5019.6(17)	5924(2)	3581.7(4)	23.6(3)
C7	6976(2)	5363(3)	4896.5(5)	44.7(5)
C8	3650(2)	10595(2)	4205.6(5)	35.5(4)
C9	5596.7(17)	1957(2)	3284.4(4)	21.2(3)
C10	4106.8(17)	2122(2)	3200.1(4)	23.8(4)
C11	3489.2(18)	1036(2)	2918.9(5)	26.2(4)
C12	4329.4(18)	-224(2)	2718.3(4)	27.5(4)
C13	5808.8(18)	-381(2)	2801.0(4)	27.1(4)
C14	6438.7(17)	707(2)	3077.7(4)	24.2(4)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for mac150002_fa. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	48.7(8)	29.5(6)	25.0(6)	-3.7(5)	-9.6(6)	9.0(6)
O2	38.3(7)	25.6(6)	32.7(6)	-4.4(5)	-1.8(5)	8.8(5)
N1	22.2(7)	26.3(7)	29.6(8)	-4.6(6)	-5.8(6)	6.8(6)
C1	18.7(8)	21.0(8)	25.5(8)	-0.9(6)	1.3(6)	-2.1(6)
C2	21.4(8)	21.1(7)	26.1(8)	2.1(6)	-3.2(7)	1.0(7)
C3	23.8(9)	25.0(8)	22.9(8)	-0.4(6)	-1.1(7)	-2.8(7)
C4	20.2(8)	18.8(7)	29.4(8)	-0.8(6)	4.1(7)	-1.1(6)
C5	19.2(8)	21.0(7)	30.0(9)	4.0(6)	-0.2(7)	0.8(7)
C6	21.8(8)	26.7(8)	22.3(8)	1.4(6)	-1.2(6)	-1.1(7)
C7	66.7(14)	37.6(10)	29.7(10)	-2.4(8)	-17.9(9)	13.3(10)
C8	47.3(11)	22.7(8)	36.5(10)	4.5(7)	9.5(9)	11.0(8)
C9	24.1(8)	19.0(7)	20.5(8)	4.0(6)	0.9(6)	-1.6(6)
C10	22.3(8)	22.9(8)	26.3(8)	1.8(6)	3.7(6)	1.0(7)
C11	21.9(8)	27.3(8)	29.4(9)	4.8(7)	-1.3(7)	-3.0(7)
C12	30.7(10)	26.4(8)	25.4(9)	-1.4(7)	-1.6(7)	-4.4(7)
C13	29.7(9)	23.5(8)	27.9(9)	-3.8(7)	5.3(7)	1.8(7)
C14	20.1(8)	25.2(8)	27.4(8)	1.2(7)	1.2(7)	1.5(7)

Table 4 Bond Lengths for mac150002_fa.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C3	1.3609(18)	C3	C4	1.408(2)
O1	C7	1.431(2)	C4	C5	1.377(2)
O2	C4	1.3705(18)	C5	C6	1.397(2)
O2	C8	1.421(2)	C9	C10	1.396(2)
N1	C1	1.404(2)	C9	C14	1.392(2)
N1	C9	1.397(2)	C10	C11	1.387(2)
C1	C2	1.404(2)	C11	C12	1.384(2)
C1	C6	1.382(2)	C12	C13	1.385(2)
C2	C3	1.382(2)	C13	C14	1.381(2)

Table 5 Bond Angles for mac150002_fa.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C3	O1	C7	117.04(13)	C5	C4	C3	119.06(14)
C4	O2	C8	116.78(13)	C4	C5	C6	120.87(14)
C9	N1	C1	128.04(14)	C1	C6	C5	120.34(14)
C2	C1	N1	117.55(14)	C10	C9	N1	122.99(14)
C6	C1	N1	123.35(14)	C14	C9	N1	118.26(14)
C6	C1	C2	119.03(14)	C14	C9	C10	118.63(14)
C3	C2	C1	120.62(14)	C11	C10	C9	120.07(15)
O1	C3	C2	124.73(14)	C12	C11	C10	120.96(15)
O1	C3	C4	115.22(14)	C11	C12	C13	118.94(15)
C2	C3	C4	120.05(14)	C14	C13	C12	120.60(15)
O2	C4	C3	115.26(14)	C13	C14	C9	120.78(15)
O2	C4	C5	125.68(14)				

Table 6 Torsion Angles for mac150002_fa.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C3	C4	O2	-1.7(2)	C4	C5	C6	C1	0.5(2)
O1	C3	C4	C5	178.33(14)	C6	C1	C2	C3	1.0(2)
O2	C4	C5	C6	−178.82(14)	C7	O1	C3	C2	3.0(2)
N1	C1	C2	C3	178.08(14)	C7	O1	C3	C4	−177.16(15)
N1	C1	C6	C5	−178.55(14)	C8	O2	C4	C3	−174.79(14)
N1	C9	C10	C11	−175.12(14)	C8	O2	C4	C5	5.2(2)
N1	C9	C14	C13	174.63(14)	C9	N1	C1	C2	150.50(15)
C1	N1	C9	C10	-21.9(2)	C9	N1	C1	C6	-32.5(2)
C1	N1	C9	C14	162.09(15)	C9	C10	C11	C12	0.1(2)
C1	C2	C3	O1	−179.41(15)	C10	C9	C14	C13	-1.6(2)
C1	C2	C3	C4	0.8(2)	C10	C11	C12	C13	-0.3(2)
C2	C1	C6	C5	-1.6(2)	C11	C12	C13	C14	-0.3(2)
C2	C3	C4	O2	178.18(14)	C12	C13	C14	C9	1.3(2)
C2	C3	C4	C5	-1.8(2)	C14	C9	C10	C11	0.9(2)
C3	C4	C5	C6	1.2(2)					

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mac150002_fa.

Atom	*x*	*y*	*z*	U(eq)
H1	7100(20)	2480(20)	3650(5)	31
H2	6690	3839	4268	27
H5	4082	8448	3653	28
H6	4783	5799	3328	28
H7A	7876	5183	4761	67
H7B	6455	4207	4911	67
H7C	7189	5799	5146	67
H8A	4143	11148	3994	53
H8B	3423	11536	4388	53
H8C	2760	10017	4122	53
H10	3528	2961	3333	29
H11	2496	1155	2864	31
H12	3907	-953	2531	33
H13	6383	-1228	2669	32
H14	7438	603	3127	29

6.7 X-ray crystal structure of *N*-phenylazaquinone (71)

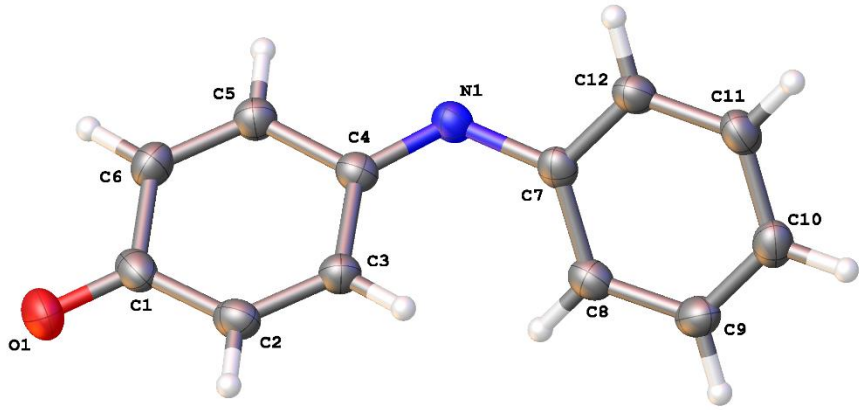


Table 1 : Crystal data and structure refinement for mac150015.

Identification code	mac150015
Empirical formula	$C_{12}H_9NO$
Formula weight	183.20
Temperature/K	150.01(10)
Crystal system	orthorhombic
Space group	$Pca2_1$
a/Å	20.3364(2)
b/Å	6.79390(10)
c/Å	13.52620(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1868.83(4)
Z	8
ρ_{calc}g/cm^3	1.302
μ/mm^{-1}	0.669
F(000)	768.0
Crystal size/mm^3	0.25 × 0.22 × 0.19
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.696 to 133.942
Index ranges	$-24 \leq h \leq 24$, $-8 \leq k \leq 8$, $-16 \leq l \leq 16$
Reflections collected	47877
Independent reflections	3313 [R_{int} = 0.0439, R_{sigma} = 0.0129]
Data/restraints/parameters	3313/1/254
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0279, wR_2 = 0.0759
Final R indexes [all data]	R_1 = 0.0298, wR_2 = 0.0772
Largest diff. peak/hole / e Å^{-3}	0.16/-0.14
Flack parameter	0.01(10)

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for mac150015. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	5547.0(8)	3234(2)	3887.7(14)	43.6(4)
O2	5932.1(8)	-2165(2)	6360.3(17)	47.1(4)
N1	3909.5(8)	9447(2)	3855.3(13)	27.3(4)
N2	4375.6(8)	4221(2)	6301.9(15)	29.2(4)
C1	5167.9(11)	4636(3)	3855.0(17)	31.5(5)
C2	4468.5(11)	4363(3)	3650.1(16)	31.4(5)
C3	4047.4(10)	5871(3)	3636.3(16)	28.3(5)
C4	4271.2(10)	7886(3)	3830.9(15)	26.1(4)
C5	4978.6(10)	8174(3)	3977.8(17)	29.6(5)
C6	5398.9(10)	6663(3)	3996.9(18)	32.6(5)
C7	3216.4(10)	9370(3)	3788.9(16)	25.4(4)
C8	2831.0(11)	8164(3)	4391.9(17)	29.4(5)
C9	2151.5(11)	8242(3)	4322.9(18)	32.3(5)
C10	1849.3(11)	9529(3)	3673.0(18)	32.0(5)
C11	2232.7(11)	10756(3)	3089.3(18)	32.4(5)
C12	2910.6(11)	10693(3)	3148.9(17)	29.2(5)
C13	5569.0(11)	-723(3)	6372.9(19)	31.9(5)
C14	4854.3(11)	-934(3)	6479.8(18)	33.3(5)
C15	4454(1)	608(3)	6465.6(17)	29.9(5)
C16	4713.4(10)	2615(3)	6339.7(17)	26.3(4)
C17	5428.4(10)	2831(3)	6284.2(18)	30.2(4)
C18	5828.4(10)	1278(3)	6293.5(18)	31.9(5)
C19	3679.8(9)	4246(3)	6286.9(17)	26.8(4)
C20	3309.6(10)	3127(3)	5625.8(18)	29.3(5)
C21	2629.5(11)	3291(3)	5623.1(19)	33.6(5)
C22	2316(1)	4561(3)	6265(2)	33.1(5)
C23	2685.6(11)	5707(3)	6906.9(18)	32.4(5)
C24	3362.4(10)	5572(3)	6914.4(17)	29.4(5)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for mac150015. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	37.3(9)	35.2(8)	58.2(11)	6.0(8)	7.7(8)	11.7(7)
O2	39.6(9)	33.1(8)	68.5(11)	-4.6(9)	-10.3(9)	11.4(7)
N1	27.5(9)	22.2(8)	32.2(10)	-0.7(8)	-1.6(8)	0.5(7)
N2	26.8(8)	24.6(8)	36.1(9)	-0.3(8)	1.0(9)	-1.3(6)
C1	34.4(12)	28.1(11)	32.1(12)	5.5(10)	5.9(10)	6.8(9)
C2	36.1(12)	22.6(10)	35.7(12)	-0.5(9)	4.2(10)	-1.1(9)
C3	26.8(10)	24.1(10)	34.1(12)	0.4(9)	0.9(9)	-1.7(8)
C4	28.2(10)	23.4(10)	26.6(10)	0.5(9)	-0.9(9)	-0.5(8)
C5	27.8(10)	26.1(10)	34.9(11)	-0.5(9)	-0.7(9)	-1.4(8)
C6	24.2(10)	34.4(12)	39.1(13)	0.4(10)	0.5(9)	-2.2(9)
C7	25.9(10)	19.6(9)	30.6(12)	-5.0(9)	-2.2(9)	0.0(7)
C8	34.6(11)	23.5(10)	30.1(11)	0.8(9)	0.0(9)	1.3(8)
C9	32.4(11)	26.4(10)	38.1(12)	0.9(9)	8.0(9)	-1.3(9)
C10	25.8(10)	27.8(10)	42.3(13)	-4.8(10)	-1(1)	1.1(8)
C11	29.6(11)	26.3(10)	41.3(13)	2.7(10)	-5.3(9)	4.4(9)
C12	30.1(11)	22.4(10)	35.0(12)	2.4(9)	-1.5(9)	-1.6(8)
C13	34.9(11)	28.8(10)	32.1(11)	-3.1(10)	-4.8(10)	6.9(9)
C14	35.2(11)	23.7(10)	40.9(13)	-0.2(9)	-0.2(10)	-2.7(8)
C15	27.1(10)	26.7(10)	35.9(12)	1.0(9)	3.8(9)	-2.5(8)
C16	28.4(9)	23.0(9)	27.7(10)	-0.7(9)	0.5(9)	-1.5(8)
C17	29.8(10)	28.3(10)	32.5(11)	0.7(10)	0.9(10)	-4.2(8)
C18	26.9(10)	34.9(10)	33.9(12)	1.4(10)	-0.6(10)	0.0(9)
C19	27.6(10)	20.1(9)	32.7(11)	3.8(9)	2.3(10)	-1.6(8)
C20	33.7(11)	21.6(10)	32.6(11)	-1.6(9)	2.3(9)	-1.1(8)
C21	34.9(12)	26.7(11)	39.3(12)	0.6(10)	-6.2(10)	-6.1(9)
C22	27.8(10)	28.4(10)	42.9(13)	6.7(10)	1.1(11)	-2.1(8)
C23	33.7(12)	26.2(10)	37.4(12)	-0.7(10)	5.3(10)	1.3(9)
C24	32.1(11)	23.1(10)	32.8(11)	-2.4(9)	-0.7(9)	-1.3(8)

Table 4 Bond Lengths for mac150015.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.226(2)	C9	C10	1.384(3)
O2	C13	1.227(2)	C10	C11	1.388(3)
N1	C4	1.291(3)	C11	C12	1.382(3)
N1	C7	1.413(3)	C13	C14	1.468(3)
N2	C16	1.290(3)	C13	C18	1.462(3)
N2	C19	1.415(3)	C14	C15	1.327(3)
C1	C2	1.461(3)	C15	C16	1.473(3)
C1	C6	1.468(3)	C16	C17	1.463(3)
C2	C3	1.335(3)	C17	C18	1.332(3)
C3	C4	1.467(3)	C19	C20	1.394(3)
C4	C5	1.465(3)	C19	C24	1.396(3)
C5	C6	1.336(3)	C20	C21	1.388(3)
C7	C8	1.397(3)	C21	C22	1.380(3)
C7	C12	1.394(3)	C22	C23	1.387(3)
C8	C9	1.386(3)	C23	C24	1.380(3)

Table 5 Bond Angles for mac150015.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C4	N1	C7	122.43(16)	C11	C12	C7	120.1(2)
C16	N2	C19	122.90(16)	O2	C13	C14	121.3(2)
O1	C1	C2	121.4(2)	O2	C13	C18	121.63(19)
O1	C1	C6	121.5(2)	C18	C13	C14	117.10(18)
C2	C1	C6	117.07(17)	C15	C14	C13	121.9(2)
C3	C2	C1	122.01(19)	C14	C15	C16	120.88(19)
C2	C3	C4	120.96(19)	N2	C16	C15	126.66(17)
N1	C4	C3	126.49(18)	N2	C16	C17	116.26(18)
N1	C4	C5	116.49(17)	C17	C16	C15	117.04(18)
C5	C4	C3	116.98(17)	C18	C17	C16	121.81(19)
C6	C5	C4	121.88(19)	C17	C18	C13	121.11(19)
C5	C6	C1	120.92(19)	C20	C19	N2	122.85(19)
C8	C7	N1	122.96(18)	C20	C19	C24	119.49(18)
C12	C7	N1	117.41(18)	C24	C19	N2	117.47(19)
C12	C7	C8	119.4(2)	C21	C20	C19	119.7(2)
C9	C8	C7	119.8(2)	C22	C21	C20	120.6(2)
C10	C9	C8	120.6(2)	C21	C22	C23	119.62(18)
C9	C10	C11	119.4(2)	C24	C23	C22	120.5(2)
C12	C11	C10	120.6(2)	C23	C24	C19	120.0(2)

Table 6 Torsion Angles for mac150015.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C1	C2	C3	178.3(2)	C8	C7	C12	C11	-2.3(3)
O1	C1	C6	C5	-178.7(2)	C8	C9	C10	C11	-0.3(3)
O2	C13	C14	C15	-178.0(3)	C9	C10	C11	C12	0.3(3)
O2	C13	C18	C17	178.4(3)	C10	C11	C12	C7	1.0(3)
N1	C4	C5	C6	178.0(2)	C12	C7	C8	C9	2.4(3)
N1	C7	C8	C9	176.52(19)	C13	C14	C15	C16	0.1(4)
N1	C7	C12	C11	-176.76(19)	C14	C13	C18	C17	-2.3(4)
N2	C16	C17	C18	-178.5(2)	C14	C15	C16	N2	179.1(2)
N2	C19	C20	C21	-177.1(2)	C14	C15	C16	C17	-3.1(3)
N2	C19	C24	C23	177.84(19)	C15	C16	C17	C18	3.5(3)
C1	C2	C3	C4	-0.2(3)	C16	N2	C19	C20	-51.1(3)
C2	C1	C6	C5	2.7(3)	C16	N2	C19	C24	134.0(2)
C2	C3	C4	N1	-178.6(2)	C16	C17	C18	C13	-0.8(4)
C2	C3	C4	C5	3.7(3)	C18	C13	C14	C15	2.7(4)
C3	C4	C5	C6	-4.1(3)	C19	N2	C16	C15	-6.1(4)
C4	N1	C7	C8	51.7(3)	C19	N2	C16	C17	176.1(2)
C4	N1	C7	C12	-134.0(2)	C19	C20	C21	C22	0.4(3)
C4	C5	C6	C1	0.9(4)	C20	C19	C24	C23	2.8(3)
C6	C1	C2	C3	-3.1(3)	C20	C21	C22	C23	1.1(3)
C7	N1	C4	C3	6.5(3)	C21	C22	C23	C24	-0.6(3)
C7	N1	C4	C5	-175.80(19)	C22	C23	C24	C19	-1.3(3)
C7	C8	C9	C10	-1.1(3)	C24	C19	C20	C21	-2.3(3)

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for mac150015.

Atom	*x*	*y*	*z*	U(eq)
H2	4308	3074	3523	38
H3	3596	5634	3498	34
H5	5143	9472	4062	36
H6	5853	6904	4104	39
H8	3034	7292	4848	35
H9	1891	7403	4726	39
H10	1383	9572	3627	38
H11	2027	11646	2645	39
H12	3169	11553	2754	35
H14	4673	-2213	6562	40
H15	3994	414	6538	36
H17	5612	4113	6240	36
H18	6290	1474	6248	38
H20	3522	2256	5179	35
H21	2377	2522	5175	40
H22	1850	4650	6268	40
H23	2471	6592	7345	39
H24	3613	6382	7347	35