Synthesis and Applications of New *N*-Functionalised Iodine Compounds

Thesis submitted for the degree of
Doctor of Philosophy
at the University of Leicester

by

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2020

Abstract

In this thesis, the synthesis, characterization and application, in a series of model organic synthetic reactions, of *N*-coordinated iodonium(I) salts and *N*-functionalised hypervalent iodine(III) chlorides and fluorides is described.

In **Chapter 2** the synthesis and characterization of novel *N*-coordinated iodonium(I) salts with multiple substituent groups based on IPy_2BF_4 is presented. Five-membered ring *N*-functionalised hypervalent Cl-I(III) and F-I(III) compounds are readily synthesized in excellent yields from *para*-substituted benzylamide compounds using TClCA and Selectfluor respectively. Their synthesis and characterization are compared with those of various *O*-functionalised hypervalent Cl-I(III) and F-I(III) compounds. X-ray crystallography reveals T-shaped geometries for these species and their structural data are compared with literature precedents. In **Chapter 3** the applications of the new *N*-coordinated iodonium(I) salts in the iodination of aromatic compounds and iodocyclisation reactions are described. In **Chapter 4** the applications of the new *N*-functionalised chlorobenzoiodazolone compounds as electrophilic chlorinating reagents in the chlorination of ethyl benzoylacetate and 1,3-diphenylpropane-1,3-dione, and the oxychlorination of styrene is presented. In addition, their reactivities are compared with those of two *O*-functionalised chlorobenziodoxolone compounds. In **Chapter 5** the applications of the new *N*-functionalised fluorobenzoiodazolone compounds as electrophilic fluorinating reagents in the fluorination of 1,3-dicarbonyl compounds, the intramolecular fluorocyclisation of unsaturated carboxylic acids and the attempted geminal difluorination of α,α'-disubstituted styrenes is described, and their reactivities are compared with those of *O*-functionalised fluoroiodane. NMR studies in hexafluoroisopropanol reveal hydrogen-bonding between the fluorobenzoiodazolones and the solvent which may activate these compounds. **Chapter 6** includes full experimental and characterization data for the chemistry outlined in Chapters 2-5.

Acknowledgement

Throughout the writing of this thesis, I have received a great deal of support and assistance.

I would first like to express the deepest appreciation to my supervisors Prof. Eric G. Hope and Dr. Alison Stuart for their expertise, assistance, guidance and patience throughout the process of research work and writing of this thesis. I have been feeling pretty fortunate to always get their encouragement, dedicated supervision and insight through my whole PhD life. This thesis would not have been possible without their continuous support.

I would also like to give my sincere thanks to Dr. Gerry Griffith and Dr. Vanessa M. Timmermann for the analysis of NMR spectra, Mr. Mick Lee and Dr. Sharad C. Mistry for the mass spectrometry and Mr. Kuldip Singh for the X-ray crystallographic structure determinations. Many thanks will be given to all the staff members in the University of Leicester who helped me as well.

In addition, I would like to appreciate all the lab partners Dr. Gregory Solan, Dr. Alex Pulis, Dr. Meshari Aljohani, Dr. Emad Zangana, Dr. Ahmed Abdoken, Dr. Rusul M. Al-Rubaay, Dr. Martyna Urbonaite, Will, Simran, Jinting, Ana, Laura and Sam for the support, friendship and all the fun we have had in the last four years we were working together.

I am also very grateful to my good friends Xi Jin, Nikki Xi, Bingxue Li, Sophie Wang, Kimmy Lee, Kun Tan, Jingjing Xing, Min Wang, Chenyiman Lou, Sharon Wong, Jack Lau, Kristy Lai and Marian Perera et al. for letting me keep positive attitudes in my study and usual life.

Finally and the most importantly, I am extremely thankful to my family. Whatever challenges come to my way, you always give me fully solid support, love and encouragement. I believe all my achievements would not have been possible without you.

Contents

Abbreviations

Å	angstrom
Ac	acetyl
Anal.	elemental analysis
Ar	aryl
ASAP	atmospheric solids analysis probe
Bn	benzyl
BODIPY	boron-dipyrromethene
bpy	2,2'-bipyridine
br, s	broad singlet
Bu	*n*-butyl
Bz	benzoyl
℃	Celsius
Calcd.	calculated
cat.	catalyst
Cbz	benzyloxycarbonyl
coll	collidine (2,4,6-trimethylpyridine)
Cp	cyclopentadienyl
d	doublet
dap	2,9-bis(p-anisyl)-1,10-phenanthroline
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet doublets
DMAP	4-(dimethylamino)pyridine
DMF	*N, N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
dt	doublet triplets
ee	enantiomeric excess
eq.	equivalents

ESI	electrospray ionization
Et	ethyl
et al.	and others
etc.	and other similar things
FAB	fast atom bombardment
g	gram
h	hour
hept	heptet
hfacac	hexafluoroacetylacetonate
HFIP	hexafluoro-2-propanol
Hz	Hertz
IR	infrared
J	NMR coupling constant
LA	Lewis acid
M	mole per litre
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
min	minute
mL	millilitre
mol	mole
m.p.	melting point
m/z	mass-to-charge ratio
Ms	mesyl (methanesulfonyl)
MS	molecular sieve; mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
oct	octet
OMe	methoxy
PFA	perfluoroalkoxy alkane
Ph	phenyl

Phen	1,10-phenanthroline
Phth	phthaloyl
Piv	pivaloyl
ppm	parts per million
Pr	*n*-propyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
q	quartet
RT	room temperature
s	singlet
t	triplet
TBAI	tetrabutylammonium iodide
TBAT	tris(benzyltriazolylmethyl)amine
t-Bu	*tert*-butyl
TClCA	trichloroisocyanuric acid
td	triplet doublets
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMP	trimethylpyridine
TMS	trimethylsilyl
Tol	*p*-tolyl
TREAT-HF	trimethylamine trihydrofluoride
Ts	tosyl (*p*-toluenesulfonyl)
V	volume
δ	delta (NMR chemical shift)

Chapter 1 General Introduction

1.1 Introduction

Iodine is the heaviest non-radioactive non-metal element that belongs to the main group p-block elements in the Periodic Table. It is also the largest, least electronegative, and the most polarizable halogen. However, the bonding description, structural features and reactivity of iodine compounds are different from those of the lighter main-group elements because of its large atomic radius. This chapter mainly introduces the applications of iodonium(I) salts and hypervalent iodine(III) in various areas.

1.2 Iodonium(I) Salts

In order to prepare iodonium(I) salts, heterolytic cleavage of the I-I bond is needed for the formation of I^+. Effectively this is a disproportionation of iodine, forming I^+ and I^-. The I^+ is then stabilized by coordination to good ligands, like pyridine. Bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) (Barluenga's reagent) **(Figure 1.1)** is one of the most widely used reagents among them. Compared with other inorganic iodonium(I) compounds such as IBr, ICl and Py·ICl, IPy_2BF_4 has better thermal stability and lower toxicity, which makes it an I^+ source that can be used under mild reaction conditions.[1-3]

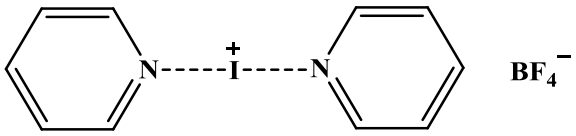
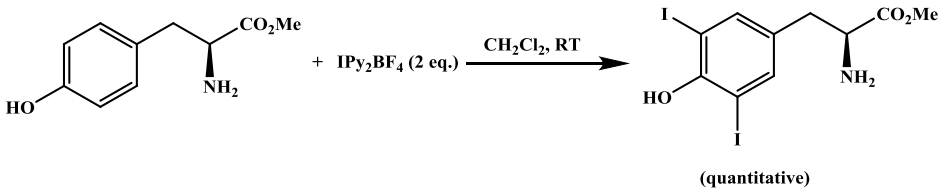


Figure 1.1 Bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) (Barluenga's reagent)

1.2.1 Application of iodonium(I) salts in the iodination of functional organic compounds

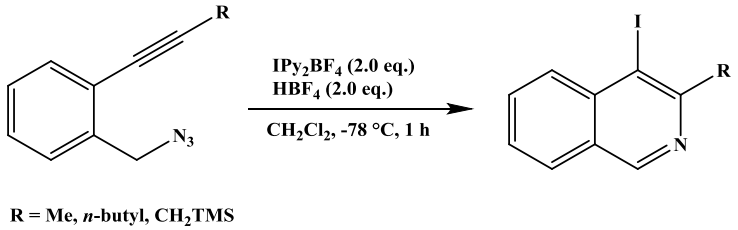
One of the most significant applications of iodination of functional organic compounds is in the field of medical nuclear imaging. In 1996, Barluenga and co-workers first reported iodination of aromatic residues in peptides by the reaction of amino acid derivatives with IPy_2BF_4 **(Scheme 1.1)**. The reaction is simple, straightforward and can be carried out at room temperature, with potential application in single emission computed tomography (SPECT) for brain studies.[4] In 2006, Valencia and co-workers extended the application of IPy_2BF_4 in protein characterization and labelling by iodination. Their results gave ample proof of the viability of using IPy_2BF_4, in that the

reaction is quantitative, fast and selective for the most accessible Tyr residues of a protein.[5]



Scheme 1.1 Di-iodination of tyrosine methyl ester using IPy_2BF_4

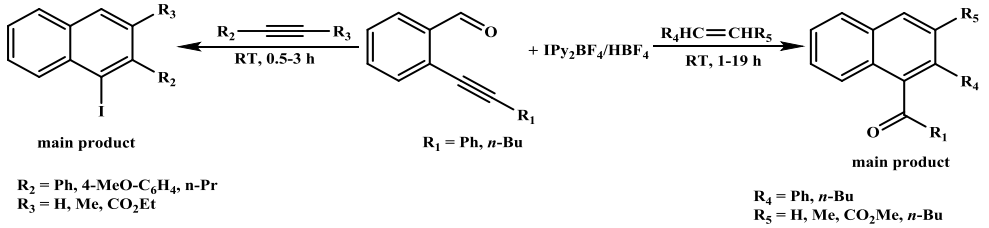
Alternatively, the reaction of 2-alkynyl-1-methylene azide aromatics with IPy_2BF_4/HBF_4 gave highly substituted cyclization products 1,3-disubstituted 4-iodoisoquinolines in good yields in an hour **(Scheme 1.2)**, which provided a new methodology in pharmaceutical synthesis, as reported by Yamamoto et al.[6]



Scheme 1.2 Iodine-mediated cyclization of 2-alkynylbenzyl azides using IPy_2BF_4

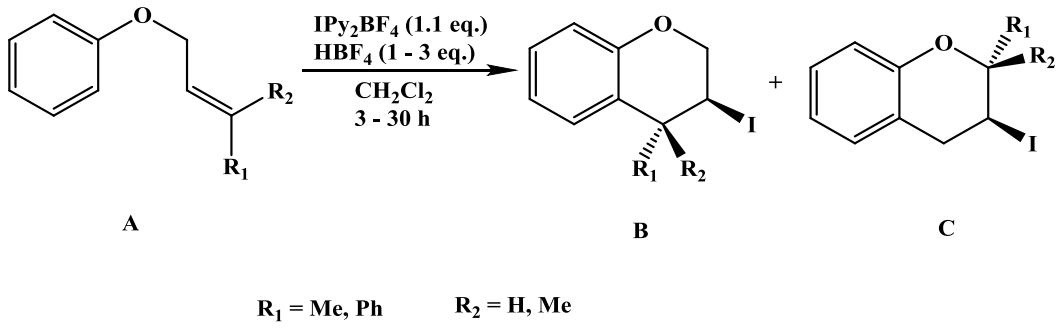
1.2.2 Application of iodonium(I) salts to build new C–C bonds

In 2003, Barluenga's group proposed, for the first time, a method to produce substituted naphthalene compounds upon treatment of *o*-(alkynyl)benzaldehyde derivatives with IPy_2BF_4/HBF_4 and subsequent addition of either an alkyne or an alkene **(Scheme 1.3)**; they thus gave a facile metal-free approach to accomplish valuable C–C bond forming reactions.[7]



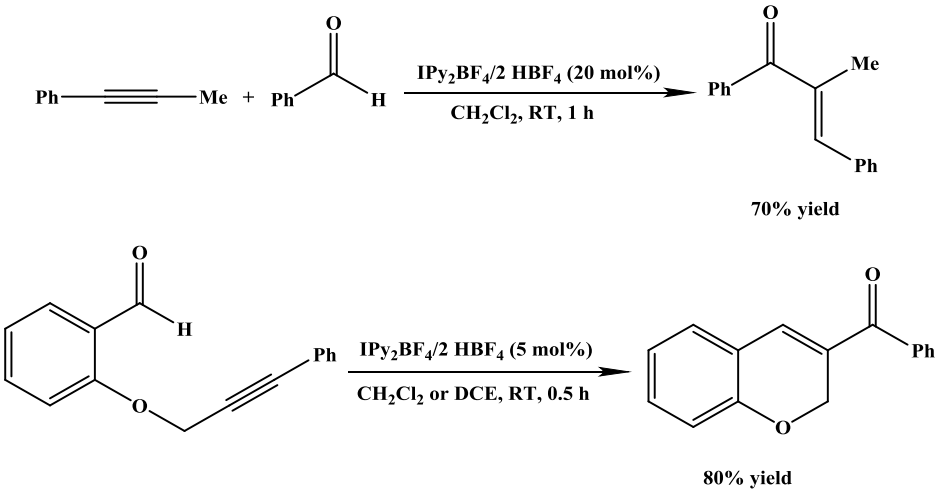
Scheme 1.3 Cycloaddition of *o*-(alkynyl)benzaldehyde derivatives by the reaction of alkynes or alkenes with IPy_2BF_4/HBF_4

In 2004, they also found that the intramolecular arylation reactions of alkenes with IPy_2BF_4/HBF_4 is a flexible approach for the synthesis of chromans, as shown in **Scheme 1.4**. At -40 ℃, the main product was **B** (92-95% yield) and at -90 ℃, the main product was **C** (85-95% yield).[8]



Scheme 1.4 Synthesis of chromans **B** and **C**

In 2016, Saito et al. reported IPy_2BF_4 with HBF_4 as an efficient catalyst for alkyne-carbonyl metathesis of unactivated alkynes (**Scheme 1.5)**. This was the first published account of a catalytic application of IPy_2BF_4 [9] based on the proposed mechanism of the involvement of IPy_2BF_4/HBF_4 in the direct intramolecular arylation of aldehydes **(Figure 1.2)** reported by Barluenga et al.[10]



Scheme 1.5 Two examples of inter- and intramolecular alkyne-carbonyl metathesis of unactivated alkynes with aldehydes.

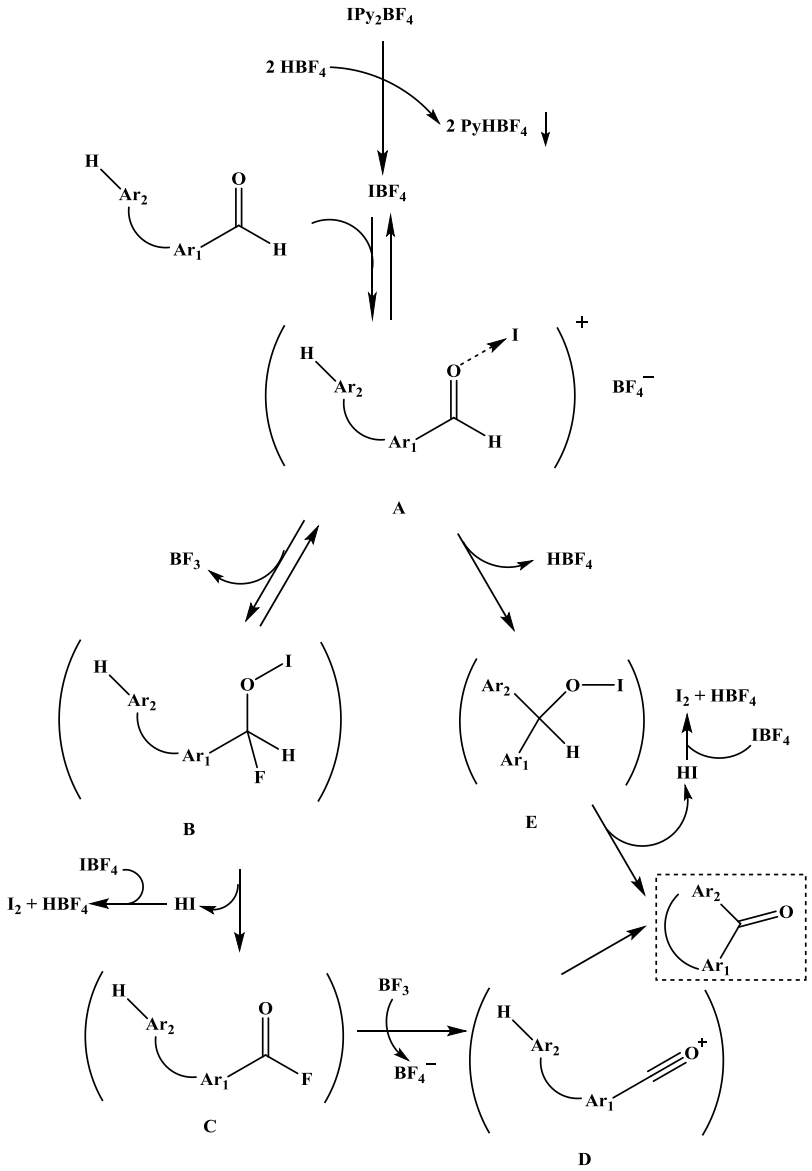
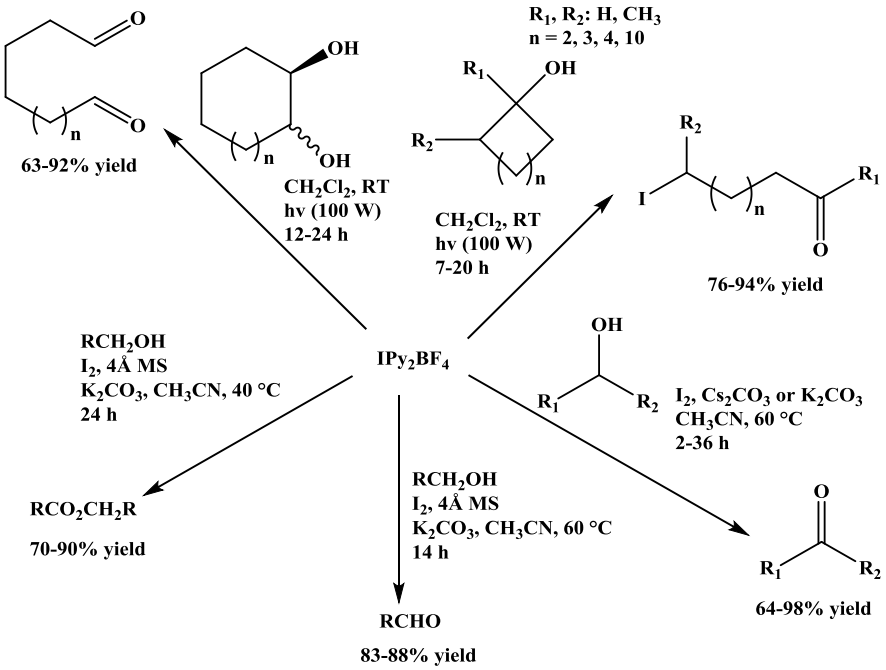


Figure 1.2 Proposed mechanism pathways that account for the observed aldehyde to ketone conversion

1.2.3 Application of iodonium(I) salts as oxidants

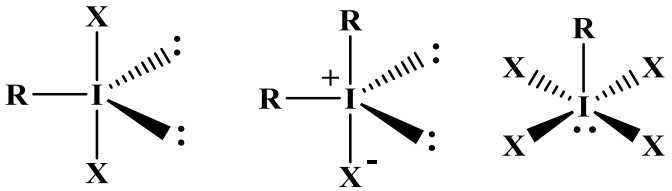
Barluenga et al. have demonstrated that IPy_2BF_4 can be used as a versatile oxidizing reagent for the preparation of ω-iodocarbonyl compounds by a regioselective ring opening reaction of cycloalkanols, the preparation of aldehydes and esters from primary and benzylic alcohols, and the oxidation of secondary alcohols and diols under photochemical or thermal conditions **(Scheme 1.6)**.[11-12]



Scheme 1.6 IPy_2BF_4 as an oxidizing reagent

1.3 Hypervalent Iodine(III) Compounds

Iodine(III) and iodine(V) compounds **(Figure 1.3)** are termed hypervalent iodine compounds with three-centre-four-electron (3c-4e) bonds, which are highly polarised, longer and weaker than regular covalent bonds, which in turn lead to their various special applications in modern organic synthesis.[13-15] We first introduce the syntheses of different types of widely used and stable organic hypervalent iodine(III) compounds.



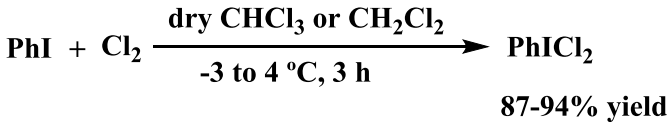
R = carbon ligand; X = halogen, O-, or N- ligand

Figure 1.3 Typical structural types of iodine(III) and iodine(V) compounds

1.3.1 Synthesis of hypervalent iodine(III) compounds

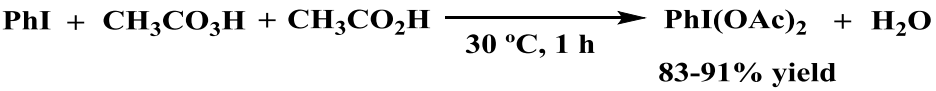
Nearly all the hypervalent iodine(III) compounds are prepared by the oxidation of iodobenzene or its derivatives.

(Dichloroiodo)benzene ($PhICl_2$), one of the most widely used hypervalent iodine(III) compounds, can be prepared on a large-scale by the reaction of iodobenzene with Cl_2 gas at low temperature **(Scheme 1.7)**.[16-17]

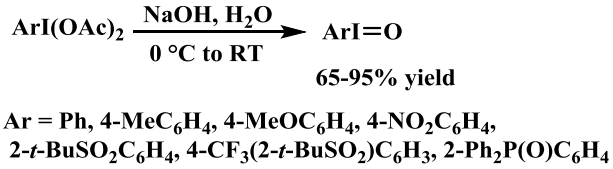


Scheme 1.7 Synthesis of $PhICl_2$

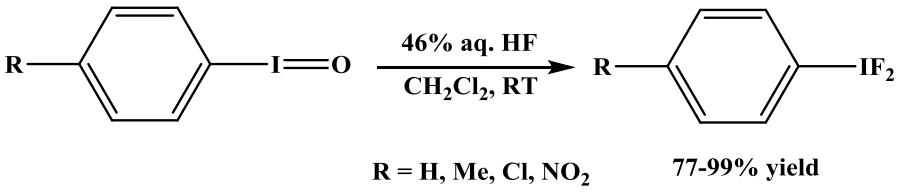
Another important hypervalent iodine(III) compound (diacetoxyiodo)benzene (DIB) is usually prepared by the reaction of iodobenzene with a mixture of acetic acid and peracetic acid **(Scheme 1.8)**.[18] DIB and its derivatives are also precursors, through hydrolysis with aqueous NaOH solution for the preparation of heat-sensitive iodosylbenzene (PhI=O) and its derivatives **(Scheme 1.9)**.[15] Subsequently, as shown in **Scheme 1.10**, PhI=O can be used for the synthesis of (difluoroiodo)benzene ($PhIF_2$) and its analogues.[15, 19] However, (difluoroiodo)benzene derivatives are usually prepared and used in solution without isolation because of their highly hydroscopic properties.[15]



Scheme 1.8 Synthesis of DIB



Scheme 1.9 Typical approach for the preparation of iodosylbenzene and its derivatives



Scheme 1.10 Preparation of $PhIF_2$ and its analogues

1.3.2 Applications of linear hypervalent iodine(III) compounds

At present, a large number of studies have reported the role of hypervalent iodine(III) compounds as electrophilic reagents in the synthesis of functional organic compounds. In particular, linear hypervalent iodine(III) compounds, such as some commercially available species, such as (dichloroiodo)benzene ($PhICl_2$), (diacetoxyiodo)benzene (DIB) and [bis(trifluoroacetoxy)iodo]benzene (BTI or PIFA) **(Figure 1.4)** as well as their analogues, are powerful tools to achieve di-functionalization of alkenes to obtain diastereoselective products. The following are some examples:

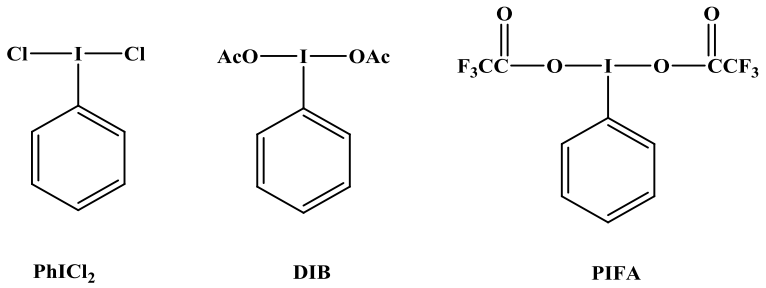
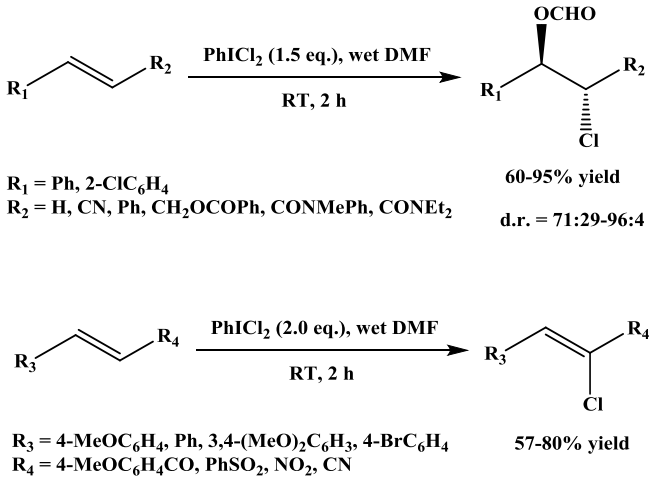


Figure 1.4 Structures of $PhICl_2$, DIB and PIFA

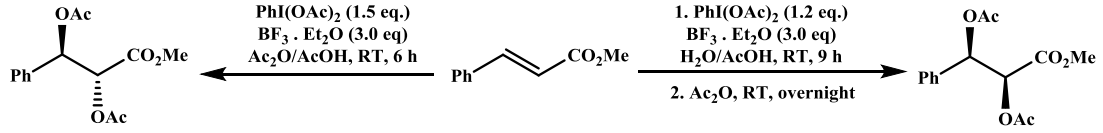
The regioselective chloroformyloxylation and α-chlorination of various alkenes can be conveniently established using $PhICl_2$ in wet DMF **(Scheme 1.11)**.[20]



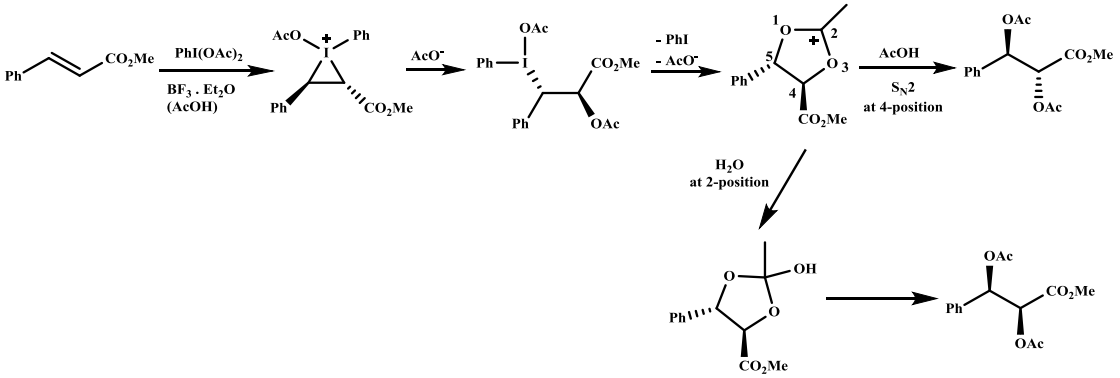
Scheme 1.11 Regioselective chloroformylation or α-chlorination of alkenes using $PhICl_2$ in wet DMF

Diacetoxylation of various alkenes using DIB/BF_3·Et_2O can produce corresponding diastereoselective products, depending on the presence or absence of water **(Scheme**

1.12). The proposed mechanism also considers that the 1,3-dioxolan-2-yl cation is the most significant intermediate **(Scheme 1.13)**.[21-22]

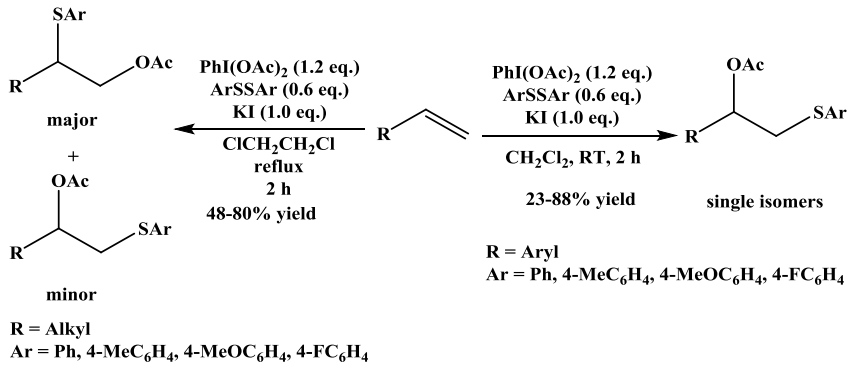


Scheme 1.12 Diastereoselective diacetoxylation of alkenes using DIB under different conditions



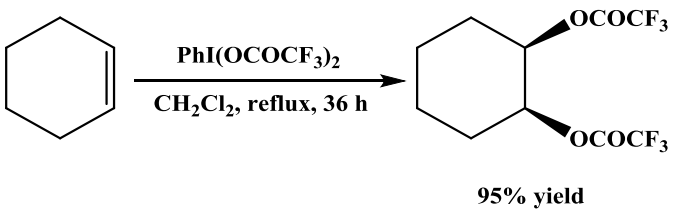
Scheme 1.13 Proposed mechanism for the diastereoselective diacetoxylation of alkenes using DIB under different conditions

Muangkaew et al. developed the DIB/KI mediated 1,2-acetoxysulfenylation of alkenes using disulfides, which is a facile method for the synthesis of β-acetoxysulfides.[23] The reaction is highly regioselective for styrene derivatives while aliphatic alkenes result in a mixture of two regioisomeric products **(Scheme 1.14)**.



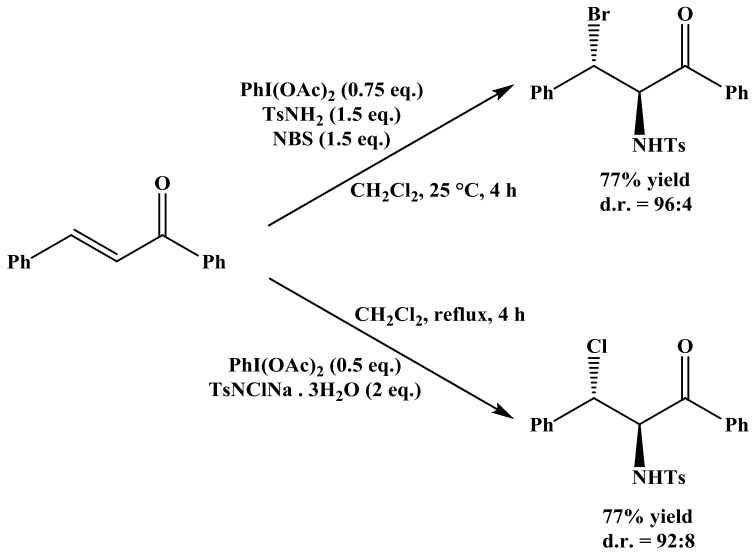
Scheme 1.14 DIB/KI mediated 1,2-acetoxysulfenylation of alkenes under different reaction conditions

In a similar way to the reactions with DIB, the trifluoroacetoxylation of alkenes can be carried out using PIFA. In particular, the treatment of cyclohexene with PIFA can result in a high yield of cis-1,2-bis(trifluoroacetate)cyclohexane, a highly diastereoselective product **(Scheme 1.15)**.[24]



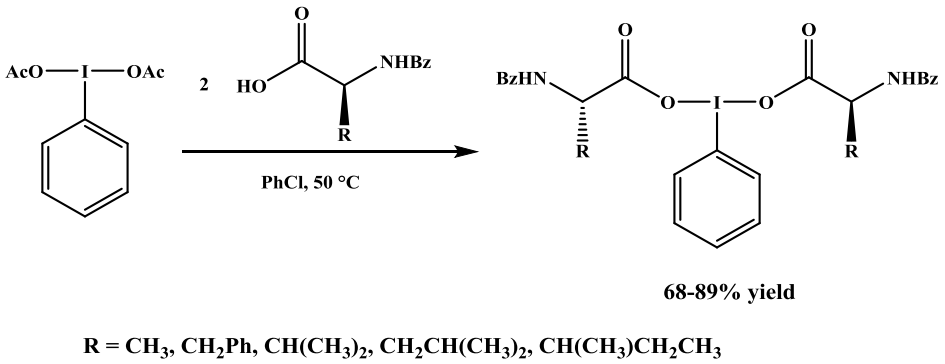
Scheme 1.15 Trifluoroacetoxylation of cyclohexene using PIFA

Linear hypervalent iodine(III) compounds can not only directly introduce functional groups into alkenes by electrophilic addition reaction but can also facilitate the introduction of other functional groups through various reactions such as aminobromination and aminochlorination of, for example, chalcone **(Scheme 1.16)** using DIB.[25] These reactions are usually metal-free and highly regio- and stereo-selective.

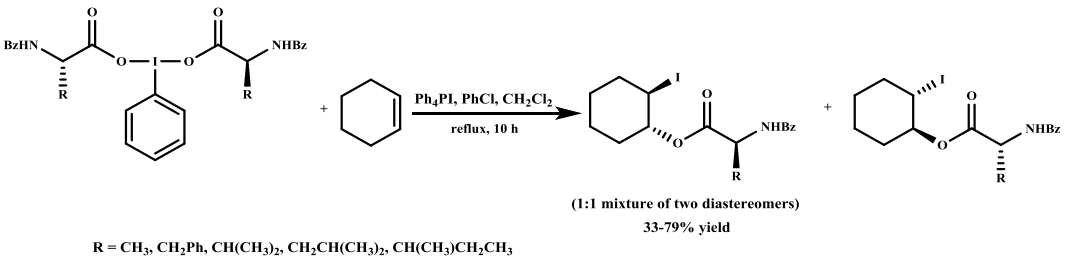


Scheme 1.16 DIB in the aminobromination and aminochlorination of chalcone

Many linear hypervalent iodine(III) compounds can transform each other by ligand exchange and hydrolysis, an aspect that greatly widens their applications. For example, amino acid-derived iodobenzene dicarboxylates can be prepared from DIB using the following approach outlined in **Scheme 1.17**. In combination with Ph_4PI, these compounds can be applied in the β-iodocarboxylation of alkenes to prepare amino acid esters **(Scheme 1.18)**.[26]

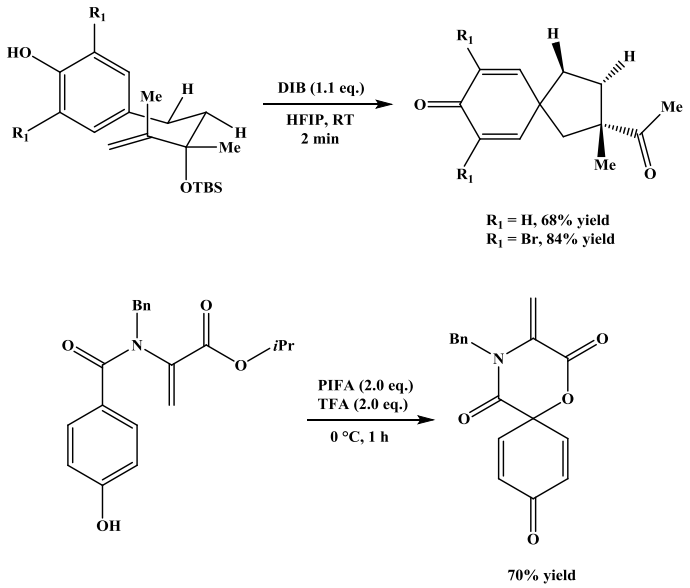


Scheme 1.17 Synthesis of amino acid-derived iodobenzene dicarboxylates from DIB



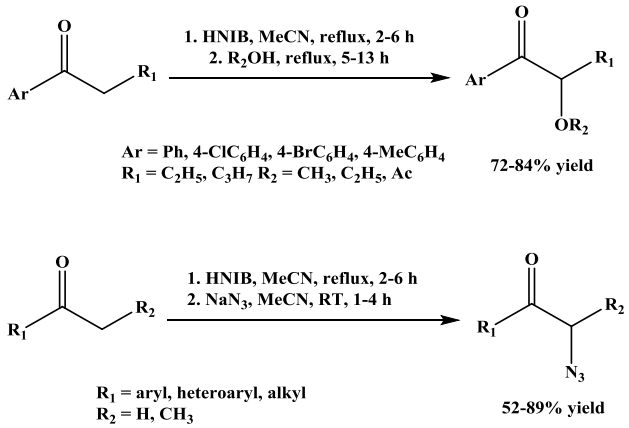
Scheme 1.18 Reaction of amino acid-derived iodobenzene dicarboxylates with cyclohexene

It is well known that hypervalent iodine(III) compounds can be employed as oxidants, which play an important roles in organic synthesis. One of the most representative applications is the dearomatisation of phenolic substrates using DIB and PIFA **(Scheme 1.19)**. This application is a powerful tool for the synthesis of natural products.[27-29]

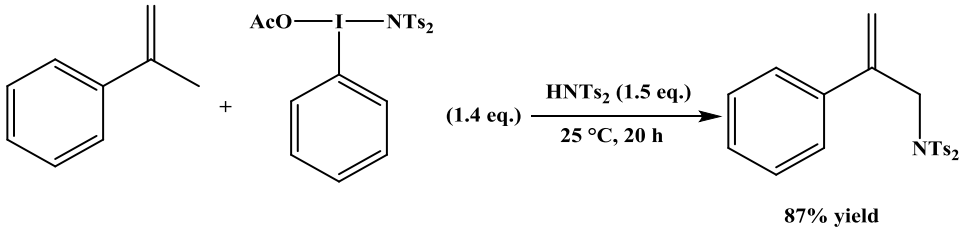


Scheme 1.19 Applications of DIB and PIFA in dearomatisation of phenolic substrates

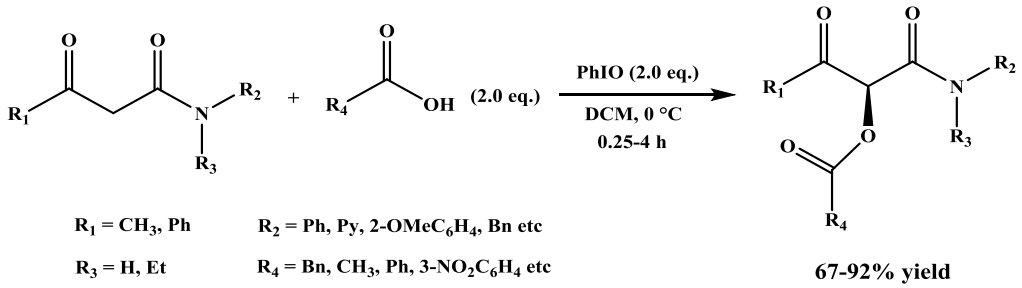
The applications of linear hypervalent iodine(III) compounds in α-functionalisation of carbonyl and alkene compounds have been extensively reported. These applications include the α-alkoxylation or α-acetoxylation of aromatic ketones and α-azidonation of aliphatic or aromatic ketones using [hydroxy(p-nitrobenzenesulfonyloxy)iodo]benzene (HNIB) **(Scheme 1.20)** [30] as well as the α-sulfonyloxylation of carbonyl compounds using [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent) and its analogues.[31] Muñiz's group discovered a new approach, reported for the first time in 2012, to direct intermolecular allylic amination through C-H activation using $PhI(OAc)NTs_2$ under metal-free conditions **(Scheme 1.21)**.[32] In 2018, Dong and co-workers presented a highly efficient direct α-acyloxylation of 1,3-dicarbonyl compounds with carboxylic acids treated by iodosylbenzene **(Schemes 1.22 and 1.23)**.[33]



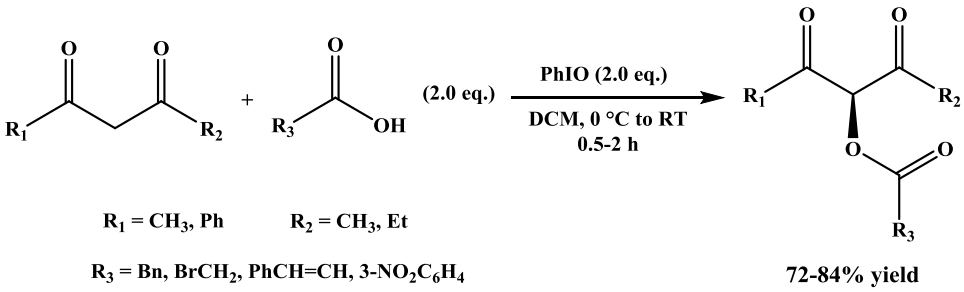
Scheme 1.20 α-alkoxylation, α-acetoxylation and α-azidonation of ketones using HNIB



Scheme 1.21 Metal-free allylic amination of α-methyl styrene using $PhI(OAc)NTs_2$

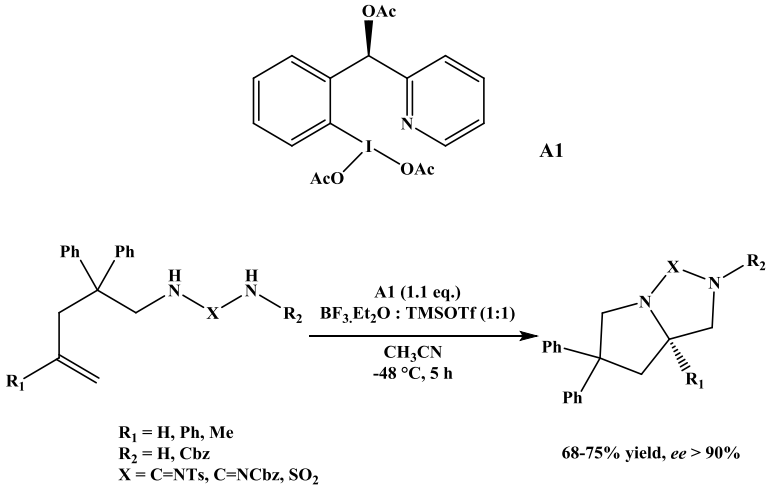


Scheme 1.22 Reaction of β-oxo amides with carboxylic acids in the presence of iodosylbenzene



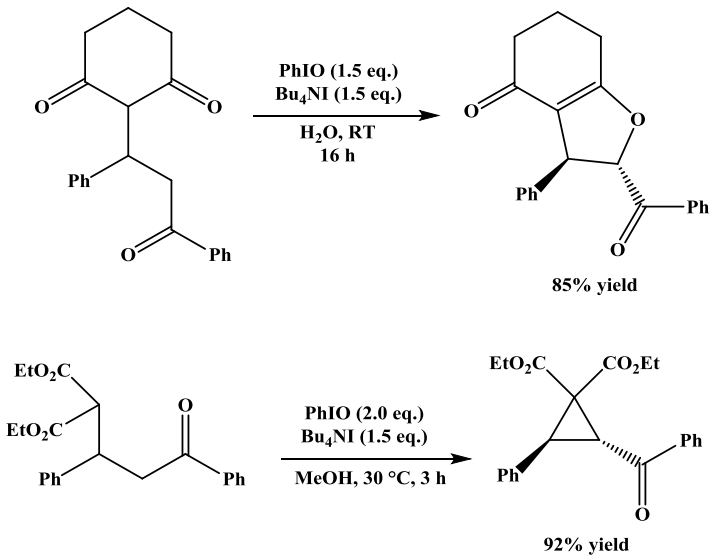
Scheme 1.23 α-Acyloxylation of 1,3-diketones in the presence of iodosylbenzene

Additionally, Wirth's group reported the application of chiral hypervalent iodine(III) compounds in stereo- and enantioselective synthesis, which offers potential for developments in pharmaceutical production in the future.[34-35] As shown in **Scheme 1.24**, they successfully synthesised bicyclic products by a stereoselective cyclisation reaction using the chiral hypervalent iodine(III) compound **A1** combined with a Lewis acid.

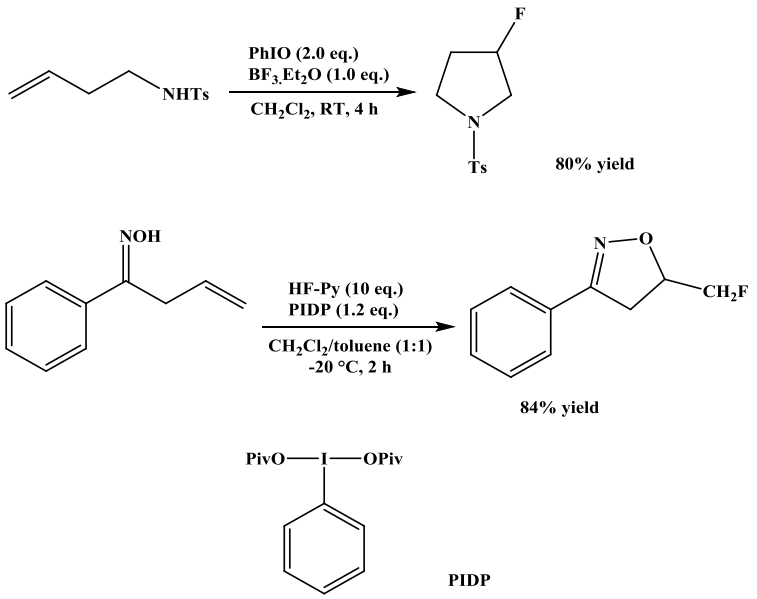


Scheme 1.24 Stereoselective cyclization reaction using chiral hypervalent iodine(III) compound **A1**

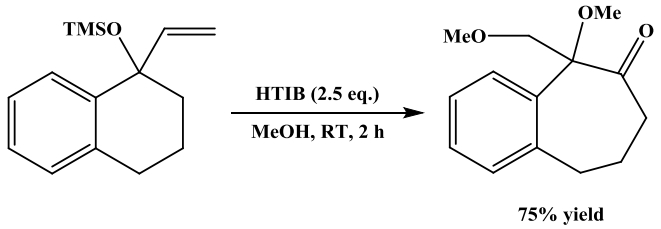
Furthermore, linear hypervalent iodine(III) compounds can be employed in intramolecular cyclisation of Michael adducts of 1,3-dicarbonyl compounds **(Scheme 1.25)**,[36-37] fluorinative cyclization **(Scheme 1.26)**,[38-39] ring expansion reactions **(Scheme 1.27)**,[40] ring contraction reactions **(Scheme 1.28)** [41] and cross-coupling reactions **(Scheme 1.29)**.[42]



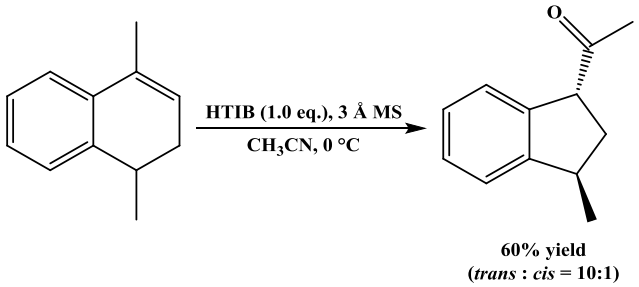
Scheme 1.25 Intramolecular cyclisation through Michael reactions using iodosylbenzene



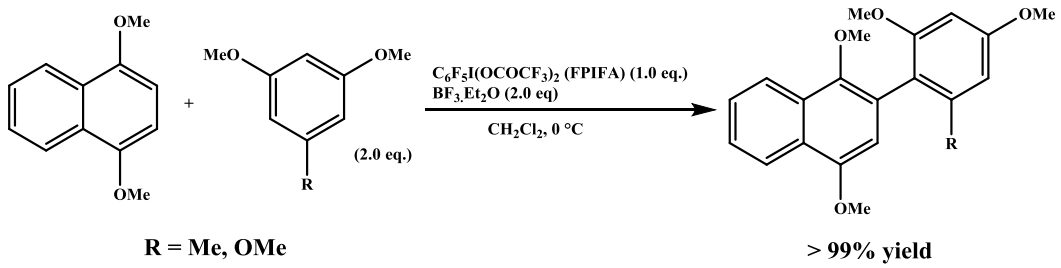
Scheme 1.26 Fluorinative cyclisation using hypervalent iodine(III) compounds



Scheme 1.27 Application of hypervalent iodine(III) compound PhI(OH)OTs (HTIB, Koser's reagent) in a ring expansion reaction

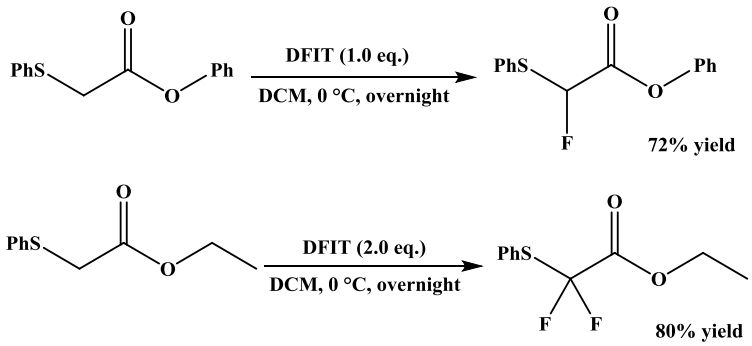


Scheme 1.28 Application of HTIB in a ring contraction reaction

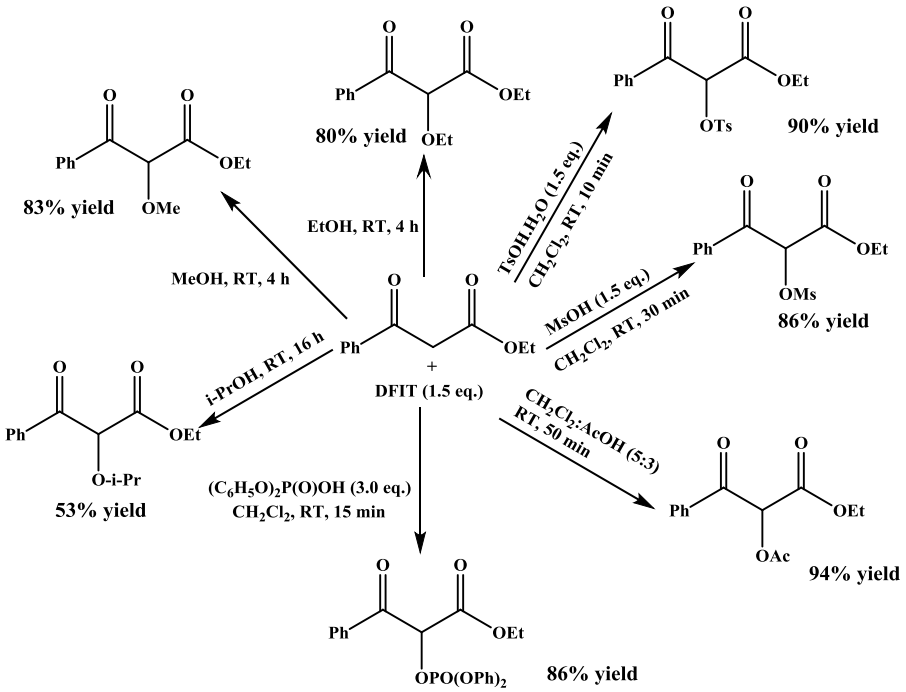


Scheme 1.29 Application of hypervalent iodine(III) compound $C_6F_5I(OCOCF_3)_2$ (FPIFA) in a cross-coupling reaction

Among all of the linear hypervalent iodine(III) compounds, (difluoroiodo)benzene ($PhIF_2$) and its analogues have been studied for a long time; they are usually used to introduce fluorine into organic compounds, especially for the α-fluorination of carbonyl compounds **(Scheme 1.30)**,[43] which play a significant role in the bio-pharmaceutical area. In an alternative, in 2010, Zhang et al. reported the role of (difluoroiodo)toluene ($TolIF_2$, DFIT) as a general reagent for the effective introduction of various O-containing functional groups, including tosyloxy, mesyloxy, acetoxy, phosphoryloxy, methoxy, ethoxy and isopropoxy, to the α-position of 1,3-dicarbonyl compounds **(Scheme 1.31)**.[44]

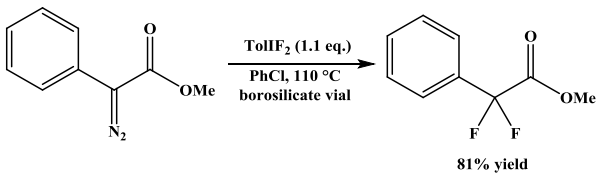


Scheme 1.30 α-Fluorination of α-phenylsulfanyl esters using (difluoroiodo)toluene ($TolIF_2$, DFIT)

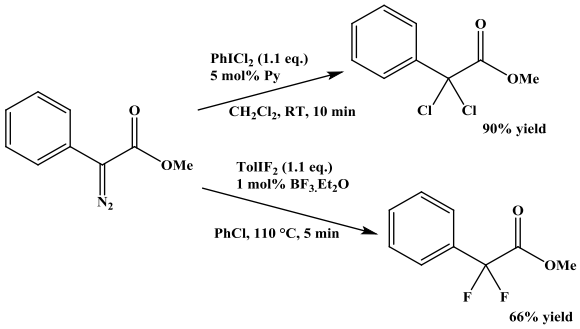


Scheme 1.31 Introduction of various O-containing functional groups at the α-position of ethyl benzoylacetate using DFIT

In 2016, Murphy et al. identified borosilicate as an effective activator for DFIT in the gem-difluorination of phenyl diazoacetate derivatives **(Scheme 1.32)**,[45] based on gem-dichlorination and difluorination of phenyl diazoacetate using $PhICl_2$ and DFIT activated by pyridine and BF_3 ÐEt_2O, respectively **(Scheme 1.33)**.[46]

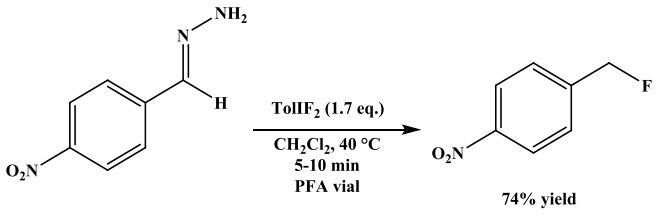


Scheme 1.32 gem-Difluorination of phenyl diazoacetate using DFIT with borosilicate activation

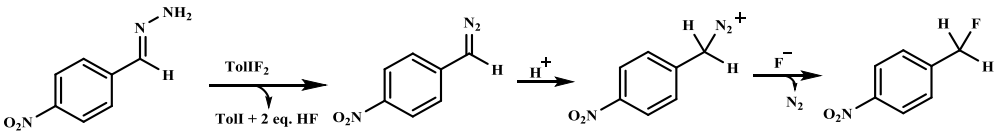


Scheme 1.33 gem-Dichlorination and difluorination of phenyl diazoacetate using DFIT with pyridine and BF_3 ÐEt_2O activation

Some reactions using DFIT must be carried out in perfluoroalkoxy alkane (PFA) vials due to the production of HF **(Schemes 1.34 and 1.35)**.[47]



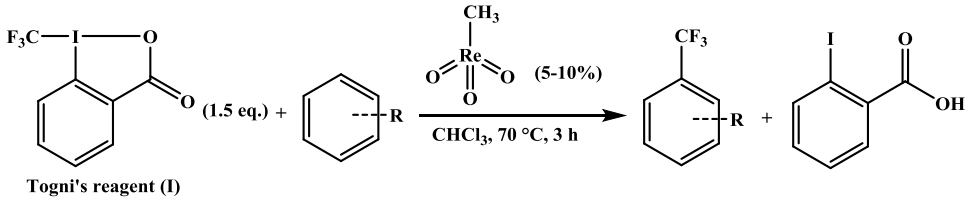
Scheme 1.34 Denitrogenative hydrofluorination of 4-nitrobenzaldehyde hydrazine using DFIT



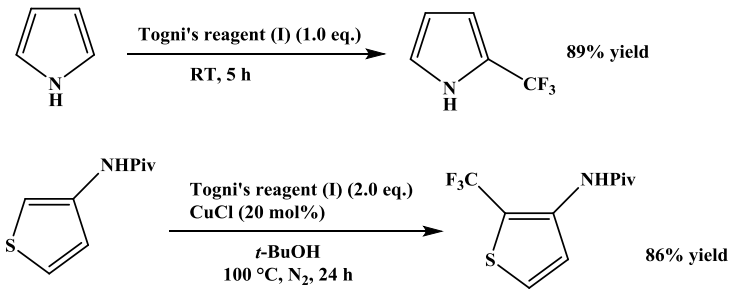
Scheme 1.35 Proposed mechanism for the denitrogenative hydrofluorination of 4-nitrobenzaldehyde hydrazine using DFIT

1.3.3 Applications of heterocyclic hypervalent iodine(III) compounds

Compared with the acyclic hypervalent iodine(III) reagents, the five-membered heterocyclic iodine(III) compounds have considerably higher thermal stability.[15] 1-Chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **(OC-1)** and 1-chloro-1,2-benziodoxol-3-(1*H*)-one **(OC-2)** are particularly important oxygen containing five-membered ring hypervalent iodine(III) compounds obtained from 2-iodobenzoic acid, which can be used to prepare other derivatives, especially those containing OH-I(III), OAc-I(III), F-I(III) and to synthesise 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one (Togni's reagent (I)) and trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (Togni's reagent (II)) by ligand exchange.[48] Many studies have reported the introduction of the CF_3 group to organic compounds using Togni's reagent (I). Trifluoromethylbenzene and its derivatives can be prepared **(Scheme 1.36)** [49] and the trifluoromethylation of other aromatic compounds **(Scheme 1.37)** [50-51] accomplished by metal-catalysed or metal-free applications of Togni's reagent (I).

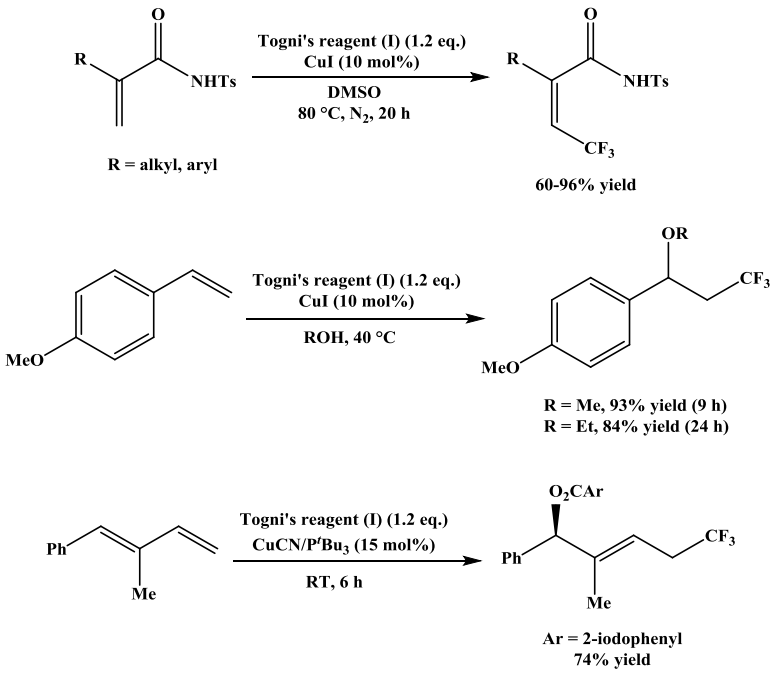


Scheme 1.36 Trifluoromethylbenzene and its derivatives prepared using Togni's reagent (I) and a metal catalyst

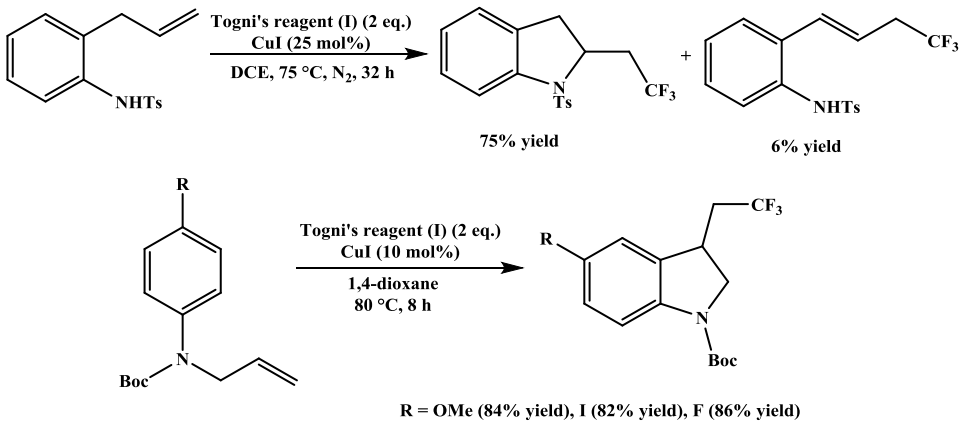


Scheme 1.37 Trifluoromethylation of other aromatic compounds using Togni's reagent (I)

Togni's reagent (I) is also a highly effective reagent for different kinds of trifluoromethylation of alkenes **(Scheme 1.38)** [52-54] and trifluoromethylated cyclization reactions **(Scheme 1.39)**.[55-56]



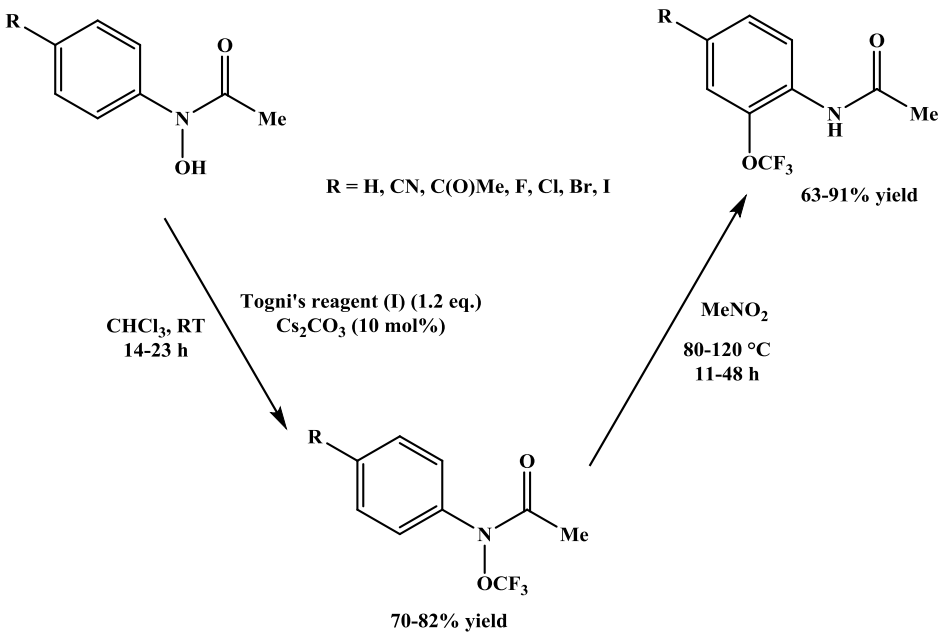
Scheme 1.38 Some examples of trifluoromethylation of alkenes using Togni's reagent (I)



Scheme 1.39 Some examples of trifluoromethylated cyclisation reactions using Togni's reagent (I)

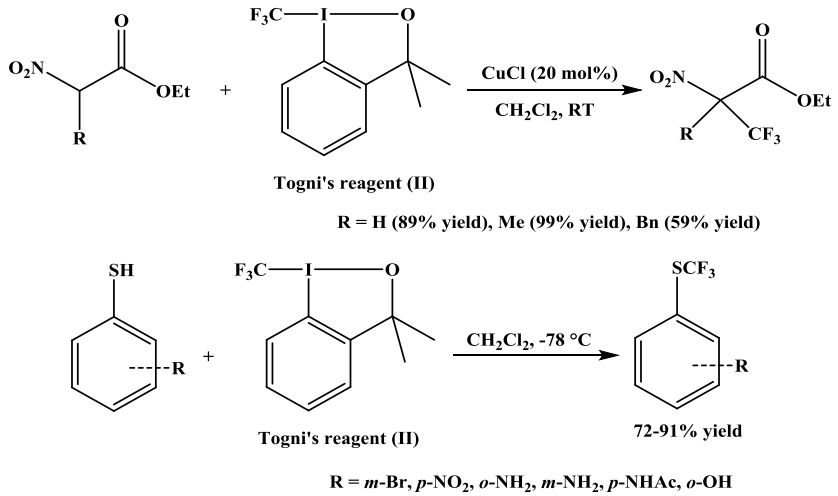
In 2014, Ngai et al. reported aryl trifluoromethoxylation in two steps: *O*-trifluoromethylation of *N*-aryl-*N*-hydroxylamine derivatives using Togni's reagent (I) and intramolecular OCF_3 migration **(Scheme 1.40)**.[57] This approach provides an easy

and accessible way to synthesise *ortho*-OCF_3 aniline derivatives, which are very important for pharmaceuticals and agrochemicals.

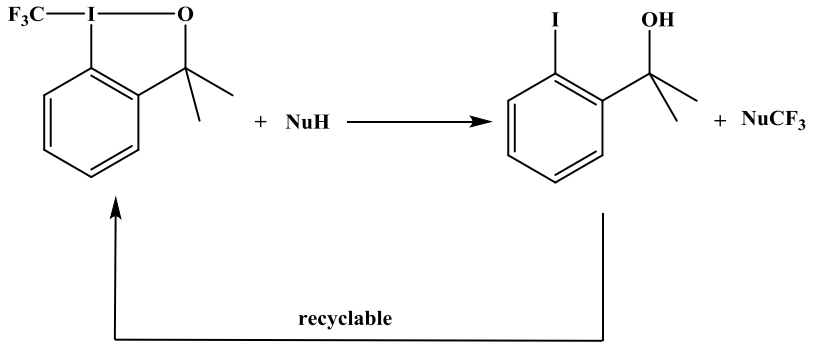


Scheme 1.40 Synthetic route for aryl trifluoromethoxylation using Togni's reagent (I)

Additionally, the applications of Togni's reagent (II) with regard to the trifluoromethylation of various substrates have been reported in many studies, where it has been compared to those with Togni's reagent (I). Togni et al. reported in 2007 that mild electrophilic trifluoromethylation of carbon- and sulfur- centred nucleophiles can be carried out with excellent results using Togni's reagent (II), such as the α-trifluoromethylation of α-nitroesters and trifluoromethylation of thiols **(Scheme 1.41)**.[58] 2-Iodophenylpropan-2-ol is formed as a by-product which can be recycled for the synthesis of more Togni's reagent (II) **(Scheme 1.42)**.

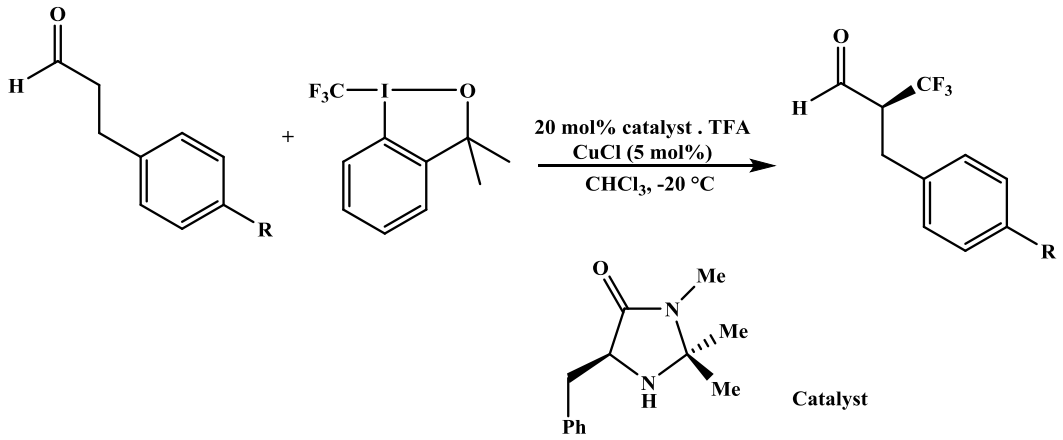


Scheme 1.41 α-Trifluoromethylation of α-nitroesters and trifluoromethylation of thiols using Togni's reagent (II)



Scheme 1.42 General straightforward stoichiometry for electrophilic trifluoromethylation reactions with Togni's reagent (II)

In 2010, MacMillan et al. first reported that enantioselective α-trifluoromethylated aldehydes can be generated under mild conditions using Togni's reagent (II) combined with CuCl as a Lewis acid catalyst together with a chiral organic catalyst **(Scheme 1.43)**.[59] The reaction mechanism is described in **Figure 1.5**.



R = H (81% yield, 94% ee), OMe (87% yield, 96% ee), CF_3 (78% yield, 93% ee)

Scheme 1.43 Catalytic enantioselective α-trifluoromethylation of *p*-benzylaldehydes using Togni's reagent (II)

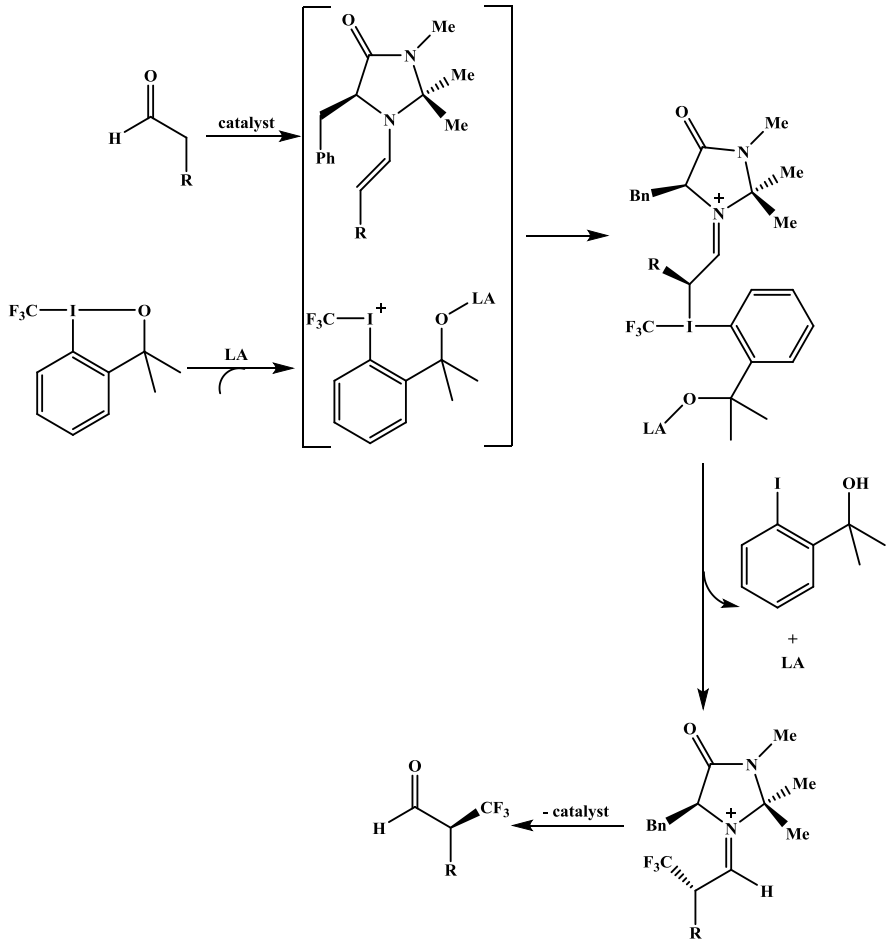
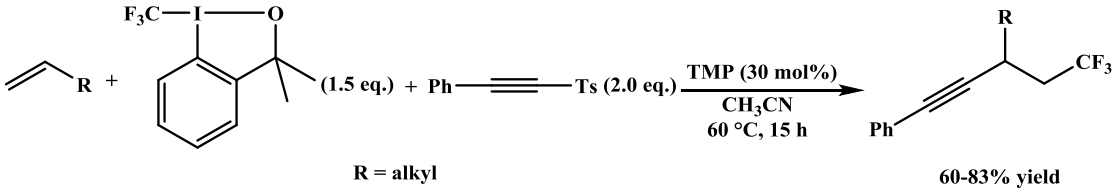


Figure 1.5 Proposed mechanism for enantioselective α-trifluoromethylation of aldehydes using Togni's reagent (II)

In 2017, Li et al. developed the trifluoromethylalkynylation of unactivated alkenes with alkynyl sulfones and Togni's reagent (II), which was catalysed by 2,4,6-trimethylpyridine (TMP) under metal-free conditions, as shown in **Scheme 1.44**. The CF_3 radical is considered to be the most significant active intermediate in the proposed mechanism **(Figure 1.6)**.[60]



Scheme 1.44 Trifluoromethyalkynylation of unactivated alkenes using Togni's reagent (II)

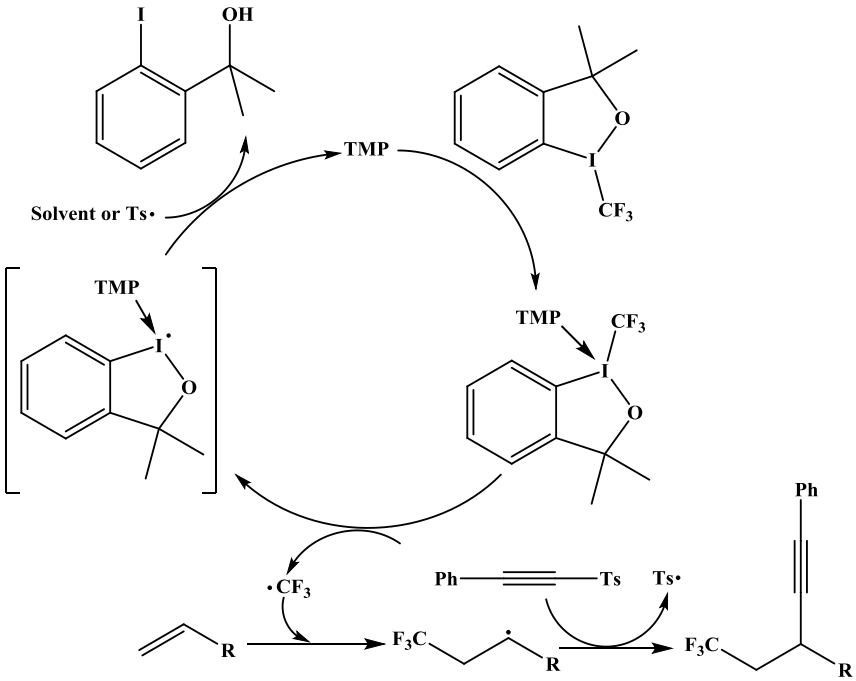
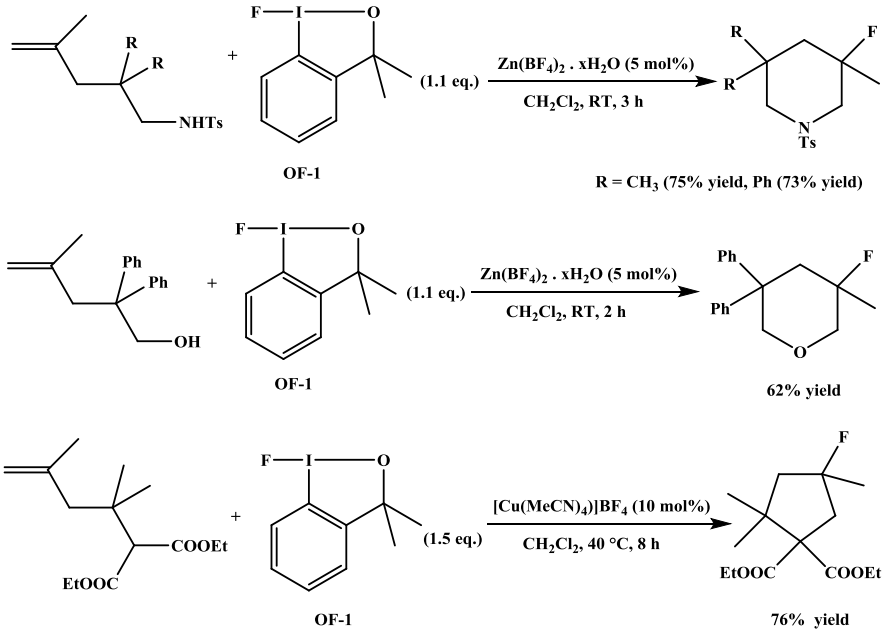


Figure 1.6 Proposed mechanism of trifluoromethylalkynylation with Togni's reagent (II)

In the process of preparation of Togni's reagent (II), 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** is treated as an important intermediate. As a reagent, **OF-1** has attracted a lot of attention from chemists as a safe, thermally stable and easily accessible electrophilic fluorination reagent. Particularly, it can be applied in the fluorocyclisation of various unsaturated compounds. In 2015, Yuan and Szabó first

presented the applications of **OF-1** in catalytic intramolecular aminofluorination, oxyfluorination and carbofluorination to build new fluorine-containing rings **(Scheme 1.45)**.[61] **Figure 1.7** gives an example of the proposed mechanism for the intramolecular aminofluorination reaction with **OF-1**.



Scheme 1.45 Selected examples of catalytic fluorocyclisation reactions using **OF-1**

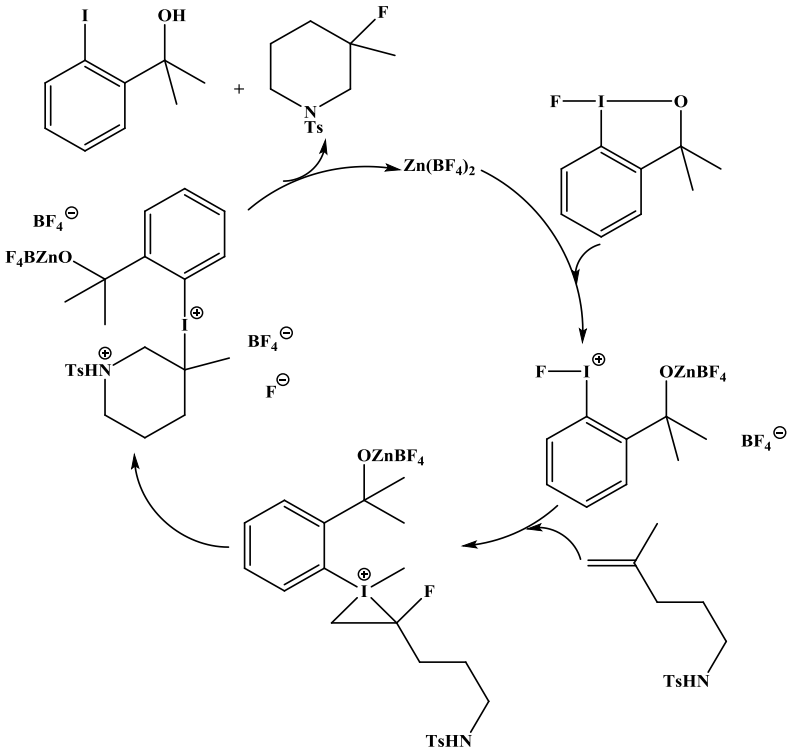
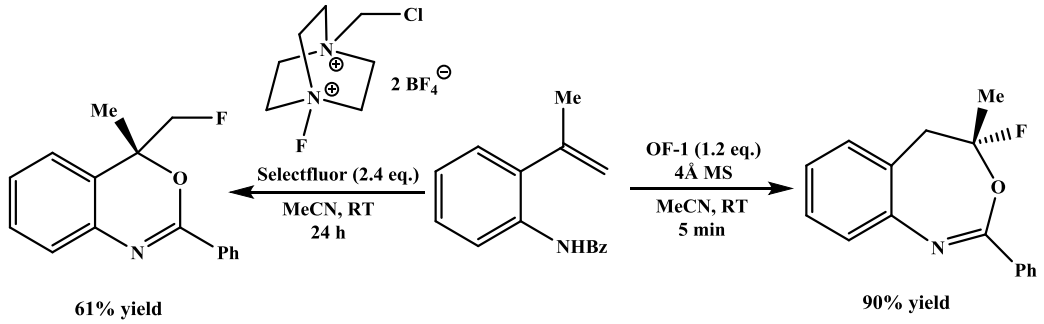


Figure 1.7 Proposed mechanism for the intramolecular aminofluorination reaction with **OF-1**

In 2016, Gulder's group demonstrated that the synthesis of the novel class of 4-fluoro-1,3-benzoxazepines using **OF-1**, through an unusual fluorination/1,2-aryl migration/cyclisation cascade **(Scheme 1.46)**, is an efficient and metal-free method for high yields and regio- and diastereo-selectivities, compared with those available with the commercially available electrophilic fluorination reagent Selectfluor. The proposed mechanism is given in **Figure 1.8**.[62] Subsequently, the results and discussion were validated by computational calculations.[63]



Scheme 1.46 Synthesis of fluoro-benzoxazepines

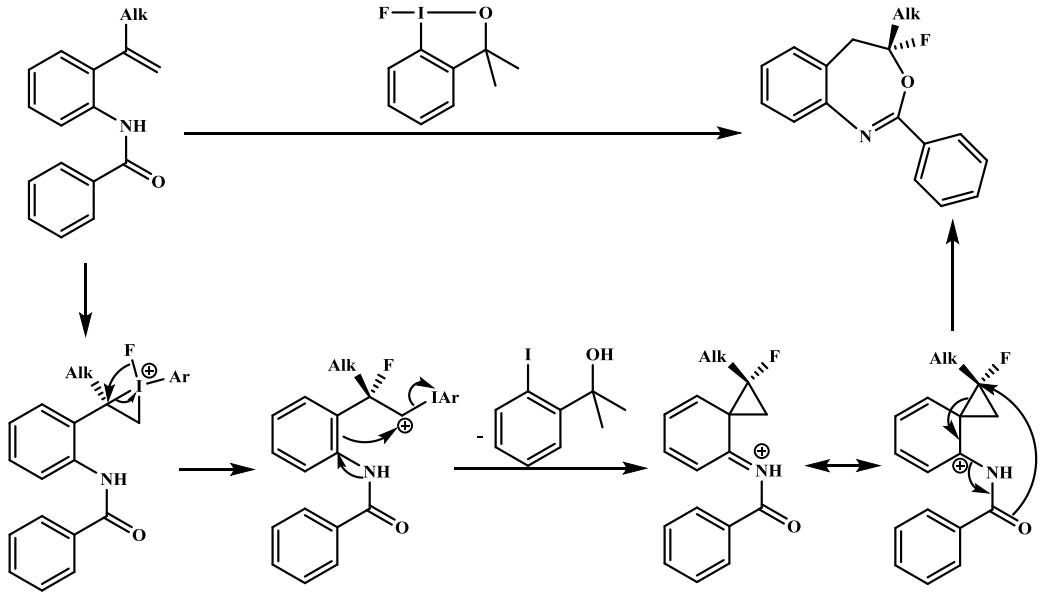
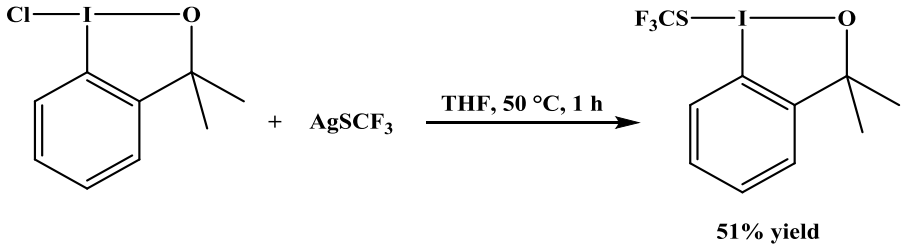


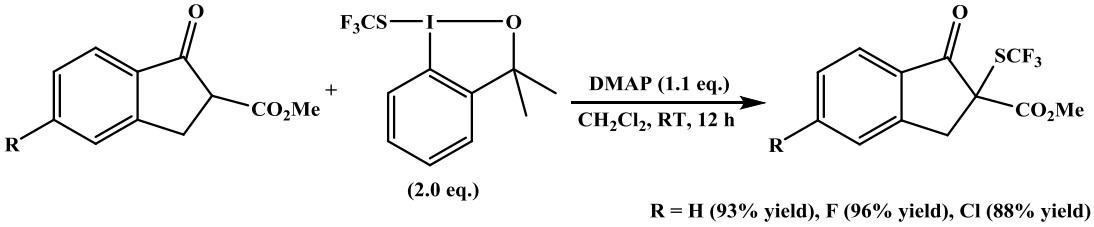
Figure 1.8 Proposed mechanism for the synthesis of 4-fluoro-1,3-benzoxazepines using **OF-1**

The air- and moisture-stable trifluoromethylthiolated hypervalent iodine(III) reagent, prepared by the reaction of **OC-1** with $AgSCF_3$, has been developed by Lu and Shen's group **(Scheme 1.47)** and applied in the α-trifluoromethylthiolation of β-ketoesters

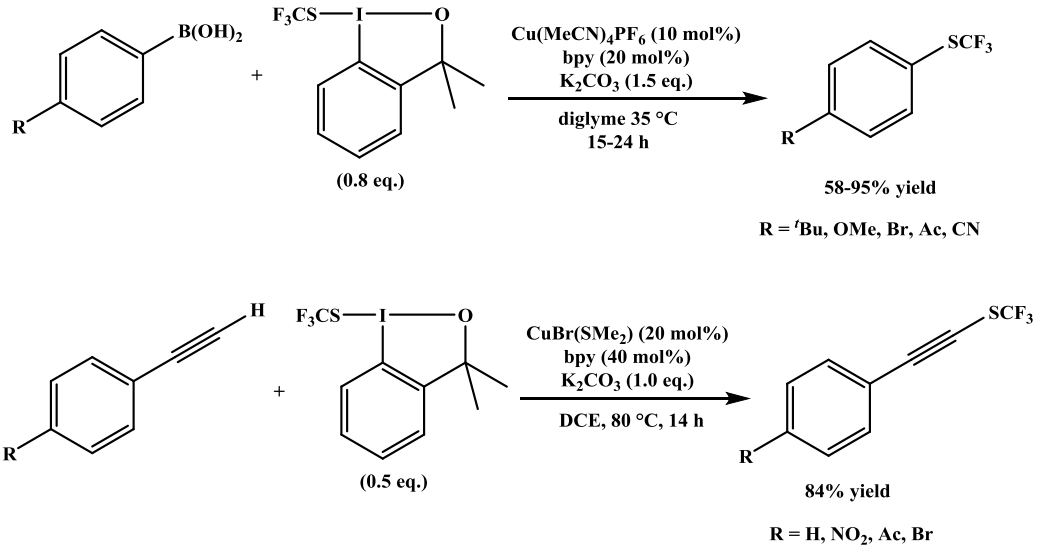
(Scheme 1.48) as well as copper-catalysed trifluoromethylthiolation of aryl boronic acids and alkynes **(Scheme 1.49)**.[64]



Scheme 1.47 Preparation of trifluoromethylthiolated hypervalent iodine(III) reagent from **OC-1**

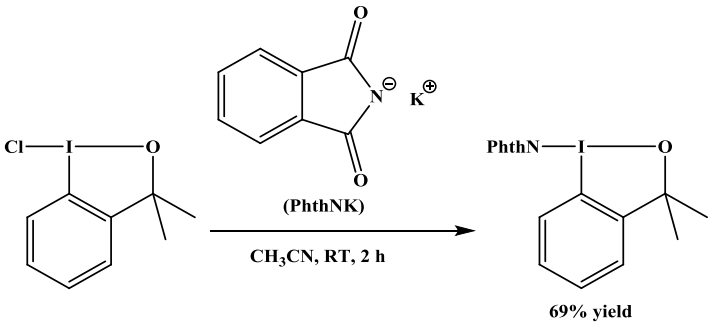


Scheme 1.48 Selected examples of α-trifluoromethylthiolation of β-ketoesters using the trifluoromethylthiolated hypervalent iodine(III) reagent

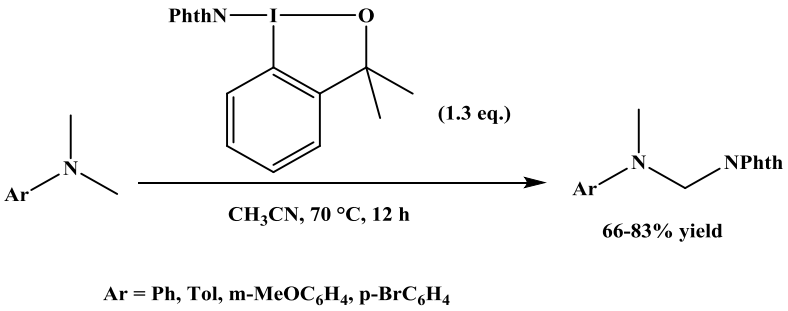


Scheme 1.49 Selected examples of copper-catalysed trifluoromethylthiolation of aryl boronic acids and alkynes using the trifluoromethylthiolated hypervalent iodine(III) reagent

Kiyokawa et al. successfully synthesised a new stable and reactive phthalimidate hypervalent iodine(III) reagent by the reaction of **OC-1** and potassium phthalimide **(Scheme 1.50)**. They found this new reagent to be highly active for oxidative amination reactions **(Scheme 1.51)**.[65]

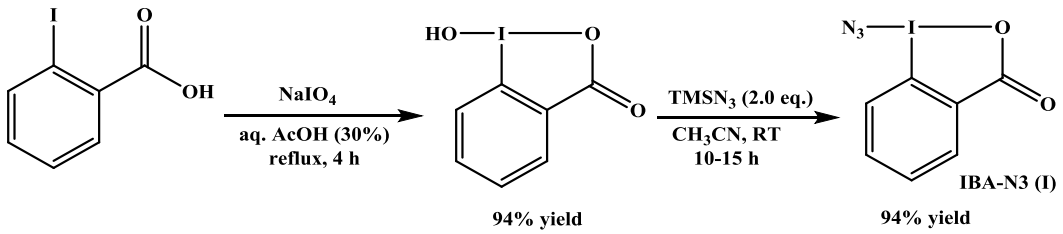


Scheme 1.50 Synthesis of phthalimidate hypervalent iodine(III) reagent from **OC-1**

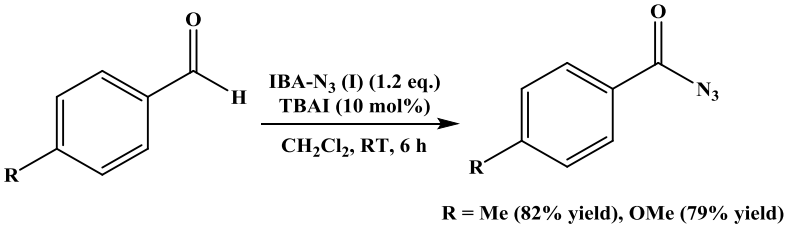


Scheme 1.51 Oxidative amination reactions using the phthalimidate hypervalent iodine(III) reagent

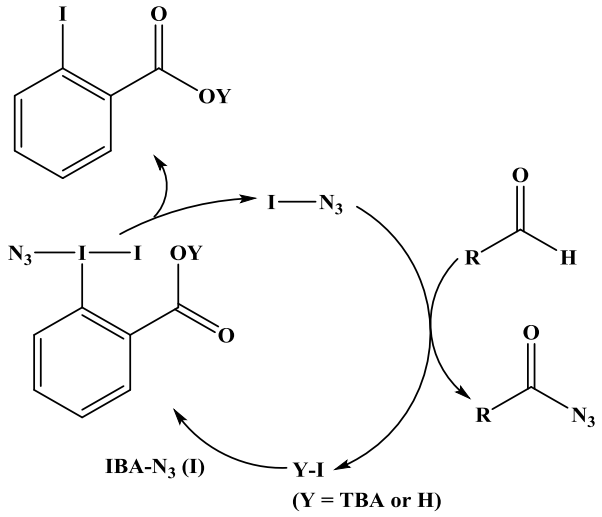
Thermally stable azidobenziodoxole IBA-N_3 (I) has a structure similar to **OC-2**. It can be synthesised from 2-iodobenzoic acid, as shown in **Scheme 1.52**, and employed as a versatile reagent for direct azidination of aldehydes **(Schemes 1.53 and 1.54)** and the preparation of azidolactones with a photoredox catalyst under blue LED irradiation **(Scheme 1.55)**.[66-68]



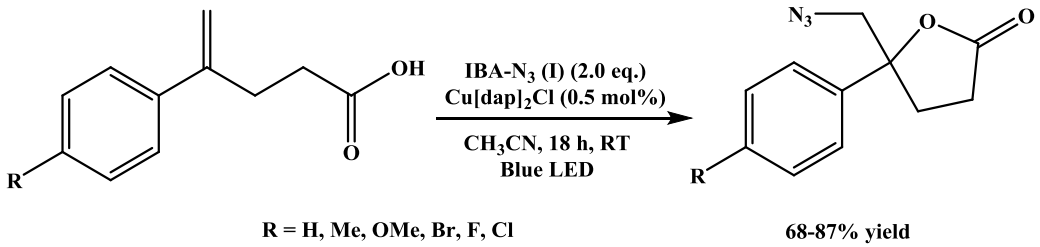
Scheme 1.52 Synthesis of azidobenziodoxole IBA-N_3 (I)



Scheme 1.53 Azidination of aldehydes with IBA-N_3 (I)



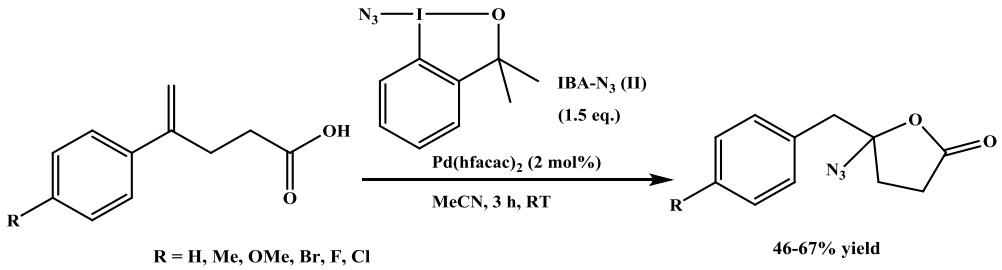
Scheme 1.54 Proposed mechanism for the azidination of aldehydes with IBA-N_3 (I)



Scheme 1.55 (1,2)-Azidolactonization of 4-phenylpent-4-enoic acid using IBA-N_3 (I)

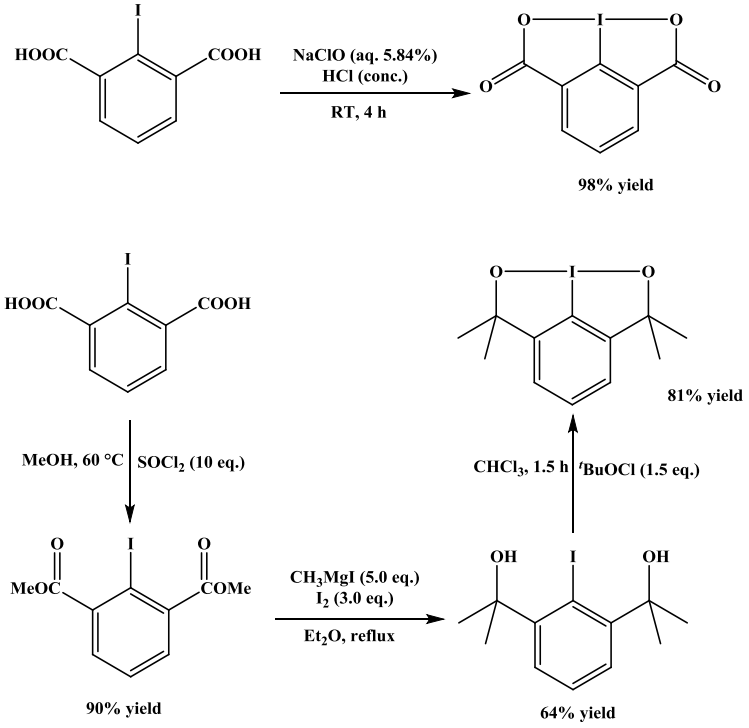
Azidobenziodoxole IBA-N_3 (II) with a structure similar to **OC-1**, has also been studied. It is less reactive than IBA-N_3 (I) in the same direct azidination reactions.[66-68] When it was used to carry out the azidolactonization of 4-phenylpent-4-enoic acid under the same conditions as that using IBA-N_3 (I), nearly no (1,2)-azidolactonization occurred. However, when Pd(hfacac)$_2$ was added as Lewis acid to carry out the azidolactonization reactions with IBA-N_3 (II) (1,1)-azidolactones were obtained instead of (1,2)-azidolactones **(Scheme 1.56)**. The proposed mechanism for (1,2)-azidolactonization using IBA-N_3 (I) is based on the production of the N_3 radical under

photoredox conditions, while that for (1,1)-azidolactonization using IBA-N_3 (II) is based on the activation by the Lewis acid; the latter is similar to that seen in the intramolecular aminofluorination reaction with **OF-1**.[61, 68]

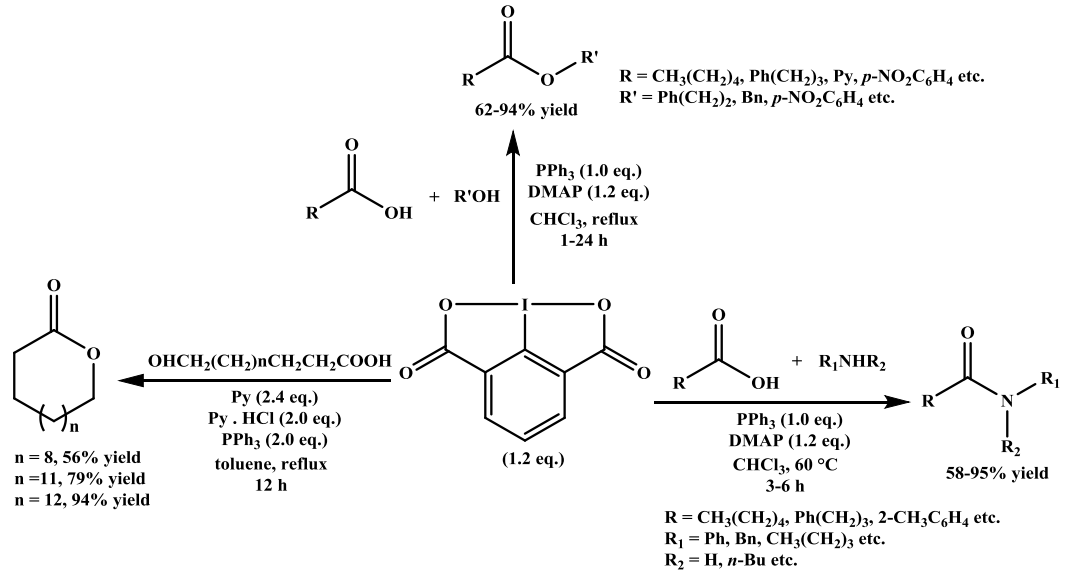


Scheme 1.56 Preparation of (1,2)-azidolactones using IBA-N_3(II)

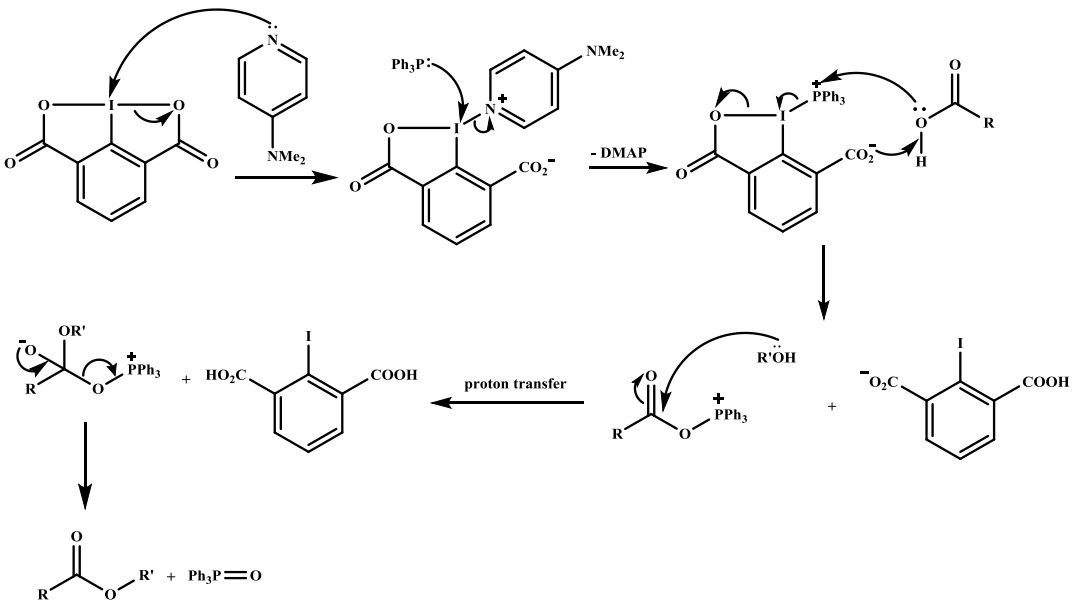
In the last 10 years, bicyclic hypervalent iodine(III) compounds have also been researched. Zhang et al. reported the synthesis of several bicyclic hypervalent iodine(III) benziodoxoles using 2-iodoisophthalic acid **(Scheme 1.57)**.[69-71] These reagents have high reactivity in direct condensation reactions between carboxylic acids and alcohols or amines to obtain esters, macrocyclic lactones, as well as amides and peptides **(Scheme 1.58)**.[69-71] The proposed mechanism for esterification is shown in **Scheme 1.59**.



Scheme 1.57 Synthesis of bicyclic hypervalent iodine(III) benziodoxoles

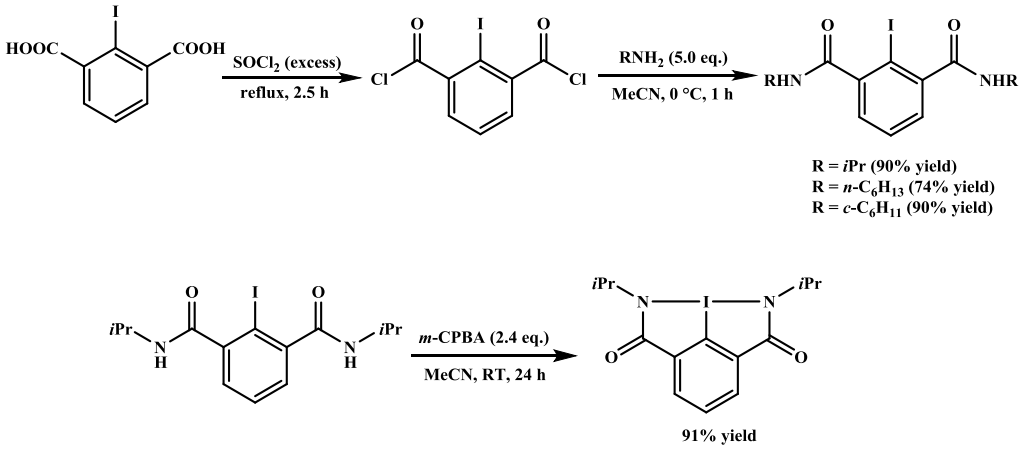


Scheme 1.58 Applications of bicyclic hypervalent iodine(III) benziodoxoles



Scheme 1.59 Proposed mechanism for the esterification of alcohols and carboxylic acids with bicyclic hypervalent iodine(III) benziodoxoles

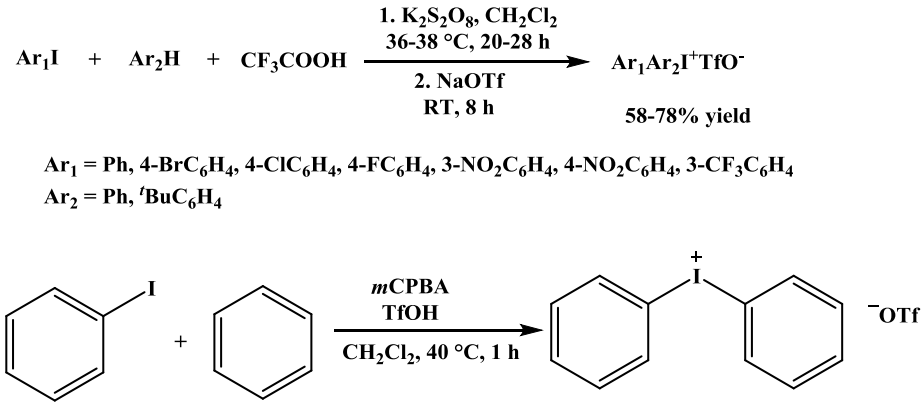
Recently, in 2018, Yoshimura et al. developed a method for the synthesis of bicyclic benziodazole compounds by the oxidation of the corresponding 2-iodo-*N*,*N*′-dialkylisophthalamides using *m*-CPBA **(Scheme 1.60)**. These new reagents have reactivities similar to those of the bicyclic hypervalent iodine(III) benziodoxoles in the same esterification and amination reactions.[72]



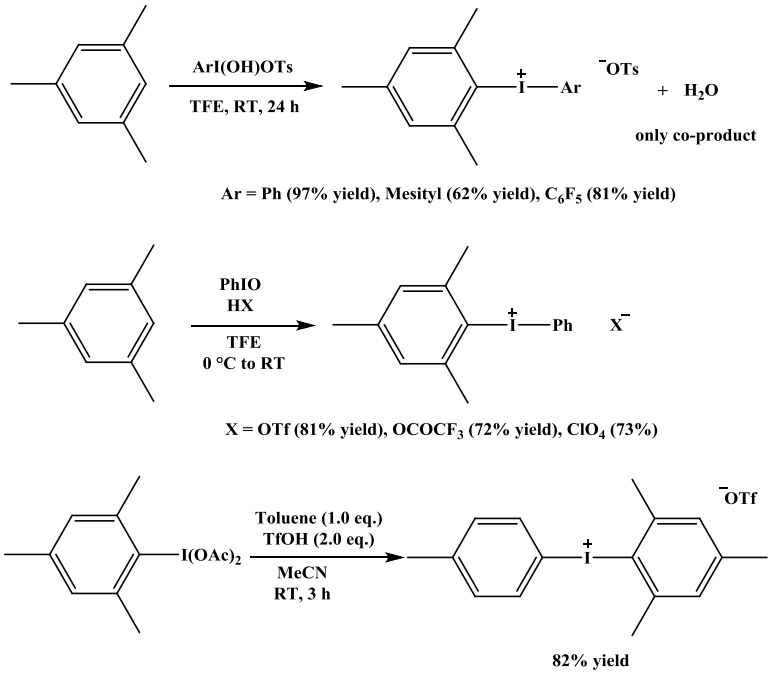
Scheme 1.60 Synthesis of bicyclic benziodazole compounds

1.3.4 Applications of iodonium(III) salts

Iodonium(III) salts $R_2I^+X^-$ are usually classified as 10-electron hypervalent compounds because of a strong secondary interaction between the iodine atom and the counterion.[15] Among them, diaryliodonium(III) salts are one of the most important types of hypervalent iodine compounds. Oxidation of iodoaromatic compounds is a widely employed approach to prepare diaryliodonium(III) salts, such as the use of potassium peroxydisulfate and *m*-CPBA, shown in **Scheme 1.61**.[73-74] Some other hypervalent iodine compounds such as HTIB (Koser's reagent), iodosylbenzene and DIB as well as their analogues, readily combine with strong acids to generate diaryliodonium(III) salts **(Scheme 1.62)**.[75-76]

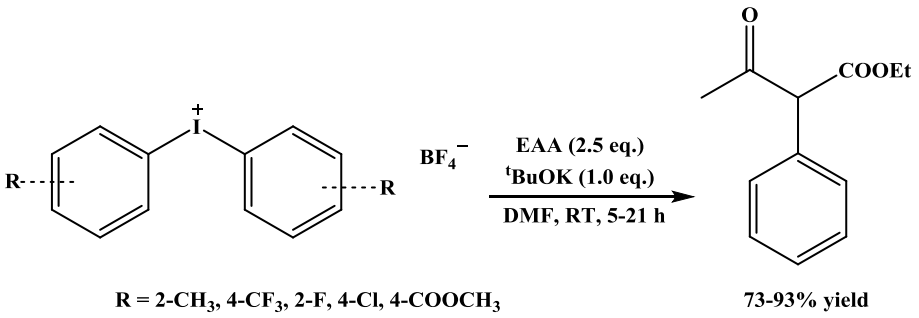


Scheme 1.61 Oxidation of iodoaromatic compounds to diaryliodonium(III) salts



Scheme 1.62 Selected examples for synthesis of diaryliodonium(III) salts

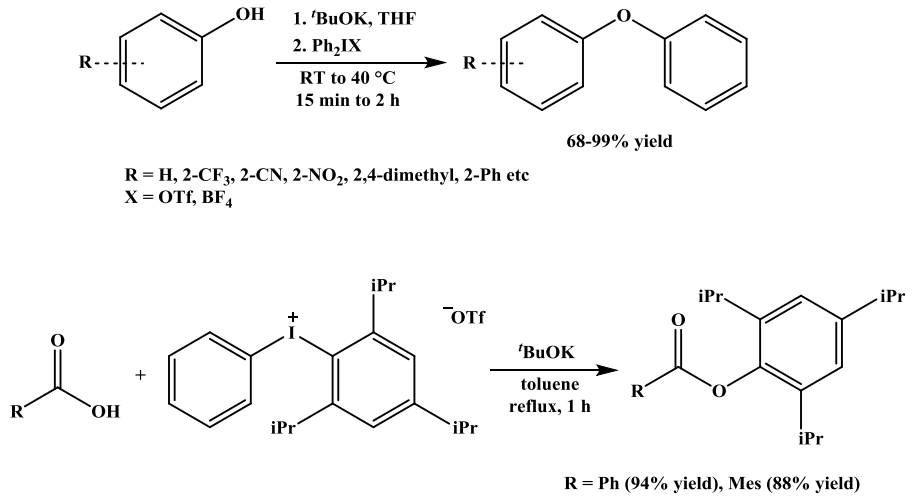
Diaryliodonium(III) salts have been widely used as arylating reagents. For example, Manetsch's group developed a clean and metal-free arylation protocol of ethyl acetoacetate (EAA) using diaryliodonium(III) salts under mild conditions **(Scheme 1.63),** which gives a new way to synthesise medicinal molecules derived from EAA.[77]



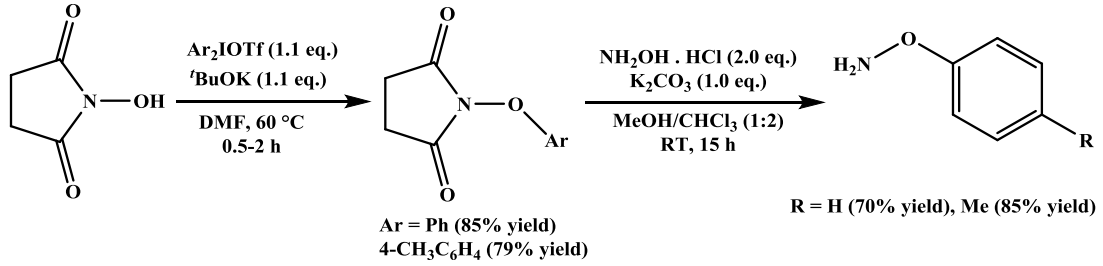
Scheme 1.63 Arylation of ethyl acetoacetate using diaryliodonium(III) salts

Not only are diaryliodonium(III) salts effective arylating reagents toward carbon nucleophiles, but also toward heteroatom nucleophiles. Olofsson et al. have reported a large number of examples of the arylation of oxygen nucleophiles with diaryliodonium(III) salts. In 2012, they reported that phenols and carboxylic acids can be arylated by diaryliodonium(III) salts to build up diaryl ethers and aryl esters **(Scheme 1.64),** which are very important structures in the pharmaceutical and

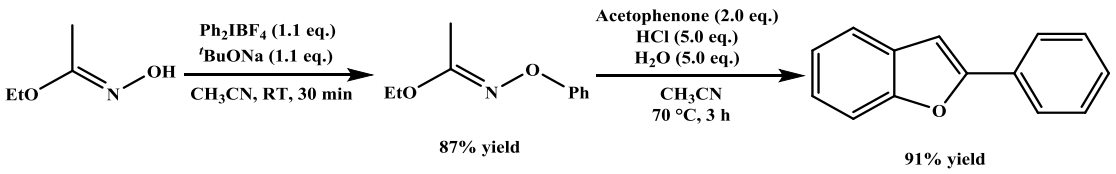
agrochemical industries.[78] In 2014, they reported a novel arylation method using diaryliodonium(III) salts combined with an excellent hydrolysis method to yield aryloxyamines **(Scheme 1.65)**, which are valuable building blocks in the synthesis of oxime ethers and benzofurans.[79] In the same year, they successfully developed the method for a simple metal-free one-pot synthesis of benzofurans by arylation of ethyl acetohydroxamate with diaryliodonium(III) salts at room temperature **(Scheme 1.66)**.[80]



Scheme 1.64 Arylation of phenols and carboxylic acids with diaryliodonium(III) salts

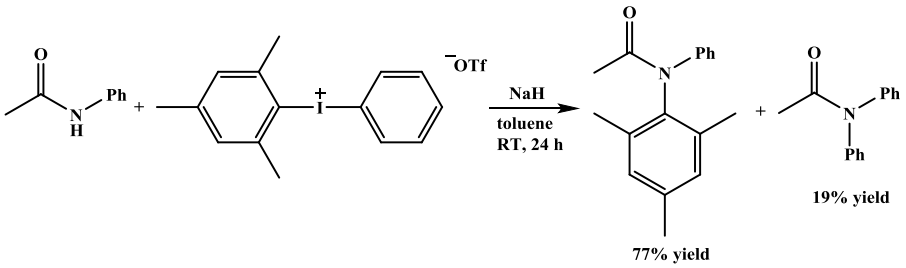


Scheme 1.65 Arylation using diaryliodonium(III) salts and hydrolysis to yield aryloxyamines

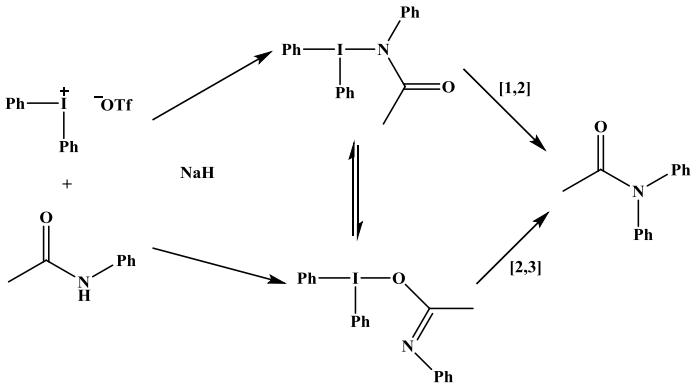


Scheme 1.66 Arylation of ethyl acetohydroxamate with diaryliodonium(III) salts for the synthesis of benzofurans

Elsewhere, the arylation of N and S nucleophiles with diaryliodonium(III) salts have been reported as well. Adolfsson and Olofsson's group developed the arylation of secondary acyclic amides with diaryliodonium(III) salts under mild conditions, which have obvious advantages, such as high chemoselectivity, as shown in **Scheme 1.67**.[81] The proposed mechanism **(Scheme 1.68)** included rearrangements from two possible T-shaped intermediates.

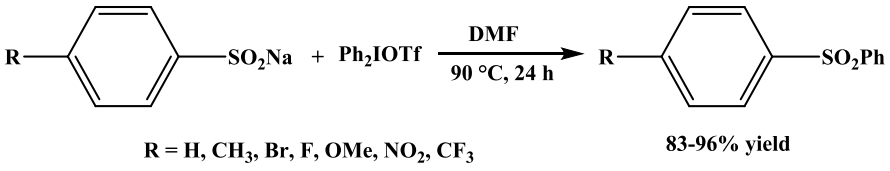


Scheme 1.67 Chemoselectivity in *N*-arylation of acetanilide with an asymmetric diaryliodonium(III) salt



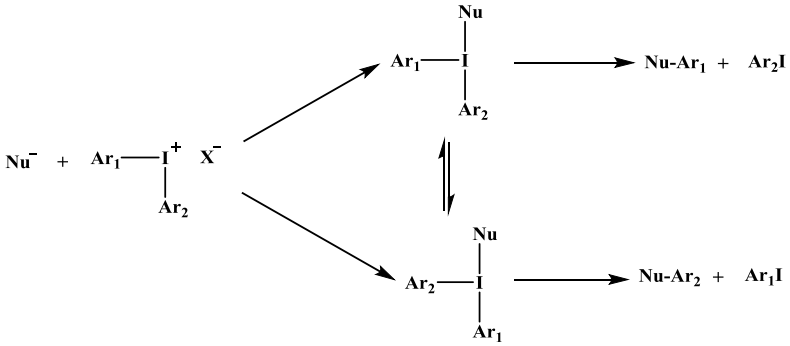
Scheme 1.68 Proposed mechanism for *N*-arylation of acetanilide

Umier and Manolikakes developed a high-yielding metal-free synthetic method to diaryl sulfones, which are useful intermediates with valuable biological properties, using the reactions of arylsulfinic acid salts with diaryliodonium(III) salts. The phenylation of arylsulfinic acid salts is shown in **Scheme 1.69**.[82]



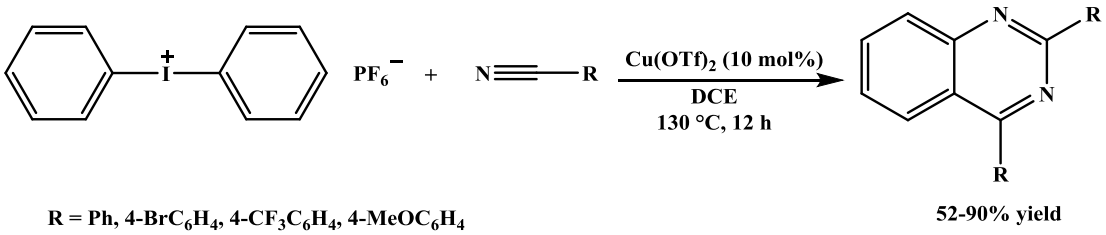
Scheme 1.69 Phenylation of arylsulfinic acid salts with diphenyliodonium triflate

The chemoselectivity in arylation reactions with diaryliodonium(III) salts is depicted in **Scheme 1.70**, as reported by Himo and Olofsson's group.[83] Diaryliodonium(III) salts combine with nucleophiles to form a T-shaped Ar_2I-Nu intermediate, and the reactions proceed by ligand coupling (reductive elimination) between the incoming nucleophile and the equatorial aryl group. In these reactions, chemoselectivitives always depend on electronic and steric factors.



Scheme 1.70 Chemoselectivity in arylation reactions with diaryliodonium(III) salts

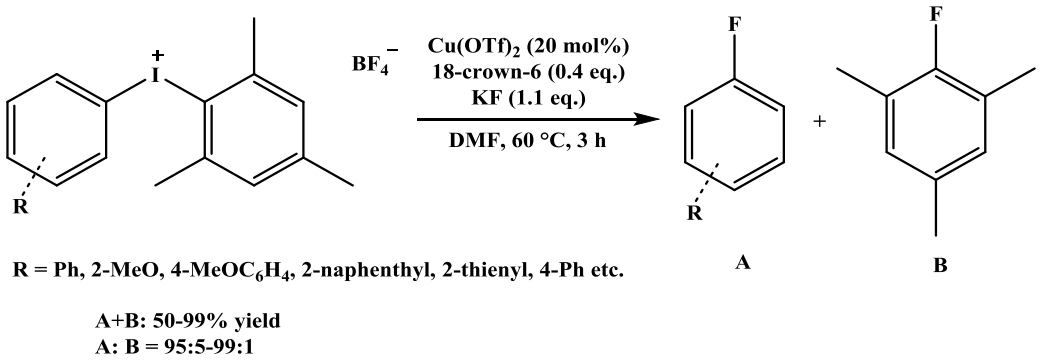
In addition, diaryliodonium(III) salts can also be treated as a powerful tool to prepare multiple heterocyclic compounds. For example, Chen et al. established a flexible one-pot approach to synthesise multiple substituted regio-selective quinazoline derivatives with diaryliodonium(III) salts **(Scheme 1.71)**.[84]



Scheme 1.71 Synthesis of multiple substituted quinazoline derivatives with diphenyliodonium hexafluorophosphate

Furthermore, the combination of diaryliodonium(III) salts and potassium fluoride can be efficiently applied to prepare aromatic compounds under copper-catalysed conditions. The reactions can be conducted with high chemoselectivities and functional group tolerance. In particular, Sanford et al. developed a series of copper-catalysed fluorinations of diaryliodonium(III) salts with KF **(Scheme 1.72)**.[85] This approach has a lot of advantages, such as fast rate of reaction, high yield, high selectivity, and no regio-

isomers, and this could find valuable application for the synthesis of ^{18}F-labelled aromatic compounds for positron emission tomography (PET) medical imaging.[86] **Figure 1.9** provides the proposed mechanism for these reactions.



Scheme 1.72 Copper-catalysed fluorination of diaryliodonium(III) salt with KF

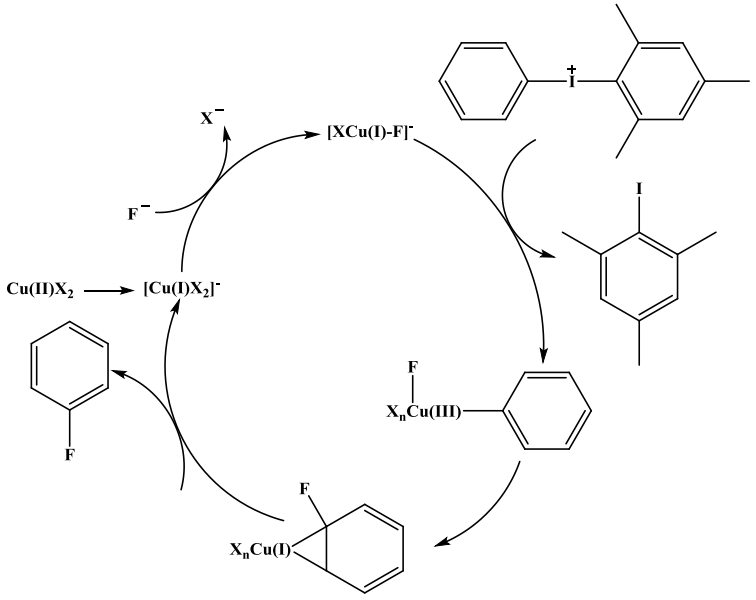


Figure 1.9 Proposed mechanism for the copper-catalysed fluorination of diaryliodonium(III) salts

1.4 Research projects in this thesis

In this thesis, we will present the synthesis and applications of novel *N*-functionalised iodine compounds.

In Chapter 2, three areas of synthetic work will be described: (i) The synthesis of various IPy_2BF_4 (Barluenga's reagent) analogues from corresponding pyridine ligands with electron-rich and electron-deficient substituents will be described, based on the

literature preparation of IPy_2BF_4 by the reaction of $AgBF_4$, pyridines and elemental iodine. (ii) Since the majority of five-membered ring Cl-I(III) compounds reported in the literature are *O*-functionalised rather than *N*-functionalised Cl-I(III) compounds, the synthesis of new five-membered ring *N*-functionalised Cl-I(III) compounds by the reactions of amide and *N*-heterocyclic compounds with trichloroisocyanuric acid (TClCA) will be described (iii) The synthesis of related *N*-functionalised F-I(III) compounds through the reaction of amides with Selectfluor will be investigated. Optimisation of the synthetic conditions will consider the reaction temperature, time, and solvent types.

All of the target novel *N*-functionalised iodine compounds will be characterised by NMR, MS, melting point and X-ray crystallography. The single crystal structures of the *N*-functionalised Cl-I(III) and F-I(III) compounds will be compared with those of various *O*-functionalised Cl-I(III) and F-I(III) compounds.

In Chapter 3, 4 and 5, the reactivities of the novel *N*-functionalised iodine compounds will be compared and contrasted in a series of model reactions. In Chapter 3, the iodination of aromatics and the iodocyclisation of alkynyl alcohols with analogues of Barluenga's reagent will be investigated. In Chapter 4, the application of *N*-functionalised Cl-I(III) compounds in the chlorination of 1,3-dicarbonyl compounds as well as the oxychlorination of styrene will be described where the reactivities will be compared with those of *O*-functionalised Cl-I(III) compounds. The effect of reaction temperature, solvent type, and time on the yield of target products will be discussed. In Chapter 5, we will focus on the applications of *N*-functionalised F-I(III) compounds in the fluorination of 1,3-dicarbonyl compounds, the intramolecular fluorocyclisation of unsaturated carboxylic acids, and the geminal difluorination of α,α'-disubstituted styrenes; a comparison of their reactivities with those of the *O*-functionalised F-I(III) compound, 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)**, will also be discussed.

All the experimental procedures and characterization data will be summarised in Chapter 6.

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Chapter 2

Synthesis and Characterization of New *N*-Functionalised Iodine Compounds

2.1 Introduction

The work in this chapter mainly presents the approaches for the synthesis of three groups of iodine compounds/complexes that have been prepared to make comparisons between their reaction chemistries, which are discussed in Chapters 3-5. The known *N*-coordinated iodonium salt, containing iodine in the +1 oxidation state, bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) **(NI-1)** and its analogues I(3,5-dimethylpyridine)$_2BF_4$ **(NI-2)**, I(2-methoxypyridine)$_2BF_4$ **(NI-3)** and I(2,4,6-trimethylpyridine)$_2BF_4$ **(NI-4)** are described first **(Figure 2.1)**. Then, the synthesis and full characterization of new *N*-functionalised Cl-I(III) compounds 2-benzyl-1-chloro-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one (**NC-1**), 1-chloro-2-(4-chlorobenzyl)-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-2)** and 1-chloro-2-(4-fluorobenzyl)-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-3)** will be discussed **(Figure 2.2)**. In addition, unsuccessful attempts to prepare cationic *N*-functionalised Cl-I(III) will be briefly summarized. Finally, the preparation and full characterization of new *N*-functionalised F-I(III) compounds 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)**, 2-(4-chlorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-2)** and 2-(4-fluorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-3) (Figure 2.3)** that have been prepared from amide precursors will be outlined.

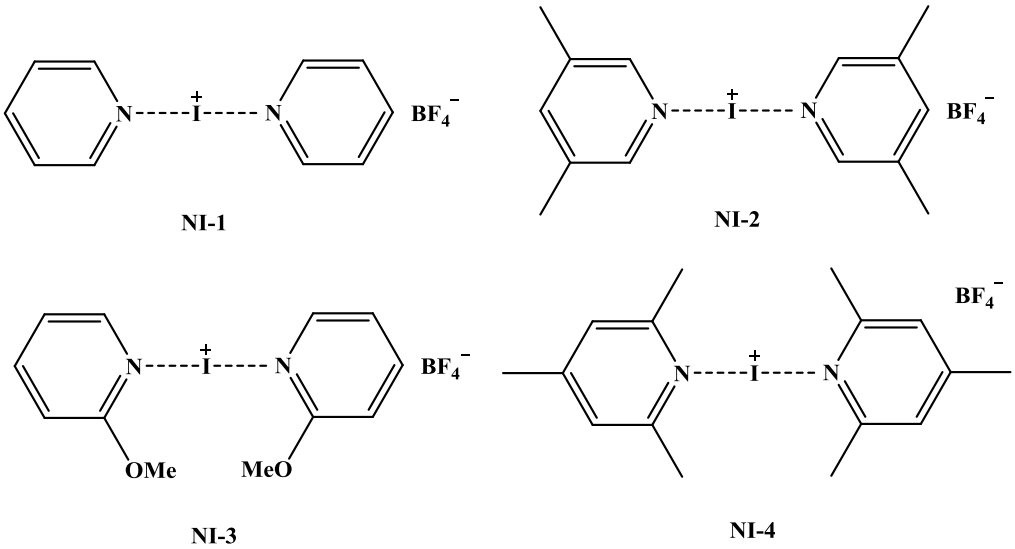
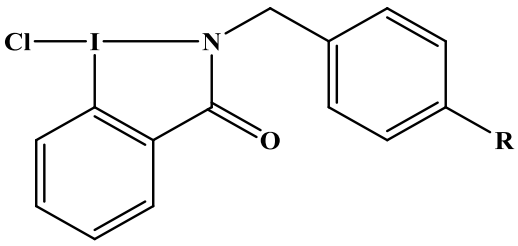
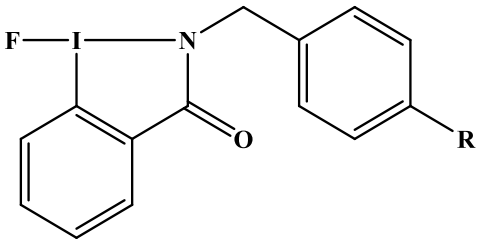


Figure 2.1 *N*-coordinated iodonium salts **NI-1**, **NI-2**, **NI-3** and **NI-4**



R = H (NC-1), Cl (NC-2), F (NC-3)

Figure 2.2 *N*-functionalised Cl-I(III) compounds **NC-1**, **NC-2** and **NC-3**



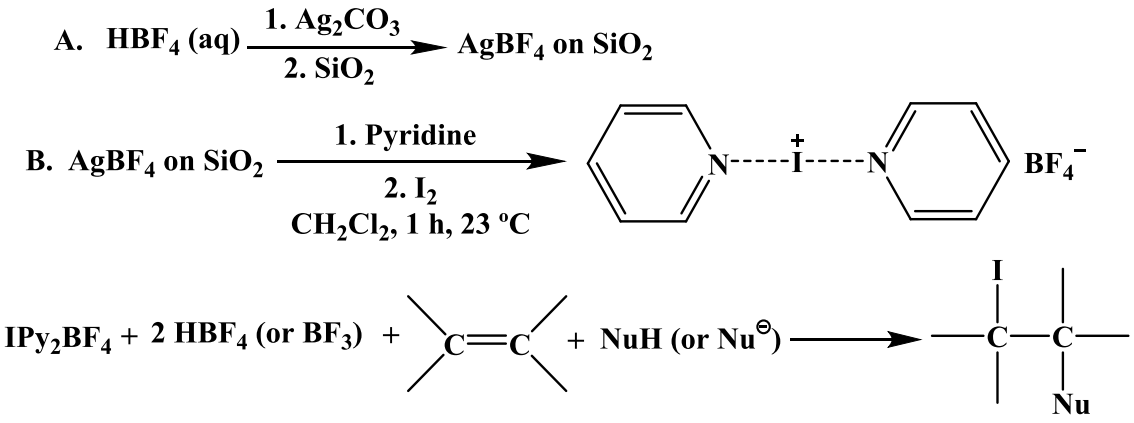
R = H (NF-1), Cl (NF-2), F (NF-3)

Figure 2.3 *N*-functionalised F-I(III) compounds **NF-1**, **NF-2** and **NF-3**

2.1.1 Iodonium(I) and Bromonium(I) Salts

Applications of various iodonium(I) salts and hypervalent iodine compounds in organic syntheses have been described in Chapter 1. In recent decades, the synthesis of new iodonium(I) salts, often with high yield and under mild reaction conditions, has attracted a lot of attention from chemists. In contrast, there have been relatively few studies of the closely-related bromonium(I) salts.

In 1985, it was reported for the first time that bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4), also termed 'Barluenga's reagent', as a novel iodonium(I) salt and iodination reagent could be used for the 1,2-iodofunctionalization of olefins **(Scheme 2.1)**.[1] It is usually prepared by the reaction of iodine with pyridine in the presence of $AgBF_4$ supported on silica gel in CH_2Cl_2 solvent, and AgI, as by-product, is precipitated out.[2] It has now become a commercially available product with low toxicity and strong thermal stability advantages.



Scheme 2.1 Structure of IPy_2BF_4 and its application in the 1,2-iodofunctionalization of olefins

Based on the approach for synthesis of Barluenga's reagent, another method for the preparation of the related bis(collidine)iodonium(I) tetrafluoroborate was reported by Evans and co-workers. In the first step, bis(*sym*-collidine)silver(I) tetrafluoroborate was synthesized from a mixture of *sym*-collidine, silver nitrate and sodium tetrafluoroborate. In the second step, the titled product was derived, after recrystallization, by the reaction of bis(*sym*-collidine)silver(I) tetrafluoroborate and elemental iodine in dry CH_2Cl_2.[3] However, the conditions of this approach are extremely rigorous, as it must be carried out in dry solvent in order to avoid decomposition of product. The bis(*sym*-collidine)silver(I) tetrafluoroborate obtained in the first step must be dried under vacuum over phosphorus pentoxide for 24 hours before the second step.

In research work pertaining to the synthesis of IPy_2BF_4 and its analogues, counterions, solvent type, moisture control are the most significant factors of study. In 2013, the solvent effect on halogen bond symmetry was reported by Erdélyi's group.[4] The symmetric arrangement of the iodine and bromine centred 3-centre-4-electron halogen bond is revealed to be preferred in a polar, aprotic solvent environment. On changing the solvent, from CH_2Cl_2 to CH_3CN, neither the N-X-N bond lengths nor the charge distribution of bis(pyridine)halonium complexes are affected by a more polar solvent. The different reactivity in these two solvents for synthesis of bis(pyridine)halonium complexes may be best explained by an altered degree of solvation and a consequent charge separation that provides an easier access to form the halonium(I) salt in CH_3CN.

In 2014, Christensen and co-workers successfully synthesized anion substituted analogues of Barluenga's reagent IPy_2PF_6, IPy_2OTf, IPy_2NO_3, IPy_2I_3 and IPy_2ClO_4 as well as bromine analogues $BrPy_2OTf$, $BrPy_2PF_6$, $BrPy_2BF_4$ and $BrPy_2ClO_4$ **(Figure 2.4)**. Meanwhile, they also investigated, in depth, differences in their molecular crystal structures.[5]

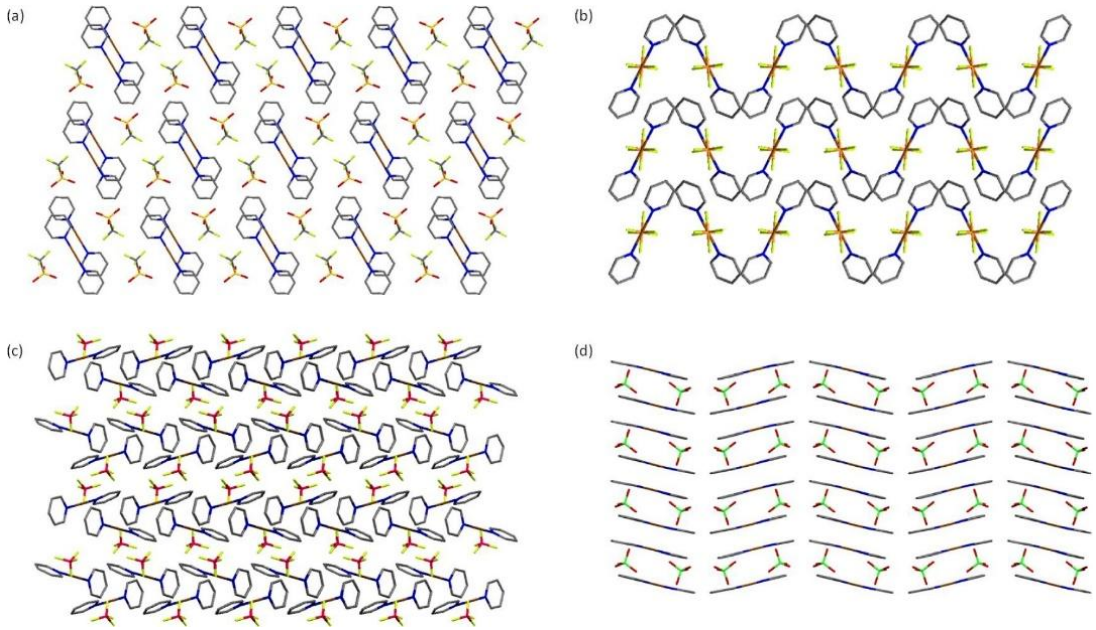


Figure 2.4 X-ray structures of the $BrPy_2^+$ salts (a) $BrPy_2OTf$, (b) $BrPy_2PF_6$, (c) $BrPy_2BF_4$, (d) $BrPy_2ClO_4$

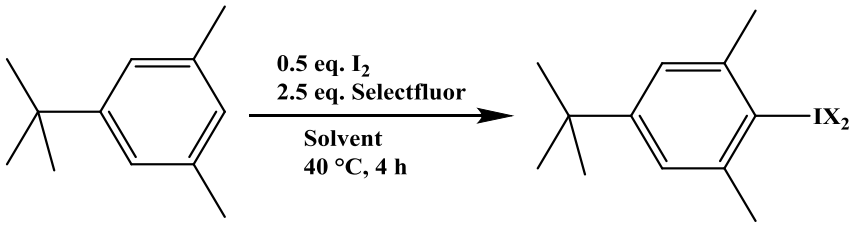
In 2015, Erdélyi's group presented a detailed investigation of the influence of counterions on the $[N\text{-}I\text{-}N]^+$ halogen bond and concluded that counterions do not influence the intrinsically preferred linear, centrosymmetric geometry of the $[N\text{-}I\text{-}N]^+$ halogen bond whether in solution or in the solid state.[6] Subsequently, they reported the *para*-substituent effects on the $[N\text{-}I\text{-}N]^+$ halogen bond in 2016.[7] It was concluded that changes in electron density do not affect the symmetric geometry of the $[N\text{-}I\text{-}N]^+$ halogen bond of the bis(pyridine) type system either in solution or in the solid state.

In this chapter, we will investigate the synthesis of various analogues of Barluenga's reagent from mono- and multi-substituted, activated and deactivated pyridine reagents with different substituents: pyridine, 3,5-dimethylpyridine, 2-methoxypyridine, 2,4,6-trimethylpyridine, 2-acetylpyridine and 2-picolinic acid which have never been reported in the literature to study the effect of substituents to their reactivities in the

iodination of aromatic compounds and iodocyclization of alkynes described in Chapter 3.

2.1.2 Hypervalent Iodine(III) Compounds

The syntheses of linear hypervalent iodine(III) compounds such as (diacetoxyiodo) benzene {$PhI(OAc)_2$, DIB}, [hydroxyl(tosyloxy)iodo]benzene {PhI(OH)OTs, Koser's reagent)} and hydroxyl(trifluoromethanesufonyloxy)]iodobenzene {PhI(OH)OTf}, which are considered as mild oxidants, catalysts or functional reagents, play an important role in modern organic chemistry (Chapter 1), and have been extensively reported in the literature.[8-16] In 2005, Shreeve and co-workers reported that aryl iodine(III) difluoride and diacetate can be synthesized from the corresponding arene with elemental iodine and Selectfluor in a one-pot procedure shown in **Scheme 2.2**.[17] Compared with the normal method to prepare (difluoroiodo)benzene ($PhIF_2$) and its analogues by the reaction of PhIO with corrosive and toxic 46% aqueous HF solution which were described in Chapter 1, this approach is more effective and can be carried out under mild reaction conditions.



Scheme 2.2 One-pot synthesis of aryl-IF_2 or -$I(OAc)_2$ from arene using I_2 and Selectfluor

Five-membered ring hypervalent iodine(III) compounds are always more stable and have lower toxicity than linear hypervalent iodine(III) compounds. The majority of five-membered ring hypervalent iodine (III) compounds are *O*-functionalised. The most popular ones are two types of Togni's reagents, acid-type 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one Togni's reagent (I) and alcohol-type trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole Togni's reagent (II) **(Figure 2.5)**, which were reported by Togni's group for the first time in 2006.[18]

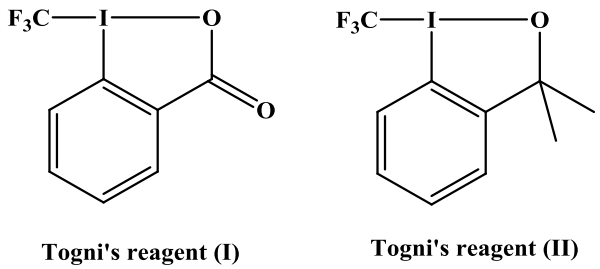
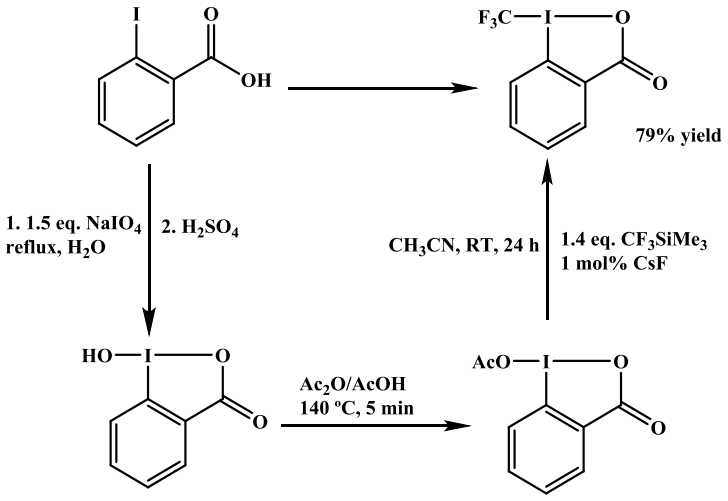
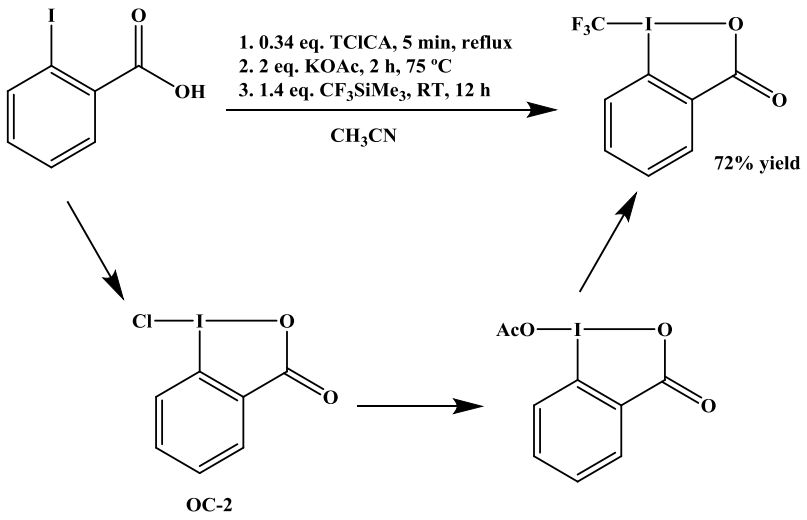


Figure 2.5 Structures of Togni's reagent (I) and Togni's reagent (II)

The two routes to Togni's reagent (I) are shown in **Scheme 2.3** and **Scheme 2.4**. In Route A **(Scheme 2.3)**, which was found and improved by Togni's group in 2008,[19] Togni's reagent (I) can be obtained in a 79% yield after aqueous oxidation of 2-iodobenzoic acid, acetylation of hydroxyiodobenziodoxolone and trifluoromethylation of acetoxyiodane. However, there are two drawbacks in this synthetic route. First, two intermediates, hydroxyiodobenziodoxolone and acetoxyiodane, are required to be isolated and thoroughly dried. Second, the hydroxylation and acetylation steps are always operated behind a safety screen due to possible adventitious traces of iodine(V) impurities or traces of sodium iodate polluting the starting material and potentially leading to violent decomposition. In 2013, the same group developed Route B **(Scheme 2.4)** and gained a 72% yield, which can be simplified to a one-pot synthesis.[20] In this synthetic route the intermediates chloroiodane and acetoxyiodane are not required to be isolated, and reactions can be carried out in a shorter time using a more desirable oxidant, trichloroisocyanuric acid (TClCA), under mild conditions.

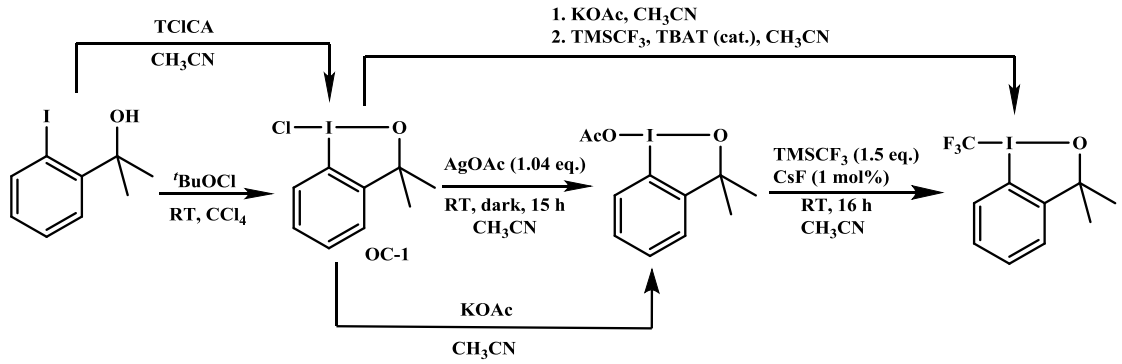


Scheme 2.3 Route A for synthesis of Togni's reagent (I)

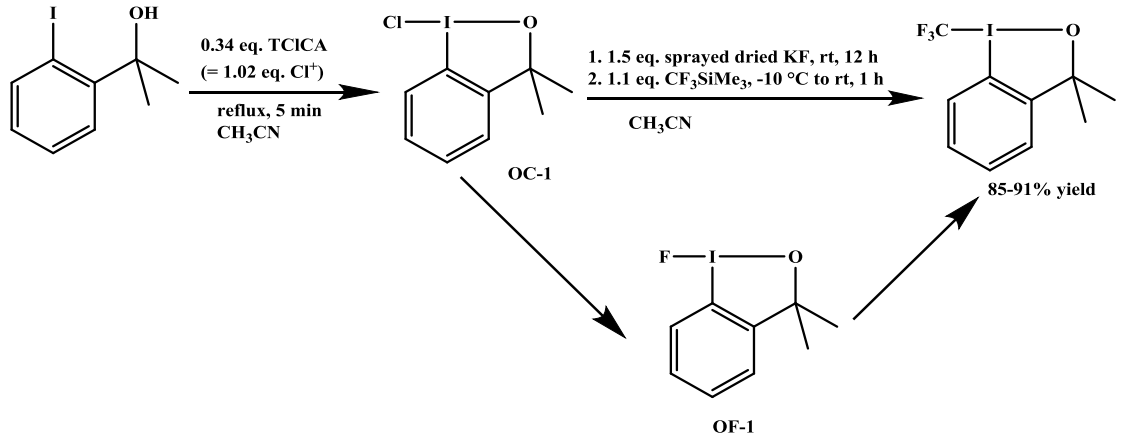


Scheme 2.4 Route B for synthesis of Togni's reagent (I)

In **Scheme 2.5** and **Scheme 2.6**, two routes toward Togni's reagent (II) are shown. In Route C **(Scheme 2.5)**,[21] the chlorination of 2-iodophenylpropan-2-ol to prepare 1-chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **(OC-1)** is done in the first step and then acetoxylation can be performed with either KOAc or AgOAc. In this process, TClCA is a better oxidant than *tert*-butyl hypochlorite, which has light- and heat-sensitive characteristics, for the chlorination of 2-iodophenylpropan-2-ol. KOAc is more strongly advised to be used, as AgOAc is more expensive and requires the absence of light. $TMSCF_3$ is used as the CF_3 source for the trifluoromethylation of the acetoxy intermediate in order to obtain Togni's reagent (II). In Route D **(Scheme 2.6)**,[20] a 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** suspension in CH_3CN is prepared as an intermediate using a 1.5 equimolar amount of spray dried KF at room temperature for 12 hours and then a 1.1 equimolar amount of $TMSCF_3$ is added to the cooled suspension. After warming the reaction mixture to room temperature, it is stirred for one hour to afford Togni's reagent (II) in an 85-91% yield. Compared with Route C, Togni's reagent (II) can be prepared via this fluoroiodane route in a shorter time and without the need for accurate temperature control to prepare the intermedia 1-acetoxy-3,3-dimethyl-1,2-benziodoxole.



Scheme 2.5 Route C for synthesis of Togni's reagent (II)

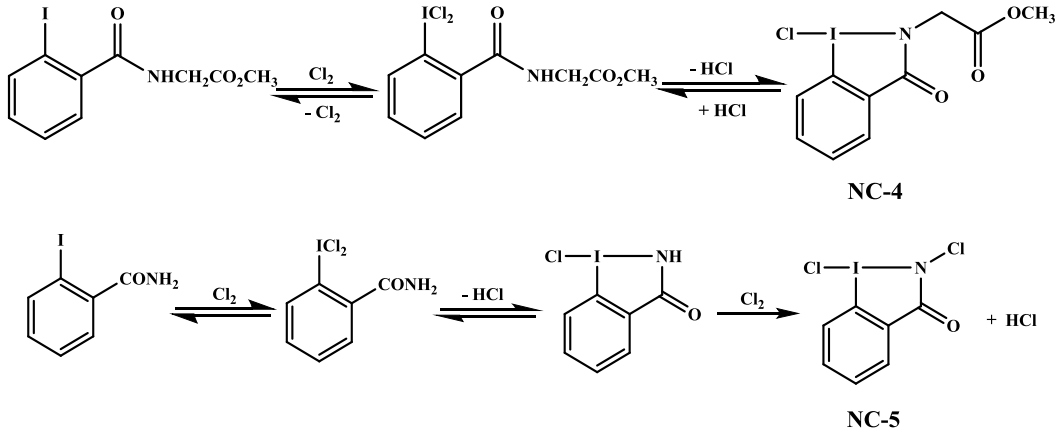


Scheme 2.6 Route D for synthesis of Togni's reagent (II)

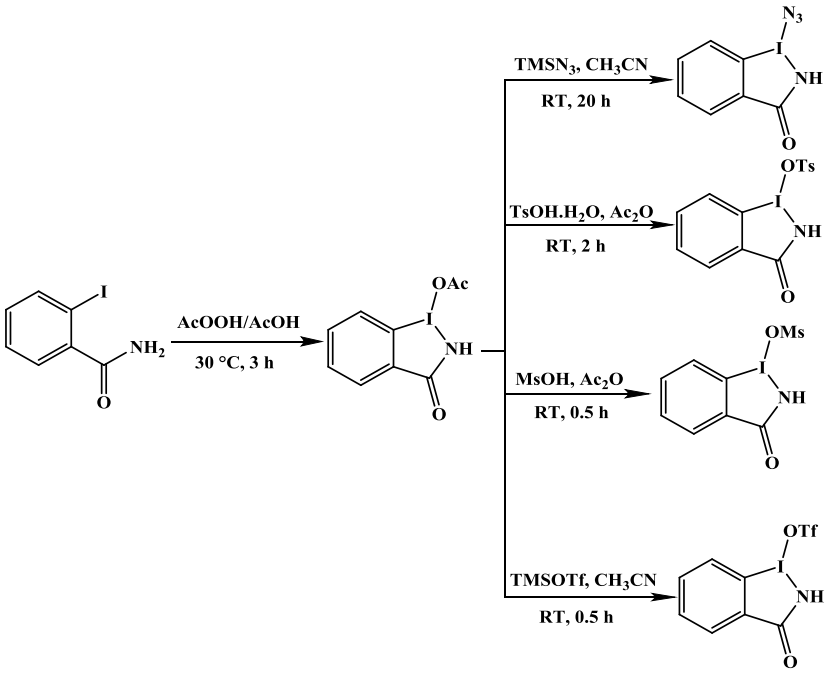
The electronic and steric effect and the *trans* influence on the reactivity of both Togni's reagents and their derivatives have also been deeply investigated through computational studies and X-ray crystallography.[22-23]

From all the synthetic routes toward Togni's reagent (I) and Togni's reagent (II), it could be seen that chlorination of starting materials to prepare the corresponding Cl-I(III) compounds 1-chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **(OC-1)** and 1-chloro-1,2-benziodoxol-3-(1*H*)-one **(OC-2)** as precursors is an initial and convenient step. Meanwhile, Cl-I(III) compounds are also good chlorinating reagents to introduce chlorine atoms into functional organic molecules as discussed in Chapter 1. In the past, the majority of five-membered ring Cl-I(III) compounds were *O*-functionalised, but few examples of *N*-functionalised Cl-I(III) compounds have also been reported in literatures. Therefore, in this chapter, we will focus on the synthesis of new *N*-functionalised five-membered ring Cl-I(III) compounds.

Traditionally, Cl_2 gas has been used as the chlorinating reagent to obtain *N*-functionalised Cl-I(III) compounds such as **NC-4** and **NC-5 (Scheme 2.7)**.[24-25] In 1998, Zhdankin, Kiprof and their co-workers successfully prepared a series of other *N*-functionalised iodine(III) compounds from 2-iodobenzamide **(Scheme 2.8)**.[26] Based on these studies, we have studied the synthesis of new *N*-functionalised five-membered ring Cl-I(III) compounds by oxidation with TClCA (as an excellent oxidant to replace Cl_2 gas) of amide *N*-substrates: *N*-benzyl-2-iodobenzamide (***N*-1**), *N*-(4-chlorobenzyl)-2-iodobenzamide (***N*-2**) and *N*-(4-fluorobenzyl)-2-iodobenzamide (***N*-3**).

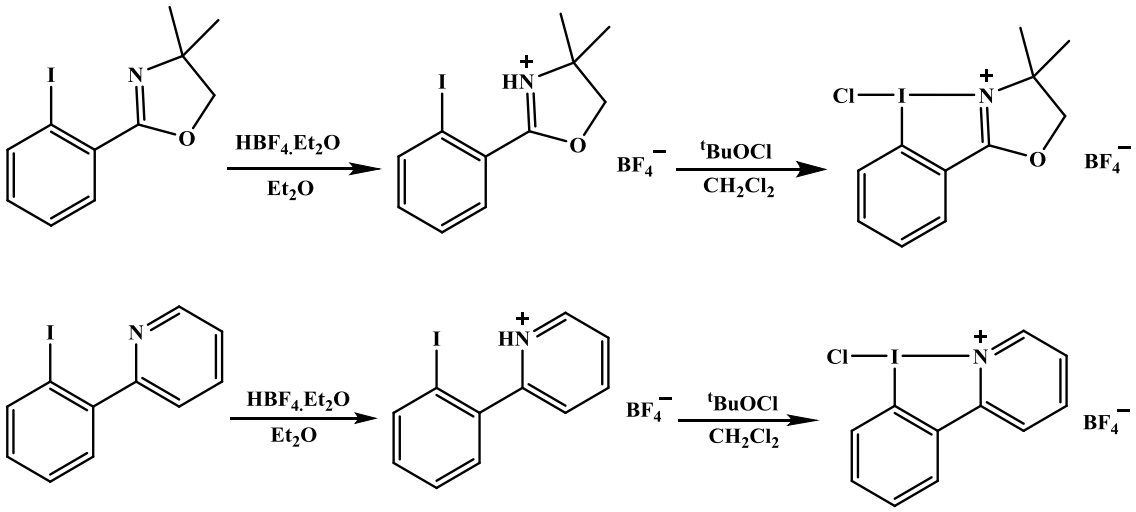


Scheme 2.7 Synthesis of *N*-functionalised Cl-I(III) compounds **NC-4** and **NC-5** using Cl_2 gas



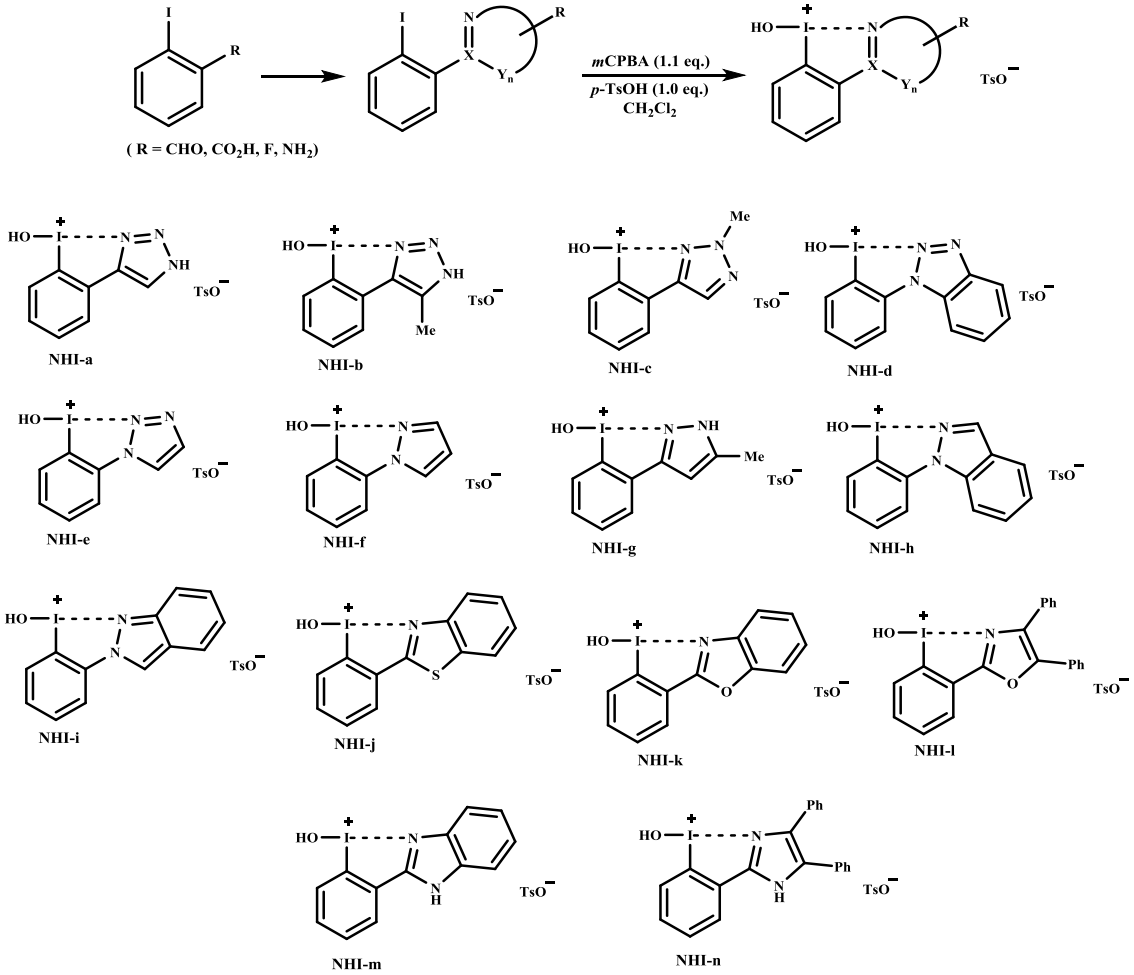
Scheme 2.8 A series of *N*-functionalised iodine (III) compounds from 2-iodobenzamide

Additionally, Togni's group reported the synthesis of two cationic 1-chloro-λ^3-iodane compounds by the protonation of oxazolidine and 2-(2-iodophenyl) pyridine using HBF_4 prior to oxidation with ^{t}BuOCl **(Scheme 2.9)** in 2010.[22]

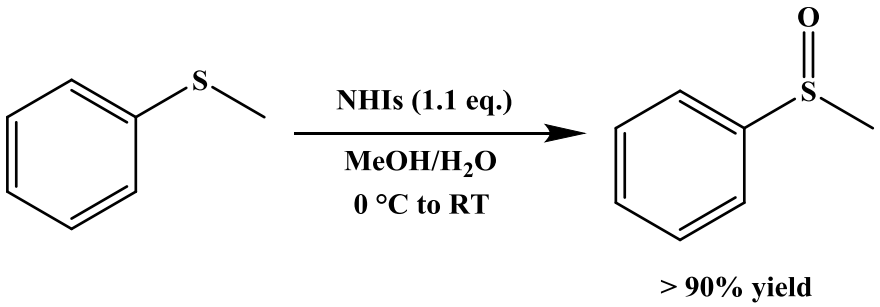


Scheme 2.9 Synthesis of two cationic 1-chloro-λ^3-iodane compounds from oxazolidine and 2-(2-iodophenyl)pyridine

During the course of this work, in 2018, Nachtsheim and co-workers successfully prepared various *N*-stabilized pseudocyclic λ^3-iodane compounds (NHIs) **(Scheme 2.10)** and found that they had high reactivity in the oxidation of thioanisole to the sulfoxide **(Scheme 2.11)** achieving full conversion within one hour.[27] Based on these works, we also attempted the preparation of some cationic *N*-heterocyclic stabilized chloroiodane compounds under mild reaction conditions. Due to the greater safety and low toxicity of TClCA than ^{t}BuOCl, in this chapter, we will describe attempts to synthesize cationic *N*-heterocycle Cl-I(III) compounds using TClCA from 2-(2-iodophenyl)pyridine **(*N*-4)**, 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole **(*N*-5)** and 2-(2-iodophenyl)-4,5-diphenyl-1*H*-imidazole **(*N*-6)**.



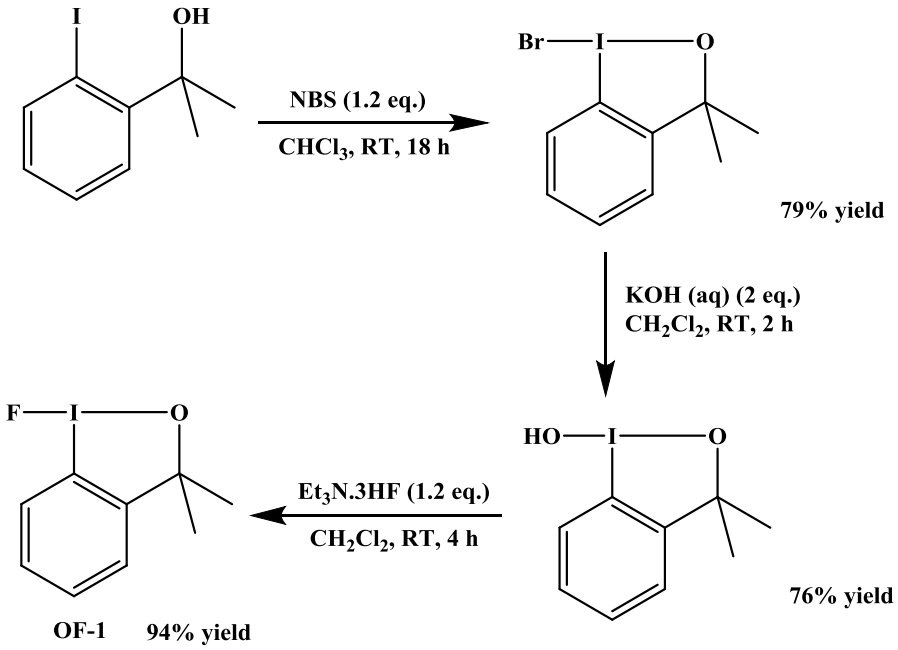
Scheme 2.10 Synthesis of *N*-heterocyclic stabilized iodane compounds (NHIs)



Scheme 2.11 Oxidation of thioanisole to sulfoxide using *N*-heterocyclic stabilized iodane compounds (NHIs)

1-Fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** has been used to introduce fluorine atoms into organic molecules; some examples have been outlined in Chapter 1 and this area will be discussed in greater detail in Chapter 5. However, Togni's fluorination for the preparation of **OF-1** has to be performed under carefully-

controlled anhydrous conditions, with dry solvents and spray-dried KF under an inert atmosphere.[22] It is also hard to prepare 1-fluoro-1,2-benziodoxol-3-(1*H*)-one **(OF-2)**, which is unstable and must be prepared in a Teflon polymer flask.[28-29] In 2012, Legault and Prévost reported the straightforward synthesis of **OF-1** using Selectfluor, but NMR spectroscopic and even yield characterization data were not presented.[30] Whilst in 2013, our group developed a novel method to synthesize **OF-1** using TREAT-HF as shown in **Scheme 2.12**, which has the most obvious advantages, including the avoidance of N_2 gas protection, careful moisture control and heating for the preparation of each product.[31]



Scheme 2.12 Synthesis of **OF-1** using TREAT-HF

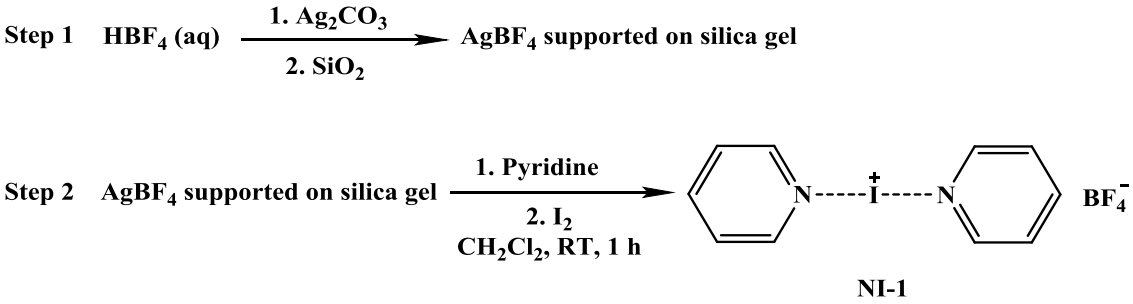
In this chapter, we will also explore approaches to gain new *N*-functionalised five-membered ring F-I(III) compounds **NF-1**, **NF-2** and **NF-3** from the same amide starting materials **(*N*-1**, ***N*-2** and ***N*-3)**.

2.2 Synthesis of iodonium(I) salts

2.2.1 Synthesis of IPy_2BF_4 and its analogues

First of all, the synthesis of bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) **(NI-1)** was repeated and modified according to the procedures found in the literature.[2] There

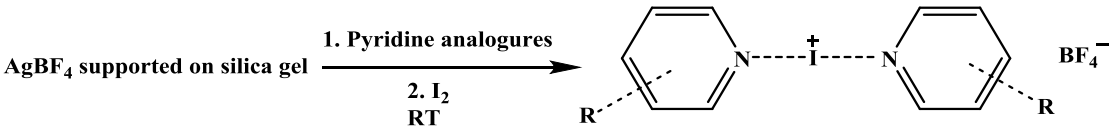
are two main steps including the preparation of $AgBF_4$ supported on silica gel as an off-white/grey free flowing powder and its subsequent reaction with iodine and pyridine **(Scheme 2.13)**. In these processes, AgI can form as yellow precipitate, which can be seen easily. It is an indicator of reaction progression. Iodine cannot be reacted totally. The pure **NI-1** can be obtained as colourless prism crystals by recrystallization in CH_2Cl_2. When the reaction time was prolonged from one hour to three hours, the final yield (65%) of the product did not change.



Scheme 2.13 Preparation of IPy_2BF_4 **(NI-1)**

This compound was sensitive to light and moisture because the cap became slightly yellow when it was kept in a sealed transparent vial at room temperature in the laboratory for three days. However, it can be stored in the freezer at -20 ℃ without any sign of decomposition over two years which was determined by the same results as a fresh sample in the ^{1}H NMR spectra of **NI-1**.

Based on this approach to synthesize **NI-1** by the reaction of iodine with pyridine in the presence of $AgBF_4$ supported on silica gel,[2] the preparation of analogues I(3,5-dimethylpyridine)$_2BF_4$ **(NI-2)**, I(2-methoxypyridine)$_2BF_4$ **(NI-3)** and I(2,4,6-trimethylpyridine)$_2BF_4$ **(NI-4)** from the respective pyridines was also studied **(Table 2.1)**. The reaction conditions were not very different, but it was found that CH_3CN was better than CH_2Cl_2 as the solvent and longer reaction times were needed than that for **NI-1**. **NI-2** and **NI-4** were gained as colourless block crystals after recrystallization. The colour of **NI-3** as block crystals was yellowish.



Entry	Iodonium Product	R	Time (h)	Solvent	Isolated Yield (%)
1	**NI-1**	H	1	CH_2Cl_2	65
2	**NI-1**	H	3	CH_2Cl_2	65
3	**NI-2**	3,5-$(CH_3)_2$	1	CH_2Cl_2	35
4	**NI-2**	3,5-$(CH_3)_2$	3	CH_2Cl_2	43
5	**NI-2**	3,5-$(CH_3)_2$	3	CH_3CN	54
6	**NI-3**	2-OMe	3	CH_3CN	51
7	**NI-4**	2,4,6-$(CH_3)_3$	3	CH_3CN	54

Table 2.1 Synthesis of IPy_2BF_4 and its analogues

When the same synthetic method was used with 2-acetylpyridine as the starting material in an attempt to prepare the corresponding iodonium salt I(2-acetylpyridine)$_2$$BF_4$, X-ray crystallographic evidence for the product, obtained as a prism, showed that it was actually H(2-acetylpyridine)BF_4 **(Figure 2.6)**. Similarly, in the attempted synthesis of the I(2-picolinic acid)$_2$$BF_4$, firstly the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the crude product was the same as the starting material of 2-picolinic acid. Secondly, no precipitate was obtained when adding Et_2O in the final step, indicating that the N atom of 2-picolinic acid did not coordinate to iodine.

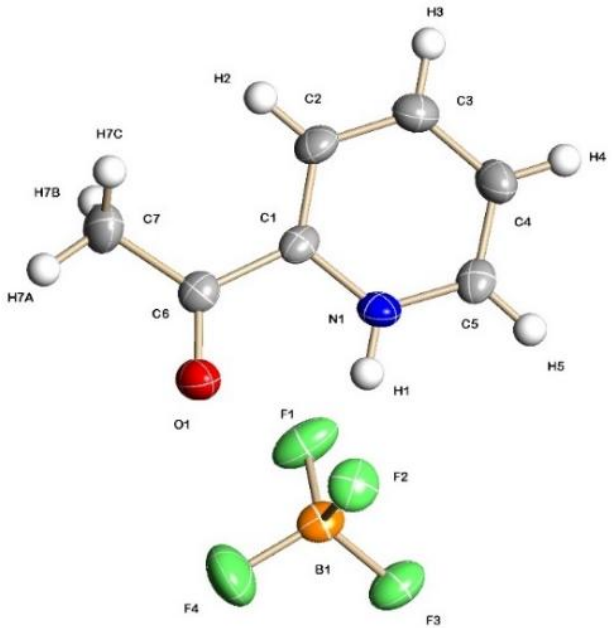


Figure 2.6 Single-crystal structure of H(2-acetylpyridine)BF_4

The mechanism for the formation of these iodonium salts has not been significantly investigated. However, it is likely that the abstraction of iodide from elemental iodine was driven by the precipitation of silver iodide and the resulting iodonium cation was then stabilized by coordination with two pyridine molecules.

2.2.2 Comparison of NMR spectroscopic data

The formation of iodonium products was first investigated using ^{1}H, ^{13}C and ^{19}F NMR spectroscopies. Among IPy_2BF_4 and its analogues, the ^{1}H NMR spectra of the iodonium products were a little different to those of the pyridine starting materials due to the change in the protons' environments. For example, in a comparison of the ^{1}H NMR (500 MHz, CD_3CN) spectra of **NI-3** and 2-methoxypyridine **(Figure 2.7)**, there are significant downfield shifts of all the proton signals from 2-methoxypyridine to **NI-3** due to the coordination of the nitrogen atom to the cationic iodine centre. This gives evidence for the formation of the iodonium salts.

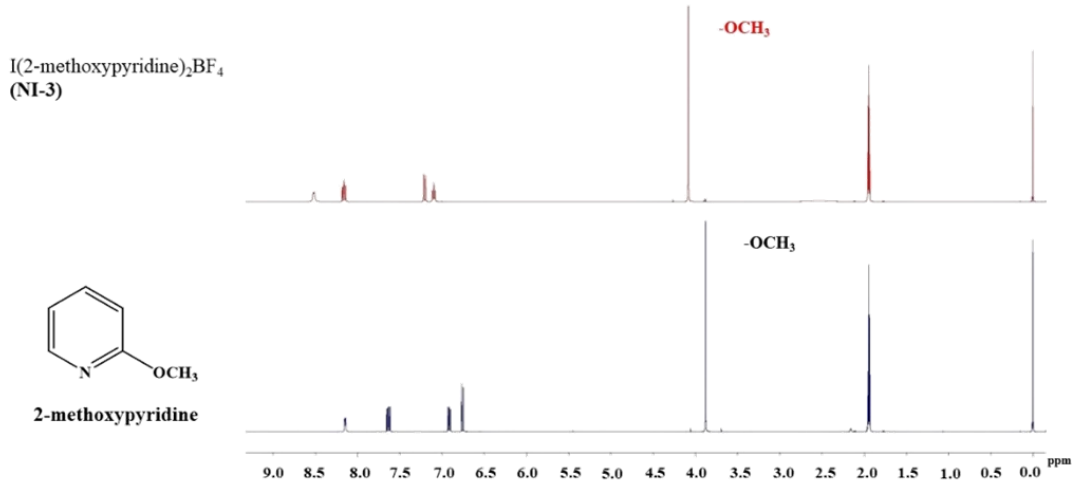


Figure 2.7 Comparison of ^{1}H NMR (500 MHz, CD_3CN) spectra of **NI-3** and 2-methoxypyridine

In an analogous comparison between the ^{13}C NMR (100 MHz, CD_3CN) spectra of **NI-3** and 2-methoxypyridine **(Figure 2.8)**, there were small downfield shifts of each of the carbon signals from 2-methoxypyridine to **NI-3**.

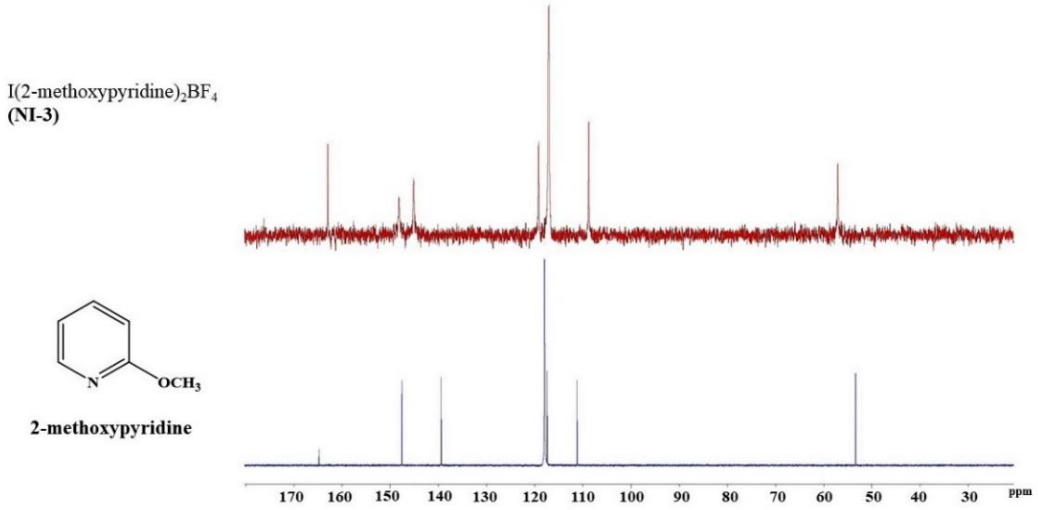


Figure 2.8 Comparison of ^{13}C $\{^{1}H\}$ NMR (100 MHz, CD_3CN) spectra of **NI-3** and 2-methoxypyridine

In the ^{19}F NMR spectra of IPy_2BF_4 and its analogues, there was a significant singlet peak. The chemical shift was at around -150.0 ppm for the BF_4^- anion.

2.2.3 Comparison of the single-crystal X-ray structures of IPy_2BF_4 and its analogues

X-Ray diffraction gave evidence to confirm the structures of IPy_2BF_4 and its analogues; the single-crystal X-ray structures of **NI-1**, **NI-2**, **NI-3** and **NI-4** are shown in **Figure 2.9**. All of them have a linear geometry from the combination of the iodine centre and the nitrogen donor sites of the two pyridine or derivative ligands. The BF_4^- units exist as free anions. It is worth mentioning that the two methoxy groups are on the same side in the structure of **NI-3**.

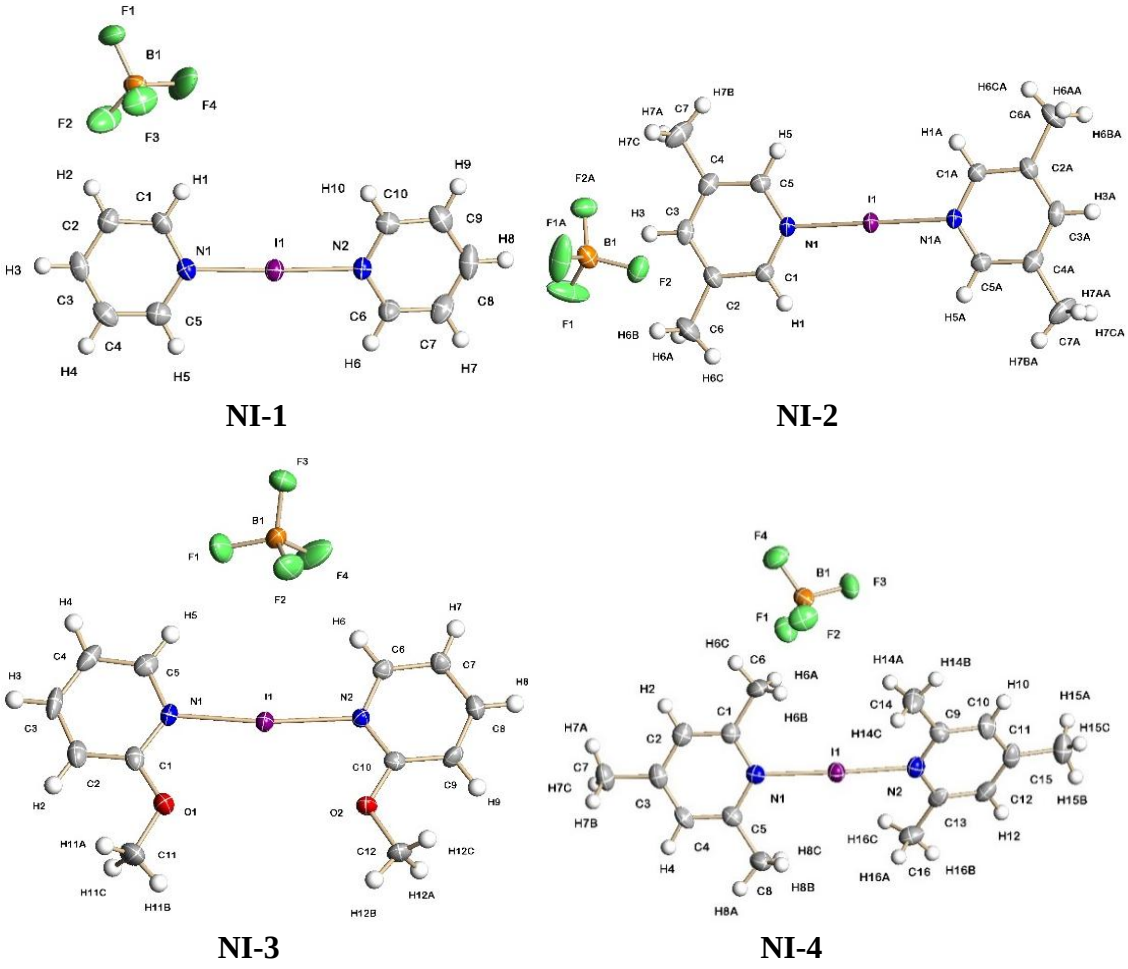


Figure 2.9 Solid-state structures of **NI-1**, **NI-2**, **NI-3** and **NI-4**

From bond length data presented in **Table 2.2**, it can be seen that the bond lengths of the two I-N bonds in all four species are crystallographically equivalent. These distances in **NI-4** are slightly longer than those in the other three species, probably due to steric repulsion arising from the *ortho*-methyl groups. From the bond angle data in **Table 2.3**, it can be seen that the N-I-N axes in **NI-1** and **NI-2** are linear. In contrast,

N(1)-I-N(2) in **NI-3** is 172 ° and N(1)-I-N(2) in **NI-4** is 176 °, which suggests that the substituents close to the N atom on the pyridine ring make the iodonium(I) salt slightly bent due to steric hindrance.

Iodonium salt	Bond lengths (Å)	
NI-1	I(1)-N(1)	2.258(3)
	I(1)-N(2)	2.259(3)
NI-2	I(1)-N(1A)	2.2525(16)
	I(1)-N(1)	2.2525(16)
NI-3	I(1)-N(1)	2.263(3)
	I(1)-N(2)	2.276(3)
NI-4	I(1)-N(2)	2.281(6)
	I(1)-N(1)	2.297(6)

Table 2.2 Bond length data for IPy_2BF_4 and its analogues

Iodonium salt	Bond	Bond Angles ( )
NI-1	N(1)-I(1)-N(2)	180.0
NI-2	N(1A)-I(1)-N(1)	180.0
NI-3	N(1)-I(1)-N(2)	172.04(10)
NI-4	N(2)-I(1)-N(1)	176.41(17)

Table 2.3 Bond angle data for IPy_2BF_4 and its analogues

2.3 Synthesis of New *N*-Functionalised Cl-I(III) Compounds

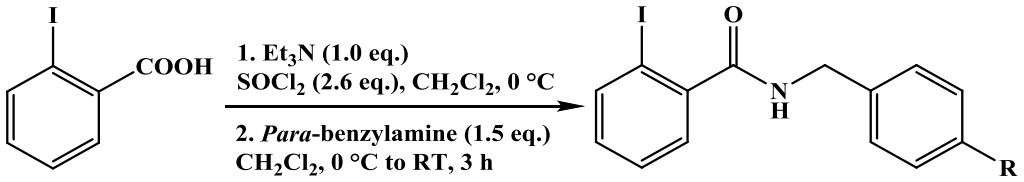
2.3.1 Synthesis of *N*-(*para*-benzyl)-2-iodobenzamides

Para-substituted *N*-benzyl-2-iodobenzamide compounds were prepared as starting materials for the synthesis of new *N*-functionalised Cl-I(III) compounds. Based on the synthetic methods reported in the literature [32-34] and the nucleophilic acyl substitution reaction mechanism, *para*-substituted *N*-benzyl-2-iodobenzamide substrates *N*-benzyl-2-iodobenzamide (***N*-1**), *N*-(4-chlorobenzyl)-2-iodobenzamide (***N*-2**) and *N*-(4-

fluorobenzyl)-2-iodobenzamide (***N*-3**) were synthesised using the *para*-substituted benzylamines.

The solubility of 2-iodobenzoic acid in CH_2Cl_2 is very low. When an equimolar amount of Et_3N was added into the mixture, all the solids dissolved. Et_3N can act as a weak base which aids in the formation of the 2-iodobenzoic acid anion which then attacks $SOCl_2$ as a nucleophile. In this process, the intermediate 2-iodobenzoyl chloride is produced, which can then react with the respective amine compounds to synthesize *para*-substituted *N*-benzyl-2-iodobenzamide derivatives easily. After stirring at room temperature for three hours, the reaction was worked up by adding a saturated aqueous solution of $NaHCO_3$ and washing with brine and water. Finally, CH_2Cl_2 was removed under reduced pressure; the crude target products were gained as yellow powders.

In the ^1H NMR (500 MHz, $CDCl_3$) spectra of the products, there is a significant broad singlet peak at around 6.00 ppm, representing the -CONH- proton and another important doublet peak at around 4.62 ppm with coupling constant of 5.6 Hz, represented by $-CH_2-$ protons connecting to -CONH-. In their ^{13}C NMR (126 MHz, $CDCl_3$) spectra, there are two important peaks. One chemical shift around 169.2 ppm, is characteristic of the C=O bond in -CONH- and the other around 43.5 ppm represents the $-CH_2-$ group connected to -CONH-. The products were purified by recrystallization from CH_3CN. Finally, the yields of ***N*-1**, ***N*-2** and ***N*-3** as colourless crystals were 75%, 78% and 80% respectively **(Table 2.4)**.

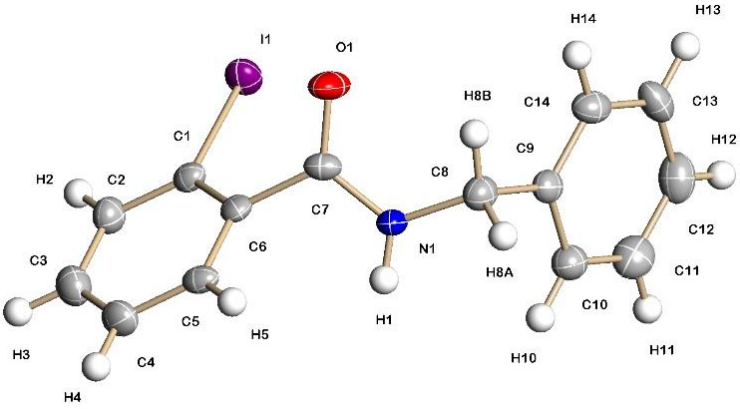


R=H, Cl, F

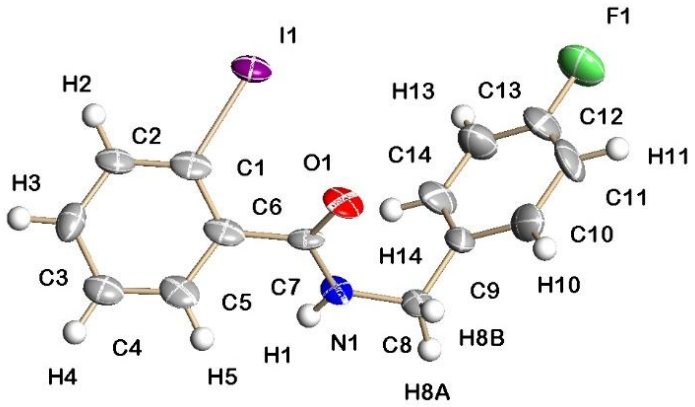
Entry	*Para*-substituted benzylamine	R	Amide Product	Yield (%)
1	Benzylamine	H	***N*-1**	75
2	4-Chlorobenzylamine	Cl	***N*-2**	78
3	4-Fluorobenzylamine	F	***N*-3**	80

Table 2.4 Synthetic results of *para*-substituted *N*-benzyl-2-iodobenzamide compounds

In the process of recrystallization, it was found that ***N*-1** and ***N*-3** could be obtained as colourless block crystals suitable for characterisation by X-ray crystallography. The single crystal structures of ***N*-1** and ***N*-3** are shown in **Figure 2.10**. The bond length and bond angle data for these two species are unremarkable.



***N*-1**



***N*-3**

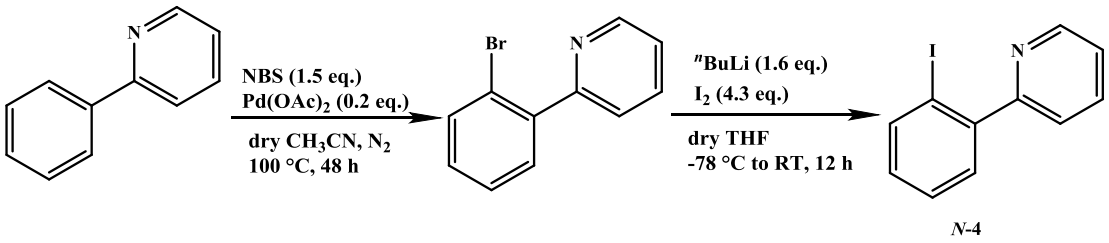
Figure 2.10 X-ray crystal for structures of ***N*-1** and ***N*-3**

Comparing the approach used here for the synthesis of ***N*-1** with other approaches in the literature, such as using 2-iodobenzoic acid reaction with oxalyl chloride $(COCl)_2$ or with DMF and $SOCl_2$ under reflux to form 2-iodobenzoyl chloride in the first step and then convert it to amide product,[32-34] the final products could be obtained in high yields, under mild conditions and in a short amount of time, and also the products could be purified easily.

2.3.2 Synthesis of *N*-heterocyclic compounds as substrates

After the preparation of three different *para*-substituted *N*-benzyl-2-iodobenzamide compounds ***N*-1**, ***N*-2** and ***N*-3** as substrates for the synthesis of new *N*-functionalised

Cl-I(III) compounds, the synthesis of various *N*-heterocyclic compounds as substrates was also investigated. 2-(2-Iodophenyl)pyridine **(*N*-4)** was synthesized by the following modified procedures **(Scheme 2.14)** based on the work presented by Togni's group in 2010.[22]

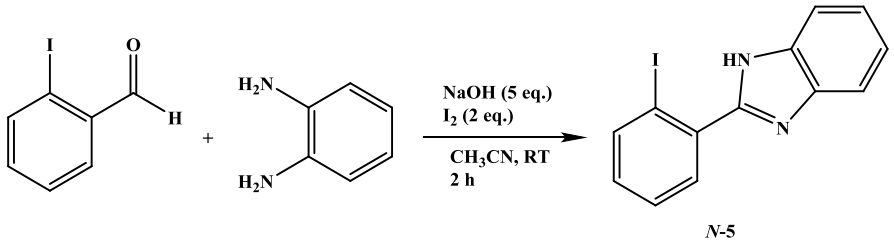


Scheme 2.14 Preparation of ***N*-4**

It was difficult to introduce the iodine atom into the benzene ring to derive ***N*-4**. In the first step to synthesize 2-(2-bromophenyl)pyridine, the NBS must exceed 1.5 equivalents and 0.2 equivalents of $Pd(OAc)_2$ were used as a catalyst for the C-H activation step. This reaction had to be carried out over 48 hours at 100 ℃ in dry CH_3CN. The pure product was gained as a yellowish oil following column chromatography on silica gel using hexane/EtOAc (V:V = 2:1), and the yield was 70%. In the second step, synthesis of ***N*-4** was accomplished by adding I_2 dissolved in THF to a solution of 2-(2-bromophenyl) pyridine and ^{n}BuLi at -78 ℃ in dry THF, warming it up to room temperature and continuously stirring it for 12 hours at room temperature. In this process, 1.6 equivalents of ^{n}BuLi and 4.3 equivalents of I_2 were added in order to replace the majority of bromine atoms by iodine atoms. Finally, a 76% yield of pure 2-(2-iodophenyl)pyridine was obtained as a yellow oil after column chromatography on silica gel using hexane/EtOAc (V:V = 3:1). The most significant characterisation data is the chemical shift at 95.7 ppm in the ^{13}C NMR spectrum which represented the C-I unit in the product.

Two other *N*-heterocyclic compounds 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole **(*N*-5)** and 2-(2-iodophenyl)-4,5-diphenyl-1*H*-imidazole **(*N*-6)** were prepared as substrates in order to study the preparation of cationic *N*-functionalised Cl-I(III) compounds. The synthesis of ***N*-5** was very easy to carry out **(Scheme 2.15)**. The proposed mechanism is detailed in **Figure 2.11**. Iodine reacts with solid NaOH to form IO_3^-, which played an important role in obtaining the product. However, during the work up of the reaction large amounts of EtOAc had to be used to extract the target product from the aqueous

phase: 600 mL of EtOAc was added to allow 1.23 g of 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole to be collected as a yellow solid after purification. The crude product could be purified by washing with acetone and drying under vacuum. The yield of ***N*-5** could reach 65% using this method.



Scheme 2.15 Synthesis of ***N*-5**

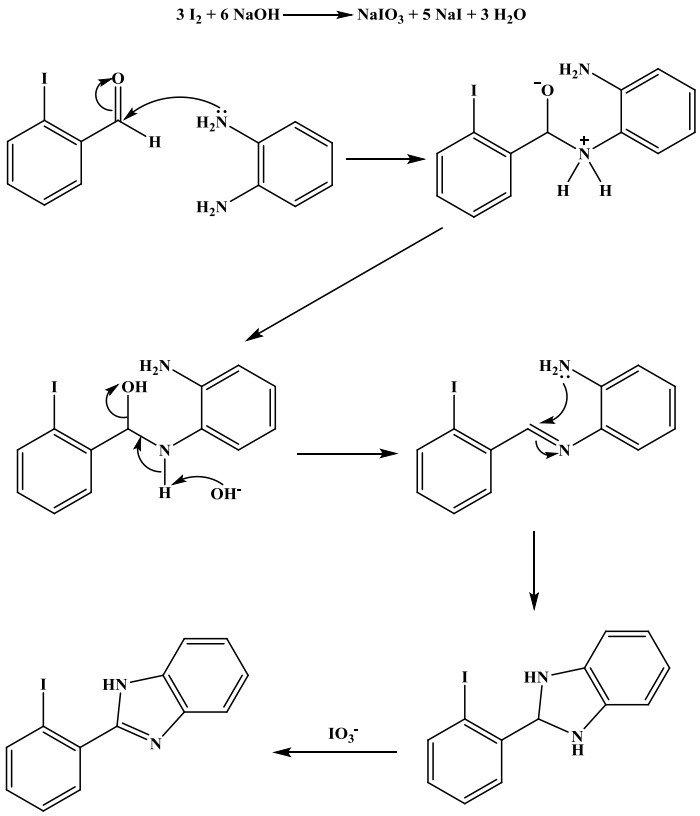
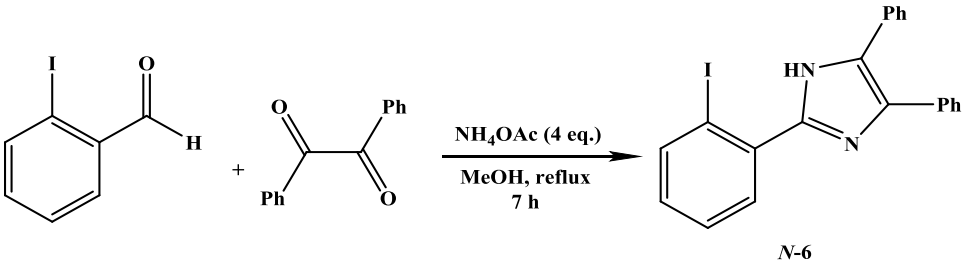


Figure 2.11 Proposed mechanism for formation of ***N*-5**

The synthesis of ***N*-6** was carried out by the following route **(Scheme 2.16)**. Benzil reacted with NH_4OAc to form 1,2-diphenylethane-1,2-diamine in methanol heated at reflux, which continued to react with 2-iodobenzaldehyde to form ***N*-6**. If the purification of crude product was attempted by washing with EtOH, as detailed in the literature, the by-product acetic acid was difficult to remove. An alternative purification procedure was devised; a 58% yield of pure 2-(2-iodophenyl)-4,5-diphenyl-1*H*-

imidazole could be gained by recrystallization in DMF, washing with EtOH and drying under vacuum. X-ray crystallography gave evidence for the single crystal structure of ***N*-6** co-crystallised with a single DMF molecule **(Figure 2.12)**.



Scheme 2.16 Synthesis of ***N*-6**

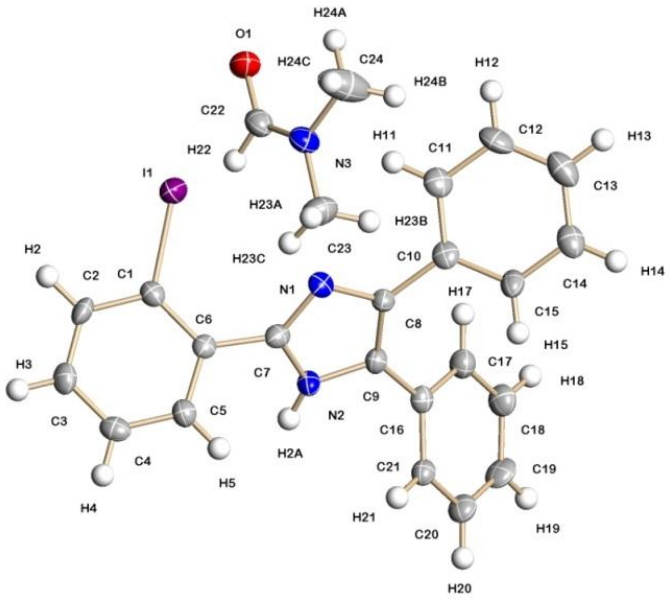


Figure 2.12 The X-ray crystal structure of ***N*-6** co-crystallized with a DMF molecule

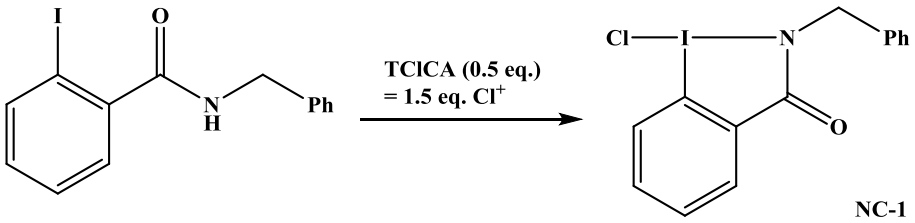
2.3.3 Synthesis of new *N*-functionalised Cl-I(III) compounds using *N*-(*para*-benzyl)-2-iodobenzamide substrates

In order to modify the literature method to obtain *N*-functionalised Cl-I(III) chlorobenzoiodazolone compounds using Cl_2 gas,[24-25] the more safe and stable reagent trichloroisocyanuric acid (TClCA) was used as the chlorine source for the synthesis of the new *N*-functionalised Cl-I(III) compound 2-benzyl-1-chloro-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-1)**.

It was found that the by-product, cyanuric acid, formed as a white precipitate, which gave evidence for the progress of the reaction. The reaction mixture must be filtered as soon as possible after the reaction is completed and whilst the solution is still hot. After the solvent has been removed, cold CH_3CN is added drop by drop to wash the crude

product in order to remove any unreacted TClCA and ***N*-1** starting materials**,** as well as a tiny amount of cyanuric acid.

Optimisation of the conditions were explored by varying the solvent, CH_2Cl_2 and CH_3CN, reaction temperatures, time and method of addition **(Table 2.5)**. It was found that CH_3CN was much more suitable as the solvent than CH_2Cl_2, presumably due to the higher solubility of TClCA in CH_3CN. A 75% yield of **NC-1** as colourless block crystals was obtained, when the reaction was carried out in dry CH_3CN, at 75 ℃ for 18 hours.



Entry	Solvent	T (℃)	Time	Yield (%)
1	**CH_2Cl_2 [a]**	RT	1 h	18
2	**CH_2Cl_2 [a]**	40	1 h	36
3	**CH_3CN [a]**	RT	1 h	20
4	**CH_3CN [a]**	40	1 h	54
5	**CH_3CN [a]**	75	5 min	18
6	**CH_3CN [b]**	75	5 min	10
7	**CH_3CN [a]**	75	1 h	60
8	**CH_3CN [b]**	**75**	**18 h**	**75**

Table 2.5 Comparison of the various reaction conditions to synthesize **NC-1**

a The three-necked round bottom flask was charged with starting materials, evacuated, and then refilled with N_2 three times before the dry solvent was added. After that, it was heated to the required temperature.

b The three-necked round bottom flask was charged with *N*-benzyl-2-iodobenzamide **(*N*-1)**, evacuated, and then refilled with N_2 three times before dry CH_3CN was added. When it was heated to 75 ℃, the solution of TClCA dissolved in the dry CH_3CN added.

In comparison with the syntheses of the two *O*-functionalised Cl-I(III) compounds 1-chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **(OC-1)** and 1-chloro-1,2-benziodoxol-3-(1*H*)-one **(OC-2)** reported by Togni's group,[19] for which an 85% yield could be obtained in dry CH_3CN at 75 ℃ in just 5 minutes, the formation of **NC-1** occurred much more slowly. The main reason for this could be that the amide nitrogen is less nucleophilic than either a carboxylic acid or a tertiary alcohol oxygen since the lone pair of electrons on the nitrogen will be delocalized onto the carbonyl group, thus forming the imidic acid tautomer with partial double bond character between the nitrogen and the carbonyl carbon **(Figure 2.13)**.

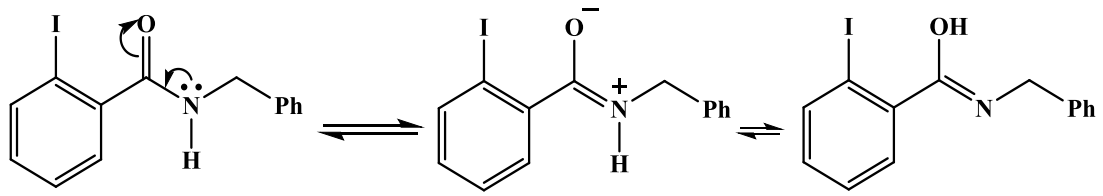
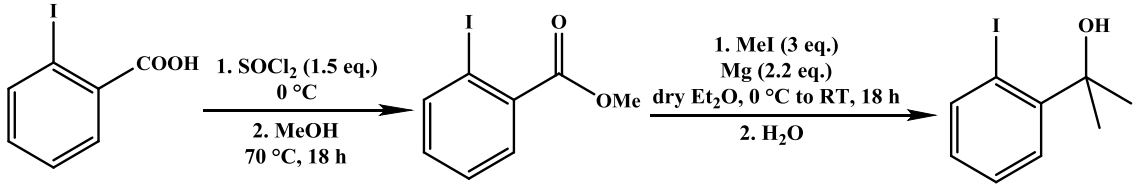


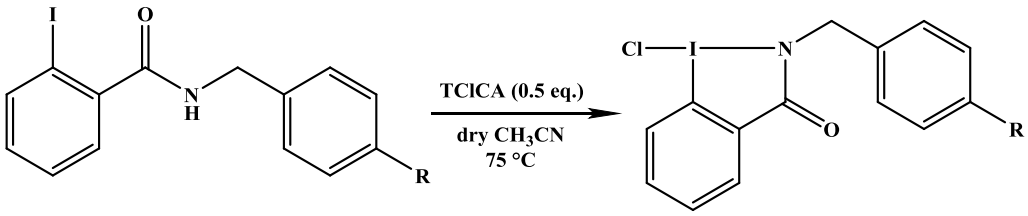
Figure 2.13 Tautormerism of *N*-benzyl-2-iodobenzamide **(*N*-1)** and (*Z*)-*N*-benzyl-2-iodobenimidic acid

Between **NC-1**, **OC-1** and **OC-2**, **OC-2** is the easiest to synthesize since the starting material, 2-iodobenzoic acid, is commercially available. **OC-1** might be considered to be easier to prepare than **NC-1** since the oxidation step is quick, but its precursor 2-(2-iodophenyl)propan-2-ol is prepared by a Grignard reaction in dry diethyl ether under N_2 gas protection **(Scheme 2.17)**, which is very sensitive to air and moisture. In comparison, the ***N*-1** starting material is straightforward to prepare such that, overall **NC-1** is easier to synthesize than **OC-1**.



Scheme 2.17 Synthesis of 2-(2-iodophenyl)propan-2-ol

Subsequently, two other new *N*-functionalised Cl-I(III) compounds 1-chloro-2-(4-chlorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-2)** and 1-chloro-2-(4-fluorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-3)** were synthesized using the same method. As seen in the synthesis of **NC-1**, it was found that the yield of the target product was very low, only 18% and 15% respectively, when the reactions were carried out for three hours. However, these reached 75% and 80% respectively **(Table 2.6)** when the reactions were carried out at 75 ℃ under N_2 for 18 hours.



***N*-2 R = Cl**
***N*-3 R = F**

NC-2 R = Cl
NC-3 R = F

Entry	Cl-I(III)	Time (h)	R	Yield (%)
1	**NC-2**	3	Cl	18
2	**NC-2**	**18**	**Cl**	**75**
3	**NC-3**	3	F	15
4	**NC-3**	**18**	**F**	**80**

Table 2.6 Comparison of syntheses of **NC-2** and **NC-3**

2.3.4 Comparison of NMR data of *N*-benzyl-2-iodobenzamides and corresponding Cl-I(III) compounds

NMR spectroscopy was one of the most essential methods to confirm the successful formation of **NC-1**, **NC-2** and **NC-3** from ***N*-1**, ***N*-2** and ***N*-3**. For example, in the ^{1}H NMR (500 MHz, $CDCl_3$) spectra of ***N*-1** and **NC-1**, the formation of *N*-functionalised Cl-I(III) compounds caused H_a to undergo a downfield shift from 7.86 ppm in ***N*-1** to 8.43 ppm in **NC-1**, H_e to undergo a downfield shift from 4.65 ppm in ***N*-1** as a doublet peak to 4.89 ppm in **NC-1** as a singlet peak **(Figure 2.14)**. Additionally, the peak for the N-H proton around 6.00 ppm disappeared due to the formation of new N-I bond. In

the ^{13}C NMR (126 MHz, $CDCl_3$) spectra, after formation of corresponding Cl-I(III) compound, the chemical shift of the C-I unit on the benzene ring of **NC-1**, **NC-2** and **NC-3** was **116.8** , **114.5** and **115.2** ppm respectively, which had changed so obviously when compared with the chemical shift of C-I unit of ***N*-1**, ***N*-2** and ***N*-3** at around **92.4** ppm, which is typically seen between related iodine(I) and iodine(III) systems. Similarly, the peak representing the –CONH- carbon atom in ***N*-1**, ***N*-2** and ***N*-3** at around 169.2 ppm changed to 165.2, 163.5 and 165.5 ppm in **NC-1**, **NC-2** and **NC-3** respectively. **Figure 2.15** illustrates the changes in the ^{13}C NMR spectra after the formation of **NC-1** from ***N*-1**.

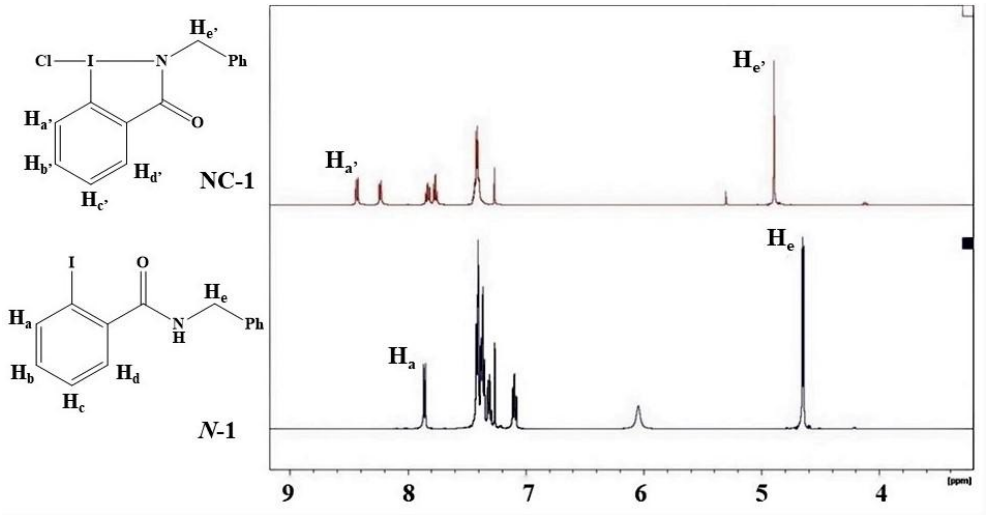


Figure 2.14 Comparison of the ^{1}H NMR spectra for ***N*-1** and **NC-1**

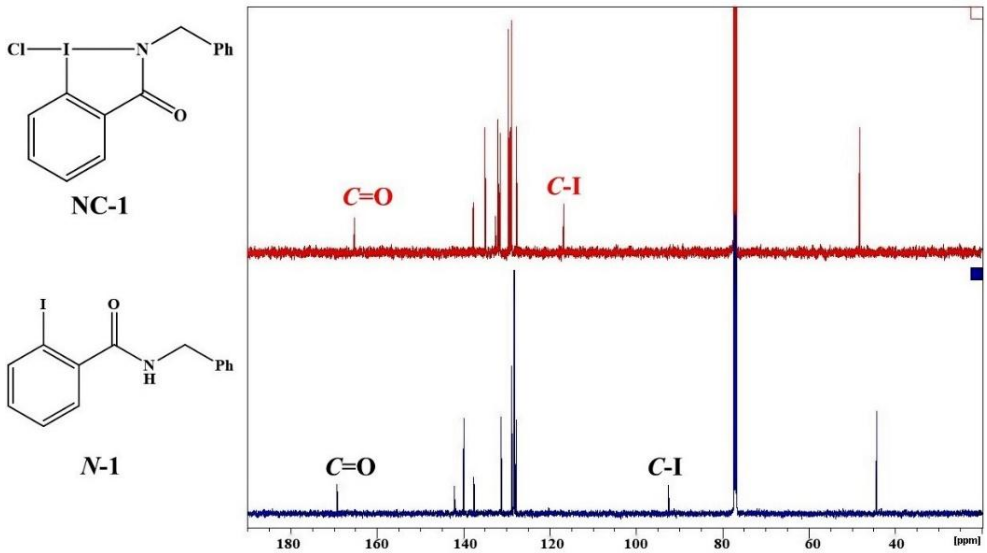
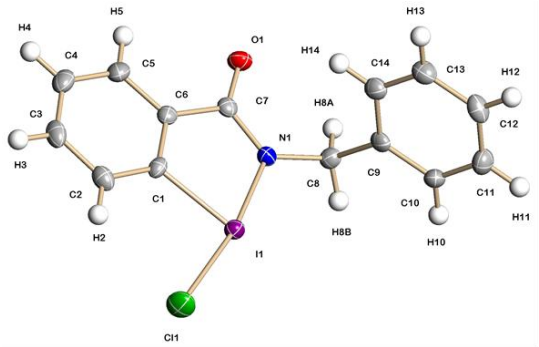


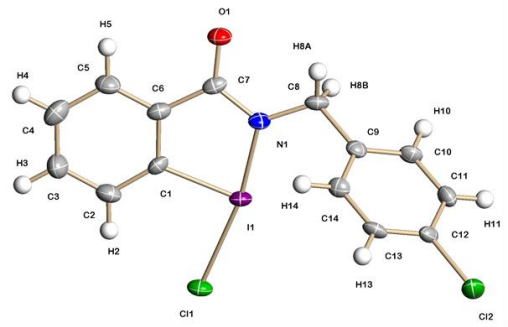
Figure 2.15 Comparison of ^{13}C {^{1}H} NMR spectra for ***N*-1** and **NC-1**

2.3.5 Comparison of the single-crystal X-ray structures of various Cl-I(III) compounds

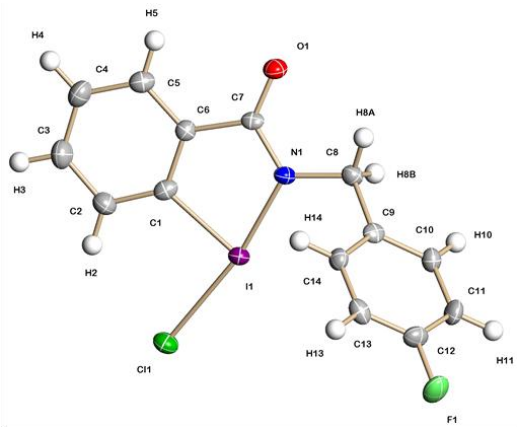
From the X-ray crystallographic diffraction results for **NC-1**, **NC-2** and **NC-3** as single crystals prepared by recrystallization, which plays the most significant role in the confirmation of structures for newly synthesized compounds, it can be seen that one Cl atom and one N atom are coordinated to the iodine centre **(Figure 2.16)**. From these structures it can be seen that the Cl and F substituents on the benzyl groups make the Cl-I bond lengths for **NC-2** and **NC-3** obviously different from that for **NC-1 (Table 2.7)**. In a comparison of the C(7)=O(1), N(1)-C(7) and N(1)-C(8) bond lengths in **NC-1** and ***N*-1**, it can be observed that the C(7)=O(1) bond length 1.233(4) Å is unchanged, but the N(1)-C(7) and N(1)-C(8) bond length increased from 1.333(5) Å to 1.355(5) Å and 1.455(4) Å to 1.468 (5) Å respectively between ***N*-1** and **NC-1** which shows that these two bonds become weaker after formation of **NC-1**. Additionally, in **NC-1**, the summation of the bond angles C(7)-N(1)-C(8) (122.5(3) ⁰), C(7)-N(1)-I(1) (117.0(2) ⁰) and C(8)-N(1)-I(1) (120.4(2) ⁰) is 360 ° (which is the same as **NC-2** and **NC-3**), and significantly shows that N is planar and sp^2 hybridised, and that the lone pair of electrons on nitrogen are delocalized by π-interactions in these species.



NC-1



NC-2



NC-3

Figure 2.16 Single crystal X-ray structures of **NC-1, NC-2** and **NC-3**

From a comparison of the single crystal structures for the three new chlorobenzoiodazolones **NC-1**, **NC-2** and **NC-3** with several other types of five-membered heterocyclic hypervalent Cl-I(III) compounds reported in the literature, including chlorobenzoiodazolones, chlorobenzoiodoxolones and chloroiodanes **(Figures 2.16 and 2.17)**, it can be seen that they all clearly show a distorted T-shaped geometry around iodine, which is typical for five-membered ring hypervalent iodine(III) compounds. The I-Cl bond lengths lie between 2.438 Å for the chlorobenzoiodoxolone with two highly electron withdrawing CF_3 substituents **(OC-3)** and 2.587 Å for **NC-3**. The I-N bond lengths lie between 2.06 and 2.123 Å, although it may be considered that the shortest of these (for **NC-5**) is unusual since it, alone, contains chlorine bound to the nitrogen. The I-O bond lengths lie between 2.017 and 2.110 Å (**Table 2.7**). The differences between the data for the various *O*-functionalised Cl-I(III) compounds in **Table 2.7** can mainly be described to electronic effects derived from the substituents that have been discussed previously by Togni's group,[22] and the differences between the *O*- and *N*-functionalised Cl-I(III) compounds can similarly be accounted for by the difference of electronegativity between N and O.

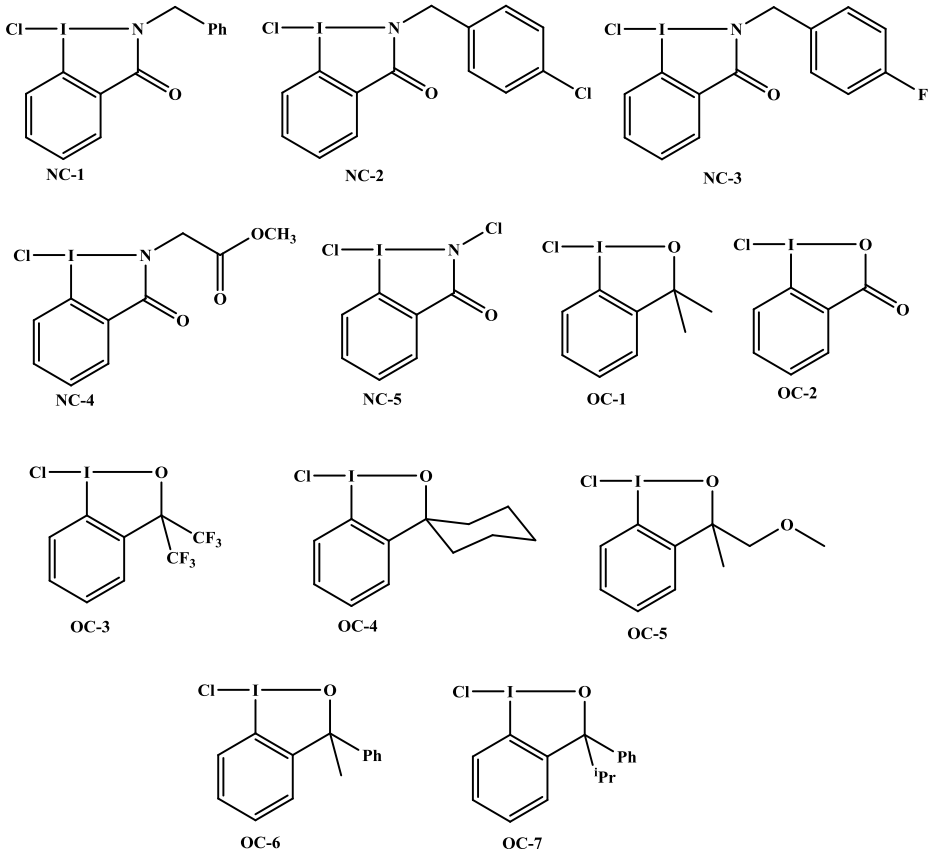


Figure 2.17 Several types of five-membered heterocyclic hypervalent Cl-I(III) compounds

Cl-I(III) Reagents	I-N	I-O	I-C(1)	I-Cl
NC-1	2.121(3)		2.106(4)	2.5330(12)
NC-2	2.123(6)		2.100(8)	2.575(2)
NC-3	2.110(3)		2.111(4)	2.5873(12)
NC-4 [22]	2.113		2.101	2.563
NC-5 [22]	2.06		2.19	2.56
OC-1 [22]		2.042(2)	2.102(3)	2.5491(8)
OC-2 [21]		2.091(3)	2.100(4)	2.461(1)
OC-3 [22]		2.110(5)	2.105(7)	2.438(2)
OC-4 [22]		2.049(2)	2.108(3)	2.5135(9)
OC-5 [22]		2.0511(18)	2.117(2)	2.5201(7)
OC-6 [22]		2.0437(2)	2.107(2)	2.5406(7)
OC-7 [21]		2.0169(14)	2.108(2)	2.5805(6)

Table 2.7 Bond lengths [Å] of various Cl-I (III) reagents

In all five-membered rings, the bond angles of Cl-I-O and Cl-I-N are obviously smaller than 180 ° due to the repulsion of the two lone pairs of electrons at iodine position (**Table 2.8**). Interesting, there are no significant differences between these for the Cl-I-O and Cl-I-N series. The N-I-C(1)-C(6) torsion angle 2.0 ° in **NC-1,** 4.4 ° in **NC-2**, 4.4 ° in **NC-3** and 1.2 ° in **NC-4** indicates almost perfect co-planarity with the adjacent phenyl ring in the structures of the three new chlorobenzoiodazolones **NC-1**, **NC-2** and **NC-3** as well as chlorobenzoiodazolone **NC-4** (**Table 2.9**). The N-I-C(1)-C(6) torsion angle 1.8 ° in chlorobenziodoxolone **OC-2**, which also contains an sp^2 hybridised C(7) atom, provides the evidence for a similar structural character for **OC-2**

to those for the chlorobenzoiodazolones **NC-1**, **NC-2**, **NC-3** and **NC-4**. A comparison between the torsion angle N-I-C(1)-C(6) in the *N*-functionalised Cl-I(III) compounds and O-I-C(1)-C(6) in the *O*-functionalised Cl-I(III) compounds, indicates that the torsion angle generally increases with larger substituents at the C(7) atom of the five-membered ring due to the steric effect.

Cl-I(III) Reagents	N-I-Cl	C(1)-I-N	C(1)-I-Cl	O-I-Cl	C(1)-I-O
NC-1	170.21(9)	78.89(14)	91.46(11)		
NC-2	170.28(18)	79.5(3)	90.8(2)		
NC-3	170.12(10)	79.24(16)	90.90(13)		
NC-4 [22]	170.6	79.0	91.6		
NC-5 [22]	171	80	91		
OC-1 [22]			91.45(8)	171.06(7)	80.57(10)
OC-2 [22]			92.6(1)	171.96(8)	79.5(1)
OC-3 [22]			93.2(2)	172.0(1)	78.9(2)
OC-4 [22]			90.77(9)	170.17(7)	80.67(10)
OC-5 [22]			90.43(7)	170.51(5)	80.20(9)
OC-6 [22]			91.15(7)	169.86(5)	79.89(9)
OC-7 [22]			91.27(6)	171.61(5)	80.5(7)

Table 2.8 Bond Angles [°] of Various Cl-I(III) Reagents

Cl-I(III) Reagents	N-I-C(1)-C(6)	Cl-I-C(1)-C(2)	O-I-C(1)-C(6)
NC-1	2.0(3)	-2.7(3)	
NC-2	4.4(6)	6.2(7)	
NC-3	4.4(3)	5.1(4)	
NC-4 [22]	1.2	2.0	
OC-1 [22]		6.0(3)	10.8(2)
OC-2 [22]		3.3(3)	1.8(3)
OC-3 [22]		-4.7(5)	-6.4(6)
OC-4 [22]		2.9(3)	10.0(2)
OC-5 [22]		3.9(2)	8.36(18)
OC-6 [22]		13.1(2)	15.82(17)
OC-7 [22]		15.18(18)	17.17(15)

Table 2.9 Torsion Angles [°] of Various Cl-I(III) Reagents

2.3.6 Mechanism for the formation of chlorobenzoiodazolones

In the proposed mechanism for the formation of **NC-1 (Figure 2.18)**, TClCA acts as an electrophilic oxidant. The lone pair of electrons on the iodine atom attacks a chlorine of TClCA, and the Cl-N bond is broken to form the iodonium intermediate. Nitrogen coordinates with iodine to form the five-membered ring Cl-I(III) compound **NC-1** from iodine(I) compound ***N*-1** by electron-transfer and deprotonation. One TClCA molecule can react with three ***N*-1** molecules. In the process of making **NC-1**, TClCA is transformed into the by-product cyanuric acid, as a white precipitate, which can act as an important indicator for the success of this reaction.

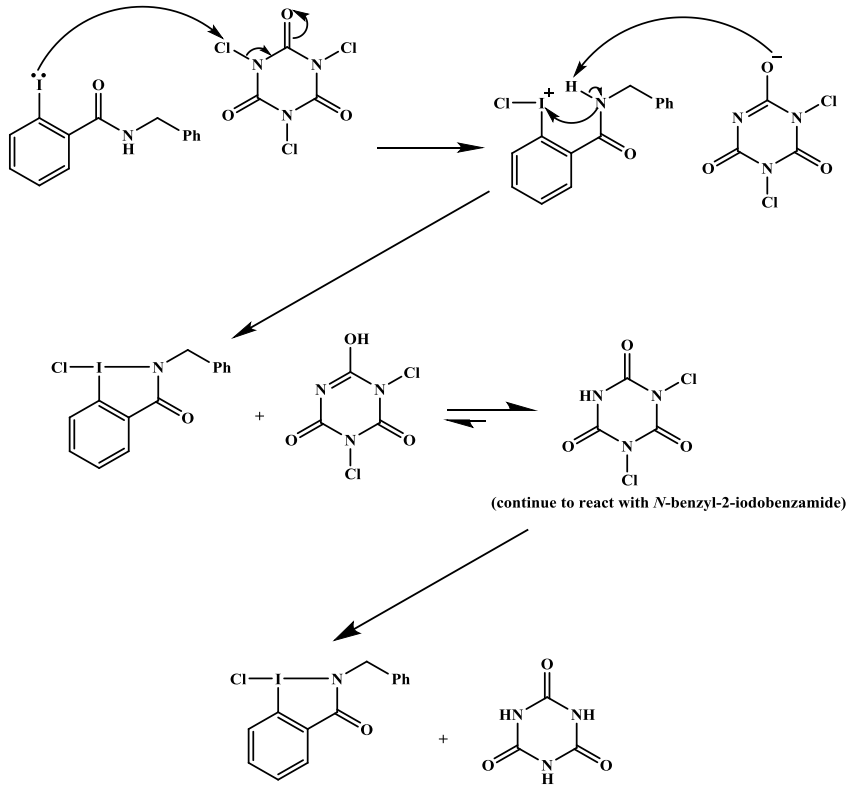
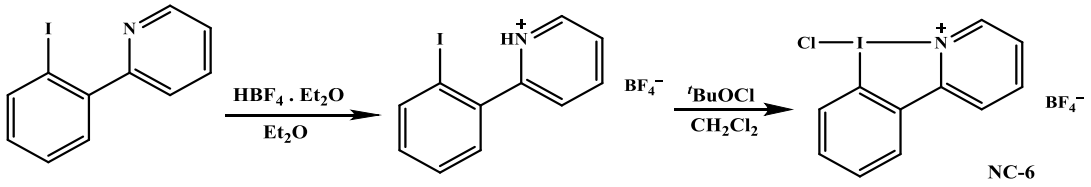


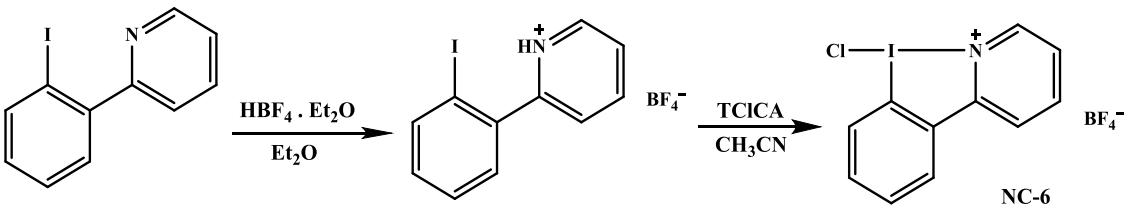
Figure 2.18 Proposed mechanism for the formation of **NC-1**

2.3.7 Attempted synthesis of new *N*-functionalised Cl-I(III) compounds using *N*-heterocyclic compounds as substrates

In 2010, Togni and his co-workers first reported the synthesis of the cationic chloroiodane **NC-6** from 2-(2-iodophenyl)pyridine, protonated using HBF_4 before oxidation with ^{t}BuOCl **(Scheme 2.18)**.[22]



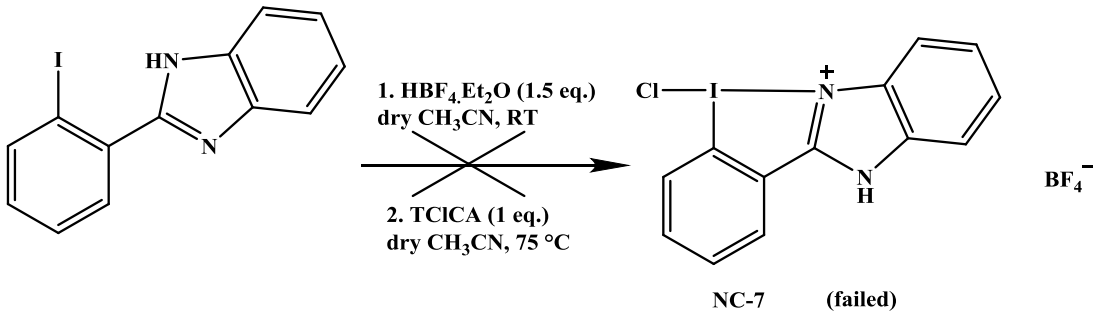
Scheme 2.18 Synthetic route of **NC-6** in Togni's work



Scheme 2.19 Synthesis of **NC-6** using TClCA

In this work, the safer and easier-to-handle chlorination reagent TClCA was used to replace ^{t}BuOCl in the synthesis of **NC-6 (Scheme 2.19)**. When 2-(2-iodophenyl)pyridine was dissolved in dry diethyl ether and HBF_4 (54% diethyl ether solution) was added, the protonated intermediate was formed as a pale brown precipitate immediately. When the solution of TClCA in dry CH_3CN was added into the Schlenk tube, the intermediate dissolved rapidly but the by-product cyanuric acid as a white precipitate, which was hoped would act as an important indicator for the success of this reaction, did not appear even when the reaction mixture was heated for over 18 hours at 75 ℃. From these results, it may be concluded that TClCA is not strong enough as an oxidant to prepare **NC-6** and that ^{t}BuOCl is better.

The synthesis of cationic chloroiodane **NC-7** from 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole was also attempted in the same way **(Scheme 2.20)**. The solubility of 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole in diethyl ether is very low, but it is much better in CH_3CN. Therefore, CH_3CN was used as the solvent in this reaction.



Scheme 2.20 Synthetic route designed for **NC-7**

When HBF_4 (54% diethyl ether solution) was added, the protonated intermediate formed easily at room temperature as a yellow solid after removing the solvent under vacuum. However, it did not react with TClCA even when it was heated at 75 ℃ for 18 hours. No evidence for the generation of cyanuric acid as a white precipitate was found,

and the protonated 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole, formed by reaction with HBF_4 was obtained by recrystallization from ethyl acetate. The same product was formed even when no TClCA had been added. X-ray diffraction gives evidence for its structure **(Figure 2.19)**.

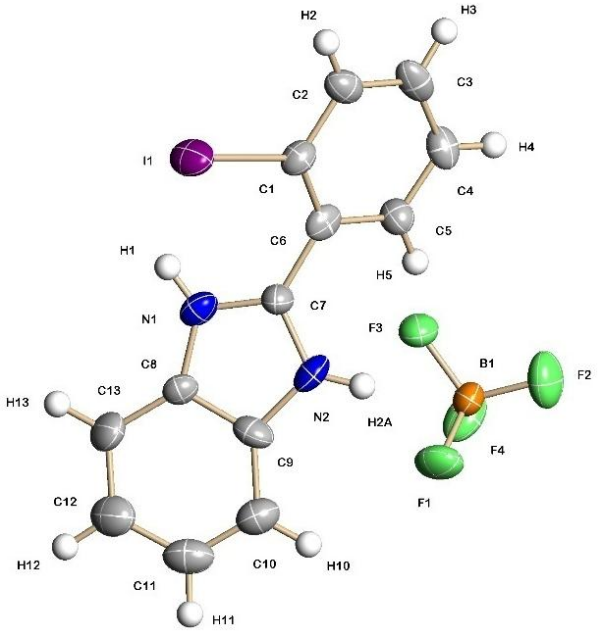


Figure 2.19 Solid-state structure of the protonated 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole product

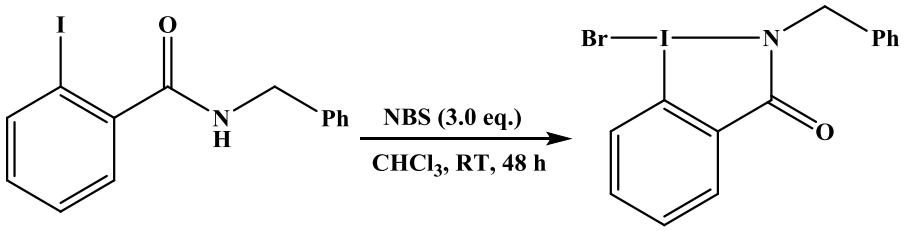
When 2-(2-iodophenyl)-4,5-diphenyl-1*H*-imidazole was used as the starting material, similar negative results were obtained.

2.4 Synthesis of new *N*-functionalised F-I(III) compounds

2.4.1 Synthesis of fluorobenzoiodazolones by halogen-transfer

Based on the synthetic route to 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** developed by our group under mild conditions at room temperature without N_2 gas protection or use of dry solvent [31] and the above work, the synthesis of the new *N*-functionalised F-I(III) compound 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)** from ***N*-1** under the same conditions was attempted. However, the reactions yielded only a mixture of starting materials after the first step using NBS, even when the reaction was carried out over 48 hours or with

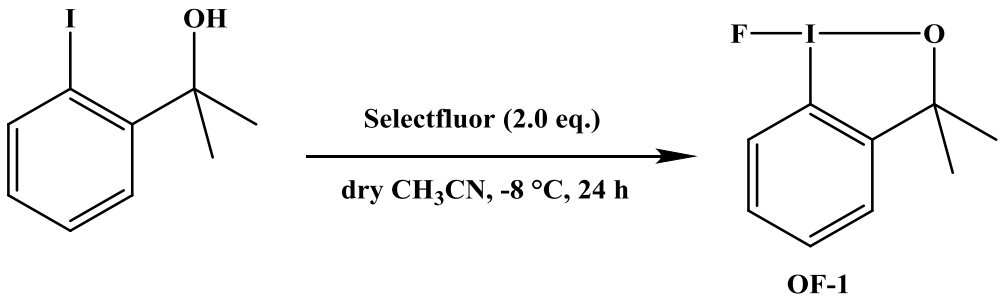
3 equivalents of NBS **(Scheme 2.21)**. These results suggest that NBS is not a strong oxidant for the preparation of the corresponding Br-I(III) compound from ***N*-1**.



Scheme 2.21 Attempted preparation of bromobenzoiodazolone from ***N*-1** using NBS

2.4.2 Synthesis of fluorobenzoiodazolones using Selectfluor

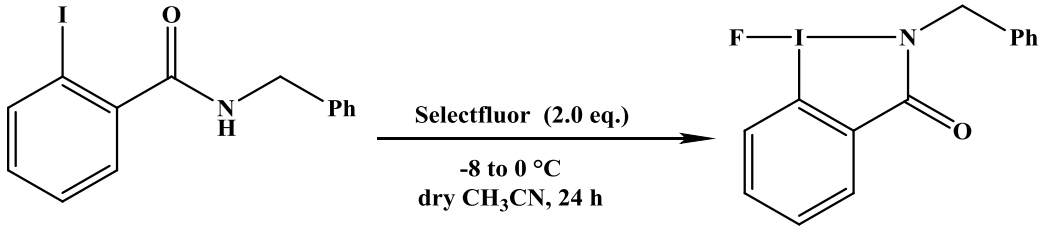
The synthesis of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** using Selectfluor in dry CH_3CN at room temperature and the structure of **OF-1** as a single crystal have been reported in the literature.[30] However, neither NMR spectroscopic data nor the yield of target product produced by this method was reported.



Scheme 2.22 Synthesis of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** using Selectfluor

Following work from our group,[35] **OF-1** was successfully prepared from 2-(2-iodophenyl)propan-2-ol using Selectfluor in dry CH_3CN at -8 ℃ for 24 hours **(Scheme 2.22)**. The pure product was gained as colourless crystals in a 37% yield after recrystallization from hexane. The low reaction temperature is necessary here to avoid over oxidation to form iodine(V) compounds as by-products if the reaction is carried out at room temperature. Then the reaction of ***N*-1** with Selectfluor **(Scheme 2.23)** was also explored at low temperatures of -8 and 0 ℃ using the same conditions. When the

reaction was completed, the CH_3CN was removed by rotary evaporation, $CHCl_3$ was added in order to separate unreacted Selectfluor and collect the target iodine(III) compound through filtration. Then, other various solvents were added in order to try to isolate the target product from other by-products such as BF_4^- salts. This was different to the synthesis of **OF-1** which can be readily extracted using hexane. Here, the crude reaction mixture including the potential new *N*-functionalised F-I(III) compound 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)**, was insoluble in hexane, but it could be extracted with ethyl acetate. After removal of the ethyl acetate by rotary evaporation, a crude product was obtained as a yellow oil which included **NF-1**, unreacted ***N*-1** and some BF_4^- salts according to analysis by ^1H and ^{19}F NMR spectroscopy.



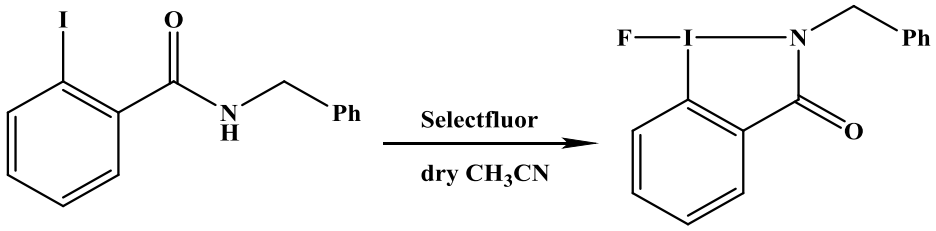
Scheme 2.23 Synthesis of 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)** using Selectfluor

2.4.3 Optimisation of reaction conditions for preparation of fluorobenzoiodazolones

From the data in **Table 2.10**, it can be seen that *N*-benzyl-2-iodobenzamide (***N*-1**) was much more difficult to convert to **NF-1** than 2-(2-iodophenyl)propan-2-ol to **OF-1** at low temperature even when three equivalents of Selectfluor were added at 0 ℃. The conversion of ***N*-1** to **NF-1**, calculated by the intergration of -CH_2- signal at 4.65 ppm in ***N*-1** and 4.79 ppm in **NF-1** in the ^1H NMR spectra, improved when the reaction was carried out at room temperature. When the reaction was carried out at room temperature using ***N*-1** with 2 equivalents of Selectfluor for 18 hours, the conversion of ***N*-1** to **NF-1** reached 100%. The most probable reason for these observations is the lower nucleophilicity of nitrogen, arising from the tautomerism of ***N*-1**, which has been discussed in the synthesis of the *N*-functionalised Cl-I(III) compound **NC-1**.

Following extraction of the crude product with ethyl acetate, the target F-I(III) product **NF-1** was purified by recrystallization from CH_3CN and obtained as colourless

block crystals, but some **NF-1** was lost in this process. Therefore, the final yield of **NF-1** was just 62%, which was much lower than the conversion of 100%.



Entry	Scale of Selectfluor (eq.)	Temperature (℃)	Time (h)	Conversion to F-I(III) Compound
1	2	-8	24	7
2	2	0	24	28
3	3	0	24	28
4	1.2	RT	18	77
5	**2**	**RT**	**18**	**100**

Table 2.10 Optimisation of reaction conditions for the preparation of **NF-1** from *N*-benzyl-2-iodobenzamide **(*N*-1)** and Selectfluor

In order to check the stability of **NF-1** to air, light and moisture, it was kept in a small open sample vial on the bench for 15 days. Then, in comparison with a fresh sample, no change was found in the ^{1}H and ^{19}F NMR spectra of **NF-1,** which could suggest that **NF-1** is a very stable new *N*-functionalised F-I(III) compound.

2.4.4 Comparison of the NMR data for *para*-substituted *N*-benzyl-2-iodobenzamide species and corresponding F-I(III) compounds

The identity of **NF-1** was confirmed by NMR spectroscopy. In the ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of **NF-1**, the broad singlet peak at 6.00 ppm for the N-H proton in ***N*-1** had disappeared because of coordination of nitrogen to iodine. As seen in the NMR spectra of the *N*-functionalised Cl-I(III) compounds, oxidation results in a downfield shift for H_a from 7.86 ppm in ***N*-1** to 8.22 ppm in **NF-1**, a downfield shift for H_e from 4.65 ppm in ***N*-1** to 4.79 ppm in **NF-1 (Figure 2.20)**. However, in the spectra for **NF-1**,

this is a doublet **(Figure 2.21)**, with a coupling constant of 6.5 Hz, which is different to the singlet resonance for the same proton in the *N*-functionalised Cl-I(III) reagent **NC-1**, which is expected to have a similar structure. The main reason for it might be that the two protons of -CH_2- connected to nitrogen in **NF-1** were coupled with the F atom. In order to confirm this, a ^{1}H {^{19}F} NMR (400 MHz, $CDCl_3$) spectrum was recorded where the peak 4.79 ppm collapsed to a singlet. Consequently, this observation confirms that these two protons show long range coupling to the F atom. The formation of the corresponding F-I(III) compound could also be readily inferred from the ^{13}C NMR spectra (126 MHz, $CDCl_3$) where the resonance due to the C-I atom **NF-1** was found at **117.8** ppm **(Figure 2.22)** which is a significant shift from that for the corresponding C-I resonance in ***N*-1** at **92.4** ppm.

In the ^{19}F NMR spectra (376 MHz, $CDCl_3$), the broad singlet peak at -104.4 ppm represents the F-I atom in **NF-1 (Figure 2.23)**. These data suggest that the new F-I(III) compound had been successfully formed from iodine(I) compound ***N*-1**.

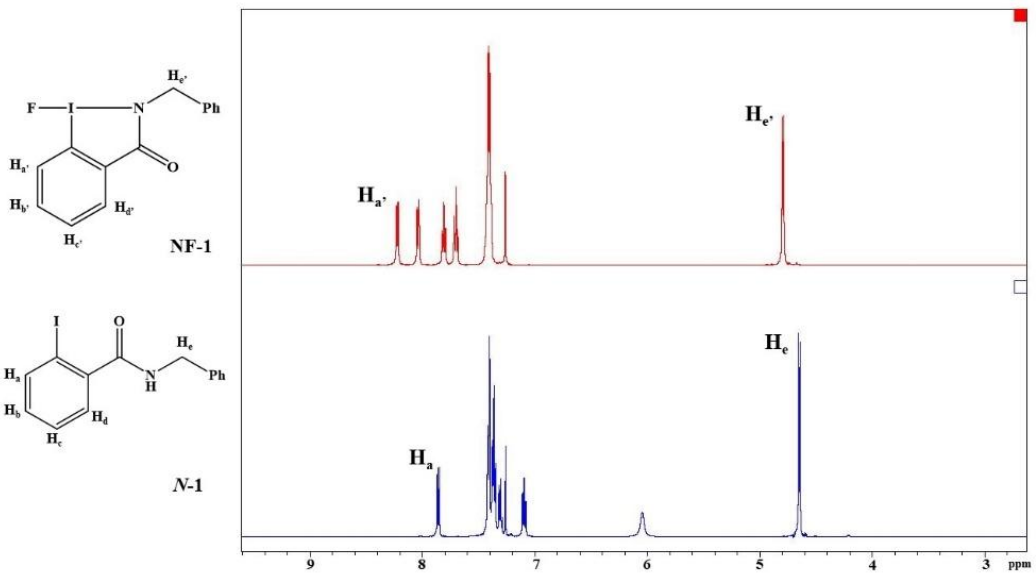


Figure 2.20 Comparison of the ^{1}H NMR spectra (500 MHz, $CDCl_3$) ***N*-1** and **NF-1**

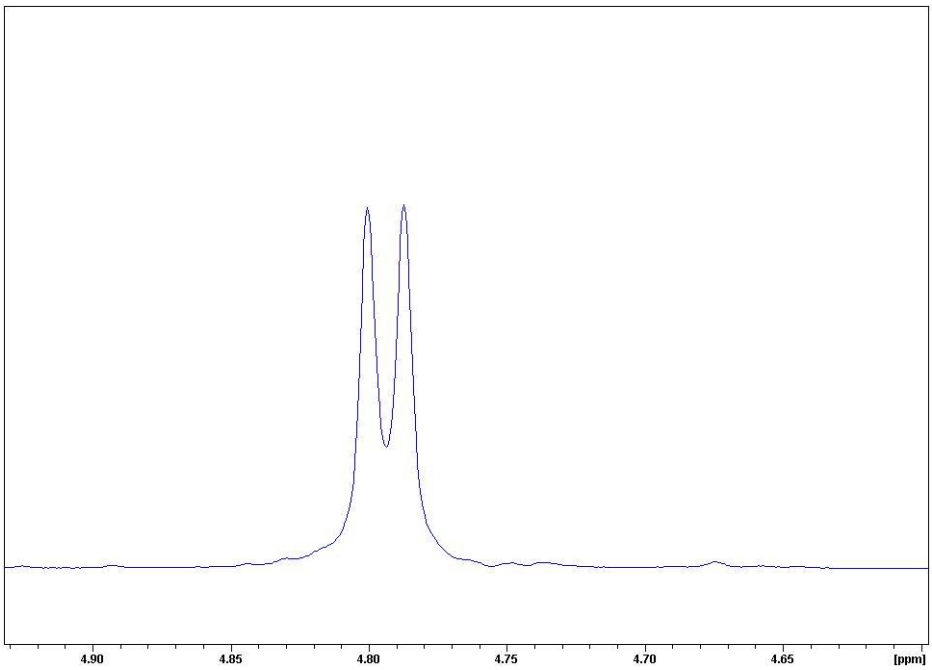


Figure 2.21 -CH_2- resonance in the ^1H NMR spectrum (500 MHz, $CDCl_3$) of **NF-1** (^1H-^{19}F coulpling)

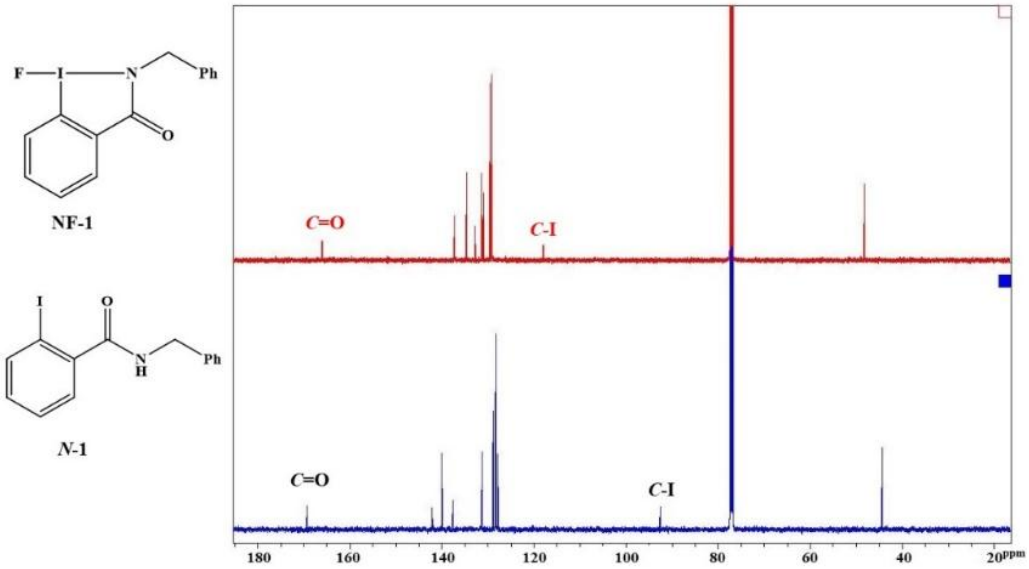


Figure 2.22 Comparison of the ^{13}C NMR spectra (126 MHz, $CDCl_3$) for ***N*-1** and **NF-1**

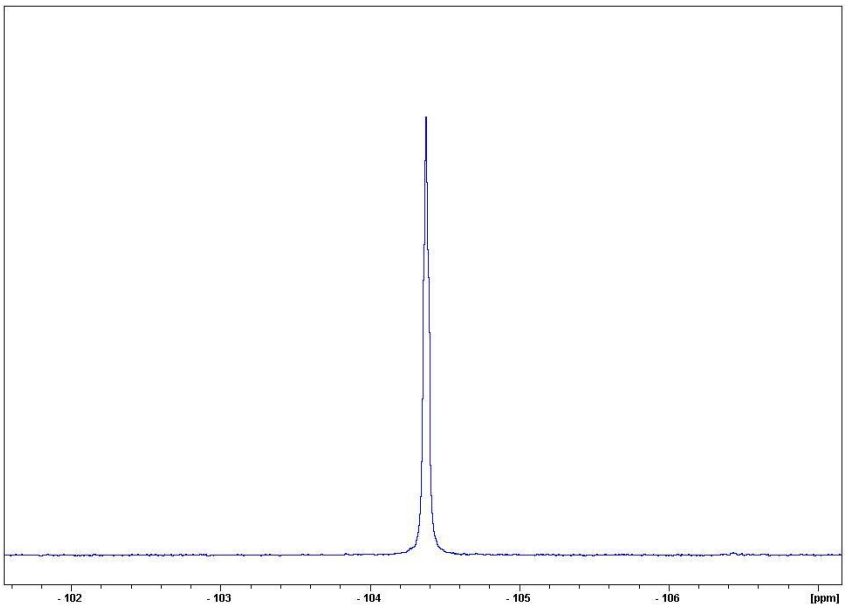


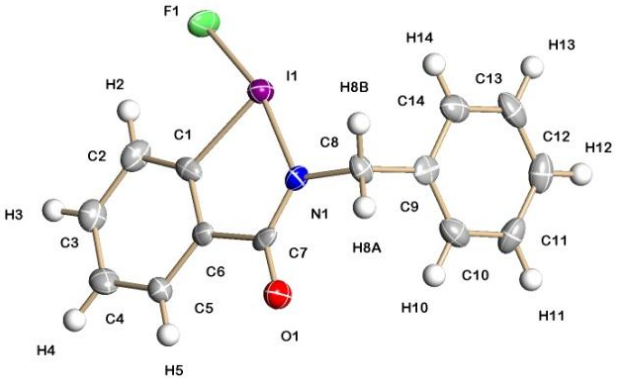
Figure 2.23 ^{19}F NMR spectrum (376 MHz, $CDCl_3$) of **NF-1** (broad ^{1}H-^{19}F coulpling)

When the same synthetic approach for **NF-1** was carried out to prepare two other analogues 2-(4-chlorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-2)** and 2-(4-fluorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-3)** using ***N*-2** and ***N*-3** with 2 equivalents of Selectfluor under the same reaction conditions at room temperature for 18 hours, the yields of **NF-2** and **NF-3** as a single crystal were 60%. These compounds were similarly characterized by NMR spectroscopy.

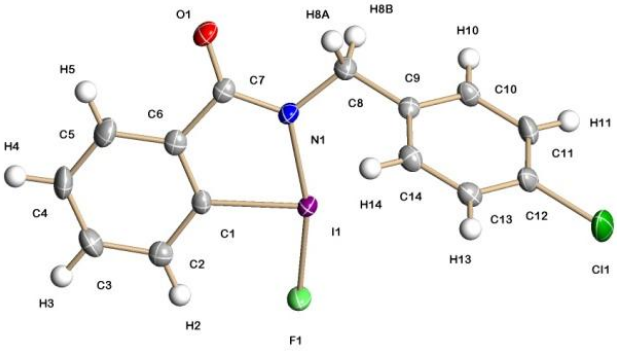
2.4.5 Comparison of the single-crystal structures of various F-I(III) compounds

X-Ray crystallography is the most important method to verify the structure of the three new F-I(III) compounds **NF-1**, **NF-2** and **NF-3 (Figure 2.24)**. Significantly, the structures of **NF-1**, **NF-2** and **NF-3** clearly show distorted T-shaped geometries around iodine, which is typical for five-membered ring hypervalent iodine(III) compounds. In a comparison of the C(7)=O(1), N(1)-C(7) and N(1)-C(8) bond lengths in **NF-1** and ***N*-1**, it can be observed that the C(7)=O(1) bond length 1.233(4) Å in ***N*-1** is unchanged after the formation of **NF-1**, but the N(1)-C(7) distance decreased from 1.333(5) Å to 1.303(9) Å, which is opposite to that seen when ***N*-1** is oxidised to **NC-1**; the N(1)-C(8) bond length increased from 1.455(4) Å to 1.477(9) Å between ***N*-1** and **NF-1**. Furthermore, in **NF-1**, the summation of bond angles C(7)-N(1)-C(8) (122.6(3) °), C(7)-N(1)-I(1) (119.2(5) °) and C(8)-N(1)-I(1) (118.0(5) °) is 360 ° which significantly shows

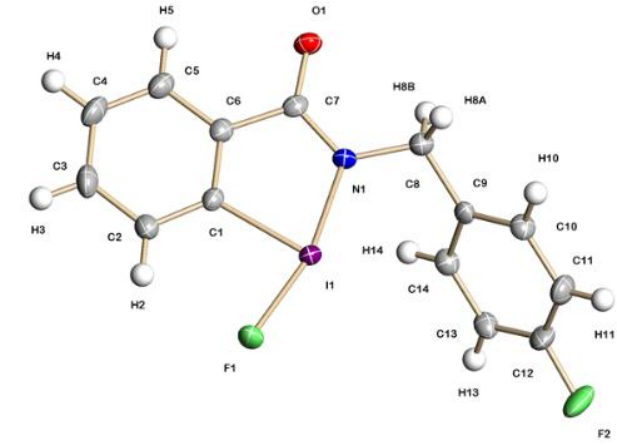
that N is planar, sp^2 hybridised, and that the lone pair of electrons on nitrogen are delocalized by π-interactions in these species.



NF-1



NF-2



NF-3

Figure 2.24 Single crystal structures of **NF-1**, **NF-2** and **NF-3**

In the single crystal structure of **NF-1**, **Figure 2.25** shows the packing diagram.

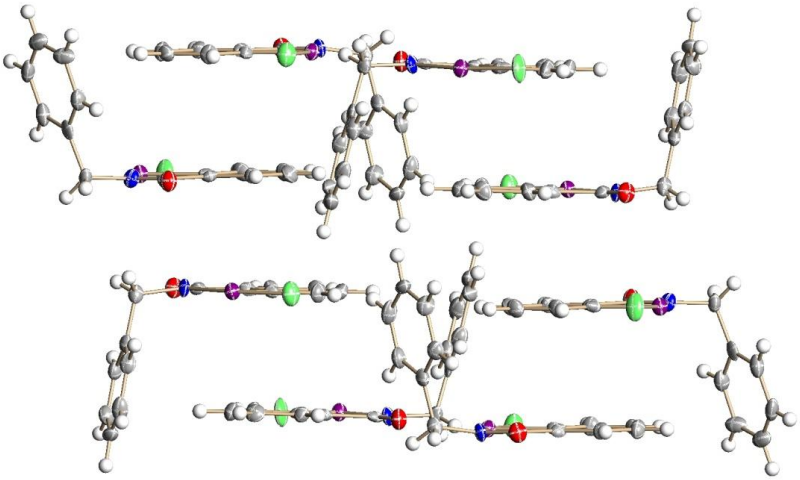


Figure 2.25 Unit cell of **NF-1** including two unique molecules

In a comparison between the single crystal X-ray structures of the *N*-functionalised F-I(III) compounds fluorobenzoiodazolones **NF-1**, **NF-2** and **NF-3** with that for the *O*-functionalised F-I(III) compound **OF-1**, it can be seen that the F-I bond lengths are either around 2.043 Å or 2.079 Å **(Table 2.11)**; the presence of a F or Cl atom in the *para* position of the benzyl ring of **NF-2** and **NF-3**, results in an increase in the F-I bond length. Lengthening of the F-I bond may result in increased reactivity. Meanwhile, the I-N and I-C(1) bond lengths are crystallographically the same, and comparable to those distances in the related chlorobenzoiodazolones **NC-1**, **NC-2** and **NC-3** indicating that the halide does not impact significantly on the structural characteristics of these iodine(III) species.

In **Table 2.12** pertaining to bond angles, there are only minor differences between F-I-O and F-I-N, C(1)-I-O and C(1)-I-N, and C(1)-I-F bond angles for **NF-1**, **NF-2**, **NF-3** and **OF-1**. The F-I-O angle of **OF-1** is 166.4 ° and the F-I-N angle for **NF-1**, **NF-2** and **NF-3** are 165.3, 165.3 and 165.2 ° respectively. All of them are obviously smaller than 180 °, which is mainly due to the repulsion of the two lone pairs of electrons at iodine. The N-I-C(1)-C(6) torsion angle is -0.9 ° in **NF-1**, 3.9 ° in **NF-2** and -4.2 ° in compound **NF-3** which indicates almost perfect co-planarity with the adjacent phenyl ring (**Table 2.13**) as seen for the analogous chlorobenzoiodazolones **(Table 2.9)**.

F-I(III) compounds	I-N	I-O	I-C(1)	I-F
NF-1	2.114(6)		2.093(7)	2.043(4)
NF-2	2.103(2)		2.0827(17)	2.079(3)
NF-3	2.103(3)		2.083(3)	2.0786(19)
OF-1 [31]		2.022(3)	2.085(4)	2.045(3)

Table 2.11 Bond Lengths [Å] of various F-I (III) compounds

F-I(III) compounds	N-I-F	C(1)-I-N	C(1)-I-F	O-I-F	C(1)-I-O
NF-1	165.3(2)	78.9(3)	86.7(3)		
NF-2	165.33(2)	78.96(11)	86.37(10)		
NF-3	165.18(9)	79.05(12)	86.13(11)		
OF-1 [31]			86.21(16)	166.40(12)	80.58(16)

Table 2.12 Bond Angles [°] of various F-I(III) compounds

F-I(III) compounds	N-I-C(1)-C(6)	F-I-C(1)-C(2)	O-I-C(1)-C(6)
NF-1	-0.9(5)	3.0(7)	
NF-2	3.9(2)	3.7(3)	
NF-3	-4.2(2)	-3.2(3)	
OF-1 [31]		-8.8(4)	-11.4(3)

Table 2.13 Torsion Angles [°] of various F-I(III) reagents

2.4.6 Mechanism of formation of fluorobenzoiodazolones

The mechanism for the formation of **NF-1** is shown in **Figure 2.26**. Selectfluor acts as a strong oxidant, making **NF-1** from ***N*-1**. Firstly, iodine is oxidized by Selectfluor. Secondly, the lone pair of electrons on nitrogen nucleophilically attacks the resulting positive charge on iodine. The base generated from Selectfluor then abstracts the proton to leave **NF-1**. In this process, hydrogen replaces the fluorine atom of Selectfluor to form the BF_4^- salt as a by-product.

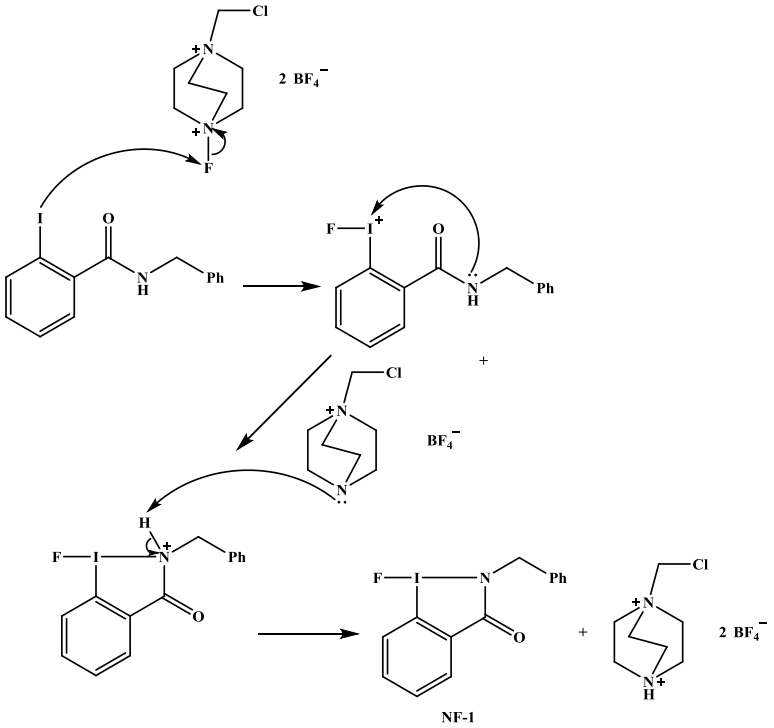


Figure 2.26 Proposed mechanism for the formation of **NF-1**

2.5 Conclusions

Bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) **(NI-1)** and its three analogues I(3,5-dimethylpyridine)$_2BF_4$ **(NI-2)**, I(2-methoxypyridine)$_2BF_4$ **(NI-3)** and I(2,4,6-trimethylpyridine)$_2BF_4$ **(NI-4)** were successfully synthesized by reactions of I_2 with pyridine derivatives in the presence of silica gel supported $AgBF_4$. CH_3CN is a better solvent than CH_2Cl_2 for the preparation of **NI-2**, **NI-3** and **NI-4**. Their exact structures as single crystals were verified and studied by X-ray crystallography. When the reaction was attempted with deactivated pyridine ligands, the corresponding iodonium salts were not formed.

Three *para*-substituted *N*-benzyl-2-iodobenzamide compounds *N*-benzyl-2-iodobenzamide (***N*-1**), *N*-(4-chlorobenzyl)-2-iodobenzamide (***N*-2**) and *N*-(4-fluorobenzyl)-2-iodobenzamide (***N*-3**) were successfully prepared under mild conditions. ***N*-1** and ***N*-3** could be gained as single crystals and their structures were confirmed by X-ray diffraction.

Three new *N*-functionalised Cl-I(III) chlorobenzoiodazolone compounds 2-benzyl-1-chloro-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one (**NC-1**), 1-chloro-2-(4-chlorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-2)** and 1-chloro-2-(4-fluorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-3)** were successfully synthesized and gained in high yields by reactions of ***N*-1**, ***N*-2** and ***N*-3** with TClCA in CH_3CN at 75 ℃ for 18 hours. Their exact structures as single crystals were also determined by X-ray crystallography, and they all have a distorted T-shaped geometry around the iodine centre.

Three N containing heterocycle compounds 2-(2-iodophenyl)pyridine **(*N*-4)**, 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole **(*N*-5)** and 2-(2-iodophenyl)-4,5-diphenyl-1*H*-imidazole **(*N*-6)** did not react with TClCA to form the corresponding cationic *N*-functionalised Cl-I(III) compounds.

Three new *N*-functionalised F-I(III) fluorobenzoiodazolone compounds 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)**, 2-(4-chlorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-2)** and 2-(4-fluorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-3)** were successfully synthesized in around 60% yields by the reactions of ***N*-1**, ***N*-2** and ***N*-3** with Selectfluor in dry CH_3CN at room temperature for 18 hours. Their exact structures as single crystals were verified by X-ray diffraction, and they all have a distorted T-shaped geometry around the iodine centre.

2.6 References

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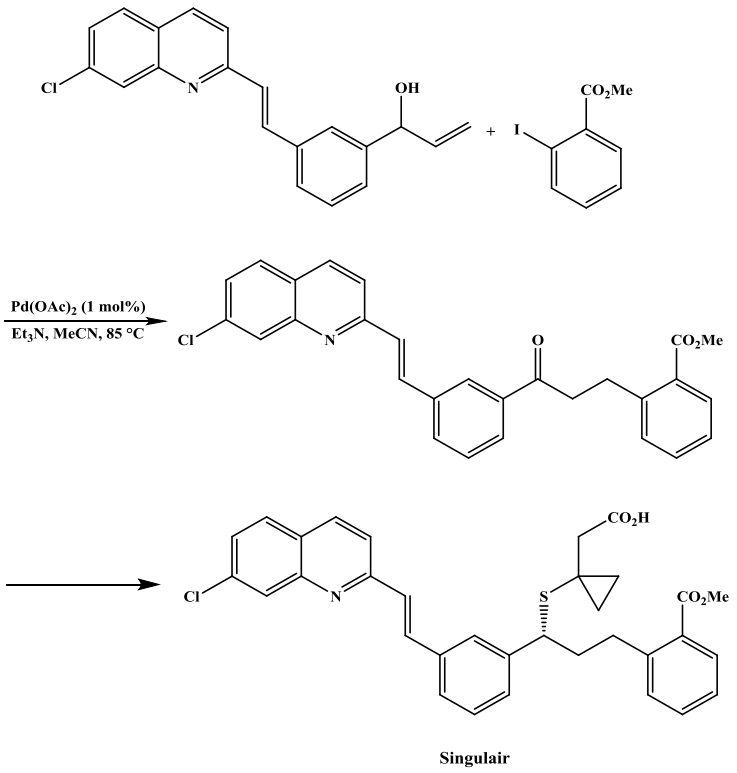
Chapter 3 Applications of Iodonium(I) Salts

3.1 Introduction

In the previous chapter the synthesis of four iodonium(I) salts, including Barluenga's reagent IPy_2BF_4 **(NI-1)** and its three derivatives: I(3,5-dimethylpyridine)$_2BF_4$ **(NI-2)**, I(2-methoxypyridine)$_2BF_4$ **(NI-3)** and I(2,4,6-trimethylpyridine)$_2BF_4$ **(NI-4)** was described. In the present chapter their applications and reactivity in different organic reactions are discussed.

One of the most essential roles of iodine-containing aromatic compounds is to act as intermediates or precursors in organic synthesis, owing to the easy formation and cleavage of the C-I bond. They are widely used in various coupling reactions with palladium catalysts, which can be subsequently functionalised to build new C-C and C-heteroatom bonds.[1-3] For example, in **Scheme 3.1**, the use of methyl *o*-iodobenzoate in the commercial synthesis of Singulair, a medication used in the maintenance treatment of asthma, is shown.[2]



Scheme 3.1 The use of an intermolecular Heck reaction in the commercial synthesis of Singulair

Iodine-containing aromatic compounds are considered to be very powerful tools in the fields of pharmaceuticals, medical imaging and therapy. For example, Iohexol is an

X-ray contrast agent, and thiiodothyronine (T_3) and thyroxine (T_4) are two hormones that increase the basal metabolic rate, affect protein synthesis and help regulate long bone growth **(Figure 3.1)**.[4] Additionally, radioactively labelled iodinated aromatic compounds have been widely used in highly sophisticated single-photon emission computed tomography (SPECT) instruments due to the high stability of aromatic C-I bonds and long half-life of ^{123}I (13.2 h).[5] For example, *m*-tyrosine **(Scheme 3.2)** can be developed into a feasible ^{123}I radiolabelling route by adding the oxidant chloramine-T (ChT) to create an electrophilic reaction.[5]

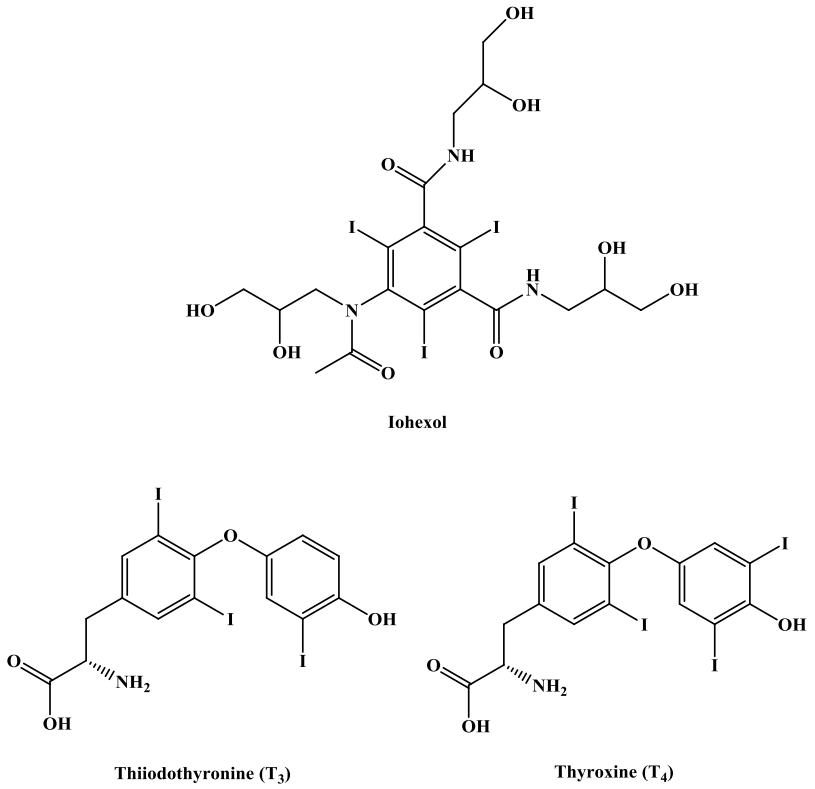
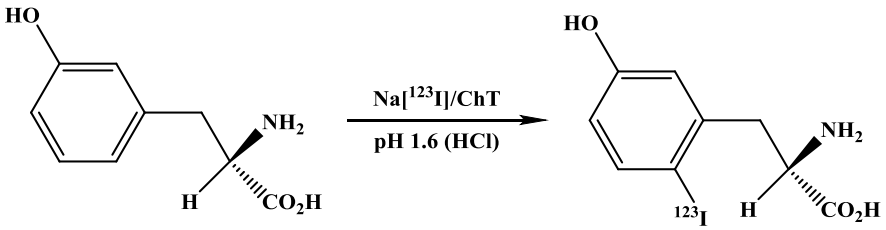


Figure 3.1 Molecular structure of Iohexol, T_3 and T_4



Scheme 3.2 Direct radioiodination of meta-tyrosine

Furthermore, iodinated aromatic compounds are significant starting materials to prepare hypervalent iodine (III) and (V) compounds that possess great value in modern organic synthesis, as described in Chapters 1 and 2.

Due to the increasing importance of iodoaromatics in various chemical applications, the development of synthetic pathways for their preparation has garnered much interest. However, the low electrophilic and reactive characteristic of elemental iodine makes its direct use difficult. To solve this problem, iodination is always performed under oxidative conditions with a strong acid. In the most well-known case, the industrial production of iodobenzene, the simplest iodinated aromatic compound, is carried out by the reaction of benzene with I_2 under reflux in the presence of concentrated nitric acid. The transformation of benzene using I_2 and sodium percarbonate (SPC) [6] or diiodine pentoxide (I_2O_5) [7] while heating under anhydrous and strong acidic conditions such as AcOH-Ac_2O-H_2SO_4 and AcOH-H_2SO_4 systems can also produce good yields of iodobenzene. However, it should be noted that in these processes, some undesirable side reactions occur. Other reaction systems such as I_2/XeF_2,[8] I_2/$Hg(NO_3)_2$ [9] and I_2/AgOTf [10] are available for the preparation of iodobenzene under mild conditions without heating and strong acidic conditions, but their biggest disadvantages are their high expense and toxicity. In the laboratory, iodobenzene and its derivatives can be prepared from aniline, using the Sandmeyer reaction to diazotize the amine functional group with hydrochloric acid and sodium nitrite and then adding potassium iodide to get the product with the release of N_2 gas.

Considering that the iodide ion, with poor nucleophilicity, is an inconvenient agent to introduce an iodine atom into organic molecules and the weak electrophilic characteristic of elemental iodine, the modification of electrophilic iodination, including iodinating reagents, is recognised as the best approach to prepare iodinated aromatic compounds. Among them, direct and regioselective iodination of benzene, naphthalene and other aromatic compounds with electron-donating groups can be conducted well in the presence of $Fe(NO_3)_3 \cdot 9H_2O$-SiO_2 (Silfen, silica gel supported ferric nitrate nonahydrate)/I_2 [11] and active-charcoal-supported $Fe(NO_3)_3 \cdot 1.5N_2O_4$/$I_2$ or $Fe(NO_3)_3 \cdot 1.5N_2O_4$/KI [12] system, at room temperature. Systems such as KI/KIO_3/HCl in MeOH,[13] KI/$NaIO_4$/NaCl in aqueous AcOH,[14] I_2/1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) in MeCN [15] or H_2O,[16] I_2/O_2 with $H_5PV_2Mo_{10}O_{40}$ as a catalyst,[17] I_2/air with $Bi(NO_3)_3$ as a catalyst,[18] I_2/30% H_2O_2 [19] can be very effective for the iodination of phenol, anisole, aniline and their

derivatives, which are important building blocks in bioactive organic molecules. In 2005, Ellervik and co-workers presented ICl/In(OTf)$_3$ as a new reagent combination for mild iodination, suitable for acid-sensitive substrates such as carbohydrates.[20] In 2009, NaI/H_2O_2 (35%) with $CeCl_3 \cdot 7H_2O$, a new environmentally catalytic method effective for the monoiodination of arenes under reflux conditions, was described by Firouzabadi and co-workers.[21] In the reactions, $CeCl_3 \cdot 7H_2O$ is not only a Lewis acid but also an electron-transfer catalyst process **(Figure 3.2)**.

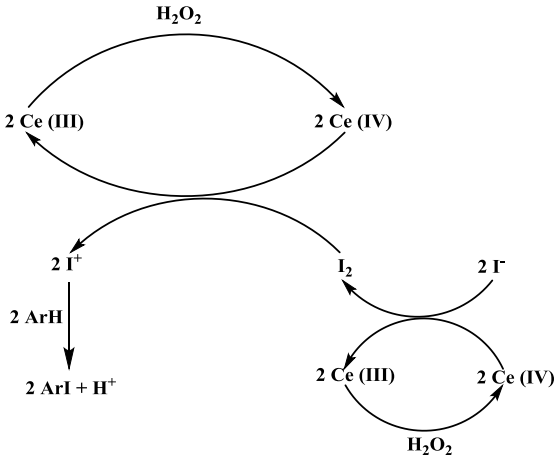


Figure 3.2 Mechanism *via* an electron-transfer process for iodination of aromatic compounds

In 2013, Iskra and co-workers reported that hydrochloric acid can activate the oxidative iodination of electron-rich aromatic compounds with the I_2/H_2O_2 system through the formation of an iodine (I) compound with dichloroiodic (I) acid ($HICl_2$) as the iodinating reagent.[22] The mechanism for this process is demonstrated in **Figure 3.3**.

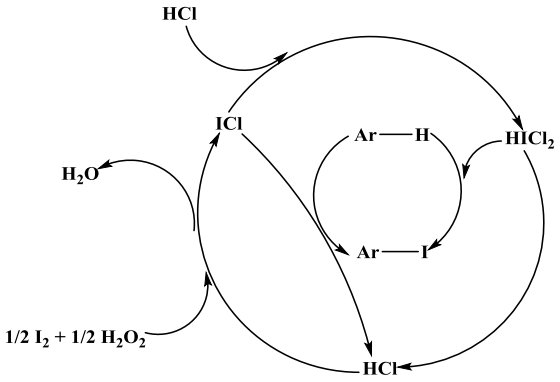


Figure 3.3 Iodination of arenes with *in situ* generated $HICl_2$

Compared to that of activated aromatic compounds, the direct iodination of deactivated aromatic compounds with strongly electron-withdrawing substituents such as NO_2, CF_3, COR and SO_2R is a difficult task. However, some methods, using I_2/SPC in AcOH-Ac_2O-H_2SO_4,[7] I_2/10% F_2 in N_2 with concentrated H_2SO_4,[23] I_2/$NaIO_3$ with concentrated H_2SO_4 [24] and *N*-iodosuccinimide (NIS)/BF_3-H_2O,[25] serve as good alternatives to the classical indirect approach using the Sandmeyer reaction.[26] Bis(pyridinium)iodonium(I) tetrafluoroborate (IPy_2BF_4), also termed as Barluenga's reagent, is a stable and commercially available solid. It can be activated by adding HBF_4 or CF_3SO_3H to generate iodonium ions **(Scheme 3.3)**, which serve as strong electrophilic sources, and can be used to prepare monoiodo derivatives of aromatic compounds with excellent regioselectivity and yields.[27-28] Compared to other methods, the iodination of aromatic compounds using IPy_2BF_4 with HBF_4 or CF_3SO_3H can be easier to handle and operate using normal laboratory glassware under mild conditions, as the intermediate iodonium ion has high reactivity.

$$\mathbf{IPy_2BF_4 \xrightarrow{HBF_4 \,.\, Et_2O} I^+BF_4^- + PyH^+BF_4^- + Py}$$

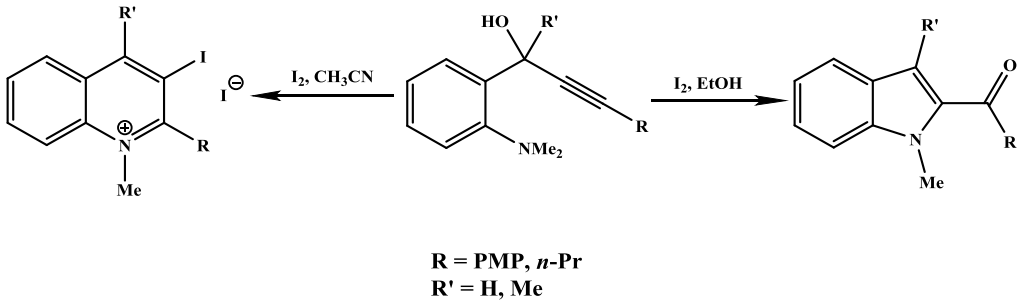
Scheme 3.3 IPy_2BF_4 activated by HBF_4 to produce I^+

In the present chapter, we will first compare the reactivity of IPy_2BF_4 **(NI-1)** and its three derivatives **NI-2**, **NI-3** and **NI-4** in the presence of HBF_4 in the iodination of 1,3,5-trimethylbenzene, chlorobenzene and 1,4-dibromobenzene. The reaction procedures are based on those in the literature.[27]

Furthermore, the electrophilic iodocyclization of alkenes and alkynes acts as a powerful tool to produce heterocyclic compounds, which are highly significant in several natural and synthetic products with a wide range of biological activities.[29-30]

In the past, the iodocyclization of carbonyl groups onto alkynes using IPy_2BF_4 was reported by Barluenga's group.[31] Okitsu et al. presented the synthesis of 2, 5-dihydroisoxazoles and isoxazoles through the iodocyclization of *N*-alkoxycarbonyl *O*-propargylic hydroxylamines using bis(2,4,6-collidine)iodonium(I) hexafluorophosphate [$I(coll)_2PF_6$] and NIS/BF_3·Et_2O, respectively, in 2011.[32] In 2014, they presented the iodocyclization of ethoxyethyl ethers into amides using $I(coll)_2PF_6$.[33] Flynn's group once reported I_2 in CH_3CN or EtOH for highly selective 5-exo- and 6-endo-diagonal

iodocyclization protocols that can provide direct access to various indoles and quinolones **(Scheme 3.4)**, as well as their application to the synthesis of analogues of potent heterocyclic tubulin polymerization inhibitors.[34]



Scheme 3.4 Synthesis of various indoles and quinolones via iodocyclization

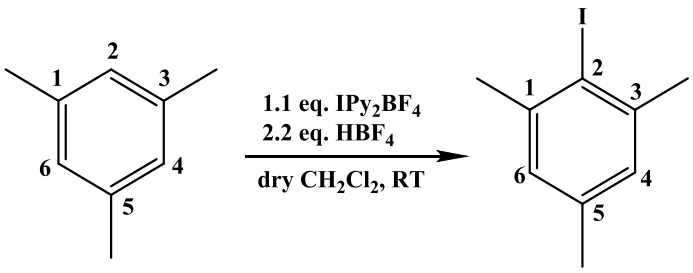
In 2005, Larock's group synthesised a series of isoindolin-1-ones through the iodocyclization of *O*-(1-alkynyl)benzamides using $I_2/NaHCO_3$ or ICl that was successfully applied to the synthesis of a biologically active alkaloid and cepharanone B.[35] In 2012, they reported a novel approach to 3-iodothiophenes through the direct iodocyclization of alkynylthiol derivatives using $I_2/NaHCO_3$ at room temperature in CH_3CN.[36] In 2017, Verma's group presented an iodocyclization strategy to construct iodo-benzo[a]phenazines using $I_2/NaHCO_3$.[37]

Based on the above, we will also study the iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol using **NI-1**, **NI-2**, **NI-3** and **NI-4** and compare these reactions with Larock's method.[38]

3.2 Iodination of aromatic compounds

3.2.1 Iodination of 1,3,5-trimethylbenzene using IPy_2BF_4 and its analogues

First, we investigated the reactivity of IPy_2BF_4 **(NI-1)** and its analogues I(3,5-dimethylpyridine)$_2BF_4$ **(NI-2)**, I(2-methoxypyridine)$_2BF_4$ **(NI-3)** and I(2,4,6-trimethylpyridine)$_2BF_4$ **(NI-4)**, in the iodination of activated aromatic compounds. To conduct the iodination reaction using **NI-1**, **NI-2**, **NI-3** and **NI-4**, 1,3,5-trimethylbenzene was chosen as the first substrate **(Scheme 3.5)** because the three methyl groups on the benzene ring make it an electron-rich system and the iodination product obtained can be easily analysed by NMR spectroscopy.

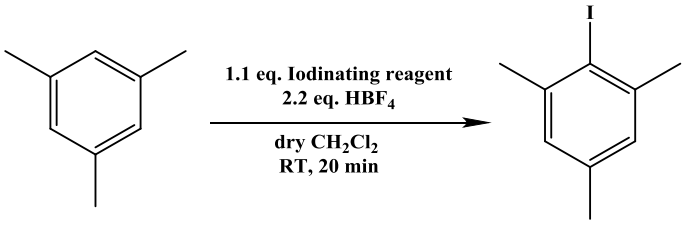


Scheme 3.5 Iodination of 1,3,5-trimethylbenzene using IPy_2BF_4

During the reaction, the mixture changed from colourless to purplish after HBF_4 (54% Et_2O solution) was added into the flask because I_2 came out as a by-product. It could be removed using a saturated $Na_2S_2O_3$ aqueous solution. In accordance with the results in the literature,[27] it was a very quick reaction. The ^1H NMR (400 MHz, $CDCl_3$) spectrum of the crude product after removing the solvent in the last step when using **NI-1** at room temperature for 20 minutes indicated 100% conversion of the substrate to monoiodinated product because of the removal of two singlet peaks represented protons of 1,3,5-trimethylbenzene and the appearance of three singlet peaks represented protons of the pure monoiodinated product 2-iodo-1,3,5-trimethylbenzene as yellow prism crystals was obtained directly. In the ^1H NMR (400 MHz, $CDCl_3$) spectrum of 1,3,5-trimethylbenzene, there are two different resonances at 6.80 ppm and 2.27 ppm. In that of 2-iodo-1,3,5-trimethylbenzene, there are three different resonances. A singlet peak at 6.89 ppm represented two protons (positions **4** and **6**), a singlet peak at 2.44 ppm represented the protons of two methyl groups at positions **1** and **3** and a singlet peak at 2.22 ppm represented the protons of the methyl group at position **5**. In the ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 1,3,5-trimethylbenzene, there are three different resonances at 137.7 ppm (representing carbons at positions **1**, **3** and **5**), at 126.9 ppm (representing carbons at positions **2**, **4** and **6**) and at 21.2 ppm (representing three methyl groups). For the product, 2-iodo-1,3,5-trimethylbenzene, there are six resonances: 141.8 ppm (carbons **1** and **3**), 137.3 ppm (carbons **5**), 128.0 ppm (carbons **4** and **6**), 95.6 (C-I), 29.5 ppm (methyl groups at **1** and **3**) and at 20.6 ppm (methyl group at position **5**). The yield of pure 2-iodo-1,3,5-trimethylbenzene was 91% using **NI-1**.

When the reaction was performed using **NI-2**, **NI-3** and **NI-4** as the iodine source, the conversion of the substrate was 100% for all of them. However, the removal by rotary evaporation of the pyridine by-products 3,5-dimethylpyridine, 2-methoxypyridine and 2,4,6-trimethylpyridine was more difficult than that of pyridine.

The pure target product can also be obtained through recrystallization or column chromatography on silica gel using hexane/ethyl acetate (V:V = 20:1), but in these processes, a small amount of the product was lost. Thus, the final yields were 87%, 78% and 81% respectively **(Table 3.1)**. These results indicate that the four reagents all had similar reactivities, but that product purification was more straightforward with **NI-1**.



Entry	Iodinating Reagent	Conversion of 1,3,5-trimethylbenzene (%) [a]	Yield of 2-iodo-1,3,5-trimethylbenzene (%)
1	**NI-1**	100	91
2	**NI-2**	100	87
3	**NI-3**	100	78
4	**NI-4**	100	81

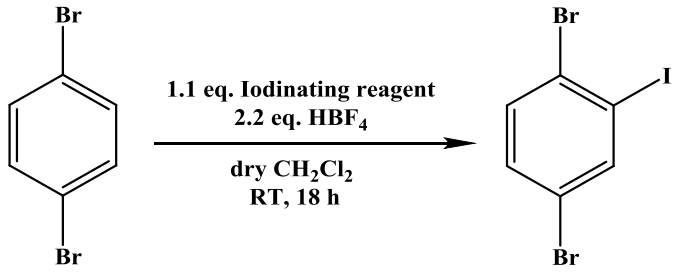
Table 3.1 Iodination of 1,3,5-trimethylbenzene using **NI-1**, **NI-2**, **NI-3** and **NI-4**
a Measured by ^{1}H NMR

3.2.2 Attempted iodination of 1,4-dibromobenzene

Based on the results of the iodination of 1,3,5-trimethylbenzene using **NI-1**, **NI-2**, **NI-3** and **NI-4**, their reactivity in the iodination of deactivated aromatic compounds was also investigated and the electron-poor, 1,4-dibromobenzene was chosen as the substrate. The reaction was performed under the same conditions as those for the iodination of 1,3,5-trimethylbenzene. It should be easy to detect whether the iodination reaction was successful by analysing the ^{1}H NMR spectrum of the reaction product, as there is only one singlet peak for 1,4-dibromobenzene.

However, the ^{1}H NMR (400 MHz, $CDCl_3$) spectra of the crude products after the reactions showed merely a mixture of unreacted starting materials with no sign of iodination. A series of reaction conditions were investigated **(Table 2.2)**, but no

evidence for iodination was observed. Consequently, using IPy_2BF_4 and its analogues for the iodination of 1,4-dibromobenzene was challenging.



Entry	Iodinating Reagent	T (℃)	Time (h)	Conversion of 1,4-dibromobenzene
1	**NI-1**	RT	0.3	0
2	**NI-1**	RT	1	0
3	**NI-1**	RT	18	0
4	**NI-1**	40	1	0
5	**NI-2**	RT	18	0
6	**NI-3**	RT	18	0
7	**NI-4**	RT	18	0

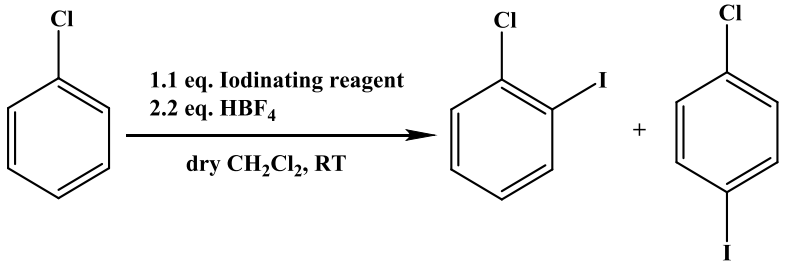
Table 3.2 Results of the attempted iodination of 1,4-dibromobenzene using **NI-1**, **NI-2**, **NI-3,** and **NI-4**

3.2.3 Iodination of chlorobenzene

The iodination of chlorobenzene as a mid-range deactivated aromatic compound using IPy_2BF_4 and its analogues was also studied.

Since the anticipated mixture of *o*- and *p*- products are very difficult to seperate, only the conversion of chlorobenzene to iodinated products was calculated by the integration of resonance at 7.40-7.29 ppm (representing five protons of chlorobenzen), 7.93 ppm (representing one proton of *o*-chloroiodobenzene) and 7.70 ppm (representing two protons of *p*-chloroiodobenzene) in ^{1}H NMR spectroscopy. In **Table 3.3**, from the low conversion of chlorobenzene, it can be concluded that the iodination of chlorobenzene was not easy to perform; *p*-chloroiodobenzene was obtained as the main product. In this

reaction, **NI-3** showed the highest conversion and no iodination was observed when **NI-4** was used as the iodine source, possibly due to steric issues with the *ortho*-methyl groups. When these results are compared to the iodination of chlorobenzene using IPy_2BF_4 with CF_3SO_3H (78%),[27] it can be concluded that this reaction was challenging with HBF_4.



Entry	Iodinating Reagent	Time (h)	Ortho isomer (%)	Para isomer (%)	Conversion of chlorobenzene (%)
1	**NI-1**	1	4	32	36
2	**NI-1**	18	7	30	37
3	**NI-2**	1	3	21	24
4	**NI-2**	18	3	22	25
5	**NI-3**	1	6	44	50
6	**NI-3**	18	6	44	50
7	**NI-4**	1	0	0	0
8	**NI-4**	18	0	0	0

Table 3.3 Results of the iodination of chlorobenzene using **NI-1**, **NI-2**, **NI-3** and **NI-4**

3.2.4 Mechanism for the iodination of aromatic compounds using IPy_2BF_4 and its analogues

Based on the literature [27] and the results above, the proposed mechanism for the iodination of 1,3,5-trimethylbenzene using **NI-1** is shown in **Figure 3.4**. This is an electrophilic substitution reaction. In the first step, IPy_2BF_4 was activated by HBF_4 to form iodonium tetrafluoroborate as an active electrophile. Then the iodonium ion was attacked by 1,3,5-trimethylbenzene to generate a positively charged benzonium

intermediate. The three methyl groups provide an electron-donating system to stabilise the cationic intermediate. Finally, hydrogen on the benzene ring was lost.

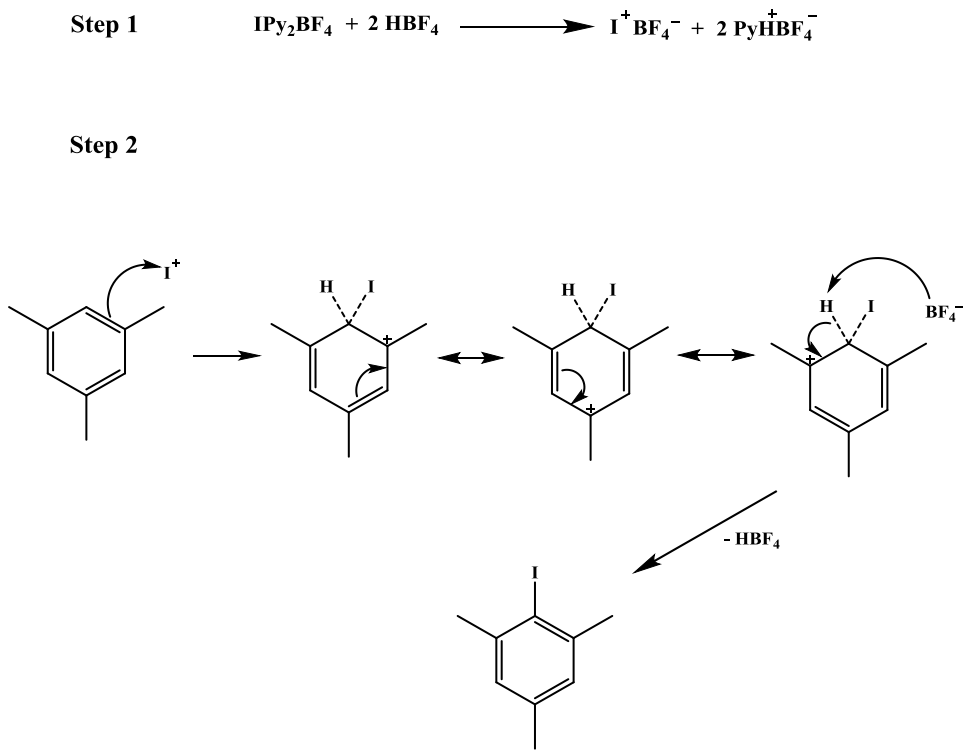


Figure 3.4 The proposed mechanism for the iodination of 1,3,5-trimethylbenzene using IPy_2BF_4 **(NI-1)**

In contrast, in the iodination of 1,4-dibromobenzene using **NI-1**, the two electron-withdrawing bromine groups reduce the nucleophilicity of the arene inhibiting the reaction. The same reason can explain the difficulty in performing the iodination of chlorobenzene using **NI-1**. However, as CF_3SO_3H is more acidic than HBF_4, it is easier to form the active $I^+CF_3SO_3^-$ that leads to easier iodination of chlorobenzene.[27]

3.3 Iodocyclization of alkynes using IPy_2BF_4 and its analogues

3.3.1 Iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol

Following on from the previous work on the iodination of aromatic compounds using IPy_2BF_4 and its analogues in the presence of HBF_4, we also studied their application in the iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol to obtain dihydroisobenzofuran, an important heterocyclic compound. We then compared this method with the one reported by Larock's group.[38]

The reaction was performed at room temperature for three hours, and the conversion of the starting material reached 100% according to the ^{1}H NMR spectrum of the crude product, as the singlet peak at 3.23 ppm representing the hydroxyl group in 2-(2-(phenylethynyl)phenyl)propan-2-ol had disappeared. After purification by column chromatography and recrystallization, the target iodocyclization product was obtained as brown-yellow crystals, and X-ray crystallography confirmed that it was obtained as the *Z*-isomer, not the *E*-isomer. The single-crystal structure of the final iodocyclization product (*Z*)-1,1-dimethyl-3-iodophenylmethylene-1,3-dihydroisobenzofuran **(IC-1)** is shown in **Figure 3.5**.

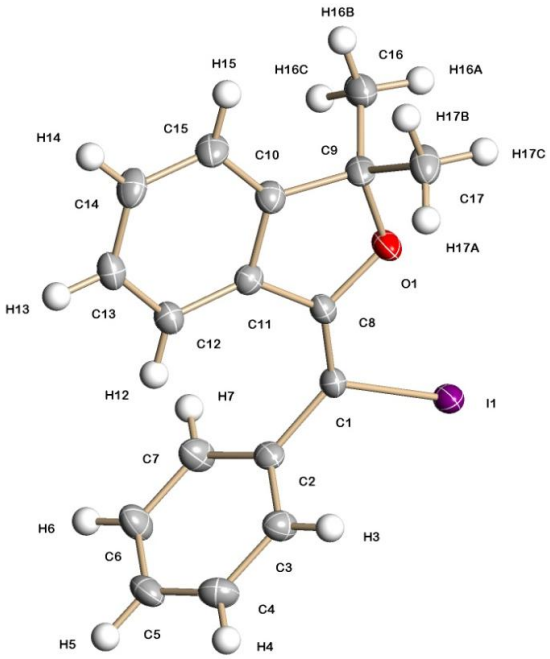
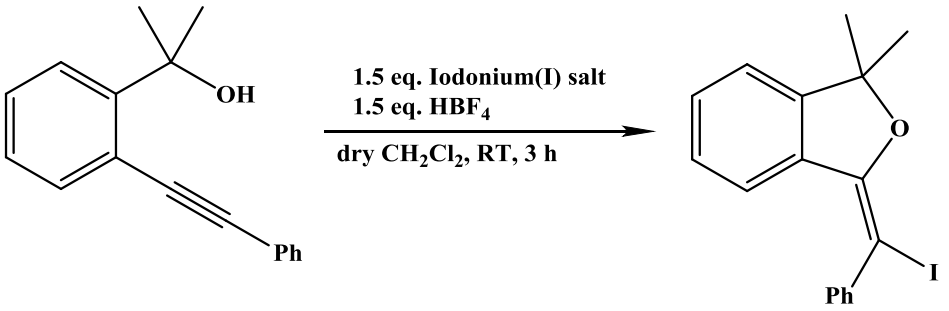


Figure 3.5 X-ray structural assignment of (*Z*)-1,1-dimethyl-3-iodophenylmethylene-1,3-dihydroisobenzofuran **(IC-1)**

The results using different iodine sources **NI-1**, **NI-2**, **NI-3**, and **NI-4** are shown in **Table 3.4**. Although the conversion of the starting material reached nearly 100% after three hours for all the reagents, the final yields of the target product were lower because some were lost in the purification processes through column chromatography and recrystallization.



Entry	Iodine Source	Conversion of 2-(2-(phenylethynyl)phenyl)propan-2-ol (%)	Yield of iodocyclization product (%)
1	**NI-1**	100	62
2	**NI-2**	100	58
3	**NI-3**	100	50
4	**NI-4**	100	53

Table 3.4 The iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol using IPy_2BF_4 and its analogues

In comparison to Larock's group's method for the same reaction (using three equivalents of I_2 with $NaHCO_3$ at room temperature for 15 hours) to give a similar yield of the same product,[38] it is easier to conduct the reaction using IPy_2BF_4 and its analogues. However, there are no significant advantages in the use of **NI-2**, **NI-3** and **NI-4** over **NI-1**.

3.3.2 Mechanism for the iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol using IPy_2BF_4 and its analogues

Based on the literature and previous studies, the proposed mechanism is shown in **Figure 3.6**. In the first step, I^+ is produced by the reaction of IPy_2BF_4 and HBF_4. The coordination of I^+ with the alkyne leads to electrophilic activation of the carbon-carbon triple bond, generating a three-membered ring iodonium intermediate; following this, the hydroxyl group attacks it. After electron transfer and isomerisation through the formation of intermediate **B"** followed by stereospecific deprotonation, the stable

product (*Z*)-1,1-dimethyl-3-iodophenylmethylene-1,3-dihydroisobenzofuran **(IC-1)** is formed.

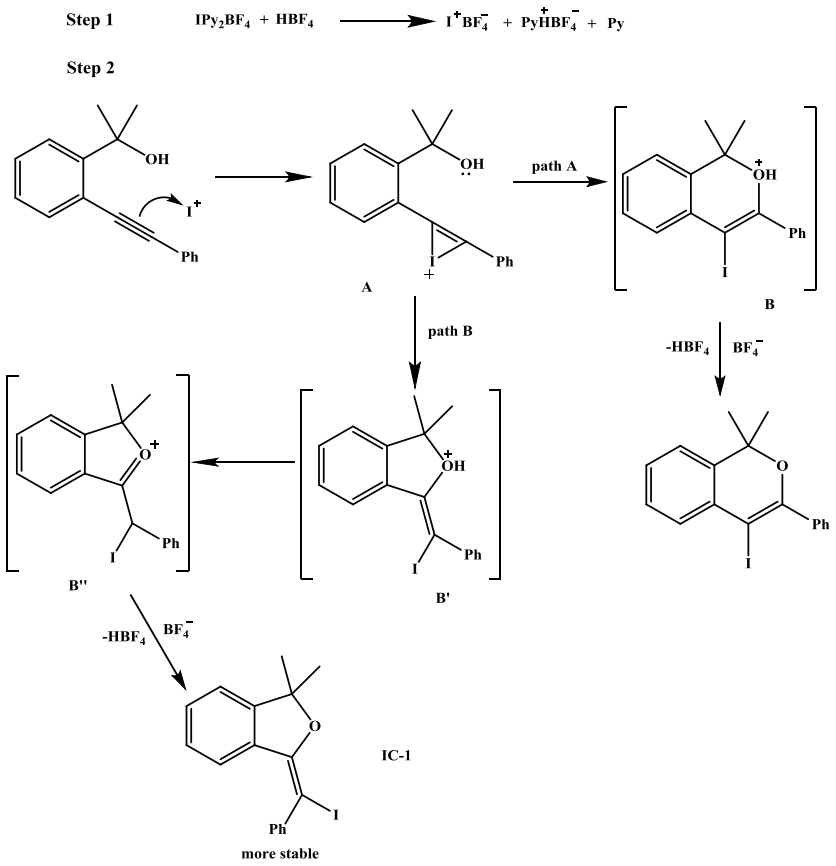


Figure 3.6 Mechanism for the iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol using IPy_2BF_4

3.4 Conclusions

IPy_2BF_4 **(NI-1)** is the best iodinating reagent, when combined with HBF_4, for iodination of 1,3,5-trimethylbenzene among all the analogues studied here. IPy_2BF_4/HBF_4 is an excellent system for the iodination of 1,3,5-trimethylbenzene at room temperature under mild conditions. However, it is unsuitable for the iodination of 1,4-dibromobenzene. Amongst the iodination of chlorobenzene reactions using IPy_2BF_4 and its analogues, in the presence of HBF_4, the reactivity of **NI-3** was the highest and the poorest one was **NI-4**. The main iodination product was *p*-iodochlorobenzene. However, whichever iodinating reagent was used, the conversion of chlorobenzene was very low. Here, HBF_4 is worse than CF_3SO_3H in the activation of IPy_2BF_4 for the iodination of chlorobenzene.

There are virtually no differences in the reactivities of IPy_2BF_4 and its analogues, in the presence of HBF_4, in the iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol. It may be concluded that IPy_2BF_4 is the best one for this reaction because pyridine is the cheapest of the ligands. The product from the iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol was (*Z*)-3-(iodo(phenyl)methylene)-1,1-dimethyl-2,3-dihydro-1*H*-indene **(IC-1)** which formed as brown crystals and has been structurally characterized. The reaction using IPy_2BF_4/HBF_4 was faster than that using $I_2/NaHCO_3$ for the iodocyclization of 2-(2-(phenylethynyl)phenyl)propan-2-ol, which will have potential application in other electrophilic iodocyclization reactions of alkynes to construct heterocyclic compounds.

3.5 References

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Chapter 4 Applications of New Chlorobenzoiodazolones

4.1 Introduction

In this chapter, we present research work on the applications in two model chlorination reaction systems of the new *N*-functionalised Cl-I(III) reagents 2-benzyl-1-chloro-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-1)**, 1-chloro-2-(4-chlorobenzyl)-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-2)** and 1-chloro-2-(4-fluorobenzyl)-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-3)**, which have been successfully synthesised and characterised in Chapter 2.

Chlorine-containing sub-units are a structural motif that can be found in natural products or applied to the synthesis of pharmaceuticals. The inclusion of these sub-units can greatly improve the activity of medicines, and it has been found that nearly 85% of all drugs, such as Plavix (heart disease drug), thiamphenicol (antibiotic), amiloride (high blood pressure drug), and griseofulvin (antifungal medication) **(Figure 4.1)**, contain or are manufactured using chlorine.[1-4] Chlorine-containing compounds also play an important role in material science [5-6] and some other organic syntheses such as cross-coupling chemistry.[7-8]

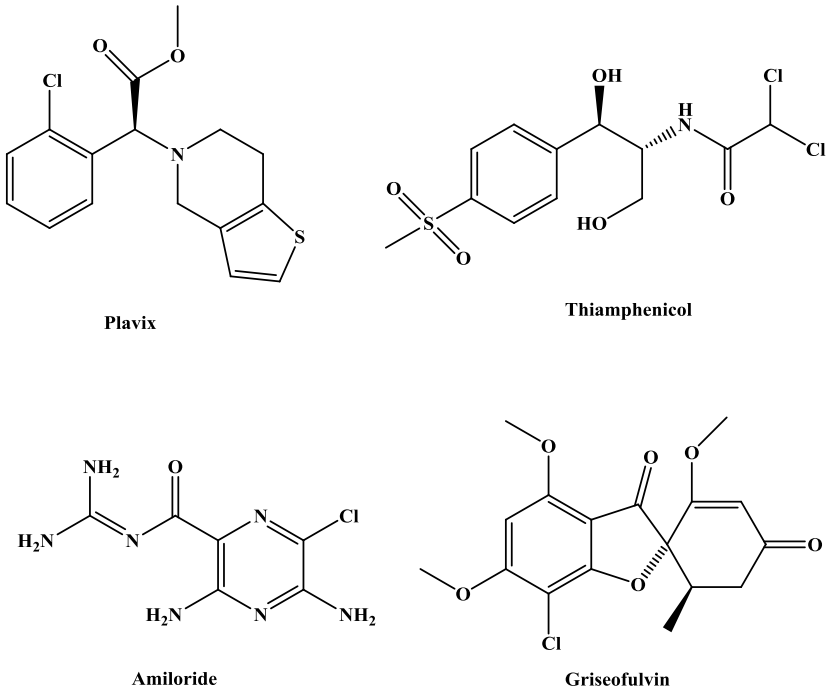


Figure 4.1 Some chlorine-containing medicines

Consequently, economical, convenient, and rapid mild reaction condition protocols for introducing chlorine atoms into organic molecules are a hot topic. In this area, an array of chlorinating reagents have been successfully developed. For instance, over the past

few decades, transition-metal-catalysed C-H activation methods using $HCl/PdCl_2$ [9] and *N*-chlorosuccinimide (NCS)/$Pd(OAc)_2$/PTSA [10-11] have emerged as powerful tools for the synthesis of aromatic chloride compounds, which are an important class of substrates utilized in drug synthesis. These conventional chlorination reagents are inexpensive and mild, but metal catalyst is essential for the reactions, and the scope of the substrates is limited. Some other traditional chlorinating reagents, such as SO_2Cl_2 and Cl_2 with high reactivities, are also widely used, but their safety liabilities and poor regio-selectivities can limit their application.[12-13]

To achieve both high reactivity and regioselectivity, often operating via a radical-based mechanism, *t*-BuOCl serves as a valuable chlorinating reagent, especially in the presence of $Ag(Phen)_2OTf$ as catalyst, and it can be applied in the decarboxylative chlorination of aliphatic carboxylic acids, which is not only efficient and general but also chemoselective [14] **(Figure 4.2** and **Scheme 4.1)**. However, *t*-BuOCl is dangerous to use as it is highly light-sensitive (decomposes with formation of acetone and methyl chloride) and heat-sensitive (release Cl_2).[15] In addition, toxicity, explosiveness, and moisture sensitivity are the main drawbacks of some other chlorinating reagents, such as PhSeCl,[16] $SbCl_5$,[17] and $TiCl_4/CF_3CO_3H$ [18] that limit their practical application.

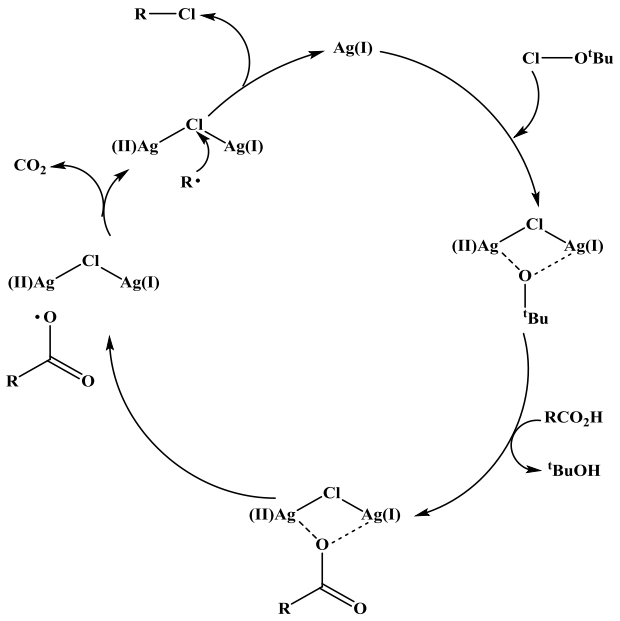
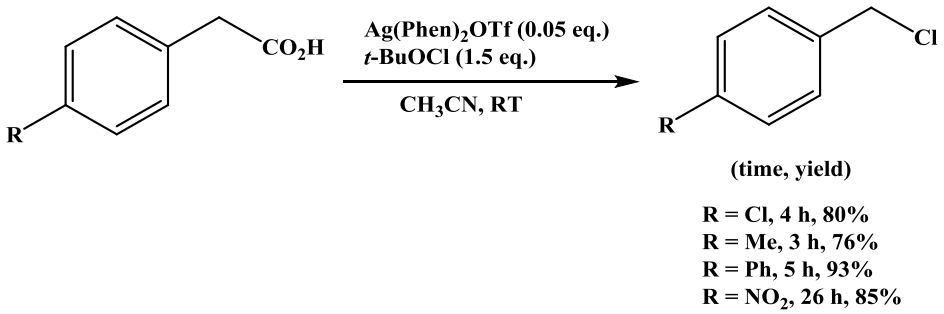
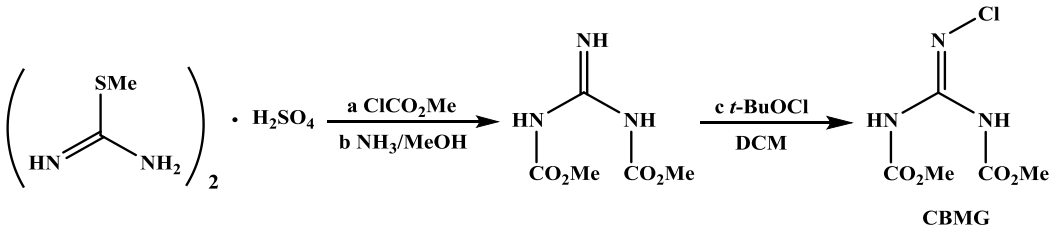


Figure 4.2 Proposed mechanism for Ag(I)-catalysed decarboxylative chlorination of carboxylic acids



Scheme 4.1 Some examples of silver-catalysed decarboxylative chlorination carboxylic acids using *t*-BuOCl

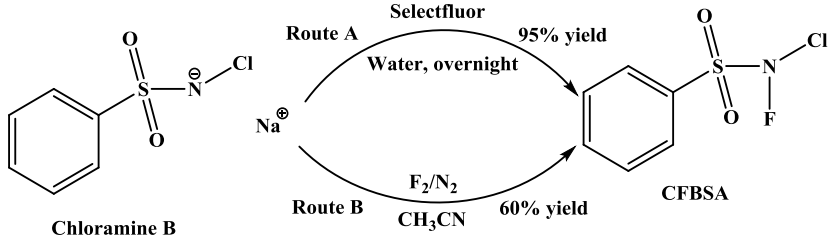
In 2014, Baran [19] and his co-workers reported the invention of a new guanidine-based chlorinating reagent, CBMG, with high reactivity. It is an air stable, free-flowing powder with good thermal stability and no chromatography characters. This direct, mild, operationally simple, and safe chlorinating reagent is excellent for a range of nitrogen-containing heterocycles. However, in its synthesis **(Scheme 4.2)**, $ClCO_2Me$ (heat- and moisture-sensitive reagent that can release phosgene) and *t*-BuOCl (light- and heat-sensitive reagent) have to be used.



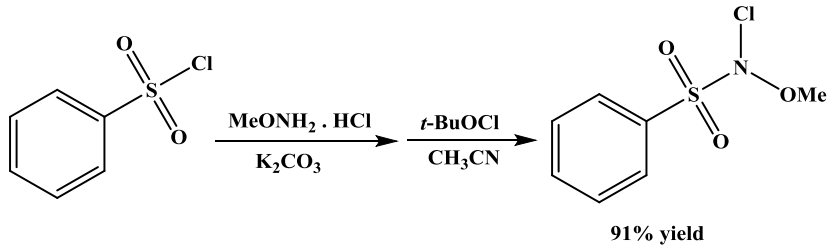
Scheme 4.2 Synthesis of CBMG

Accordingly, the development of easily accessible and recyclable chlorinating reagents is still a significant topic in synthetic chemistry. Among them, the five-membered ring Cl-I(III) compounds present exceptional stability, reactivity and recyclability, together with low toxicity, which strongly attract chemists. In 2016, the practical and efficient chlorination of nitrogen-containing heterocycles, some selected classes of arenes, BODIPY dyes, and pharmaceuticals by the use of 1-chloro-1,2-benziodoxol-3-one **(OC-2)** have been reported by Xue and co-workers.[20] When compared with other classical methods that use iodine (III) reagents such as aryl and alkyl iodine(III) dichlorides,[21] $PhI(OAc)_2$/MeSiCl,[22] and even with two other newer chlorinating reagents *N*-chloro-*N*-fluorobenzenesulfonylamide (CFBSA) and *N*-chloro-

N-methoxybenzenesulfonamide (CMOBSA) **(Schemes 4.3 and 4.4)** developed by Yang and co-workers [23-24] for the same reaction to introduce chlorine into 1,3-dicarbonyl compounds, **OC-2** was found to be more convenient and economical.

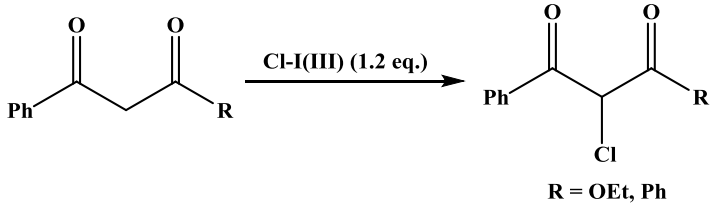


Scheme 4.3 Two synthetic ways to prepare CFBSA



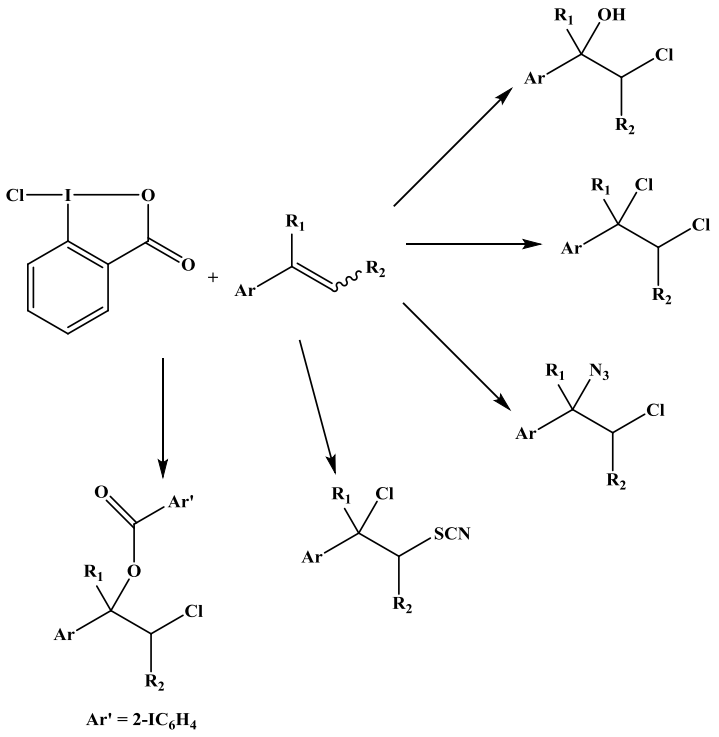
Scheme 4.4 Preparation of CMOBSA

In view of the advantages of the five-membered ring Cl-I(III) compounds above, we are first going to study the application of the three new *N*-functionalised Cl-I(III) reagents **NC-1**, **NC-2**, and **NC-3** (described in Chapter 2) as well as two closely-related *O*-functionalised Cl-I(III) reagents 1-chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole **(OC-1)** and 1-chloro-1,2-benziodoxol-3-one **(OC-2)** in the chlorination of 1,3-dicarbonyl compounds to introduce chlorine onto a C(sp^3) centre **(Scheme 4.5)**, which are useful building blocks or intermediates in organic synthesis.[25-26] Ethyl benzoylacetate and 1,3-diphenylpropane-1,3-dione will be used as substrates for this study, and variations in the reaction solvent, temperature, and time will be taken into consideration.



Scheme 4.5 Chlorination of ethyl benzoylacetate and 1,3-diphenylpropane-1,3-dione

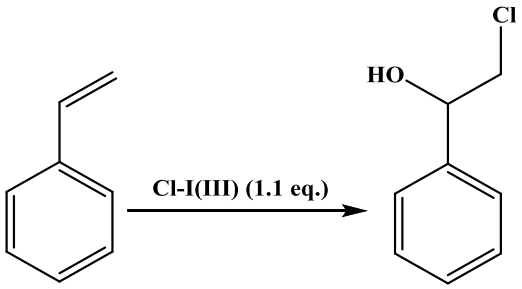
The second area of study is the difunctionalisation of alkenes using five-membered ring Cl-I(III) compounds. This is an important area for research since the difunctionalisation of alkenes and unsaturated compounds gives a powerful method to generate two new σ bonds and two stereogenic centres in one step. Consequently, the halofunctionalisation of alkenes is a useful tool for various organic transformations and to build up complex multifunctional alkane derivatives.[27-31] In 2016, Egami's group examined the oxychlorination, dichlorination, azidochlorination, chlorothiocyanation, and iodoesterfication of several styrene derivatives using **OC-2 (Scheme 4.6)**.[32] The mild conditions for these reactions enabled convenient site-selective difunctionalisations of substrates with two alkene moieties and have provided a new guide to the chlorofunctionalisation of alkenes using chlorine-containing hypervalent iodine reagents. When compared with traditional reagents such as iodobenzene dichloride [33] or the NCS/Ph_2Se system [34] for the chlorofunctionalisation of alkenes, **OC-2** has advantages such as high reactivity and safety, and low toxicity.



Scheme 4.6 Difunctionalisation of alkenes with **OC-2**

Thus, in this chapter, we will focus on comparing the reactivity of the three new *N*-functionalised Cl-I(III) reagents **NC-1**, **NC-2**, and **NC-3** with *O*-functionalised Cl-I(III) reagents **OC-1** and **OC-2** in the oxychlorination of styrene **(Scheme 4.7)** to provide

direction for further chlorofunctionalisation of alkenes in the future. The reaction procedure are based on those in the literature.[32]



Scheme 4.7 Oxychlorination of styrene

4.2 Chlorination of 1,3-dicarbonyl compounds

Two different 1,3-dicarbonyl compounds, ethyl benzoylacetate and 1,3-diphenylpropane-1,3-dione, were chosen as substrates for these chlorination reactions.

4.2.1 Chlorination of ethyl benzoylacetate

In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl benzoylacetate, it can be seen that both the ketone (singlet peak, δ = 3.98 ppm assigned to the two protons of the CH_2 group in the α positon) and the enol tautomer (singlet peak, δ = 5.20 ppm assigned to the C=CH proton) exist in solution **(Figure 4.3)**, in a 5:1 ratio respectively. Hypervalent iodine(III) reagents usually act as electrophiles that react with the enol tautomer of ethyl benzoylacetate.

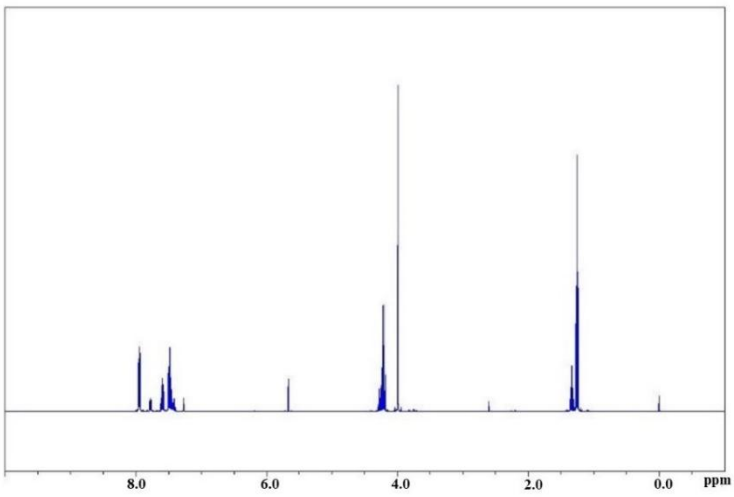


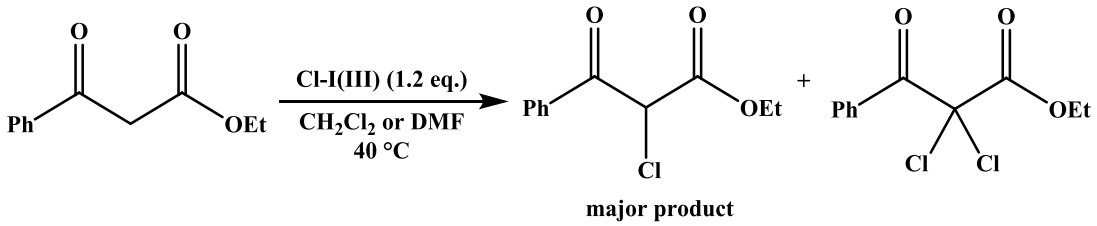
Figure 4.3 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ethyl benzoylacetate

The reactivities of the new *N*-functionalised Cl-I(III) compounds **NC-1**, **NC-2**, and **NC-3** in the chlorination of ethyl benzoylacetate have been compared with those of the *O*-functionalised Cl-I(III) compounds **OC-1** and **OC-2** according to the yield of mono-chlorination product ethyl 2-chloro-3-oxo-3-phenylpropanoate; this is the major product when 1.2 equivalents of the Cl-I(III) reagents are used. In these processes, the di-chlorination product, ethyl 2,2-dichloro-3-oxo-3-phenylpropanoate, may also be observed as a by-product. The reaction was carried out under various conditions. The mono-chlorination and di-chlorination products can be separated easily by column chromatography using petroleum ether (40-60 ℃)/CH_2Cl_2 (V:V = 2:1) on silica gel. The identities of the known products were made by comparison of NMR data with the literature. The results are summarised in **Tables 4.1** and **4.2**.

When the reaction was carried out at 40 ℃ under N_2 in dry CH_2Cl_2 for one hour, no chlorination product was obtained with **NC-1**; **NC-2** and **NC-3** gave identical results. In contrast, after just one hour, 68% mono-chlorination and 5% di-chlorination were observed with **OC-1** and 24% mono-chlorination was observed with **OC-2**. Extending the reaction time to three hours increased the mono-chlorination yield to 79% for **OC-1** and to 43% for **OC-2**. Significantly, 30% conversion was obtained after three hours when **NC-1** (or **NC-2** or **NC-3**) was used as the chlorinating agent. By extending the reaction time further, to 18 hours, the yields of the mono-chlorination and the di-chlorination products for four of the Cl-I(III) compounds (**NC-1**, **NC-2**, **NC-3** and **OC-1**), were now very similar and greater than those obtained with **OC-2**. These results clearly indicate that the *N*-functionalised Cl-I(III) reagents **NC-1**, **NC-2** and **NC-3** are less reactive than, in particular, **OC-1**, but that they are chlorinating agents in this reaction.

During this work, we found that the solubility of the Cl-I(III) compounds in DMF is higher than that in CH_2Cl_2. Therefore, we initially predicted that the chlorination of 1,3-dicarbonyl compounds using the Cl-I(III) reagents in dry DMF may be easier to carry out than that in dry CH_2Cl_2. Using the *N*-functionalised Cl-I(III) reagents **NC-1, NC-2,** and **NC-3**, as seen at 40 ℃ when CH_2Cl_2 was used as the solvent, after one hour in DMF no chlorination was observed. However, after three hours in DMF, the yields of the mono-chlorination product were better than those observed after 18 hours in CH_2Cl_2 with, significantly, no evidence for the di-chlorinated product **(Tables 4.1** and **4.2)**. Increasing the reaction time to 18 hours in DMF did not improve the yields of the mono-chlorinated product, but some di-chlorination had now occurred **(Table 4.3)**.

These results suggested that, indeed, the Cl-I(III) reagents are more reactive in DMF, so a series of experiments were undertaken at room temperature for 18 hours. Moderate yields of the mono-chlorinated product were observed in all cases.



Entry	Cl-I (III) Reagents	Time (h)	Monochlorination Yield (%)	Dichlorination Yield (%)
1	**NC-1**	1	0	0
2	**NC-1**	3	30	0
3	**NC-1**	18	74	11
4	**NC-2**	18	80	6
5	**NC-3**	18	79	6
6	**OC-2**	18	70	-
7	**OC-1**	18	75	9
8	**OC-2**	1	24	0
9	**OC-2**	3	43	0
10	**OC-1**	1	68	5
11	**OC-1**	3	79	5

Table 4.1 Chlorination of ethyl benzoylacetate with various Cl-I(III) reagents at 40 ℃ in dry CH_2Cl_2

Entry	Cl-I (III) Reagents	Time (h)	Monochlorination Yield (%)	Dichlorination Yield (%)
1	**NC-1**	1	0	0
2	**NC-1**	3	86	0
3	**NC-2**	3	87	0
4	**NC-3**	3	85	0
5	**OC-2**	3	70	5
6	**OC-1**	3	78	0

Table 4.2 Chlorination of ethyl benzoylacetate with various Cl-I(III) reagents at 40 ℃ in dry DMF for three hours

Entry	Cl-I (III) Reagents	Solvent	T (°C)	Monochlorination Yield (%)	Dichlorination Yield (%)
1	**NC-1**	DMF	40	78	7
2	**NC-2**	DMF	40	83	7
3	**NC-3**	DMF	40	81	6
4	**OC-2**	DMF	40	75	5
5	**OC-1**	DMF	40	78	8
6	**NC-1**	DMF	RT	37	-
7	**NC-2**	DMF	RT	39	-
8	**OC-2**	DMF	RT	37	-
9	**OC-1**	DMF	RT	44	-

Table 4.3 Chlorination of ethyl benzoylacetate with various Cl-I(III) reagents at 40 ℃ or room temperature in DMF for 18 hours

From the results above, it can be summarised that the chlorination of ethyl benzoylacetate using Cl-I(III) reagents is very difficult to carry out without heating. For the *N*-functionalised Cl-I(III) compounds **NC-1**, **NC-2**, **NC-3**, and the *O*-functionalised Cl-I(III) compound **OC-2**, dry DMF is a more suitable solvent than CH_2Cl_2. For the *O*-

functionalised Cl-I(III) compound **OC-1**, the amount of dry DMF used as solvent for the chlorination of ethyl benzoylacetate is smaller than that used with CH_2Cl_2, but it needs more saturated $NaHCO_3$ aqueous solution, brine, and water to remove the DMF and obtain the product. Finally, the best conditions for the chlorination of ethyl benzoylacetate using **OC-1** is in dry CH_2Cl_2 at 40 ℃ under N_2.

4.2.2 Chlorination of 1,3-diphenylpropane-1,3-dione

In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1,3-diphenylpropane-1,3-dione, it can be seen that there is nearly 100% of the enol tautomer (singlet, 6.89 ppm assigned to the –C=C*H* proton) **(Figure 4.4)**.

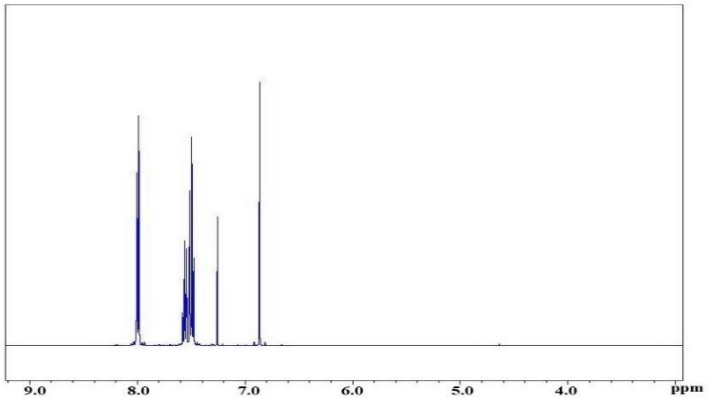


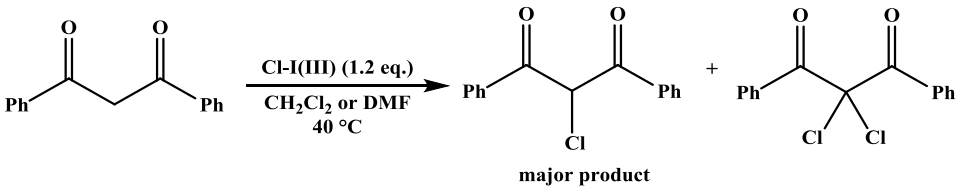
Figure 4.4 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1,3-diphenylpropane-1,3-dione

The chlorination of 1,3-diphenylpropane-1,3-dione using various Cl-I(III) reagents was carried out in either CH_2Cl_2 or DMF. The mono-chlorination and di-chlorination products can be separated easily by column chromatography using petroleum ether (40-60 ℃)/CH_2Cl_2 (V:V = 2:1) on silica gel. The identities of the known products was made by comparison of NMR data with the literature. The results are summarised in **Table 4.4**.

For the *O*-functionalised Cl-I(III) compounds moderate yields of the mono-chlorinated products could be obtained in dry CH_2Cl_2 at 40 ℃ under N_2 for 18 hours, but only a trace of this product was obtained when the *N*-functionalised Cl-I(III) compounds, such as **NC-1**, where used. This appeared to be due to solubility issues, but since all the Cl-I(III) compounds and 1,3-diphenylpropane-1,3-dione dissolved easily in DMF the reactions were subsequently studied in this solvent.

When the reactions were run for three hours, the yields of the mono-chlorination product was around 50%, and the di-chlorination product was around 9% when **NC-1**,

NC-2, **NC-3** and **OC-2** were used as the chlorine source. However, when **OC-1** acted as the chlorine source in this reaction, the yield of mono-chlorination product increased to 84%, and no di-chlorination product was obtained after three hours. When these reactions were run for 18 hours, the resulting products contained mono-chlorination product (67–79%) and di-chlorination product (8–13%). The differences between the chlorination results were not very obvious when using **NC-1**, **NC-2**, **NC-3**, and **OC-1**. However, when **OC-2** was taken as the chlorine source, the yields of the chlorination products were much lower than those with the other reagents.



major product

Entry	Cl-I (III) Reagents	Solvent	Time (h)	Monochlorination Yield (%)	Dichlorination Yield (%)
1	**NC-1**	DMF	3	50	8
2	**NC-1**	DMF	18	77	13
3	**NC-1**	DCM	18	trace	0
4	**NC-2**	DMF	3	50	9
5	**NC-2**	DMF	18	79	12
6	**NC-3**	DMF	3	49	9
7	**NC-3**	DMF	18	77	11
8	**OC-2**	DMF	3	58	8
9	**OC-2**	DMF	18	67	8
10	**OC-2**	DCM	18	49	0
11	**OC-1**	DMF	3	84	0
12	**OC-1**	DMF	18	77	9
13	**OC-1**	DCM	18	69	0

Table 4.4 Chlorination of 1,3-diphenylpropane-1,3-dione with various Cl-I(III) reagents in dry DMF and DCM at 40 ℃

In CH_2Cl_2, the chlorination of 1,3-diphenylpropane-1,3-dione using Cl-I(III) reagents was more difficult to carry out than that of ethyl benzoylacetate under the same reaction conditions. In contrast, when DMF was used as the solvent, chlorinations of ethyl benzoylacetate and 1,3-diphenylpropane-1,3-dione under the same conditions gave very similar results.

4.2.3 Reaction mechanism

The probable mechanism for these chlorination reactions is shown in **Figure 4.5**. The determining step is the formation of enol tautomer of the substrate and the chlorinating hypervalent iodine(III) compounds act as electrophiles. The proportion of enol tautomer will increase, and the Cl-I bond will be easier to break on warming. As the reaction time increases, the mono-chlorination product can react further with the Cl-I(III) compound to bring about di-chlorination.

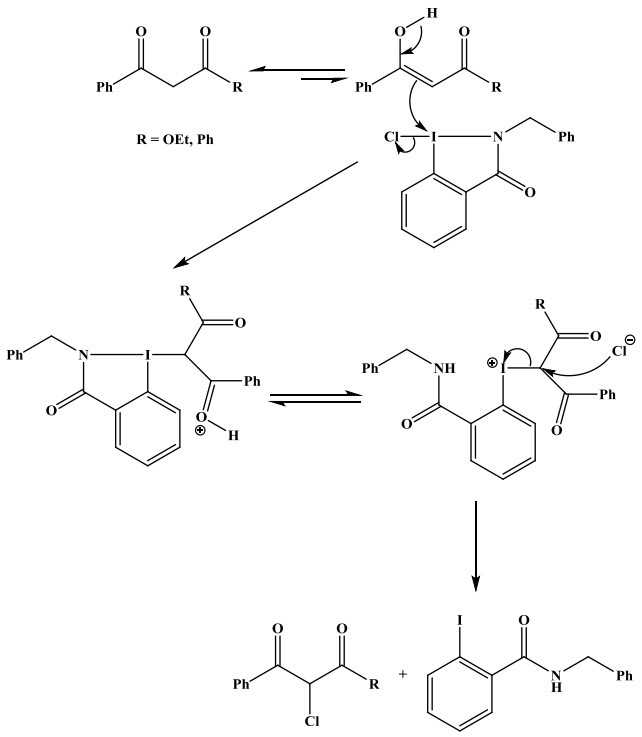


Figure 4.5 Mechanism for the chlorination of 1,3-dicarbonyl compounds using **NC-1**

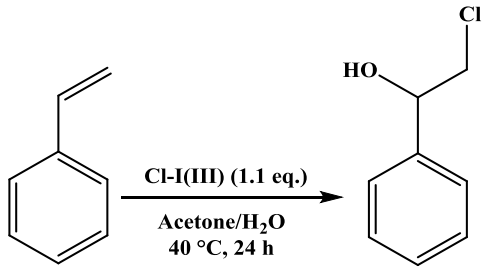
Additionally, the reactivity of the Cl-I(III) reagents in these chlorination reactions may depend on the bond length of Cl-I and the ability of the reagent to stabilise the positive charge on the resulting iodonium ion. In this work, the Cl-I bond length for the three new *N*-functionalised Cl-I(III) compounds, **NC-1**, **NC-2**, and **NC-3** and **OC-1** are

very similar, whilst that for **OC-2** is much shorter. This may explain why the conversions of ethyl benzoylacetate and 1,3-diphenylpropane-1,3-dione to chlorination products using **OC-2** over 18 hours were a little lower than those of the other reagents. In terms of the relative stability of the intermediate iodonium ion and consequent increased reactivity, this may arise from the electron donating methyl substituents present in **OC-1**.

4.3 Oxychlorination of styrene

4.3.1 Oxychlorination of styrene using Cl-I(III) reagents

Oxychlorination of styrene using Cl-I(III) reagents was carried out in a mixture of acetone and water at 40 ℃ for 24 hours. When the reactivity of the three new *N*-functionalised Cl-I(III) compounds, **NC-1**, **NC-2**, and **NC-3** was compared with that of the *O*-functionalised Cl-I(III) compound **OC-2** in the oxychlorination of styrene, the yields of the target product, 2-chloro-1-phenylethan-1-ol as yellowish oil, were the same (75%). However, in the reaction using **OC-1** none of the target product, 2-chloro-1-phenylethan-1-ol, from the oxychlorination of styrene was obtained. The results are summarized in **Table 4.5**.



Entry	Cl-I(III) Reagents	Yield of 2-chloro-1-phenylethan-1-ol (%)
1	**NC-1**	75
2	**NC-2**	75
3	**NC-3**	75
4	**OC-1**	-
5	**OC-2**	75

Table 4.5 Results of the oxychlorination of styrene

4.3.2 NMR and mechanism

The target product, 2-chloro-1-phenylethan-1-ol, is a known compound that is readily identified by NMR spectroscopy.[32] In the ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 2-chloro-1-phenylethan-1-ol, a mutiplet peak in the 4.92-4.89 ppm range can be assigned to the -OH proton, two protons on the terminal site are diastereotopic (a doublet of the doublet peak at 3.65 ppm and a doublet peak at 2.64 ppm) and a doublet of doublets peak at 3.75 ppm is assigned to the CH-OH proton. In the ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of 2-chloro-1-phenylethan-1-ol, the most significant two peaks at 74.1 ppm and 50.9 ppm represent the two carbons of -CHOH- and -CH_2Cl, respectively.

When **OC-1** was used to carry out this reaction, it did not yield the same product. The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of the crude reaction mixture showed many peaks in the 3.5-5.5 ppm range, and no peaks due to the product were found. The reasons for this were not investigated further.

The proposed reaction mechanism using **OC-2** is shown in **Figure 4.6**. No matter which Cl-I(III) reagent (**NC-1**, **NC-2**, **NC-3** and **OC-2**) was used, the reactivity of the significant intermediate iodonium ion does not change, so the final yields from these reactions were the same.

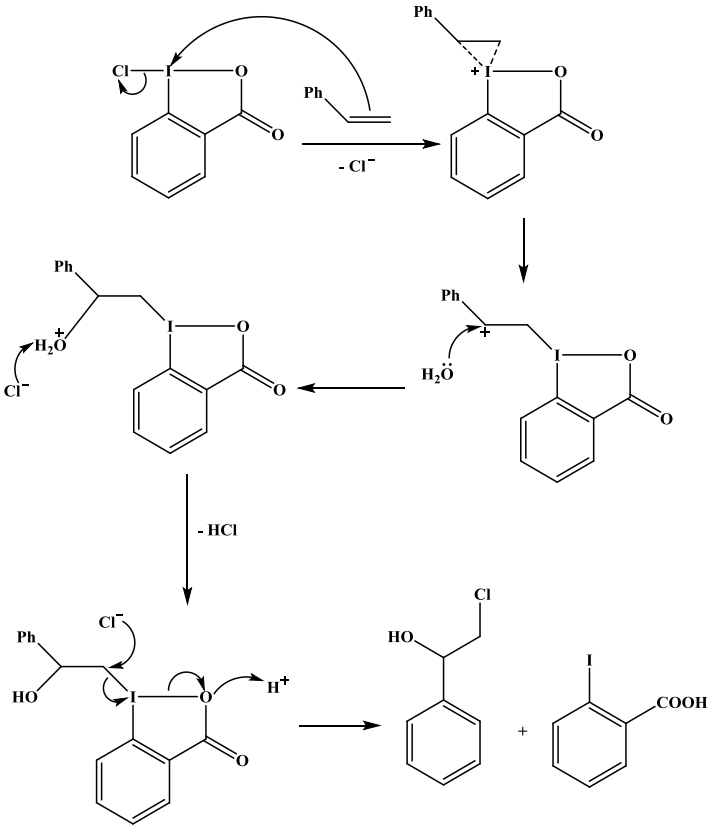


Figure 4.6 Proposed mechanism for oxychlorination of styrene using **OC-2**

4.4 Conclusions

The reactivities of three new *N*-functionalised Cl-I(III) reagents, **NC-1**, **NC-2**, and **NC-3** in the chlorination of the 1,3-dicarbonyl compound ethyl benzoylacetate, were found to be almost the same. The substituents on the *para* position of benzene ring of the benzylamine unit do not affect the reactivity of **NC-1**, **NC-2**, and **NC-3**. When the reaction was carried out at 40 ℃ in CH_2Cl_2 as solvent, the reactivity of the *O*-functionalised Cl-I(III) reagent **OC-1** was found to be higher. However, when DMF was used as the reaction solvent, the differences in reactivity between all of the Cl-I(III) reagents became very small. The best conditions in which to prepare ethyl 2-chloro-3-oxo-3-phenylpropanoate are using 1.2 equivalents of **NC-1** in DMF at 40 °C for three hours.

The chlorination of the 1,3-dicarbonyl compound 1,3-diphenylpropane-1,3-dione was very difficult to carry out using **NC-1** in CH_2Cl_2. DMF is better than CH_2Cl_2 as a solvent for all of the Cl-I(III) reagents studied here. The best conditions to prepare 2-chloro-1,3-diphenylpropane-1,3-dione are using 1.2 equivalents of **OC-1** in DMF at 40 ℃ for three hours.

In the oxychlorination of styrene using Cl-I(III) reagents, it was easy to get good results with a 75% yield of the target product 2-chloro-1-phenylethan-1-ol using the three new *N*-functionalised Cl-I(III) reagents, **NC-1**, **NC-2** and **NC-3** and the *O*-functionalised Cl-I(III) reagent **OC-2** at 40 ℃ in acetone/H_2O for 24 hours. When **OC-1** was used to carry out this reaction, it did not yield the same product.

4.5 References

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Chapter 5 Applications of New Fluorobenzoiodazolones

5.1 Introduction

This chapter focuses on the study of fluorination applications of the new *N*-functionalised F-I(III) reagents 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)**, 2-(4-chlorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-2)**, and 2-(4-fluorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-3)**, which have been successfully synthesised and characterised in Chapter 2.

The unique physical and chemical properties of fluorine-containing compounds have led to their increasingly widespread application in medicinal chemistry,[1-2] agrochemicals,[3] functional materials,[4] and several other areas of research.[5] For example, at present, 20-30% of all pharmaceuticals on the market contain at least one fluorine atom such as Lipitor (cholesterol-lowering drug), Prozac (antidepressant), Faslodex (anticancer), Flurithromycin (antibacterial) and Efavirenz (antiviral), following 5-fluorouracil (antimetabolite) which was first synthesised in 1957 **(Figure 5.1)**.[2, 6-7]

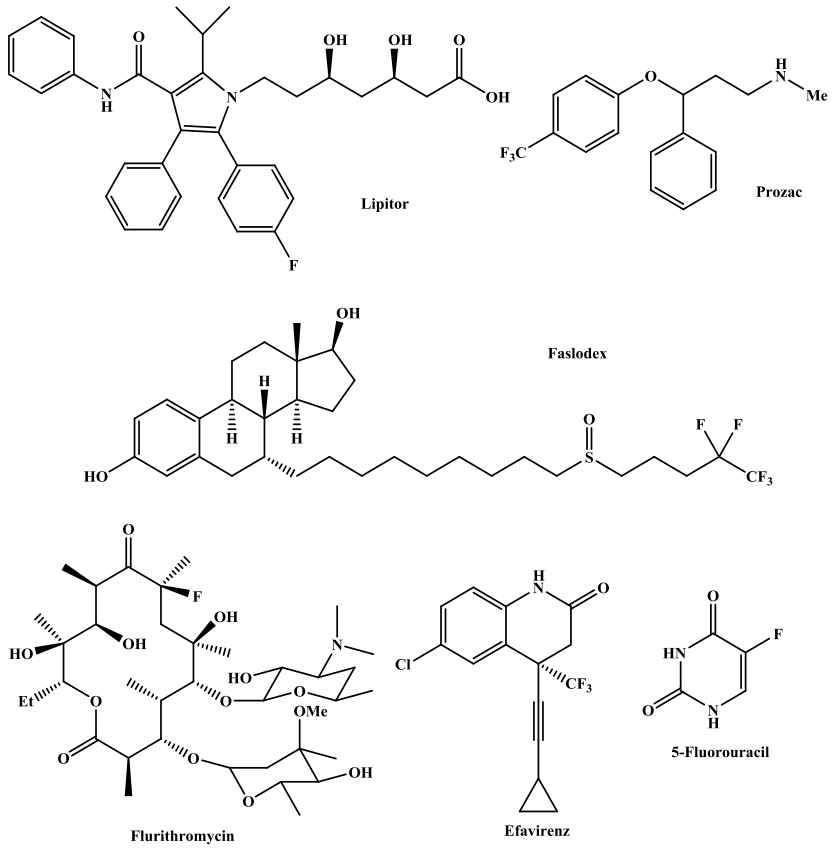


Figure 5.1 Some popular fluorine-containing drugs

Another significant fluorine application is in the field of ^{18}F-labelled positron emission tomography (PET) scans, a nuclear medical imaging modality mapping functional processes in vivo. ^{18}F tracers are advantageous owing to their longer half-lives ($t_{1/2}$ = 110 minutes), as compared to other commonly used radionuclides, such as ^{11}C ($t_{1/2}$ = 20 minutes), ^{13}N ($t_{1/2}$ = 10 minutes), and ^{15}O ($t_{1/2}$ = 2 minutes).[2] The most frequently used radiopharmaceutical for PET in biodistribution and drug occupancy studies are 2-deoxy-2-[^{18}F] fluoro-D-glucose (also termed [^{18}F]FDG) and [^{18}F]SPA-RQC **(Figures 5.2 and 5.3)**.

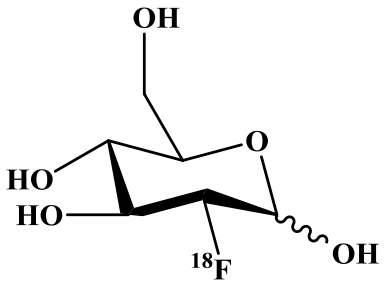


Figure 5.2 2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG)

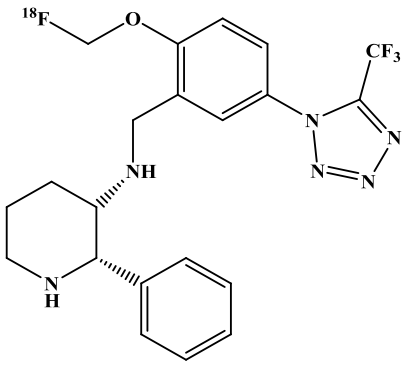


Figure 5.3 [^{18}F]SPA-RQC

Almost all target fluorinated organic molecules have to be chemically synthesised, since organofluorine compounds in natural products are extremely rare.[8-9] The replacement of hydrogen atoms with fluorine substituents in organic substrates is of great interest in synthetic chemistry owing to fluorine's strong electronegativity (Pauling electronegativity 4.0) as well as the small size of the fluorine atom (van der Waals radius: 1.35 Å; hydrogen: 1.20 Å).[10-11] However, these contribute to the weak nucleophilicity of fluoride that limits the access to C-F bonds via nucleophilic

substitution reactions.[12] Consequently, over the past several decades, several significant efforts have focussed on developing methods to generate C-F bonds.

Some nucleophilic fluorine sources, such as diethylaminosulfur trifluoride (DAST),[13] 2,2-difluoro-1,3-dimethylimidazolidine (DFI),[14] bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor),[15] trimethylamine trihydrofluoride (TREAT-HF),[16] CsF, AgF, AgF_2, and anhydrous tetrabutylammonium fluoride (Bu_4NF) [17] **(Figure 5.4)** are available for the introduction of fluorine into organic molecules. However, the developement and commercialisation of various new electrophilic fluorinating reagents containing R_2N-F or R_3N^+-F units such as N-fluoropyridinium triflate, 2,4,6-trimethyl-1-fluoropyridinium triflate (FP-T300), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (FTEDA-PF_6), 1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor II), 1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) (Selectfluor II-PF_6), N-fluorobenzenesulfonimide (NFSI), N-fluoromethylsulfonimide (Me-NFSI), 1-fluoro-4-hydroxyl-1, and 4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (NFTh) **(Figure 5.5)** as replacement for traditional electrophilic fluorinating agents (F_2, XeF_2, CF_3OF, and $FClO_3$) are making electrophilic fluorination a most promising and efficient tool in synthesising organic fluorine compounds with pharmacological activity.[18]

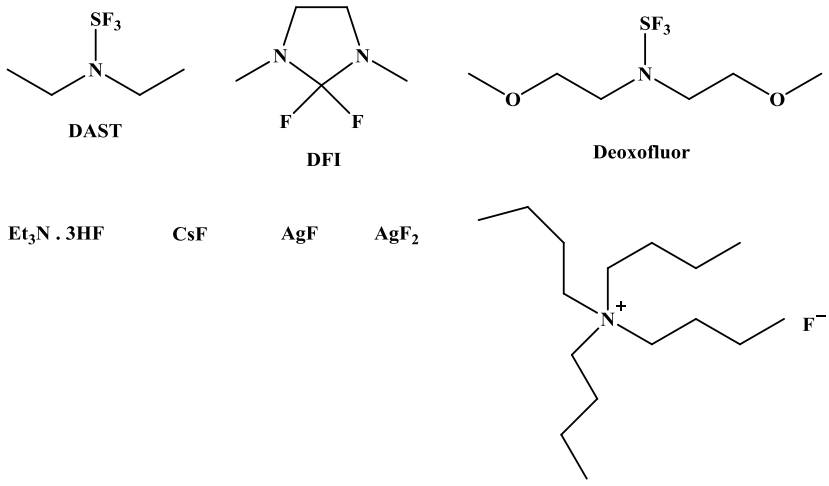


Figure 5.4 Some classical nucleophilic fluorine reagents

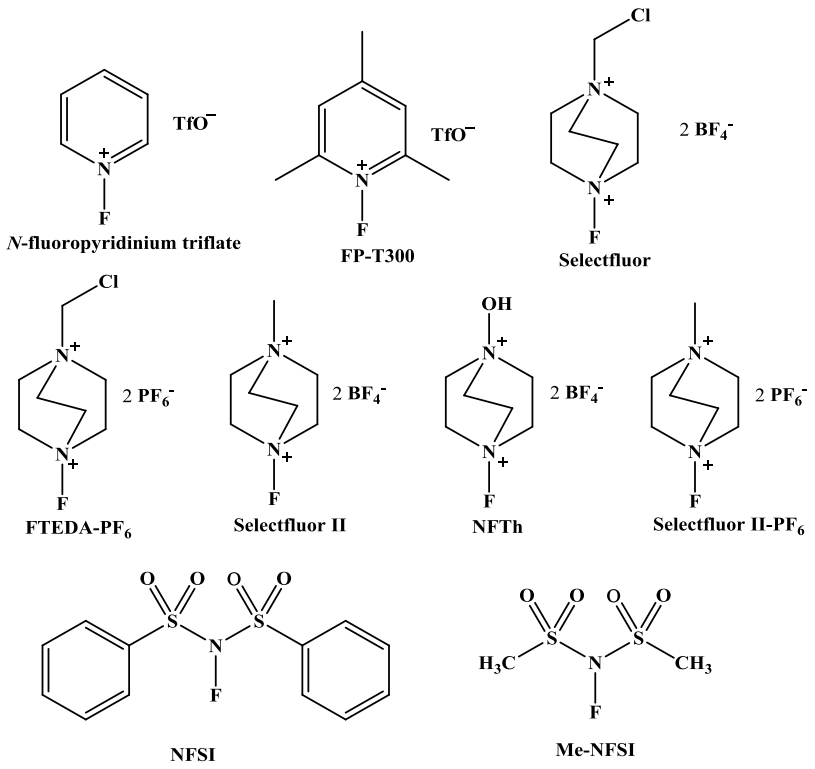
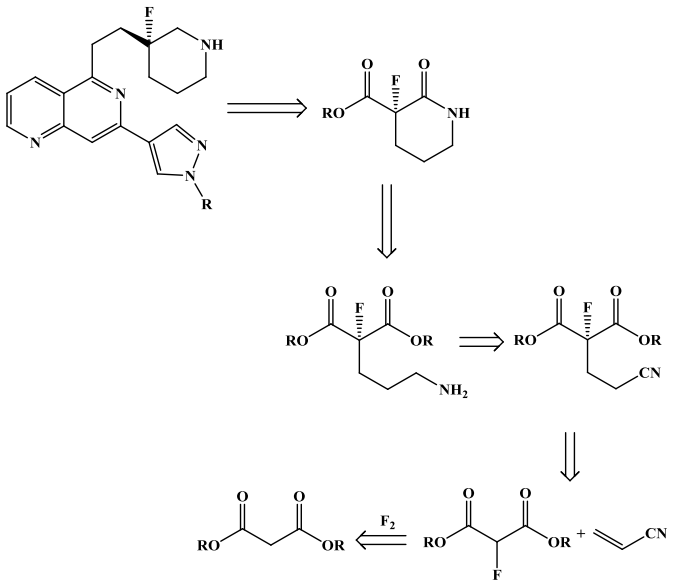


Figure 5.5 Some N–F electrophilic fluorinating reagents

In several fluorinating applications, the fluorination of 1,3-dicarbonyl compounds has attracted major attention from chemists and has oftern been used as a model reaction for evaluating new electrophilic fluorinating agents. 1,3-dicarbonyl compounds can be used as important precursors to synthesise pyrazoles, which are useful intermediates in preparing new pharmacologically active compounds, especially fluorinated pyrazoles, a class of compounds with potential in medicinal chemistry.[19] Sale et al. (2012) prepared a range of flavone derivatives to evaluate their potential as anti-prostate cancer agents through the α-fluorination of 1,3-dicarbonyl derivatives.[20] Additionally, Sandford et al. (2016) designed the retrosynthetic approach to potential pre-clinical candidate spleen tyrosine kinase (Syk) inhibitors from the synthesis of chiral fluorolactam derivatives by a route involving $Cu(NO_3)_2 \cdot 2.5H_2O$ catalysed selective direct fluorination using fluorine gas **(Scheme 5.1)**.[21]



Scheme 5.1 Retrosynthetic approach to Syk inhibitors

The fluorination of 1,3-dicarbonyl compounds employing the hypervalent fluoroiodane reagent 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** was first reported by our group.[22-23] Compared with other methods for the same reactions, such as using F_2 [24] and XeF_2,[25] Selectfluor with $CpTiCl_3$ as a catalyst,[26] aqueous HF in the presence of iodosylbenzene,[27] and Ar-I/HF·Py/*m*CPBA,[28] using **OF-1** for the fluorination of 1,3-dicarbonyl compounds is metal-free, easily-handled, low-toxicity, recyclable, safe, allows high regioselectivities, and yields target products under mild conditions. **OF-1** provides a most powerful synthetic method for direct fluorination to build new C-F bonds.

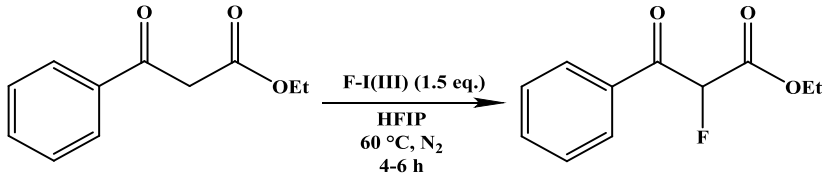
Following this work, a new class of fluorinated lactones was prepared by the intramolecular fluorocyclisations of unsaturated carboxylic acids using **OF-1** in combination with $AgBF_4$, which has potential application in developing new ^{18}F-labelled radiotracers for PET imaging.[29] In 2014, Szabó's group demonstrated mild silver-mediated geminal difluorination of styrenes using **OF-1** as an excellent means to obtain various products bearing the CHF_2 [30] unit, which is important for fine-tuning the biological properties of drug molecules.[31-32] Based on this, in 2017, they reported that **OF-1** was good for the geminal difluorination of α, α'-disubstituted styrenes.[33] More recently, our group has demonstrated that hexafluoroisopropanol (HFIP) is an excellent solvent for promoting fluorinating with **OF-1** which can be activated by formation of a hydrogen-bonded adduct with HFIP. Crucially, it removes the need for transition metals or TREAT-HF activators in fluorination reactions.[34]

The work in this chapter thus aims to test the reactivity of the new *N*-functionalised F-I(III) reagents **NF-1**, **NF-2**, and **NF-3** in the fluorination of 1,3-dicarbonyl compounds, the intramolecular fluorocyclisation of unsaturated carboxylic acids, and the geminal difluorination of α,α'-disubstituted styrenes in HFIP. Furthermore, this chapter aims to provide a comparison between the reactivities of the *N*-functionalized F-I(III) reagents with those of the *O*-functionalised F-I(III) reagent **OF-1**.

5.2 Applications in the fluorination of 1,3-dicarbonyl compounds

5.2.1 Fluorination of 1,3-ketoesters and 1,3-ketoamide in hexafluoroisopropanol using various fluorobenzoiodazolones and fluoroiodane

First of all, we chose ethyl benzoylacetate as a substrate to compare the reactivity of the three new *N*-functionalised F-I(III) reagents **NF-1**, **NF-2** and **NF-3**, which have been successfully synthesised and described in Chapter 2 with the established *O*-functionalised **OF-1** for the fluorination of 1,3-dicarbonyl compounds in HFIP. The data are summarised in **Table 5.1**.



Entry	F-I(III) Reagents	Time (h)	Yield of Monofluorination Product (%)
1	**OF-1** [34]	4	73
2	**NF-1**	4	45
3	**NF-1**	6	71
4	**NF-2**	6	72
5	**NF-3**	6	72

Table 5.1 Fluorination of ethyl benzoylacetate using various F-I(III) reagents

Following the same reaction procedures reported in the literature,[34] it was observed that the fluorination of ethyl benzoylacetate using **OF-1** could be conducted very quickly,

such that a 73% yield of the monofluorination product, ethyl 2-fluoro-3-oxo-3-phenylpropanoate, was achieved in HFIP at 60 ℃ for four hours.[34] The literature product, ethyl 2-fluoro-3-oxo-3-phenylpropanoate, was readily identifed by NMR spectroscopy. In the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum, a doublet peak at round 5.85 ppm ($^{2}J_{HF}$ = 49.0 Hz) is observed for the remaining proton at the fluorinated carbon atom. It simlifies to a singlet on fluorine decoupling. In the ^{13}C NMR (100 MHz, $CDCl_3$) spectrum, two quaternary carbon doublet peaks are observed at 188.0 ppm ($^{2}J_{CF}$ = 20.0 Hz) and at 165.0 ppm ($^{2}J_{CF}$ = 24.5 Hz) and are assigned to the carbonyl carbons. A wide doublet peak at 90.0 ppm ($^{1}J_{CF}$ = 197.5 Hz) is assigned to the fluorinated carbon atom. In the ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) spectrum, the product has a characteristic singlet peak at -190.0 ppm.

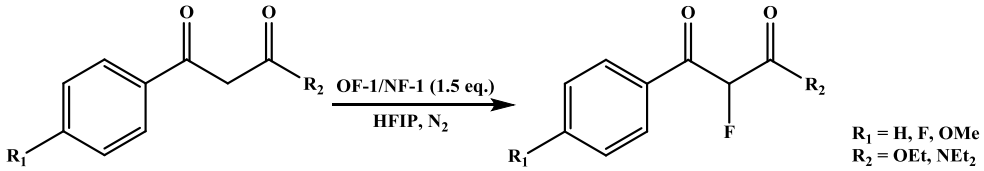
When the fluorination reagent was changed to **NF-1** and the reaction was run under the same conditions, the yield of the monofluorination product was only 45% after the initial four hours period. By extending the reaction time to six hours, the yield of monofluorination product increased to 71%. This slight difference in reactivities between the *O*- and *N*-functionalised F-I(III) reagents is much less than the differences in electrophilic chlorination reactivities of **OC-1** and **NC-1** in dichloromethane (Chapter 4). Similar results were obtained when the reaction was run with **NF-2** and **NF-3**; under the same conditions the yields were 72%; thus, there are negligible differences in the reactivities of **NF-1**, **NF-2**, and **NF-3** with different *para*-benzyl substitutions. These results mirror those for electrophilic chlorination of ethyl benzoylacetate using **NC-1**, **NC-2** and **NC-3** (Chapter 4).

In summary, the reactivities of the *O*-functionalised F-I(III) reagent **OF-1** and *N*-functionalised F-I(III) reagents **NF-1**, **NF-2**, and **NF-3** for the fluorination of ethyl benzoylacetate in HFIP are similar. Consequently, **NF-1** was chosen as the reagent for the fluorination of a series of 1,3-dicarbonyl compounds, since it is easy to synthesise and the starting material benzylamine is much cheaper than *p*-chlorobenzylamine and *p*-fluorobenzylamine making **NF-1** a cheaper reagent. Using **NF-1** the yields of the monofluorination product from the fluorination of ethyl (4-fluorobenzoyl)acetate and ethyl (4-methoxybenzoyl)acetate were 94% and 90%, respectively.

Based on the reaction conditions for the fluorination of a 1,3-ketoamide reported in the literature [34] and the NMR spectrum of the chosen substrate, *N*,*N*-diethyl-3-oxo-3-phenylpropanoate, it can be concluded that *N*,*N*-diethyl-3-oxo-3-phenylpropanoate is more active than 1,3-ketoesters in fluorination reactions as a result of the higher

percentage of the enol tautomer. Consequently, the fluorination of *N*,*N*-diethyl-3-oxo-3-phenylpropanoate with **NF-1** was carried out at room temperature for one hour. From the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude product after removal of the solvent, it was found that the conversion of substrate to the monofluorination product was only 50% which was much lower than that using **OF-1** under the same conditions. At the same time, the target product could not be seperated from the resulting amide by-product ***N*-1**. Consequently, the usefulness of **NF-1** in the fluorination of *N*,*N*-diethyl-3-oxo-3-phenylpropanoate is worse than that of **OF-1**.

All of the results of the fluorination of 1,3-ketoesters and 1,3-ketoamide with **OF-1** and **NF-1** are summarised in **Table 5.2**. The use of **OF-1** and **NF-1** for these reactions in HFIP was straightforward.

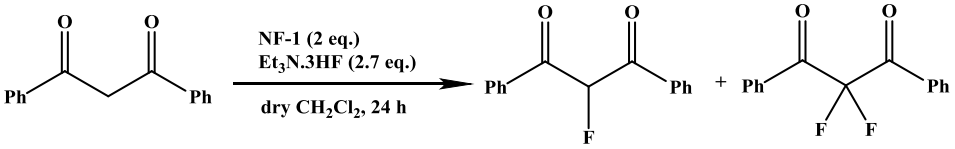


Entry	R1	R2	F-I(III) Reagents	T (℃)	Time (h)	Yield of Monofluorination (%)
1	**H**	**OEt**	**OF-1** [34]	60	4	73
2	**H**	**OEt**	**NF-1**	60	4	45
3	**H**	**OEt**	**NF-1**	60	6	71
4	**F**	**OEt**	**OF-1** [34]	60	4	90
5	**F**	**OEt**	**NF-1**	60	6	90
6	**OMe**	**OEt**	**OF-1** [34]	60	4	93
7	**OMe**	**OEt**	**NF-1**	60	6	94
8	**H**	**NEt_2**	**OF-1** [34]	RT	1	77
9	**H**	**NEt_2**	**NF-1**	RT	1	*

Table 5.2 Fluorination of 1,3-ketoesters and 1,3-ketoamide. * The pure product was not gained so the yield cannot be calculated.

5.2.2 Fluorination of a 1,3-diketone using fluorobenzoiodazolone and fluoroiodane with $Et_3N{\cdot}3HF$ as an additive

1,3-Diketones are generally more reactive to electrophiles than 1,3-ketoesters. Our group has reported that the fluorination of 1,3-diphenylpropane-1,3-dione with **OF-1** in the presence of $Et_3N{\cdot}3HF$ (TREAT-HF) gave the difluorination product as the major product.[22] The presence of the monofluorination product, 1,3-diphenyl-2-fluoro-1,3-propanedione, was made by NMR spectroscopy. In the ^1H NMR (400 MHz, $CDCl_3$) spectrum, a doublet peak at 6.51 ppm ($^2J_{HF}$ = 49.2 Hz) is observed for the remaining proton at the fluorinated carbon atom. In the ^{19}F {^1H} NMR (376 MHz, $CDCl_3$) spectrum, a singlet peak at -186.6 ppm is observed. The difluorination product, 1,3-diphenyl-2,2-fluoro-1,3-propanedione, has a characteristic singlet peak at -102.6 ppm in the ^{19}F NMR (376 MHz, $CDCl_3$) spectrum. When **NF-1** was used as the fluorinating agent under the same reactions, the ^1H NMR (400 MHz, $CDCl_3$) and ^{19}F NMR (376 MHz, $CDCl_3$) spectra of crude product revealed a very small amount of the monofluorination product and the difluorination product, 1,3-diphenyl-2,2-difluoro-1,3-propanedione, was clearly the major product. After purification by column chromatography using petroleum ether (40-60 ℃): CH_2Cl_2 (V:V = 1:2) on silica gel, a 77% isolated yield of difluorinated product was obtained. When the reaction temperature was raised to 60 ℃, only the difluorination product was gained in an 85% isolated yield. When the reactivities of **NF-1** and **OF-1** are compared in this reaction, in the presence of $Et_3N{\cdot}3HF$ (TREAT-HF), **NF-1 (Table 5.3)** is greater.



Entry	F-I(III) Reagent	T (℃)	Yield of Monofluorination Product (%)	Yield of Difluorination Product (%)
1	**OF-1** [22]	40	30	55
2	**OF-1** [22]	60	11	76
3	**NF-1**	40	-	77
4	**NF-1**	60	-	85

Table 5.3 Fluorination of 1,3-diphenylpropane-1,3-dione using **NF-1** and **OF-1**

5.2.3 Discussion of reaction mechanism and supporting NMR studies

The fluorination mechanism using **NF-1 (Figure 5.6)** is similar to that reported in the literature for fluorination reactions with **OF-1**.[23, 27] The reaction of ethyl benzoylacetate with **NF-1** proceeds effectively after enolisation. **NF-1** acts as an electrophilic reagent in reaction with the enol form of substrate releasing fluoride. After the five-membered ring opens, the fluoride ion attacks the α carbon centre of the iodonium ion intermediate releasing the aryl iodide *N*-benzyl-2-iodobenzamide **(*N*-1)** as a good leaving group resulting in the formation of the fluorine-containing product ethyl 2-fluoro-3-oxo-3-phenylpropanoate. Neither the difference in the electronegativity between N and O nor the different structures of **NF-1** and **OF-1** are likely to influence this mechanism.

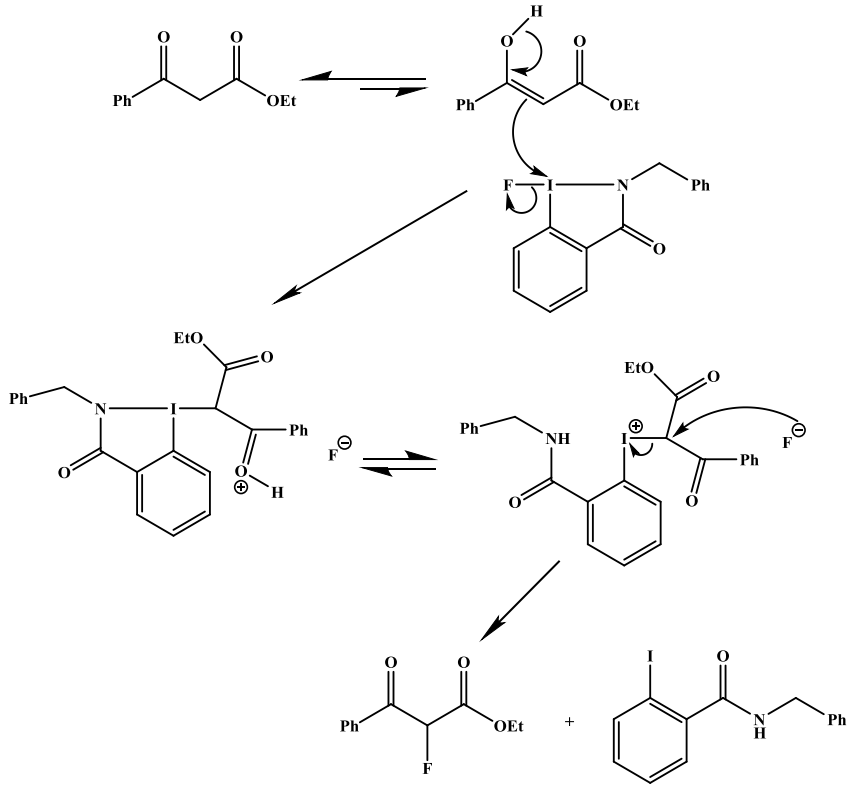


Figure 5.6 Proposed mechanism of fluorination of ethyl benzolyacetate using **NF-1**

In the literature, NMR data suggests the formation of a hydrogen-bonded adduct between HFIP and **OF-1** and that **OF-1** is activated as an electrophilic fluorinating agent by this hydrogen bonding.[34] Therefore, the possible role of HFIP in activating **NF-1** was investigated using NMR spectroscopy. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded for the following: (a) **NF-1**, (b) HFIP, and (c) a 1:1 mixture of **NF-1**:

HFIP. The three ^{1}H NMR spectra are shown in **Figure 5.7** and the spectroscopic data together with their assignments are listed in **Table 5.4**. An obvious and significant downfield shift of the OH signal from 3.01 in HFIP (broad singlet peak) to 5.45 ppm in the 1:1 mixture of **NF-1** and HFIP (doublet peak) (**Δ δ = 2.44**) was observed. The shift associated with this signal is slightly larger than that seen for the 1:1 mixture of **OF-1** and HFIP (**Δ δ = 2.12**).[34] Additionally, there was a small upfield shift of the -CH_2- signal on the position **8** from 4.79 in **NF-1** to 4.77 ppm in the 1:1 mixture of **NF-1** and HFIP (**Δ δ = -0.02**). Furthermore, this resonance changed from a doublet (due to long range H-F coupling; Chapter 2) in the ^{1}H NMR spectrum of **NF-1** to a singlet. These factors provide evidence of the formation of a hydrogen-bonded adduct between the solvent and **NF-1**, with clear evidence for a change in the fluorine environment, and providing supporting evidence for how **NF-1** is activated by hydrogen bonding to HFIP in the same way as seen for **OF-1**.[34] Based on these results, the hydrogen bonding between HFIP and **NF-1** is stronger than that between HFIP and **OF-1** enhancing the fluorination reactivity of **NF-1** more that of **OF-1**. The ^{19}F NMR data for **NF-1**, HFIP, and a 1:1 **NF-1**:HFIP mixture are shown in **Table 5.5**. The differences in the chemical shifts of both F-I and CF_3 between the substrates and the adduct are very small. In **Table 5.6**, the comparison of the ^{13}C NMR data is shown.

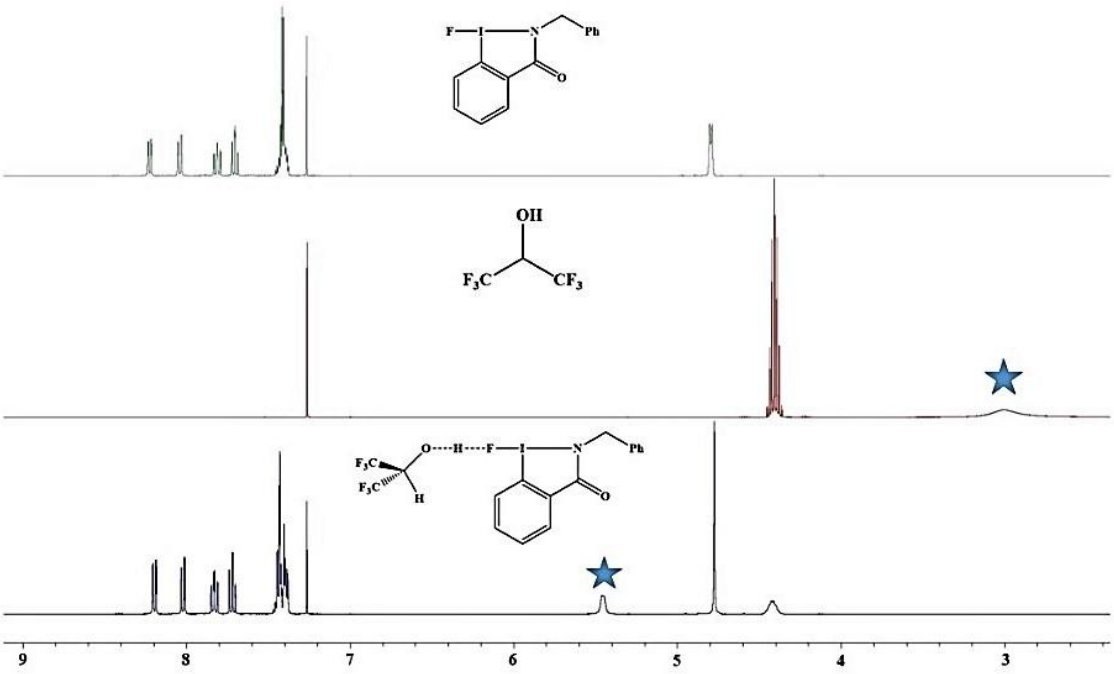
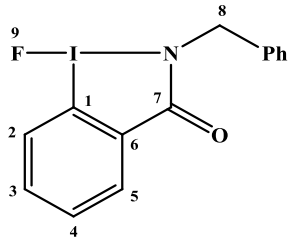
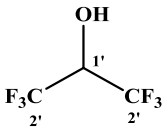


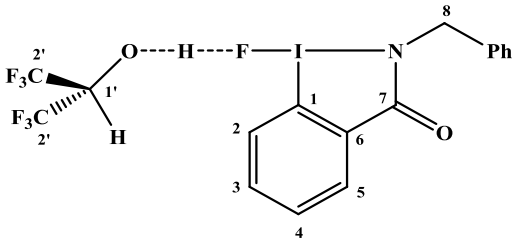
Figure 5.7 ^{1}H NMR spectra of (a) **NF-1**, (b) HFIP, and (c) a 1:1 mixture of **NF-1**: HFIP



(a) NF-1



(b) HFIP



(c) 1:1 mixture of NF-1: HFIP

Assignment	NF-1	HFIP	Adduct	Δ δ
2	8.22, dd, *J* = 7.5, 1.6 Hz	-	8.19, dd, *J* = 7.4, 1.6 Hz	-0.03
3	7.81, td, *J* = 7.5, 1.6 Hz	-	7.83, td, *J* = 7.4, 1.6 Hz	0.02
4	7.70, td, *J* = 7.5, 1.0 Hz	-	7.72, td, *J* = 7.4, 1.0 Hz	0.02
5	8.04, d, *J* = 7.5 Hz	-	8.02, d, *J* = 7.4 Hz	-0.02
8	4.79, d, *J* = 5.6 Hz	-	4.77, s	-0.02
1'	-	4.42, octet, *J* = 6.2 Hz	4.41, hept, *J* = 5.9 Hz	-0.01
OH	-	3.01, broad s	5.45, d, *J* = 4.0 Hz	2.44

Table 5.4 Comparison of ^{1}H NMR (400 MHz, $CDCl_3$) data for (a) **NF-1**, (b) HFIP, and (c) 1:1 mixture of **NF-1**:HFIP

Assignment	NF-1	HFIP	Adduct	Δ δ
9	-104.4, s	-	-105.1, s	-0.7
2'	-	-75.7, d, *J* = 6.6 Hz	-75.7, d, *J* = 6.6 Hz	0

Table 5.5 Comparison of ^{19}F NMR (376 MHz, $CDCl_3$) data for (a) **NF-1**, (b) HFIP, and (c) 1:1 mixture of **NF-1**:HFIP

Assignment	NF-1	HFIP	Adduct	Δ δ
1	117.8	-	117.9	0.1
2	131.4	-	131.4	0
3	134.6	-	134.9	0.3
4	132.7	-	132.5	-0.2
5	130.9	-	131.1	0.2
6	137.2	-	136.8	-0.4
7	165.9	-	166.4	0.5
8	48.1	-	48.4	0.3
1'	-	69.7, hept, *J* = 33.4 Hz	69.5, hept, *J* = 33.7 Hz	-0.2
2'	-	121.4, q, *J* = 283.4 Hz	121.7, q, *J* = 283.4 Hz	0.3

Table 5.6 Comparison of ^{13}C NMR (100 MHz, $CDCl_3$) data for (a) **NF-1**, (b) HFIP, and (c) 1:1 mixture of **NF-1**:HFIP

5.3 Applications in intramolecular fluorocyclisation of unsaturated carboxylic acids in hexafluoroisopropanol

5.3.1 Intramolecular fluorocyclisation of unsaturated carboxylic acids in hexafluoroisopropanol using fluorobenzoiodazolone and fluoroiodane

Based on the fluorination of the 1,3-dicarbonyl compounds in HFIP, the differences in the reactivity between **NF-1**, **NF-2**, and **NF-3** are small, so **NF-1** is used as the fluorinating reagent for this study.

Using the established reaction conditions from the literature,[34] the reactivity of **NF-1** and **OF-1** for the intramolecular fluorocyclisation of unsaturated carboxylic acids in HFIP at 40 ℃ for one hour has been compared. In this process, 4 Å molecular sieves has been added in order to prevent water competing with fluoride as a nucleophile. After purification, the literature products were readily identified by NMR spectroscopy where the most significant observation in the ^{1}H NMR spectra is that each of the protons on positions **1**, **3** and **4 (Figure 5.8)** were not only coupled with the adjacent protons but also with the fluorine on position **2**. Using 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one as an example, in the (400 MHz, $CDCl_3$) spectrum the two protons on position **1** are observed as a doublet at 3.29 ppm ($^{3}J_{HF}$ = 14.5 Hz), which collapses to a singlet on fluorine decoupling. Two protons on position **4** are diastererotopic and appear as two doublets of doublets of doublets at 2.42 ppm and 2.74 ppm on fluorine decoupling. The two diastereotopic protons on position **3** appear as a complicated multiplet. In the ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one a wide doublet peak at 119.2 ppm ($^{1}J_{CF}$ = 230.7 Hz) is assigned to C on position **2** and narrower doublets at 42.7 ppm ($^{2}J_{CF}$ = 28.2 Hz) and 30.9 ppm ($^{2}J_{CF}$ = 27.7 Hz) are assigned to C on the positions **1** and **3** respectively. In the ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) spectrum of 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one, a singlet resonance at -97.0 ppm is observed.

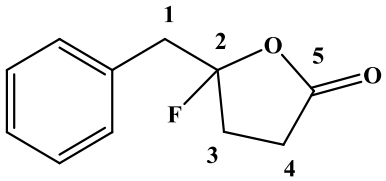


Figure 5.8 Structure of 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one

In **Table 5.7**, the results for the intramolecular fluorocyclisation in HFIP from the four different substrates, 4-phenylpent-4-enoic acid, 4-(4-fluorophenyl)pent-4-enoic acid, 2-(1-phenylvinyl)benzoic acid and 2-(1-(4-fluorophenyl)vinyl)benzoic acid using **NF-1** and **OF-1** under the same conditions are compared. These show that the reactivities of **NF-1** and **OF-1** are identical. Furthermore, it can be seen that these reactions are very quick since a 77% yield of the fluorocyclised product from 4-phenylpent-4-enoic acid was reached using **NF-1** after only 30 minutes **(Entry 1)**.

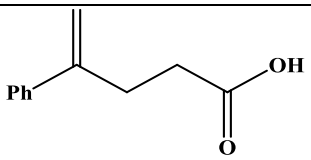
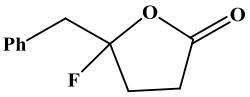
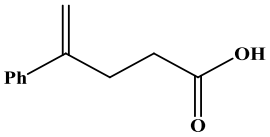
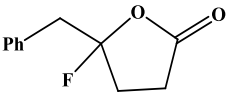
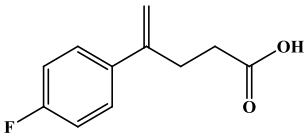
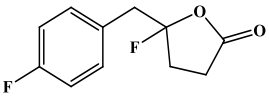
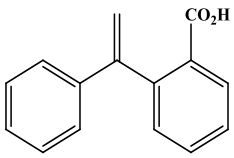
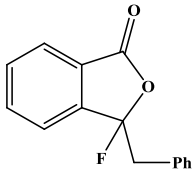
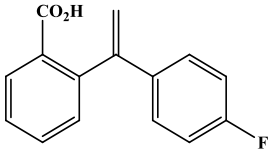
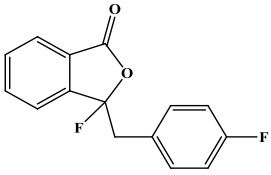
Entry	Substrate	Product	Time (h)	Yield with OF-1 (%)[34]	Yield with NF-1 (%)
1			0.5	-	77
2			1	84	85
3			1	80	79
4			1	79	78
5			1	81	82

Table 5.7 Fluorocyclisation of unsaturated carboxylic acids using **NF-1** and **OF-1**

5.3.2 NMR and mechanism

From the results it can be concluded that the reactivities, and hence the reaction mechanisms, for the fluorocyclisation using the *N*-functionalised F-I(III) **NF-1** and the *O*-functionalised F-I(III) **OF-1** are the same. The mechanism for the fluorocyclisation of 4-phenylpent-4-enoic acid using **NF-1** is shown in **Figure 5.9**. Here **NF-1** is activated by hydrogen bonding to HFIP, making the fluoride a better leaving group, increasing the electrophilicity of the I(III) centre and promoting reaction with the C = C bond of the substrate.

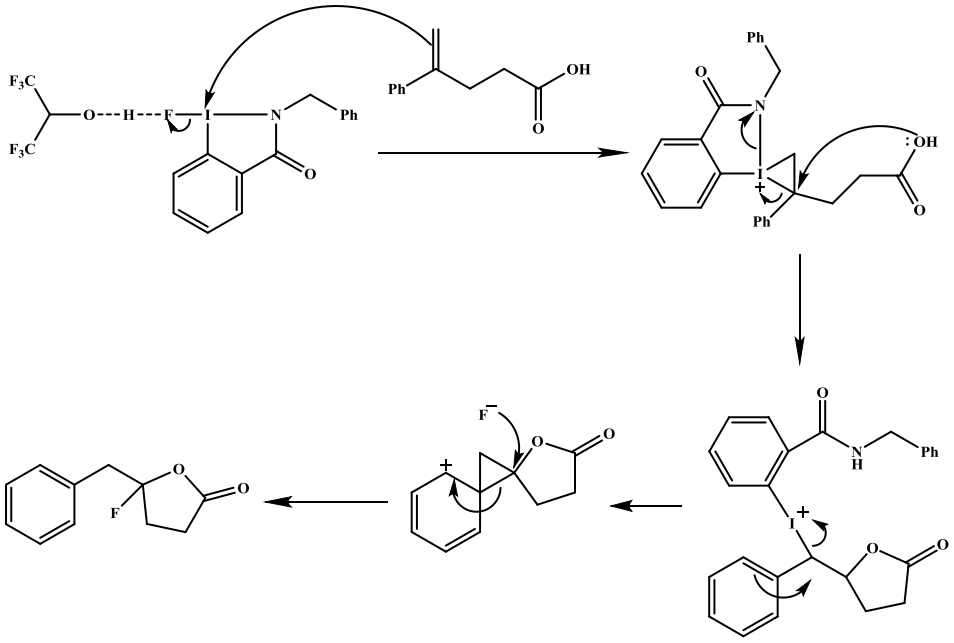


Figure 5.9 The mechanism of fluorocyclisation of 4-phenylpent-4-enoic acid using **NF-1** in HFIP

5.4 Attempted geminal difluorination of α,α'-disubstituted styrenes in hexafluoroisopropanol using fluorobenzoiodazolone

Following the success in the intramolecular fluorocyclisation of unsaturated carboxylic acids in HFIP using **NF-1** and from a consideration of Szabó's groups' studies on the geminal difluorination of styrenes using one equimolecular amount of **OF-1** with $AgBF_4$ [30] as well as the geminal difluorination of α, α'-disubstituted styrenes using **OF-1** with catalytic amounts (20 mol%) of $Pd(MeCN)_4BF_4$ and $Cu(MeCN)_4PF_6$ as the catalyst,[33] we next investgated if activation of **NF-1** by hydrogen bonding to HFIP could be applied to the geminal difluorination of α,α'-disubstituted styrenes directly. It is important to note that in the mechanisms **(Figure 5.10, 5.11)** proposed from Szabó's

work, one of C-F bonds is from **OF-1** whilst the other one is from the BF_4^- counterion in the metal salts.

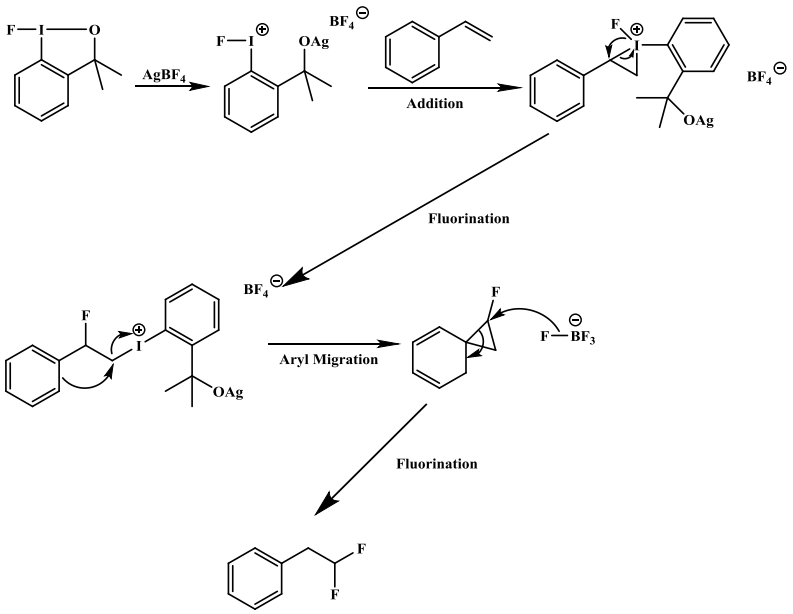


Figure 5.10 Proposed mechanism of difluorination styrene using **OF-1** with $AgBF_4$

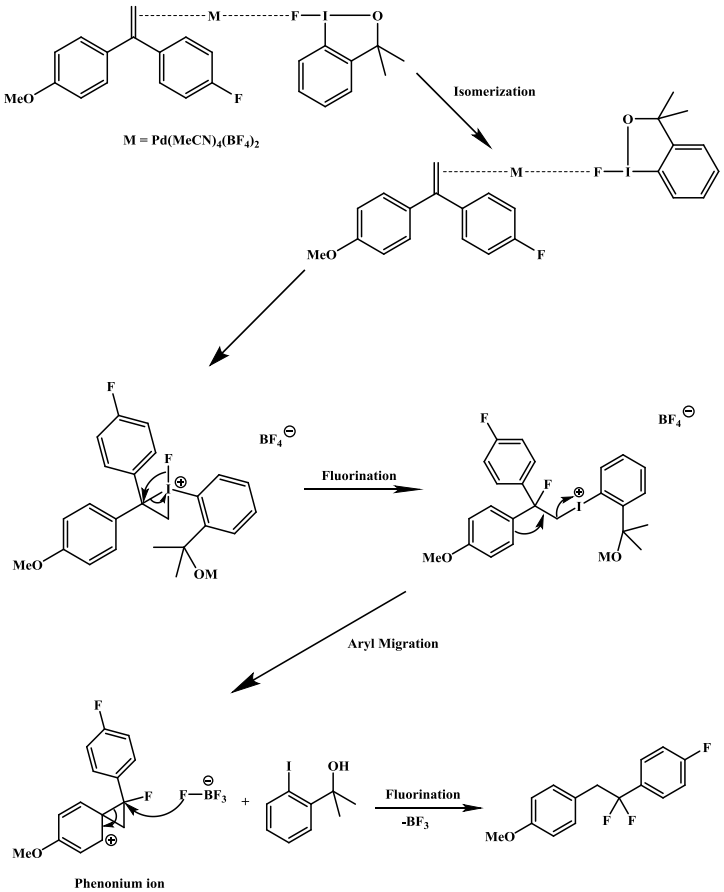


Figure 5.11 Proposed mechanism of geminal difluorination of α, α'-disubstituted styrenes using **OF-1** with $Pd(MeCN)_4(BF_4)_2$

1,1-Diphenylethylene was chosen as the substrate. In this process, the reason for the addition of 4 Å molecular sieves was similar to that in the intramolecular fluorocyclisation of unsaturated carboxylic acids in HFIP, i.e. removing water as a competing nucleophile. Firstly, the reaction was attempted using 2.2 equivalents of **NF-1** in HFIP (the solution was 1.25 M) at room temperature for one hour. However, only starting materials were seen in the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude reaction mixture after removal of the solvent. Neither increasing the reaction time to five hours, nor increasing the amount of **NF-1** (three equivalents), nor increasing the reaction temperature to 40 ℃ had any effect; only starting materials were recovered. Finally the solvent system for this reaction was considered. It was noted that Szabó's group had employed $CDCl_3$ instead of $CHCl_3$ as the solvent for this reaction to allow the crude reaction mixture to be analysed and the conversion of starting material to be monitored using ^{1}H NMR spectroscopy.[33] Based on this, we tried HFIP/$CHCl_3$ (0.1 mL/1.0 mL) and HFIP/$CDCl_3$ (0.3 mL/1.0 mL) as the solvent system with three and 2.2 equivalents of **NF-1** respectively, or 18 hours at 40 ℃, but found no evidence for the desired fluorinated product.

These results showed that activation of **NF-1** by HFIP could not be applied to the geminal difluorination of α, α'-disubstituted styrenes.

5.5 Conclusions

The reactivity of three new *N*-functionalised F-I(III) reagents **NF-1**, **NF-2** and **NF-3** in the fluorination of the 1,3-dicarbonyl compound ethyl benzoylacetate gave virtually identical isolated yields of the target fluorinated product. In comparison with the reactivity of the *O*-functionalized F-I(III) reagent **OF-1** in HFIP under the same reaction conditions comparable isolated yields of the monofluorination product, ethyl 2-fluoro-3-oxo-3-phenylpropanoate were obtained after 4 **(OF-1)** and 6 **(NF-1)** hours respectively. These differences in reactivity can nearly be ignored. **NF-1** was also used in the fluorination of ethyl (4-fluorobenzoyl)acetate and ethyl (4-methoxybenzoyl)acetate and the results were very similar to those using **OF-1**. It can be concluded that both **NF-1** and **OF-1** are good reagents for the fluorination of 1,3-ketoesters.

In an example of the fluorination of a 1,3-ketoamide, *N*,*N*-diethyl-3-oxo-3-phenylpropanamide, **NF-1** performed worse than **OF-1**. Using a 1,3-diketone as the substrate, it was easier to obtain the difluorination product from 1,3-diphenylpropane-

1,3-dione using **NF-1** than **OF-1** with the addition of TREAT-HF under the same conditions and no monofluorination product was obtained.

The evidence from the ^{1}H, ^{19}F and ^{13}C NMR spectra for a 1:1 mixture of **NF-1**: HFIP, when compared to those for either **NF-1** or HFIP alone revealed hydrogen bonding between HFIP and NF-1 that may activate NF-1 for the fluorination of organic molecules.

In the intramolecular fluorocyclisations of unsaturated carboxylic acids, the results using **NF-1** and **OF-1** were almost same. This is a very quick reaction when HFIP is used as the solvent. In contrast, the activation of **NF-1** by HFIP cannot be applied in the geminal difluorination of α, α'-disubstituted styrenes.

5.6 References

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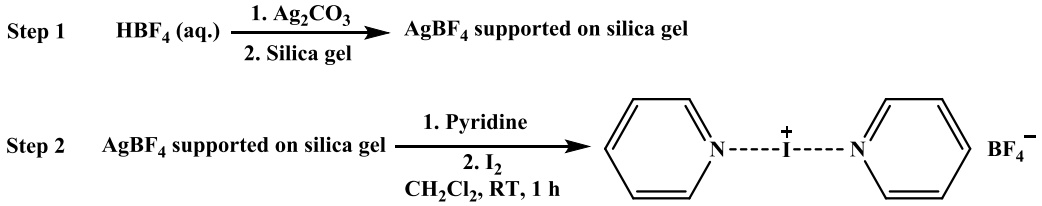
Chapter 6 Experimental

6.1 General information

All reactions were carried out using oven-dried glassware and syringes. Dry CH_2Cl_2, Et_3N and CH_3CN were obtained by distillation under dry, oxygen-free N_2 after they were stirred with calcium hydride as drying agent overnight. Dry Et_2O and THF were prepared by distillation after they were heated with sodium wire and sodium benzophenone at reflux under dry, oxygen-free N_2 for several hours until the colour turned deep blue. Dry DMF was commercially available. Dry toluene was prepared by distillation after being heated with sodium wire for two hours. Starting materials for synthesis were purchased from Sigma-Aldrich, Apollo Scientific, Alfa Aesar and Fluorochem. All the general solvents, iodine, anhydrous sodium sulfate, sodium thiosulfate pentahydrate, anhydrous magnesium sulfate, magnesium turnings, sodium chloride and ammonium chloride were obtained from Fisher Scientific. TLC was performed on aluminium-backed plates coated with silica gel 60 with F_{254} indicator. Flash column chromatography was carried out on silica gel 60, 200-425 mesh. ^{1}H NMR (400 MHz), ^{1}H NMR (500 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376 MHz) and ^{31}P NMR (161 MHz) spectra were recorded on Bruker DRX400, DRX500 and AV-400 instruments at room temperature. Fast atom bombardment (FAB), electrospray ionization (ESI) and atmospheric solids analysis probe (ASAP) mass spectrometry were recorded on a Waters XevoQToF mass spectrometer. Infrared spectra were recorded in the solid state on a Perkin Elmer Spectrum One FT-IR instrument. Single crystal X-ray diffraction data were collected on a Bruker Apex 2000 CCD diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Structure solution by direct methods and structure refinement on F^2 employed SHELXTL-97. Melting points were measured on a Gallenkamp melting point apparatus (model MFB-595) in open capillary tubes. Element analyses were obtained at the Science Technical Support Unit, London Metropolitan University.

6.2 Experimental procedures for Chapter 2

6.2.1 Synthesis of $[IPy_2][BF_4]$ and its analogues



Scheme 6.1 Synthesis of $[IPy_2][BF_4]$ **(NI-1)**

These procedures were modified and based on that described by the Davis group **(Scheme 6.1)**.[1] To a 500 mL round bottom flask was added deionized H_2O (50 mL) and HBF_4 (6.5 mL of a 48 wt.% aqueous solution, 50 mmol). Ag_2CO_3 (6.89 g, 25.0 mmol) was added to the stirred solution in several portions. The mixture was stirred vigorously until all the solids had dissolved and then carried on for 20 minutes. Silica gel (10.0 g) was added to the resulting solution. The slurry was stirred at room temperature for 5 minutes. After this time, the stirrer bar was removed, and the water was evaporated under high vacuum at 60 ℃ for three hours to give $AgBF_4$ on silica gel. The flask was cooled to room temperature and then carried on to the next step. Accordingly, CH_2Cl_2 (300 mL) was added and the mixture stirred. Care was taken to ensure all the silica gel was suspended in the solvent. Pyridine (20 mL, 250 mmol) and iodine (12.69 g, 50.0 mmol) were added sequentially to the reaction flask. AgI as a yellow powder precipitated immediately. The flask was stoppered, and the reaction mixture was stirred vigorously at room temperature for one hour. Subsequently, solids (AgI and silica gel) were removed by filtration. The filter cake was washed with CH_2Cl_2 (100 mL). The filtrate was concentrated by rotary evaporation to give a red solid. The solid was dissolved in CH_2Cl_2 (100 mL) and stirred at 0 ℃. Et_2O (200 mL) was poured into the stirred solution to precipitate the product which was isolated by filtration and dried under vacuum to give crude **NI-1** as a white powder. After recrystallization from CH_2Cl_2, the title compound was obtained as colourless prisms crystals 12.08 g (65% yield). m.p. = 149-150 ℃ (Lit [1]: 148-151 ℃). IR cm^{-1}: 1603, 1455, 1208, 1049, 1033, 758, 688, 637. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.90 (4H, dd, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 1.4 Hz, H-2), 8.20 (2H, tt, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.4 Hz, H-4), 7.64 (4H, dd, $^3J_{HH}$ = 7.7 Hz,

$^{3}J_{HH}$ = 6.4 Hz, H-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.1 (C-2), 143.1 (C-4), 129.5 (C-3). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -152.5 (BF_4^-). MS (FAB) m/z = 285 ($[IPy_2]^+$, 100%), 206 ($[IPy]^+$, 85%). These data are consistent with those reported in the literature.[1]

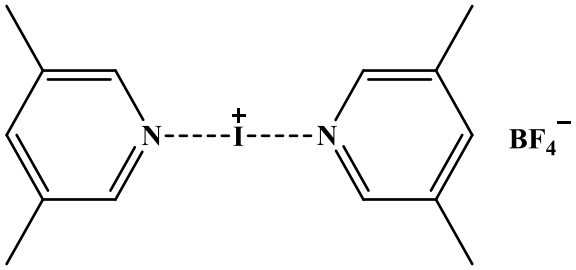


Figure 6.1 NI-2

CH_3CN was employed as the solvent in the synthesis of [I(3,5-dimethylpyridine)$_2$][BF_4] **(NI-2)** , [I(2-methoxypyridine)$_2$][BF_4] **(NI-3)** and [I(2,4,6-trimethylpyridine)$_2$][BF_4] **(NI-4)**. After recrystallization from CH_3CN, pure **NI-2 (Figure 6.1)** from 3,5-dimethylpyridine was obtained as colourless block crystals in a 54% yield. m.p. = 192-194 ℃. IR cm^{-1}: 1601, 1465, 1383, 1266, 1091, 1046, 875, 766, 694. ^{1}H NMR (400 MHz, CD_3CN) δ = 8.44 (4H, s, H-2), 7.66 (2H, s, H-4), 2.39 (12H, s, -CH_3). ^{13}C NMR (100 MHz, CD_3CN) δ = 146.5 (C-2), 143.1 (C-4), 138.0 (C-3), 17.1 (-CH_3). ^{19}F NMR (376 MHz, CD_3CN) δ = -152.4 (BF_4^-). MS (FAB) m/z = 341 ($[I(3,5\text{-}Me_2Py)_2]^+$, 95%), 234 ($[I(3,5\text{-}Me_2Py)]^+$, 100%). Anal. Calcd. for $C_{14}H_{18}BF_4IN_2$: C, 39.29; H, 4.24; N, 6.55. Found C, 39.33; H, 4.08; N, 6.54.

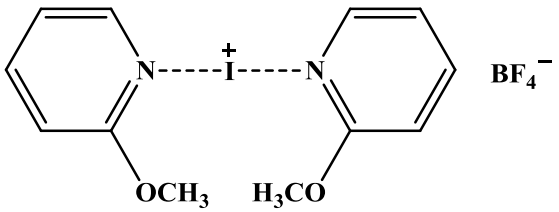


Figure 6.2 NI-3

Pure **NI-3 (Figure 6.2)** from 2-methoxypyridine was obtained as yellow block crystals in a 51% yield. m.p. = 138-140 ℃. IR cm^{-1}: 1606, 1575, 1489, 1285, 1047, 802, 766, 638. ^{1}H NMR (500 MHz, CD_3CN) δ = 8.52 (2H, d, $^{3}J_{HH}$ = 7.3 Hz, H-6), 8.15 (2H, t, $^{3}J_{HH}$ = 7.5 Hz, H-5), 7.20 (2H, d, $^{3}J_{HH}$ = 8.3 Hz, H-3), 7.09 (2H, tt, $^{3}J_{HH}$ = 8.0, $^{4}J_{HH}$ = 1.3 Hz, H-4), 4.08 (6H, s, -OCH_3). ^{13}C NMR (100 MHz, CD_3CN) δ = 162.9 (C-6),

148.1 (C-2), 145.1 (C-4), 119.1 (C-3), 108.7 (C-5), 57.0 (-OCH_3). ^{19}F NMR (376 MHz, CD_3CN) δ = -151.8 (BF_4^-). MS (FAB) m/z = 345 ($[I(2\text{-}OMePy)_2]^+$, 45%), 236 ($[I(2\text{-}OMePy)]^+$, 100%). Anal. Calcd. for $C_{12}H_{14}BF_4IN_2O_2$: C, 33.37; H, 3.27; N, 6.49. Found C, 33.23, H, 3.21; N, 6.38.

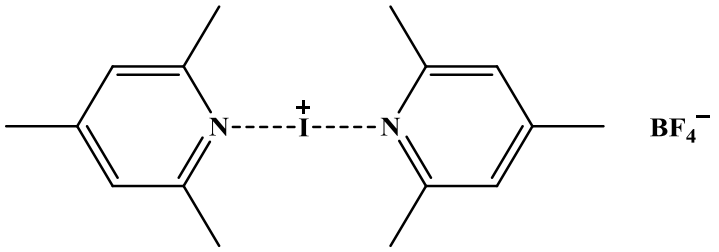
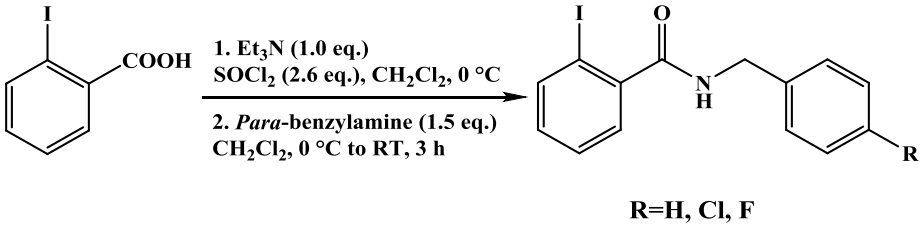


Figure 6.3 NI-4

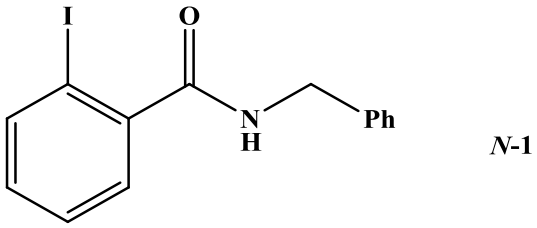
Pure **NI-4 (Figure 6.3)** from 2,4,6-trimethylpyridine was obtained as colourless block crystals in a 54% yield. The following analytical data was obtained from crystals: m.p. = 217-219 ℃. IR cm^{-1}: 1636, 1441, 1399, 1280, 1204, 1054, 957, 763. ^1H NMR (400 MHz, CD_3CN) δ = 7.14 (4H, s, H-3, H-5), 2.74 (12H, s, -CH_3-2, -CH_3-6), 2.47 (6H, s, -CH_3-4). ^{13}C NMR (100 MHz, CD_3CN) δ = 126.1 (C-3), 31.2 (-CH_3-2, -CH_3-6), 21.2 (-CH_3-4). ^{19}F NMR (376 MHz, CD_3CN) δ = -149.5 (BF_4^-). MS (FAB) m/z = 369 ($[I(2,4,6\text{-}Me_3Py)_2]^+$, $C_{16}H_{22}IN_2^+$ requires 369.0828, 45%), 248 ($[I(2,4,6\text{-}Me_3Py)]^+$, $C_8H_{11}IN^+$ requires 247.9936, 100%).

When the same method was used to attempt to synthesise $[I(2\text{-picolinic acid})_2][BF_4]$ from 2-picolinic acid and $[I(2\text{-acetylpyridine})_2][BF_4]$ from 2-acetylpyridine the reactions failed to work. The ^1H NMR spectrum (400 MHz, $CDCl_3$) of the product from the attempted synthesis of $[I(2\text{-acetylpy})_2][BF_4]$ showed peaks at 8.86 (2H, m), 8.62 (1H, d, *J* = 7.8 Hz), 8.29 (1H, td, *J* = 5.9, 1.1 Hz), 2.80 (3H, s, -CH_3) and a singlet in the ^{19}F NMR (376 MHz, $CDCl_3$) spectrum at -151.9 (BF_4^-). The single crystal X-ray evidence showed the product was $[H(2\text{-acetylpy})]BF_4$.

6.2.2 Synthesis of *N*-benzyl-2-iodobenzamide (*N*-1)



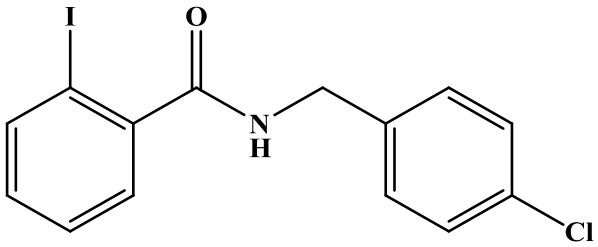
Scheme 6.2 Synthesis of *N*-(*para*-benzyl)-2-iodobenzamides



***N*-1**

Following a modified literature procedure **(Scheme 6.2)**,[2-3] Et_3N (1.4 mL, 10 mmol) was added to a solution of 2-iodobenzoic acid (2.48 g, 10 mmol) in CH_2Cl_2 (20 mL) until the solid disappeared and then $SOCl_2$ (2 mL, 26.6 mmol) was added dropwise at 0 ℃ with stirring. A solution of benzylamine (1.7 mL, 15 mmol) in CH_2Cl_2 (20 mL) was added to the mixture carefully and it was stirred at room temperature for three hours. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL) three times. Then combined organic layers were washed with brine (20 mL) and water (20 mL), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by recrystallization in CH_3CN. Colourless block crystals were obtained (2.52 g, 75% yield) that were suitable for analysis by X-ray crystallography. m.p. = 122-124 ℃ (Lit [2]: 123-125 ℃). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.86 (1H, dd, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 0.8 Hz, ArH), 7.43-7.28 (7H, m, ArH), 7.11-7.07 (1H, m, ArH), 6.03 (1H, broad s, -NH-), 4.65 (2H, d, $^3J_{HH}$ = 5.6 Hz, -CH_2-). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.2 (-CONH-), 142.0 (C), 139.9 (CH), 137.5 (C), 131.2 (CH), 130.7 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 92.4 (C-I), 44.3(CH_2). MS (ES^+) m/z: 338 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[2-3]

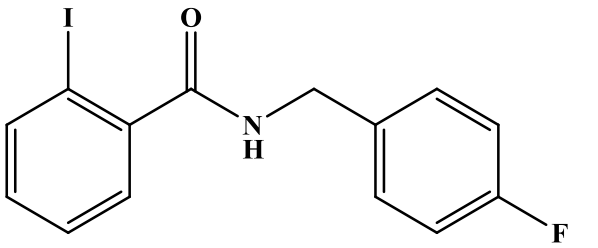
6.2.3 Synthesis of *N*-(4-chlorobenzyl)-2-iodobenzamide (*N*-2) (R = Cl)



***N*-2**

The same procedure was employed to synthesise *N*-(4-chlorobenzyl)-2-iodobenzamide **(*N*-2) (R = Cl)** as colourless needle-like crystals in a 78% yield. m.p. = 162-164 ℃ (Lit [4]: 164-165 ℃). IR cm^{-1}: 1646, 1538, 1489, 1323, 1087, 1013, 994, 826, 791, 746, 716, 650, 637. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (1H, dd, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 0.6 Hz, ArH), 7.42-7.32 (6H, m, ArH), 7.11 (1H, td, $^{3}J_{HH}$ = 5.9 Hz, $^{4}J_{HH}$ = 1.3 Hz, ArH), 6.05 (1H, broad s, -CONH-), 4.62 (2H, d, $^{3}J_{HH}$ = 5.8 Hz, -CH_2-). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.2 (-CONH-), 141.8 (C), 140.0 (CH), 136.1(C), 133.6 (CH), 131.3 (C), 129.5 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 92.4 (C-I), 43.5 (CH_2). MS (ESI) m/z: 372 ($[MH]^+$, 100%, ^{35}Cl), 374 ($[MH]^+$, 35%, ^{37}Cl). These data are consistent with those reported in the literature.[4]

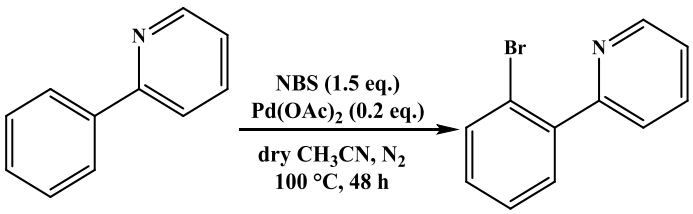
6.2.4 Synthesis of *N*-(4-fluorobenzyl)-2-iodobenzamide (*N*-3) (R = F)



***N*-3**

When the same procedures were employed to synthesise *N*-(4-fluorobenzyl)-2-iodobenzamide **(*N*-3) (R = F)**, colourless block crystals were obtained in an 80% yield. m.p. = 102-105 ℃. IR cm^{-1}: 1648, 1640, 1535, 1506, 1314, 1218, 990, 838, 818, 758, 743, 691, 642. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, ArH), 7.42-7.36 (4H, m, ArH), 7.12-7.03 (3H, m, ArH), 6.04 (1H, broad s, -CONH-), 4.62 (2H, d, $^{3}J_{HH}$ = 5.6 Hz, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.2 (-CONH-), 162.3 (d, $^{1}J_{CF}$ = 245.0 Hz, C-F) 141.9 (C), 139.9 (CH), 136.1(CH), 133.4 (CH), 131.3 (CH), 129.9 (d, $^{4}J_{CF}$ = 8.0 Hz, C), 128.3 (d, $^{3}J_{CF}$ = 12.9 Hz, CH), 115.7 (d, $^{2}J_{CF}$ = 21.3 Hz, CH), 92.4 (C-I), 43.5 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -114.5 (s, C-*F*). MS (ESI) m/z: 355.9953 ($[MH]^+$, $C_{14}H_{12}FINO^+$ requires 355.9948, 100%).

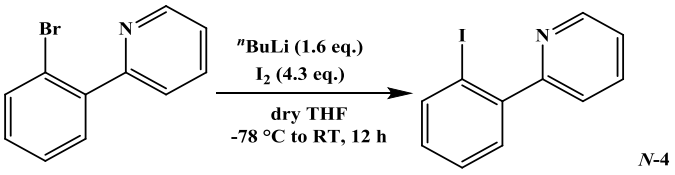
6.2.5 Synthesis of 2-(2-bromophenyl)pyridine



Scheme 6.3 Synthesis of 2-(2-bromophenyl)pyridine

In a Schlenk tube with a glass cap, $Pd(OAc)_2$ (0.08 g, 0.36 mmol, 0.2 eq.), NBS (0.457 g, 2.56 mmol, 1.5 eq.) and 2-phenylpyridine (0.25 mL, 1.75 mmol) were dissolved in dry acetonitrile (10 mL) under N_2. The solution was warmed to 100 ℃ and the tube was closed. The mixture was heated at reflux for 48 h **(Scheme 6.3)**, then cooled to the room temperature, filtered through Celite and the solids were washed with CH_3CN (20 mL). The filtrate was concentrated under reduced pressure and purified by column chromatography using ethyl acetate/hexane (V:V = 1:2) on silica gel. The title product was obtained as a yellowish oil (0.286 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (1H, dd, $^3J_{HH}$ = 4.2 Hz, $^4J_{HH}$ = 1.0 Hz), 7.77 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ =1.8 Hz), 7.68 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz), 7.61 (1H, dt, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.0 Hz), 7.53 (1H, dd, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.7 Hz), 7.41 (2H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz), 7.32-7.24 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3 (C), 149.4 (CH), 141.2 (C), 135.9 (CH), 133.3 (CH), 131.4 (CH), 129.8 (CH), 127.6 (CH), 124.8 (CH), 122.5 (CH), 121.8 (C). MS (ASAP) m/z: 234 ($[MH]^+$, 100%, ^{79}Br), 236 ($[MH]^+$, 98%, ^{81}Br). These data are consistent with those reported in the literature.[5]

6.2.6 Synthesis of 2-(2-iodophenyl)pyridine (*N*-4)

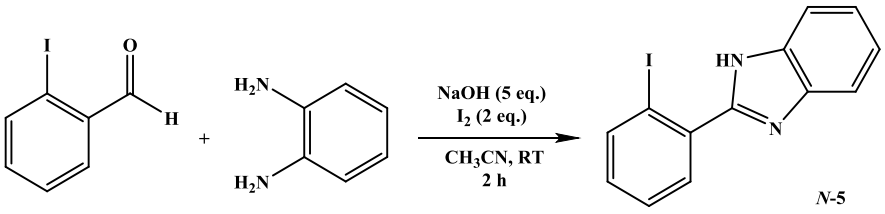


Scheme 6.4 Synthesis of 2-(2-iodophenyl)pyridine

In a 100 mL three-necked flask, 2-(2-bromophenyl)pyridine (0.234 g, 1.0 mmol) was dissolved in dry THF (10 mL), then cooled to -78 ℃ and ^{n}BuLi (1.0 mL, 1.6 M in

hexane, 1.6 mmol) was added. The lithiation was complete after 1 h and the reaction mixture was quenched with I_2 (1.15 g, 4.5 mmol) in dry THF (6 mL). After that, dry THF (5 mL) was added and the mixture was allowed to warm up to room temperature and stirred for 12 h **(Scheme 6.4)**. It was quenched with a saturated NH_4Cl solution (15 mL), a saturated $Na_2S_2O_3$ solution (15 mL) was added and the mixture extracted with ethyl acetate (20 mL) three times. The organic layers were combined and washed with brine (10 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The pure product (0.216 g, 0.76 mmol, 76% yield) was obtained as a yellow oil after purification by column chromatography using ethyl acetate/hexane (V:V = 1:3) on silica gel. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.64 (1H, d, $^3J_{HH}$ = 4.9 Hz), 7.89 (1H, d, $^3J_{HH}$ = 7.8 Hz), 7.70 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ =1.8 Hz), 7.39-7.30 (3H, m), 7.24 (1H, ddd, $^3J_{HH}$ = 6.5 Hz, $^3J_{HH}$ = 5.0 Hz, $^4J_{HH}$ =1.1 Hz), 7.02 (1H, ddd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ =2.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.8 (C), 148.2 (CH), 144.0 (C), 138.7 (CH), 135.0 (CH), 129.3 (CH), 128.7 (CH), 123.4 (CH), 121.5 (CH), 95.7 (C-I). MS (ASAP) m/z: 282 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[5]

6.2.7 Synthesis of 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole (*N*-5)

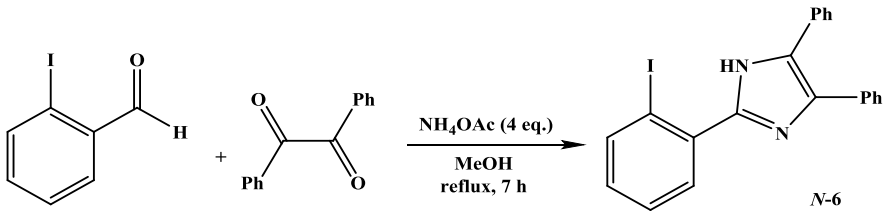


Scheme 6.5 Synthetic route for 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole **(*N*-5)**

Following a modified literature procedure,[6] 2-iodobenzaldehyde (1.16 g, 5.00 mmol) and 1,2-phenylenediamine (0.54 g, 5.00 mmol) were dissolved in CH_3CN (20 mL) and stirred at room temperature for 1 h. Then, NaOH (1.00 g, 25 mmol) and I_2 (2.54 g, 10 mmol) were added and the reaction mixture continued to be stirred at room temperature for 1 h **(Scheme 6.5)**. After that, a saturated $Na_2S_2O_3$ aqueous solution (100 mL) was added and the mixture was extracted with EtOAc (200 mL) three times. The combined organic layers were washed with brine (50 mL) and, water (50 mL), dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The crude product, a

brown solid, was washed with acetone (10 mL) and dried in vacuum to give the pure product as a yellowish solid (1.03 g, 65% yield). m.p. = 237-239 ℃ (Lit [6]: 238-240 ℃). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.89 (1H, broad s, -NH-), 7.99 (2H, dd, $^{3}J_{HH}$ = 7.9 Hz, $^{4}J_{HH}$ = 1.0 Hz, ArH), 7.80 (2H, dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.2 Hz, ArH), 7.48 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.2 Hz, ArH), 7.34-7.31 (2H, m, ArH), 7.17 (1H, td, $^{3}J_{HH}$ = 7.6, $^{4}J_{HH}$ = 1.7 Hz, ArH). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.4 (C), 140.5 (C), 135.2 (C), 135.0 (CH), 132.4 (CH), 131.3 (CH), 128.5 (CH), 123.2 (CH), 120.4 (CH), 94.6 (C-I). MS (ES^+) m/z = 321 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[6]

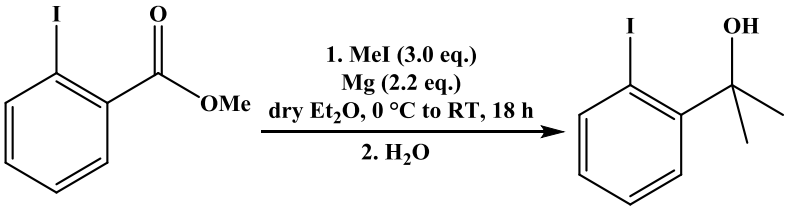
6.2.8 Synthesis of 2-(2-iodophenyl)-4,5-diphenyl-1*H*-imidazole (*N*-6)



Scheme 6.6 Synthetic route for 2-(2-iodophenyl)-4,5-diphenyl-1*H*-imidazole **(*N*-6)**

2-Iodobenzaldehyde (1.16 g, 5.0 mmol) was dissolved in MeOH (10 mL) and benzil (1.05 g, 5.0 mmol) and NH_4OAc (1.54 g, 20.0 mmol) were added. The mixture was heated at 70 ℃ for 7 hours **(Scheme 6.6)**. After the resulting suspension was cooled to room temperature, the solvent was decanted by syringe. The residual solid was recrystallized in DMF and block crystals were obtained which were suitable for X-ray crystallographic analysis. The title product was obtained as a white solid (1.23 g, 58% yield). m.p. = 237-239 ℃ (The related data could not be found in the literature). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.93 (1H, broad s, -NH-), 8.13 (1H, dd, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.6 Hz, ArH), 7.96 (1H, dd, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 1.0 Hz, ArH), 7.69 (2H, d, $^{3}J_{HH}$ = 5.5 Hz, ArH), 7.52-7.33 (10H, m, ArH), 7.08 (1H, td, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.7 Hz, ArH). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.3 (C), 140.5 (C), 138.0 (C), 134.6 (CH), 134.4 (CH), 131.6 (CH), 130.9 (CH), 130.2 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 127.0 (CH), 93.4 (C-I). MS (ES^+) m/z = 423 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[6]

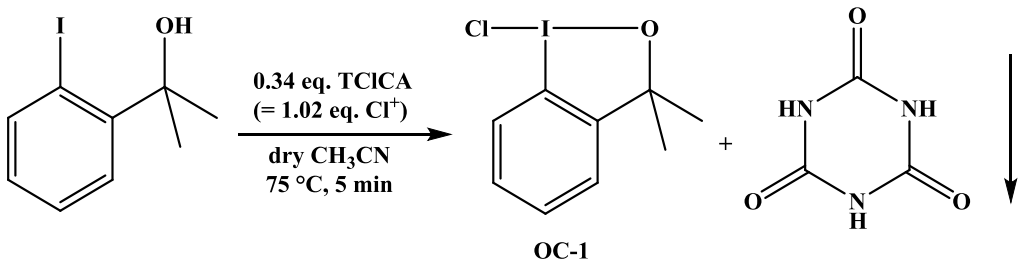
6.2.9 Synthesis of 2-(2-iodophenyl)propan-2-ol



Scheme 6.7 Synthetic route for 2-(2-iodophenyl)propan-2-ol

A dry, three-necked 250 mL round bottom flask equipped with a reflux condenser and, dropping funnel was charged with magnesium turnings (5.12 g, 210 mmol) and then evacuated for half an hour, refilled with N_2 three times before dry Et_2O (15 mL) was added. A solution of MeI (18 mL, 287 mmol) in dry Et_2O (15 mL) was charged to the dropping funnel and then added to the flask dropwise. Initiation of the reaction was observed after the addition of nearly 2 mL of the MeI under N_2. At this point, the mixture was diluted with dry Et_2O (20 mL) and addition of the MeI solution was held at a rate that kept the reaction mixture at reflux. After all of the MeI solution had been added, the flask was cooled to the room temperature. The mixture was stirred for a further 15 minutes and then cooled to 0 ℃. A solution of methyl-2-iodobenzoate (25.0 g, 95.4 mmol) in dry Et_2O (10 mL) was then added to the MeMgI solution over 10 minutes followed slowly by dry Et_2O (10 mL) and the mixture was stirred for 18 hours **(Scheme 6.7)**. An ice cold saturated solution of NH_4Cl (75 mL) was then added into the mixture dropwise carefully at 0 ℃. Water (150 mL) was added and the mixture was stirred for half an hour until all of the precipitate had dissolved. After filtration through a pad of Celite, the organic layer was separated, and the aqueous layer was extracted with Et_2O (150 mL) four times. The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The pure product was obtained as a dark brown oil (21.25 g, 85% yield) after the solvent had been removed. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (1H, d, $^3J_{HH}$ = 7.8 Hz, ArH), 7.63 (1H, dd, $^3J_{HH}$ = 6.5 Hz, $^4J_{HH}$ = 1.4 Hz, ArH), 7.33 (1H, td, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 0.7 Hz, ArH), 6.90 (1H, td, $^3J_{HH}$ = 6.3 Hz, $^4J_{HH}$ = 1.1 Hz, ArH), 2.49 (1H, s, -OH), 1.76 (6H, s, $-CH_3$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.5 (C), 142.7 (CH), 128.6 (CH), 128.2 (CH), 126.7 (CH), 93.2 (C-I), 73.6 (CO), 29.8 ($-CH_3$). MS (ASAP) m/z: 244.9882 ($[M\text{-}OH]^+$, 5%). These data are consistent with those reported in the literature.[7]

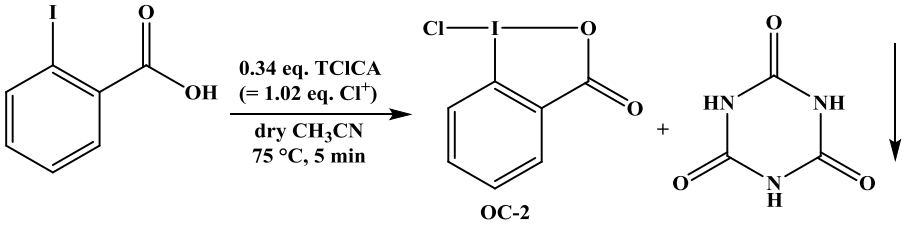
6.2.10 Synthesis of 1-chloro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[*d*][1,2]iodoxole (OC-1)



Scheme 6.8 Synthetic route for 1-chloro-3,3-dimethyl-1,3-dihydro-1λ^3-benzo[d][1,2]iodoxole **(OC-1)**

A 100 mL three-necked round bottom flask equipped with a magnetic stirring bar, N_2 adapter, glass stopper and a rubber stopper was charged with 2-(2-iodophenyl)propan-2-ol (1.05 g, 4.0 mmol), evacuated and refilled with N_2 three times before dry CH_3CN (15 mL) was added. Then, a solution of TClCA (0.32 g, 1.4 mmol) in dry CH_3CN (5 mL) was added to the flask carefully. After that, the mixture was heated to 75 ℃ under N_2 and stirred for five minutes. During the addition of the TClCA solution, formation of insoluble isocyanuric acid as a white solid was observed **(Scheme 6.8)**. The resulting mixture was filtered hot over a preheated sintered-glass funnel covered with a pad of Celite (approximately 1 cm thick). Solvent from the filtrate was removed under vacuum. Yellow-brown crystals were obtained which were washed with a little cold CH_3CN. The final product was obtained as yellow block crystals (1.0 g, 85% yield). m.p. = 143 - 145 ℃ (Lit [8]: 143-145 ℃). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (1H, d, $^3J_{HH}$ = 8.2 Hz, ArH), 7.59-7.51 (2H, m, ArH), 7.18 (1H, d, $^3J_{HH}$ = 7.4 Hz, ArH), 1.55 (6H, s, -CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 149.4 (C), 130.9 (CH), 130.4 (CH), 128.4 (CH), 126.1 (CH), 114.6 (C-I), 85.1 (CO), 29.2 (-CH_3). MS (ASAP) m/z: 297 ($[MH]^+$, 10%), 261 ($[MH-Cl]^+$, 100%). These data are consistent with those reported in the literature.[8]

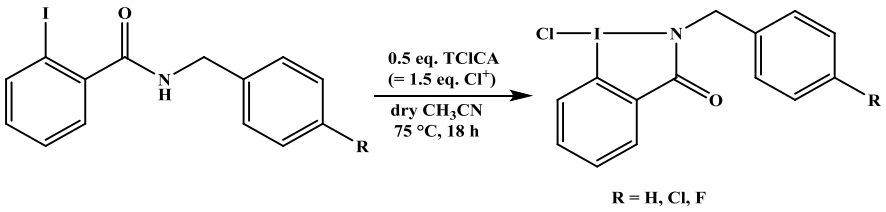
6.2.11 Synthesis of 1-chloro-1,2-benziodoxol-3-(1*H*)-one (OC-2)



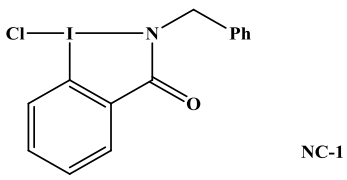
Scheme 6.9 Synthetic route for 1-chloro-1,2-benziodoxol-3-(1*H*)-one **(OC-2)**

1-Chloro-1,2-benziodoxol-3-(1*H*)-one **(OC-2)** was prepared similarly from 2-iodobenzoic acid (1.0 g, 4.0 mmol) and TClCA (0.32 g, 1.4 mmol) **(Scheme 6.9)**. The final product was obtained as light yellow block crystals (0.96 g, 85% yield). m.p. = 168-170 ℃ (Lit [8]: 167-170 ℃). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.28-8.21 (2H, m, ArH), 8.00 (1H, td, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.1 Hz, ArH), 7.80 (1H, t, $^{3}J_{HH}$ = 7.3 Hz, ArH). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.1 (C=O), 136.6 (C), 133.4 (CH), 131.9 (CH), 128.7 (CH), 126.9 (CH), 117.1 (C-I). MS (ASAP) m/z: 283 ($[MH]^+$, 10%), 248 ($[MH-Cl]^+$,100%). These data are consistent with those reported in the literatures.[8]

6.2.12 Synthesis of 2-benzyl-1-chloro-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one (NC-1)



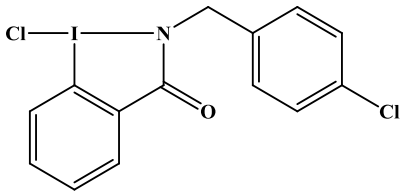
Scheme 6.10 Synthetic route for 2-benzyl-1-chloro-1,2-dihydro-3*H*-λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-1)** and its analogues



A 100 mL three-necked round bottom flask equipped with a magnetic stirring bar, N_2 adapter, glass stopper and a rubber stopper was charged with solid *N*-benzyl-2-

iodobenzamide (0.50 g, 1.48 mmol), then evacuated and refilled with N_2 three times before dry CH_3CN (15 mL) was added. TClCA (0.18 g, 0.74 mmol) dissolved in dry CH_3CN (5 mL) was added carefully and the resulting mixture was heated to 75 ℃ and stirred for 18 hours **(Scheme 6.10)**. During the process of heating, insoluble isocyanuric acid became apparent. After that, the reaction mixture was filtered over a funnel with a pad of Celite and the filter cake was washed with CH_3CN (5 mL). The filtrates were combined, the solvent was removed under reduced pressure and the crude product was obtained as a white solid. When it was recrystallized from EtOAc, the pure title product **NC-1** was obtained as colourless block crystals (0.42 g, 75% yield) which were suitable for the X-ray crystallographic analysis. m.p. = 152-154 ℃. IR cm^{-1}: 1608, 1586, 1563, 1437, 1375, 1346, 1035, 963, 785, 743, 735, 698, 686. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 0.7 Hz, ArH), 8.24 (1H, dd, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 1.8 Hz, ArH), 7.85-7.75 (2H, m, ArH), 7.45-7.40 (5H, m, ArH), 4.89 (2H, s, -CH_2-). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.2 (C=O), 137.7 (C), 134.9 (CH), 132.5 (CH), 132.0 (CH), 131.5 (CH), 129.6 (C), 129.1 (CH), 128.9 (CH), 127.8 (CH), 116.8 (C-I), 48.2 (CH_2). MS (ASAP) m/z = 371.9662 ($[MH]^+$, $C_{14}H_{12}ClINO^+$ (^{35}Cl) requires 371.9652, 100%). Anal. Calcd. for $C_{14}H_{11}ClINO$: C, 45.25; H, 2.98; N, 3.77. Found C, 45.08; H, 3.14; N, 3.83.

6.2.13 Synthesis of 1-chloro-2-(4-chlorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one (NC-2) (R = Cl)

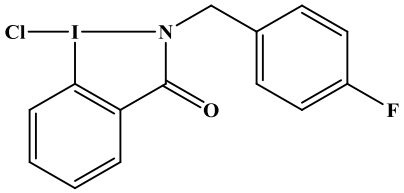


NC-2

1-Chloro-2-(4-chlorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-2) (R = Cl)** was prepared similarly in a 78% yield. Single crystals suitable for X-ray crystallographic analysis were obtained by keeping a saturated CH_3CN solution at -20 ℃ for 18 hours. m.p. = 130-132 ℃. IR cm^{-1}: 1635, 1587, 1438, 1350, 1337, 1088, 1009, 968, 819, 798, 732, 664, 652. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (1H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 8.23 (1H, dd, $^3J_{HH}$ = 5.7 Hz, $^4J_{HH}$ = 1.7 Hz, ArH), 7.85 (1H, td, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ = 1.7 Hz, ArH), 7.77 (1H, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 0.7 Hz, ArH), 7.39-7.32 (4H, m, ArH), 4.86 (2H, s, -CH_2-). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.5 (C=O), 134.2 (C), 133.2 (CH), 132.9 (CH), 130.2 (CH), 130.1 (C), 129.6 (CH), 128.1 (CH),

127.7 (C), 125.7 (CH), 114.5 (C-I), 45.2 (CH_2). MS (ASAP) m/z = 405.9262 ($[MH]^+$, $C_{14}H_{11}Cl_2INO^+$ requires 405.9263, 100%).

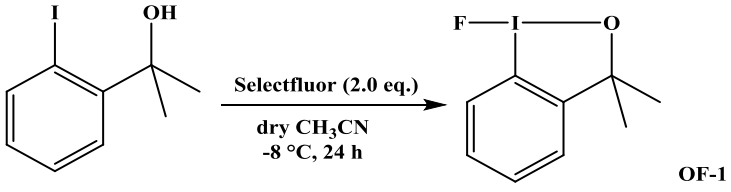
6.2.14 Synthesis of 1-chloro-2-(4-fluorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one (NC-3) (R = F)



NC-3

1-Chloro-2-(4-fluorobenzyl)-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-3) (R = F)** was obtained as a pale yellow powder in an 80% yield. Single crystals suitable for X-ray crystallographic analysis were obtained from CH_3CN solution held at -20 ℃ for 18 hours. m.p. = 150-152 ℃. IR cm^{-1}: 1699, 1604, 1587, 1440, 1418, 1402, 1376, 1220, 834, 823, 761, 742, 666. ^{1}H NMR (500 MHz, CD_3CN): δ = 8.45 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.8 Hz, ArH), 8.10 (1H, dd, $^3J_{HH}$ = 5.6 Hz, $^4J_{HH}$ = 1.8 Hz, ArH), 7.93-7.89 (1H, m, ArH), 7.80 (1H, td, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 0.9 Hz, ArH), 7.43-7.40 (2H, m, ArH), 7.13-7.07 (2H, m, ArH), 4.82 (2H, s, -CH_2-). ^{13}C NMR (126 MHz, CD_3CN): δ = 165.5 (C=O), 162.9 (d, $^1J_{CF}$ = 248.7 Hz, C-F), 134.8 (C), 134.3 (CH), 131.7 (CH), 131.1 (CH), 131.0 (CH), 129.8 (d, $^3J_{CF}$ = 9.2 Hz, CH), 127.4 (C), 116.4 (C-I), 115.2 (d, $^2J_{CF}$ = 21.9 Hz, CH), 45.6 (CH_2). ^{19}F NMR (376 MHz, CD_3CN): δ = -116.3 (s, C-F). MS (ASAP) m/z = 389.9558 ($[MH]^+$, $C_{14}H_{11}ClFINO^+$ requires 389.9558, 100%).

6.2.15 Synthesis of 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole (OF-1) using Selectfluor



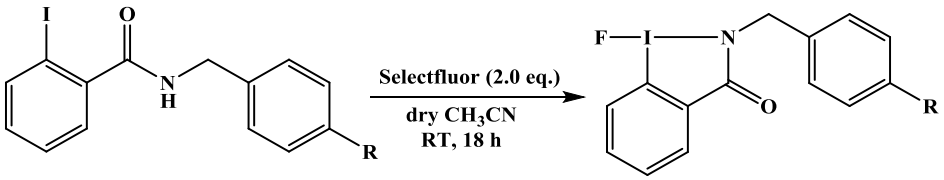
OF-1

Scheme 6.11 Synthetic route for 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)** using Selectfluor

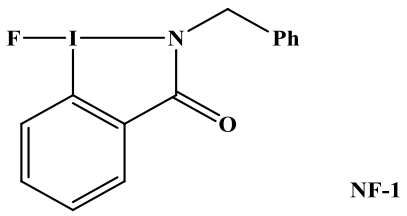
A 250 mL three-necked flask containing a solution of 2-(2-iodophenyl)propan-2-ol (1.04 g, 3.97 mmol) in dry CH_3CN (80 mL) under N_2 was cooled to -8 ℃. After

stirring the solution for 10 minutes, Selectfluor (2.81 g, 7.94 mmol) was added and the reaction mixture was stirred at -8 ℃ for 24 hours **(Scheme 6.11)**. The solvent was removed on a rotary evaporator and the resulting white solid which was extracted with CH_3Cl (15 mL) three times. The combined CH_3Cl extractions were concentrated under reduced pressure to give a yelloow oil. After that, it was extracted with hexane (15 mL) three times. The pure product, 1-fluoro-3,3-dimethyl-1,3-dihydro-λ^3-benzo[d][1,2]iodoxole **(OF-1)**, was obtained as colourless crystals (0.41 g, 37% yield) after the hexane solution was concentrated on a rotary evaporator. m.p. = 82-84 ℃ (Lit [9]: 82-84 ℃). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz, ArH), 7.55 (1H, td, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 7.47 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, ArH), 7.17 (1H, dt, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5 Hz, ArH), 1.52 (6H, s, -CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.5 (C), 130.5 (CH), 130.2 (CH), 128.6 (CH), 125.9 (CH), 115.9 (C-I), 85.2 (C), 29.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -142.9 (s, F-I). MS (ASAP) m/z: 280.9944 ($[MH]^+$, 5%), 260.9773 ($[M-F]^+$, 100%). These data are consistent with those reported in the literature.[9]

6.2.16 Synthesis of 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one (NF-1)



Scheme 6.12 Synthetic route for 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)** and its analogues

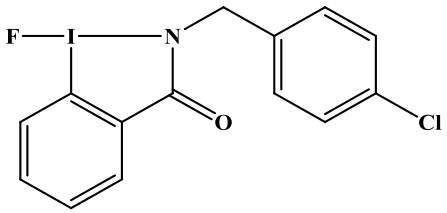


NF-1

A solution of *N*-benzyl-2-iodobenzamide (***N*-1**) (2.7 g, 8.05 mmol) in dry CH_3CN (240 mL) was prepared under N_2 in a 500 mL three-necked flask and stirred at room

temperature. To this system Selectfluor (5.73 g, 16.09 mmol) was added and the mixture was stirred at room temperature for 18 hours **(Scheme 6.12)**. The solvent was removed under reduced pressure to give a white solid which was extracted with $CHCl_3$ (120 mL) three times. The combined chloroform solutions were concentrated under reduced pressure to give a white solid mixed with a yellow oil. The product was extracted with ethyl acetate (200 mL) and the solvent was removed under reduced pressure to give a yellow oil. From the ^{1}H NMR (400 MHz, $CDCl_3$) and ^{19}F NMR (376 MHz, $CDCl_3$) spectra of crude product, it could be seen that it was impure. Finally, CH_3CN (5 mL) was added to dissolve the crude product and kept at -18 ℃ overnight to give colourless single crystals of the title compound 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1) (R = H)** (1.83 g, 62% yield) which were suitable for X-ray crystallography. m.p. = 108-110 ℃. ^{1}H NMR (500MHz, $CDCl_3$): δ = 8.22 (1H, d, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 8.04 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.81 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 7.70 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, ArH), 7.45-7.37 (5H, m, ArH), 4.79 (2H, d, $^4J_{HF}$ = 5.6 Hz, -CH_2-, on fluorine decoupling simplifies to a singlet). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.9 (C=O), 137.2 (C), 134.6 (CH), 132.7 (CH), 132.0 (CH), 131.3 (CH), 130.9 (CH), 129.5 (C), 129.1 (CH), 129.0 (CH), 117.8 (C-I), 48.1 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -104.4 (s, F-I). MS (ESI) m/z: 355.9954 ($[MH]^+$, $C_{14}H_{12}FINO^+$ requires 355.9948, 100%). Anal. Calcd. for $C_{14}H_{11}FIO$: C, 47.35; H, 3.12; N, 3.94. Found C, 47.31, H, 3.12; N, 3.94.

6.2.17 Synthesis of 2-(4-chlorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one (NF-2) (R = Cl)

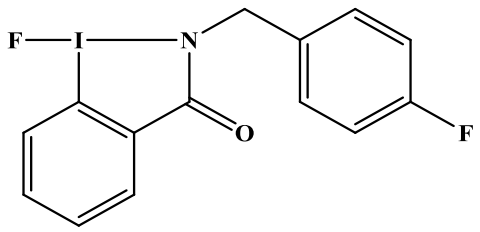


NF-2

2-(4-Chlorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-2) (R = Cl)** from *N*-(4-chlorobenzyl)-2-iodobenzamide (***N*-2**) was obtained as colourless block crystals by the same method. The yield was 60%. m.p. = 116-119 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 8.05 (1H, d, $^3J_{HH}$ = 7.5 Hz,

ArH), 7.83 (1H, td, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.2 Hz, ArH), 7.71 (1H, td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.0 Hz, ArH), 7.40-7.30 (4H, m, ArH), 4.77 (2H, d, $^{4}J_{HF}$ = 6.5 Hz, -CH_2-, on fluorine decoupling simplifies to a singlet). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.1 (C=O), 135.7 (C), 134.8 (CH), 132.3 (CH), 131.5 (CH), 131.0 (CH), 130.1 (CH), 129.6 (C), 129.1 (C), 129.0 (CH), 117.6 (C-I), 47.0 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -105.1 (s, F-I). MS (ASAP) m/z: 389.9565 ($[MH]^+$, $C_{14}H_{11}ClFINO^+$ (^{35}Cl) requires 389.9558, 100%).

6.2.18 Synthesis of 2-(4-fluorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one (NF-3) (R = F)

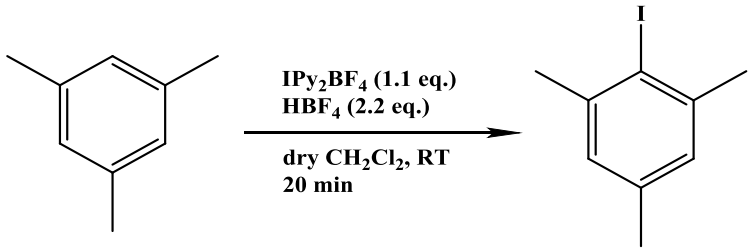


NF-3

2-(4-Fluorobenzyl)-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-3) (R = F)** from *N*-(4-fluorobenzyl)-2-iodobenzamide (***N*-3**) was obtained as colourless block crystals in a 60% yield. m.p. = 113-115 ℃. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (1H, dd, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.4 Hz, ArH), 8.05 (1H, d, $^{3}J_{HH}$ = 7.6 Hz, ArH), 7.83 (1H, td, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.6 Hz, ArH), 7.71 (1H, td, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.0 Hz, ArH), 7.39-7.35 (2H, m, ArH), 7.13-7.08 (2H, m, ArH), 4.77 (2H, d, $^{4}J_{HF}$ = 6.1 Hz, -CH_2-, on fluorine decoupling simplifies to a singlet). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.0 (C=O), 163.4 (d, $^{1}J_{CF}$ = 248.2 Hz, C-F), 134.7 (C), 133.1 (CH), 132.5 (CH), 131.4 (CH), 131.0 (CH), 130.7 (d, $^{4}J_{CF}$ = 8.2 Hz, C), 129.1 (d, $^{3}J_{CF}$ = 9.2 Hz, CH), 117.7 (C-I), 116.4 (d, $^{2}J_{CF}$ = 21.8 Hz, CH), 47.1 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -104.7 (s, F-I), -112.3 (s, C-*F*). MS (ASAP) m/z: 373.9867 ($[MH]^+$, $C_{14}H_{11}F_2INO^+$ requires 373.9854, 100%).

6.3 Experimental procedures for Chapter 3

6.3.1 Preparation of 2-iodo-1,3,5-trimethylbenzene using $[IPy_2][BF_4]$ and its analogues



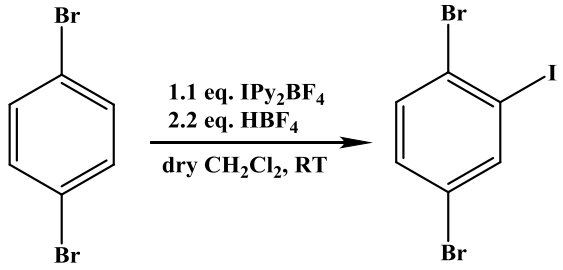
Scheme 6.13 Synthesis of 2-iodo-1,3,5-trimethylbenzene using $[IPy_2][BF_4]$ **(NI-1)**

These procedures were based on those described by Barluenga's group **(Scheme 6.13)**.[10] A 100 mL three-necked round bottom flask equipped with a magnetic stirring bar, N_2 adapter, glass stopper and a rubber stopper was charged with IPy_2BF_4 **(NI-1)** (1.00 g, 2.7 mmol), then evacuated for 20 minutes, refilled with N_2 three times at room temperature before dry CH_2Cl_2 (30 mL) was syringed into the flask to dissolve all the solids. Then, 1,3,5-trimethylbenzene (0.34 mL, 2.45 mmol) was added to the solution. A solution of HBF_4 (1 mL of a 54% diethyl ether solution) mixed with dry CH_2Cl_2 (5 mL) was added over 5 minutes to the magnetically stirred mixture, which was stirred for a further 15 minutes. After that, the reaction mixture was treated with a saturated $Na_2S_2O_3$ aqueous solution (10 mL) and extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the pure product as yellow crystals was obtained (0.546 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89 (2H, s, ArH-4, ArH-6), 2.44 (6H, s, -CH_3-1, -CH_3-3), 2.22 (3H, s, -CH_3-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.8 (C-5), 137.3 (C-1, C-3), 128.0 (C-4, C-6), 95.6 (C-I), 29.5 (-CH_3-1, -CH_3-3), 20.6 (-CH_3-5). MS (ASAP) m/z: 246 (M^+, 100%). These data are consistent with those reported in the literature.[10]

When $[I(3,5\text{-dimethylpyridine})_2][BF_4]$ **(NI-2)**, $[I(2\text{-methoxypyridine})_2][BF_4]$ **(NI-3)** and $[I(2,4,6\text{-trimethylpyridine})_2][BF_4]$ **(NI-4)** were used, the conversions of 1,3,5-trimethylbenzene were all 100%. The final yields of 2-iodo-trimethylbenzene as yellow crystals were 87%, 78% and 81% respectively. It is worth mentioning that with **NI-3** the crude product needed to be purified by column chromatography on silica gel using hexane/ethyl acetate (V:V = 20:1). The pure 2-iodo-1,3,5-trimethylbenzene as yellow

crystals could be obtained directly from the reactions with **NI-2** and **NI-4** after the solvent was removed by rotary evaporation and recrystallization in CH_2Cl_2.

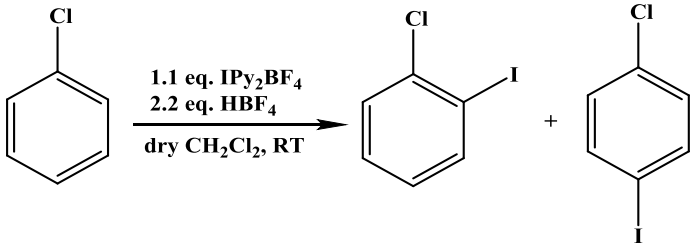
6.3.2 Attempted iodination of 1,4-dibromobenzene using $[IPy_2][BF_4]$



Scheme 6.14 Attempted iodination of 1,4-dibromobenzene using $[IPy_2][BF_4]$

When the same procedures were used for the iodination of 1,4-dibromobenzene **(Scheme 6.14)**, only starting materials were recovered. The reactions were attempted at room temperature for one hour and 18 hours, and at 40 ℃ for one hour.

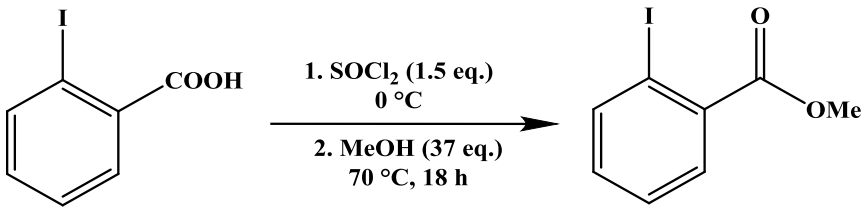
6.3.3 Iodination of chlorobenzene using $[IPy_2][BF_4]$ and its analogues



Scheme 6.15 Iodination of chlorobenzene using $[IPy_2][BF_4]$

The same procedures were used for the iodination of chlorobenzene **(Scheme 6.15)**. The products, obtained as colourless oils, were mixtures of *o*- and *p*-chloroiodobenzene. After 18 hours, the ^{1}H NMR (400 MHz, CD_3CN) spectra were recorded 7.93 (1H, d, $^3J_{HH}$ = 7.7 Hz, *o*-chloroiodobenzene), 7.70 (2H, d, $^3J_{HH}$ = 8.6 Hz, *p*-chloroiodobenzene), 7.54-7.48 (3H, m, *o*-chloroiodobenzene), 7.40-7.29 (5H, m, chlorobenzene), 7.17 (2H, d, $^3J_{HH}$ = 8.6 Hz, *p*-chloroiodobenzene). From integration, it was found that the conversions of chlorobenzene using **NI-1**, **NI-2**, **NI-3** and **NI-4** were 37%, 25%, 50% and 0 respectively. The two isomers *o*- and *p*-chloroiodobenzene were not separated.

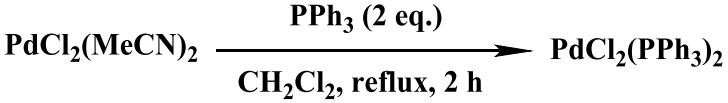
6.3.4 Preparation of methyl 2-iodobenzoate



Scheme 6.16 Synthesis of methyl 2-iodobenzoate

These procedures were based on those described by Pinto *et al.* (**Scheme 6.16**).[11] 2-Iodobenzoic acid (12.5 g, 51 mmol) was dissolved in methanol (75.5 mL) at 0 ℃ before thionyl chloride (5.5 mL, 76 mmol) was added drop wise over 30 minutes. The solution was heated to reflux at 70 ℃ for 18 hours and then concentrated on a rotary evaporator giving a yellow oil. Ethyl acetate (50 mL) was added to the crude product and it was washed with brine (50 mL) three times. The organic layers were combined, dried over anhydrous Mg_2SO_4 and concentrated on a rotary evaporator. The pure product was obtained as a yellow oil (11.77 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (1H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 7.79 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.39 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 7.5 Hz, ArH), 7.14 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 7.5 Hz, ArH), 3.93 (3H, s, -OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0 (C=O), 141.3 (CH), 135.2 (C), 132.6 (CH), 130.9 (CH), 127.9 (CH), 94.1 (C-I), 52.5 (-OCH_3). MS (ASAP) m/z: 262.9569 ($[MH]^+$, 100%), 230.9324 ($[M\text{-}OCH_3]^+$, 50%). These data are consistent with those reported in the literature.[11]

6.3.5 Preparation of $PdCl_2(PPh_3)_2$

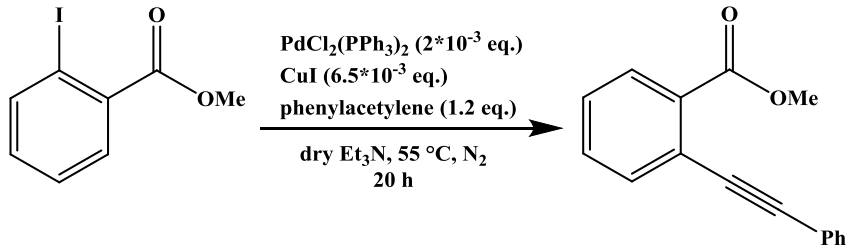


Scheme 6.17 Preparation of $PdCl_2(PPh_3)_2$

These procedures were based on those described by Li *et al.* **(Scheme 6.17)**.[12] To a 100 mL round bottom flask was added PPh_3 (0.750 g, 2.85 mmol) in CH_2Cl_2 (60 mL) and $PdCl_2(MeCN)_2$ (0.371 g, 1.42 mmol) and then heated at reflux for 2 hours with vigorous stirring. After cooling to room temperature, the product was filtered and dried

in vacuo as a bright yellow powder (0.982 g, 98.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73-7.68 (m, 5H, ArH), 7.43-7.36 (m, 5H, ArH). ^{31}P NMR (161 MHz, $CDCl_3$): δ = 23.36. MS (ESI) m/z: 667 ($[M\text{-}Cl]^+$, 50%), 631 ($[M\text{-}Cl\text{-}Cl]^+$, 100%). These data are consistent with those reported in the literature.[12]

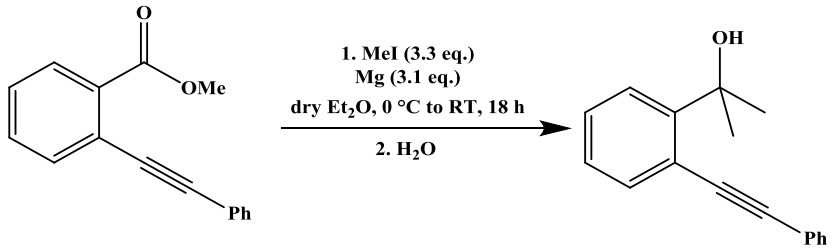
6.3.6 Preparation of methyl 2-(phenylethynyl)benzoate



Scheme 6.18 Preparation of methyl 2-(phenylethynyl)benzoate

This procedure was based on a Sonogashira coupling reaction described by Blum and Yanai **(Scheme 6.18)**.[13-14] A 250 mL three-necked flask was charged with methyl 2-iodobenzoate (5.24 g, 3 mL, 20 mmol), $PdCl_2(PPh_3)_2$ (0.028 g, 0.04 mmol), CuI (0.024 g, 0.13 mmol) and then evacuated, refilled with N_2 three times before dry Et_3N (80 mL) was added. After that, phenylacetylene (2.7 mL, 24 mmol) was syringed into the flask. The resulting mixture was then heated under N_2 at 55 ℃ for 20 hours. When the reaction was completed, the mixture was allowed to cool to room temperature, and the solids removed by filtration through a pad of Celite. The yellow reaction filtrate was dissolved in ethyl acetate (100 mL) and washed with a saturated aqueous solution of NH_4Cl (45 mL), water (45 mL) and brine (45 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed by rotary evaporation and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (V:V = 20:1). The final product was obtained as a yellow oil (4.24 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (1H, td, $^{3}J_{HH}$ = 7.7 Hz, $^{4}J_{HH}$ = 1.4 Hz, ArH), 7.65 (1H, td, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.3 Hz, ArH), 7.59-7.56 (2H, m, ArH), 7.49 (1H, td, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.4 Hz, ArH), 7.40-7.34 (4H, m, ArH), 3.97 (3H, s, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2 (C=O), 134.7 (CH), 132.8 (CH), 132.5 (CH), 130.6 (CH), 130.5 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.2 (C), 124.1 (C), 99.5 (C≡C), 93.2 (C≡C), 51.8 ($-OCH_3$). MS (ASAP) m/z: 237.0906 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[14]

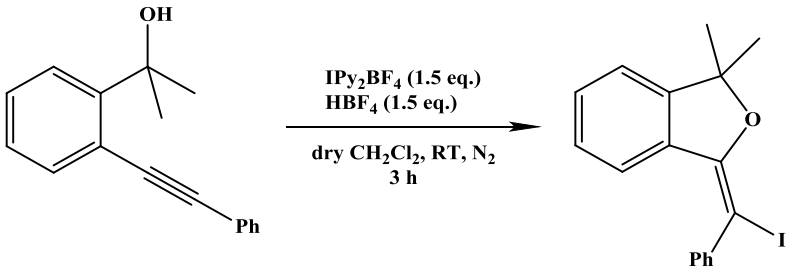
6.3.7 Preparation of 2-(2-(phenylethynyl)phenyl)propan-2-ol



Scheme 6.19 Preparation of 2-(2-(Phenylethynyl)phenyl)propan-2-ol

This procedure was based on the Grignard reaction described by Larock's group (**Scheme 6.19**).[15] A solution of MeI (3.1 mL, 49.5 mmol) in dry diethyl ether (40 mL) was added dropwise into a 250 mL three-necked round bottom flask charged with magnesium powder (1.12 g, 46.5 mmol) and dry diethyl ether (20 mL) until the reaction mixture started to reflux under N_2. Then, dry diethyl ether (10 mL) was added and the remainder of the MeI solution was added at a rate that kept the reaction mixture at reflux. The mixture was stirred for a further 15 minutes and then was cooled to 0 ℃. Methyl 2-(phenylethynyl)benzoate (3.54 g, 15 mmol) dissolved in dry diethyl ether (10 mL) was charged into a syringe and added dropwise to the mixture over 20 minutes. After that, the mixture was warmed to room temperature and stirred for 18 hours before being heated at reflux for 1.5 hours. After cooling to room temperature, the mixture was quenched with a saturated aqueous solution of NH_4Cl at 0 ℃ and extracted with ethyl acetate (15 mL) three times. The organic layers were combined, washed with H_2O (20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed on a rotary evaporator to give the crude product which was purified by column chromatography on silica gel using petroleum ether (40-60)/ethyl acetate (V:V = 9:1) to give pure 2-(2-(phenylethynyl)phenyl)propan-2-ol as a yellow solid (1.52 g, 43% yield). m.p. = 52-55 ℃ (The related data could not be found in the literature). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.52 (4H, m, ArH), 7.36 (3H, m, ArH), 7.32 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 7.24 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 3.23 (1H, s, -OH), 1.80 (6H, s, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8 (C), 133.9 (CH), 131.3 (CH), 131.2 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 125.8 (CH), 125.6 (C), 122.0 (C), 98.3 (C), 92.0 (C), 75.8 (C), 30.0 (CH_3). MS (ASAP) m/z: 219.1173 ([MH-OH_2]$^+$, 100%), 204.0944 ([MH-OH_2-CH_3]$^+$, 20%), 237.1328 ([MH]$^+$, $C_{17}H_{17}O$, 10%). These data are consistent with those reported in the literature.[15]

6.3.8 Preparation of (*Z*)-1,1-dimethyl-3-iodophenylmethylene-1,3-dihydroisobenzofuran using $[IPy_2][BF_4]$ and its analogues



Scheme 6.20 Preparation of (*Z*)-1,1-dimethyl-3-iodophenylmethylene-1,3-dihydroisobenfuran using $[IPy_2][BF_4]$

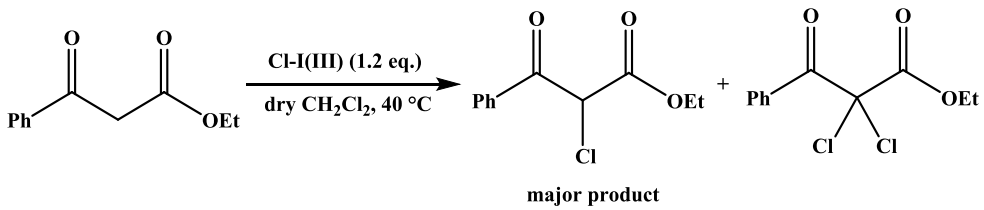
This procedure was based on that described by Larock group **(Scheme 6.20)**.[15] A 100 mL three-necked flask was charged with $[IPy_2][BF_4]$ (0.473 g, 1.27 mmol), evacuated for 15 minutes, refilled with N_2 three times before dry CH_2Cl_2 (15 mL) was added. After that, HBF_4 (0.18 mL, 1.27 mmol, a 54% diethyl ether solution) dissolved in dry CH_2Cl_2 (5 mL) was syringed into the flask carefully under N_2 at 0 ℃ and the mixture stirred for 20 minutes. Then, 2-(2-(phenylethynyl)phenyl)propan-2-ol (0.2 g, 0.85 mmol) dissolved in dry CH_2Cl_2 (5 mL) was syringed into the reaction mixture. After stirring for 15 minutes, the mixture was warmed to the room temperature and stirred for three hours. Then, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the mixture was vigorously stirred for a further 5 minutes to quench the reaction. The mixture was extracted with CH_2Cl_2 (10 mL) three times and the organic layers were combined and washed with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL) three times. The organic layers were combined and dried over anhydrous $MgSO_4$, and the solvent was removed to give the crude product which was purified by column chromatography on silica gel using petroleum ether (40-60)/ethyl acetate (V:V = 5:1). The pure (*Z*)-3-(iodo(phenyl)methylene)-1,1-dimethyl-2,3-dihydro-1*H*-indene was obtained as little block brown crystals (0.19 g, 62% yield) after recrystallization in CH_2Cl_2. These were suitable for X-ray crystallographic analysis. m.p. = 113-116 ℃ (The related data could not be found in the literature). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42 (5H, m, ArH), 7.24 (1H, t, $^3J_{HH}$ = 7.5 Hz, ArH), 7.14 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 6.96 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 6.40 (1H, d, $^3J_{HH}$ = 8.0 Hz, ArH), 1.66 (6H, s, -CH_3). ^{13}C NMR (100 MHz,

$CDCl_3$) δ = 155.1 (C), 150.6 (C), 141.3 (C), 130.7 (CH), 129.9 (C), 128.9 (CH), 128.2 (CH), 127.6 (CH), 123.2 (CH), 121.9 (CH), 120.6 (CH), 87.3 (C), 63.1 (C-I), 28.3 (-CH_3). MS (ASAP) m/z: 362 $[M]^+$, 236 $[MH\text{-}I]^+$. These data are consistent with those reported in the literature.[15] The structure of the product was confirmed by X-ray diffraction.

The same method was followed using **NI-2**, **NI-3** and **NI-4**. The final yields of (*Z*)-3-(iodo(phenyl)methylene)-1,1-dimethyl-2,3-dihydro-1*H*-indene as little block brown crystals were 58%, 50% and 53%, respectively.

6.4 Experimental procedures for Chapter 4

6.4.1 Chlorination of ethyl benzoylacetate using Cl-I(III) compounds



Scheme 6.21 Chlorination of ethyl benzoylacetate using Cl-I(III) compounds in dry CH_2Cl_2

A Schlenk tube with a glass cap was charged with 2-benzyl-1-chloro-1,2-dihydro-3*H*-1λ^3-benzo[*d*][1,2]iodazol-3-one **(NC-1)** (0.3 g, 0.81 mmol) and then evacuated, refilled with N_2 three times before dry CH_2Cl_2 (3 mL) was added to dissolve the solid. After that, ethyl benzoylacetate (0.12 mL, 0.675 mmol) was added and the mixture was stirred at 40 ℃ for 18 hours **(Scheme 6.21)**. Then, the solution was allowed to cool to the room temperature and the solvent was removed under reduced pressure. Both the monochlorinated and the dichlorinated product were identified in the crude product, which was purified by column chromatography on silica gel using CH_2Cl_2/petroleum ether (40-60 ℃) (V:V = 2:1).

Finally, the monochlorinated product ethyl 2-chloro-3-oxo-3-phenylpropanoate was obtained as a pale yellow oil (0.113 g, 74% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (2H, dt, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.64 (1H, tt, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 7.51 (2H, td, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 5.62 (1H, s, CClH), 4.29

(2H, q, $^{3}J_{HH}$ = 7.1 Hz, -OCH_2), 1.25 (3H, t, $^{3}J_{HH}$ = 7.2 Hz, -CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.2 (C=O), 165.3 (C=O), 134.4 (CH), 133.3 (C), 129.3 (CH), 128.9 (CH), 63.2 (CClH), 58.0 (OCH_2), 13.9 (CH_3). MS (ASAP) m/z = 105.0305 ([MH-OEt-Ph]$^{+}$, 30%), 181.0062 ([M-OEt]$^{+}$, 100%). These data are consistent with those reported in the literature.[16]

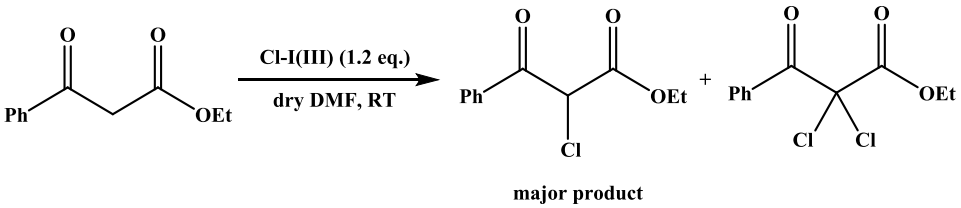
The dichlorinated product ethyl 2,2-dichloro-3-oxo-3-phenylpropanoate was obtained as a pale yellow oil (0.02 g, 11% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (2H, dd, $^{3}J_{HH}$ = 7.3 Hz, $^{4}J_{HH}$ = 1.3 Hz, ArH), 7.62 (1H, tt, $^{3}J_{HH}$ = 7.4 Hz, $^{4}J_{HH}$ = 1.1 Hz, ArH), 7.48 (2H, t, $^{3}J_{HH}$ = 7.7 Hz, ArH), 4.31 (2H, q, $^{3}J_{HH}$ = 7.1 Hz, OCH_2), 1.18 (3H, t, $^{3}J_{HH}$ = 7.1 Hz, C*H*$_3$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 184.2 (C=O), 165.5 (C=O), 135.2 (CH), 133.0 (C), 130.0 (CH), 129.1 (CH), 81.0 (CCl_2), 66.7 (OCH_2), 14.1 (CH_3). MS (ASAP) m/z = 261 (MH^{+}, 100%, ^{35}Cl), 263 (MH^{+}, 70%, ^{37}Cl). These data are consistent with those reported in the literature.[17]

When 1-chloro-2-(4-chlorobenzyl)-1,2-dihydro-3*H*-1λ^{3}-benzo[*d*][1,2]iodazol-3-one **(NC-2)** was used, the yields of ethyl 2-chloro-3-oxo-3-phenylpropanoate and 2,2-dichloro-3-oxo-3-phenylpropanoate were 79% and 6%, respectively.

When 1-chloro-2-(4-fluorobenzyl)-1,2-dihydro-3*H*-1λ^{3}-benzo[*d*][1,2]iodazol-3-one **(NC-3)** was used, the yields of ethyl 2-chloro-3-oxo-3-phenylpropanoate and 2,2-dichloro-3-oxo-3-phenylpropanoate were 80% and 6%, respectively.

When 1-chloro-3,3-dimethyl-1,3-dihydro-1λ^{3}-benzo[*d*][1,2]iodoxole **(OC-1)** was used, the yields of ethyl 2-chloro-3-oxo-3-phenylpropanoate and 2,2-dichloro-3-oxo-3-phenylpropanoate were 75% and 9%, respectively.

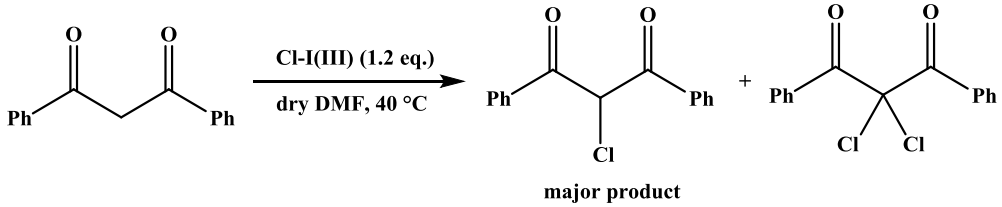
When 1-chloro-1λ^{3}-benzo[*d*][1,2]iodoxol-3(1*H*)-one **(OC-2)** was used, the yield of ethyl 2-chloro-3-oxo-3-phenylpropanoate was 70%.



Scheme 6.22 Chlorination of ethyl benzoylacetate using Cl-I(III) compounds in dry DMF

Dry DMF was used as the solvent for the chlorination of ethyl benzylacetate **(Scheme 6.22)**. A Schlenk tube was charged with **NC-1** (0.3 g, 0.81 mmol) then evacuated, refilled with N_2 three times before dry DMF (2 mL) was added to dissolve the solid. After that, ethyl benzoylacetate (0.12 mL, 0.675 mmol) was added and the mixture was stirred at room temperature for 18 hours. Then, the mixture were quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ethyl acetate (5 mL) three times. The organic layers were combined, washed with brine (10 mL) and water (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Finally, the crude product was purified by column chromatography on silica gel using CH_2Cl_2/petroleum ether (40-60 ℃) (V:V = 2:1). The yield of the monochlorinated product ethyl 2-chloro-3-oxo-3-phenylpropanoate was 37%. When **NC-2**, **OC-1** and **OC-2** were employed, the yields of the monochlorinated product ethyl 2-chloro-3-oxo-3-phenylpropanoate were 39%, 44% and 37%, respectively.

6.4.2 Chlorination of 1,3-diphenylpropane-1,3-dione using Cl-I(III) compounds



Scheme 6.23 Chlorination of 1,3-diphenylpropane-1,3-dione using Cl-I(III) compounds in dry DMF

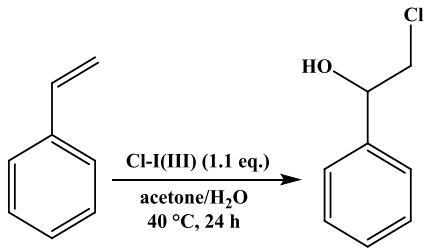
A Schlenk tube with a glass cap charged with **NC-1** (0.2 g, 0.54 mmol) and 1,3-diphenylpropane-1,3-dione (0.100 g, 0.45 mmol) was evacuated, refilled with N_2 three times before dry DMF (2 mL) was added to dissolve all the solids. The mixture was stirred at 40 ℃ for 18 hours **(Scheme 6.23)**. Then, it was cooled to room temperature and quenched with a saturated aqueous $NaHCO_3$ (30 mL) and extracted with ethyl acetate (10 mL) three times. The organic layers were combined and washed with brine (15 mL) and water (15 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using CH_2Cl_2/petroleum ether (40-60 ℃) (V:V = 2:1). Finally, the monochlorinated product 2-chloro-1,3-diphenylpropane-1,3-dione was

obtained as pale yellow microcrystals (0.079 g, 77% yield). m.p. = 70-72 ℃ (Lit [18]: 71-72.5 ℃). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (4H, dd, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 1.1 Hz, ArH), 7.60 (2H, tt, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.8 Hz, ArH), 7.47 (4H, t, $^{3}J_{HH}$ = 7.5 Hz, ArH), 6.41 (1H, s, -CHCl-). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3 (C=O), 134.3 (CH), 133.9 (C), 129.3 (CH), 129.0 (CH), 62.9 (-CHCl-). MS (ASAP) m/z = 259 ($[MH]^+$, 20%, ^{35}Cl), 261 ($[MH]^+$, 5%, ^{37}Cl), 181 ($[M\text{-}Ph]^+$, 35%, ^{35}Cl), 183 ($[M\text{-}Ph]^+$, 15%, ^{37}Cl), 105 ($[C(O)Ph]^+$, 100%), 77 (Ph^+, 20%). These data are consistent with those reported in the literature.[18]

The dichlorinated product 2,2-dichloro-1,3-diphenylpropane-1,3-dione was obtained as a pale yellow oil (0.017 g, 13% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (4H, d, $^{3}J_{HH}$ = 7.4 Hz, ArH), 7.54 (2H, t, $^{3}J_{HH}$ = 7.4 Hz, ArH), 7.40 (4H, t, $^{3}J_{HH}$ = 7.6 Hz, ArH). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 183.5 (C=O), 132.4 (CH), 129.6 (C), 128.6 (CH), 126.8 (CH), 85.7 (CCl_2). MS (ASAP) m/z = 259 ($[M\text{-}Cl]^+$, 45%, ^{37}Cl), 257 ($[M\text{-}Cl]^+$, 100%, ^{35}Cl), 105 ($[C(O)Ph]^+$, 100%), 77 (Ph^+, 60%). These data are consistent with those reported in the literature.[19-21]

When **NC-2**, **NC-3**, **OC-1** and **OC-2** was used, the yields of the monochlorinated product 2-chloro-1,3-diphenylpropane-1,3-dione were 77%, 79%, 77% and 67% respectively and those of the dichlorinated product 2,2-dichloro-1,3-diphenylpropane-1,3-dione were 12%, 13%, 11%, 9% and 8% respectively.

6.4.3 Oxychlorination of styrene using Cl-I(III) compounds



Scheme 6.24 Oxychlorination of styrene using Cl-I(III) compounds

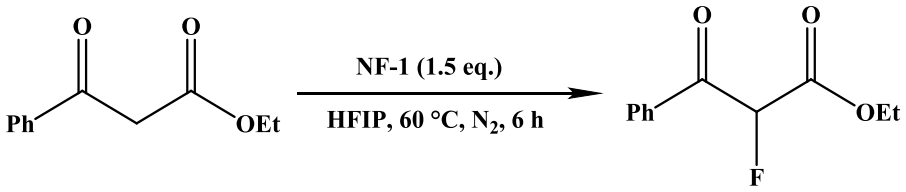
To a suspension of **NC-1** (0.408 g, 1.1 mmol) in acetone/H_2O (15 mL/10 mL) was added styrene (0.11 mL, 1 mmol) and the mixture was stirred for 15 minutes at room temperature. After that, it was heated to 40 ℃ and stirred for 24 hours **(Scheme 6.24)**. Then, it was cooled to room temperature, washed with water (5 mL) and extracted with ethyl acetate (10 mL) three times. The organic layers were combined and dried over

anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (V:V = 5:1) to provide 2-chloro-1-phenylethan-1-ol as a yellowish oil (0.116 g, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.31 (5H, m, ArH), 4.92-4.89 (1H, m, -OH), 3.75 (1H, dd, $^3J_{HH}$ = 3.4 Hz, $^3J_{HH}$ = 11.2 Hz, -C*H*OH-), 3.65 (1H, dd, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 11.2 Hz, -C*H*HCl), 2.64 (1H, d, $^2J_{HH}$ = 3.2 Hz, -CH*H*Cl). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 139.9 (C), 128.7 (CH), 128.5 (CH), 126.1 (CH), 74.1 (-CHOH-), 50.9 (-CH_2Cl). MS (ASAP) m/z = 157 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[22]

When **NC-2**, **NC-3** and **OC-2** were used, the yields of 2-chloro-1-phenylethan-1-ol were the same.

6.5 Experimental procedures for Chapter 5

6.5.1 Fluorination of ethyl benzoylacetate using F-I(III) compounds



Scheme 6.25 Fluorination of ethyl benzoylacetate

A Schlenk flask fitted with a glass cap was charged with 2-benzyl-1-fluoro-1,2-dihydro-3*H*-λ^3-benzo[d][1,2]iodazol-3-one **(NF-1)** (0.300 g, 0.84 mmol) and then evacuated, refilled with N_2 three times before dry HFIP (1.2 mL) was added. Ethyl benzoylacetate (0.1 mL, 0.56 mmol) was added and the mixture was stirred at 60 ℃ for six hours **(Scheme 6.25)**. The solution was allowed to cool to room temperature and the solvent was removed under vacuum. The crude product was purified by column chromatography using CH_2Cl_2 on silica gel. Finally, the monofluorination product ethyl 2-fluoro-3-oxo-3-phenylpropanoate was obtained as a pale yellow oil (0.083 g, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (2H, dt, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 7.64 (1H, tt, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.3 Hz, ArH), 7.51 (2H, t, $^3J_{HH}$ = 8.1 Hz, ArH), 5.87 (1H, d, $^2J_{HF}$ = 49.0 Hz, CHF), 4.30 (2H, dq, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 7.2 Hz, OCH_AH_B), 1.26 (3H, t, $^3J_{HH}$ = 7.1 Hz, -CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 189.5 (d, $^2J_{CF}$ = 20.1 Hz, C=O), 164.9 (d, $^2J_{CF}$ = 24.2 Hz, C=O), 134.2 (CH), 133.4 (C), 129.5

(CH), 128.8 (CH), 90.0 (d, $^{1}J_{CF}$ = 197.7 Hz, CHF), 62.7 (OCH_2), 14.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -190.3 (s, CHF). MS (ASAP) m/z: 211 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[23] When **NF-2** and **NF-3** were used, the yields of the monofluorinated product ethyl 2-fluoro-3-oxo-3-phenylpropanoate were both 72%.

6.5.2 Fluorination of ethyl (4-fluorobenzoyl)acetate using NF-1

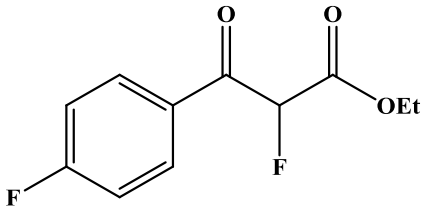


Figure 6.4 Ethyl 2-fluoro-3-(4-fluorophenyl)-3-oxo-propanoate

The same method was used for the fluorination of ethyl (4-fluorobenzoyl)acetate using **NF-1** which gave ethyl 2-fluoro-3-(4-fluorophenyl)-3-oxo-propanoate (**Figure 6.4**) as a colourless oil in a 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14-8.08 (2H, m, ArH), 7.19 (2H, t, $^{3}J_{HH}$ = 8.9 Hz, ArH), 5.84 (1H, d, $^{2}J_{HF}$ = 48.9 Hz, CHF), 4.31 (2H, m_{AB}, qm, $^{3}J_{HH}$ = 7.1 Hz, -OCH_AH_B-), 1.28 (3H, t, $^{3}J_{HH}$ = 7.2 Hz, -CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 188.0 (d, $^{2}J_{CF}$ = 20.9 Hz, C=O), 166.5 (d, $^{1}J_{CF}$ = 257.7 Hz, C-F), 164.8 (d, $^{2}J_{CF}$ = 24.8 Hz, C=O), 132.5 (dd, $^{3}J_{CF}$ = 9.4 Hz, $^{4}J_{CF}$ = 3.7 Hz, CH), 129.8 (C), 116.2 (d, $^{2}J_{CF}$ = 22.5 Hz, CH), 90.3 (d, $^{1}J_{CF}$ = 197.9 Hz, CHF), 62.8 (OCH_2), 14.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -101.8 (1F, s, Ar*F*), -189.6 (1F, s, CH*F*). MS (ESI) m/z: 229 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[23]

6.5.3 Fluorination of ethyl (4-methoxybenzoyl)acetate using NF-1

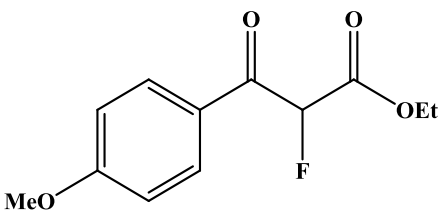
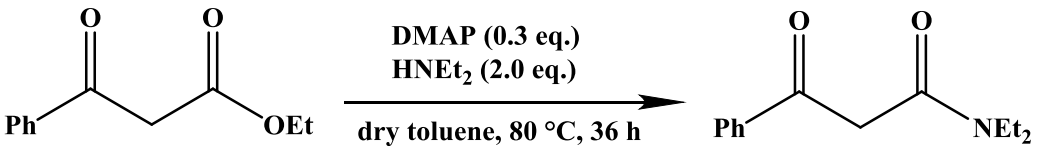


Figure 6.5 Ethyl 2-fluoro-3-(4-methoxyphenyl)-3-oxo-propanoate

When the same method was used for the fluorination of ethyl (4-methoxybenzoyl)acetate with **NF-1**, the pure monofluorination product ethyl 2-fluoro-

3-(4-methoxyphenyl)-3-oxo-propanoate **(Figure 6.5)** was obtained as a colourless oil after purification by column chromatography using 1% MeOH/CH_2Cl_2 on silica gel in an 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (2H, dd, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 1.2 Hz, ArH), 6.97 (2H, d, $^3J_{HH}$ = 8.9 Hz, ArH), 5.82 (1H, d, $^2J_{HF}$ = 49.1 Hz, C*H*F), 4.30 (2H, m_{AB}, dq, $^2J_{HH}$ = 10.3 Hz, $^3J_{HH}$ = 7.2 Hz, -OCH_AH_B-), 3.89 (3H, s, -OCH_3), 1.27 (3H, t, $^3J_{HH}$ = 7.1 Hz, -CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 187.8 (d, $^2J_{CF}$ = 19.9 Hz, C=O), 165.2 (d, $^2J_{CF}$ = 24.4 Hz, C=O), 164.7 (C), 132.1 (d, $^4J_{CF}$ = 3.7 Hz, CH), 126.3 (C), 114.1 (CH), 90.2 (d, $^1J_{CF}$ = 197.2 Hz, CHF), 62.6 (-OCH_2-), 55.6 (-OCH_3), 14.0 (-CH_3). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -189.5 (1F, s, CH*F*). MS (ESI) m/z: 241 ($[MH]^+$, 100%). These data are consistent with those reported in the literature.[23]

6.5.4 Preparation of *N*, *N*-diethyl-3-oxo-3-phenylpropanamide

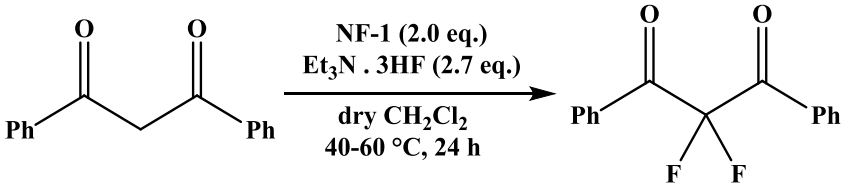


Scheme 6.26 Synthesis of *N*,*N*-diethyl-3-oxo-3-phenylpropanamide

A three-necked flask was charged with 4-dimethylaminopyridine (DMAP) (0.42 g, 3.47 mmol) and then evacuated, refilled with N_2 three times before dry toluene (20 mL) was added. $HNEt_2$ (2.4 mL, 23.2 mmol) and ethyl benzoylacetate (2.0 mL, 11.2 mmol) were added and the mixture was stirred under N_2 at 80 ℃ for 36 hours **(Scheme 6.26)**. After cooling to room temperature, the mixture was concentrated under reduced pressure to give the crude product which was purified by column chromatography using hexane/ethyl acetate (V:V = 5:1) on silica gel to give *N*,*N*-diethyl-3-oxo-3-phenylpropanamide as a yellow oil (0.654 g, 26% yield, 46% enol: 54% keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (2H, dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.2 Hz, keto, ArH), 7.79-7.76 (2H, m, enol, ArH), 7.58 (1H, tt, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 2.0 Hz, keto, ArH), 7.48 (2H, t, $^3J_{HH}$ = 7.4 Hz, enol, ArH), 7.44-7.38 (3H, m, enol, ArH), 5.73 (1H, s, enol, CH), 4.07 (2H, s, keto, -CH_2-), 3.48-3.34 (4H, m, enol and keto, -CH_2-), 1.26-1.13 (6H, m, enol and keto, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3 (C=O), 171.4 (C=O), 171.3 (C=O), 166.0 (C), 136.4 (C), 135.3 (C), 133.6 (CH), 130.5 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 125.9 (CH), 84.9 (CH, enol), 45.9 (CH_2, keto), 42.8 (CH_2),

40.2 (CH_2), 14.2 (CH_3), 12.9 (CH_3). MS (ES^+) m/z: 220 ($[MH]^+$, 100%), 242 ($[MNa]^+$, 65%). These data are consistent with those reported in the literature.[24]

6.5.5 Fluorination of 1,3-diphenylpropane-1,3-dione using NF-1 with $Et_3N{\cdot}3HF$ as an additive



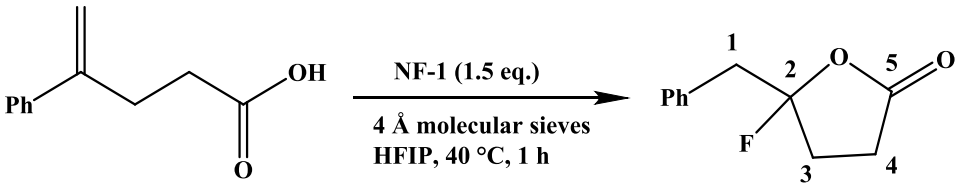
Scheme 6.27 Difluorination of 1,3-diphenylpropane-1,3-dione using **NF-1** with $Et_3N{\cdot}3HF$

A Schlenk flask was charged with **NF-1** (0.334 g, 0.96 mmol) and 1,3-diphenylpropane-1,3-dione (0.106 g, 0.48 mmol) and then evacuated, refilled with N_2 three times before dry CH_2Cl_2 (1 mL) was added, $Et_3N{\cdot}3HF$ (0.2 mL, 1.28 mmol) was added to the solution and the mixture was stirred at 40 ℃ for 24 hours **(Scheme 6.27)**. The solution was allowed to cool to room temperature, washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL) three times. The organic layers were combined and washed with brine (10 mL) and water (10 mL). After being dried over anhydrous $MgSO_4$, the organic phase was filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography using petroleum ether (40-60 ℃)/CH_2Cl_2 (V:V = 1:2) on silica gel. The difluorinated product 1,3-diphenyl-2,2-difluoro-1,3-propanedione was obtained as a colourless solid (0.094 g, 77% yield). When the reaction temperature was raised to 60 ℃, the yield increased to 85%. m.p. = 57-59 ℃ (Lit [25] = 58-60 ℃). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (4H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.66 (2H, d, $^3J_{HH}$ = 7.4 Hz, ArH), 7.50 (4H, d, $^3J_{HH}$ = 7.5 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4 (t, $^2J_{CF}$ = 27.0 Hz, C=O), 135.0 (CH), 131.6 (C), 130.3 (t, $^4J_{CF}$ = 2.7 Hz, CH), 128.9 (CH), 112.7 (t, $^1J_{CF}$ = 265.5 Hz, CF_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -102.6 (s, CF_2). MS (ESI) m/z: 241 ($[M\text{-}F]^+$, 100%). These data are consistent with those reported in the literature.[25]

6.5.6 General procedure for the intramolecular fluorocyclisation of unsaturated carboxylic acids using NF-1

A Schlenk flask with a glass cap was charged with **NF-1** (0.304 g, 0.86 mmol), the unsaturated carboxylic acid substrate (0.57 mmol), and powdered 4 Å molecular sieves (0.1 g). The flask was then evacuated and refilled with N_2 three times before dry HFIP (2 mL) was added. The mixture was heated under N_2 to 40 ℃ and stirred for one hour. After cooling to room temperature, the mixture was concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel using a dichloromethane.

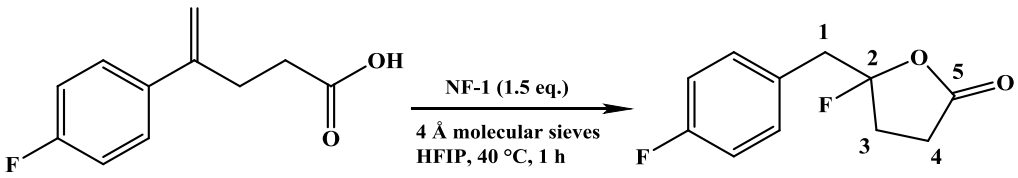
6.5.7 Synthesis of 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one



Scheme 6.28 Fluorocyclisation of 4-phenylpent-4-enoic acid using **NF-1**

The fluorocyclisation of 4-phenylpent-4-enoic acid (0.10 g, 0.57 mmol) using **NF-1** (0.304 g, 0.86 mmol) gave 5-benzyl-5-fluorodihydrofuran-2(3*H*)-one **(Scheme 6.28)**, as a colourless oil (0.094 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.28 (5H, m, ArH), 3.29 (2H, d, $^{3}J_{HF}$ = 14.5 Hz, on fluorine decoupling simplifies to a singlet, H_1 and $H_{1'}$), 2.74 (1H, ddd, $^{2}J_{HH}$ = 18.0 Hz, $^{3}J_{HH}$ = 10.0 Hz, $^{3}J_{HH}$ = 9.5 Hz, $H_{4'}$), 2.45-2.38 (1H, m, on fluorine decoupling simplifies to a ddd, δ = 2.42, $^{2}J_{HH}$ = 18.0 Hz, $^{3}J_{HH}$ = 10.0 Hz, $^{3}J_{HH}$ = 9.5 Hz, H_4), 2.30-2.17 (2H, m, H_3 and $H_{3'}$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.7 (C=O), 133.0 (d, $^{3}J_{CF}$ = 5.5 Hz, C), 130.4 (CH), 128.8 (CH), 127.6 (CH), 119.2 (d, $^{1}J_{CF}$ = 230.7 Hz, CF), 42.7 (d, $^{2}J_{CF}$ = 28.2 Hz, CH_2), 30.9 (d, $^{2}J_{CF}$ = 27.7 Hz, CH_2), 27.0 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -97.0 (s, C*F*). MS (ESI) m/z: 175 ($[M-F]^+$, 100%). These data are consistent with those reported in the literature.[23]

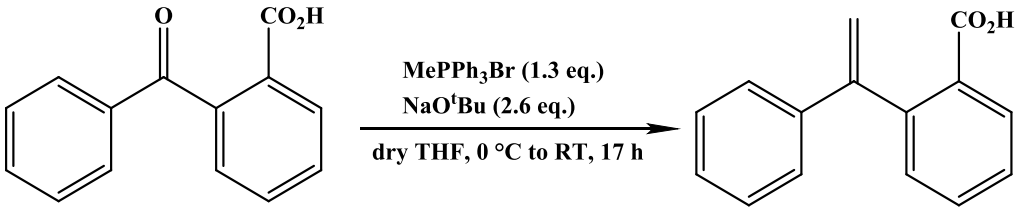
6.5.8 Synthesis of 5-fluoro-5-(4-fluorobenzyl)dihydrofuran-2(3*H*)-one



Scheme 6.29 Fluorocyclisation of 4-(4-fluorophenyl)pent-4-enoic acid

The fluorocyclisation of 4-(4-fluorophenyl)pent-4-enoic acid (0.11 g, 0.57 mmol) using **NF-1** (0.304 g, 0.86 mmol) gave 5-fluoro-5-(4-fluorobenzyl)dihydrofuran-2(3*H*)-one **(Scheme 6.29)** as a pale yellow oil (0.096 g, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (2H, dd, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HF}$ = 5.5 Hz, ArH), 7.03 (2H, t, $^{3}J_{HH}$ = $^{3}J_{HF}$ = 8.7 Hz, ArH), 3.26 (2H, d, $^{3}J_{HF}$ = 14.8 Hz, on fluorine decoupling simplifies to a singlet, H_1 and $H_{1'}$), 2.75 (1H, ddd, $^{2}J_{HH}$ = 18.1 Hz, $^{3}J_{HH}$ = 10.6 Hz, $^{3}J_{HH}$ = 8.6 Hz, $H_{4'}$), 2.48-2.42 (1H, m, on fluorine decoupling simplifies to a ddd, δ = 2.45, $^{2}J_{HH}$ = 18.2 Hz, $^{3}J_{HH}$ = 8.6 Hz, $^{3}J_{HH}$ = 2.3 Hz, H_4), 2.32-2.14 (2H, m, H_3 and $H_{3'}$). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.5 (C=O), 162.4 (d, $^{1}J_{CF}$ = 247.0 Hz, CF), 131.9 (d, $^{3}J_{CF}$ = 7.7 Hz, CH), 128.7 (C), 118.9 (d, $^{1}J_{CF}$ = 230.7 Hz, CF), 115.5 (d, $^{2}J_{CF}$ = 21.2 Hz, CH), 41.9 (d, $^{2}J_{CF}$ = 28.1 Hz, CH_2), 30.9 (d, $^{2}J_{CF}$ = 28.5 Hz, CH_2), 26.9 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -97.7 (s, C*F*), -114.8 (s, Ar*F*). MS (ESI) m/z: 193 ($[M-F]^+$, 100%). These data are consistent with those reported in the literature.[23]

6.5.9 Synthesis of 2-(1-phenylvinyl)benzoic acid

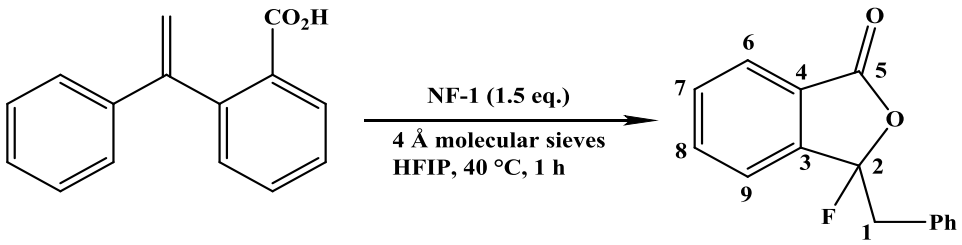


Scheme 6.30 Preparation of 2-(1-phenylvinyl)benzoic acid

A three-necked flask was charged with methyltriphenylphosphonium bromide (2.06 g, 5.78 mmol) and then evacuated, refilled with N_2 three times before dry THF (20 mL) was added with stirring. NaO^tBu (1.11 g, 11.57 mmol) was added quickly to the suspension at 0 ℃ and the reaction mixture was stirred for 30 minutes. After adding 2-

benzoylbenzoic acid (1.0 g, 4.42 mmol), the reaction mixture was warmed to room temperature and stirred for 18 hours **(Scheme 6.30)**. The reaction was quenched by using 1 M NaOH aqueous solution (25 mL) followed by CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) for three times. Organic layers were combined and the aqueous layer was acidified to pH = 2 using 12 M HCl and then the product was extracted into CH_2Cl_2 (20 mL) for three times. All the organic layers were combined, dried over the anhydrous $MgSO_4$ and filtrated. The solvent was removed under reduced pressure to get crude product. Finally, the pure product was obtained as white solid (0.453 g, 46% yield) by chromatography using petroleum ether (40-60)/ethyl acetate (V:V = 1:1) on silica gel. m.p. = 129-130 ℃ (Lit [26]: 130-131 ℃). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 1.5 Hz, ArH), 7.56 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 1.4 Hz, ArH), 7.43 (1H, td, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 1.4 Hz, ArH), 7.37 (1H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 1.4 Hz, ArH), 7.26-7.20 (5H, m, ArH), 5.67 (1H, d, $^2J_{HH}$ = 1.1 Hz, C*H*H), 5.22 (1H, d, $^2J_{HH}$ = 1.0 Hz, CH*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3 (C=O), 149.5 (C), 143.6 (C), 140.8 (C), 132.4 (CH), 131.6 (CH), 130.7 (CH), 129.4 (C), 128.1 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 114.4 (C=CHH). MS (ESI) m/z: 225 ($[MH]^+$, 15%), 207 ($[M\text{-}OH]^+$, 100%).. These data are consistent with those reported in the literature.[27]

6.5.10 Synthesis of 3-benzyl-3-fluoroisobenzofuran-1(3*H*)-one

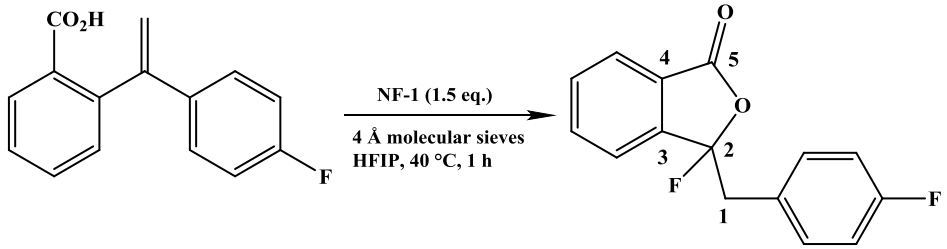


Scheme 6.31 Fluorocyclisation of 2-(1-phenylvinyl)benzoic acid

The fluorocyclisation of 2-(1-phenylvinyl)benzoic acid (0.1 g, 0.44 mmol) using **NF-1** (0.239 g, 0.66 mmol) gave the title product 3-benzyl-3-fluoroisobenzofuran-1(3*H*)-one **(Scheme 6.31)** as a colourless oil (0.085 g, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.67 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.58 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.33 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.26-7.19 (5H, m, ArH), 3.61 (1H, dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HF}$ = 12.3 Hz, $H_{1'}$), 3.52 (1H, dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HF}$ = 15.0 Hz, H_1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8 (C=O), 144.6 (d, $^2J_{CF}$ = 21.1 Hz, C), 134.6 (CH), 130.2 (d, $^3J_{CF}$ = 4.5 Hz, C), 129.8 (CH), 128.8 (CH), 126.7 (CH), 125.9 (CH), 124.5 (C), 124.0 (CH), 121.4 (CH), 113.4 (d, $^1J_{CF}$ = 232.4 Hz, CF), 42.4 (d, $^2J_{CF}$ = 30.0 Hz, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -100.6 (s, C*F*). MS (ESI) m/z: 223 ($[M-F]^+$, 100%). These data are consistent with those reported in the literature.[23]

6.5.11 Synthesis of 3-Fluoro-3-(4-fluorobenzyl)isobenzofuran-1(3*H*)-one



Scheme 6.32 Fluorocyclisation of 2-(1-(4-fluorophenyl)vinyl)benzoic acid

The fluorocyclisation of 2-(1-(4-fluorophenyl)vinyl)benzoic acid (0.1 g, 0.42 mmol) using **NF-1** (0.227 g, 0.63 mmol) gave the title product, 3-fluoro-3-(4-fluorobenzyl)isobenzofuran-1(3*H*)-one **(Scheme 6.32)**, as a white solid (0.090 g, 82% yield). m.p. = 68-70 ℃ (Lit [23]: 69-71 ℃). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (1H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.69 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.60 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.37 (1H, t, $^3J_{HH}$ = 7.6 Hz, ArH), 7.17 (2H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HF}$ = 5.5 Hz, ArH), 6.93 (2H, t, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, ArH), 3.57 (1H, dd, $^2J_{HH}$ = 14.3 Hz, $^3J_{HF}$ = 12.6 Hz, $H_{1'}$), 3.51 (1H, dd, $^2J_{HH}$ = 14.5 Hz, $^3J_{HF}$ = 14.2 Hz, H_1). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.4 (d, $^3J_{CF}$ = 1.8 Hz, C=O), 162.8 (d, $^1J_{CF}$ = 247.1 Hz, CF), 144.5 (d, $^2J_{CF}$ = 21.2 Hz, C), 132.2 (d, $^3J_{CF}$ = 8.2 Hz, CH), 131.7 (d, $^3J_{CF}$ = 2.7 Hz, CH), 127.8 (dd, $^3J_{CF}$ = 5.6 Hz, $^4J_{CF}$ = 3.3 Hz, C), 126.3 (C), 125.8 (CH), 123.0 (CH), 115.4 (d, $^2J_{CF}$ = 21.4 Hz, CH), 115.0 (d, $^1J_{CF}$ = 233.0 Hz, CF), 41.6 (d, $^2J_{CF}$ = 30.9 Hz, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -101.1 (s, C*F*), -114.6 (s, Ar*F*). MS (ASAP) m/z: 261 ($[MH]^+$, 20%), 241 ($[M-F]^+$, 100%). These data are consistent with those reported in the literature.[23]

6.5.12 NF-1/HFIP NMR experiments

HFIP (0.020 g) was dissolved in $CDCl_3$ (0.6 mL), and then the NMR experiments for this solution was carried out. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.42 (1H, octet, $^3J_{HF}$ = 6.2 Hz, CH), 3.01 (1H, broad s, -OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.4 (q, $^1J_{CF}$

= 283.4 Hz, CF_3), 69.7 (hept, $^2J_{CF}$ = 33.4 Hz, CH). ^{19}F NMR (376 MHz, $CDCl_3$): δ = -75.7 (d, $^1J_{FF}$ = 6.6 Hz, CF_3). These data are consistent with those reported in the literature.[23]

NF-1 (0.02 g, 0.056 mmol) with 0.1 mL HFLP solution (0.095 g HFIP (0.56 mmol) mixed with 1mL $CDCl_3$) was dissolved in $CDCl_3$ (0.6 mL), and then the NMR experiments for this solution was carried out. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (1H, dd, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 8.02 (1H, d, $^3J_{HH}$ = 7.4 Hz, ArH), 7.83 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 7.72 (1H, td, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.0 Hz, ArH), 7.46-7.36 (5H, m, ArH), 5.45 (1H, d, $^1J_{HF}$ = 4.0 Hz, -OH), 4.77 (2H, s, CH_2), 4.41 (1H, hept, $^3J_{HF}$ = 5.9 Hz, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (C=O), 136.8 (C), 134.9 (CH), 132.5 (CH), 131.4 (CH), 131.1 (CH), 130.9 (CH), 129.5 (C), 129.1 (CH), 129.0 (CH), 121.7 (q, $^1J_{CF}$ = 283.4 Hz, CF_3), 117.9 (C-I), 69.5 (hept, $^2J_{CF}$ = 33.7 Hz, CH), 48.4 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ = (d, $^1J_{FF}$ = 6.6 Hz, CF_3).

6.6 References

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Appendix

Table A1 Crystal data and structure refinement for **NI-1**, **NI-2**, **NI-3** and **NI-4**

Name	NI-1	NI-2	NI-3	NI-4
Empirical formula	C10 H10 B F4 I N2	C14 H18 B F4 I N2	C12 H14 B F4 I N2 O2	C16 H22 B F4 I N2
Formula weight	371.91	428.01	431.96	456.07
Temperature	150(2) K	150(2) K	150(2) K	150(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	P2(1)/n	C2/c	P-1	I2/a
Unit cell dimensions	a = 12.221(3) Å b = 15.815(4) Å c = 14.644(4) Å α = 90° β = 113.366(4) ° γ = 90°	a = 12.766(2) Å b = 8.9885(17) Å c = 15.380(3) Å α = 90° β = 108.144(3)° γ = 90°	a = 8.0341(18) Å b = 8.3742(19) Å c = 12.038(3) Å α = 80.536(4)° β = 85.632(4)° γ = 76.585(4)°	a = 22.536(19) Å b = 10.952(9) Å c = 23.33(3) Å α = 90° β =106.556(11) ° γ = 90°
Volume	2598.2(11) $Å^3$	1677.0(5) $Å^3$	776.5(3) $Å^3$	5520(9) $Å^3$
Z	8	4	2	12
Density (calculated)	1.902 Mg/m^3	1.695 Mg/m^3	1.848 Mg/m^3	1.646 Mg/m^3
Absorption coefficient	2.495 mm^{-1}	1.945 mm^{-1}	2.110 mm^{-1}	1.778 mm^{-1}
F(000)	1424	840	420	2712
Crystal size	0.31 x 0.27 x 0.18 mm^3	0.31 x 0.23 x 0.21 mm^3	0.18 x 0.11 x 0.04 mm^3	0.35 x 0.23 x 0.16 mm^3
Theta range for data collection	1.99 to 27.00 °	2.79 to 27.00 °	2.53 to 27.00 °	1.82 to 27.00 °
Index ranges	-15<=h<=15, -20<=k<=20, -18<=l<=18	-16<=h<=15, -11<=k<=11, -19<=l<=19	-10<=h<=10, -10<=k<=10, -15<=l<=15	-27<=h<=27, -13<=k<=13, -28<=l<=28
Reflections collected	20971	6700	6582	21016
Independent reflections	5652 [R(int) = 0.0457]	1820 [R(int) = 0.0262]	3330 [R(int) = 0.0477]	5431 [R(int) = 0.1567]
Completeness to theta = 27.00 °	99.7 %	99.8 %	98.3 %	99.9 %
Absorption correction	Empirical	Empirical	Empirical	Empirical
Max. and min. transmission	0.894 and 0.605	0.894 and 0.781	0.862 and 0.219	0.894 and 0.312
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	5652 / 0 / 328	1820 / 0 / 104	3330 / 0 / 201	5431 / 13 / 336
Goodness-of-fit on F^2	1.028	1.071	0.967	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0419, wR2 = 0.0888	R1 = 0.0218, wR2 = 0.0531	R1 = 0.0354, wR2 = 0.0689	R1 = 0.0616, wR2 = 0.1641
R indices (all data)	R1 = 0.0757, wR2 = 0.0991	R1 = 0.0260, wR2 = 0.0546	R1 = 0.0436, wR2 = 0.0718	R1 = 0.0769, wR2 = 0.1803
Largest diff. peak and hole	0.740 and -0.589 $e.Å^{-3}$	0.477 and -0.446 $e.Å^{-3}$	0.848 and -0.739 $e.Å^{-3}$	2.449 and -1.360 $e.Å^{-3}$

Table A2 Crystal data and structure refinement for H(2-acetylpyridine)BF_4, ***N*-1**, ***N*-3** and ***N*-6** ·DMF

Name	H(2-acetylpyridine)BF_4	***N*-1**	***N*-3**	***N*-6** ·DMF
Empirical formula	C7 H8 B F4 N O	C14 H12 I N O	C14 H11 F I N O	C24 H22 I N3 O
Formula weight	208.95	337.15	355.14	495.35
Temperature	150(2) K	150(2) K	150(2) K	150(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic
Space group	P2(1)2(1)2(1)	Pca2(1)	P2(1)/c	Pbca
Unit cell dimensions	a = 5.396(2) Å b = 12.680(5) Å c = 13.024(5) Å α = 90° β = 90° γ = 90°	a = 12.955(3) Å b = 10.132(3) Å c = 9.805(3) Å α = 90° β = 90° γ = 90°	a = 25.252(13) Å b = 4.985(3) Å c = 22.795(11) Å α = 90° β = 114.236(9)° γ = 90°	a = 9.303(2) Å b = 19.108(5) Å c = 23.950(6) Å α = 90° β = 90° γ = 90°
Volume	891.1(6) $Å^3$	1287.0(6) $Å^3$	2617(2) $Å^3$	4257.5(18) $Å^3$
Z	4	4	8	8
Density (calculated)	1.557 Mg/m^3	1.740 Mg/m^3	1.803 Mg/m^3	1.546 Mg/m^3
Absorption coefficient	0.157 mm^{-1}	2.471 mm^{-1}	2.446 mm^{-1}	1.524 mm^{-1}
F(000)	424	656	1376	1984
Crystal size	0.25 x 0.18 x 0.05 mm^3	0.49 x 0.22 x 0.15 mm^3	0.27 x 0.14 x 0.03 mm^3	0.48 x 0.06 x 0.05 mm^3
Theta range for data collection	2.24 to 26.00 °	2.01 to 26.00 °	0.88 to 26.00 °	1.70 to 26.00 °
Index ranges	-6<=h<=6, -14<=k<=7, -15<=l<=8	-15<=h<=15, -12<=k<=12, -12<=l<=12	-31<=h<=30, - 6<=k<=6, -28<=l<=28	-11<=h<=11, -23<=k<=23, -29<=l<=29
Reflections collected	2459	9362	19317	31649
Independent reflections	1531 [R(int) = 0.0581]	2513 [R(int) = 0.0431]	5137 [R(int) = 0.1780]	4189 [R(int) = 0.1419]
Completeness to theta = 26.00 °	98.5 %	99.9 %	99.9 %	99.9 %
Absorption correction	Empirical	Empirical	Empirical	Empirical
Max. and min. transmission	0.894 and 0.474	0.894 and 0.406	0.901 and 0.459	0.894 and 0.678
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	1531 / 0 / 128	2513 / 1 / 154	5137 / 78 / 326	4189 / 0 / 264
Goodness-of-fit on F^2	0.985	1.036	1.084	0.899
Final R indices [I>2sigma(I)]	R1 = 0.0500, wR2 = 0.1007	R1 = 0.0282, wR2 = 0.0629	R1 = 0.1078, wR2 = 0.2595	R1 = 0.0502, wR2 = 0.0827
R indices (all data)	R1 = 0.0775, wR2 = 0.1260	R1 = 0.0336, wR2 = 0.0650	R1 = 0.1828, wR2 = 0.2851	R1 = 0.0945, wR2 = 0.0945
Largest diff. peak and hole	0.206 and -0.184 $e.Å^{-3}$	0.495 and -0.590 $e.Å^{-3}$	2.620 and -1.547 $e.Å^{-3}$	0.607 and -0.727 $e.Å^{-3}$

Table A3 Crystal data and structure refinement for **NC-1**, **NC-2**, **NC-3** and H(***N*-5**)BF_4

Name	**NC-1**	**NC-2**	**NC-3**	**H(*N*-5)BF_4**
Empirical formula	C14 H11 Cl I N O	C14 H10 Cl2 I N O	C14 H10 Cl F I N O	C13 H10 B F4 I N2
Formula weight	371.59	406.03	389.58	407.94
Temperature	150(2) K	150(2) K	150(2) K	150(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic	Trigonal
Space group	P2(1)/c	C2/c	C2/c	P3(1)
Unit cell dimensions	a = 8.125(3) Å b = 15.332(6) Å c = 11.191(4) Å α = 90° β = 103.855(6)° γ = 90°	a = 27.911(8) Å b = 5.7353(17) Å c = 19.332(6) Å α = 90° β = 114.652(5)° γ = 90°	a = 27.049(7) Å b = 5.6867(14) Å c = 19.531(5) Å α = 90° β = 117.459(4) ° γ = 90°	a = 9.0285(14) Å b = 9.0285(14) Å c = 14.991(3) Å α = 90° β = 90° γ = 120 °
Volume	1353.5(9) $Å^3$	2812.6(15) $Å^3$	2665.8(11) $Å^3$	1058.3(3) $Å^3$
Z	4	8	8	3
Density (calculated)	1.823 Mg/m^3	1.918 Mg/m^3	1.941 Mg/m^3	1.920 Mg/m^3
Absorption coefficient	2.550 mm^{-1}	2.647 mm^{-1}	2.604 mm^{-1}	2.307 mm^{-1}
F(000)	720	1568	1504	588
Crystal size	0.28 x 0.20 x 0.14 mm^3	0.19 x 0.15 x 0.03 mm^3	0.26 x 0.14 x 0.03 mm^3	0.24 x 0.08 x 0.07 mm^3
Theta range for data collection	2.30 to 26.00 °	1.61 to 26.00 °	1.70 to 26.00 °	2.60 to 26.00 °
Index ranges	-10<=h<=9, -18<=k<=18, -13<=l<=13	-34<=h<=34, -7<=k<=7, -23<=l<=23	-33<=h<=30, - 6<=k<=7, -24<=l<=24	-11<=h<=11, -11<=k<=11, -18<=l<=18
Reflections collected	10259	10287	9743	8295
Independent reflections	2648 [R(int) = 0.0530]	2751 [R(int) = 0.0957]	2594 [R(int) = 0.0633]	2695 [R(int) = 0.0925]
Completeness to theta = 26.00 °	99.7 %	99.9 %	99.7 %	99.9 %
Absorption correction	Empirical	Empirical	Empirical	Empirical
Max. and min. transmission	0.894 and 0.635	0.888 and 0.525	0.928 and 0.598	0.894 and 0.654
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	2648 / 0 / 163	2751 / 0 / 172	2594 / 0 / 172	2695 / 2 / 190
Goodness-of-fit on F^2	1.051	1.003	0.987	0.923
Final R indices [I>2sigma(I)]	R1 = 0.0345, wR2 = 0.0715	R1 = 0.0582, wR2 = 0.1253	R1 = 0.0373, wR2 = 0.0762	R1 = 0.0528, wR2 = 0.0789
R indices (all data)	R1 = 0.0416, wR2 = 0.0741	R1 = 0.0866, wR2 = 0.1347	R1 = 0.0479, wR2 = 0.0798	R1 = 0.0777, wR2 = 0.0842
Largest diff. peak and hole	0.945 and -0.531 e.$Å^{-3}$	2.770 and -1.544 e.$Å^{-3}$	1.118 and -0.860 e.$Å^{-3}$	0.815 and -0.565 e.$Å^{-3}$

Table A4 Crystal data and structure refinement for **NF-1**, **NF-2**, **NF-3** and **IC-1**

Name	NF-1	NF-2	NF-3	IC-1
Empirical formula	C14 H11 F I N O	C14 H10 Cl F I N O	C14 H10 F2 I N O	C17 H15 I O
Formula weight	355.14	389.58	373.13	362.19
Temperature	150(2) K	150(2) K	150(2) K	150(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P2(1)/c	C2/c	C2/c	P2(1)/n
Unit cell dimensions	a = 13.079(2) Å b = 13.890(2) Å c = 14.747(2) Å α = 90° β = 108.966(3) ° γ = 90°	a = 26.105(5) Å b = 5.6191(11) Å c = 18.635(4) Å α = 90° β = 101.142(3) ° γ = 90°	a = 24.623(9) Å b = 5.638(2) Å c = 18.587(7) Å α = 90° β = 100.026(6) ° γ = 90°	a = 8.087(3) Å b = 18.042(6) Å c = 10.473(3) Å α = 90° β = 105.576(5)° γ = 90 °
Volume	2533.6(7) $Å^3$	2682.1(9) $Å^3$	2540.9(16) $Å^3$	1471.9(8) $Å^3$
Z	8	8	8	4
Density (calculated)	1.862 Mg/m^3	1.930 Mg/m^3	1.951 Mg/m^3	1.634 Mg/m^3
Absorption coefficient	2.527 mm^{-1}	2.589 mm^{-1}	2.535 mm^{-1}	2.165 mm^{-1}
F(000)	1376	1504	1440	712
Crystal size	0.27 x 0.22 x 0.10 mm^3	0.39 x 0.28 x 0.16 mm^3	0.31 x 0.24 x 0.10 mm^3	0.49 x 0.17 x 0.13 mm^3
Theta range for data collection	1.65 to 26.00 °	1.59 to 26.00 °	1.68 to 26.00 °	2.26 to 26.00 °
Index ranges	-16<=h<=16, -16<=k<=17, -18<=l<=18	-32<=h<=31, -6<=k<=6, -22<=l<=22	-30<=h<=31, - 7<=k<=7, -23<=l<=23	-9<=h<=9, -22<=k<=21, -12<=l<=12
Reflections collected	19564	9737	9923	11269
Independent reflections	4976 [R(int) = 0.1227]	2624 [R(int) = 0.0350]	2766 [R(int) = 0.0466]	2881 [R(int) = 0.0487]
Completeness to theta = 26.00 °	99.9 %	99.7 %	99.7 %	99.9 %
Absorption correction	Empirical	Empirical	Empirical	Empirical
Max. and min. transmission	0.894 and 0.491	0.888 and 0.658	0.894 and 0.652	0.914 and 0.581
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	4976 / 0 / 325	2624 / 0 / 172	2766 / 0 / 172	2881 / 0 / 174
Goodness-of-fit on F^2	0.853	1.069	1.061	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0525, wR2 = 0.0870	R1 = 0.0267, wR2 = 0.0616	R1 = 0.0314, wR2 = 0.0672	R1 = 0.0323, wR2 = 0.0736
R indices (all data)	R1 = 0.0994, wR2 = 0.0995	R1 = 0.0340, wR2 = 0.0644	R1 = 0.0453, wR2 = 0.0719	R1 = 0.0395, wR2 = 0.0761
Largest diff. peak and hole	1.754 and -1.012 e.$Å^{-3}$	0.476 and -0.524 e.$Å^{-3}$	0.936 and -0.580 e.$Å^{-3}$	1.225 and -0.412 e.$Å^{-3}$