New Perspectives in Aromatic Aminations Using Hypervalent Iodine(III) Reagents

Nicola Lucchetti

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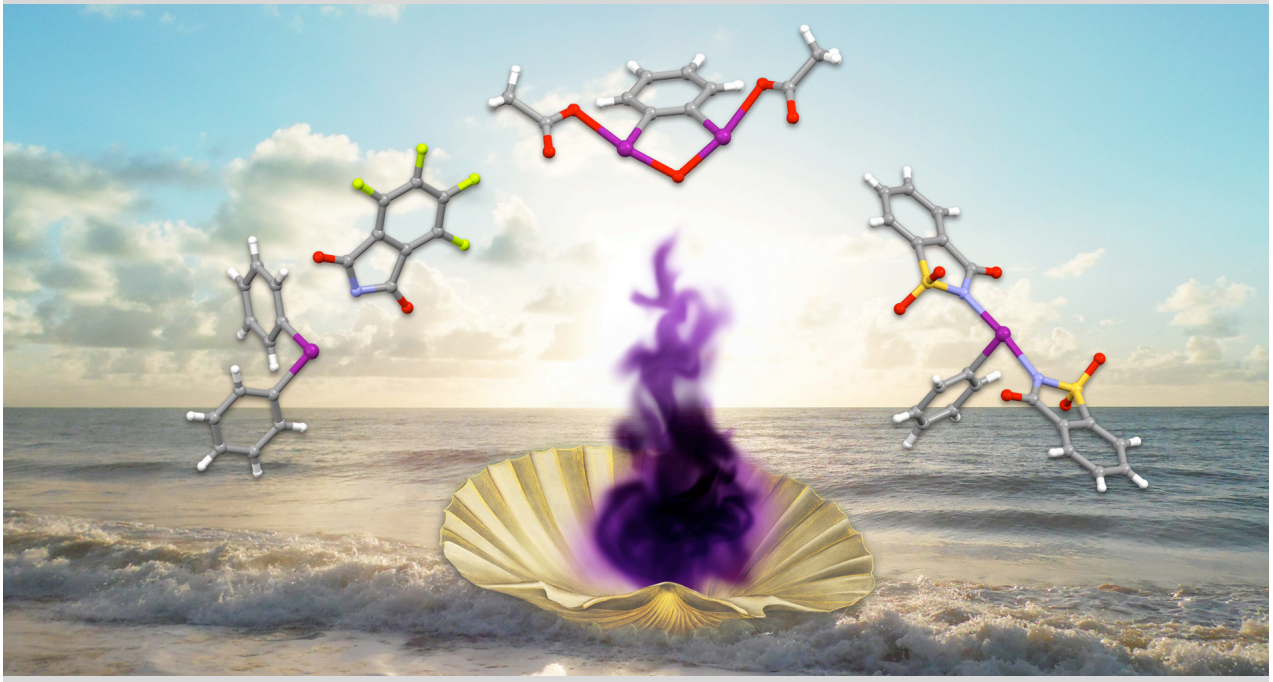

DOCTORAL THESIS
2017

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Doctoral Thesis

Supervised by Prof. Kilian Muñiz Klein

Institute of Chemical Research of Catalonia (ICIQ)

Tarragona

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Prof. Dr. Kilian Muñiz Klein, Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) and Research Professor of the Catalan Institution for Research and Advanced Studies (ICREA),

I STATE that the present study, entitled "New Perspectives in Aromatic Aminations Using Hypervalent Iodine(III) Reagents", presented by NICOLA LUCCHETTI for the award of the Degree of Doctor, has been carried out under my supervision at Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, May 31st, 2017

Doctoral Thesis Supervisor

Prof. Dr. Kilian Muñiz Klein

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List of Publications

Some of the results presented in this thesis have been published:

• "Sterically Congested 2,6-Disubstituted Anilines from Direct C−N Bond Formation at an Iodine(III) Center"
Nicola Lucchetti, Michelangelo Scalone, Serena Fantasia and Kilian Muñiz.
Angew. Chem. Int. Ed. **2016**, *55*, 13335.

• "An Improved Catalyst for Iodine(I/III)-Catalysed Intermolecular C−H Amination"
Nicola Lucchetti, Michelangelo Scalone, Serena Fantasia and Kilian Muñiz.
Adv. Synth. Catal. **2016**, *358*, 2093. Selected as Very Important Publication.

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"Tutti sanno che una cosa è impossibile da realizzare,
finchè arriva uno sprovveduto che non lo sa e la inventa."
Albert Einstein

"Audentes fortuna iuvat."
Virgilio

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List of Abbreviations and Acronyms

^{4F}Phth…….Tetrafluorophthalimide
Ac……..Acetyl
Ar……...Aryl
BHT……...……Butylated hydroxytoluene
BDE……...Bond dissocation energy
Bn……..Benzyl
Boc……*Tert*-butyloxy carbonyl
Bs……..Benzenesulphonyl
bpy…….2,2'-bipyridine
Cbz……Benzylcarbamoyl
DAIB…….(Diacetoxyiodo)benzene
DCE……..1,2-Dichloroethane
DCM……..Dichloromethane
DDQ……..2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DG…….Directing group
DMAP……...4-Dimethylaminopyridine
DMF……..Dimethylformamide
DMP……..Dess-Martin periodinane
DMSO……...Dimethylsulphoxide
dtbbpy……4,4'-di-*tert*-butyl-2,2'-dipyridyl
DTBP…….Di-*tert*-butyl peroxide
EDA complex……Electron donor-acceptor complex
ee……...Enantiomeric excess
Equiv…….Equivalent
ESI…….Electrospray ionization
ESR……Electron spin resonance
fac……..Facial
FT-IR…….Fourier-transform infrared spectroscopy
gem……Geminal
HFIP……..1,1,1,3,3,3-Hexafluoroisopropanol
HRMS……High resolution mass spectrometry
IBX……2-Iodobenzoic acid
IUPAC……...International Union of Pure and Applied Chemistry
KIE……Kinetic isotope effect

m.p……...Melting point
MALDI……Matrix-assisted laser desorption ionization
*m*CPBA……*meta*-Chloroperbenzoic acid
MHz……....Megahertz
Ms……Methanesulphonyl
MTBE……..Metyl-*tert*-butyl-ether
NMR……Nuclear magnetic resonance
Ns…….4-Nitrobenzenesulphonyl
ºC…….Celsius degree
PET……..Positron emission tomography
Ph…….Phenyl
Phth……..Phthalimide
PIDA……see DAIB
PIFA…….[Bis(trifluoroacetoxy)iodo]benzene
PMB…….*Para*-methoxy benzene
PPTS……Pyridinium *para*-toluenesulphonate
ppy……2-Phenyl pyridine
Py…….Pyridine
r.t……..Room temperature
SET……..Single electron transfer
TBAB……..Tetrabutylammonium bromide
TBACl……Tetrabutylammonium chloride
TBAI……Tetrabutylammonium iodide
TBAOH……Tetrabutylammonium hydroxide
TBHP……*Tert*-butyl hydroperoxide
TCICA…….Trichloroisocyanuric acid
TEMPO……2,2,6,6-Tetramethyl-1-piperidinyloxy
TFA……..Trifluoroacetic acid
TFE……..2,2,2-Trifluoroethanol
THF……..Tetrahydrofuran
TLC……..Thin layer chromatography
TMP…….Trimethoxyphenyl
TMSCl…….Chlorotrimethylsilane
Ts……..4-Toluenesulphonyl
UV……Ultraviolet

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Chapter I

General Overview

1.1 Carbon-nitrogen bonds in biological synthesis

Nitrogen- and oxygen-containing functional groups are ubiquitous features of biologically active molecules. The balance of heteroatom substituents is fundamental to both biological activity and potentiality as target drugs. In fact, in many cases the function of a specific molecule requires the presence of carbon-nitrogen bonds in strategic positions.[1] The importance of nitrogen-containing fragments is related both to the basic character of the nitrogen lone pair and the hydrogen bond-donating ability of the NH group. This last aspect can be modulated by the substitution pattern. A classical example is found in DNA.
Modulation of the substitution at the nitrogen leads to marked pharmacological effects. This delicate equilibrium between steric and electronic factors renders the nitrogen-based group a target for chemical synthesis and for studies of the structure and activity of biologically active molecules.

1.1.1 Aromatic amines

As the main aim of this dissertation is the development of suitable synthetic methodologies with high potential applicability from an industrial perspective, a brief historical introduction on the synthesis of aromatic compounds containing nitrogen functional groups is provided.
Aromatic amines are compounds of notable industrial and commercial importance.[2] They are used as intermediates in the synthesis of numerous organic compounds including azo dyes, and as antioxidants in consumer goods. Also, they are produced when plants and other organic materials are burned. As important structural fragments, these aminated compounds often show significant biological properties. For this reason,

[1] Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284.
[2] a) Skeen, J. R. *Chem. Eng. News* **1948**, *26*, 3827; b) Radomski, J. L. *Ann. Rev. Pharmacol. Toxicol.* **1979**, *19*, 129.

they have been of prominent research interest in synthetic, material and medicinal chemistry.

Aniline was first isolated from indigo in 1826 by Otto Unverdorben.[3] In 1842, the Russian chemist Nikolai N. Zinin reduced nitrobenzene with hydrogen sulfide to a new molecule called "Binzid".[4] In 1845, August Wilhelm von Hofmann purified aniline from coal tar. The first industrial application of aniline was the manufacture of mauveine (Perkin's mauve, Fig. 1.1), a dye discovered in 1856 by William Henry Perkin.[4]

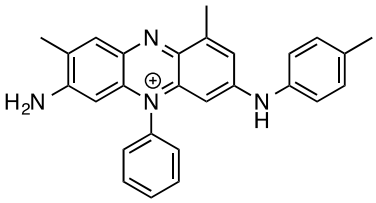


Figure 1.1 Perkin's mauve.

Historically, arylamine synthesis was carried out by electrophilic aromatic substitution in two steps: nitration or nitrosation of the arene core followed by catalytic reduction with a metal salt.[5] However, these protocols encountered some limitations. Nitration requires harsh acidic and oxidising conditions, and is incompatible with many functional groups. Sequential steps of protection-deprotection are demanded as consequence. Regioselectivity represents another significant issue, with the production of *ortho*/*para* mixtures. On the other hand, nucleophilic substitutions have the advantage to be a single synthetic step. However, they are restricted to substrates possessing electron-withdrawing groups.

From Perkin's serendipitous discovery on, aromatic amines became a generic class of organic chemicals with profound consequences. Moreover, this scaffold is nowadays incorporated in series of relevant compounds of pharmaceutical and herbicidal interest (Fig. 1.2).

[3] Brooks, N. M. *Bull. Hist. Chem.* **2002**, *27*, 26.
[4] *The Chemistry of Anilines*, Vol. 1,2, Ed. Z. Rappoport, Wiley, New York, **2007**.
[5] Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399.

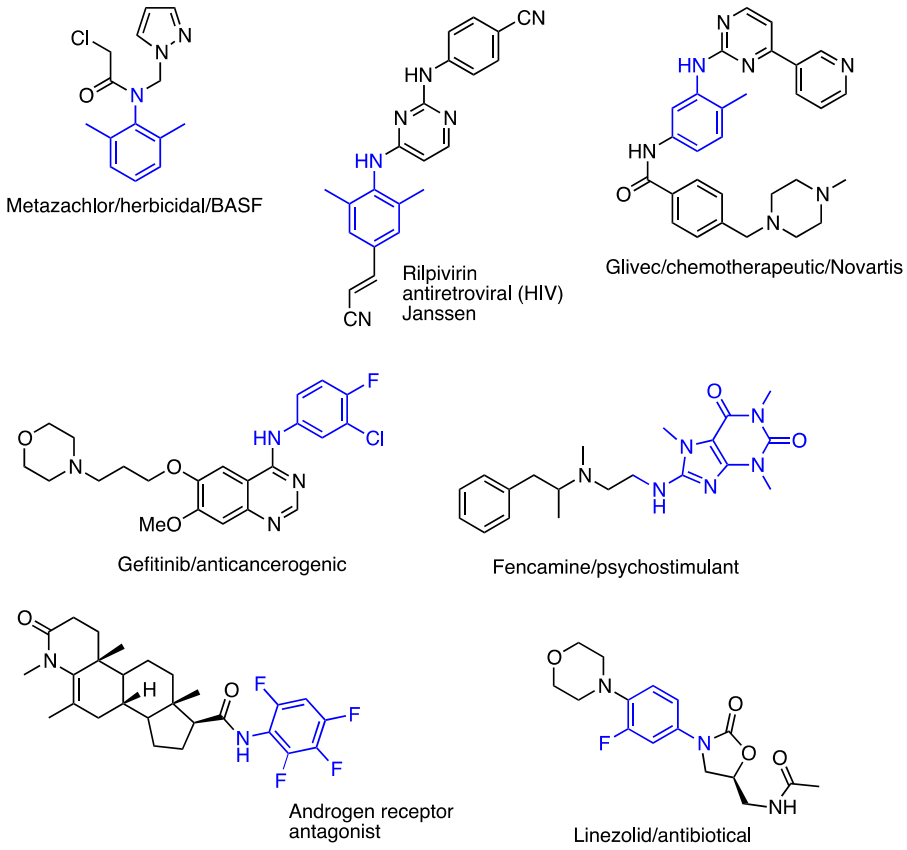


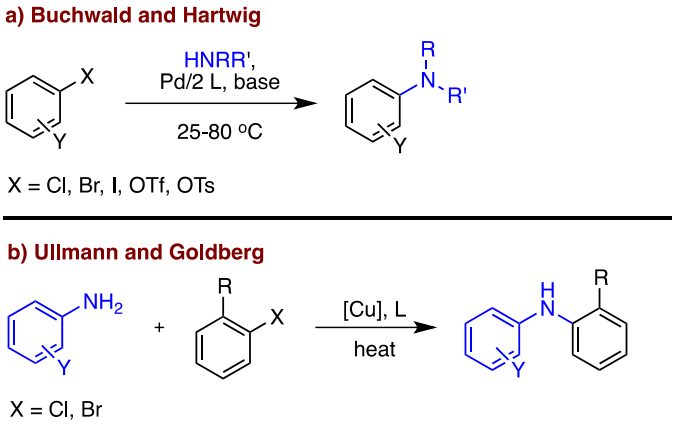
Figure 1.2 Aromatic amines of biological interest.

1.2 C–H oxidative amination: metal catalysis

In contrast to the many natural ways of oxygen transfer, nature does not provide much inspiration for direct oxidative nitrogen transfer to organic molecules. However, non-natural oxidation systems, which deliver carbon-nitrogen fragments to organic molecules in a direct fashion, do exist. A particular prominent example of innovative C–N bond installation is the synthesis of anilines by transition-metal-catalysed coupling between amine sources and pre-functionalised arenes. In this field, palladium[6] and

[6] For selected reviews, see: a) Jiang, L.; Buchwald, L. S. in *Metal-Catalysed Cross-Coupling Reactions*, *Vol. 2*, 2nd ed., Wiley-VCH, Weinheim, **2004**, p. 699; b) Hartwig, J. F. in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Ed. E. Negishi, Wiley-Interscience, New-York, **2002**, p. 1051; c) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; d) Hartwig, J. F. *Synlett*, **2006**, 1283; e) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.

copper[7] have received most of the attention since the mid-1990s (Scheme 1.1). These widely investigated protocols require the presence of a halogen atom (Cl, Br or I) or of good leaving groups, such as sulphonates or triflates (prepared from the corresponding phenols) in the arenes. Moreover, the scope of the amine nucleophiles is restricted to primary and secondary amines. Sulphonylamines, carbamates, and nitrogen-containing heterocycles are not suitable substrates. Herein, attention will focus on direct C−H oxidative aminations of aromatic cores, as they represent cheaper and more elegant alternatives to Buchwald-Hartwig and Ullmann couplings.

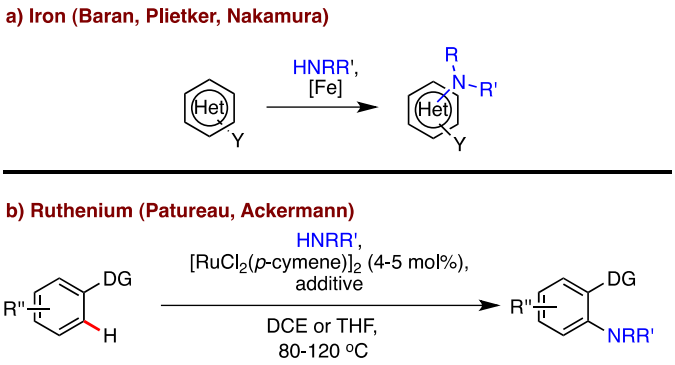


Scheme 1.1 Classical transition-metal-catalysed C−N bond formation.

Regarding metals from group VII, heterogeneous, porous γ-MnO_2 catalyses amination of benzoxazoles using molecular oxygen as green oxidant.[8] Among group VIII, the earth abundant iron was efficiently used to promote catalytic amination (Scheme 1.2a).[9] Recently, Baran reported a scalable *N*-succinimidyl perester enabling imidations in combination with ferrocene as electron shuttle.[9b] Remarkable recent progress has been accomplished in direct C−H functionalisations for the formation of C−N bonds through the use of readily accessible ruthenium catalysts (Scheme 1.2b).[10] Valuable directing

[7] a) Ullmann, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2174; b) Ullmann, F. *Justus Liebigs Ann. Chem.* **1904**, *332*, 38; c) Evano, E.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054; d) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.
[8] Pal, P.; Giri, A. K.; Singh, H.; Ghosh, S. C.; Panda, A. B. *Chem. Asian J.* **2014**, *9*, 2392.
[9] a) Majumdar, K. C.; De, N.; Ghosh, T.; Roy, B. *Tetrahedron* **2014**, *70*, 4827; b) Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5279; c) Legnani, L.; Prina Cerai, G.; Morandi, B. *ACS Catal.* **2016**, *6*, 8162; d) Legnani, L.; Bhawal, B. N.; Morandi, B. *Synthesis* **2017**, *49*, 776.
[10] Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29.

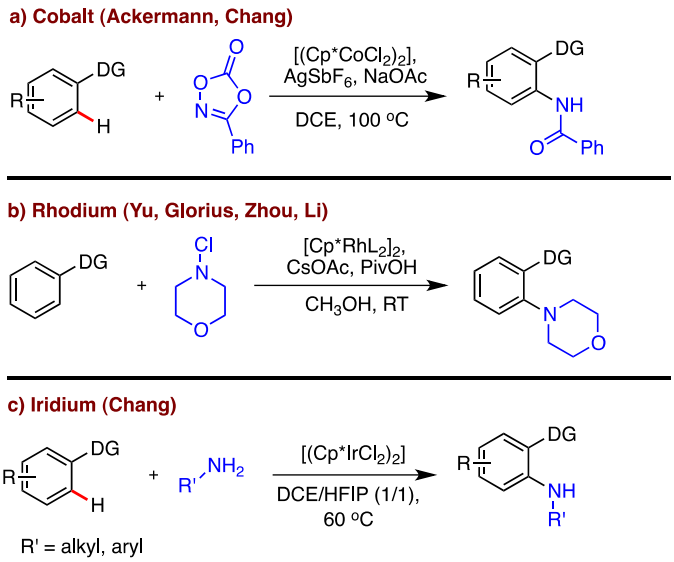
groups allow chelation-assisted amidations of arenes with various alkyl and aryl sulphonyl amides, providing C−N bond instalment in excellent yields.



Scheme 1.2 Group VIII catalysed C−N bond formation.

High-valent cobalt(III) catalysts (group IX) afford versatile amidations with high levels of regio- and chemoselectivities (Scheme 1.3a).[11] Dioxazolones are easy to handle and possess high coordination affinity to the metal centres of metallacycle intermediates depicting a common reagent for amidation reactions.[12] Later, researchers explored Rh(III)-catalysed C−H amination reactions by assuming a coupling between the rhodacyclic intermediate with a proper amino source instead of the previously described nucleophiles (Scheme 1.3b).[13] In 2012, Yu[14] and Glorius[15] independently reported such transformations using *N*-chloroamines as aminating agents. Also, dirhodium species catalysed C−H arene amination using hydroxylamines.[16] Newly developed systems based on iridium catalysis were successfully applied to the C−H amination of arenes with challenging alkylamine reactants as nitrogen sources (Scheme 1.3c).[17] The reaction was proposed to proceed through an Ir(IV)-imido species, which was in accordance to the oxidative conversion and poor reactivity of secondary amines.

[11] Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498.
[12] a) Park, J.; Chang, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 14103; b) Mei, R.; Loup, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 793.
[13] a) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040; b) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017** DOI: 10.1021/acs.chemrev.6b00644.
[14] Ka-Ho, N.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272.
[15] Grohmann, C.; Wang. H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.
[16] Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck, J. R. *Science* **2016**, *353*, 1144.
[17] Kim, H.; Chang, S. *ACS Catal.* **2016**, 6, 2341.

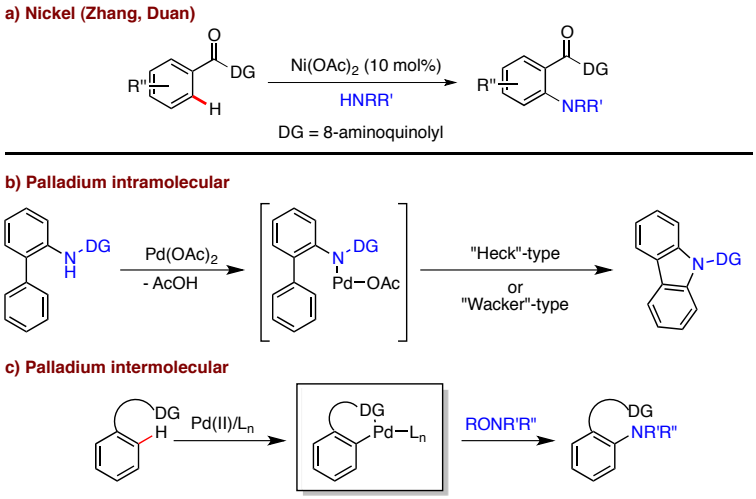


Scheme 1.3 Group IX catalysed C−N bond formation.

Since nickel is the least expensive and most abundant element among the group X it has been at the centre of attention. Great achievements have been accomplished in Ni-catalysed amination reactions within the last few years (Scheme 1.4a).[18] In 2012, Duan[18a] reported a direct amination of benzaxoles with secondary amines, under acidic conditions in an oxygen atmosphere. On the other hand, palladium-catalysed, ligand-directed C−H functionalisations were historically mostly used for the introduction of C−N bonds.[19] This field of chemical reactions can be divided in two main categories: C−N bonds are formed in an intramolecular way, or the nitrogen is transferred from an external reagent (Scheme 1.4b). Buchwald[20] and Gaunt[21] reported an oxidative Pd(II)-catalysed amination of carbazoles. Chen described highly efficient syntheses of lactams via intramolecular amination at γ and δ positions.[22] Diverse 4-aryl-2-quinolines were prepared from propionamides via ligand-enabled triple activation.[23] As alternative approach, chelation assisted C−H bond activation represents a powerful tool for the

[18] a) Li, Y.; Liu, J.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. *Org. Biomol. Chem.* **2012**, *10*, 3715; b) Marín, M.; Rama, R. J.; Nicasio, M. C. *Chem. Rec.* **2016**, *16*, 1819;
[19] For selected reviews, see: a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; b) SanMartin, R.; Herrero, M. T.; Domínguez, E. *Chem. Rec.* **2016**, *16*, 1082; c) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610.
[20] Tsang, P. W. C.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560.
[21] Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184.
[22] He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.
[23] Deng, Y.; Gong, W.; He, J.; Yu, J.-Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 6692.

deprotonation of inert C–H bonds (Scheme 1.4c). In 2006, Che published an intermolecular *ortho*-amidation of 2-arylpyridines via nitrene insertion.[24] *Ortho*-amination of aryl iodides was achieved using $Pd(OAc)_2$ and norbornene as ligand.[25] Recently, Yu and co-workers described a suitable approach to *ortho*- and *meta*-amination[26] of arenes via Pd(II) catalysis using *N*-benzoyl morpholine as aminating agent. In this reaction the addition of a modified norbornene as transient mediator was crucial. Only a few intramolecular platinum-catalysed examples have become available.[27]

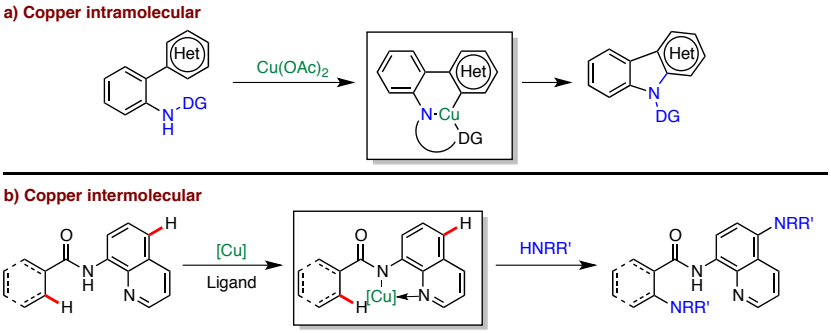


Scheme 1.4 Group X catalysed C–N bond formation.

Among first row transition-metals, copper complexes (group XI) show unique and versatile reactivities and good functional group tolerance. A broad range of oxidation states of copper (mainly from Cu^0 to Cu^{III}) enables the promotion of redox reactions in either a single-electron or a two-electron-transfer fashion. For the versatility shown by this metal, most investigations have been directed towards the synthesis of nitrogen-

[24] Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048.
[25] a) Shi, H.; Babinski, D. J.; Ritter, T. *J. Am. Chem. Soc.* **2015**, *137*, 3775; b) Della Ca`, N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389.
[26] a) Zhu, D.; Yang, G.; He, J.; Chu, L.; Chen, G.; Gong, W.; Chen, K.; Eastgate, M. D.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 2497; b) Wang, P.; Li, G.-C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 14092.
[27] a) Yamamoto, M.; Matsubara, S. *Chem. Lett.* **2007**, *36*, 172; b) Matsubara, S.; Asano, K.; Kajita, Y.; Yamamoto, M. *Synthesis* **2007**, *13*, 2055.

containing species.[28] Intramolecular oxidative C−N bond formations have been developed for the preparation of carbazoles under copper catalysis using hypervalent iodine(III)[29] or MnO_2[30] as oxidants. Imidazo[1,2-*a*]pyridines were efficiently synthesised by oxidative C−H amination (Scheme 1.5a).[31] In most intermolecular reactions however, the presence of a chelating group for the transition-metal catalyst is required (Scheme 1.5b). In 2016, Daugulis[32] and Baidya[33] described a C(sp^2)−H amination of heterocycles using bidentate directing groups incorporated in the same molecule. (NHC)−Cu complexes were found to successfully furnish the amidation of heteroarenes under mild conditions allowing the subsequent easy deprotection of the carbamate groups.[34] Recently, Bolm afforded a direct sulphoximination of heteroaromatic *N*-oxides by dual C−H/N−H dehydrogenative cross coupling.[35]



Scheme 1.5 Copper catalysed C−N bond formation.

Silver, the less expensive among the noble metals, has been widely used for various organic transformations in the past few decades.[36] Its application as potential catalyst for C−N bond formation is still not thoroughly investigated. An example is the synthesis of dimeric 1,2-dihydro-2,2,4-trimethylquinoline derivatives.[36a] In 2013, Ritter provided

[28] For selected reviews, see: a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622; b) Zhu, X.; Chiba, S. *Chem. Soc. Rev.* **2016**, *45*, 4504; c) Liu, J.; Chen, G.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 1174.
[29] Cho, H. S.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996.
[30] Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 2892.
[31] Kielesinski, Ł.; Tasior, M.; Gryko, D. T. *Org. Chem. Front.* **2015**, *2*, 21.
[32] Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016**, *138*, 4601.
[33] Sahoo, H.; Reddy, M. K.; Ramakrishna, I.; Baidya, M. *Chem. Eur. J.* **2016**, *22*, 1592.
[34] Xie, W.; Yoon, J. H.; Chang, S. *J. Am. Chem. Soc.* **2016**, *138*, 12605.
[35] Yu, H.; Dannenberg, C. A.; Li, Z.; Bolm, C. *Chem. Asian J.* **2016**, *11*, 54.
[36] a) Fotie, J.; Rhodus, J. L.; Taha, H. A.; Reid, C. S. *Heteroatom Chem.* **2012**, *23*, 598; b) Zheng, Q.-Z.; Jiao, N. *Chem. Soc. Rev.* **2016**, *45*, 4590.

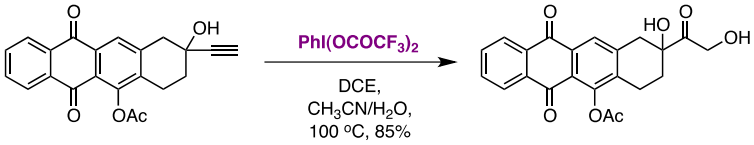
a co-catalysed C–H imidation of arenes.[37] Only few examples of gold catalysis in oxidative aminations are reported. In 2007, He reported a gold(III)-catalysed nitrene insertion into aromatics with iodonium ylides.[38] Recently, a regioselective gold(I)-catalysed oxidative C–N bond formation with phthalimide was performed.[39]

1.3 Hypervalent iodine(III) as alternative to metal catalysis

Iodine is an element that is quite different in reactivity to its halogen homologues. Its behaviour often resembles that of a transition-metal when used in organic transformations.[40] It is the largest, least electronegative and, as consequence, the most polarisable element among the halogen elements. As a result, it has been used as helpful alternative to replace highly toxic heavy-metal oxidants, such as lead(IV), mercury(II), and thallium(III). Additional benefits of iodine-based oxidants are the high stability and easy handling of these compounds.[41]

1.3.1 General features

In 1969, Musher stated: *"Hypervalent species are molecules and ions formed by elements in Groups 15-18 bearing more than eight electrons in their valence shells"*.[42] According to this definition, trivalent and pentavalent iodine compounds can be included in this category. The first hypervalent iodine(III) $PhICl_2$ was prepared by Willgerodt in 1886.[43] About 30-years ago, a hypervalent iodine(III) reagent was used in the synthesis of a natural product for the first time (Scheme 1.6).[44]



Scheme 1.6 Synthesis of ethynylcarbinol.

[37] Boursalian, G. B.; Ngai, M.-Y.; Hojczyk, K. N.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 13278.
[38] Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058.
[39] Marchetti, L.; Kantak, A.; Davis, R.; DeBoef, B. *Org. Lett.* **2015**, *17*, 358.
[40] Zhdankin, V. V. *Hypervalent Iodine Chemistry Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Chichester, **2013**.
[41] Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073.
[42] Musher, J. I. *Angew. Chem. Int. Ed.* **1969**, *8*, 54.
[43] Willgerodt, C. *J. Prakt. Chem.* **1886**, *33*, 154.
[44] a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 3837; b) Kita, Y.; Dohi, T. *Chem. Rec.* **2015**, *15*, 886.

Historically, I(III) compounds were called iodinanes, while I(V) compounds were referred to as periodinanes. Nowadays, the IUPAC nomenclature is depicting those compounds as λ^3-iodanes and λ^5-iodanes, respectively. Aryl-λ^3-iodanes possess pseudotrigonal bypiramid geometry, where the aryl and the lone pairs are directing to the equatorial positions (T-shaped structure). The aryl group and the iodine are connected by two σ-bonds described by molecular orbital theory as a three-centre-four-electron (3c-4e) system (Fig. 1.3).

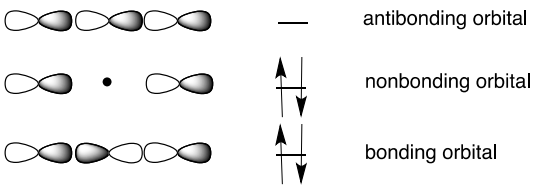


Figure 1.3 Molecular orbital diagram for aryl-λ^3-iodanes.

Due to the node present in the centre of the HOMO orbital, the hypervalent bond shows a highly polarised nature. A partial positive charge is localised on the iodine atom, while a partial negative charge is located on each of the ligands. The electrophilicity is explicitly demonstrated by a strong dipolar moment as well the apical disposition of the ligands. The most common classes of aryl-λ^3-iodanes are depicted in Fig. 1.4.[45] Among them, the most known are (diacetoxyiodo)benzene (PIDA), [bis(trifluoroacetoxy)iodo]benzene (PIFA), [hydroxyl(tosyloxy)iodo]benzene (Koser's reagent),[46] and 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni's I reagent).[47]

[45] a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123; b) *Issue in Honor of Prof. A. Varvoglis*, Arkivoc **2003**, *6*, 1.
[46] Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, *7*, 365.
[47] Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650.

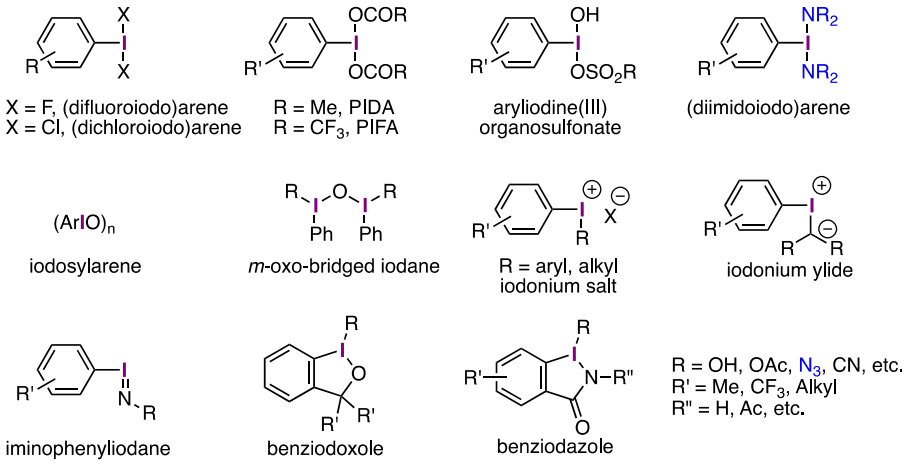


Figure 1.4 General structures for aryl-λ^3-iodanes.

Aryl-λ^5-iodanes are square pyramidal with an aryl group in the apical position connected by two σ-bonds to the iodine centre. Similarly to aryl-λ^3-iodanes, these compounds exhibit two orthogonal hypervalent three-centre-four-electron bonds with the ligands (Fig. 1.5).[48]

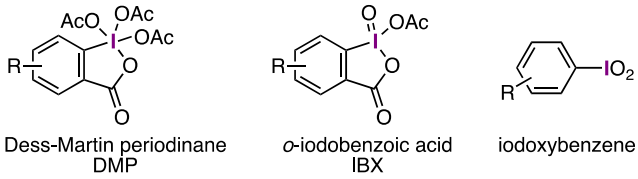


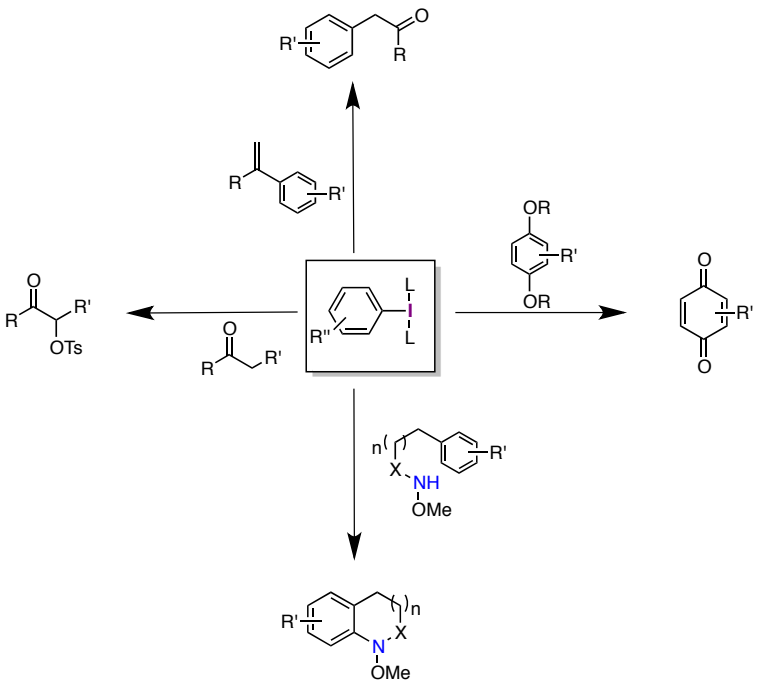
Figure 1.5 General structures for aryl-λ^5-iodanes.

1.3.2 General reactivity

Organic molecules bearing hypervalent iodine moieties have turned from laboratory curiosities to useful and routinely employed reagents in synthetic chemistry.[49] Several reagents in which the oxidation state at the iodine differs from the elemental state are now accessible. In the early stage of their application, they have been used as stoichiometric oxidants with a main focus on palladium and copper-catalysed processes.

[48] For selected reviews, see: a) Skulski, L. *Molecules* **2000**, *5*, 1331; b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523; c) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997; d) Ochiai, M. *Chem. Rec.* **2007**, *7*, 12; e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
[49] Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656.

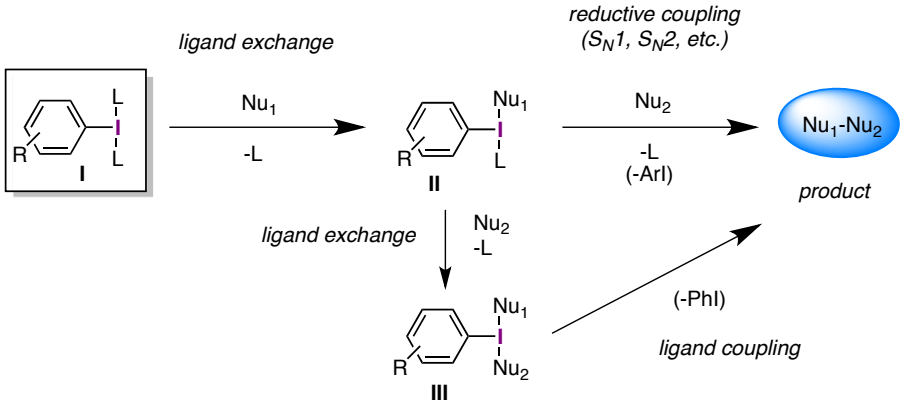
Their applications however, are not only limited to the role of oxidants as many other synthetic transformations of non-oxygenative nature such as cyclisations, α-functionalisations of carbonyl compounds, atom-transfer reactions, and oxidative rearrangements have been established utilising hypervalent iodine(III) species (Scheme 1.7).[50]



Scheme 1.7 General reactivity of aryl-λ^3-iodanes.

The two-electron-transfer processes involved in most hypervalent-iodine(III)-mediated transformations are generally discussed in a generalised mechanistic Scheme, which focuses on the changes in redox states and ligands (Scheme 1.8).

[50] a) Parra, A.; Reboredo, S. *Chem. Eur. J.* **2013**, *19*, 17224; b) Singh, F. V.; Wirth, T. *Chem. Asian J.* **2014**, *9*, 950; c) Romero, R. M.; Wöste, T. H.; Muñiz, K. *Chem. Asian J.* **2014**, *9*, 972.



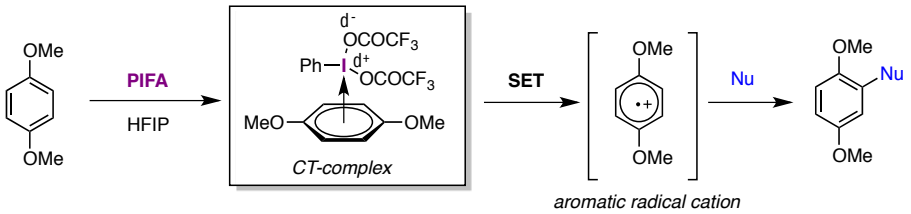
Scheme 1.8 General reactivity of aryl-λ^3-iodanes towards nucleophiles.

The ligand exchange at the iodine centre by the nucleophile (Nu_1) usually depicts the first step in the conversion of **I** to the final product. When $ArIL_2$ **I** gets converted, the ligand L is released forming the new specie **II**. For the coupling with a second nucleophile Nu_2, a reductive coupling or a ligand coupling process can be assumed starting from $ArINu_1L$ **II**. In the first pathway, the direct attack of the nucleophile Nu_1 at the iodine centre can take place by a S_N1 (dissociative) or S_N2 (associative) mechanism with releasing of aryl iodide and the ligand to afford the product. A dissociative pathway seems to be more unlikely due to the instability of a positive-charged intermediate. However, experiments in gas phase or during titrations of PhI(OH)OTs and PhI(OH)OMs by detection of charged intermediates clearly demonstrated that this pathway depicts an alternative to yield **II**.[51] As hypervalent iodine(III) compounds possess a strong electrophilic character, the two ligands could also both serve as leaving groups generating compound **III** directly. The ligand coupling leading to **III** is suggested to proceed through a reductive elimination step releasing ArI. This behaviour is common for diaryliodonium salts, which will be discussed in Chapter II. In conclusion, due to the change of the oxidation state at the iodine centre, this chemistry strongly resembles that of transition-metals.[52]

Hypervalent iodine(III) compounds also show single-electron-transfer (SET) oxidation abilities for the activation of aromatic systems. In this case, electron-donor and electron-

[51] Richter, H. W.; Cherry, B. R.; Zook, T. D.; Koser, G. F. *J. Am. Chem. Soc.* **1997**, *119*, 9614.
[52] a) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244; b) Grushin, V. V. *Acc. Chem. Res.* **1992**, *25*, 529; c) Ochiai, M. *Top. Curr. Chem.* **2003**, *224*, 5; d) *Ligand Coupling Reactions with Heteroaromatic Compounds, Tetrahedron Organic Series, Vol. 18*, Ed. P. Finet, Pergamon, Oxford, **1998**.

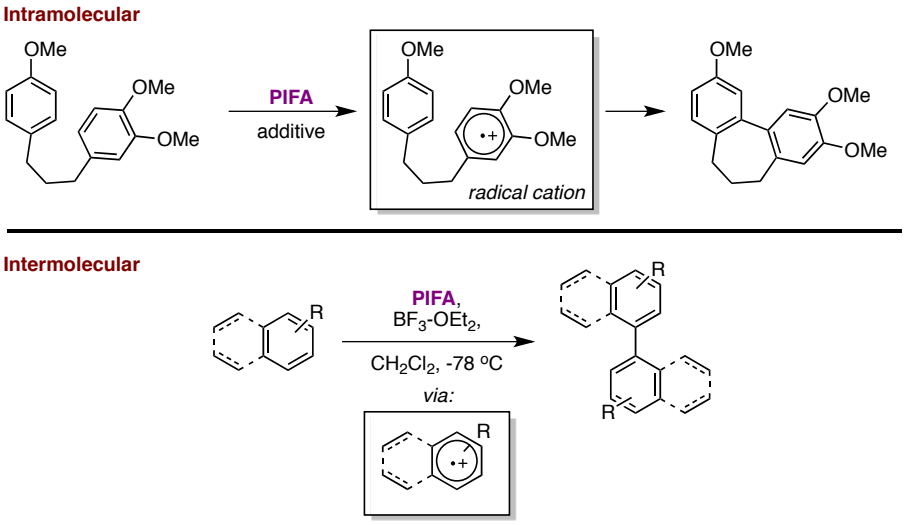
acceptor compounds generate an EDA (electron donor-acceptor) complex (Scheme 1.9).[53]



Scheme 1.9 Reaction mechanism: aromatic ring activation by SET oxidation.

In 1991, Kita and co-workers found that *para*-substituted phenol ethers afforded, when treated with trimethylsilyl azide, aromatic azides.[54] The use of fluoroalcohols as solvents dramatically affected the result of this reaction. A few years later, they determined the involvement of an aromatic cation radical during the reaction by performing detailed mechanistic studies based on UV and ESR spectroscopic measurement.[55] Later on, SET methodology was extended to the synthesis of biaryls in high yields (Scheme 1.10).[44b,56]

[53] For an extensive review about EDA complexes in organic synthesis, see: Rathore, R.; Kochi, J. K. *Adv. Phys. Org. Chem.* **2000**, *35*, 193.
[54] Aromatic cation radicals generation: a) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakura, Y. *Tetrahedron Lett.* **1991**, *32*, 4321; b) Kita, Y.; Takada, T.; Tohma, T. *Pure Appl. Chem.* **1996**, *68*, 627; c) Zhao, J.; Li, S. *J. Org. Chem.* **2017**, *82*, 2984.
[55] Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.
[56] a) Tohma, H.; Morioka, H.; Tazikawa, S.; Arisawa, M.; Kita, Y. *Tetrahedron* **2001**, *57*, 345; b) Tohma, H.; Iwata, M.; Maegawa, T.; Kita, Y. *Tetrahedron* **2002**, *43*, 9241.



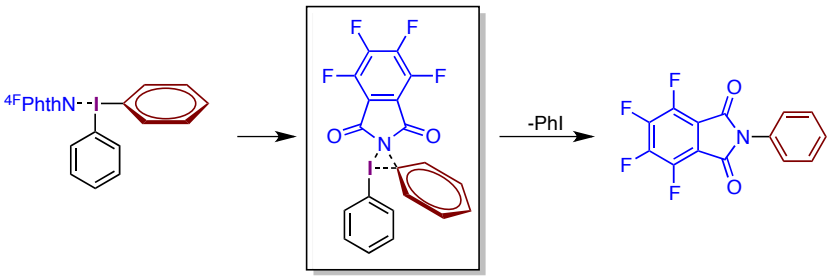
Scheme 1.10 Oxidative coupling of phenyl ether rings.

1.4 General objectives and summary

The main objective of this doctoral thesis is the development of new stoichiometric and catalytic methodologies for the metal-free amination of aromatic cores. Our approach relies only on the innate reactivity of the substrates, without the required presence of directing groups to provide the regioselectivity. The major issue associated with their use is the necessity of harsh conditions for the removal. Furthermore, in contrast with transition-metal catalysis we do not utilise expensive phosphine ligands or N-heterocyclic carbenes (NHC) to facilitate our reactions. The research studies have been divided in three main parts. First, iodine(III) compounds of the general formula Ar_2I-NPhth (HNPhth = phthalimide), prepared from ligand-exchange by pre-formed diaryliodonium salts, were applied to efficiently promote a direct reductive $C(sp^2)$–N bond formation. Second, the improvement of a catalyst for the iodine(I/III)-catalysed intermolecular aromatic amination has been investigated. Third, a synthetic procedure for aromatic and heteroaromatic aminations under photochemical conditions has been established utilising a combination of molecular iodine and bis(imido)iodanes.

1.4.1 Reductive elimination at an iodine centre

In Chapter II, the development of a synthetic procedure towards 2,6-disubstituted anilines by the direct reaction between amides and diaryliodonum salts is reported (Scheme 1.11).

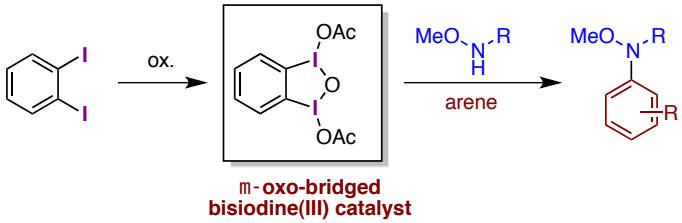


Scheme 1.11 Direct reductive C(sp^2)–N bond formation to afford protected anilines.

The reaction reported is of unusually broad scope in respect to the sterically congested arenes and nitrogen sources. Halogen substituents are tolerated as well as lactams as nitrogen sources. The reaction proceeds without any additional transition-metal promoters, while the efficiency of the coupling methodology was further demonstrated by a short chemoselective synthesis of a chemerin binding inhibitor. The proposed reaction mechanism was supported by the isolation of reaction intermediates, which were also characterised by X-ray diffraction. The intermediates were probed under the reaction conditions to calculate the activation energy parameters, as derived from Arrhenius and Eyring plots.

1.4.2 Advanced iodine(I/III) catalysis

In Chapter III, a novel catalytic amination methodology via iodine(I/III) is described. 1,2-Diiodobenzene was utilised as an efficient catalyst precursor for the intermolecular amination of arenes under homogeneous conditions (Scheme 1.12). The key feature of the catalyst is a strained μ-oxo-bridged conformation of the bisiodine(III) intermediate, which induces unparalleled high reactivity. This geometry differs with that of the example previously reported in literature.



Scheme 1.12 Direct C(sp^2)–N coupling promoted by a strained μ-oxo-bridged bisiodine(III) catalyst.

A wide variety of nitrogen-protecting groups was suitable in the reported approach, with the highest turnover numbers (TON) compared to other methodologies. Preliminary mechanistic investigations suggested an involvement of both iodine(III) centres during the process.

1.4.3 Title

This doctoral thesis is a collaboration with F. Hoffmann-La Roche Ltd. The content of this paragraph has not been included in this version of the document since is confidential.

UNIVERSITAT ROVIRA I VIRGILI
New Perspectives in Aromatic Aminations Using
Hypervalent Iodine(III) Reagents
Nicola Lucchetti

Chapter II

Synthesis of Congested 2,6-Disubstituted Anilines via Reductive Elimination at an Iodine Centre

2.1 Introduction to diaryliodonium salts

Iodine(III) reagents with two carbon ligands have properties resembling those of Hg, Pb, and Pd complexes and can be used in reaction pathways similar to metal-catalysed reactions.[1] Diaryliodonium salts are the most known compounds of this class.[2] Owing to their marked electron-deficient nature and excellent leaving group ability, they serve as versatile arylating agents with a variety of nucleophiles.

Diaryliodonium reagents are air- and moisture-stable compounds, prepared for the first time in 1894 by Hartmann and Meyer.[3] Their structure consists of two aromatic moieties and an anion X (Fig. 2.1a). An attractive property of these compounds is the lack of nucleophilicity of the counter ion, especially when it is a halogen. In this chapter, however, we will demonstrate the dramatic change in reactivity of I(III) species bearing imido ligands. The nitrogen-containing counter ions X possess a relevant nucleophilic character, which is the key aspect to demonstrate the possible reductive elimination pathway involved in the C–N bond forming reactions.

The work discussed in this chapter has already been published, see: Lucchetti, N.; Scalone, M.; Fantasia, S.; Muñiz, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 13335.

[1] Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997.

[2] a) Varvoglis, A., *The Organic Chemistry of Polycoordinated Iodine*, VCH, Weinheim, **1992**; b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179; c) Grushin, V. V. *Chem. Soc. Rev.* **2000**, *29*, 315; d) *Hypervalent Iodine Chemistry*, *Top. Curr. Chem.* **2003**, *224*, Ed. T. Wirth, Springer, Berlin; e) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052.

[3] Hartmann, C.; Meyer, V. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 426.

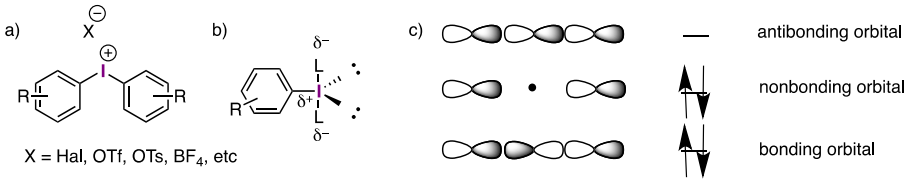
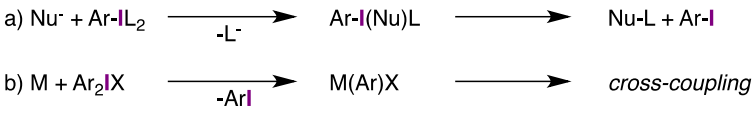


Figure 2.1 a) General structure of diaryliodonium salts. b) T-shaped geometry demonstrated by X-ray analysis. c) Orbitals in the hypervalent bond.

The term "salt" is deceptive, as they posses the same T-shaped geometry as related I(III) compounds (see Chapter I), but differ in the ability to dissolve in organic solvents. The retention of the spatial geometry depends both on the anion X and the solvent.

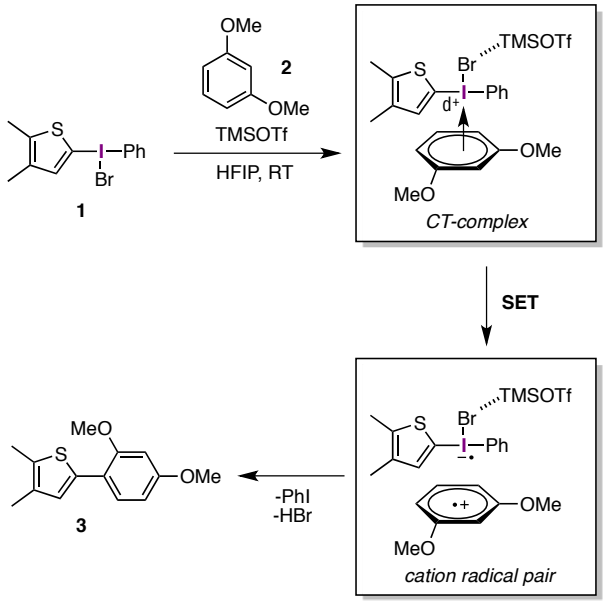
Diaryliodonium salts, also called diaryl-λ^3-iodanes according to the IUPAC nomenclature, generally react through a reductive elimination pathway connecting one of the aryl moieties to the nucleophile (Scheme 2.1a). In metal-catalysed reactions, they behave as a more reactive version of aryl iodides and easily undergo oxidative additions to the metal centre, leading ultimately to cross-coupling products (Scheme 2.1b).[1]



Scheme 2.1 General reactivity of diaryliodonium salts in a) reactions with nucleophiles, b) metal-catalysed reactions.

A moderate SET oxidising ability of the diaryliodonium salts towards electron-rich SET-sensitive aromatic compounds, such as alkoxybenzenes **2**, was observed by spectroscopic studies (Scheme 2.3).[4] Coordination to a Lewis acid seems to enhance the electrophilicity at the iodine atom of the salt.

[4] a) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 3334; b) Yamaoka, N.; Sumida, K.; Itani, I.; Kubo, H.; Ohnishi, Y.; Sekiguchi, S.; Dohi, T.; Kita, Y. *Chem. Eur. J.* **2013**, *19*, 15004.

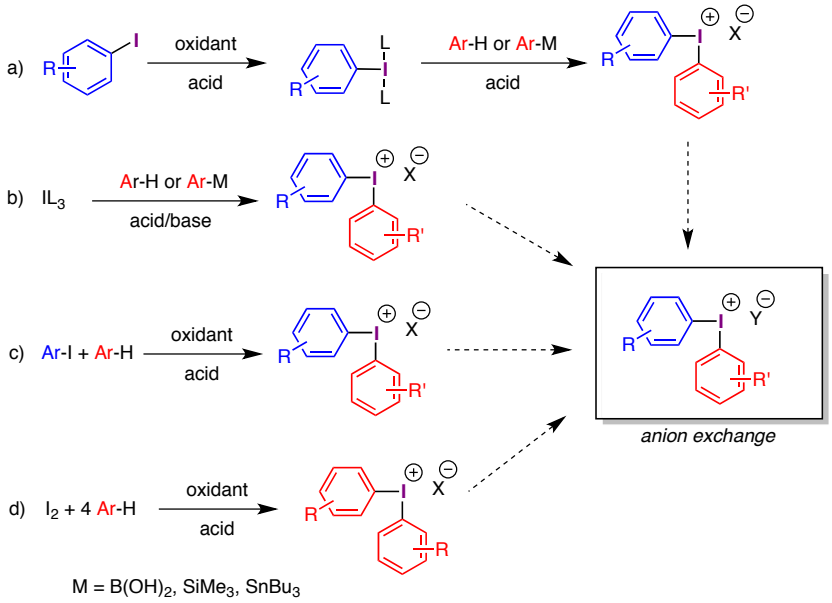


Scheme 2.3 Cross-coupling of heteroaromatic diaryliodonium salts **1** with alkoxybenzenes **2** initiated by a SET oxidation process.

2.1.1 Synthesis

Beringer and co-workers made considerable contributions to the synthesis of iodonium salts in the 1950s.[5] Nowadays, synthetic routes to diaryliodonium salts generally involve two or three steps, with initial oxidation of an aryl iodide to iodine(III) and then ligand-exchange with an arene partner or an organometallic reagent to furnish the desired salt (Scheme 2.4).[2,6]

[5] Beringer, M.; Drexler, M.; Gindler, M. E.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2705.
[6] Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *Arkivoc* **2011**, *1*, 370.



Scheme 2.4 Synthetic strategies for the preparation of diaryliodonium salts.

To shorten the synthetic route, preformed iodine(III) reagents can be employed. In fact, the electrophilic aromatic substitution of an arene onto an iodine(III) intermediate is a quite common strategy. Other progresses in the field involve one-pot oxidation and ligand-exchange reactions to obtain diaryliodonium salts directly from arenes and iodo arenes or molecular iodine respectively.[7] The majority of the reactions are performed under acidic conditions. Moreover, Kita and co-workers observed that fluoroalcoholic media could facilitate their preparation.[8] A limited number of protocols involves lithiated arenes, stannanes or silanes.[9] Examples of iodine(III) salts bearing heteroaromatic ligands were also described.[10] In addition, Wirth and Olofsson provided a route to chiral iodonium salts in 2015.[11]

---

[7] For recent advances, see: a) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610; b) Kraszkiewicz, L.; Skulski, L. *Synthesis* **2008**, *15*, 2373; c) Dohi, T.; Yamaoka, N.; Itani, I.; Kita, Y. *Aust. J. Chem.* **2011**, *64*, 529; d) Hu, B.; Miller, W. H.; Neumann, K. D.; Linstad, E. J.; DiMagno, S. G. *Chem. Eur. J.* **2015**, *21*, 6394.

[8] a) Dohi, T.; Ito, M.; Morimoto, K.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 4152; b) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

[9] a) Koser, G. F.; Wettach, R. H.; Smith, C. S. *J. Org. Chem.* **1980**, *45*, 1543; b) Chun, J.-H.; Lu, S.; Lee, Y.-S.; Pike, V. W. *J. Org. Chem.* **2010**, *75*, 3332.

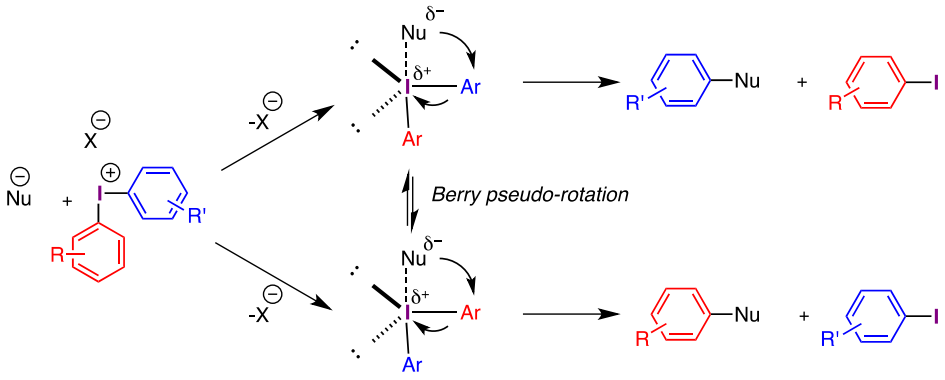
[10] a) Carman, C. S.; Koser, G. F. *J. Org. Chem.* **1983**, *48*, 2534; b) Bielawski, M.; Malmgren, J.; Pardo, L. M.; Wikmark, Y.; Olofsson, B. *Chem. Open* **2014**, *3*, 19.

[11] Brown, M.; Delorme, M.; Malmedy, F.; Malmgren, J.; Olofsson, B.; Wirth, T. *Synlett* **2015**, *26*, 1573.

2.2 Unsymmetrical aryl-λ³-iodanes: chemoselectivity

Unsymmetrical diaryl-λ³-iodanes (Ar ≠ Ar') are the desirable choice when the starting materials are expensive, as only one aryl moiety can be transferred with the other behaving as a "dummy" ligand. From this point of view, the use of a non-expensive arene as non-transferable group will dramatically reduce cost. Moreover, such as unsymmetrical diaryliodonium synthesis is facilitated by the combination of an electron-rich arene and an electron-poor partner.

The electronic as well as the steric factors modulate the selectivity in unsymmetrical iodonium salts during the reductive elimination step. Depending on the presence of a transition-metal catalyst, the selectivity is different. Olofsson thoroughly investigated non-metal catalysed reactions of unsymmetrical diaryliodonium salts.[12] Mechanistically it is widely accepted that they react with nucleophiles to form a T-shaped Ar_2I-Nu intermediate, with a subsequent three-centre-four-electron bond between the nucleophile and one of the arenes (Scheme 2.13). In a later step, the reaction affords the product by reductive elimination event. Reactions with unsymmetrical salts furnish T-shaped intermediates that are in fast equilibrium through Berry pseudo-rotation.[13] As consequence two pairs of different reaction products are observed.



Scheme 2.13 Chemoselectivity in metal-free arylation reactions with diaryliodonium salts.

For reactions with enolates and heteroatoms, the insertion of nucleophiles takes place onto the more electron-deficient *ipso* carbon. This behaviour can be rationalised by a better stabilisation of the partial charges in the polarised ligand-coupling transition state.

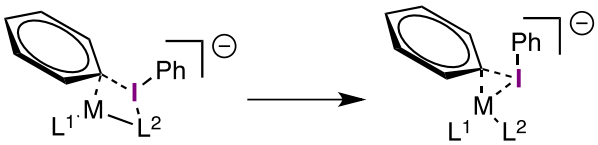
[12] Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem. Eur. J.* **2013**, *19*, 10334.
[13] Ochiai, M. *Top. Curr. Chem.* **2003**, *224*, 5.

However, extremely electron-rich diaryliodonium salts are prone to side-reactions involving redox and inner-sphere electron transfer, leading to a limitation of the use of the electronic control to achieve chemoselectivity.

The steric effects can be explained as a consequence of the spatial disposition of different aryl ligands. Substituents *ortho* to the iodine(III) centre offer a moderate acceleration in elimination rates, so that there is a preference for the more substituted product to be functionalised.[14] The origins for this so called "*ortho* effect" are: 1) the preference of the more-sterically demanding aromatic ring to occupy an equatorial position *syn* to the nucleophile, and 2) the favouritism of the *ortho*-substituted aromatic ring to a conformation, in which the π-system aligns with the incoming nucleophile.[15] However, exceptions to this empirical rule are reported in literature.[16]

2.2.1 Transition-metal catalysed reactions: chemoselectivity

The selectivity of the transition-metal catalysed reactions remains still unclear, albeit some mechanistic investigations have been performed. According to experimental data, the electronic balance favours the transfer of the more electron-rich arene. However, when bulkiness is involved, the less sterically hindered group is transferred. This trend is in pure contrast to the metal-free approach. Here, mesityl- and triisopropyl phenyl groups are most often used as "dummy" ligands.[17] DFT calculations revealed that the reaction might involve a π-interaction between the metal centre and one of the aryl groups. This then leads to a transfer of "Ar^+" to the metal centre with the release of PhI (Scheme 2.14).



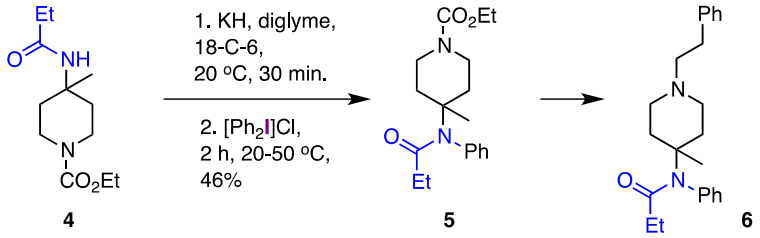
Scheme 2.14 Transition-model structures for metal-catalysed reactions.

[14] Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4079.
[15] a) Grushin, V. V. *Acc. Chem. Res.* **1992**, *25*, 529; b) Grushin, V. V.; Demkina, I. I.; Tolstaya, T. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 505; c) Carroll, M. A.; Martin-Santamaria, S.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2707.
[16] a) Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999**, *121*, 9233; b) Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358; c) Sundalam, S. K.; Stuart, D. R. *J. Org. Chem.* **2015**, *80*, 6456.
[17] Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

The trend in selectivity for electron-rich arenes finds evidences in a better π-interaction with the electrophilic metal centre. The preference for the less hindered ligands is also supported by the *ipso* reductive step.

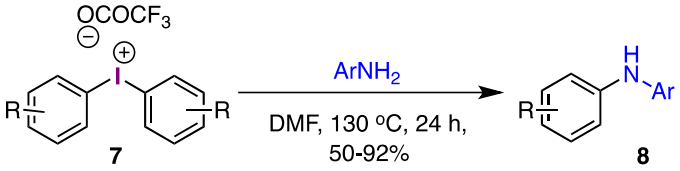
2.3 Reactivity: diaryliodonium-mediated metal-free aminations

The use of diaryliodonium salts in arylation reactions of heteroatom nucleophiles has been known for more than 80 years. Due to the biological activity shown by nitrogen-containing molecules, metal-free C–N coupling reactions have recently attracted considerable attentions. In 2000, diphenyliodonium chloride was used in the multistep synthesis of 4-methyl fentanyl **6**, a narcotic analgesic (Scheme 2.5).[18]



Scheme 2.5 Synthesis of 4-methyl fentanyl **(6)**.

Recently, Carroll[19] reported a transition-metal-free route to diarylamines **8**, in which also the influence of the anion and chemoselectivity aspects of the reductive coupling was investigated (Scheme 2.6).



Scheme 2.6 Metal-free arylation of anilines.

Other examples include aniline syntheses by arylation of amides,[20] methoxyamines,[21] ammonia,[22] $NaNO_2$,[23] nitrones,[24] heterocycles,[25] and pyrazoles.[26]

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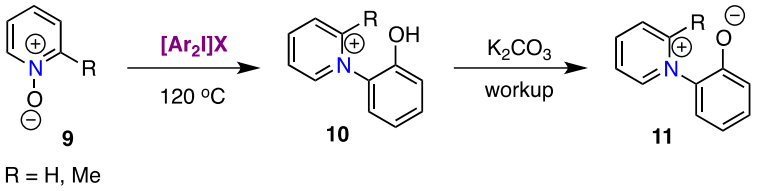
[18] Mićović, I. V.; Ivanović, M. D.; Vuckovic, S. M.; Prostran, M. Š.; Došen-Mićović, L.; Kiricojević, V. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2011.
[19] Carroll, M. A.; Wood, R. A. *Tetrahedron* **2007**, *63*, 11349.

With respect to a new arylation of nitrogen groups, in 2013 Chen afforded a vicinal disubstitution of diaryliodonium salts with pyridine *N*-oxides **9** by a 1,3-radical rearrangement (Scheme 2.7).[27]



Scheme 2.7 Vicinal disubstitution of pyridine *N*-oxides by 1,3-radical rearrangement.

2.4 Reactivity: diaryliodonium-mediated metal-catalysed aminations

On the other hand, diaryliodonium salts are also employed as suitable coupling partners in transition-metal-catalysed transformations. Recently, Suna and co-workers have accomplished notable progresses in copper-catalysed amination of heteroaromatics **13** (Scheme 2.8).[28] Although the indicated reaction mechanism for this transformation appears plausible, they have not been able to isolate the putative heteroaryl-λ^3-iodane intermediate.

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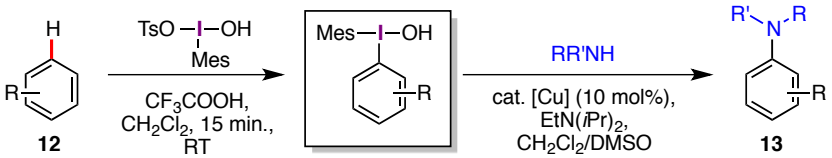
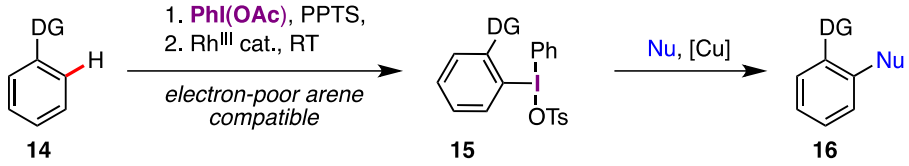
[20] a) Landge, K. P.; Jang, K. S.; Lee, S. Y.; Chi, D. Y. *J. Org. Chem.* **2012**, *77*, 5705; b) Bergman, J.; Stensland, B. *J. Heterocycl. Chem.* **2014**, *51*, 1; c) Tinnis, F.; Stridfeldt, E.; Lundberg, H.; Adolfsson, H.; Olofsson, B. *Org. Lett.* **2015**, *17*, 2688.
[21] Lucchetti, N.; Scalone, M.; Fantasia, S.; Muñiz, K. *Adv. Synth. Catal.* **2016**, *358*, 2093.
[22] Li, J.; Liu, L. *RSC Adv.* **2012**, *2*, 10485.
[23] Reitti, M.; Villo, P.; Olofsson, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 8928.
[24] Wu, S.-Y.; Ma, X.-P.; Liang, C.; Mo, D.-L. *J. Org. Chem.* **2017**, *82*, 3232.
[25] a) Guo, F.; Wang, L.; Wang, P.; Yu, J.; Han, J. *Asian J. Org. Chem.* **2012**, *1*, 218; b) Gonda, Z.; Novák, Z. *Chem. Eur. J.* **2015**, *21*, 16801; c) Bihari, T.; Babinszki, B.; Gonda, Z.; Kovács, S.; Novák, Z.; Stirling, A. *J. Org. Chem.* **2016**, *81*, 5417.
[26] Teskey, C. J.; Sohel, S. M. A.; Bunting, D. L.; Modha, S. G.; Greaney M. F. *Angew. Chem. Int. Ed.* **2017**, *56*, 5263.
[27] Peng, J.; Chen, C.; Wang, Y.; Lou, Z.; Li, M.; Xi, C.; Chen, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7574.
[28] a) Lubriks, D.; Sokolovs, I.; Suna, E. *J. Am. Chem. Soc.* **2012**, *134*, 15436; b) Sokolovs, I.; Lubriks, D.; Suna, E. *J. Am. Chem. Soc.* **2014**, *136*, 6920; c) Berzina, B.; Sokolovs, I.; Suna, E. *ACS Catal.* **2015**, *5*, 7008.



Scheme 2.8 Copper-catalysed amination of heteroaromatics.

Other examples include the copper-catalysed[29] synthesis of diarylimidazolium salts,[30] diarylamines,[31] substituted quinolines,[32] quinazolines,[33] arylurea derivatives,[34] *N*-arylsulphoximines,[35] and 2-pyridones.[36] In 2015, Li described the first synthesis of diaryliodonium reagents by rhodium(III)-catalysed C−H hyperiodination of electron-poor arenes under chelation assistance.[37] Subsequent nucleophilic functionalisation, under copper catalysis, allowed the easy construction of C−N bonds (Scheme 2.9).



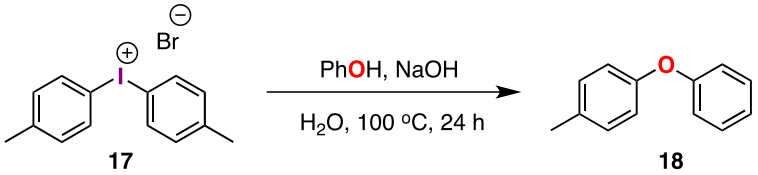
Scheme 2.9 Rhodium-catalysed syntheses of diaryliodonium salts.

2.5 Reactivity: arylation of other heteroatoms

In 2015, Muñiz demonstrated a metal-free synthesis of aryl boronic esters via borylation with diaryliodonium salts in absence of catalysts or additives with an anti-*ortho* selectivity.[38] In group XV, arylphosphonates were prepared under metal-free or palladium-catalysed arylation of *O*,*O*-dialkyl phosphites.[39] Gaunt and co-workers

[29] Fañanás-Mastral, M. *Synthesis* **2017**, *49*, 1905.
[30] Lv, T.-Y.; Yang, L.; Zhao, Y.-S.; Song, F.-J.; Lan, J.-B.; You, J.-S.; Gao, G. *Chin. Chem. Lett.* **2013**, *24*, 773.
[31] Matsuzaki, K.; Okuyama, K.; Tokunaga, E.; Saito, N.; Shiro, M.; Shibata, N. *Org. Lett.* **2015**, *17*, 3038.
[32] Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 5323.
[33] Su, X.; Chen, C.; Wang, Y.; Chen, J.; Lou, Z.; Li, M. *Chem. Commun.* **2013**, *49*, 6752.
[34] Li, P.; Cheng, G.; Zhang, H.; Xu, X.; Gao, J.; Cui, X. *J. Org. Chem.* **2014**, *79*, 8156.
[35] Vaddula, B.; Leazer, J.; Varma, R. S. *Adv. Synth. Catal.* **2012**, *354*, 986.
[36] Jung, S.-H.; Sung, D.-B.; Park, C.-H.; Kim, W.-S. *J. Org. Chem.* **2016**, *81*, 7717.
[37] Xie, F.; Zhang, Z.; Yu, X.; Tang, G.; Li, X. *Angew. Chem. Int. Ed.* **2015**, *54*, 7405.
[38] Miralles, N.; Romero, R. M.; Fernández, E.; Muñiz, K. *Chem. Commun.* **2015**, *51*, 14068.
[39] a) Liu, Z.-D.; Chen, Z.-C. *Synthesis* **1993**, 373; b) Zhou, T.; Chen, Z.-C. *Synth. Commun.* **2001**, *31*, 3289.

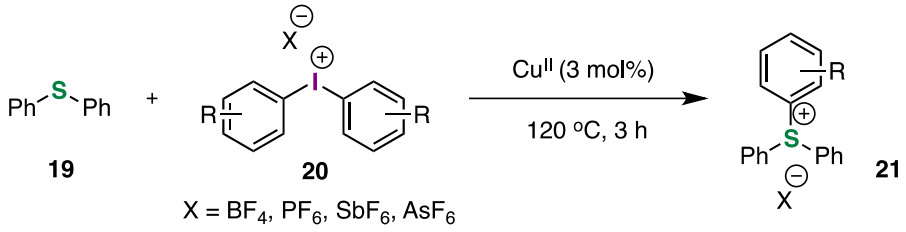
reported an enantioselective copper-catalysed arylation of secondary phosphine oxides with diaryliodonium salts toward the synthesis of P-chiral phosphines.[40] Nucleophiles that belong to group XVI have been the object of many investigations. Crowder in 1963 reported the first example of the synthesis of diphenyl ethers **18** using diphenyliodonium bromides, which were refluxed in water in the presence of stoichiometric amounts of sodium phenoxide (Scheme 2.10).[41]



Scheme 2.10 Arylation of sodium phenoxide.

Independently, Olofsson and Kürti demonstrated the arylation of *N*-oximes for the synthesis of complex benzo[*b*]furans.[42] They found that even carboxylic acids were suitable substrates for this reaction process.[43]

Arylation of sulphur nucleophiles using diaryliodonium salts allows the preparation of thioethers, sulphonium species and *S*-aryl thiocarboxylates.[44] In 1978, Crivello and Lam reported a copper(II)-catalysed arylation of diarylsulphides **19** to sulphonium salts **21** (Scheme 2.11).[45]



Scheme 2.11 Arylation of diarylsulphides.

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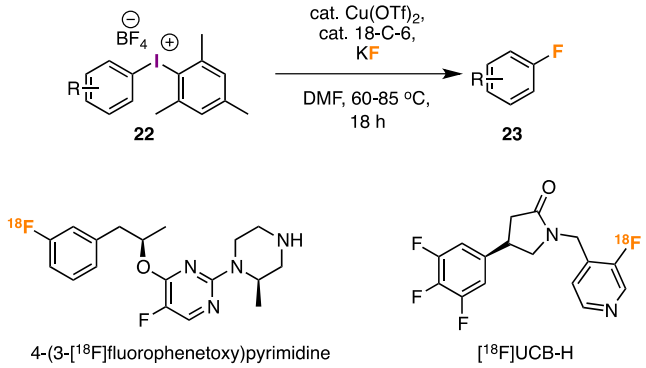
[40] Beaud, R.; Phipps, R. J.; Gaunt, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 13183.
[41] Crowder, J. R.; Glover, E. E., Grundon, M. F.; Kaempfen, H. X. *J. Chem. Soc.* **1963**, 4578.
[42] a) Gao, H.; Xu, Q.-L.; Keene, C.; Kürti, L. *Chem. Eur. J.* **2014**, *20*, 8883; b) Ghosh, R.; Stridfeldt, E.; Olofsson, B. *Chem. Eur. J.* **2014**, *20*, 8888; c) Ghosh, R.; Olofsson, B. *Org. Lett.* **2014**, *16*, 1830.
[43] Petersen, T. B.; Khan, R.; Olofsson, B. *Org. Lett.* **2011**, *13*, 3462.
[44] a) Wagner, A. M.; Sanford, M. S. *J. Org. Chem.* **2014**, *79*, 2263; b) Racicot, L.; Kasahara, T.; Ciufolini, M. A. *Org. Lett.* **2014**, *16*, 6382.
[45] Crivello, J. V.; Lam, J. H. W. *J. Org. Chem.* **1978**, *43*, 3055.

Selenium and tellurium nucleophiles exhibit analogue reactivity compared to sulphur.[46] Fluorine-18 labeled arenes and heteroarenes are widely used in positron-emission tomography (PET). As consequence, the synthesis of such radiolabeled species through nucleophilic attack of [^{18}F]fluoride on diaryliodonium salts has been extensively studied by Sanford[47] and DiMagno[48] (Scheme 2.12). Many applications toward the synthesis of molecules showing biological activity have been reported.[49]



Scheme 2.12 Synthesis of labeled fluoroarenes.

2.6 Target of the project

Although in literature several examples of metal-free amination reactions promoted by diaryliodonium salts are reported (see Section 2.3), none of them allow for the synthesis of simple aniline building blocks. Our interest was to establish a powerful methodology enabling the synthesis of nitrogen-containing compounds with a subsequent easy deprotection step. In addition, only little evidence for C–N bond formation to yield

[46] a) You, J.-Z.; Chen, Z.-C. *Synth. Commun.* **1992**, *22*, 1441; b) You, J.-Z.; Chen, Z.-C. *Synthesis* **1992**, 633; c) Liu, Z.-D.; Zeng, H.; Chen, Z.-C. *Synth. Commun.* **1994**, *24*, 475.
[47] a) Ichiishi, N.; Canty, A. J. Yates, B. F.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5134; b) Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Organometallics* **2014**, *33*, 5525; c) Ichiishi, N.; Brooks, A. F.; Topczewski, J. J.; Rodnick, M. E.; Sanford, M. S.; Scott, P. J. H. *Org. Lett.* **2014**, *16*, 3224.
[48] Wang, B.; Cerny, R. L.; Uppaluri, S.; Kempinger, J. J.; DiMagno, S. G. *J. Fluorine Chem.* **2010**, *131*, 1113.
[49] For recent examples, see: a) Warnier, C.; Lemarie, C.; Becker, G.; Zaragoza, G.; Giacomelli, F.; Aerts, J.; Otabashi, M.; Bahri, M. A.; Mercier, J.; Plenevaux, A.; Luxen, A. *J. Med. Chem.* **2016**, *59*, 8955; b) Kim, J.; Moon, B. S.; Lee, B. C.; Lee, H.-Y.; Kim, H.-J.; Choo, H.; Pae, A. N.; Cho, Y. S.; Min, S.-J. *ACS Chem. Neurosci.* **2017**, *8*, 996.

congested 2,6-disubstituted anilines exists in literature, wherein the use of toxic pentavalent triarylbismuth compounds was involved.[50]

In order to provide mechanistic elucidations by experiments, we envisioned isolation of the hypothetical reaction intermediates, which could also be used for the calculation of the energetic parameters.

2.7 Results and discussion

2.7.1 Optimisation studies

We started out our optimisation studies with the search for a suitable nitrogen source for the desired transformation. Phthalimide has already been used in metal-free aminations of arenes,[51] and in general represents a successful ammonia surrogate due to the ease of deprotection. On the other side, phthalimides usually may lack in reactivity due to poor solubilities, high pKa values and the delocalisation of the negative charge of the nitrogen atom.

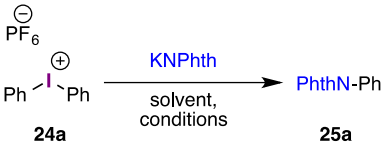
The reaction conditions were initially investigated for the diphenyliodonium salt **24a** and phthalimide potassium salt as the nucleophilic nitrogen source (Table 2.1). Aryl-λ^3-iodanes with halide anions are generally weakly soluble in most organic solvents. Therefore, we decided to start our investigations with the commercially available hexafluorophosphate salt. Treatment of **24a** with a fivefold excess of potassium phthalimide in dichloromethane at refluxing temperature led to a low yield of the desired product **25a** (entry 1). A change of the solvent allowed for the optimisation of the reaction, leading to yields of 60% and 54%, when dry toluene with either 4 or 3 equivalents of phthalimide were used (entries 3 and 4). Alternative solvents such as dichloroethane, dioxane, or DMF provided little to no conversion. Increasing the reaction temperature to 100 ºC (dry toluene as solvent) slightly increased the yield to 67% (entry 7). No change in conversion was observed stirring the reaction at reflux. Addition of chlorobenzene as co-solvent allowed a better solubilisation of the potassium phthalimide, albeit at expense of the yields (entries 9-11). Finally, tetrafluorophthalimide was tested (entry 13). The potassium salt was pre-formed,

[50] Fedorov, A.; Combes, S.; Finet, J.-P. *Tetrahedron* **1999**, *55*, 1341.

[51] a) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382; b) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960; c) Shrestha, R.; Mukherjee, P.; Tan, Y.; Litman, Z. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 8480; d) Greulich, T. W.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2015**, *17*, 254.

mixing *t*BuOK and the imide in dry THF. Under the former best conditions, the tetrafluoro derivative afforded the isolated aniline **25b** in an improved 75% yield.

Table 2.1 Metal-free C–N bond formation from diphenyliodonium salts: reaction optimisation.



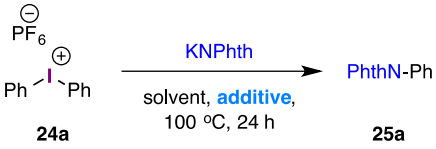
24a **25a**

Entry	Amide (eq)	Solvent	Time (h)	Temperature (°C)	Yield%
1	Phthalimide (5.0)	CH_2Cl_2	44	Reflux	9
2	Phthalimide (5.0)	DCE	36	84	NR
3	Phthalimide (4.0)	toluene	24	84	60
4	Phthalimide (3.0)	toluene	24	84	54
5	Phthalimide (3.0)	toluene	48	84	49
6	Phthalimide (3.0)	dry toluene	24	Reflux	67
7	Phthalimide (3.0)	dry toluene	24	100	67
8	Phthalimide (3.0)	DMF	24	130	NR
9	Phthalimide (2.0)	dry Tol/PhCl	24	100	23
10	Phthalimide (2.0)	dry Tol/PhCl	24	110	50
11	Phthalimide (2.0)	dry Tol/PhCl	24	120	50
12	Phthalimide (2.0)	dioxane	24	100	NR
13	^{4F}Phthalimide (3.0)	dry toluene	24	100	75

Reactions carried out on a 0.24 mmol scale. Yields reported as isolated compounds after column chromatography. NR = no reaction.

Encouraged by the good yields, we tried to improve the solubility of the nitrogen nucleophile by addition of phase-transfer agents (Table 2.2). Using the optimised conditions, we added catalytic amounts of tetrabutyl ammonium salts (bromide, chloride, iodide and hydroxide, entries 1-4). However, these modifications led to little to no conversion. The highest conversion was found with TBACl (entry 6). In conclusion, phase-transfer agents exhibited only a negative effect on the progress of the reaction.

Table 2.2 Metal-free C–N bond formation from diphenyliodonium salts: additives optimisation.



24a **25a**

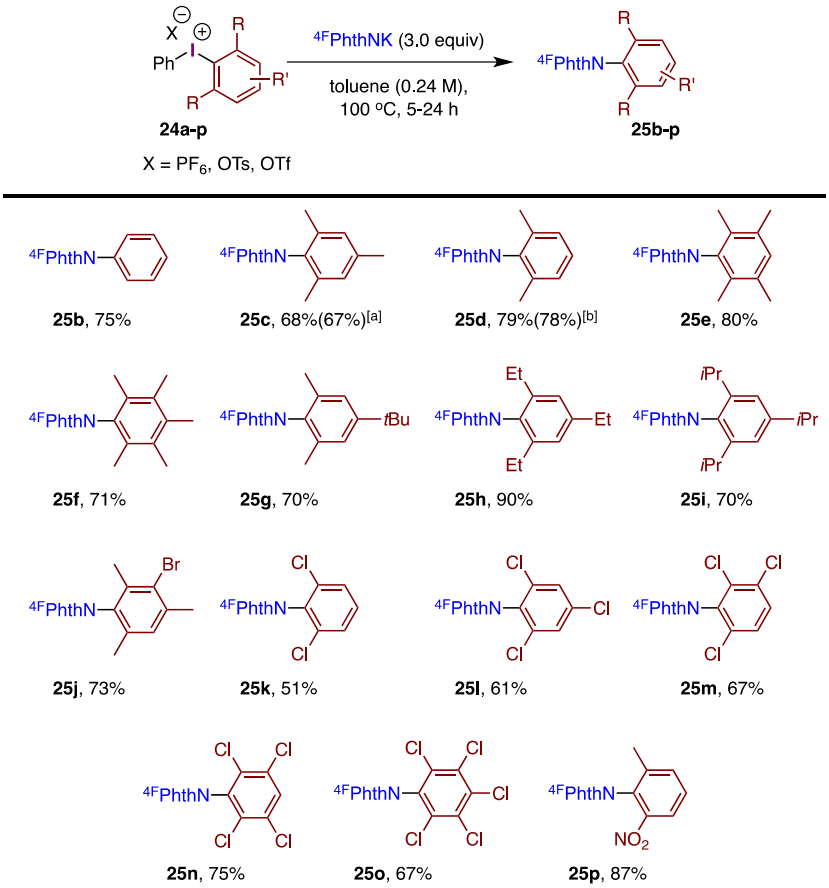
Entry	Solvent	Additive (eq)	Yield%
1	dry toluene	TBAB (10 mol%)	30[a]
2	dry toluene	TBAB (15 mol%)	15[a]
3	dry toluene	TBAI (10 mol%)	18[a]
4	dry toluene	TBAOH (1.0)	15
5	dry Tol/PhCl	TBAB (10 mol%)	NR
6	dry Tol/PhCl	TBACl (10 mol%)	31
7	dry Tol/PhCl	TBAI (10 mol%)	19

Reactions carried out on a 0.24 mmol scale. [a] = Conversion determined by ^{1}H-NMR analysis of the crude mixture compared to unreacted starting material. NR = no reaction.

With the optimised conditions in hand, we evaluated the scope of 2,6-disubstituted unsymmetrical diaryliodonium salts with diverse nitrogen nucleophiles.

2.7.2 Reaction scope

Replacement of the diphenyliodonium salt **24a** by the mixed reagent [MesIPh]OTs (**24c)** led to exclusive formation of a C–N bond involving the transfer of a mesityl group. *N*-mesityl tetrafluorophthalimide (**25c)** was thus obtained in 68% yield (Fig. 2.15).

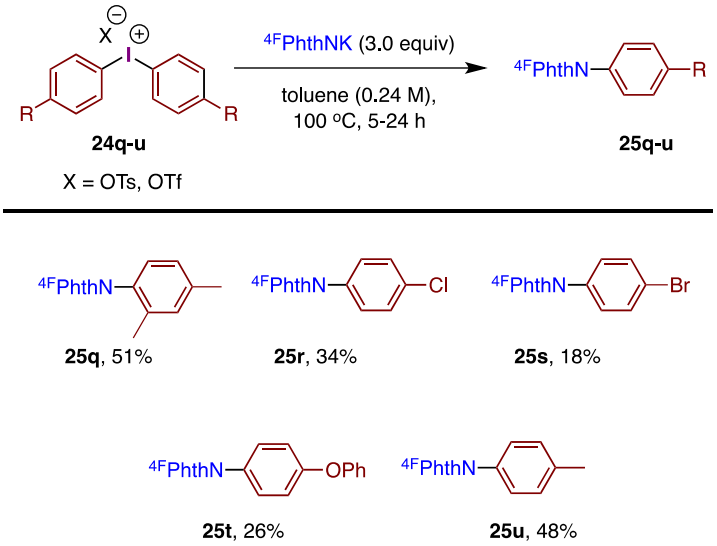


Scheme 2.15 Amination of 2,6-disubstituted arenes: reaction scope. [a] = Reaction with [Mes2I]OTf (**26**). [b] = Reaction on 4.6 mmol scale.

According to this observation, we investigated the amination of aryls with sterically congested substitution pattern, where preference was given to various 2,6-disubstitution motifs. Performing the reaction with symmetrical [Mes2I]OTf (**26**) revealed an identical outcome for the synthesis of **25c**. As a result of their more economical synthesis, mixed aryl(phenyl)iodonium salts were employed for the investigation of the scope. In this way, purification of the title compound was facilitated, as PhI was formed as by-product and the compounds **25** could also be isolated by simple crystallisation. Importantly, the reaction proved to be robust affording the product aniline **25d** in up to 4.6 mmol (1.5 g). *Ortho* substituents larger than methyl, such as ethyl or even 2-propyl, were well tolerated (**25h** and **25i**; 90 and 70% yield). Halogen substitution was readily compatible, as demonstrated for compound **25j**. This result demonstrates a notable advantage

compared to the classical metal-catalysed protocols. The 2,6-dichloro motif and higher-substituted derivatives thereof were explored by using **24k-o** (51-75% yields). Finally, the formation of the mixed 2-nitro-6-methyl derivative (**25p**) showed that also the stereo-electronically demanding nitro substituent could be employed (87% yield). In all these reactions, exclusive transfer of the higher substituted arene was observed.

Additionally, a short investigation of the amination of symmetrical *para*-substituted iodonium salts was carried out (Scheme 2.16).



Scheme 2.16 Amination of *para*-disubstituted arenes: reaction scope.

2,4-Dimethyl substituted aniline **25q** was synthesised in acceptable yield due to the presence of a reduced *ortho* effect. However, the yield dramatically decreased when only the *para*-position was substituted. Besides the steric factors, the weak solubility of the anilines with bromo or chloro substituents (products **25r**,**s**) was found to reduce the yield of the process. An alternative purification method by simple crystallisation was not feasible as the iodoarene by-products co-crystallised with the products.

In summary, we have demonstrated the crucial role of the *ortho* effect in metal-free amination reactions promoted by iodonium salts and verified our hypothesis on the ortho-effect in C−N bond formation.

Our attention was also directed to the challenging 2,6-difluorosubstituted motifs **24v-y** (Fig. 2.2).

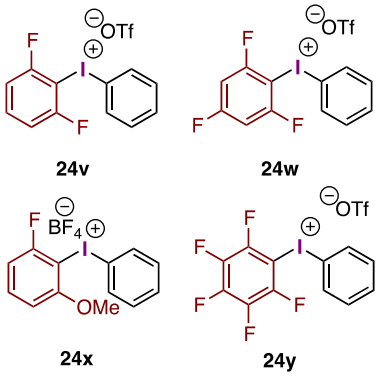
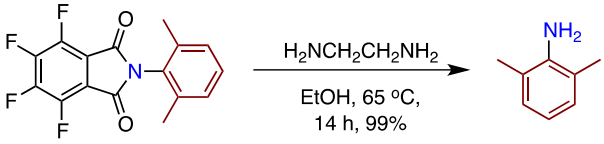


Figure 2.2 Amination of 2,6-difluorosubstituted arenes.

However, when applying these compounds, no conversions to the desired aniline were observed. Probably, the electronic effects of the electronegative fluorine atoms were more relevant than the steric in these cases. Another reason for the reduced yields may be that the electron-deficient arene could impair the reductive elimination, which ultimately inhibits the formation of the desired products.

The attractiveness of tetrafluorophthalimide as nitrogen precursor was later demonstrated by the deprotection of **25d** in a convenient aminolysis protocol providing 2,6-dimethylaniline (**25d'**) in quantitative yield (Scheme 2.17).

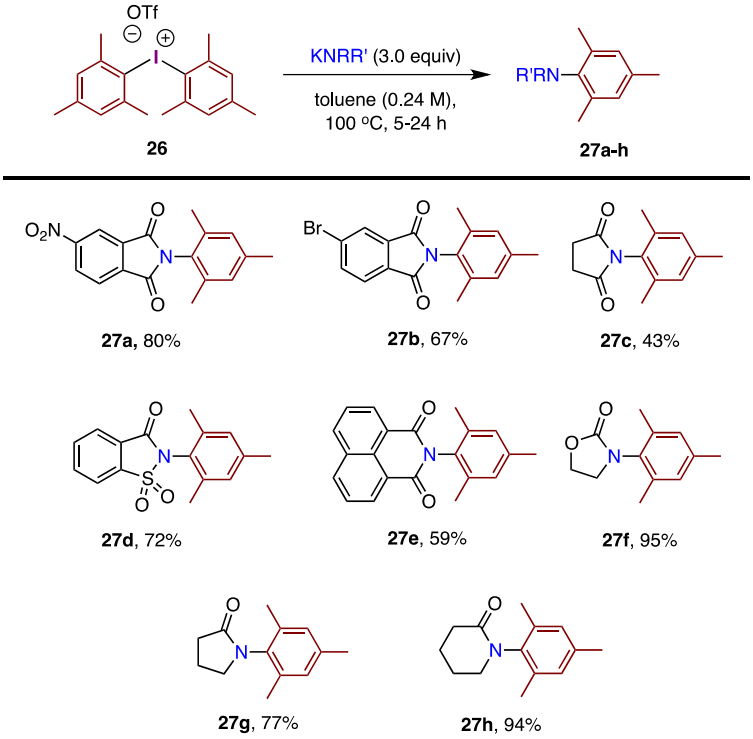


Scheme 2.17 Deprotection of 2,6-dimethylsubstituted aniline **25d**.

Classical deprotection conditions using methyl hydrazine and hydrazine monohydrate were found to be less effective, affording **25d'** in 43 and 27% yields respectively. When methanol was used as solvent, the reaction provided the desired aniline in 59% yield.

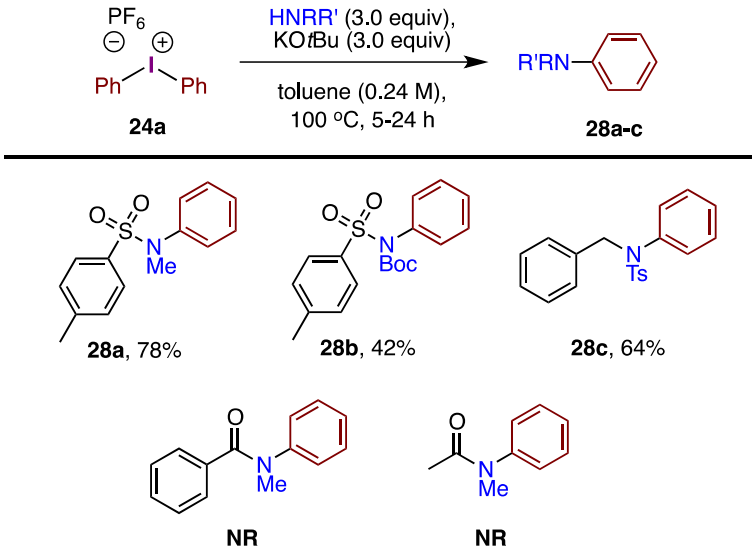
Additionally, we found that the present amination protocol was not limited to phthalimide and its tetrafluoro derivative (Scheme 2.18). By employing dimesityliodonium(III) triflate (**26**) as the representative arylating agent, the utilisation of other phthalimides such as 4-nitrophthalimide and 4-bromophthalimide provided

good results (products **27a,b**). Different nitrogen sources successfully applied in this reaction included succinimide (**27c**), saccharin (**27d**), and 1,8-naphthalimide (**27e**), which afforded the corresponding products in 43-72% yields. Moreover, the pharmaceutically important classes of oxalidinones and lactams also underwent arylation under the optimised conditions (products **27f-h**, 77-95% yields).



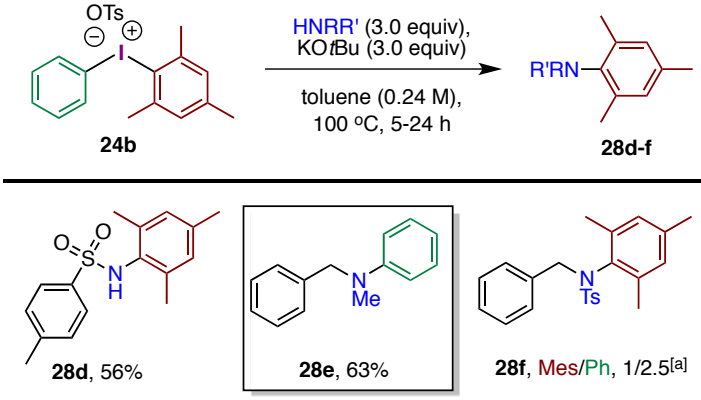
Scheme 2.18 Amination of [Mes$_2$I]OTf (**26**) with different nitrogen source: scope.

To extend the scope of the methodology, we performed also amination reactions of tosylimides and amines with the symmetrical iodonium compound **24a** (Scheme 2.19).



Scheme 2.19 Amination of $[Ph_2I]PF_6$ (**24a**) with different amides and amines: scope.

In this case, the potassium salt of the amide was generated *in situ* by the addition of an equimolar amount of *t*BuOK. Methyl and *tert*-butyloxycarbonyl protecting groups were well tolerated (**28a**,**b**, 78 and 42%, respectively). Moreover, the protected benzylamine afforded the aniline **28c** in 64% yield. On the other hand, benzamides and acetamides failed. As a logical extension, we studied the chemoselectivity of the reaction using the unsymmetrical reagent [PhIMes]OTs (**24b**) (Scheme 2.20).

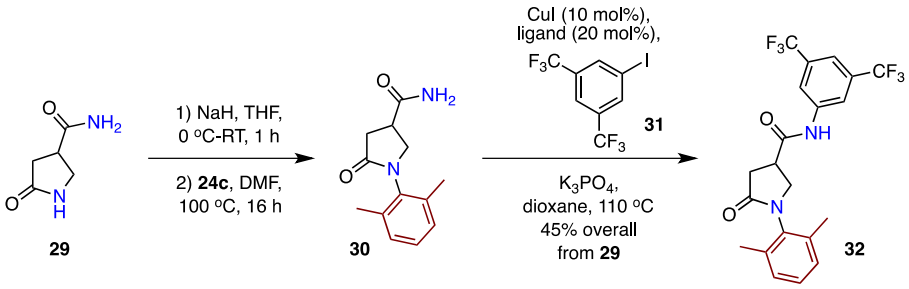


Scheme 2.20 Study of the chemoselectivity with [PhIMes]OTs (**24b**): scope. [a] = Ratio calculated on the crude ^{1}H-NMR spectrum.

Tosylimide underwent a clean and selective arylation reaction to form **28d** (56% yield). Surprisingly, *N*-methylbenzamine gave **28e** as single product after purification, which is an outcome reminiscent to transition-metal-catalysed aminations. A logical explanation can be found in the lower steric congestion of the amine, which is in sharp contrast to the bulky phthalimide nucleophile. In the transition state, the mesityl group could act as a "dummy ligand" as in related copper or palladium catalysis. Stuart and co-workers observed the same behaviour using the 1,3,5-trimethoxybenzene (TMP) as blocking group in iodonium salts with cyclic amines as coupling partners.[52] The role of steric factors involving the nitrogen centre on the reductive elimination pattern was stressed out replacing the methyl with a tosyl group on benzylamine, obtaining a 1:2.5 mixture for product **28f**.

[52] Sandtorv, A. H.; Stuart, D. R. *Angew. Chem. Int. Ed.* **2016**, *55*, 15812.

The synthetic utility of the coupling was demonstrated within a short synthesis of the *N*,*N*'-diarylated pyrrolidinone carboxamide **32** (Scheme 2.21).



Scheme 2.21 Synthesis of *N*,*N'*-diarylated pyrrolidinone carboxamide **32**.

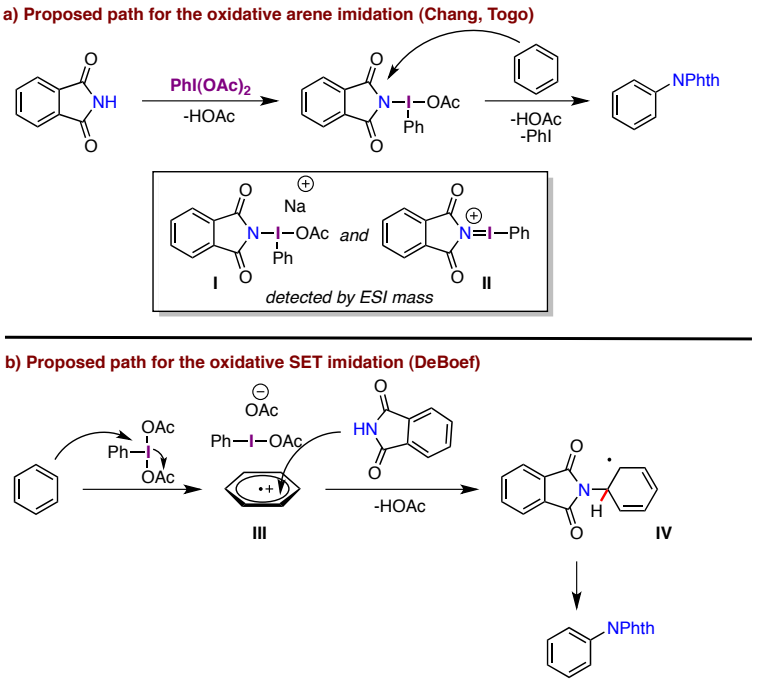
This compound represents a family of binding inhibitors of the chemo-attractant peptide chemerin to the G-protein coupled receptor ChemR23, which is commonly prepared by a linear synthesis starting from preformed anilines.[53] The protecting-group-free two-step synthesis started with selective *N*-arylation at the lactam moiety of commercially available pyrrolidinone carboxamide **29**. It was isolated in 35% yield (64% NMR yield using 1,3,5-trimethoxybenzene as internal standard). Notably, the symmetrical compound **24c** and unsymmetrical iodonium salts gave the same conversion. We chose the symmetrical reagent because of the lower boiling point of the by-product (PhI). As the purification of **30** was complicated due to polarity reasons, we decided to perform the second step with the crude mixture. The present change of solvent from toluene, used in the general protocol of the methodology, to DMF was necessary due to the low solubility of the lactam **29**. The second *N*-arylation (Ullmann coupling)[54] at the free amide group in **30** yielded inhibitor **32**, which was obtained in an overall 45% yield from **29**. A protocol utilising K_3PO_4 as base and racemic *trans*-1,2-diaminocyclohexane as ligand, was found to work best for the coupling reaction. When diethylenediamine was applied as ligand the product was formed although in lower yield; while when *N*,*N'*-dimethylenediamine was applied the starting material was not fully consumed. Our protocol represents a notable advance in the synthesis of these target molecules. The previously described procedure involved a total of five steps, starting from the condensation of pre-formed anilines with carboxylic acids at high temperature to install the pyrrolidinone ring.[53] Despite of this, we shortened the synthesis using commercially

[53] Charvat, T. T.; Chu, H.; Krasinski, A.; Lange, C. W.; Leleti, M. R.; Powers, J. P.; Punna, S.; Sullivan, T. J.; Ungashe, S. WO 035332A1, **2011**.
[54] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

available starting materials, with an enhancement of the chemoselectivity and isolated yield after only one purification step.

2.7.3 Mechanistic insights

Two different proposals for a plausible mechanism for the C–H imidation of arenes with hypervalent iodine(III) compounds and phthalimides are described in literature (Scheme 2.22).

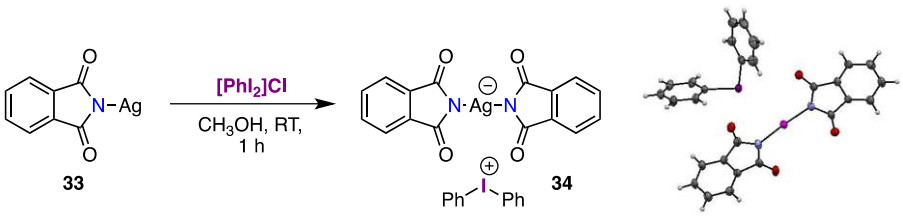


Scheme 2.22 Proposed mechanism for the imidation of arenes with hypervalent iodine(III) and phthalimide.

Chang[51a] and Togo[55] proposed an electrophilic aromatic substitution pathway for aryl C(sp^2)–H bond imidations based on high resolution ESI mass analysis evidences (Scheme 2.22a). It was postulated that the treatment of phthalimide with $PhI(OAc)_2$ furnished a *N*-(phenylacetoxyiodo)imido species **I** or **II**. Then, a nucleophilic attack of the arene at the iodoimido species **I** would afford the imidated product upon release of acetic acid and iodobenzene. On the other hand, DeBoef[51b] hypothesised on a single

[55] Moriyama, K.; Ishida, K.; Togo, H. *Org. Lett.* **2012**, *14*, 3.

electron-transfer (SET) mechanism (Scheme 2.22b). $PhI(OAc)_2$ could oxidise an electron-rich arene to a radical cation **III** and a subsequent nucleophilic attack of the phthalimide. The consecutive radical intermediate **IV** (one mesomeric structure shown) could be oxidised to form a Wheland-type arenium ion. Despite these hypotheses, we assumed that our amination reaction should proceed by an anion exchange at the iodine centre, where the tetrafluorophthalimidato ligand was incorporated prior to the aniline formation. To investigate this direct C–N bond formation from diaryliodonium compounds containing defined imidato groups,[56] we planned the synthesis of suitable compounds with different nitrogen entities. Our initial idea was to prepare the silver salt of phthalimide **33**[57] to react this compound with a stoichiometric amount of diphenyliodonium chloride (Scheme 2.23), where precipitation of AgCl would drive the reaction.



Scheme 2.23 Synthesis of diaryliodonium compounds with an imidato ligand via silver salt and solid-state structure of **34** (ellipsoids at 50% probabability).

However, instead of the anticipated product we isolated a negatively charged bisimido-silver complex **34** with the hypervalent iodine(III) species as counter ion.[58] In a subsequent attempt, we decided to start from preformed iodine(III) derivatives containing the bistosylimide moiety, which represents the standard nitrogen source in the recent amination chemistry of our group (Scheme 2.24).[59]

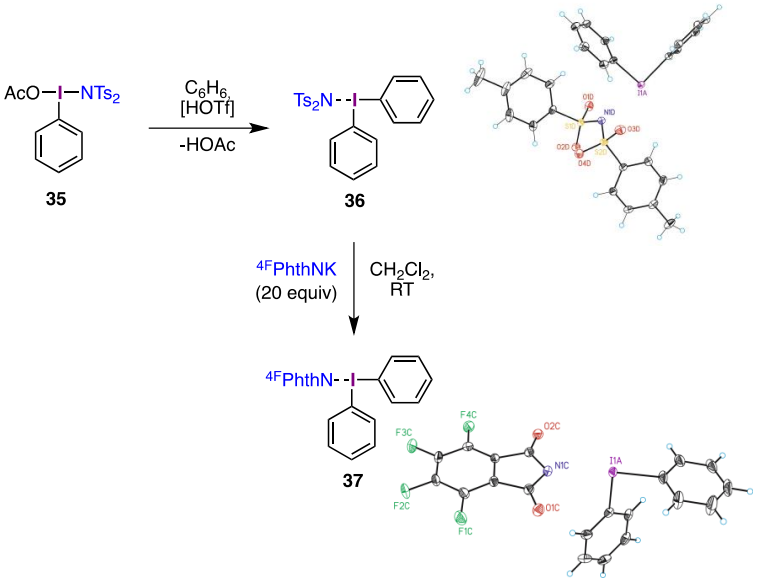
---

[56] For some examples, see: a) Montanari, V.; DesMarteau, D. D.; Pennington, W. T. *J. Mol. Structure* **2000**, *550*, 337; b) Hirschberg, M. E.; Wenda, A.; Frohn, H.-J.; Ignat'ev, N. V. *J. Fluorine Chem.* **2012**, *138*, 24; c) Ishida, K.; Togo, H.; Moriyama, K. *Chem. Asian J.* **2016**, *11*, 3583.

[57] Whitcomb, D. R.; Rajeswaran, M. *J. Chem. Cryst.* **2006**, *36*, 587.

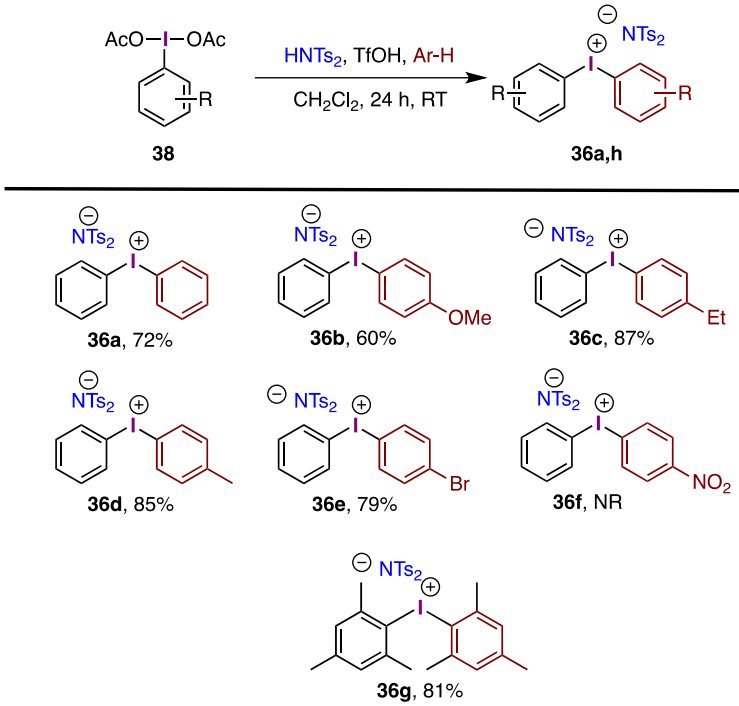
[58] For related examples of silver-amide complexes, see: a) Huot, J.-Y.; Serve, D.; Lessard, J. *Can. J. Chem.* **1983**, *61*, 1890; b) Perron, J.; Beauchamp, A. L. *Inorg. Chem.* **1984**, *23*, 2853.

[59] For selected examples, see: a) Souto, J. A.; González, Y.; Iglesias, Á.; Zian, D.; Lishchynskyi, A.; Muñiz, K. *Chem. Asian J.* **2012**, *7*, 1103; b) Souto, J. A.; Martínez, C.; Velilla, I.; Muñiz, K. *Angew. Chem. Int. Ed.* **2013**, *125*, 1363; c) Fra, L.; Millán, A.; Souto, J. A.; Muñiz, K. *Angew. Chem. Int. Ed.* **2014**, *53*, 7349.



Scheme 2.24 Synthesis of the diaryliodonium(III) amidato complexes **36**, **37** and solid-state structures (ellipsoids at 50% probabability).

Compound **36** was conveniently accessed from the known iodine(III) derivative **35** by electrophilic activation of benzene. It could also be prepared starting from commercial $PhI(OAc)_2$ and $HNTs_2$ (dichloromethane, 24 h, 72% yield). To demonstrate the effectiveness of the protocol, we synthesised a series of symmetrical and unsymmetrical diaryliodonium(III) amidato complexes **36a-g** (Scheme 2.25).



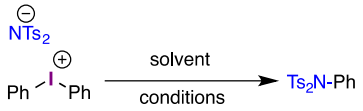
Scheme 2.25 Synthesis of diaryliodonium(III) imidato complexes **36a**,**g**.

Compound **37** contains the tetrafluorophthalimide anion and was generated from **36a** through amide exchange with potassium tetrafluorophthalimide. The preparation of the potassium salt of the amide was particularly difficult, as the synthesis was only possible by the use of a KH dispersion in mineral oil. In the case of *t*BuOK as base, we isolated mixtures of diaryliodonium salts with chlorine or *tert*-butoxide as counter ion. According to X-ray diffraction analysis, both species **36a** and **37** display the expected T-shaped disposition at the iodine centre with only small deviation of the N−I−C bond angle from linearity. The respective iodine-nitrogen bond lengths of 2.874(1) and 2.758(2) Å are comparable. They are longer than the I−N bond in a related phthalimidato iodine(III) derivative reported by Minakata and co-workers (2.197(4) Å).[60] The present reaction scenario confirmed an anionic character of the tetrafluorophthalimide in **37**, which excluded involvement of an electrophilic amination pathway as postulated by Chang.[51a] However, **36a** and **37** displayed significantly different chemical performances. As a consequence of the highly stabilised bistosylimide group as nitrogen source, iodine(III) compound **36a** was stable with

[60] Kiyokawa, K.; Kosaka, T.; Kojima, T.; Minakata, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 13719.

respect to reductive elimination and the formation of a carbon-nitrogen bond (Table 2.3).

Table 2.3 Metal-free C−N bond formation from diphenyliodonium salts: reaction optimisation for **36a**.



36a **39**

Entry	Solvent	Time (h)	Temperature (°C)	Yield%
1	THF	13	100	NR
2	DCE	24	80	NR
3	DCE	48	80	NR
4	DCE	13	100	NR
5	DMF	24	100	NR
6	dry toluene	24	100	NR
7	*m*-xylene	24	100	NR
8	dry CH_3CN	48	80	NR
9	*t*-BuOH	48	80	NR
10	benzene	24	100	NR
11	dioxane	24	100	NR

Reactions carried out on a 0.24 mmol scale. NR = no reaction.

Even upon prolonged heating in toluene solution, only starting material was recovered. In contrast, isolated compound **37** underwent a thermally induced quantitative transformation to the C−N coupling product **25b** with a clear first order dependence and expected temperature dependence (Fig. 2.3).

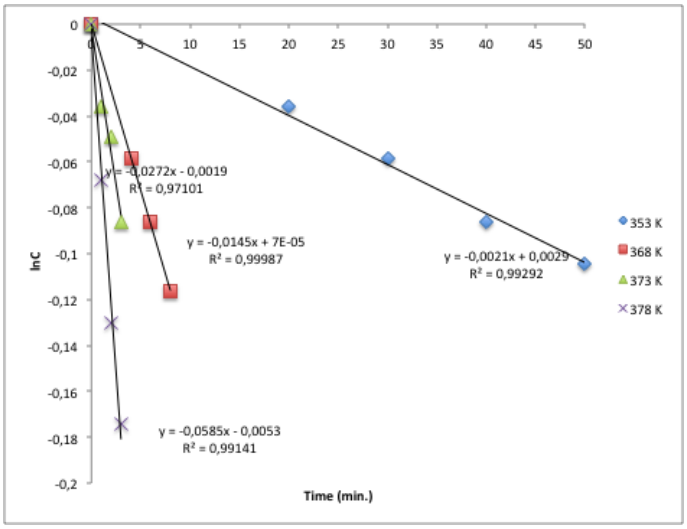


Figure 2.3 Correlation of lnC versus Time: temperature dependence.

The reaction could thus be monitored by ^{19}F-NMR spectroscopy at different temperatures in the range 80-110 °C. An Arrhenius plot provided the activation energy of 34.8 kcal mol^{-1} for the C–N bond formation of **37**, which was in agreement with high reaction temperatures required experimentally (Fig. 2.4).

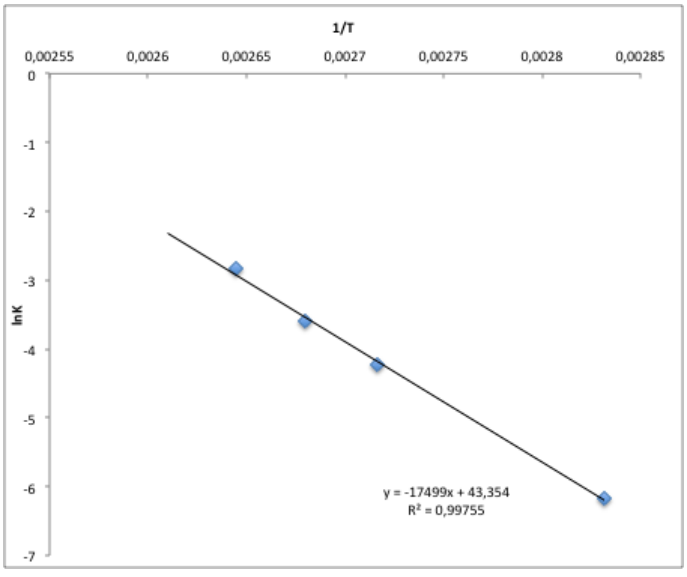


Figure 2.4 Arrhenius plot, lnK vs 1/T.

The corresponding Eyring plot revealed an activation enthalpy $\Delta\Delta H^{\ddagger}$ of 34.1 kcal mol^{-1} and an entropy of $\Delta\Delta S^{\ddagger} = 105.5$ JK^{-1} (Fig. 2.5).

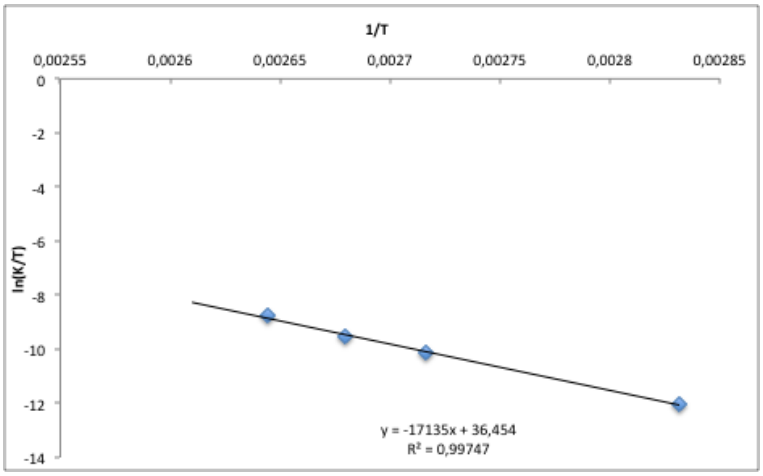
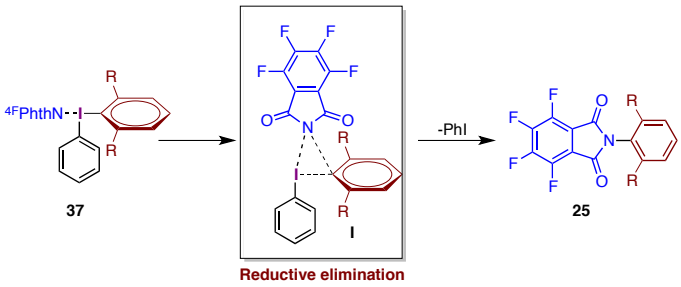


Figure 2.5 Eyring plot, ln(K/T) vs 1/T.

This scenario supports the assumption of an ordered monomeric transition state **I**, in which the original N−I bond has partially dissociated and in which product formation proceeds through a three-centre-four-electron state (Scheme 2.26). This pathway resembles related mechanisms in transition-metal chemistry. It is further aided by the 2,6-disubstitution motif at the arene, which adds steric bulk to the transition state **I** promoting reductive elimination with a predictable regioselectivity. Reductive elimination on diaryliodonium(III) derivatives through a transition state analogous to **I** was reported previously by Ochiai and others.[12,14,20b,61]

[61] a) Lancer, K. M.; Wiegand, G. H. *J. Org. Chem.* **1976**, *41*, 3360; b) Ochiai, M.; Takaoka, Y.; Sumi, K.; Nagao, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1382; c) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai. M. *J. Am. Chem. Soc.* **1995**, *117*, 3360; d) Ochiai, M.; Shu, T.; Nagaoka, T.; Kitagawa, Y. *J. Org. Chem.* **1997**, *62*, 2130; e) Lee, Y.-S.; Chun, J.-H.; Hodošček, M.; Pike, V. W. *Chem. Eur. J.* **2017**, *23*, 4353.



Scheme 2.26 Mechanism of the C−N bond formation.

2.8 Conclusions and remarks

In this Chapter we have reported a new procedure for the effective synthesis of 2,6-disubstituted anilines and their higher-substituted derivatives. It proceeds through a direct reductive C−N bond formation, which constitutes a transition-metal-like performance of the iodine(III) centre. This mechanistic conclusion was supported by isolation of reaction intermediates and kinetic experiments. This approach was suitable for a wide range of aryl groups as well nitrogen sources. It significantly streamlines the synthetic path to this class of compounds and should allow a larger structural diversification of these aniline motifs in the screening of molecular structures of pharmaceutical interest.

2.9 Experimental section

General information: Column chromatography was performed with silica gel (Merck, type 60, 0.063-0.2 mm). NMR spectra were recorded on a Bruker Avance 400 MHz or 500 MHz spectrometers, respectively. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following calibrations were used: $CDCl_3$ δ = 7.26 and 77.0 ppm, CD_3OD δ = 31.0 and 49.0 ppm, DMSO-d_6 δ = 2.50 and 39.52 ppm. MS (ESI-LCMS) experiments were performed using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). MS (EI) and HRMS were performed on a Kratos MS 50 within the service center at ICIQ. IR spectra were taken in a Bruker Alpha instrument in the solid state.

Materials: All solvents, reagents and all deuterated solvents were purchased from Aldrich, TCI, Alfa Aesar, Fluorochem and Apollo Scientific commercial suppliers. The commercially available compounds were used as received.

General procedure for the synthesis of starting diaryliodonium salts (GP1): To a stirred solution of (diacetoxyiodo)benzene (1.0 equiv.) in a 2,2,2-trifluoroethanol (TFE) and CH_2Cl_2 mixture (10/1, v/v) was added the arene (1.5 equiv.) and TsOH-H_2O (2.0 equiv.) and the solution was stirred at room temperature. After the disappearance of the arene (checked by TLC), water was added and the organic layer was extracted with CH_2Cl_2 (3 x 10 mL), and then dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude oily product was triturated with diethyl ether to afford the final diaryliodonium salt as solid.

General procedure for the synthesis of starting diaryliodonium salts (GP2): Iodine (1.0 equiv.), *m*CPBA 77% (2.5 equiv.) and diphenyl ether (3.5 equiv.) were dissolved in CH_2Cl_2 (15.0 mL). Then TsOH-H_2O (3.4 equiv.) was added to the solution and the mixture was stirred at room temperature for 17 h. The solution was quenched with water, extracted with CH_2Cl_2 (3 x 10 mL) and dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the crude oil was triturated with diethyl ether to afford the desired diaryliodonium salt as a solid.

General procedure for the synthesis of starting diaryliodonium salts (GP3): [62] In a flamed and dried Schlenk flask, the iodoarene (1.0 equiv.) was dissolved in 5.0 mL of dry CH_2Cl_2. *m*CPBA 77% (1.08 equiv.) and BF_3-OEt_2 46% (2.48 equiv.) were added and the mixture was stirred at room temperature for 30 min. Then it was cooled down to 0 ºC with an ice-bath and phenylboronic acid (1.08 equiv.) was added. The mixture was stirred warming to room temperature for 15 min. and then TfOH (1.08 equiv.) was added. The mixture was stirred for other 15 min. at room temperature and then the solvent was removed under reduced pressure. The crude oil was triturated with diethyl ether to afford the desired compound as solid.

General procedure for the synthesis of (diacetoxyiodo)arenes (GP4): Arene (1.0 equiv.) was dissolved in AcOH (2.4 mL) and AcOOH 35 wt% (2.6 equiv.) was added and the final mixture was stirred at room temperature for 20 h. The solvent was removed under reduced pressure. The (diacetoxyiodo)arene was recrystallised in CH_2Cl_2/*n*-hexane.

General procedure for the synthesis of starting diaryliodonium salts (GP5): Arylboronic acid (1.1 equiv.) was dissolved in dry CH_2Cl_2 (3.0 mL) under an inert

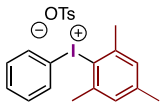
[62] Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602.

atmosphere. At 0 ºC, BF_3-OEt_2 46% (1.5 equiv.) was added and the mixture was stirred at this temperature during 10 min. Then, (diacetoxyiodo)arene (1.0 equiv.) was added and the final mixture was stirred at room temperature for 1 h. After re-cooling again to 0 ºC, TfOH (1.1 equiv.) was added and the mixture was stirred warming to room temperature for 30 min. The solvent was removed under reduced pressure and Et_2O was added to the residual mixture. The resulting mixture was cooled to -20 ºC overnight and the precipitate (diaryliodonium triflate) was collected by filtration and then washed with cold diethyl ether.

General procedure for the synthesis of starting diaryliodonium salts (GP6): 1,3,5-Triisopropylbenzene (0.692 mL, 2.72 mmol) was added to a solution of iodobenzene (0.274 mL, 2.45 mmol) and *m*CPBA 77% (0.61 g, 2.72 mmol) in CH_2Cl_2 (10.0 mL) and the solution cooled to 0 ºC. Trifluoromethanesulfonic acid (0.36 mL, 4.09 mmol) was added drop-wise over 5 min. and the reaction allowed to slowly warm to room temperature over the course of 2 h. The solvent was removed under reduced pressure and diethyl ether added. The crystallisation was completed in the fridge and the white solid was collected by filtration.

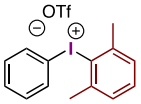
General procedure for the synthesis of starting diaryliodonium salts (GP7): Iodoarene (1.0 equiv.) was dissolved in CH_2Cl_2, *m*CPBA 77% (1.1 equiv.), and the arene (1.1 equiv.) were added. The mixture was cooled down to 0 ºC with an ice-bath and triflic acid (3.0 equiv.) was added drop-wise. The mixture was stirred for the indicated time while allowed warming to room temperature. The solvent was removed under reduced pressure and the crude was triturated with diethyl ether. After filtration the desired diaryliodonium salt was collected as solid.

Mesityl(phenyl)iodonium tosylate (24c).



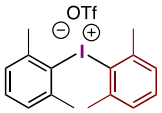
Synthesised by GP1. White solid, 93% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.31 (s, 3H), 2.32 (s, 3H), 2.58 (s, 6H), 7.00-7.03 (m, 4H), 7.30-7.33 (m, 2H), 7.43-7.44 (m, 1H), 7.50-7.53 (m, 2H), 7.67-7.69 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 21.2, 21.4, 27.3, 113.6, 122.0, 126.1, 128.5, 130.1, 131.2, 131.9, 133.1, 139.3, 142.5, 143.0, 143.8. **IR ν(cm^{-1}):** 1442, 1164, 1007, 678, 562. **m.p.(ºC):** 183-185 ºC.

(2,6-Dimethylphenyl)(phenyl)iodonium triflate (24d).



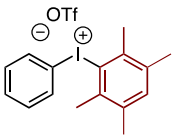
Synthesised by GP5. Brownish solid, 93% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.69 (s, 6H), 7.30-7.32 (m, 2H), 7.40-7.46 (m, 3H), 7.53-7.57 (m, 1H), 7.70-7.73 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.5 (s, 3F). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 27.5, 111.7, 120.4 (q, J_{C-F} = 319.8 Hz), 124.5, 129.7, 132.1, 132.5, 133.4, 133.7, 142.9. **IR ν(cm^{-1}):** 1469, 1239, 1219, 1159, 1024, 734, 633, 514. **HRMS (ESI^{+}):** calc. for $[C_{14}H_{14}I]^{+}$: 309.0135; found: 309.0136. **m.p.(ºC):** 168-170 ºC.

Bis(2,4-dimethylphenyl)iodonium triflate (24d').



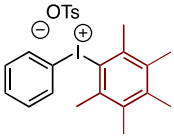
Synthesised by GP5. Brownish solid, 71% yield. **^{1}H-NMR (400 MHz, CD_3OD):** δ = 2.59 (s, 12H), 7.38 (d, J = 8.1 Hz, 4H), 7.47-7.51 (m, 2H). **^{19}F-NMR (376 MHz, CD_3OD):** δ = -80.1 (s, 3F). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 26.3, 122.8, 131.1, 134.2, 144.0. **IR ν(cm^{-1}):** 1461, 1241, 1172, 1157, 1020, 788, 630. **HRMS (ESI^{+}):** calc. for $[C_{16}H_{18}I]^{+}$: 337.0441; found: 337.0448. **m.p.(ºC):** 204-206 ºC.

Phenyl(2,3,5,6-tetramethylphenyl)iodonium triflate (24e).



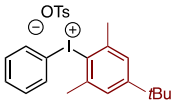
Synthesised by GP5. Brownish solid, 60% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.35 (s, 6H), 2.99 (s, 6H), 7.20 (s, 1H), 7.40-7.44 (m, 2H), 7.53-7.57 (m, 1H), 7.68-7.70 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.4 (s, 3F). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 21.9, 25.1, 111.9, 127.7, 132.1, 132.5, 133.2, 137.1, 137.5, 138.5. **IR ν(cm^{-1}):** 1444, 1239, 1220, 1155, 1022, 727, 633, 516. **HRMS (ESI^{+}):** calc. for $[C_{16}H_{18}I]^{+}$: 337.0448; found: 337.0436. **m.p.(ºC):** 178-179 ºC.

(2,3,4,5,6-Pentamethylphenyl)(phenyl)iodonium tosylate (24f).



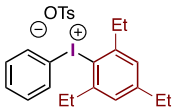
Synthesised by GP1 using 1.0 equiv. of arene. Brownish solid, 65% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.26 (s, 9H), 2.30 (s, 3H), 2.62 (s, 6H), 7.00-7.02 (m, 2H), 7.29-7.34 (m, 2H), 7.44 (tt, J = 7.5, 1.1 Hz, 1H), 7.52-7.55 (m, 2H), 7.66-7.69 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 17.6, 18.8, 21.4, 26.5, 113.7, 126.1, 127.0, 128.5, 131.2, 131.9, 133.1, 135.8, 137.3, 139.3, 141.1, 142.9. **IR ν(cm^{-1}):** 2919, 1565, 1442, 1232, 1155, 1008, 739, 679, 560. **HRMS (ESI^{+}):** calc. for $[C_{17}H_{20}I]^{+}$: 351.0604; found: 351.0594. **m.p.(ºC):** 157-159 ºC.

(4-(*Tert*-butyl)-2,6-dimethylphenyl)(phenyl)iodonium tosylate (24g).



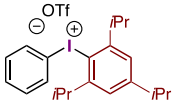
Synthesised by GP1. White solid, 77% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.30 (s, 9H), 2.30 (s, 3H), 2.62 (s, 6H), 7.04 (d, *J* = 7.9 Hz, 2H), 7.20 (s, 2H), 7.32-7.36 (m, 2H), 7.44-7.49 (m, 1H), 7.52-7.55 (m, 2H), 7.70-7.72 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 21.4, 27.6, 31.2, 35.0, 113.5, 121.9, 126.1, 126.7, 128.6, 131.3, 131.9, 133.3, 139.4, 142.2, 143.0, 156.6.

Phenyl(2,4,6-triethylphenyl)iodonium tosylate (24h).



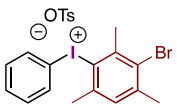
Synthesised by GP1 using CH_2Cl_2 as solvent. White solid, 67% yield. **^{1}H-NMR (400 MHz, CD_3OD):** δ = 1.24-1.29 (m, 9H), 2.36 (s, 3H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.99 (q, *J* = 7.5 Hz, 4H), 7.21-7.23 (m, 2H), 7.30 (s, 2H), 7.48-7.52 (m, 2H), 7.61-7.65 (m, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.81-7.83 (m, 2H). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 15.63, 15.65, 21.3, 29.5, 34.6, 114.5, 121.6, 127.0, 129.3, 129.8, 133.1, 133.3, 134.5, 141.6, 143.6, 149.1, 152.5. **IR ν(cm^{-1}):** 1433, 1236, 1017, 821, 685, 572. **HRMS (MALDI$^+$):** calc. for $[C_{18}H_{22}I]^+$: 365.0761; found: 365.0765. **m.p.(ºC):** 133-135 ºC.

Phenyl(2,4,6-triisopropylphenyl)iodonium triflate (24i).



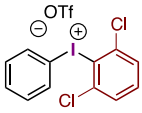
Synthesised by GP6. White powder, 39% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.27 (d, *J* = 6.7 Hz, 12H), 1.30 (d, *J* = 6.9 Hz, 6H), 2.99 (hept, *J* = 6.9 Hz, 1H), 3.28 (hept, *J* = 6.7 Hz, 2H), 7.21 (s, 2H), 7.43-7.48 (m, 2H), 7.55-7.59 (m, 1H), 7.68-7.71 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.4 (s, 3F). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 23.8, 24.4, 34.4, 39.7, 113.0, 120.5, 125.5, 132.0, 132.5, 132.7, 152.5, 155.9.

(3-Bromo-2,4,6-trimethylphenyl)(phenyl)iodonium tosylate (24j).



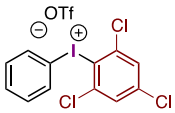
Synthesised by GP1. White solid, 74% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.31 (s, 3H), 2.40 (s, 3H), 2.61 (s, 3H), 2.83 (s, 3H), 6.99-7.01 (m, 2H), 7.11 (s, 1H), 7.29-7.32 (m, 2H), 7.40-7.44 (m, 3H), 7.71-7.73 (m, 2H). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 21.3, 24.4, 27.3, 29.7, 115.0, 125.8, 126.9, 129.8, 132.4, 133.4, 133.45, 133.49, 141.6, 142.1, 142.6, 143.5, 145.9. **IR ν(cm^{-1}):** 1439, 1224, 1165, 1028, 1006, 743, 678, 565. **HRMS (ESI$^+$):** calc. for $[C_{15}H_{15}BrI]^+$: 400.9396; found: 400.9395. **m.p.(ºC):** 171-173 ºC.

(2,6-Dichlorophenyl)(phenyl)iodonium triflate (24k).



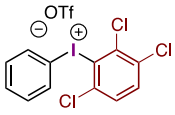
Synthesised by GP3. White crystals, 29% yield. **^{1}H-NMR (400 MHz, CD_3OD):** δ = 7.56-7.60 (m, 2H), 7.64-7.68 (m, 1H), 7.71-7.76 (m, 3H), 8.20-8.22 (m, 2H). **^{19}F-NMR (376 MHz, CD_3OD):** δ = -80.1 (s, 3F). **^{13}C-NMR (75 MHz, CD_3OD):** δ = 116.9, 123.9, 130.2, 133.4, 134.2, 136.6, 136.9, 140.6. **IR ν(cm^{-1}):** 1428, 1238, 1221, 1158, 1024, 784, 741, 634, 514. **HRMS (ESI^{+}):** calc. for $[C_{12}H_8Cl_2I]^{+}$: 348.9042; found: 348.9040. **m.p.(ºC):** 178-180 ºC.

Phenyl(2,4,6-trichlorophenyl)iodonium triflate (24l).



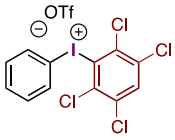
Synthesised by GP3. White solid, 23% yield. **^{1}H-NMR (400 MHz, CD_3OD):** δ = 7.57-7.61 (m, 2H), 7.72-7.77 (m, 1H), 7.90 (s, 2H), 8.20-8.23 (m, 2H). **^{19}F-NMR (376 MHz, CD_3OD):** δ = -80.1 (s, 3F). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 117.1, 121.8 (q, $J_{C\text{-}F}$ = 318.4 Hz), 122.4, 130.2, 133.5, 134.3, 136.6, 141.5, 142.4. **IR ν(cm^{-1}):** 1546, 1220, 1020, 634, 514. **HRMS (ESI^{+}):** calc. for $[C_{12}H_7Cl_3]^{+}$: 382.8634; found: 382.8653. **m.p.(ºC):** 181-183 ºC.

Phenyl(2,3,6-trichlorophenyl)iodonium triflate (24m).



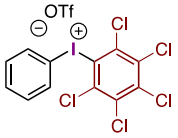
Synthesised by GP3. White solid, 30% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.46-7.53 (m, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.61-7.65 (m, 2H), 8.07-8.09 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.4 (s, 3F). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 117.1, 121.8 (q, $J_{C\text{-}F}$ = 318.4 Hz), 125.2, 131.0, 133.3, 133.5, 134.4, 136.7, 137.0, 138.7, 139.1. **IR ν(cm^{-1}):** 1421, 1274, 1219, 1160, 1019, 988, 734, 633, 515. **HRMS (ESI^{+}):** calc. for $[C_{12}H_7Cl_3I]^{+}$: 382.8653; found: 386.8657. **m.p.(ºC):** 219-220 ºC.

Phenyl(2,3,5,6-tetrachlorophenyl)iodonium triflate (24n).



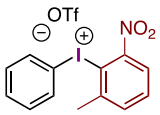
Synthesised by GP3. Brownish solid, 36% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.46-7.51 (m, 2H), 7.62-7.66 (m, 1H), 7.80 (s, 1H), 8.08-8.10 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.4 (s, 3F). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 117.3, 121.8 (q, $J_{C\text{-}F}$ = 318.5 Hz), 126.1, 133.6, 133.8, 134.6, 136.8, 136.9, 137.6. **IR ν(cm^{-1}):** 1391, 1212, 1162, 1018, 987, 633, 517. **HRMS (ESI^{+}):** calc. for $[C_{12}H_6Cl_4I]^{+}$: 416.8263; found: 416.8251. **m.p.(ºC):** 208-209 ºC.

(Perchlorophenyl)(phenyl)iodonium triflate (24o).



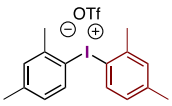
Synthesised by GP3. Brownish solid, 29% yield. **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 7.59-7.63 (m, 2H), 7.75-7.79 (m, 1H), 8.27-8.29 (m, 2H). **^{19}F-NMR (376 MHz, CD$_3$OD):** δ = -80.1 (s, 3F). **^{13}C-NMR (100 MHz, CD$_3$OD):** δ = 117.4, 123.9, 133.5, 133.6, 134.6, 136.8, 138.2, 140.4. **IR ν(cm^{-1}):** 1222, 987, 737, 635, 516. **HRMS (ESI$^+$):** calc. for $[C_{12}H_5Cl_5I]^+$: 450.7873; found: 450.7870. **m.p.(ºC):** 213-215 ºC.

(2-Methyl-6-nitrophenyl)(phenyl)iodonium triflate (24p).



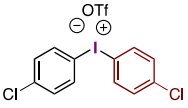
Synthesised by GP3. Beige solid, 40% yield. **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 2.85 (s, 3H), 7.42-7.47 (m, 2H), 7.56-7.61 (m, 1H), 7.64-7.68 (m, 1H), 7.73-7.75 (m, 1H), 7.98-8.04 (m, 3H). **^{19}F-NMR (376 MHz, CDCl$_3$):** δ = -77.9 (s, 3F). **^{13}C-NMR (100 MHz, CDCl$_3$):** δ = 27.8, 110.9, 114.7, 120.0 (q, $J_{C\text{-}F}$ = 319.8 Hz), 124.6, 132.2, 132.7, 133.8, 135.1, 136.6, 145.9, 150.3. **IR ν(cm^{-1}):** 1536, 1223, 1154, 1024, 731, 633, 515. **HRMS (MALDI$^+$):** calc. for $[C_{13}H_{11}INO_2]^+$: 339.9829; found: 339.9824. **m.p.(ºC):** 128-130 ºC.

Bis(2,4-dimethylphenyl)iodonium triflate (24q).



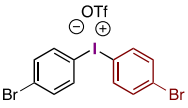
Synthesised by GP5. Brownish solid, 74% yield. **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 2.37 (s, 6H), 2.60 (s, 6H), 7.11-7.14 (m, 2H), 7.38-7.39 (m, 2H), 8.03 (d, J = 8.2 Hz, 2H). **^{19}F-NMR (376 MHz, CD$_3$OD):** δ = -80.1 (s, 3F). **^{13}C-NMR (100 MHz, CD$_3$OD):** δ = 21.1, 25.3, 116.3, 131.4, 133.8, 138.2, 142.2, 145.7.

Bis(4-chlorophenyl)iodonium triflate (24r).



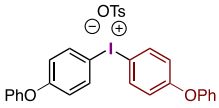
Synthesised by GP7, reaction time: 19 h. White solid, 74% yield. **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 7.54-7.58 (m, 4H), 8.15-8.18 (m, 4H). **^{19}F-NMR (376 MHz, CD$_3$OD):** δ = -80.1 (s, 3F). **^{13}C-NMR (100 MHz, CD$_3$OD):** δ = 113.7, 121.8 (q, $J_{C\text{-}F}$ = 318.6 Hz), 133.3, 138.1, 140.6.

Bis(4-bromophenyl)iodonium triflate (24s).



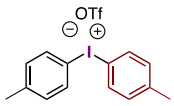
Synthesised by GP7, reaction time: 1 h. White solid, 82% yield. **^{1}H-NMR (400 MHz, CD$_3$OD):** δ = 7.70-7.72 (m, 4H), 8.06-8.10 (m, 4H). **^{19}F-NMR (376 MHz, CD$_3$OD):** δ = -79.8 (s, 3F). **^{13}C-NMR (100 MHz, CD$_3$OD):** δ = 114.4, 121.8 (q, $J_{C\text{-}F}$ = 318.5 Hz) 128.8, 136.4, 138.1.

Bis(4-phenoxyphenyl)iodonium tosylate (24t).



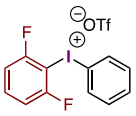
Synthesised by GP2. Yellowish solid, 97% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.30 (s, 3H), 6.83-6.87 (m, 4H), 6.98-7.05 (m, 6H), 7.18-7.22 (m, 2H), 7.35-7.40 (m, 4H), 7.48-7.51 (m, 2H), 7.85-7.90 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 21.5, 107.1, 120.4, 125.2, 126.1, 128.6, 130.3, 137.2, 139.5, 142.8, 155.0, 161.0. **IR ν(cm^{-1}):** 3059, 1569, 1478, 1222, 1152, 1006, 750, 678, 562. **HRMS (ESI$^+$):** calc. for $[C_{24}H_{18}IO_2]^+$: 465.0346; found: 465.0331. **m.p.(ºC):** 161-163 ºC.

Di-*p*-tolyliodonium triflate (24u).



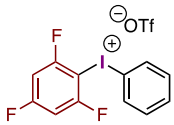
Synthesised by GP5. Brownish solid, 82% yield. **^{1}H-NMR (400 MHz, CD_3OD):** δ = 2.48 (s, 6H), 7.40-7.44 (m, 4H), 8.07-8.10 (m, 4H). **^{19}F-NMR (376 MHz, CD_3OD):** δ = -80.1 (s, 3F). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 21.3, 112.4, 133.8, 136.2, 145.0.

(2,6-Difluorophenyl)(phenyl)iodonium triflate (24v).



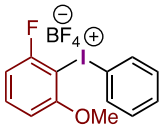
Synthesised by GP5. White solid, 86% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.12-7.16 (m, 2H), 7.42-7.47 (m, 2H), 7.58-7.64 (m, 2H), 8.03-8.06 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.5 (s, 3F), -94.0 (s, 2F). **^{13}C-NMR (100 MHz, CD_3OD):** δ = 93.4 (t, $J_{C\text{-}F}$ = 27.4 Hz), 114.0-114.2 (m), 116.5, 121.8 (q, $J_{C\text{-}F}$ = 318.5 Hz), 133.5, 134.2, 136.6, 138.8 (t, $J_{C\text{-}F}$ = 10.0 Hz), 162.2 (d, $J_{C\text{-}F}$ = 248.0 Hz), 162.2 (d, $J_{C\text{-}F}$ = 257.7 Hz). **IR ν(cm^{-1}):** 3089, 1593, 1468, 1219, 1162, 998, 746, 633, 515. **HRMS (ESI$^+$):** calc. for $[C_{12}H_8F_2I]^+$: 316.9633; found: 316.9642. **m.p.(ºC):** 179-180 ºC.

Phenyl(2,4,6-trifluorophenyl)iodonium triflate (24w).



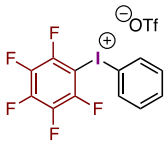
Synthetized by GP5. White solid, 91% yield. **^{1}H-NMR (400 MHz, CD_3OD):** δ = 7.29-7.36 (m, 2H), 7.55-7.60 (m, 2H), 7.72-7.76 (m, 1H), 8.18-8.21 (m, 2H). **^{19}F-NMR (376 MHz, CD_3OD):** δ = -80.1 (s, 3F), -94.4 (d, J = 9.7 Hz, 2F), -98.3 (t, J = 9.9 Hz, 1F). **^{13}C-NMR (125 MHz, CD_3OD):** δ = 88.8-89.5 (m), 103.4, (td, $J_{C\text{-}F}$ = 27.8, 3.5 Hz), 121.8 (t, $J_{C\text{-}F}$ = 318.4 Hz), 133.6, 134.3, 136.6, 161.9 (dd, $J_{C\text{-}F}$ = 16.0, 7.9 Hz), 164.4 (dd, $J_{C\text{-}F}$ = 15.9, 7.9 Hz), 167.6 (t, $J_{C\text{-}F}$ = 15.2 Hz), 170.1 (t, $J_{C\text{-}F}$ = 15.2 Hz). **IR ν(cm^{-1}):** 1597, 1440, 1223, 1022, 738, 632, 507. **HRMS (ESI$^+$):** calc. for $[C_{15}H_7F_3I]^+$: 334.9539; found: 334.9547. **m.p.(ºC):** 151-153 ºC.

(2-Fluoro-6-methoxyphenyl)(phenyl)iodonium tetrafluoroborate (24x).



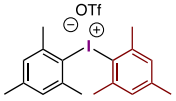
Synthesised by GP5 without the addition of TfOH. White solid, 95% yield. **^{1}H-NMR (400 MHz, CD_3OD):** δ = 4.05 (s, 3H), 7.04-7.08 (m, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.50-7.55 (m, 2H), 7.66-7.72 (m, 2H), 8.08-8.11 (m, 2H). **^{19}F-NMR (376 MHz, CD_3OD):** δ = -97.8 (s, 1F), -154.8 (s, 4F). **^{13}C-NMR (75 MHz, CD_3OD):** δ = 56.3, 95.7 (d, J_{C-F} = 25.3 Hz), 109.81 (d, J_{C-F} = 2.8 Hz), 109.84 (d, J_{C-F} = 22.7 Hz), 115.8, 133.1, 133.7, 136.5, 138.3 (d, J_{C-F} = 10.3 Hz), 160.2 (d, J_{C-F} = 4.7 Hz), 162.6 (d, J_{C-F} = 250.2 Hz). **IR ν(cm^{-1}):** 3209, 1476, 1247, 1020, 988, 676. **HRMS (ESI^{+}):** calc. for $[C_{13}H_{11}FIO]^{+}$: 328.9833; found: 328.9832. **m.p.(ºC):** 182-184 ºC.

(Perfluorophenyl)(phenyl)iodonium triflate (24y).



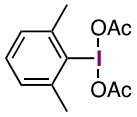
Synthesised by GP5. White crystals, 83% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.47-7.51 (m, 2H), 7.64-7.68 (m, 1H), 8.05-8.07 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.68- -78.73 (m, 3F), -121.3- -121.4 (m, 2F), -141.8 (s, 1F), -154.9- -155.1 (m, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 114.9, 119.7 (q, J_{C-F} = 318.8 Hz), 132.7, 133.4, 135.9, 136.3-136.7 (m), 138.4-138.7 (m), 144.3-144.5 (m), 145.4-145.7 (m), 146.5-146.7 (m), 147.4-147.6 (m). **IR ν(cm^{-1}):** 1502, 1278, 1221, 1169, 976, 730, 633, 517. **HRMS (ESI^{+}):** calc. for $[C_{12}H_5F_5I]^{+}$: 370.9351; found: 370.9352. **m.p.(ºC):** 115-117 ºC.

Dimesityliodonium triflate (26).



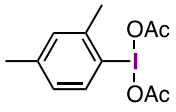
Synthesised by GP6. White powder, 70% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.33 (s, 6H), 2.51 (s, 12H), 7.05 (s, 4H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -78.4 (s, 3F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 20.9, 26.1, 117.2, 120.5 (q, J_{C-F} = 320.2 Hz), 130.9, 142.2, 143.8.

(2,6-Dimethylphenyl)- λ^{3}-iodanediyl diacetate.



Synthesised by GP4. Yellowish solid, 94%. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.97 (s, 6H), 2.75 (s, 6H), 7.28-7.30 (m, 2H), 7.38 (dd, *J* = 8.3, 6.6 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 20.4, 27.1, 128.3, 132.7, 133.1, 141.6, 176.6.

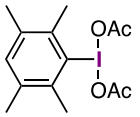
(2,4-Dimethylphenyl)-λ^{3}-iodanediyl diacetate.



Synthesised by GP4. Yellow solid, 95% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.97 (s, 6H), 2.40 (s, 3H), 2.67 (s, 3H), 7.03-7.06 (m,

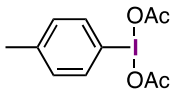
1H), 7.30-7.31 (m, 1H), 8.04 (d, *J* = 8.1 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 20.5, 21.6, 25.5, 124.1, 129.3, 131.8, 137.3, 140.6, 143.7, 176.5. **IR ν(cm^{-1}):** 2928, 1643, 1367, 1265, 1008, 667. **HRMS (MALDI$^+$):** calc. for $[C_{10}H_{12}IO_2]^+$: 290.9876; found: 290.9875. **m.p.(ºC):** 120-122 ºC.

(2,3,5,6-Tetramethylphenyl)-λ^3-iodanediyl diacetate.



Synthesised by GP4. Yellow solid, 83%. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.97 (s, 6H), 2.36 (s, 6H), 2.65 (s, 6H), 7.14 (s, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 20.5, 21.8, 24.7, 135.6, 136.0, 136.1, 137.1, 176.6. **IR ν(cm^{-1}):** 2919, 1650, 1269, 666, 494. **HRMS (MALDI$^+$):** calc. for $[C_{12}H_{16}IO_2]^+$: 319.0189; found: 319.0189. **m.p.(ºC):** 155-157 ºC.

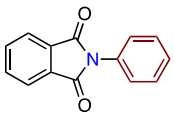
***p*-Tolyl-λ^3-iodanediyl diacetate.**



Synthesised by GP4. Yellow solid, 90% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.00 (s, 6H), 2.44 (s, 3H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 20.6, 21.7, 118.5, 131.9, 135.1, 142.8, 176.6.

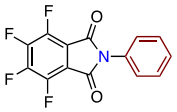
General procedure for the synthesis of protected anilines (GP8): A Schlenk tube equipped with a stirring bar was charged with the potassium or sodium salt of the amide (0.7 mmol, 3.0 equiv.) in 10.0 mL of dry toluene (0.24 M). The diaryliodonium salt (0.24 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at 100 ºC for the indicated time. After cooling to room temperature the suspension was filtered over a short pad of Celite® washing with CH_2Cl_2 and the solvent was removed under reduced pressure. After purification by column chromatography (*n*-hexane/EtOAc, 95/5 v/v) the final protected aniline was isolated as solid.

2-Phenylisoindoline-1,3-dione (25a).



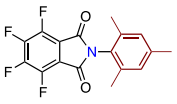
Synthesised by GP8. White solid, 67% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.39-7.43 (m, 1H), 7.44-7.46 (m, 2H), 7.49-7.53 (m, 2H), 7.79-7.80 (m, 2H), 7.95-7.97 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 123.9, 126.7, 128.2, 129.3, 131.9, 132.0, 134.5, 167.4.

4,5,6,7-Tetrafluoro-2-phenylisoindoline-1,3-dione (25b).



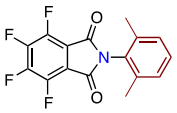
Synthesised by GP8. Yellowish solid, 75% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.37-7.40 (m, 2H), 7.43-7.47 (m, 1H), 7.50-7.55 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -135.1 (q, *J* = 9.5 Hz, 2F), -141.6 (q, *J* = 9.5 Hz, 2F). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 113.6-113.7 (m), 126.6, 129.0, 129.5, 130.6, 142.4-142.6 (m), 143.9-144.2 (m), 145.0-145.3 (m), 146.6-146.9 (m), 161.5.

4,5,6,7-Tetrafluoro-2-mesitylisoindoline-1,3-dione (25c).



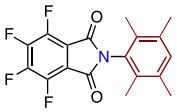
Synthesised by GP8. Yellowish solid, 69% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.10 (s, 6H), 2.34 (s, 3H), 7.51 (s, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.8 (q, *J* = 9.6 Hz, 2F), -141.9 (q, *J* = 11.1 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 18.0, 21.3, 113.83-113.88 (m), 126.0, 129.6, 136.3, 140.2, 142.38-142.43 (m), 144.0-144.2 (m), 145.0-145.2 (m), 146.7-146.8 (m), 161.5. **IR ν(cm^{-1}):** 2924, 1725, 1498, 1400, 1362, 1314, 1138, 946, 885, 731, 533. **HRMS (APCI$^+$):** calc. for $[C_{17}H_{12}F_4NO_2]^+$: 338.0799; found: 338.0798. **m.p.(ºC):** 155-157 ºC.

2-(2,6-Dimethylphenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione (25d).



Synthesised by GP8. Yellowish solid, 79% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.15 (s, 6H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.26-7.32 (m, 1H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.7 (q, *J* = 9.6 Hz, 2F), -141.8 (q, *J* = 9.5 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 18.1, 113.8, 128.75, 128.84, 136.8, 142.65-142.74 (m), 144.2-144.5 (m), 144.8-144.9 (m), 146.5-146.6 (m), 161.3. **IR ν(cm^{-1}):** 2978, 1715, 1504, 1359, 1091, 940, 756, 685, 541. **HRMS (MALDI$^-$):** calc. for $[C_{16}H_9F_4NO_2]^-$: 323.0569; found: 323.0569. **m.p.(ºC):** 151-153 ºC.

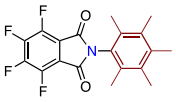
4,5,6,7-Tetrafluoro-2-(2,3,5,6-tetramethylphenyl)isoindoline-1,3-dione (25e).



Synthesised by GP8. Yellowish solid, 80% yield. Reaction time: 20 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.99 (s, 6H), 2.27 (s, 6H), 7.10 (s, 1H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.7 (q, *J* = 9.4 Hz, 2F), -141.9 (q, *J* = 9.5 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 14.7, 20.2, 113.8-113.9 (m), 128.5, 132.2, 133.5, 135.1, 142.6-142.8 (m), 144.2-144.5 (m), 144.8-144.9 (m), 146.3-146.6 (m), 161.7. **IR ν(cm^{-1}):** 2926, 1722, 1496, 1400, 1092, 944, 743, 649.

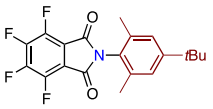
HRMS (ESI$^+$): calc. for $[C_{18}H_{13}F_4NNaO_2]^+$: 374.0775; found: 374.0784. **m.p.(ºC):** 193-195 ºC.

4,5,6,7-Tetrafluoro-2-(2,3,4,5,6-pentamethylphenyl)isoindoline-1,3-dione (25f).



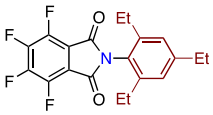
Synthesised by GP8. Pale yellow solid, 77% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.03 (s, 6H), 2.25 (s, 6H), 2.27 (s, 3H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.3 (q, *J* = 9.5 Hz, 2F), -141.6 (q, *J* = 9.4 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 15.6, 16.9, 17.2, 113.8-113.9 (m), 126.1, 131.6, 134.0, 137.6, 142.6-142.7 (m), 144.2-144.4 (m), 144.8-144.9 (m), 146.3-146.5 (m), 161.8. **IR ν(cm^{-1}):** 2932, 1719, 1506, 1404, 1146, 1095, 943, 754, 650. **HRMS (ESI$^+$):** calc. for $[C_{19}H_{15}F_4NNaO_2]^+$: 388.0931; found: 388.0927. **m.p.(ºC):** 223-225 ºC.

2-(4-(*Tert*-butyl)-2,6-dimethylphenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione (25g).



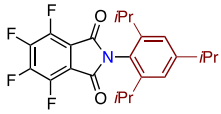
Synthesised by GP8. Yellowish solid, 70% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.32 (s, 9H), 2.13 (s, 6H), 7.18 (s, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.8 (q, *J* = 9.4 Hz, 2F), -142.0 (q, *J* = 9.5 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 18.4, 31.4, 34.7, 113.8-113.9 (m), 125.96, 126.0, 135.8, 142.6-142.7 (m), 144.2-144.4 (m), 144.8-144.9 (m), 146.3-146.6 (m), 153.0, 161.5. **IR ν(cm^{-1}):** 2973, 1721, 1500, 1365, 1140, 1090, 943, 713, 536. **HRMS (ESI$^+$):** calc. for $[C_{20}H_{17}F_4NNaO_2]^+$: 402.1088; found: 402.1085. **m.p.(ºC):** 182-184 ºC.

4,5,6,7-Tetrafluoro-2-(2,4,6-triethylphenyl)isoindoline-1,3-dione (25h).



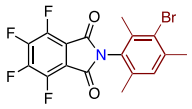
Synthesised by GP8. Yellow amorphous solid, 90% yield. Reaction time: 20 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.13 (t, *J* = 7.5 Hz, 6H), 1.27 (t, *J* = 7.6 Hz, 3H), 2.39 (q, *J* = 7.6 Hz, 4H), 2.67 (q, *J* = 7.7 Hz, 2H), 7.05 (s, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.7 (q, *J* = 9.6 Hz, 2F), -141.9 (q, *J* = 9.4 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 14.6, 15.4, 24.8, 28.9, 113.7-113.8 (m), 124.9, 126.6, 142.1, 142.2-142.4 (m), 143.9-144.2 (m), 144.7-145.1 (m), 146.6, 146.6-146.9 (m), 162.2. **IR ν(cm^{-1}):** 2968, 1727, 1367, 1094, 947. **HRMS (ESI$^+$):** calc. for $[C_{20}H_{17}F_4NNaO_2]^+$: 402.1088; found: 402.1085. **m.p.(ºC):** 105-107 ºC.

4,5,6,7-Tetrafluoro-2-(2,4,6-triisopropylphenyl)isoindoline-1,3-dione (25i).



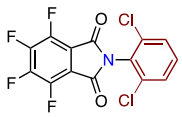
Synthesised by GP8. Yellowish solid, 70% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.16 (d, *J* = 6.9 Hz, 12H), 1.29 (d, *J* = 7.0 Hz, 6H), 2.60 (hept, *J* = 7.2 Hz, 2H), 2.95 (hept, *J* = 7.1 Hz, 1H), 7.11 (s, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.2 (q, *J* = 9.5 Hz, 2F), -141.6 (q, *J* = 9.5 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 24.1, 24.2, 29.6, 34.5, 113.76-113.83 (m), 122.4, 123.2, 142.6-142.7 (m), 144.2-144.5 (m), 144.8-144.9 (m), 146.7, 151.3, 162.5. **IR ν(cm^{-1}):** 2965, 1728, 1502, 1366, 1092, 944, 720, 552. **HRMS (ESI^{+}):** calc. for $[C_{23}H_{23}F_4NNaO_2]^{+}$: 444.1557; found: 444.1552. **m.p.(ºC):** 174-176 ºC.

2-(3-Bromo-2,4,6-trimethylphenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione (25j).



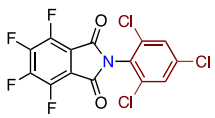
Synthesised by GP8. White solid, 73% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.07 (s, 3H), 2.23 (s, 3H), 2.44 (s, 3H), 7.12 (s, 1H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.3 (q, *J* = 9.8 Hz, 2F), -141.3 (q, *J* = 9.6 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 18.0, 19.4, 24.2, 113.6-113.7 (m), 125.8, 127.0, 130.5, 135.3, 137.0, 140.7, 142.7-142.8 (m), 144.3-144.6 (m), 144.9-145.0 (m), 146.5-146.7 (m), 161.2. **IR ν(cm^{-1}):** 2928, 1723, 1501, 1402, 1094, 942, 753, 541. **HRMS (ESI^{+}):** calc. for $[C_{18}H_{14}BrF_4NNaO_3]^{+}$: 469.9985; found: 469.9985. **m.p.(ºC):** 122-124 ºC.

2-(2,6-Dichlorophenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione (25k).



Synthesised by GP8. Yellowish solid, 51% yield. Reaction time: 24 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.40-7.45 (m, 1H), 7.49-7.51 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -133.9 (q, *J* = 9.9 Hz, 2F), -141.1 (q, *J* = 9.8 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 113.7-113.8 (m), 126.9, 128.9, 132.0, 135.5, 142.9-143.0 (m), 144.4-144.6 (m), 145.0-145.1 (m), 146.7-146.8 (m), 159.8. **IR ν(cm^{-1}):** 2963, 1731, 1506, 1463, 1089, 941, 777, 645. **HRMS (ESI^{+}):** calc. for $[C_{15}H_7Cl_2F_4NNaO_3]^{+}$: 417.9631; found: 417.9634. **m.p.(ºC):** 159-161 ºC.

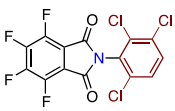
4,5,6,7-Tetrafluoro-2-(2,4,6-trichlorophenyl)isoindoline-1,3-dione (25l).



Synthesised by GP8. Yellow solid, 61% yield. Reaction time: 19 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.52 (s, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -133.6 (q, *J* = 10.0 Hz, 2F), -140.8 (q, *J* = 9.9 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 113.6-113.7 (m), 125.7, 129.1, 136.1,

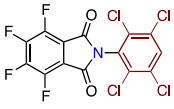
137.5, 142.6-142.8 (m), 144.2-144.5 (m), 145.3-145.5 (m), 146.9-147.2 (m), 159.6. **IR ν(cm^{-1}):** 1737, 1471, 1401, 1095, 947, 817. **HRMS (ESI$^+$):** calc. for $[C_{15}H_6Cl_3F_4NNaO_3]^+$: 451.9242; found: 451.9244. **m.p.(ºC):** 186-188 ºC.

4,5,6,7-Tetrafluoro-2-(2,3,6-trichlorophenyl)isoindoline-1,3-dione (25m).



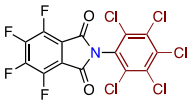
Synthesised by GP8. White solid, 67% yield. Reaction time: 17 h. **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 7.45 (d, *J* = 8.8 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H). **^{19}F-NMR (376 MHz, CDCl$_3$):** δ = -133.5 (q, *J* = 9.9 Hz, 2F), -140.7 (q, *J* = 9.9 Hz, 2F). **^{13}C-NMR (125 MHz, CDCl$_3$):** δ = 113.6-113.7 (m), 128.4, 128.8, 132.6, 133.0, 133.8, 134.5, 142.95-143.0 (m), 144.6-144.8 (m), 145.1-145.2 (m), 146.8-146.9 (m), 159.5. **IR ν(cm^{-1}):** 1731, 1502, 1402, 1093, 942, 795, 653. **HRMS (ESI$^+$):** calc. for $[C_{15}H_6Cl_3F_4NNaO_3]^+$: 451.9242; found: 451.9233. **m.p.(ºC):** 127-129 ºC.

4,5,6,7-Tetrafluoro-2-(2,3,5,6-tetrachlorophenyl)isoindoline-1,3-dione (25n).



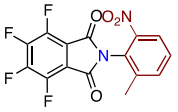
Synthesised by GP8. Yellowish solid, 75% yield. Reaction time: 20 h. **^{1}H-NMR (500 MHz, CDCl$_3$):** δ = 7.79 (s, 1H). **^{19}F-NMR (376 MHz, CDCl$_3$):** δ = -133.1 (q, *J* = 10.1 Hz, 2F), -140.3 (q, *J* = 10.0 Hz, 2F). **^{13}C-NMR (125 MHz, CDCl$_3$):** δ = 113.5-113.6 (m), 129.5, 132.87, 132.89, 133.0, 142.7-142.9 (m), 144.3-144.6 (m), 145.5-145.6 (m), 147.0-147.3 (m), 159.3. **IR ν(cm^{-1}):** 1738, 1504, 1404, 1091, 946, 738, 525. **HRMS (ESI$^+$):** calc. for $[C_{15}H_5Cl_4F_4NNaO_3]^+$: 485.8852; found: 485.8854. **m.p.(ºC):** 256-258 ºC.

4,5,6,7-Tetrafluoro-2-(perchlorophenyl)isoindoline-1,3-dione (25o).



Synthesised by GP8. Yellow solid, 67% yield. Reaction time: 17 h. **^{19}F-NMR (376 MHz, CDCl$_3$):** δ = -135.0 (q, *J* = 9.4 Hz, 2F), -142.0 (q, *J* = 9.3 Hz, 2F). **^{13}C-NMR (125 MHz, CDCl$_3$):** δ = 113.5-113.6 (m), 127.3, 133.0, 133.7, 136.8, 143.05-143.14 (m), 144.7-145.3 (m), 146.8-147.0 (m), 159.2. **IR ν(cm^{-1}):** 1732, 1502, 1402, 1094, 944, 755, 558. **HRMS (ESI$^+$):** calc. for $[C_{15}H_4Cl_5F_4NNaO_3]^+$: 519.8462; found: 519.8467. **m.p.(ºC):** 151-153 ºC.

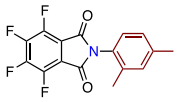
4,5,6,7-Tetrafluoro-2-(2-methyl-6-nitrophenyl)isoindoline-1,3-dione (25p).



Synthesised by GP8. White foam, 87% yield. Reaction time: 17 h. Purification by column chromatography (CH_2Cl_2/MeOH, 200/1 v/v). **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 2.33 (s, 3H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.68-7.70 (m, 1H), 8.07-8.09 (m, 1H). **^{19}F-NMR (376 MHz, CDCl$_3$):** δ = -133.9

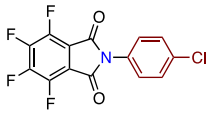
(q, *J* = 10.0 Hz, 2F), -141.0 (q, *J* = 9.9 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 18.2, 113.96-114.0 (m), 123.6, 124.1, 130.7, 136.6, 140.8, 142.9-143.0 (m), 144.5-144.7 (m), 145.0-145.1 (m), 146.4, 146.7-146.8 (m), 160.8. **IR ν(cm^{-1}):** 1731, 1501, 1340, 1089, 944, 809, 728, 652. **HRMS (ESI$^+$):** calc. for $[C_{15}H_6F_4N_2NaO_4]^+$: 377.0156; found: 377.0151. **m.p.(ºC):** 167-169 ºC.

2-(2,4-Dimethylphenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione (25q).



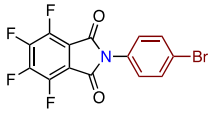
Synthesised by GP8. Yellow solid, 51% yield. Reaction time: 17 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.15 (s, 3H), 2.38 (s, 3H), 7.03 (d, *J* = 8.0 Hz, 1H) 7.12-7.15 (m, 1H), 7.18-7.19 (m, 1H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -135.0 (q, *J* = 9.4 Hz, 2F), -142.0 (q, *J* = 9.3 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 18.0, 21.3, 113.86-113.90 (m), 126.8, 128.0, 128.3, 132.2, 136.1, 140.3, 142.6-142.7 (m), 144.1-144.4 (m), 144.4-144.7 (m), 146.3-146.5 (m), 162.6. **IR ν(cm^{-1}):** 2925, 1719, 1479, 1371, 1090, 939, 734, 538. **HRMS (ESI$^+$):** calc. for $[C_{17}H_{13}F_4NNaO_3]^+$: 378.0724; found: 378.0724. **m.p.(ºC):** 154-156 ºC.

2-(4-Chlorophenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione (25r).



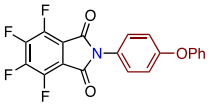
Synthesised by GP8. Yellow solid, 34% yield. Reaction time: 17 h. Recrystallisation (EtOAc/*n*-hexane). **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 7.47-7.49 (m, 2H), 7.62-7.66 (m, 2H). **^{19}F-NMR (376 MHz, DMSO-*d*$_6$):** δ = -(139.2-139.3) (m, 2F), -(144.0-144.1) (m, 2F). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** δ = 113.96-114.03 (m), 129.1, 129.2, 129.8, 133.3, 141.5-141.6 (m), 143.0-143.3 (m), 143.6-143.7 (m), 145.2-145.3 (m), 161.6. **IR ν(cm^{-1}):** 1716, 1506, 1085, 941, 731. **HRMS (ESI$^+$):** calc. for $[C_{15}H_8ClF_4NNaO_3]^+$: 384.0021; found: 384.0039. **m.p.(ºC):** 267-269 ºC.

2-(4-Bromophenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione (25s).



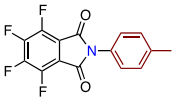
Synthesised by GP8. Yellowish solid, 18% yield. Reaction time: 14 h. Recrystallisation (EtOAc/*n*-hexane). **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 7.39-7.43 (m, 2H), 7.76-7.79 (m, 2H). **^{19}F-NMR (376 MHz, DMSO-*d*$_6$):** δ = -(139.1-139.3) (m, 2F), -(144.0-144.1) (m, 2F). **^{13}C-NMR (125 MHz, DMSO-*d*$_6$):** δ = 113.96-114.03 (m), 121.8, 129.4, 130.2, 132.1, 141.5-141.6 (m), 143.0-143.3 (m), 143.6-143.7 (m), 145.2-145.3 (m), 161.5. **IR ν(cm^{-1}):** 1712, 1491, 1404, 1086, 940, 731, 506. **HRMS (ESI$^+$):** calc. for $[C_{15}H_8BrF_4NNaO_3]^+$: 427.9516; found: 427.9513. **m.p.(ºC):** 255-257 ºC.

4,5,6,7-Tetrafluoro-2-(4-phenoxyphenyl)isoindoline-1,3-dione (25t).



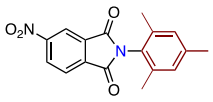
Synthesised by GP8. Yellowish solid, 26% yield. Reaction time: 14 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 7.09-7.14 (m, 4H), 7.17-7.22 (m, 1H), 7.32-7.36 (m, 2H), 7.37-7.43 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -134.7 (q, *J* = 9.6 Hz, 2F), -141.2 (q, *J* = 9.5 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 113.6-113.7 (m), 118.9, 119.9, 124.3, 125.0, 128.1, 130.1, 142.4-142.6 (m), 142.9-144.2 (m), 145.1-145.3 (m), 146.5-146.9 (m), 156.3, 158.1, 161.7. **IR ν(cm^{-1}):** 1714, 1503, 1487, 1244, 1089, 945, 733, 691. **HRMS (ESI^{+}):** calc. for $[C_{20}H_{10}F_4NO_3]^{+}$: 388.0591; found: 388.0595. **m.p.(ºC):** 194-196 ºC.

4,5,6,7-Tetrafluoro-2-(*p*-tolyl)isoindoline-1,3-dione (25v).



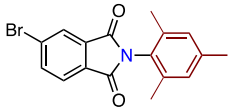
Synthesised by GP8. Yellowish solid, 48% yield. Reaction time: 15 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.42 (s, 3H), 7.24-7.26 (m, 2H), 7.31-7.33 (m, 2H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = -135.2 (q, *J* = 9.4 Hz, 2F), -141.9 (q, *J* = 9.4 Hz, 2F). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 21.4, 113.7-113.8 (m), 126.4, 127.9, 130.1, 139.2, 142.2-142.5 (m), 143.9-144.2 (m), 145.0-145.2 (m), 146.5-146.8 (m), 161.7. **IR ν(cm^{-1}):** 2923, 1720, 1496, 1402, 1090, 942, 725, 509. **HRMS (ESI^{+}):** calc. for $[C_{16}H_{11}F_4NNaO_3]^{+}$: 364.0567; found: 364.0572. **m.p.(ºC):** 230-232 ºC.

2-Mesityl-5-nitroisoindoline-1,3-dione (27a).



Synthesised by GP8. Yellowish solid, 80% yield. Reaction time: 20 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.11 (s, 6H), 2.35 (s, 3H), 7.03 (s, 2H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.68 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.78-8.79 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 18.1, 21.3, 119.4, 125.2, 126.5, 129.6, 129.7, 133.5, 136.3, 136.5, 140.1, 152.1, 165.1, 165.4. **IR ν(cm^{-1}):** 3101, 1720, 1537, 1343, 1106, 1030. **HRMS (ESI^{+}):** calc. for $[C_{17}H_{14}N_2NaO_4]^{+}$: 333.0846; found: 333.0852. **m.p.(ºC):** 214-216 ºC.

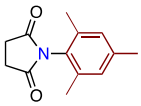
5-Bromo-2-mesitylisoindoline-1,3-dione (27b).



Synthesised by GP8. White solid, 67% yield. Reaction time: 15 h. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.10 (s, 6H), 2.33 (s, 3H), 7.00 (s, 2H), 7.82 (dd, *J* = 7.9, 0.6 Hz, 1H), 7.94 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.10 (dd, *J* = 1.7, 0.6 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 18.1, 21.3, 125.3, 126.9, 127.3, 129.4, 129.5, 130.6, 133.8, 136.5, 137.4, 139.7, 166.2, 166.7.

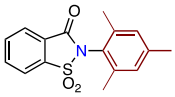
IR ν(cm^{-1}): 2917, 1709, 1370, 1096, 853, 744. **HRMS (ESI$^+$):** calc. for $[C_{17}H_{14}BrNNaO_2]^+$: 366.0100; found: 366.0104. **m.p.(ºC):** 194-196 ºC.

1-Mesitylpyrrolidine-2,5-dione (27c).



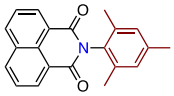
Synthesised by GP8. White solid, 43% yield. Reaction time: 20 h. Purification by column chromatography (*n*-hexane/EtOAc, 3/2 v/v). **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.07 (s, 6H), 2.30 (s, 3H), 2.93 (s, 4H), 6.97 (s, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 17.8, 21.2, 28.8, 127.6, 129.5, 135.4, 139.6, 176.3.

2-Mesitylbenzo[D]isothiazol-3(2*H*)-one-1,1-dioxide (27d).



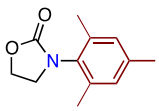
Synthesised by GP8. White solid, 72% yield. Reaction time: 24 h. Purification by column chromatography (*n*-hexane/CH_2Cl_2, 1/4 v/v). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.29 (s, 6H), 2.34 (s, 3H), 7.03 (s, 2H), 7.91 (dtd, *J* = 18.0, 7.4, 1.3 Hz, 2H), 7.99-8.01 (m, 1H), 8.16-8.18 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 18.5, 21.3, 121.4, 123.6, 125.8, 127.2, 130.1, 134.5, 135.1, 138.6, 139.6, 140.9, 158.5. **IR ν(cm^{-1}):** 2927, 1725, 1463, 1262, 1183, 984, 747, 580, 505. **HRMS (ESI$^+$):** calc. for $[C_{16}H_{16}NO_3S]^+$: 302.0845; found: 302.0847. **m.p.(ºC):** 207-209 ºC.

2-Mesityl-1*H*-benzo[DE]isoquinoline-1,3(2*H*)-dione (27e).



Synthesised by GP8. Yellowish solid, 59% yield. Reaction time: 16 h. Purification by column chromatography (*n*-hexane/EtOAc, 85/15 v/v). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.12 (s, 6H), 2.36 (s, 3H), 7.04 (s, 2H), 7.81 (dd, *J* = 8.2, 7.3 Hz, 2H), 8.29 (dd, *J* = 8.3, 1.1 Hz, 2H), 8.68 (dd, *J* = 7.3, 1.2 Hz, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 17.9, 21.3, 122.9, 127.1, 129.0, 129.5, 131.4, 131.8, 132.0, 134.4, 135.4, 138.6, 163.7. **IR ν(cm^{-1}):** 2920, 1659, 1347, 1234, 774, 526. **HRMS (ESI$^+$):** calc. for $[C_{21}H_{18}NO_2]^+$: 316.1332; found: 316.1333. **m.p.(ºC):** 232-234 ºC.

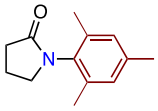
3-Mesityloxazolidin-2-one (27f).



Synthesised by GP8. White solid, 95% yield. Reaction time: 16 h. Purification by column chromatography (*n*-hexane/EtOAc, 65/35 v/v). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.24 (s, 6H), 2.28 (s, 3H), 3.79-3.83 (m, 2H), 4.51-4.55 (m, 2H), 6.92 (s, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 17.8, 21.1, 46.4, 62.5, 129.6, 131.6, 136.5, 138.6, 156.9. **IR ν(cm^{-1}):** 2921, 1744, 1411, 1111, 758,

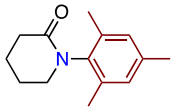
618. **HRMS (ESI$^+$):** calc. for $[C_{12}H_{16}NO_2]^+$: 206.1176; found: 206.1174. **m.p.(ºC):** 87-89 ºC.

1-Mesitylpyrrolidin-2-one (27g).



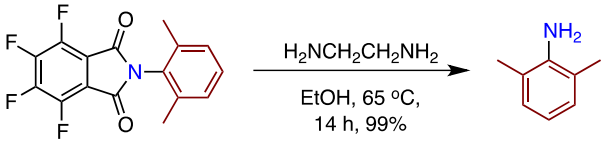
Synthesised by GP8. Colourless solid, 77% yield. Reaction time: 16 h. Purification by column chromatography (CH_2Cl_2/MeOH, 97/3 v/v). **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.17 (s, 6H), 2.22-2.25 (m, 2H), 2.27 (s, 3H), 2.57 (t, *J* = 8.1 Hz, 2H), 3.59 (t, *J* = 7.0 Hz, 2H), 6.91 (s, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 17.8, 19.5, 21.1, 31.0, 49.1, 129.4, 133.3, 135.7, 138.0, 174.6. **IR ν(cm^{-1}):** 2915, 1680, 1404, 1283, 867, 500. **HRMS (ESI$^+$):** calc. for $[C_{13}H_{18}NO]^+$: 204.1383; found: 204.1381. **m.p.(ºC):** 77-79 ºC.

1-Mesitylpiperidin-2-one (27h).



Synthesised by GP8. White solid, 94% yield. Reaction time: 14 h. Purification by column chromatography (CH_2Cl_2/MeOH, 96/4 v/v). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.94-1.96 (m, 4H), 2.15 (s, 6H), 2.27 (s, 3H), 2.56-2.58 (m, 2H), 3.37-3.39 (m, 2H), 6.91 (s, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 17.6, 21.1, 21.7, 23.7, 32.6, 49.7, 129.6, 134.7, 137.4, 138.1, 169.4. **IR ν(cm^{-1}):** 2944, 2922, 1637, 1435, 1301, 1161, 859. **HRMS (ESI$^+$):** calc. for $[C_{14}H_{20}NO]^+$: 218.1539; found: 218.1532. **m.p.(ºC):** 103-105 ºC.

General procedure for the deprotection of protected anilines (GP9).



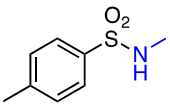
25d **25d'**

Scheme 2.27 Deprotection of 2,6-dimethylsubstituted aniline **25d**.

To a solution of 2-(2,6-dimethylphenyl)-4,5,6,7-tetrafluoroisoindoline-1,3-dione **25d** (1.0 equiv.) in ethanol (2.0 mL) was added ethylenediamine (21.1 equiv.). The mixture was heated at 65 ºC for 14 h. After cooling the reaction mixture to room temperature, it was concentrated under reduced pressure and the crude mixture was purified by column chromatography (CH_2Cl_2) to afford the aniline **25d'** as yellow oil in 99% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.20 (s, 6H), 3.57 (bs, 2H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 17.7, 118.1, 121.8, 128.4, 142.8.

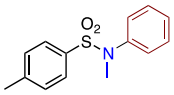
General procedure for the synthesis of protected anilines (GP10): A Schlenk tube equipped with a stirring bar was charged with the amide (0.7 mmol, 3.0 equiv.) and *t*BuOK (0.7 mmol, 3.0 equiv.) in 10.0 mL of dry toluene (0.24 M). The diaryliodonium salt (0.24 mmol, 1.0 equiv.) was added and the reaction mixture was stirred at 100 ºC for the indicated time. After cooling to room temperature, the suspension was filtered over a short pad of Celite® washing with CH_2Cl_2 and the solvent was removed under reduced pressure. After purification by column chromatography (*n*-hexane/EtOAc, 95/5 v/v) the final protected aniline was isolated as solid.

***N*-4-Dimethylbenzenesulphonamide.**



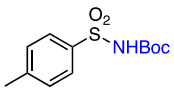
White solid, 95% yield. Purification by crystallisation (CH_2Cl_2/*n*-hexane). Spectroscopic data according to previous literature.[63] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.46 (s, 3H), 2.67 (d, *J* = 5.4 Hz, 3H), 4.36-4.37 (m, 1H), 7.33-7.36 (m, 2H), 7.47-7.50 (m, 1H), 7.76-7.79 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 26.8, 126.8, 128.5, 131.3, 134.7, 168.2.

***N*-4-Dimethyl-*N*-phenylbenzenesulphonamide (28a).**



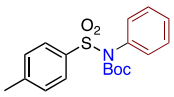
Synthesised by GP10. White solid, 78% yield. Reaction time: 17 h. Purification by column chromatography (*n*-hexane/EtOAc, 95/5 v/v). **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.42 (s, 3H), 3.17 (s, 3H), 7.09-7.11 (m, 2H), 7.23-7.32 (m, 5H), 7.42-7.44 (m, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 21.7, 38.2, 126.7, 127.4, 128.0, 128.9, 129.5, 141.8, 143.6.

***Tert*-butyl tosylcarbamate.**



White solid, 84% yield. Purification by crystallisation (CH_2Cl_2/*n*-hexane). Spectroscopic data according to previous literature.[64] **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 1.39 (s, 9H), 2.45 (s, 3H), 7.14 (bs, 1H), 7.32-7.35 (m, 2H), 7.88-7.91 (m, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 21.8, 28.0, 84.2, 128.4, 129.7, 136.1, 144.9, 149.1.

***Tert*-butyl phenyl(tosyl)carbamate (28b).**

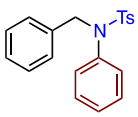


Synthesised by GP10. Yellowish solid, 42% yield. Reaction time: 21 h. Purification by column chromatography (*n*-hexane/EtOAc, 85/15 v/v). **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 1.34 (s, 9H), 2.47 (s, 3H),

[63] Alazet, S.; Zimmer, L.; Billar, T. *Chem. Eur. J.* **2014**, *80*, 8589.
[64] Barrett, S.; O'Brien, P.; Steffens, H. C.; Towers, T. D.; Voith, M. *Tetrahedron* **2000**, *56*, 9633.

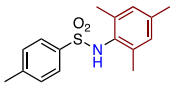
7.24-7.26 (m, 2H), 7.33-7.36 (m, 2H), 7.40-7.44 (m, 3H), 7.86-7.89 (m, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 21.8, 28.0, 84.5, 128.8, 129.1, 129.2, 129.5, 129.9, 136.7, 137.0, 144.6, 151.1.

***N*-Benzyl-4-methyl-*N*-phenylbenzenesulphonamide (28c).**



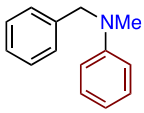
Synthesised by GP10. White solid, 64% yield. Reaction time: 17 h. Purification by column chromatography (*n*-hexane/EtOAc, 9/1 v/v). **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.45 (s, 3H), 4.72 (s, 2H), 6.96-7.00 (m, 2H), 7.18-7.23 (m, 8H), 7.26-7.29 (m, 2H), 7.53-7.56 (m, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 21.7, 54.9, 127.7, 127.9, 128.5, 128.7, 129.0, 129.1, 129.6, 135.8, 136.1, 139.2, 143.6.

***N*-Mesityl-*N*-toluensulphonamide (28d).**



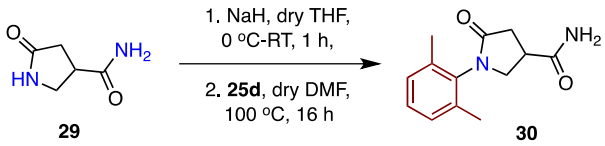
Synthesised by GP10. White solid, 56% yield. Reaction time: 17 h. Purification by column chromatography (CH_2Cl_2/MeOH, 96/4 v/v). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.44 (s, 6H), 2.69 (s, 3H), 2.86 (s, 3H), 6.74 (s, 1H), 7.67-7.70 (m, 2H), 8.05-8.08 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 18.6, 20.8, 21.5, 127.1, 129.4, 129.5, 129.9, 137.4, 137.9, 143.4.

***N*-Benzyl-*N*-methylaniline (28e).**



Synthesised by GP10. Yellow oil, 63% yield. Reaction time: 17 h. Purification by column chromatography (*n*-hexane/EtOAc, 9/1 v/v). **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 3.02 (s, 3H), 4.54 (s, 2H), 6.70-6.80 (m, 3H), 7.21-7.26 (m, 5H), 7.30-7.34 (m, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 38.6, 56.8, 112.5, 116.7, 126.9, 127.0, 128.7, 129.3, 139.2, 149.9.

Application of the methodology.

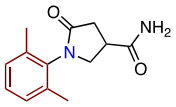


Scheme 2.28 Chemoselective synthesis of *N*-arylated lactam **30**.

In a flamed and dried Schlenk tube under argon atmosphere, NaH 55 wt% (0.035 g, 6.9 equiv.) was washed with 20.0 mL of dry hexane. After that the solvent was removed, and dry THF (5.0 mL) and 5-oxopyrrolidine-3-carboxamide **29** (0.045 g, 3.0 equiv.)

were added at 0 ºC. The reaction mixture was stirred for 1 h while warming to room temperature. The solvent was removed under vacuum and the iodonium salt **25d** (0.055 g, 1.0 equiv.) and dry DMF (2.5 mL) were added. The reaction was stirred for 16 h at 100 ºC. The solvent was removed under vacuum at 60 ºC and the crude was dissolved in EtOAc, filtered over a short pad of Celite® and concentrated under reduced pressure. The crude was used without further purification in the following step.

1-(2,6-Dimethylphenyl)-5-oxopyrrolidine-3-carboxamide (30).



Brownish solid. For the X-ray analysis the compound was purified by Al_2O_3 column chromatography (CH_2Cl_2/MeOH, 92.5/7.5 v/v) and recrystallised (CH_2Cl_2/*n*-hexane). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.17 (s, 3H), 2.21 (s, 3H), 2.79-2.85 (m, 1H), 2.90-2.95 (m, 1H), 3.30-3.36 (m, 1H), 3.72 (dd, *J* = 10.1, 8.6 Hz, 1H), 3.92 (dd, *J* = 10.1, 6.7 Hz, 1H), 7.09-7.11 (m, 2H), 7.14-7.17 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 17.89, 17.94, 34.7, 38.0, 50.9, 128.6, 129.0, 135.2, 135.9, 136.7, 171.9, 173.9. **IR ν(cm^{-1}):** 3407, 3207, 2921, 1679, 1650, 1483, 1277, 789, 612. **HRMS (ESI$^+$):** calc. for $[C_{13}H_{16}N_2NaO_2]^+$: 255.1104; found: 255.1107. **m.p.(ºC):** 215-217 ºC.

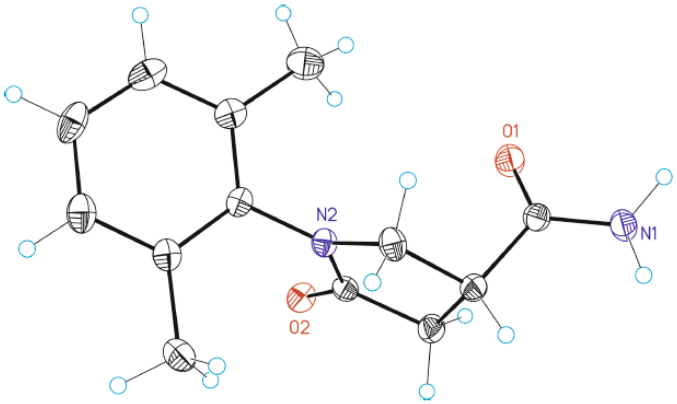
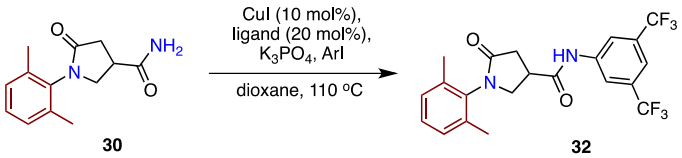


Table 2.4. Crystal data and structure refinement for **30**.

Identification code	mo_NL1678_0m
Empirical formula	C13 H16 N2 O2
Formula weight	232.28
Temperature	100(2) K

Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 9.2926(11)Å a= 90°. b= 10.7562(14)Å b = 105.593(4)°. c = 12.5718(16)Å g = 90°.
Volume	1210.3(3) $Å^3$
Z	4
Density (calculated)	1.275 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	496
Crystal size	0.20 x 0.12 x 0.08 mm^3
Theta range for data collection	2.439 to 28.724°.
Index ranges	-12<=h<=6,-14<=k<=14,-16<=l<=16
Reflections collected	14409
Independent reflections	3131[R(int) = 0.0503]
Completeness to theta =28.724°	99.7%
Absorption correction	Empirical
Max. and min. transmission	0.993 and 0.934
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3131/ 3/ 162
Goodness-of-fit on F^2	1.034
Final R indices [I>2sigma(I)]	R1 = 0.0491, wR2 = 0.1095
R indices (all data)	R1 = 0.0777, wR2 = 0.1235
Largest diff. peak and hole	0.315 and -0.225 $e.Å^{-3}$

***N*-(3,5-Bis(trifluoromethyl)phenyl)-1-(2,6-dimethylphenyl)-5-oxopyrrolidine-3-carboxamide (32).**



Scheme 2.29 Synthesis of the chemoreceptor **32**: Ullmann coupling.

In a flamed and dried Schlenk tube under argon atmosphere, 1-(2,6-dimethylphenyl)-5-oxopyrrolidine-3-carboxamide **30** (1.0 equiv.), potassium phosphate (2.0 equiv.) and CuI (10 mol%) were dissolved in 1.0 mL of dry dioxane. 1-Iodo-3,5-bis(trifluoromethyl)benzene **31** (1.2 equiv.) and racemic *trans*-1,2-diaminocyclohexane (20 mol%) were added and the reaction was stirred for 21 h at 110 ºC. The mixture was cooled down to room temperature, filtered over a short pad of Celite® and washed down with EtOAc before being concentrated under reduced pressure. The crude compound was purified by column chromatography (*n*-hexane/EtOAc, 3/7 v/v). Brownish solid, 45% yield over two steps (0.024 g). **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 2.15 (s, 3H), 2.17 (s, 3H), 2.69-2.85 (m, 2H), 3.55-3.62 (m, 1H), 3.71-3.75 (m, 1H), 3.81-3.86 (m, 1H), 7.10-7.18 (m, 3H), 7.79 (s, 1H), 8.29 (s, 2H), 10.8 (s, 1H). **^{19}F-NMR (376 MHz, DMSO-*d*$_6$):** δ = -61.8 (s, 6F). **^{13}C-NMR (125 MHz, DMSO-*d*$_6$):** δ = 17.2, 17.3, 33.6, 38.1, 50.2, 116.2-116.3 (m), 119.0-119.1 (m), 123.2 (q, $J_{C\text{-}F}$ = 272.8 Hz), 127.9, 128.2 (d, $J_{C\text{-}F}$ = 10.2 Hz), 130.8 (q, $J_{C\text{-}F}$ = 32.8 Hz), 135.7, 135.9, 136.2, 140.8, 171.4, 172.4. **IR ν(cm^{-1}):** 3293, 2925, 1671, 1382, 1276, 1130, 776. **HRMS (ESI^{+}):** calc. for $[C_{21}H_{18}F_6N_2NaO_2]^+$: 467.1165; found: 467.1181. **m.p.(ºC):** 233-235 ºC.

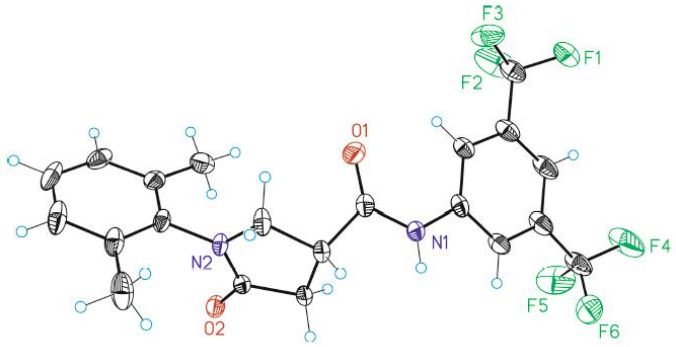
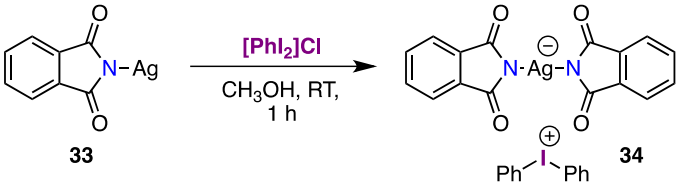


Table 2.5 Crystal data and structure refinement for **32**.

Identification code	mo_NL1699
Empirical formula	C21 H18 F6 N2 O2
Formula weight	444.37
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P2(1)/c
Unit cell dimensions	a = 11.1092(5)Å a= 90°. b = 16.8278(8)Å b = 95.0660(16)°. c = 10.6784(4)Å g = 90°.
Volume	1988.46(15) $Å^3$
Z	4
Density (calculated)	1.484 Mg/m^3
Absorption coefficient	0.134 mm^{-1}
F(000)	912
Crystal size	0.20 x 0.10 x 0.05 mm^3
Theta range for data collection	1.840 to 25.426°.
Index ranges	-13<=h<=12,-20<=k<=18,-12<=l<=12
Reflections collected	20676
Independent reflections	3561[R(int) = 0.0317]
Completeness to theta =25.426°	97.1%
Absorption correction	Multi-scan
Max. and min. transmission	0.993 and 0.764
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3561/ 18/ 282
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.1317
R indices (all data)	R1 = 0.0650, wR2 = 0.1399
Largest diff. peak and hole	0.712 and -0.417 $e.Å^{-3}$

Diphenyliodonium bis(1,3-dioxoisoindolin-2-yl)argentate(I) (34).



33 **34**

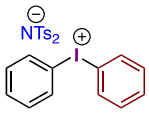
Scheme 2.30 Synthesis of the silver complex **34**.

To a stirred solution of diphenyliodonium chloride (0.05 g, 0.16 mmol) in methanol (2.0 mL) was added the silver phthalimide **33** (0.04 g, 0.16 mmol) and the reaction was

stirred at room temperature for 1 h. Then it was filtered over a short pad of Celite® washing with methanol, and the solvent was removed under reduced pressure. Compound **34** was afforded as yellow solid in 56% yield. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 7.48-7.52 (m, 5H), 7.61-7.67 (m, 8H), 8.19-8.21 (m, 5H). **^{13}C-NMR (125 MHz, DMSO-*d*$_6$):** δ = 118.4, 120.7, 130.9, 131.0, 131.7, 134.4, 135.8, 178.4. **IR ν(cm^{-1}):** 3190, 3049, 1773, 1650, 1440, 1305, 1090, 986, 679, 535. **HRMS (ESI$^+$):** calc. for $[C_{12}H_{10}I]^+$: 280.9822; found: 280.9818. **m.p.(ºC):** 160-163 ºC.

General procedure for the synthesis of diaryliodonium salts with bistosylamide as counter ion (GP11): A Schlenk tube equipped with a stirring bar was charged with PhI(OAc)(NTs_2) **35** (0.1 g, 0.17 mmol) and dry CH_2Cl_2 (2.0 mL) under argon atmosphere. In the order were added the arene (1.0 equiv.) and trifluoromethanesulfonic acid (1.0 equiv.) and the reaction mixture was stirred at room temperature for 24 h. The mixture was quenched with $NaHCO_3$ sat., extracted with CH_2Cl_2 (3 x 10 mL) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the crude oil was triturated with diethyl ether. The crystallisation was completed at 8 ºC.

Diphenyliodonium ditosylamide (36a).



Synthesised by GP11. Brownish solid, 82% yield. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 2.32 (s, 6H), 7.15 (d, *J* = 7.9 Hz, 4H), 7.50-7.58 (m, 8H), 7.65-7.71 (m, 2H), 8.22-8.24 (m, 4H). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** δ = 20.8, 116.5, 126.1, 128.1, 131.8, 132.0, 135.1, 139.4, 144.0. **IR ν(cm^{-1}):** 1127, 1108, 1076, 1030, 1009, 741, 662, 553. **HRMS (ESI$^+$):** calc. for $[C_{12}H_{10}I]^+$: 280.9822; found: 280.9829. **m.p.(ºC):** 201-203 ºC.

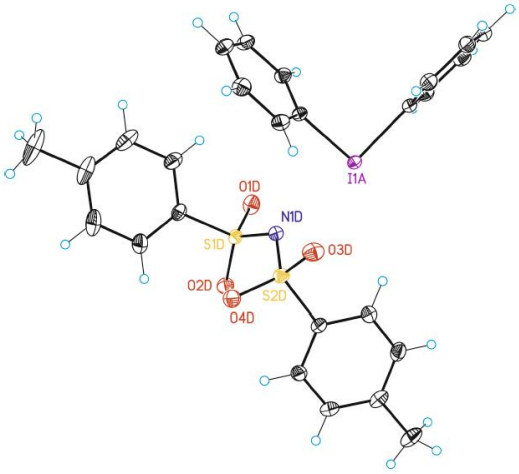
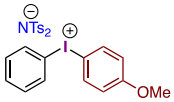


Table 2.6 Crystal data and structure refinement for **36a**.

Identification code	mo_NL209_0m
Empirical formula	C26 H24 I N O4 S2
Formula weight	605.48
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 13.0359(8)Å a = 80.703(2)°. b = 13.3667(8)Å b = 84.314(2)°. c = 14.4397(9)Å g = 85.978(2)°.
Volume	2467.0(3) $Å^3$
Z	4
Density (calculated)	1.630 Mg/m^3
Absorption coefficient	1.501 mm^{-1}
F(000)	1216
Crystal size	0.25 x 0.20 x 0.20 mm^3
Theta range for data collection	1.546 to 30.156°.
Index ranges	-18<=h<=18,-17<=k<=18,-18<=l<=20
Reflections collected	89262
Independent reflections	12850[R(int) = 0.0216]

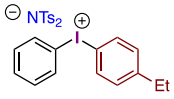
Completeness to theta =30.156°	88.1%
Absorption correction	Empirical
Max. and min. transmission	0.753 and 0.663
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12850/ 0/ 617
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma(I)]	R1 = 0.0203, wR2 = 0.0532
R indices (all data)	R1 = 0.0223, wR2 = 0.0550
Largest diff. peak and hole	1.369 and -0.624 e.Å^{-3}

(4-Methoxyphenyl)(phenyl)iodonium ditosylamide (36b).



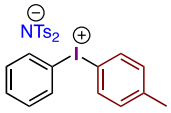
Synthesised by GP11. Brownish solid, 60% yield. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 2.31 (s, 6H), 3.79 (s, 3H), 7.05-7.09 (m, 2H), 7.13-7.15 (m, 4H), 7.50-7.54 (m, 6H), 7.63-7.67 (m, 1H), 8.16-8.20 (m, 4H). **^{13}C-NMR (125 MHz, DMSO-*d*$_6$):** δ = 20.8, 55.7, 105.3, 117.0, 117.5, 126.1, 128.1, 131.6, 131.8, 134.8, 137.2, 139.4, 144.0, 162.0. **IR ν(cm^{-1}):** 3055, 1488, 1269, 1140, 1069, 814, 749. **HRMS (ESI$^+$):** calc. for $[C_{13}H_{12}I]^+$: 310.9927; found: 310.9942. **m.p.(ºC):** 89-92 ºC.

(4-Ethylphenyl)(phenyl)iodonium ditosylamide (36c).



Synthesised by GP11. Brownish solid, 87% yield. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 1.15 (t, *J* = 7.6 Hz, 3H), 2.31 (s, 6H), 2.63 (q, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 4H), 7.36 (d, *J* = 8.9 Hz, 2H), 7.51-7.54 (m, 6H), 7.64-7.68 (m, 1H), 8.13-8.15 (m, 2H) 8.21-8.24 (m, 2H). **^{13}C-NMR (125 MHz, DMSO-*d*$_6$):** δ = 15.3, 21.0, 28.0, 113.2, 116.7, 126.3, 128.3, 131.4, 131.9, 132.1, 135.2, 135.4, 139.6, 144.1, 148.7. **IR ν(cm^{-1}):** 3052, 2970, 1404, 1151, 835, 706. **HRMS (ESI$^+$):** calc. for $[C_{14}H_{14}I]^+$: 309.0134; found: 309.0138. **m.p.(ºC):** 156-158 ºC.

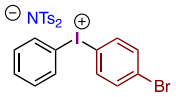
Phenyl(*p*-tolyl)iodonium ditosylamide (36d).



Synthesised by GP11. Brownish solid, 85% yield. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 2.32 (s, 6H), 2.34 (s, 3H), 7.14 (d, *J* = 8.0 Hz, 4H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.51-7.54 (m, 6H), 7.64-7.68 (m, 1H), 8.11-8.14 (m, 2H), 8.19-8.23 (m, 2H). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** δ = 20.82, 20.84, 112.9, 116.6, 126.1, 128.1, 131.7, 131.9, 132.4, 135.0, 135.1, 139.4, 142.6,

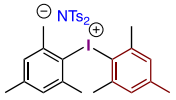
144.0. **IR ν(cm^{-1}):** 3052, 2919, 1581, 1126, 807, 741. **HRMS (ESI$^+$):** calc. for $[C_{13}H_{12}I]^+$: 294.9978; found: 294.9984. **m.p.(ºC):** 183-184 ºC.

(4-Bromophenyl)(phenyl)iodonium ditosylamide (36e).



Synthesised by GP11. Brownish solid, 79% yield. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 2.31 (s, 6H), 7.14 (d, *J* = 8.1 Hz, 4H), 7.51-7.56 (m, 6H), 7.66-7.70 (m, 1H), 7.73-7.78 (m, 2H), 8.15-8.19 (m, 2H), 8.23-8.27 (m, 2H). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** δ = 20.7, 114.9, 116.6, 125.9, 126.0, 128.0, 131.6, 132.0, 134.5, 135.0, 136.9, 139.3, 143.8. **IR ν(cm^{-1}):** 3058, 2920, 1597, 1136, 988, 763. **HRMS (ESI$^+$):** calc. for $[C_{12}H_9BrI]^+$: 358.8927; found: 358.8932. **m.p.(ºC):** 116-118 ºC.

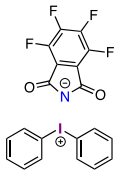
Dimesityliodonium ditosylamide (36g).



Synthesised by GP11. White crystals, 81% yield. **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 2.29 (s, 6H), 2.32 (s, 6H), 2.54 (s, 12H), 6.97-6.99 (m, 4H), 7.01 (4H), 7.52-7.54 (m, 4H). **^{13}C-NMR (100 MHz, CDCl$_3$):** δ = 21.1, 21.5, 26.4, 117.9, 126.9, 128.5, 130.8, 140.6, 141.9, 142.7, 143.5. **IR ν(cm^{-1}):** 2969, 2873, 1451, 1257, 1146, 1073, 1046, 759, 551. **HRMS (ESI$^+$):** calc. for $[C_{12}H_{10}I]^+$: 280.9822; found: 280.9829. **m.p.(ºC):** 135-136 ºC.

General procedure for the synthesis of diaryliodonium salts with tetrafluorophthalimide as counter ion (GP12): The potassium salt of tetrafluorophthalimide was prepared previously by stirring the amide (1.0 equiv.) with KH 35 wt% (1.0 equiv.) in dry THF for 1 h, while the temperature was slowly raised from 0 ºC to room temperature. A Schlenk tube equipped with a stirring bar was charged with $[Ph_2I]NTs_2$ (**36a**) (0.19 g, 0.29 mmol) and dry CH_2Cl_2 (20.0 mL) under argon atmosphere. The potassium salt of tetrafluorophthalimide (1.5 g, 5.8 mmol) was added and the slurry was stirred at room temperature overnight. The mixture was filtrated over a short pad of Celite® and washed down with dry CH_2Cl_2. After concentration under reduced pressure the crude oil was triturated with dry diethyl ether to afford the desired diphenyliodonium salt **37** as brownish solid in 34% yield.

Diphenyliodonium 4,5,6,7-tetrafluoro-1,3-dioxoisoindolin-2-ide (37).



^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ = 7.51 (t, *J* = 7.7 Hz, 4H), 7.62-7.66 (m, 2H), 8.22 (d, *J* = 7.7 Hz, 4H). **^{19}F-NMR (376 MHz, DMSO-*d*$_6$):** δ = -(144.38-144.43) (m, 2F), -(151.19-151.22) (m, 2F). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$, 313 K):** δ = 119.0 (m), 126.6, 128.6, 131.8, 135.4, 139.2-139.4 (m), 141.2-141.4 (m), 143.1-143.4 (m), 176.4. **IR ν(cm^{-1}):** 3052, 1639, 1615, 1489, 1262, 1063, 915, 731, 681, 556, 466. **HRMS (ESI^{+}):** calc. for $[C_{12}H_{10}I]^{+}$: 280.9822; found: 280.9825. **HRMS (ESI^{-}):** calc. for $[C_8F_4NO_2]^{-}$: 217.9871; found: 217.9873. **m.p.(ºC):** 139-141 ºC.

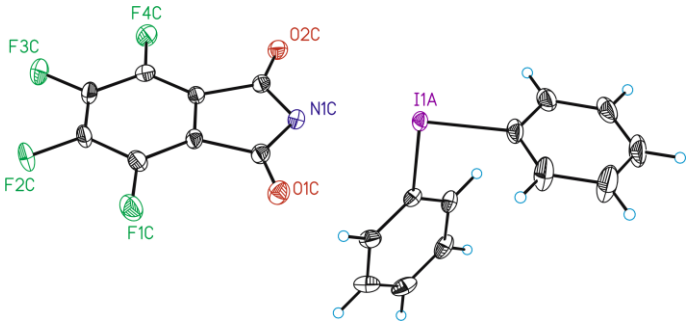


Table 2.7 Crystal data and structure refinement for **37**.

Identification code	mo_NL1064_0m
Empirical formula	C32 H20 Cl F4 I2 N O2
Formula weight	815.74
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 11.7732(10)Å a= 112.617(2)°. b = 12.2213(10)Å b = 105.411(2)°. c = 13.1241(10)Å g = 105.987(3)°.
Volume	1521.6(2) Å^3
Z	2
Density (calculated)	1.780 Mg/m^3

Absorption coefficient	2.209 mm^{-1}
F(000)	788
Crystal size	0.25 x 0.15 x 0.04 mm^3
Theta range for data collection	1.851 to 30.560°.
Index ranges	-16<=h<=15,-17<=k<=15,-12<=l<=18
Reflections collected	28705
Independent reflections	9225[R(int) = 0.0292]
Completeness to theta =30.560°	98.799995%
Absorption correction	Empirical
Max. and min. transmission	0.917 and 0.761
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9225/ 0/ 380
Goodness-of-fit on F^2	1.032
Final R indices [I>2sigma(I)]	R1 = 0.0269, wR2 = 0.0620
R indices (all data)	R1 = 0.0350, wR2 = 0.0664
Largest diff. peak and hole	1.164 and -0.695 e.$Å^{-3}$

Thermodynamic data for the reductive elimination reaction: To calculate the activation barrier for the reductive elimination, the reaction was carried out in a NMR tube using a mixture PhCl/1,2,4-trichlorobenzene (2/1, v/v), *N*,*N*-dimethyl-formamide-d_7 as reference, at different temperatures (353 K, 368 K, 373 K, 378 K) to determinate the corresponding reaction rates.

Chapter III

An Improved Catalyst for Iodine(I/III)-Catalysed Intermolecular Aromatic Aminations

3.1 Introduction

Aryl-λ^3-iodanes are known to promote oxidative transformations of a variety of functional groups such as olefins, alkynes, carbonyl compounds, alcohols, amines, amides, sulphoxides, alkyl halides and aromatic compounds.[1] They show mild, safe and environmentally friendly characteristics compared to the traditional heavy metal-based oxidants. Usually oxidations of this type involve the use of stoichiometric or excess amounts of iodine(III) reagents and, as consequence, release large amounts of aryl iodides as inevitable waste products resulting in special considerations for the purification steps. For these reasons, organoiodines are rarely utilised in scale processes. On the contrary, when the aryl iodide is selectively re-oxidised *in situ* to a hypervalent aryl-λ^3-iodane under the reaction conditions, a greener scenario is provided (Fig. 3.1).

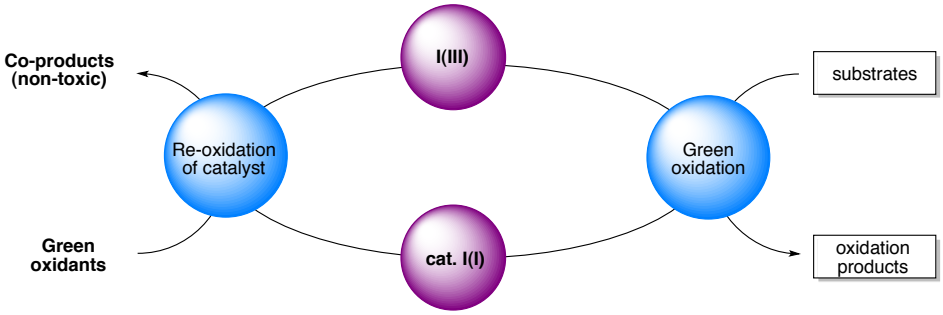
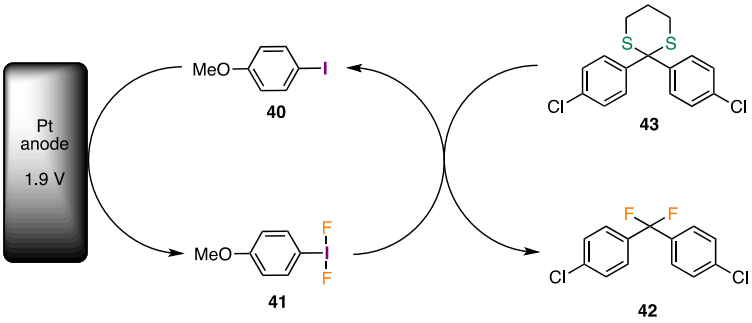


Figure 3.1 General behaviour for iodine(I/III) oxidations.

The work discussed in this chapter has already been published, see: Lucchetti, N.; Scalone, M.; Fantasia, S.; Muñiz, K. *Adv. Synth. Catal.* **2016**, *358*, 2093.

[1] For selected reviews, see: a) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402; b) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229; c) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086; d) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073.

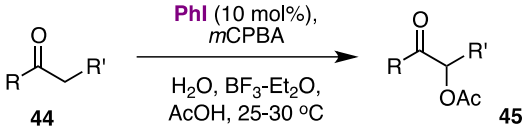
In 1994, Fuchigami and Fujita reported a pioneering study of iodobenzene-catalysed oxidations based on an electrochemical method (Scheme 3.1).[2] They performed the anodic *gem*-difluorination of cyclic dithioacetal **42** in the presence of 5 mol% of *p*-methoxyiodobenzene **40** and $Et_3N{\cdot}3HF$ as fluorine source.



Scheme 3.1 The first success of the catalytic approach under electrochemical conditions.

Under electrochemical conditions, the oxidation potentials of the catalysts have to be lower than those of the substrates and products in order to avoid any non-iodine(III)-involved background reactions. Hence, catalytic reactions are problematic when easily oxidisable substrates are utilised.

The first example of an iodobenzene-catalysed oxidation that generates active hypervalent phenyl-λ^3-iodanes *in situ* as primary oxidants by applying a second oxidant was presented by Ochiai.[3] The reaction provided an efficient route for the synthesis of α-substituted carbonyl compounds (Scheme 3.2).

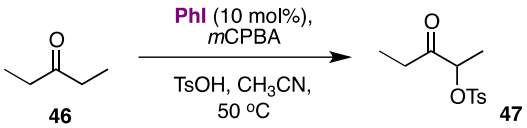


Scheme 3.2 Iodobenzene-catalysed α-acetoxylation of carbonyl compounds.

In this work, *m*-chloroperbenzoic acid (*m*CPBA) acted as a stoichiometric terminal oxidant in the PhI-catalysed α-acetoxylation of ketones where iodobenzene was oxidised to (diacetoxyiodo)benzene in acetic acid at room temperature. The hypervalent

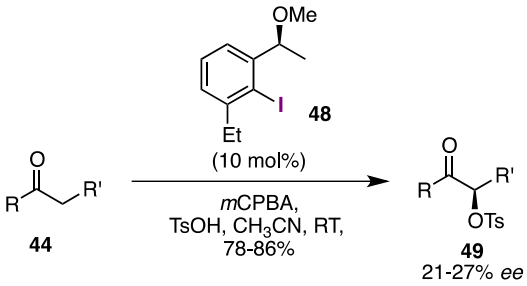
[2] a) Fuchigami, T.; Fujita, T. *J. Org. Chem.* **1994**, *59*, 7190; b) Fujita, T.; Fuchigami, T. *Tetrahedron Lett.* **1996**, *37*, 4725.
[3] a) Takeuchi, Y.; Sueda, T.; Ueda, E.; Ochiai, M. *Annual Meeting of the Pharmaceutical Society of Japan*, Nagasaki, **2003**; b) Ochiai, M.; Takeuchi, Y.; Katayama, T.; Sueda, T.; Miyamoto, K. *J. Am. Chem. Soc.* **2005**, *127*, 12244.

iodine(III) underwent a ligand-exchange with an enolate and a subsequent S_N2 displacement by acetic acid provided the final product regenerating iodobenzene, which restarted the catalytic cycle. In the absence of iodobenzene, only the Baeyer-Villiger product was observed. The regeneration of hypervalent iodine(III) species by inorganic oxidants and peracetic acid seemed, compared to *m*CPBA, to be not feasible due to uncontrolled background reactions. Moreover, *m*CPBA also served as oxidant in the iodobenzene-catalysed α-tosyloxylation of ketones **47** (Scheme 3.3).[4] A further improvement of this concept involved the use of iodobenzene supported on ionic liquids, which allowed the recovery of the catalysts.[5]



Scheme 3.3 Iodobenzene-catalysed α-tosyloxylation of carbonyl compounds.

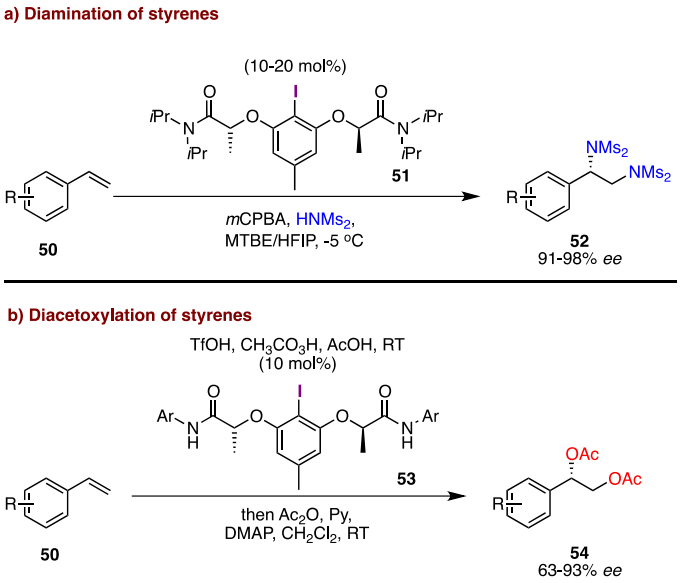
Wirth and co-workers described the first iodobenzene-catalysed enantioselective α-tosyloxylation of ketones using a chiral iodine(I) catalyst **48** (Scheme 3.4).[6] The enantioselectivity observed in this process was modest, but in good agreement with the previously developed stoichiometric protocol. This concludes that product **49** was exclusively formed through the catalytic pathway.



Scheme 3.4 Enantioselective iodobenzene-catalysed α-tosyloxylation of carbonyl compounds.

[4] a) Yamamoto, Y.; Togo, H. *Synlett* **2006**, 798; b) Yamamoto, Y.; Kawano, Y.; Toy, P. H.; Togo, H. *Tetrahedron* **2007**, *63*, 4680.
[5] Akiike, J.; Yamamoto, Y.; Togo, H. *Synlett* **2007**, 2168.
[6] a) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674; b) Richardson, R. D.; Page, T. K.; Altermann, S.; Paradine, S. M.; French, A. N.; Wirth, T. *Synlett* **2007**, 538.

Recently, Muñiz reported an elegant approach to diacetoxylated and diaminated styrenes in an enantioselective manner with up to 98% *ee*, using a new class of chiral iodine(I) catalysts (Scheme 3.5).[7]



Scheme 3.5 Enantioselective iodine(I)-catalysed a) diamination of styrenes, b) diacetoxylation of styrenes.

3.2 C–N bond formation with the stoichiometric use of hypervalent iodanes

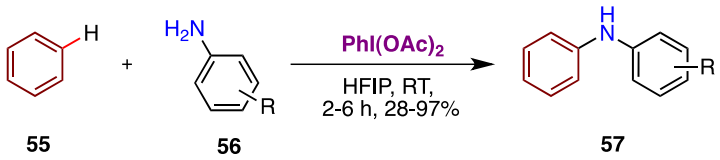
Among all the carbon-heteroatom bond formation reactions, C–N bond-forming methods are of huge importance due to the wide occurrence of nitrogen-containing compounds in natural products and in material science. Due to the necessity of greener protocols, metal-free and organocatalytic transformations attracted the attention of the academic and industrial communities. The direct oxidation of suitably functionalised

[7] a) Haubenreisser, S.; Wöste, T. H.; Martínez, C.; Ishihara, K.; Muñiz, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 413; b) Wöste, T. H.; Muñiz, K. *Synthesis* **2016**, *48*, 816; c) Muñiz, K.; Barreiro, L.; Romero, R. M.; Martínez, C. *J. Am. Chem. Soc.* **2017**, *139*, 4354.

amides by application of hypervalent iodine(III) reagents allows straightforward access to a variety of nitrogen-containing heterocycles.[8]

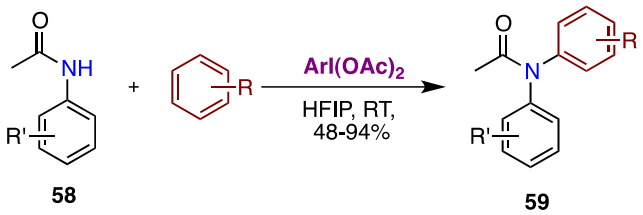
3.2.1 (Diacetoxy)iodoarenes

Antonchick developed a metal-free approach for the C−H bond amination of non-functionalised arenes with nitrogen-containing heterocycles for the synthesis of bioactive compounds (Scheme 3.6). Various hypervalent iodine(III) reagents were screened, where $PhI(OAc)_2$, when applied as stoichiometric oxidant, provided the aminated products **57** in the highest yield at room temperature.[9]



Scheme 3.6 Cross-dehydrogenative amination of arenes with amino heterocycles.

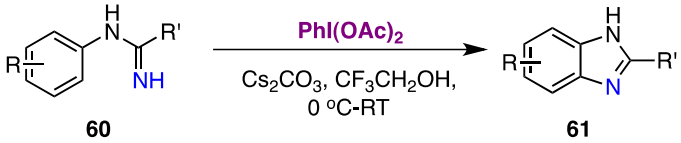
N-arylation and *para*-selective diarylation of acetanilides were obtained by cross coupling of arenes mediated by hypervalent iodine(III) (Scheme 3.7).[10] The desired products **59** were obtained regioselectively at ambient temperature, but the scope was limited to electron-rich substrates.



Scheme 3.7 Metal-free monoarylation and *para*-selective diarylation of acetanilides.

[8] For selected reviews, see: a) Samanta, R.; Antonchick, A. P. *Synlett* **2012**, *23*, 809; b) Samanta, R.; Matcha, K.; Antonchick, A. P. *Eur. J. Org. Chem.* **2013**, 5769; c) Narayan, R.; Manna, S.; Antonchick, A. P. *Synlett* **2015**, *26*, 1785; d) Muñiz, K. *Top. Curr. Chem.* **2016**, *373*, 105.
[9] Manna, S.; Serebrennikova, P. O.; Utepova, I. A.; Antonchick, A. P.; Chupakin, O. N. *Org. Lett.* **2015**, *17*, 4588.
[10] Samanta, R.; Lategahn, J.; Antonchick, A. P. *Chem. Commun.* **2012**, *48*, 3194.

Zhu and co-workers developed an alternative approach to Pd- and Cu-catalysed methods for the synthesis of 2-substituted benzimidazoles **61** by PIDA-mediated intramolecular oxidative imidation of C(sp^2)–H bonds from *N*-arylamidines **60** (Scheme 3.8).[11]



60 **61**

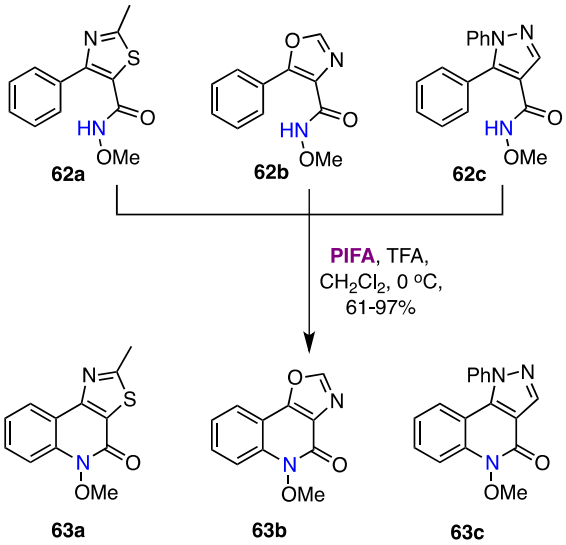
Scheme 3.8 PIDA-mediated oxidative intramolecular imidations.

Long reported a complementary approach to substituted benzimidazoles utilising *N*-benzyl-*N'*-phenyl benzimidamide and $PhI(OAc)_2$ in polar solvents. Moving to non-polar solvents, they observed the formation of substituted quinazolines.[12] Intramolecular C–N cyclisations of *N*-(biphenyl)pyridine-2-amines furnished the formation of 6-arylbenzimidazoles.[13]

3.2.2 [Bis(trifluoroacetoxy)iodo]benzene (PIFA)

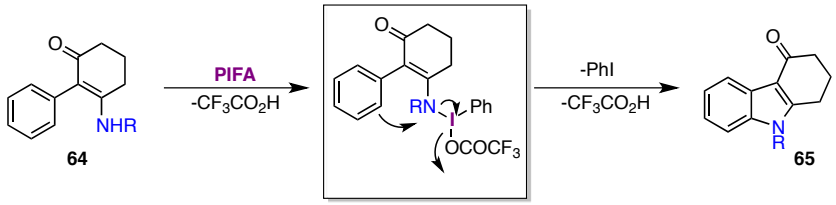
In 1984, Kikugawa reported an electrophilic aromatic substitution reaction that involved a *N*-chlorination step followed by an oxidative cyclisation using silver or zinc salts.[14] Alternatively, ferric chloride could be used with the same purpose.[15] Later, the limitations associated with these protocols were overcome by using the [bis(trifluoroacetoxy)iodo]benzene (PIFA) as promoter for the cyclisations. In 2002, Domínguez established a protocol for the synthesis of a number of heterocycle-fused quinolinones **63a**,**c** starting from the corresponding 1,2-phenyl-carbamoyl-substituted thiophenes, isoxazoles and pyrazoles **62a**,**c** by electrophilic amidation with [bis(trifluoroacetoxy)iodo]benzene in dichloromethane at 0 ºC (Scheme 3.9).[16]

[11] Huang, J.; He, Y.; Wang, Y.; Zhu, Q. *Chem. Eur. J.* **2012**, *18*, 13964.
[12] Lin, J.-P.; Zhang, F.-H.; Long, Y.-Q. *Org. Lett.* **2014**, *16*, 2822.
[13] Chu, J.-H.; Hsu, W.-T.; Wu, Y.-H.; Chiang, M.-F.; Hsu, N.-H.; Huang, H.-P.; Wu, M.-J. *J. Org. Chem.* **2014**, *79*, 11395.
[14] Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728.
[15] Cherest, M.; Lusinchi, X. *Tetrahedron Lett.* **1989**, *30*, 715.
[16] Tellitu, I.; Domínguez, E. *Synlett* **2012**, *23*, 2165.



Scheme 3.9 Preparation of heterocycle-fused quinolones **63a**,**c** using PIFA.

In 2009, a convenient approach to fused indeno-1,4-diazepinones through hypervalent iodine(III) chemistry was described.[17] Other PIFA-mediated syntheses of nitrogen-containing heterocycles include the preparations of *N*-substituted indoles,[18] 2-aminobenzimidazoles,[19] and carbazolones **65** (Scheme 3.10).[20]

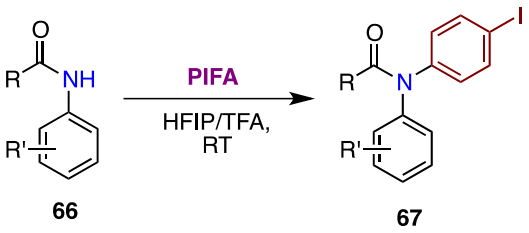


Scheme 3.10 PIFA-mediated synthesis of carbazolones **65**: proposed mechanism.

The reaction of anilides with phenyliodine(III) bis(trifluoroacetate) provided acetyldiarylamines in polar protic solvents (Scheme 3.11).[21] When the acyl group of the

[17] Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Hadjipavlou-Litina, D. *J. Org. Chem.* **2009**, *74*, 7315.
[18] Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919.
[19] Chi, Y.; Zhang, W.-X.; Xi, Z. *Org. Lett.* **2014**, *16*, 6274.
[20] Ban, X.; Pan, Y.; Lin, Y.; Wang, S.; Du, Y.; Zhao, K. *Org. Biomol. Chem.* **2012**, *10*, 3606.
[21] Itoh, N.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *J. Org. Chem.* **2002**, *67*, 7424.

anilide was strongly electronegative, the 4-iodophenyl group was transferred from PIFA to the nitrogen of the amide.

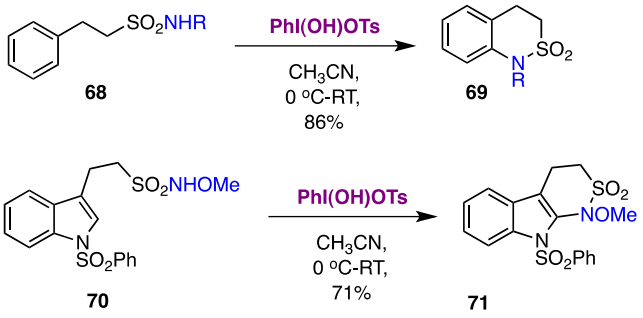


66 **67**

Scheme 3.11 PIFA-mediated arylation of anilides.

3.2.3 [Hydroxy(tosyloxy)iodo]arenes (Koser's reagent)

In 2003, Togo reported the cyclisation of sulphonamides **68** and **70** bearing an aromatic ring at the β-position utilising [hydroxyl(tosyloxy)iodo]arenes (Koser's derivatives). The C–H amination provided the corresponding 1,2-benzothiazine derivatives **69** and **71** (Scheme 3.12).[22]



68 **69** **70** **71**

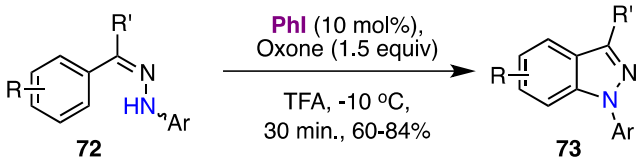
Scheme 3.12 [Hydroxy(tosyloxy)iodo]arenes-promoted syntheses of 1,2-benzothiazines **69**,**71**.

3.3 Iodine(I/III)-catalysed C–N functionalisations

The catalytic utilisation of hypervalent iodine reagents is a promising strategy to perform green chemical oxidations. For this reason, many studies were performed to replace the stoichiometric amounts of these oxidants by more economically and friendly alternatives. As nitrogen-containing heterocycles are structural motifs in many

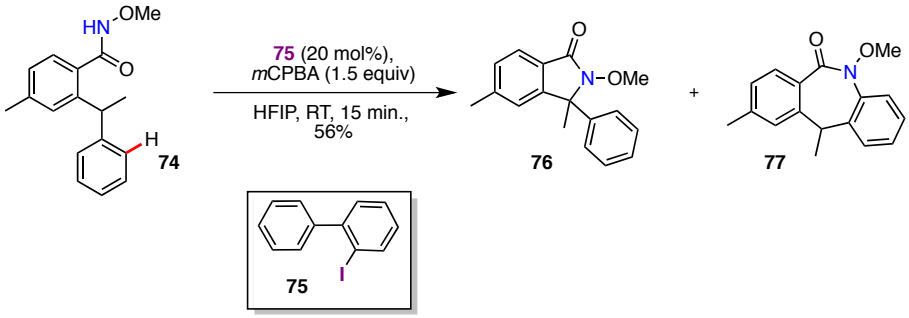
[22] Misu, Y.; Togo, H. *Org. Biomol. Chem.* **2003**, *1*, 1342.

biologically active molecules, Tanimori investigated a pathway to give facile access to 1*H*-indazoles **73** through iodobenzene-catalysed C−H amination (Scheme 3.13).[23] Arylhydrazones **72** were easily converted using PhI as catalyst with 10 mol% loading and oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as terminal oxidant in neat trifluoroacetic acid as solvent at -10 ºC.



Scheme 3.13 Cyclisation of hydrazones **72** to 1*H*-indazoles **73**.

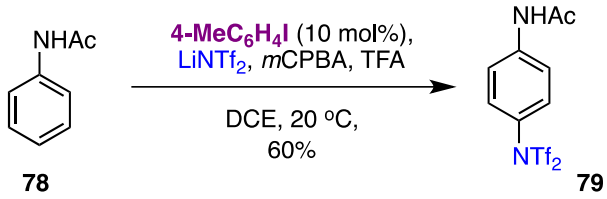
Moreover, iodine(I/III)-catalysed methodologies for the preparation of fused heterocycles include the syntheses of carbazoles,[24] benzimidazoles,[25] and pyrido[1,2-*a*]benzimidazoles.[26] In 2015, Shi and Houk reported an iodoarene-catalysed stereospecific intramolecular sp^3 and sp^2 amination protocols to furnish the formation of functionalised caprolactams **77** (Scheme 3.14).[27] Under the reaction conditions, a mixture of aminated products **76**/**77** with a ratio of 42/58 was observed upon oxidation of **74** indicating a small energy gap between the formations of the five- and seven-membered ring systems and the C(sp^3)−H and C(sp^2)−H activation, respectively.



Scheme 3.14 Chemoselectivity between sp^3 and sp^2 C−H aminations.

[23] Kashiwa, M.; Sonoda, M.; Tanimori, S. *Eur. J. Org. Chem.* **2014**, 4720.
[24] Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 8605.
[25] Alla, S. K.; Kumar, R. K.; Sadhu, P.; Punniyamurthy, T. *Org. Lett.* **2013**, *15*, 1334.
[26] He, Y.; Huang, J.; Liang, D.; Liu, L.; Zhu, Q. *Chem. Commun.* **2013**, *49*, 7352.
[27] Zhu, C.; Liang, Y.; Hong, X.; Sun, H.; Sun, W.-Y.; Houk, K. N.; Shi, Z. *J. Am. Chem. Soc.* **2015**, *137*, 7564.

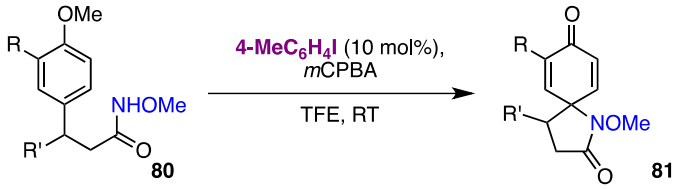
In contrast to the previously reported protocols for the *N*-arylation of anilides using stoichiometric amounts of hypervalent iodine(III) oxidants, Taillefer described an 4-iodotoluene-mediated *para*-functionalisation of **78** using lithium triflimide ($LiNTf_2$) as nitrogen source (Scheme 3.15).[28] In this process Li^+ acted as a weak Lewis acid to activate the hypervalent iodine(III) reagent towards the poorly electrophilic anilide starting materials **78**.



Scheme 3.15 *Para*-selective functionalisation of anilides **78**.

3.3.1 Spirocyclisations

In 2006, Kita reported the first hypervalent iodine(III)-catalysed spirocyclisation of amides to *N*-fused spirolactams.[29] Applying catalytic amounts of iodotoluene and *m*CPBA as terminal oxidant in 2,2,2-trifluoroethanol (TFE) solvent, five-membered spirodienone lactams **81** were obtained up to 83% yield (Scheme 3.16).

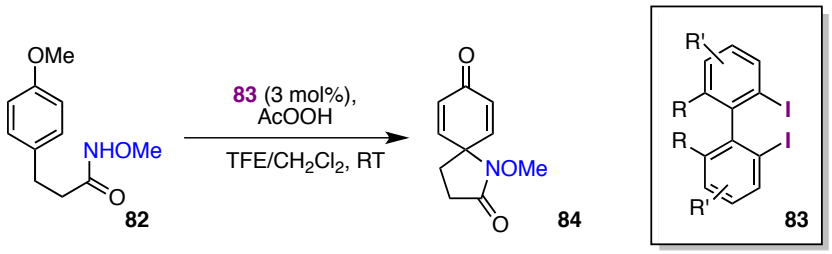


Scheme 3.16 The first iodoarene-catalysed C–N bond forming reaction.

Later, μ-oxo-bridged hypervalent iodine(III) compounds and their iodoarene precursors were screened in the oxidative spirocyclisations of amides.[30] The bis(iodoarene) pre-catalysts **83** showed a very promising catalytic activity in the presence of peracetic acid, whilst the general monoiodoarenes and the corresponding trivalent diacetates did not

[28] Pialat, A.; Bergès, J.; Sabourin, A.; Vinck, R.; Liégault, B.; Taillefer, M. *Chem. Eur. J.* **2015**, *21*, 10014.
[29] Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224.
[30] Dohi, T.; Takenaga, N.; Fukushima, K.; Uchiyama, T.; Kato, D.; Shiro, M.; Fujioka, H.; Kita, Y. *Chem. Commun.* **2010**, *46*, 7697.

work as efficiently in this transformation (Scheme 3.17). In 2017, Ciufolini reported a chiral spirocyclisation of sulphonamides using Ishihara's chiral lactate-based aryliodine.[31]



Scheme 3.17 Bis(iodo)arene-catalysed spirocyclisation of amides **82**.

3.4 Target of the project

The *status quo* in the field of oxidative metal-free C–N bond formation of aromatic substrates still allows further improvements regarding the application of iodine(I/III) catalysis. In this context, we were looking for an improved catalytic system that could enhance the turnover number of the intermolecular approach using less harsh conditions than those reported in the literature. At the same time, our goal was to increase the reaction scope by broadening the applicable substitution pattern, while improving the level of regioselectivity.

From a mechanistic viewpoint, our interest was to understand the active role of both iodine centres in the catalyst derived from type **83** during the electrophilic activation. For this reason, intermediary catalyst states should be isolated and successively characterised by X-ray diffraction.

3.5 Results and discussion

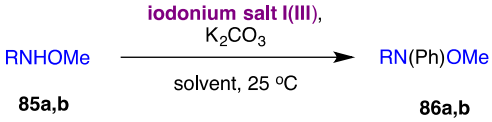
3.5.1 Optimisation studies

We started investigating the possible stoichiometric amination of arenes using preformed diaryliodonium salts with *N*-tosyl-*N*-methoxyamine **85a** as the most

[31] Jain, N.; Xu, S.; Ciufolini, M. A. *Chem. Eur. J.* **2017**, *23*, 4542.

promising nitrogen-coupling partner (Table 3.1).[32] The goal of this investigation was to obtain detailed insights on the transferability of different aryl groups in order to identify an optimum aryl monoiodine(I) catalyst.

Table 3.1 Stoichiometric amination using preformed diaryliodonium salts.



Entry	R	Iodine(III)	Solvent	Yield%[a]
1	Ts (**85a**)	$[Ph_2I]Cl$	DCE	73
2[b]	Ts (**85a**)	$[Ph_2I]Cl$	DCE	NR
3	Ts (**85a**)	$[Ph_2I]PF_6$	DCE	82
4	Ts (**85a**)	$[Ph_2I]OAc$	DCE	79
5	Ts (**85a**)	$[Ph_2I]NO_3$	DCE	77
6	Ts (**85a**)	[PhIAn]OTs[c]	DCE	63
7	Ts (**85a**)	[PhIAn]OTs	CH_2Cl_2	73
8	Ts (**85a**)	[PhIAn]OTs	$CHCl_3$	75
9	Ts (**85a**)	[PhIAn]OTs	TFE	NR
10	Ts (**85a**)	[PhIAn]OTs	HFIP	NR
11	Bn (**85b**)	$[Ph_2I]Cl$	DCE	38
12[b]	Bn (**85b**)	$[Ph_2I]Cl$	DCE	20

[a] = Isolated yields after purification. [b] = Reaction at 40 °C. [c] = An: 4-anisyl.
NR = no reaction

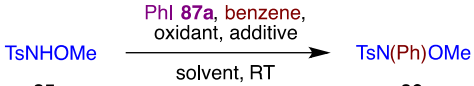
We started testing several iodonium salts,[33] which were either commercially available or known from literature. Only a small counter ion effect was observed during these studies. For diphenyliodoniums, the chloride anion furnished **85a** in 73% yield (entry 1) due to the reduced solubility, which could be increased by using hexafluorophosphate,

[32] For recent aminations with *N*-alkoxyamines, see: a) Sheradsky, T.; Nov, E. *J. Chem. Soc., Perkin Trans 1*, **1980**, 2781; b) Samanta, R.; Bauer, J. O.; Strohmann, C.; Antonchick, A. P. *Org. Lett.* **2012**, *14*, 5518; c) Yang, Y.; Wu, X.; Han, J.; Mao, S.; Qian, X.; Wang, L. *Eur. J. Org. Chem.* **2014**, 6854.
[33] Tinnis, F.; Stridfeldt, E.; Lundberg, H.; Adolfsson, H.; Olofsson, B. *Org. Lett.* **2015**, *17*, 2688.

acetate or nitrate derivatives (77-82% yields, entries 3-5). Chemoselective phenylation was detected with an unsymmetrical iodonium reagent containing 4-anisyl as arene ligand (entry 6). 1,2-Dichloroethane (DCE) was identified as the best solvent, while dichloromethane, chloroform and fluorinated solvents resulted in drastically reduced yields or no product formation at all (entries 7-10). Changing the protecting group on the nitrogen from tosyl to benzoyl (compound **85b**) provided a less efficient reaction to **86b** (entry 11). Reactions at higher temperature (40 ºC) resulted in reduced conversions. The base used in this process was not varied as the economic K_2CO_3 utilised in the previous reactions already led to high conversions.

Next, we looked for appropriate catalytic conditions for the corresponding iodine(III)-mediated arylamine formation. To this end, we investigated the influence of various oxidants, additives, solvents and temperatures on the reaction process using *N*-tosyl-*N*-methoxyamine **85a** as nitrogen source and iodobenzene **87a** as catalyst precursor. The reaction for the synthesis of **86a** was investigated for the direct C−H amination of benzene (Table 2). We tested the classic terminal oxidants for iodine(I/III) catalysis, using *m*CPBA, oxone or hydrogen peroxide in combination with different additives, but the formation of the desired product was not observed (entries 1-4). Only traces of **86a** were isolated, when peracetic acid was applied as oxidant and trifluoroacetic acid was used as addive in DCE (entry 10).

Table 3.2 Catalytic amination of benzene using iodobenzene as catalyst.



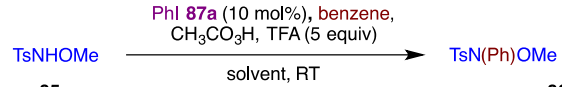
Entry	Oxidant	Additive	Solvent	Yield%[a]
1	*m*CPBA	TsOH	CH_2Cl_2	NR
2	*m*CPBA	TfOH	CH_2Cl_2	NR
3	Oxone	TsOH	CH_2Cl_2	NR
4	H_2O_2 35%	Ac_2O	CH_2Cl_2	NR
5	AcOOH 35%		CH_2Cl_2	NR
6	AcOOH 35%		HFIP	NR
7	AcOOH 35%		$CHCl_3$	NR
8	AcOOH 35%		DCE	NR
9	AcOOH 35%	AcOH	DCE	NR
10	AcOOH 35%	TFA	DCE	7

[a] = Isolated yields after purification. TFA = trifluoroacetic acid. NR = no reaction.

Once the most promising oxidant and additive were identified, we focused on the optimisation of the stoichiometry of the reagents and the reaction conditions (Table 3.3). With 2.5 equivalents of peracetic acid as oxidant, the reaction provided 46% yield of **86a**, when 10 equivalents of benzene were present (entry 2). Decreasing the amount of oxidant to 2.0 or 1.5 equivalents improved the yield to 55% (entries 3,4). Comparable results were obtained in the absence of DCE (benzene as solvent) or with 20 equivalents of benzene (entries 5,6). At this point fluorinated solvents, known to accelerate and facilitate the iodine(I/III) catalysis,[34] were tested. While the addition of 2,2,2-trifluoroethanol (TFE) provided a complex non-separable mixture, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) increased the yield to 70% (entry 8). Lowering the temperature and changing the ratio of DCE/HFIP from 1/1 v/v to 2/1 or 1/2 v/v had little effect (entries 9-11). Using an equimolar amount of oxidant led to a dramatic drop of the yield to 22% (entry 12).

[34] Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

Table 3.3 Catalytic amination of benzene using iodobenzene as catalyst: optimisation.

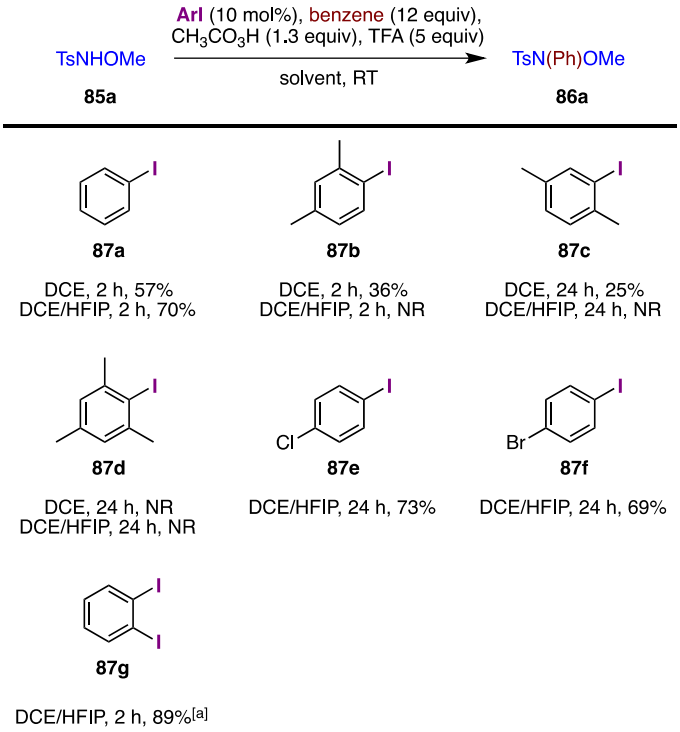


85a **86a**

Entry	CH_3CO_3H (eq)	C_6H_6 (eq)	Solvent	Temperature (°C)	Time (h)	Yield%[a]
1	2.5	10.0	-	40	23	9
2	2.5	10.0	DCE	RT	7	46
3	2.0	10.0	DCE	RT	3	55
4	1.5	10.0	DCE	RT	3	55
5	1.5	10.0	-	RT	3	52
6	1.5	20.0	DCE	RT	2	57
7	1.5	20.0	DCE/TFE	RT	18	Mixture
8	1.5	20.0	DCE/HFIP	RT	2	70
9	1.5	20.0	DCE/HFIP	0	16	73
10	1.5	20.0	DCE/HFIP 1/2	0	17	62
11	1.5	20.0	DCE/HFIP 2/1	0	17	68
12	1.0	10.0	DCE	RT	22	22

[a] = Isolated yields after purification.

Next, different sterically demanding iodine derivatives were investigated as catalysts in this transformation (Tab. 3.3). Under the optimised conditions these compounds were subjected to improve future C−H amination reactions with substituted iodoarenes (Scheme 3.18). Moreover, changing the substitution pattern and the electron density of the aromatic core of the catalysts, we desired to promote the re-oxidation and to improve the regioselectivity of the reaction. Iodoarenes bearing methyl substituents (**87b-d**) led to low performances due to over-oxidation of the pre-catalyst. While iodobenzene **87a** as standard formed **86a** in yields of 57% and 70% depending on the solvent mixture, dimethylated derivatives **87b** and **87c** reacted less efficiently in DCE and did not provide any product in the presence of HFIP. Iodomesitylene **87d** was observed to be entirely non-reactive. However, halogenated iodoarenes **87e** and **87f** led to comparable yields, although requiring significantly prolonged reaction times.



Scheme 3.18 Evaluation of iodoarenes for the catalytic amination of benzene with **85a**.
[a] = With 3 mol% catalyst loading. NR = no reaction.

Finally, the 1,2-diiodobenzene **87g** was found to be surprisingly efficient and furnished the reaction even at a reduced catalyst loading of 3 mol% in 89% yield within 2 h of reaction time. Increasing the catalyst loading of the 1,2-diiodobenze to 6 mol% or decreasing to 2 mol% did not lead to improved yields. Changing the additive from trifluoroacetic acid to NaOAc, TMSOTf or TMSCl led to no conversion. Interestingly, using TMSCl as mild Lewis acid for the activation of the iodine(III) species resulted in the formation of the dimeric form of the amide **85a** with a N−N single bond (Fig. 3.2).

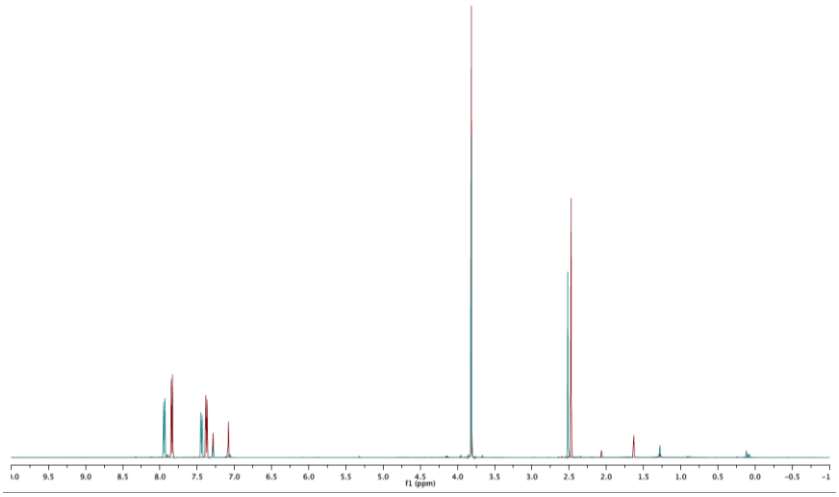
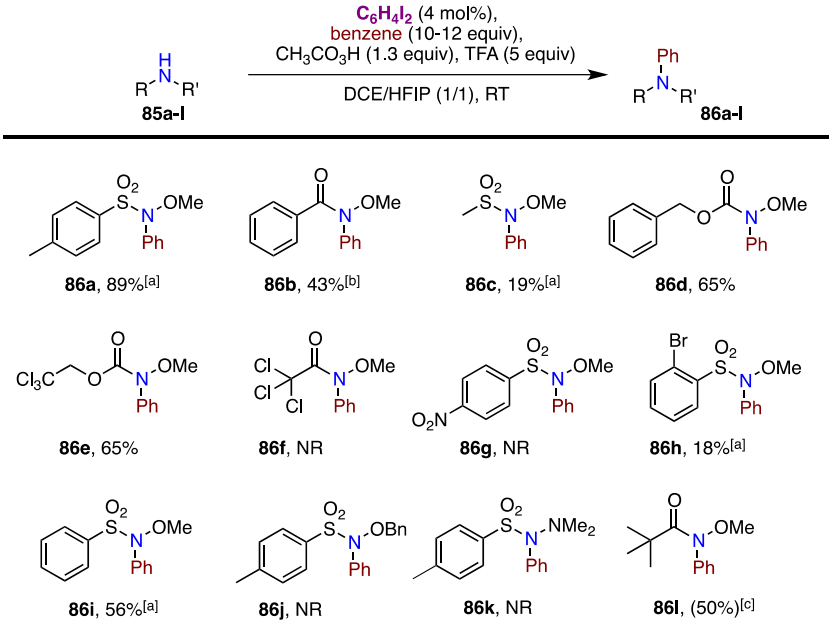


Figure 3.2 ^{1}H-NMR spectra for the reaction using TMSCl as Lewis acid additive: comparison between starting material (red) and new compound (green).

3.5.2 Reaction scope

At this point, different nitrogen sources were applied on the reaction utilising 1,2-diiodobenzene **87g** as catalyst (Scheme 3.19).



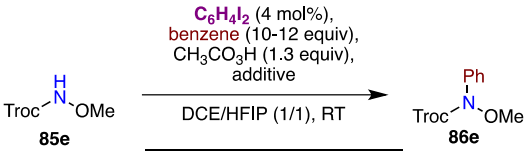
Scheme 3.19 Variation of nitrogen sources in the amination of benzene catalysed by **87g**. [a] = With 3 mol% catalyst loading. [b] = With 6 mol% catalyst loading. [c] = NMR conversion. NR = no reaction.

Various substituents at the nitrogen were well tolerated under the optimised conditions. The benzoyl-protected product **86b** was obtained in 43% yield when increasing the catalyst loading to 6 mol%. While the nosyl and 2-bromo sulphonyl derivatives (**86g,h**) gave low to no conversion due the destabilisation of the positively charged nitrogen intermediate, the phenylsulphonyl compound **86i** was obtained in 56% yield. The mesyl derivative **86c** gave a low yield of 19% due to low solubility of the substrate. Cbz and Troc carbamates **85d** and **85e** formed the corresponding products **86d** and **86e** in 65% yield. Replacing the *N*-methoxy group by a benzoyl or dimethylamino derivative (**86j**,**k**) did not result in any yields. The acetates **86f** and **86l** were not stable enough under the acidic reaction conditions, or then led to decomposition during the purification process. Although **86a** formed in the highest yield, further attempts using

different substituted arenes failed to give substantial regio- and chemoselectivity for this nitrogen source.

Due to the interesting deprotecting properties of the Troc group,[35] we first tried to improve the yield of **86e** by screening different additives (Table 3.4).

Table 3.4 Catalytic amination of benzene with **85e**: screening of additives.

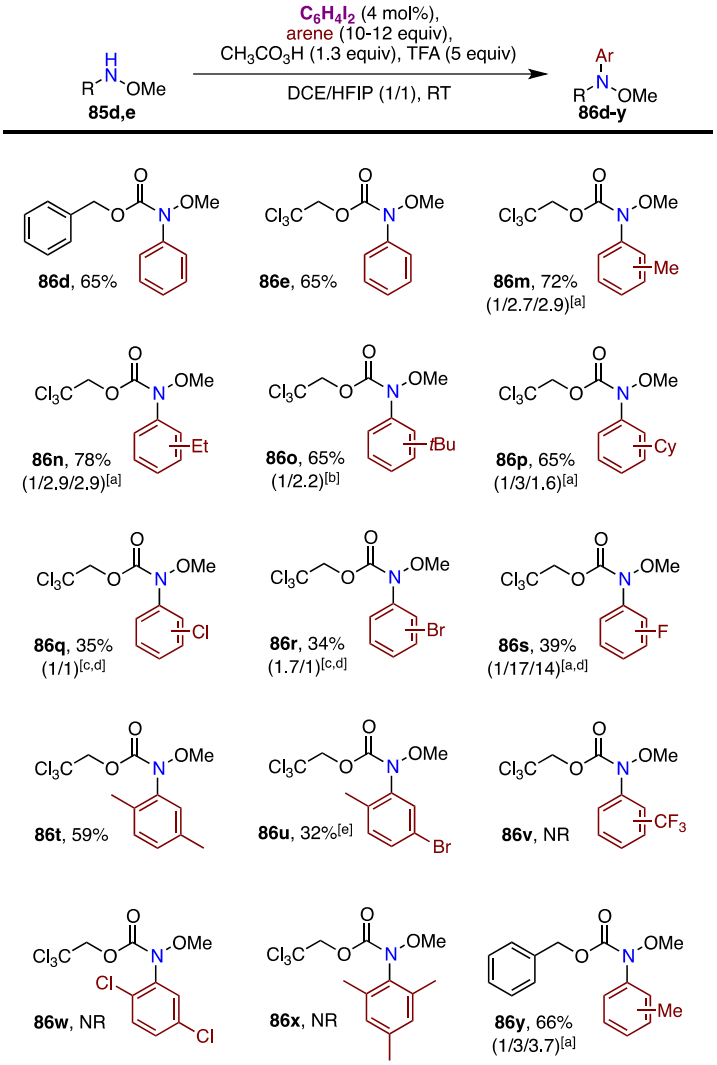


Entry	Additive	Yield%[a]
1	CCl_3CO_2H	NR
2	*m*CBA	NR
3	H_3PO_4 85%	NR
4	TMSCl	dimer
5	TFA	65
6[b]	TFA	23

[a] = Isolated yields after purification. [b] = Addition by syringe pump over 2 h.
TFA = trifluoroacetic acid. NR = no reaction.

Brønsted acids such as trichloroacetic acid, *meta*-chlorobenzoic acid and phosphoric acid were not successful additives in the formation of compound **86e (**entries 1-3). When TMSCl was used (entry 4), the N–N coupling product was obtained as in the case of *N*-tosyl-*N*-methoxyamine **85a** (see pag. 93). The best additive again was trifluoroacetic acid (entry 5). Slow addition of this acid by a syringe pump over 2 hours did not provide any improvement (entry 6). With the optimised conditions in hand, we then investigated the conversion of several arenes using carbamates **85d**,**e** as nitrogen sources (Scheme 3.20).

[35] For a previous report on copper-catalysed C–H amination with Troc-amides, see: John, A.; Byun, J.; Nicholas, K. M. *Chem. Commun.* **2013**, *49*, 10965.

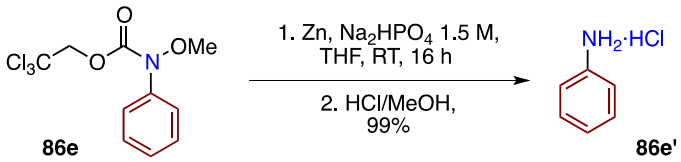


Scheme 3.20 Scope of the amine arylation catalysed by **87g**. [a] = Ratio of *o*,*m*,*p*-regioisomers (unseparated and undetermined regarding the position). [b] = Ratio of *m*,*p*-regioisomers (unseparated). [c] = The *o*,*p*-regioisomers were fully separated by column chromatography. [d] = Reaction temperature of 40 ºC. [e] = 2.0 equivs. of arene were used. NR = No reaction.

In the presence of 4 mol% of **87g** as catalyst, **85e** underwent several arylation reactions with different arene partners, which included hydrocarbons such as toluene, ethylbenzene, *tert*-butylbenzene and cyclohexylbenzene. The corresponding products **86m-p** were isolated in good yields (65-78%) and good regioselectivities. Halogenated arenes such as chlorobenzene, bromobenzene and fluorobenzene were also tolerated

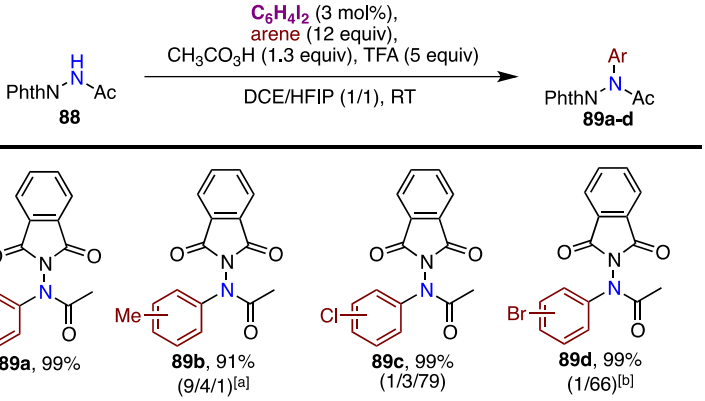
well. For the chloro **86q** and bromo derivatives **86r**, it was even possible to separate and isolate the regioisomers by column chromatography. However, trifluoromethylbenzene and 1,4-dichlorobenzene were too deactivated to undergo the reaction process. Disubstituted arenes also allowed the amination reaction to occur as demonstrated by compounds **86u**,**v**. Mesitylene did not represent a suitable substrate due to the oxidation of the aromatic system to phenol derivatives. In order to demonstrate other nitrogen sources to be applicable, Cbz derivative **85d** was arylated with toluene giving regioisomeric derivatives **86y** in an outcome comparable to that of **86m**.

Later, the attractiveness of Troc carbamate as nitrogen precursor was demonstrated by the deprotection of **86e** in a one-pot aminolysis reaction to form the aniline hydrochloride (**86e'**) in quantitative yield (Scheme 3.21).[36] Using elemental zinc as reagent, both the Troc group and the methoxy group were removed at the same time.



Scheme 3.21 One-pot deprotection of **86e** to aniline hydrochloride (**86e'**).

In order to compare the catalytic activity of 1,2-diiodobenzene (**87g)** with Antonchick's 2,2'-diiodo-biaryl-catalyst, *N*-acetylaminophthalimide **88** was used as nitrogen source (Scheme 3.22).



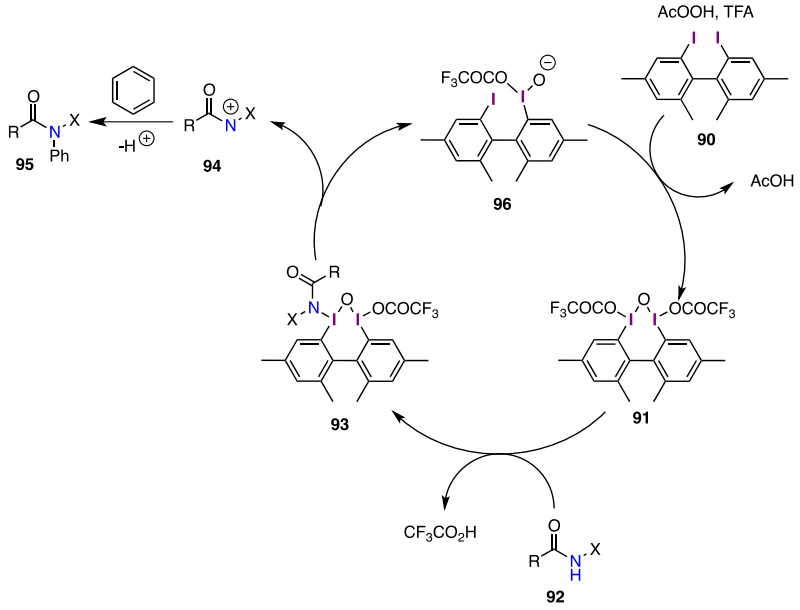
Scheme 3.22 Catalytic arylation of *N*-acetylaminophthalimide (**88**) with **87g** as catalyst. [a] = Ratio of *o*,*m*,*p*-regioisomers [b] = Ratio of *o*,*p*-regioisomers.

[36] Kim, S.; Park, J. O. *J. Org. Chem.* **1988**, *53*, 3111.

Excellent yields were obtained for the four C–N coupling products **89a-d** using benzene, toluene, chlorobenzene and bromobenzene. In addition, for **89c** and **89d** the 1,4-derivatives were predominantly isolated showing an excellent regioselectivity. These values surpass previous results and demonstrate the effectiveness of 1,2-diiodobenzene (**87g**) as powerful pre-catalyst in iodine(I/III) catalysis.

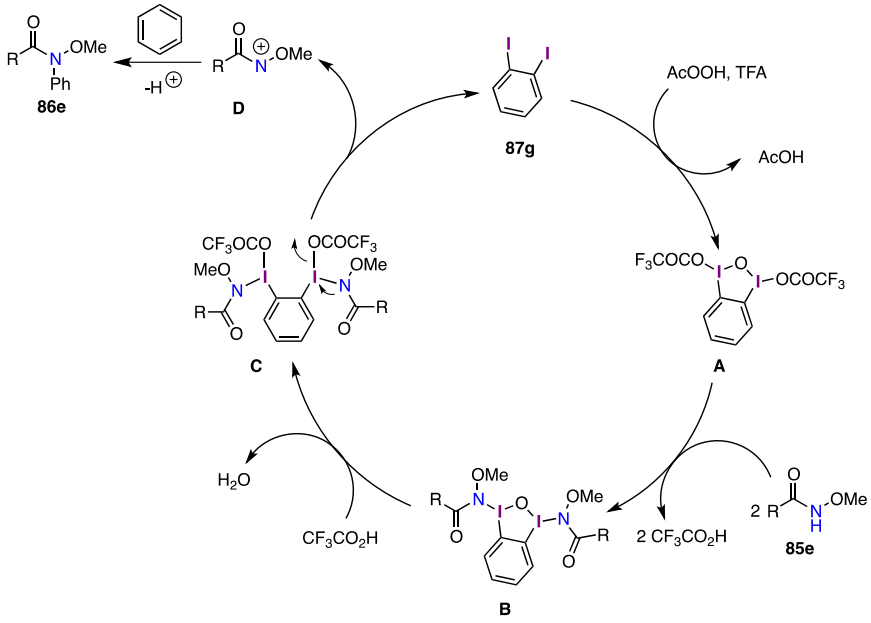
3.5.3 Mechanistic insights

In 2012, Antonchick proposed a plausible mechanism for iodine(I/III) intermolecular aminations with bisiodine pre-catalysts (Scheme 3.23). The Kita-type bisiodine pre-catalyst **90** is first oxidised by peracetic acid to form the active μ-oxo-bridged intermediate **91**. Ligand substitution at the iodine(III) by amide **92** then generates the intermediate **93**, where one of the trifluoroacetate ligands is displaced by the amino group. After oxidative fragmentation of **93**, a nitrenium ion **94** and the active specie **96** are formed. Later, **96** is re-oxidised to **91** under the reaction conditions. The positively charged species **94** undergoes a nucleophilic attack by the arene to furnish the final aniline product **95**.



Scheme 3.23 Antonchick's proposed mechanism for electrophilic aromatic amination involving the bisiodine pre-catalysts **90**.

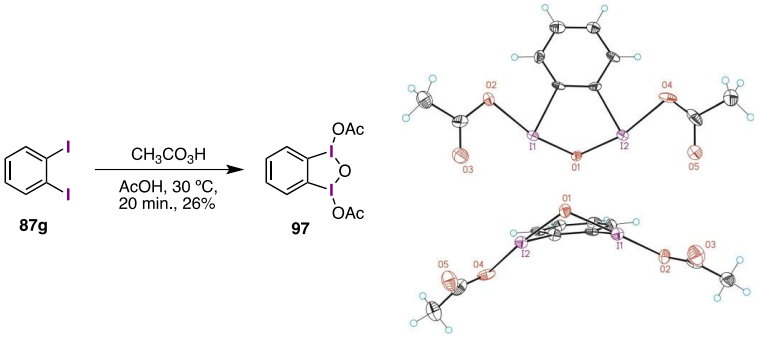
In contrast to this proposal, our idea was that both iodine atoms in the pre-catalyst should be playing an active role in the catalysis (Scheme 3.24). After the oxidation of **87g** to **A**, both iodine centres could coordinate to the amino group **85e** to generate the intermediate **B**. The protic trifluoroacetic acid can open the strained five-membered ring in **B** to form **C**, with subsequent elimination of H_2O and disappearance of the μ-oxo-bridged displacement. After oxidative fragmentation, nitrenium species **D** and **87g** are formed. Similar to Antonchick's proposal, the positive-charged species **D** is attacked by the nucleophilic arene to generate the final aniline product **86e**.



Scheme 3.24 Our mechanistic proposal based on experimental evidences.

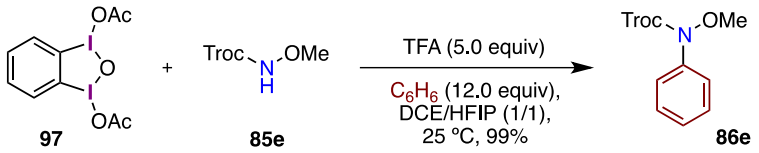
To gain mechanistic insights, the reaction of pre-catalyst 1,2-diiodobenzene (**87g**) with peracetic acid was investigated (Scheme 3.25). The oxidation[37] of 1,2-diiodobenzene (**87g**) provided the expected μ-oxo-bridged bisiodine(III) derivative **97**, which due to its high reactivity was isolated in only 26% yield.

[37] a) Wolf, W.; Chalekson, E.; Kobata, D. *J. Org. Chem.* **1967**, *32*, 3239; b) for the bis-tosylate analogue, see: Koser, G. F.; Wettach, R. H. *J. Org. Chem.* **1980**, *45*, 1542.



Scheme 3.25 Synthesis of μ-oxo-bridged bisiodine(III) derivative (**97**) and solid-state structure (ellipsoid at 50% probability), top and side views.

The structure of **97** shows mayor deviation from linearity for the central I−O−I group. The observed higher reactivity in the catalysis with **87g** may therefore result from the prominent strain of the five-membered μ-oxo-core. As demonstrated in the reaction scope, the diiodoaryl-catalyst **87g** shows a greater activity in comparison to other diiodine derivatives such as **90**, where the μ-oxo-arrengement forms an extended seven-membered ring system. To further elucidate the mechanism of the reaction, the pre-formed **97** was subjected to the phenylation of **85e** under conditions comparable to the catalysis approach (Scheme 3.26). The formation of **86e** as the only product was observed confirming that **97** was a real intermediate in the catalytic reaction process.



Scheme 3.26 Control experiment regarding the reactivity of **97**.

Importantly, when changing the ratio between **85e** and **97** to 2/1, we recovered less than 30% of unreacted nitrogen source **85e** (Figs. 3.3 and 3.4). In sharp contrast to earlier systems, both iodine(III) centres of **97** are capable of promoting arylation in the process. Moreover, clear evidences for supporting this mechanistic proposal were given, which strongly differs from earlier suggestions.

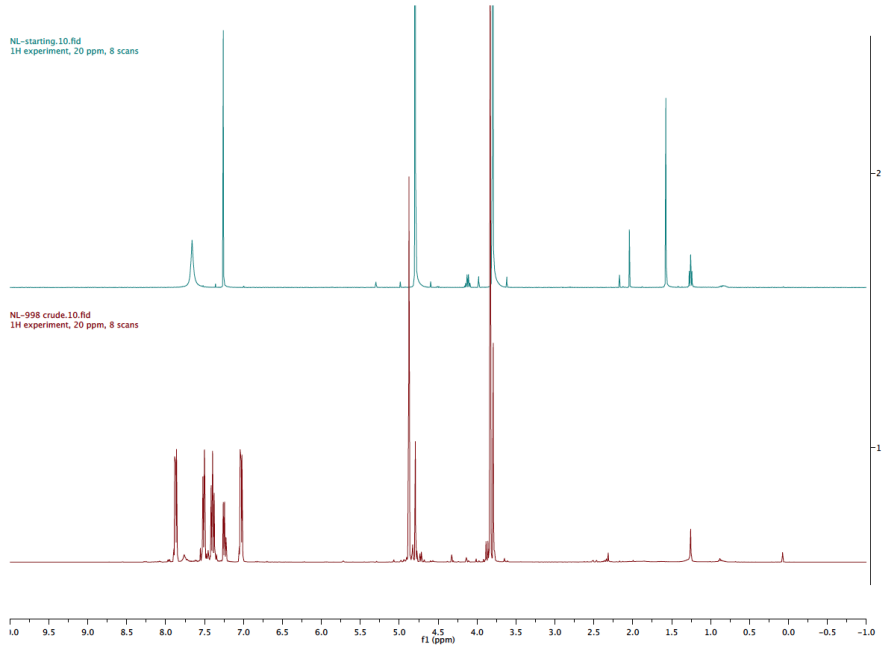


Figure 3.3 Comparison between ^{1}H-NMR spectra of Troc amino source **85e** (green) and reaction mixture performed with a ratio of **85e**/**97** 2/1 (red).

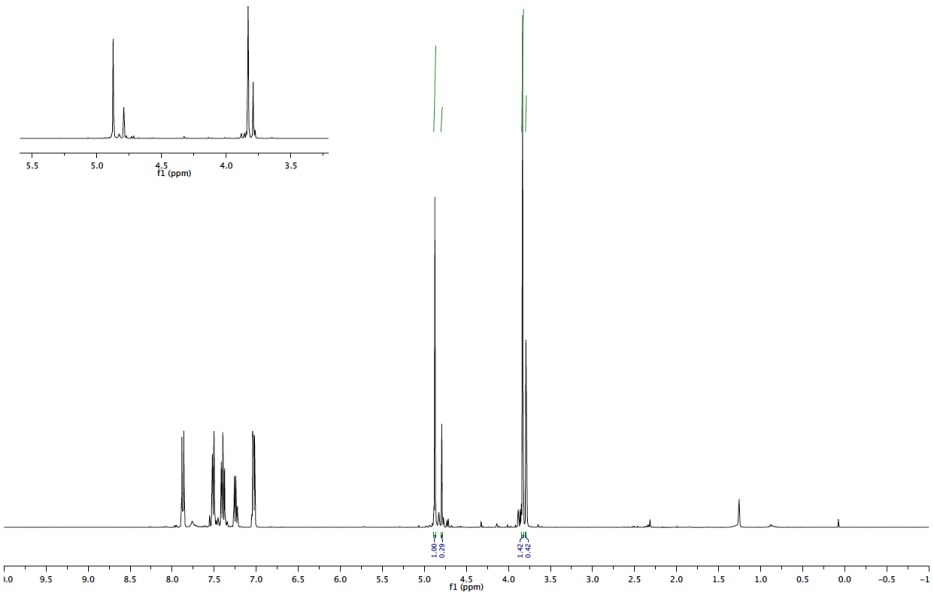
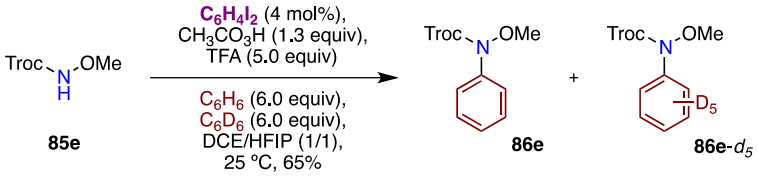


Figure 3.4 ^{1}H-NMR spectrum of the crude reaction mixture performed with a ratio of **85e**/**97** 2/1.

The opening of the five-membered I–O–I ring in **97** and therefore the arylation at the electrophilic iodine(III) centre is not rate-limiting as control experiments with C_6H_6 **86e** and C_6D_6 **86e**-d_5 suggested (Scheme 3.27). A value for the kinetic isotope effect (KIE) of 1.18 suggested that the arylation step is rather fast and therefore the C–H bond cleavage not rate-determining. This implies other events as the slow step of the overall catalysis, which may rest with the introduction of the amino source into the coordination sphere of the iodine(III) or with the final C–N bond formation.



Scheme 3.27 Control experiment: kinetic isotope effect.

3.6 Conclusions and remarks

In this Chapter we have described the use of a new bisiodine(I) pre-catalyst for the direct C–H amination of arenes. The 1,2-diidobenzene (**87g**) in its oxidised state had been known since 1967, but had not found application in catalysis until now. The reaction proceeded with exceptionally low catalyst loading (3-4 mol%) and under mild reaction conditions (peracetic acid as oxidant, TFA as additive at room temperature). It allowed the amination reaction of multiple nitrogen sources, including sulphonamides, carbamates and hydrazines, with up to 66/1 of regioisomeric control. From a mechanistic viewpoint, the active role of both iodine centres in the active species was confirmed, where the proposed mechanism is in sharp contrast to the previously reported mechanistic proposals. In fact, according to the experimental data (isolation of the reaction intermediates) we had to propose a different mechanism for the catalytic cycle, in disagreement with Antonchick's hypothesis.

3.7 Experimental section

General information: Column chromatography was performed with silica gel (Merck, type 60, 0.063-0.2 mm). NMR spectra were recorded on a Bruker Avance 300 MHz, 400 MHz or 500 MHz spectrometer and Varian Mercury 400 MHz. All chemical shifts in NMR experiments were reported as ppm downfield from TMS. The following

calibrations were used: $CDCl_3$ δ = 7.26 and 77.0 ppm, CD_3OD δ = 3.31 and 49.0 ppm, DMSO-d_6 δ = 2.50 and 39.5 ppm. GC analysis were performed using an Agilent 7890A GC system with a FID detector. An achiral HP-5 5% Phenyl Methyl Syloxan (30 m x 250 μm x 0.25 μm) column was used. Temperature range of 40–280 ºC, with a ramp of 10 ºC/min and a flow rate of 1.5 mL/min. MS (ESI) and HRMS experiments were performed on a Kratos MS 50 within the service centres at ICIQ. IR spectra were measured on a Bruker Alpha instrument in the solid state.

Materials: All solvents, reagents and deuterated solvents were purchased from Aldrich, TCI, Alfa Aesar, Fluorochem and Apollo Scientific commercial suppliers. The commercially available compounds were used as received. Diphenyliodonium acetate, diphenyliodonium nitrate and (4-methoxyphenyl)(phenyl)iodonium tosylate were synthesised according to procedures described previously in literature.[38]

General procedure for the synthesis of starting sulphonamides (GP1): Tosyl chloride (1.05 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5.0 mL) and *O*-methoxyhydroxylamine hydrochloride (1.0 equiv.) was added. Pyridine (2.0 equiv.) was added and the mixture was stirred at room temperature for 4 h. The mixture was quenched with water, extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. The final crude was triturated with *n*-hexane and filtered to afford the desired sulphonamide.

General procedure for the synthesis of starting sulphonamides (GP2): *O*-methoxyhydroxylamine hydrochloride (1.2 mmol, 1.0 equiv.) was dissolved in water (1.0 mL) at 0 ºC and potassium carbonate (1.0 equiv.) in water (1.0 mL) was added drop-wise. The internal temperature was maintained between 5 ºC and 15 ºC. The mixture was stirred for 15 min. and then THF (3.0 mL) and MeOH (0.75 mL) were added at temperature below to 15 ºC. The mixture was stirred while allowed warming to room temperature. The volatiles were removed under reduced pressure and the crude was extracted with diethyl ether (10 mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. The final crude was triturated with *n*-hexane and filtered to afford the desired sulphonamide.

[38] a) Beringer, F. M.; Galton, S. A.; Huang, S. J. *J. Am. Chem. Soc.* **1962**, *84*, 2819; b) Kazmierczak, P.; Skulski, L. *Synthesis* **1995**, *8*, 1027.

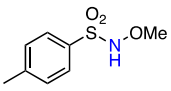
General procedure for the synthesis of starting carbamates (GP3):[39] *O*-methoxyhydroxylamine hydrochloride (1.2 mmol, 1.0 equiv.) was dissolved in water/benzene (1/1, v/v) and sodium carbonate (1.8 equiv.) was added and the mixture was cooled down to 0 ºC. Chloroformate (0.9 equiv.) was added and the mixture was stirred while allowed to warm to room temperature. The mixture was extracted with EtOAc (10 mL x 3), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the desired carbamate without further purifications.

General procedure for the synthesis of benzamides (GP4):[40] *O*-methoxyhydroxylamine hydrochloride (2.1 mmol, 1.0 equiv.) and potassium carbonate (2.0 equiv.) were dissolved in water/EtOAc (1/2, v/v) and the mixture was cooled down to 0 ºC. Benzoyl chloride (1.0 equiv.) was added drop-wise and the mixture was stirred while allowed warming to room temperature. The mixture was extracted with EtOAc (10 mL x 3), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (*n*-hexane/EtOAc, 1/1 v/v).

General procedure for the synthesis of starting acetamides (GP5): Acetyl chloride (2.4 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5.0 mL) and *O*-methoxyhydroxylamine hydrochloride (1.0 equiv.) was added and the mixture was cooled down to 0 ºC. Pyridine (2.0 equiv.) was added and the mixture was stirred while allowed warming to room temperature. The mixture was quenched with water, extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. The final crude was triturated with *n*-hexane and filtered to afford the desired acetamide.

General procedure for the synthesis of starting hydrazines (GP6): *N*-aminophthalimide (3.1 mmol, 1.0 equiv.) was dissolved in acetic anhydride (5.0 equiv.) and the mixture was stirred at 120 ºC for 1 h. The mixture was cooled to room temperature, filtered washing with Et_2O to afford the desired hydrazine.

***N*-Methoxy-4-methylbenzenesulphonamide (85a).**

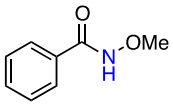


Synthesised according to GP1. Yellowish solid, 96% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.45 (s, 3H), 3.79 (s, 3H), 7.05 (bs, 1H),

[39] Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394.
[40] Wrigglesworth, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326.

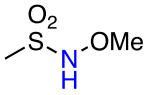
7.35 (d, *J* = 8.0 Hz, 2H), 7.80-7.83 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 21.4, 64.8, 128.2, 129.5, 133.2, 144.7. **IR ν(cm^{-1}):** 3220, 2964, 1595, 1330, 1162, 1044, 907, 819, 703, 545. **HRMS (ESI$^+$):** calc. for $[C_8H_{11}NNaO_3S]^+$: 224.0352; found: 224.0347. **m.p.(ºC):** 114-116 ºC.

_N_-Methoxybenzamide (85b).



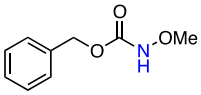
Synthesised according to GP4. Colourless solid, 65% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 3.82 (s, 3H), 7.36-7.40 (m, 2H), 7.46-7.50 (m, 1H), 7.73-7.76 (m, 2H), 9.67 (bs, 1H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 64.5, 127.3, 128.7, 131.9, 132.1, 166.6.

_N_-Methoxymethanesulphonamide (85c).



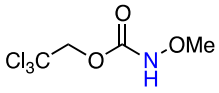
Synthesised according to GP2. White solid, 50% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.06 (s, 3H), 3.83 (s, 3H), 7.16 (bs, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 36.8, 65.4. **IR ν(cm^{-1}):** 3221, 1399, 1314, 1151, 917, 771, 690, 520, 483. **HRMS (ESI$^-$):** calc. for $[C_2H_6NO_3S]^-$: 124.0070; found: 124.0074. **m.p.(ºC):** 101-103 ºC.

Benzyl methoxycarbamate (85d).



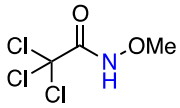
Synthesised according to GP3. Colourless oil, 99% yield. Data in agreement with those reported previously.[41] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.75 (s, 3H), 5.18 (s, 2H), 7.36-7.38 (m, 5H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 64.9, 67.7, 128.5, 128.6, 128.8, 135.7, 157.5.

2,2,2-Trichloroethylcarbamate (85e).



Synthesised according to GP3. White solid, 99% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 3.80 (s, 3H), 4.79 (s, 2H), 7.65 (bs, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 65.1, 74.9, 95.0, 155.5. **IR ν(cm^{-1}):** 3276, 2939, 1737, 1457, 1233, 1129, 813, 703, 558. **HRMS (ESI$^+$):** calc. for $[C_4H_6Cl_3NNaO_3]^+$: 243.9305; found: 243.9303. **m.p.(ºC):** 64-65 ºC.

2,2,2-Trichloro-_N_-methoxyacetamide (85f).

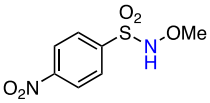


Synthesised according to GP5. Brownish solid, 76% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.88 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$):**

[41] Kukosha, T.; Trufilina, N.; Belyakov, S.; Katkevics, M. *Synthesis* **2012**, *44*, 2413.

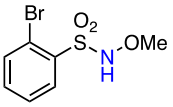
δ = 64.7, 159.1. **IR ν(cm^{-1}):** 3236, 2944, 1699, 1479, 937, 816, 757, 577. **HRMS (ESI$^+$):** calc. for $[C_3H_3Cl_3NNaO_2]^+$: 189.9235; found: 189.9238. **m.p.(ºC):** 66-68 ºC.

***N*-Methoxy-4-nitrobenzenesulphonamide (85g).**



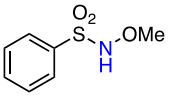
Synthesised according to GP1. Yellow solid, 86% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.85 (s, 3H), 7.20 (bs, 1H), 8.12-8.14 (m, 2H), 8.39-8.41 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 65.7, 124.4, 130.1, 142.3, 150.1. **IR ν(cm^{-1}):** 3226, 1527, 1344, 1311, 1167, 854, 742, 680, 555. **HRMS (ESI$^-$):** calc. for $[C_7H_7N_2O_5S]^-$: 231.0081; found: 231.0076. **m.p.(ºC):** 141-143 ºC.

2-Bromo-*N*-methoxybenzenesulphonamide (85h).



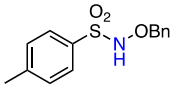
Synthesised according to GP1. Orange solid, 78% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.79 (s, 3H), 7.46 (td, *J* = 7.6, 2.0 Hz, 2H), 7.53 (td, *J* = 7.6, 1.6 Hz, 1H), 8.21 (dd, *J* = 7.7, 1.9 Hz, 1H), 8.04 (bs, 1H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 65.4, 119.9, 128.2, 133.6, 134.9, 135.2, 136.0. **IR ν(cm^{-1}):** 2936, 1367, 1177, 1024, 762, 571. **HRMS (ESI$^+$):** calc. for $[C_7H_8BrNNaO_3S]^+$: 287.9300; found: 287.9292. **m.p.(ºC):** 63-65 ºC.

***N*-Methoxybenzenesulphonamide (85i).**



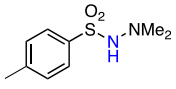
Synthesised according to GP2. White solid, 77% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 3.80 (s, 3H), 7.06 (bs, 1H), 7.54-7.58 (m, 2H), 7.64-7.68 (m, 1H), 7.93-7.95 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 65.3, 128.6, 129.2, 134.0, 136.7. **IR ν(cm^{-1}):** 3233, 1331, 1166, 905, 690, 665, 557. **HRMS (ESI$^-$):** calc. for $[C_7H_8NO_3S]^-$: 186.0230; found: 186.0231. **m.p.(ºC):** 80-82 ºC.

***N*-Benzyloxy-4-methylbenzenesulphonamide (85j).**



Synthesised according to GP1. White solid, 38% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.43 (s, 3H), 4.97 (s, 2H), 7.26-7.37 (m, 7H), 7.80-7.82 (d, *J* = 8.0 Hz, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 21.7, 128.5, 128.6, 128.7, 129.3, 129.8, 133.7, 135.3, 144.9.

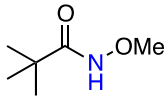
***N*',*N*'-4-Trimethylbenzenesulphonylhydrazide (85k).**



Synthesised according to GP1. Colourless solid, 65% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.40 (s, 6H), 2.45 (s, 3H), 5.14 (bs,

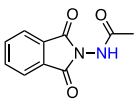
1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 21.6, 48.5, 128.2, 129.5, 135.8, 143.8.

***N*-Methoxypivalamide (85l).**



Synthesised according to GP5. Colourless oil, 83% yield. Data in agreement with those reported previously.[42] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.20 (s, 9H), 3.76 (s, 3H), 8.34 (bs, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 27.4, 38.1, 64.4, 176.4.

***N*-(1,3-Dioxoisoindolin-2-yl)acetamide (88).**



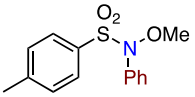
Synthesised according to GP6. White solid, 59% yield. **^{1}H-NMR (400 MHz, DMSO-*d*$_6$):** δ = 2.05 (s, 3H), 7.93-7.96 (m, 4H). **^{13}C-NMR (100 MHz, DMSO-*d*$_6$):** δ = 20.2, 123.7, 129.5, 135.3, 165.2, 168.6.

Stoichiometric synthesis of protected anilines using preformed diaryliodonium salts (GP7): The respective nitrogen source (0.15 mmol, 1.0 equiv.) was dissolved in 1,2-dichloroethane (0.5 mL), K_2CO_3 (1.0 equiv.) and diphenyliodonium hexafluorophosphate (1.0 equiv.) were added. The mixture was stirred at room temperature for 24 h and then washed with water, extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (*n*-hexane/EtOAc, 95/5 v/v).

Catalytic synthesis of protected anilines using catalyst 87g (GP8): The respective nitrogen source (0.15 mmol, 1.0 equiv.) was dissolved in a mixture of 1,2-dichloroethane and 1,1,1,3,3,3-hexafluoroisopropanol (1/1, v/v) (0.5 mL). 1,2-Diiodobenzene **87g** (3 mol%), benzene (12.0 equiv.), peracetic acid 35 wt% (1.3 equiv.) and trifluoroacetic acid (5.0 equiv.) were added in that order. The mixture was stirred at room temperature for the time indicated and then washed with water, extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane/EtOAc, 95/5 v/v).

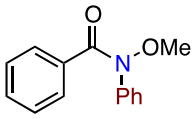
[42] Johnson, J. E.; Ghafouripour, A.; Haug, Y. K.; Cordes, A. W.; Pennington, W. T.; Exner, O. *J. Org. Chem.* **1985**, *50*, 993.

***N*-Methoxy-4-methyl-*N*-phenylbenzenesulphonamide (86a).**



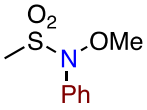
Synthesised according to GP7 as a yellowish solid in 82% yield. Synthesised according to GP8 in 89% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.41 (s, 3H), 3.88 (s, 3H), 7.10-7.12 (m, 2H), 7.20-7.21 (m, 2H), 7.23-7.27 (m, 3H), 7.40-7.42 (m, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 21.8, 64.4, 123.7, 127.6, 128.4, 129.1, 129.8, 130.2, 141.0, 144.8. **IR ν(cm^{-1}):** 2938, 1597, 1485, 1359, 1170, 1019, 813, 763, 692, 567, 541. **HRMS (ESI$^+$):** calc. for $[C_{14}H_{15}NNaO_3S]^+$: 300.0665; found: 300.0663. **m.p.(ºC):** 91-93 ºC.

***N*-Phenyl-*N*-methoxybenzamide (86b).**



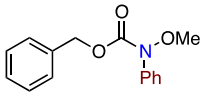
Synthesised according to GP7 as yellow oil in 38% yield. Synthetized according to GP8 using 1,2-diidobenzene (6 mol%) and benzene (10.0 equiv.) in 49% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 3.70 (s, 3H), 7.23-7.27 (m, 1H), 7.33-7.38 (m, 4H), 7.40-7.45 (m, 3H), 7.60-7.62 (m, 2H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 61.8, 124.5, 127.2, 128.1, 128.6, 129.1, 130.8, 134.7, 139.4, 168.2.

***N*-Methoxy-4-methyl-*N*-phenylbenzenesulphonamide (86c).**



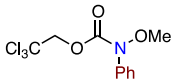
Synthesised according to GP7 as a yellowish solid in 82% yield. Synthesised according to GP8 in 19% yield. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 2.83 (s, 3H), 3.90 (s, 3H), 7.29-7.32 (m, 1H), 7.38-7.41 (m, 2H), 7.45-7.47 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 32.0, 64.5, 122.8, 127.8, 129.0, 140.8. **IR ν(cm^{-1}):** 3016, 1347, 1167, 1020, 967, 778, 534, 516. **HRMS (ESI$^+$):** calc. for $[C_8H_{11}NNaO_3S]^+$: 224.0352; found: 224.0347. **m.p.(ºC):** 57-59 ºC.

Benzyl methoxy(phenyl)carbamate (86d).



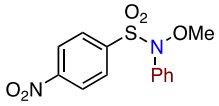
Synthesised according to GP7 as pale yellow oil in 63% yield. Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and benzene (10.0 equiv.) in 65% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.77 (s, 3H), 5.29 (s, 2H), 7.18-7.23 (m, 1H), 7.34-7.43 (m, 7H), 7.47-7.51 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 62.4, 68.0, 122.0, 126.0, 128.2, 128.4, 128.7, 128.9, 136.0, 139.6, 154.3.

2,2,2-Trichloroethyl methoxy(phenyl)carbamate (86e).



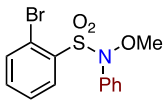
Synthesised according to GP7 as yellow oil in 46% yield. Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and benzene (10.0 equiv.) in 65% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.83 (s, 3H), 4.88 (s, 2H), 7.23-7.26 (m, 1H), 7.38-7.42 (m, 2H), 7.50-7.53 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 62.6, 75.4, 95.2, 122.4, 126.6, 129.0, 138.8, 152.6. **IR ν(cm^{-1}):** 2936, 1719, 1379, 1337, 1117, 712, 690, 568. **HRMS (ESI$^+$):** calc. for $[C_{10}H_{10}Cl_3NNaO_3]^+$: 319.9609; found: 319.9618.

***N*-Methoxy-4-nitrophenylbenzenesulphonamide (86g).**



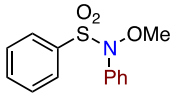
Synthesised according to GP7 as yellowish solid in 12% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.93 (s, 3H), 7.08-7.10 (m, 2H), 7.26-7.29 (m, 3H), 7.69-7.72 (m, 2H), 8.25-8.26 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 64.8, 123.3, 123.6, 128.3, 128.8, 131.0, 138.7, 140.1, 150.9. **IR ν(cm^{-1}):** 2939, 1525, 1345, 1178, 1016, 854, 739, 694, 567. **HRMS (ESI$^+$):** calc. for $[C_{13}H_{12}N_2NaO_5S]^+$: 331.0359; found: 331.0357. **m.p.(ºC):** 166-168 ºC.

2-Bromo-*N*-methoxy-*N*-phenylbenzenesulphonamide (86h).



Synthesised according to GP8 as pale yellow oil in 18% yield. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.76 (s, 3H), 7.26-7.33 (m, 5H), 7.40 (td, *J* = 7.4, 1.8 Hz, 2H), 7.72-7.74 (m, 1H), 7.85 (dd, *J* = 7.6, 2.1 Hz, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 63.8, 122.6, 124.5, 127.3, 128.2, 128.7, 133.9, 134.4, 134.6, 135.9, 139.9. **IR ν(cm^{-1}):** 2936, 1367, 1177, 1024, 762, 571. **HRMS (ESI$^+$):** calc. for $[C_{13}H_{12}BrNNaO_3S]^+$: 363.9616; found: 363.9624.

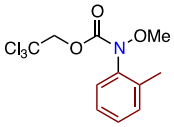
***N*-Methoxy-*N*-phenylbenzenesulphonamide (86i).**



Synthesised according to GP8. Yellow solid, 56% yield. Data in agreement with those reported previously.[43] **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.89 (s, 3H), 7.08-7.11 (m, 2H), 7.22-7.26 (m, 3H), 7.39-7.43 (m, 2H), 7.52-7.54 (m, 2H), 7.57-7.61 (m, 1H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 64.4, 123.6, 127.7, 128.4, 129.7, 133.1, 133.8, 140.8.

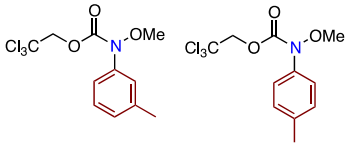
[43] Conway, T. T.; DeMaster, E. G.; Lee, M. J. C.; Nagasawa, H. T. *J. Med. Chem.* **1998**, *41*, 2903.

3,3,3-Trichloro-*N*-methoxy-*N*-(*o*-tolyl)propanamide (86m).



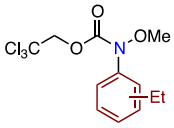
Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and toluene (10.0 equiv.) as a pale yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.34 (s, 3H), 3.79 (s, 3H), 4.83 (s, 2H), 7.23-7.32 (m, 4H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 18.0, 62.1, 75.2, 95.3, 126.6, 128.2, 129.4, 131.2, 136.7, 137.2, 153.5. **IR ν(cm^{-1}):** 2934, 1722, 1234, 1108, 758, 712, 569. **HRMS (ESI$^+$):** calc. for $[C_{11}H_{12}Cl_3NNaO_3]^+$: 333.9775; found: 333.9778.

3,3,3-Trichloro-*N*-methoxy-*N*-(*m*-tolyl)propanamide and 3,3,3-trichloro-*N*-methoxy-*N*-(*p*-tolyl)propanamide (86m).



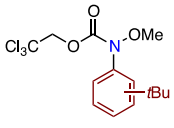
Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and toluene (10.0 equiv.) as a pale yellow oil in a non-separated regioisomeric mixture *m*/*p* 1.0/6.0. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = (*Para*-regioisomer) 2.36 (s, 3H), 3.81 (s, 3H), 4.86 (s, 2H), 7.18-7.22 (m, 2H), 7.35-7.39 (m, 2H). **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = (*Meta*-regioisomer) 2.38 (s, 3H), 3.82 (s, 3H), 4.87 (s, 2H), 7.05-7.08 (m, 1H), 7.27-7.34 (m, 3H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 21.1, 21.6, 62.4, 62.6, 75.3, 75.4, 95.2, 95.3, 119.7, 123.1, 123.3, 127.5, 128.9, 129.6, 136.2, 136.9, 138.6, 139.0, 152.6, 152.7.

3,3,3-Trichloro-*N*-(ethylphenyl)-*N*-methoxypropanamide (86n).



Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and ethylbenzene (15.0 equiv.) as yellow oil in 78% yield. Undefined ratio of regioisomers of 2.9/1.0/2.9. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.22-1.28 (m, 9H), 2.61-2.74 (m, 6H), 3.79 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 4.82 (s, 2H), 4.87 (m, 4H), 7.09-7.42 (m, 12H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 15.5, 15.6, 28.5, 28.9, 62.4, 62.5, 75.3, 95.2, 95.3, 119.9, 122.2, 123.0, 126.3, 128.4, 128.8, 136.3, 138.7, 143.1, 145.3, 152.6, 152.7.

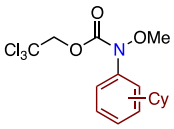
***N*-((*Tert*-butyl)phenyl)-3,3,3-trichloro-*N*-methoxypropanamide (86o).**



Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and *tert*-butyl benzene (15.0 equiv.) as yellow oil in 65% yield. Undefined ratio of regioisomers of 1.0/1.8/4.8. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 1.33 (s, 9H), 1.34 (s, 9H), 3.83 (s, 3H), 4.87 (s, 2H), 4.88 (s, 2H), 7.28-7.33 (m, 2H), 7.39-7.44 (m, 4H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 31.41, 31.44, 31.5, 34.7, 35.0, 36.1, 60.3, 62.5, 75.2, 75.3, 75.4, 95.2, 95.3, 95.4, 120.1,

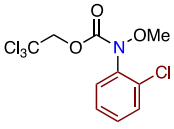
122.3, 124.0, 125.9, 126.5, 128.6, 129.2, 130.1, 132.1, 134.6, 136.1, 138.5, 149.2, 149.8, 152.4, 152.7, 152.8.

3,3,3-Trichloro-*N*-(cyclohexylphenyl)-*N*-methoxypropanamide (86p).



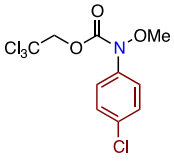
Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and cyclohexylbenzene (15.0 equiv.) as yellow oil in 65% yield. Undefined ratio of regioisomers of 1.0/1.6/3.0. **^{1}H-NMR ($CDCl_3$, 500 MHz)** δ = 1.23-1.46 (m, 16H), 1.73-1.90 (m, 16H), 2.48-2.52 (m, 2H), 2.77-2.82 (m, 1H), 3.78 (s, 3H), 3.82 (m, 6H), 4.84-4.87 (m, 6H), 7.21-7.41 (m, 12H). **^{13}C-NMR ($CDCl_3$, 125 MHz)** δ = 26.23, 26.24, 26.3, 26.96, 26.98, 27.0, 34.50, 34.54, 38.9, 44.3, 44.7, 61.7, 62.5, 62.6, 75.2, 75.3, 75.4, 95.25, 95.30, 95.5, 122.9, 126.3, 127.4, 127.8, 128.8, 128.9, 129.9, 135.7, 136.4, 138.7, 146.6, 146.9, 149.2, 152.7, 152.8, 153.8.

3,3,3-Trichloroethyl-2-chlorophenyl(methoxy)carbamate (86q).



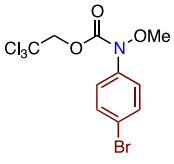
Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%), peracetic acid 35 wt% (1.5 equiv.) and chlorobenzene (15.0 equiv.) warming at 40 °C, as yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ = 3.86 (s, 3H), 4.83 (s, 2H), 7.32-7.38 (m, 2H), 7.44-7.46 (m, 1H), 7.48-7.52 (m, 1H). **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ = 62.9, 75.5, 95.0, 122.7, 130.0, 130.5, 130.7, 133.4, 136.5, 153.3. **IR ν(cm^{-1}):** 2936, 1729, 1236, 1111, 715, 569. **HRMS (ESI$^+$):** calc. for $[C_{10}H_{10}Cl_4NNaO_3]^+$: 353.9229; found: 353.9231.

3,3,3-Trichloroethyl-4-chlorophenyl(methoxy)carbamate (86q).



Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%), peracetic acid 35 wt% (1.5 equiv.) and chlorobenzene (15.0 equiv.) warming at 40 °C, as yellow oil. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.83 (s, 3H), 4.87 (s, 2H), 7.34-7.38 (m, 2H), 7.43-7.48 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 62.8, 75.5, 95.0, 123.2, 129.1, 131.8, 137.4, 152.4. **IR ν(cm^{-1}):** 2936, 1722, 1485, 1324, 1112, 787, 716, 570. **HRMS (ESI$^+$):** calc. for $[C_{10}H_{10}Cl_4NNaO_3]^+$: 353.9229; found: 353.9234.

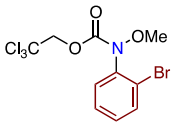
***N*-(4-Bromophenyl)-3,3,3-trichloro-*N*-methoxypropanamide (86r).**



Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%), peracetic acid 35 wt% (1.5 equiv.) and bromobenzene (15.0 equiv.) warming at 40 °C, as a pale yellow oil. **^{1}H-NMR (500 MHz,**

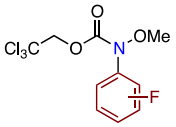
$CDCl_3$): δ = 3.83 (s, 3H), 4.87 (s, 2H), 7.40-7.42 (m, 2H), 7.50-7.52 (m, 2H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 62.8, 75.5, 95.0, 119.6, 123.4, 129.2, 138.0, 152.3. **IR ν(cm^{-1}):** 2936, 1722, 1486, 1378, 1325, 1112, 824, 787, 717, 570. **HRMS (ESI^+):** calc. for $[C_{10}H_9BrCl_3NNaO_3]^+$: 397.8724; found: 397.8717.

***N*-(2-Bromophenyl)-3,3,3-trichloro-*N*-methoxypropanamide (86r).**



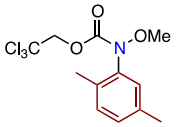
Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%), peracetic acid 35 wt% (1.5 equiv.) and bromobenzene (15.0 equiv.) warming at 40 ºC, as a pale yellow oil. **^{1}H-NMR (500 MHz, $CDCl_3$):** δ = 3.87 (s, 3H), 4.83 (s, 2H), 7.26-7.29 (m, 1H), 7.39 (td , *J* = 7.6, 1.4 Hz, 1H), 7.44 (dd , *J* = 7.9, 1.8 Hz, 1H), 7.68 (dd, *J* = 8.1, 1.4 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 63.0, 75.5, 95.0, 123.6, 128.4, 130.1, 133.7, 138.1, 153.2. **IR ν(cm^{-1}):** 2935, 1727, 1235, 1110, 714, 569. **HRMS (ESI^+):** calc. for $[C_{10}H_9BrCl_3NNaO_3]^+$: 397.8724; found: 397.8731.

3,3,3-Trichloro-*N*-(fluorophenyl)-*N*-methoxypropanamide (86s).



Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%), peracetic acid 35 wt% (1.5 equiv.) and fluorobenzene (15.0 equiv.) warming at 40 ºC, as a pale yellow oil in 39% yield. Undefined ratio of regioisomers of 1.0/17.0/14.0. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 3.82 (s, 3H), 3.85 (s, 3H), 4.83 (s, 2H), 4.85 (s, 2H), 7.06-7.11 (m, 2H), 7.16-7.23 (m, 2H), 7.35-7.48 (m, 4H). **^{19}F-NMR (376 MHz, $CDCl_3$):** δ = 111.6, 115.0, 119.2. **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 62.6, 62.8, 63.0, 75.4, 75.5, 95.0, 95.1, 115.9 (d, $J_{C\text{-}F}$ = 23.0 Hz), 116.7 (d, $J_{C\text{-}F}$ = 20.0 Hz), 124.7 (d, $J_{C\text{-}F}$ = 4.1 Hz), 124.9, 126.7 (d, $J_{C\text{-}F}$ = 12.9 Hz), 129.1, 130.9 (d, $J_{C\text{-}F}$ = 7.9 Hz), 134.9 (d, $J_{C\text{-}F}$ = 3.1 Hz), 152.8, 153.3, 157.9 (d, $J_{C\text{-}F}$ = 253.3 Hz), 161.2 (d, $J_{C\text{-}F}$ = 246.8 Hz).

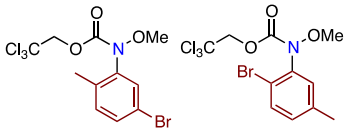
3,3,3-Trichloro-*N*-(2,5-dimethylphenyl)-*N*-methoxypropanamide (86t).



Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%) and *p*-xylene (10.0 equiv.) as a pale yellow oil in 59% yield. Mixture of rotamers, major/minor 1.4/1.0. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = (Mixture of rotamers) 2.29 (s, 3H), 2.30 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 4.83 (m, 2H), 7.03-7.05 (m, 1H), 7.09-7.13 (m, 3H), 7.15-7.19 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ = 17.4, 17.7, 20.8, 21.2, 61.8, 62.0, 75.1, 95.3, 127.2, 128.0, 128.5, 130.1, 130.8, 131.8, 133.3, 134.5, 136.3, 136.8, 139.4,

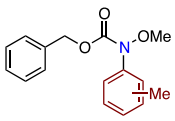
153.4, 153.5. **IR ν(cm^{-1}):** 2957, 2932, 1722, 1382, 1108, 711, 570. **HRMS (ESI$^+$):** calc. for $[C_{12}H_{14}Cl_3NNaO_3]^+$: 347.9931; found: 347.9927.

***N*-(5-Bromo-2-methylphenyl)-3,3,3-trichloro-*N*-methoxypropanamide and *N*-(2-bromo-5-methylphenyl)-3,3,3-trichloro-*N*-methoxypropanamide (86u).**



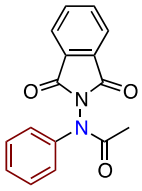
Synthesised according to GP8 using 1,2-diiodobenzene (4 mol%), peracetic acid 35 wt% (1.5 equiv.) and 1-bromo-4-methylbenzene (2.0 equiv.) at 40 ºC, as yellow oil in 32% yield. Ratio of regioisomers of 2.8/1.0. The minor regioisomer was present as a mixture of rotamers, major/minor 1.6/1.0. **^{1}H-NMR (500 MHz, $CDCl_3$):** (Major regioisomer) δ = 2.34 (s, 3H), 3.86 (s, 3H), 4.82-4.84 (m, 2H), 7.07-7.09 (m, 1H), 7.24-7.25 (m, 1H), 7.53 (d, *J* = 8.2 Hz, 1H). **^{13}C-NMR (125 MHz, $CDCl_3$):** δ = 17.5, 17.7, 20.8, 62.8, 75.15, 75.18, 75.3, 94.95, 95.03, 119.0, 119.8, 129.7, 130.5, 131.6, 132.2, 132.3, 132.5, 133.1, 133.8, 134.0, 135.5, 136.3, 137.6, 138.4, 138.6, 138.7, 153.1.

***N*-Benzyl-*O*-methyl-*N*-(tolyl)hydroxylamine (86y).**



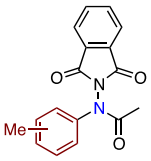
Synthesised according to GP8 using toluene as solvent, as yellowish oil in 66% yield. Undefined ratio of regioisomers of 1.0/3.0/3.7. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 2.27 (s, 3H), 2.36 (s, 3H), 2.37 (s, 3H), 3.75 (s, 6H), 3.76 (s, 3H), 5.24 (s, 2H), 5.28 (s, 2H), 5.29 (s, 2H), 7.16-7.43 (m, 27H). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ = 17.8, 21.0, 21.5, 62.0, 62.2, 62.4, 67.8, 67.91, 67.94, 119.3, 122.7, 122.9, 126.5, 126.9, 128.0, 128.1, 128.2, 128.21, 128.29, 128.31, 128.5, 128.62, 128.63, 129.0, 129.4, 131.0, 136.0, 136.1, 136.11, 136.2, 136.6, 137.0, 138.2, 138.7, 139.4, 154.4, 154.5, 155.4.

***N*-(1,3-Dioxoisoindolin-2-yl)-*N*-phenylacetamide (89a).**



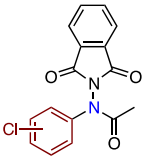
Synthesised according to GP8 as a yellowish solid in 99% yield. Mixture of rotamers (1.0/0.18). Purification by crystallisation CH_2Cl_2/*n*-hexane. **^{1}H-NMR (400 MHz, $CDCl_3$):** (Major rotamer) δ = 2.11 (s, 3H), 7.40-7.47 (m, 3H), 7.68-7.70 (m, 2H), 7.74-7.78 (m, 2H), 7.87-7.91 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$):** (Major rotamer) δ = 21.8, 124.1, 129.0, 129.7, 130.0, 130.2, 134.8, 140.8, 165.0, 168.5.

***N*-(1,3-Dioxoisoindolin-2-yl)-*N*-tolylacetamide (89b).**



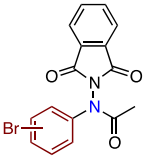
Synthesised according to GP8 as a yellowish solid in 91% yield. Purification by column chromatography (*n*-hexane/EtOAc, 75/25 v/v). Ratio *o*/*m*/*p* 9.0/4.0/1.0. **^{1}H-NMR (400 MHz, CDCl$_3$):** δ = 2.04 (s, 3H), 2.10-2.11 (m, 6H), 2.38-2.39 (m, 6H), 2.65 (s, 3H), 7.23-7.27 (m, 4H), 7.32-7.33 (m, 2H), 7.55-7.57 (m, 4H), 7.74-7.80 (m, 8H), 7.86-7.90 (m, 6H). **^{13}C-NMR (100 MHz, CDCl$_3$):** δ = 18.2, 18.4, 21.0, 21.4, 21.8, 124.1, 124.4, 127.5, 127.6, 128.8, 129.8, 129.9, 130.3, 130.6, 131.9, 134.7, 135.3, 137.6, 138.3, 139.6, 140.0, 165.0, 168.7, 168.9.

***N*-(1,3-Dioxoisoindolin-2-yl)-*N*-chlorophenylacetamide (89c).**



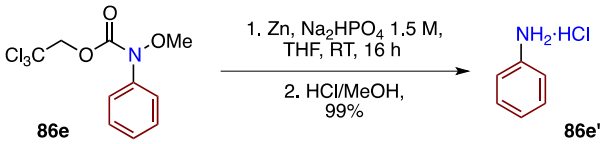
Synthesised according to GP8 as a yellowish solid in 99% yield. Purification by crystallisation CH_2Cl_2/*n*-hexane. Ratio of regioisomers *o*/*m*/*p* 3.0/1.0/79.0. **^{1}H-NMR (400 MHz, CDCl$_3$):** (*Para*-regioisomer) δ = 2.11 (s, 3H), 7.42-7.44 (m, 2H), 7.62-7.64 (m, 2H), 7.76-7.79 (m, 2H), 7.84-7.92 (m, 2H). **^{13}C-NMR (125 MHz, CDCl$_3$):** (*Para*-regioisomer) δ = 21.8, 124.2, 130.1, 130.3, 130.4, 134.9, 135.8, 139.3, 165.0, 168.2.

***N*-(1,3-Dioxoisoindolin-2-yl)-*N*-bromophenylacetamide (89d).**



Synthesised according to GP8 as a brownish solid in 99% yield. Purification by crystallisation CH_2Cl_2/*n*-hexane. Ratio *o*/*p* 1.0/66.0. **^{1}H-NMR (400 MHz, CDCl$_3$):** (*Para*-regioisomer) δ = 2.11 (s, 3H), 7.55-7.60 (m, 4H), 7.76-7.79 (m, 2H), 7.87-7.91 (m, 2H). **^{13}C-NMR (125 MHz, CDCl$_3$):** (*Para*-regioisomer) δ = 21.8, 123.9, 124.2, 130.1, 130.7, 133.3, 134.9, 139.8, 165.0, 168.1.

Deprotection of 2,2,2-trichloroethylmethoxy(phenyl)carbamate (GP9):

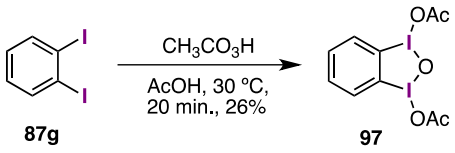


Scheme 3.28 One-pot deprotection of **86e** to aniline hydrochloride (**86e'**).

In a Schlenck tube under argon atmosphere, the 2,2,2-trichloroethylmethoxy(phenyl)carbamate **86e** (0.1 g, 0.33 mmol) was dissolved in dry

THF. Zn dust (57.0 equiv.) and aq. NaH_2PO_4 1.5 M (1.26 mL) were added and the reaction mixture was stirred at room temperature. The crude was filtered over a short pad of Celite® washing with THF. The crude was washed with NaOH 5% wt/wt and extracted with CH_2Cl_2 (10 mL x 3) and dried over Na_2SO_4. The crude was treated with HCl/MeOH and, after the removal of the solvent, the aniline hydrochloric salt **86e'** was obtained in quantitative yield as brownish solid. **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ = 7.40-7.43 (m, 2H), 7.48-7.57 (m, 3H). **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ = 124.1, 130.3, 131.3, 131.9.

Synthesis of 1,3-diacetoxy-1,3-dihydro-1,3,2-benzodiiodooxazole (97) (GP10):



87g **97**

Scheme 3.29 Synthesis of the intermediate iodine(III) **97**.

In a Schlenck tube under argon atmosphere, 1,2-diiodobenzene (**87g**) (40 μL, 0.3 mmol) was dissolved in glacial acetic acid (2.0 mL) and the mixture was warmed to 30 ºC. Peracetic acid 35 wt% (1.2 mmol) was added drop-wise. After that all the peracetic acid was added, the mixture was stirred for 20 min. Distilled water was added and a white precipitate formed. The white solid was filtered, washed with water and diethyl ether and afforded the desired title compound in 26% yield. **^{1}H-NMR ($CDCl_3$, 500 MHz):** δ = 2.09 (s, 6H), 7.61-7.65 (m, 2H), 8.01-8.05 (m, 2H). **^{13}C-NMR ($CDCl_3$, 125 MHz):** δ = 21.6, 120.1, 131.9, 135.3, 178.4. **IR (cm^{-1}):** 1629, 1364, 1301, 740, 666, 550, 471. **HRMS (MALDI$^+$):** calc. for $[C_8H_7I_2O_3]^+$: 404.8479; found: 404.8443 [M-OAc]. **m.p.(ºC):** 172-175 ºC.

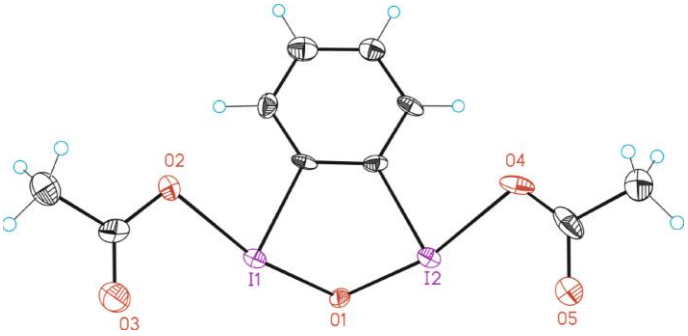
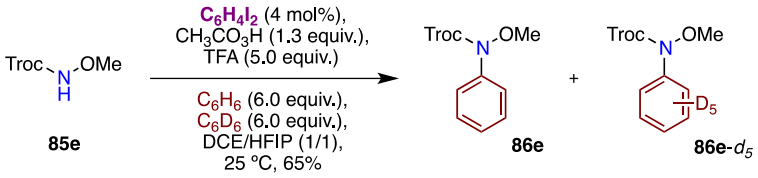


Table 3.5 Crystal data and structure refinement for 1,3-diacetoxy-1,3-dihydro-1,3,2-benzodiiodooxole (**97**).

Identification code	CCDC 1451743
Empirical formula	C11 H12 Cl2 I2 O5
Formula weight	548.91
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 36.559(10)Å a= 90°. b = 3.9392(9)Å b = 129.586(9)°. c = 27.643(8)Å g = 90°.
Volume	3068.0(15) $Å^3$
Z	8
Density (calculated)	2.377 Mg/m^3
Absorption coefficient	4.462 mm^{-1}
F(000)	2064
Crystal size	0.20 x 0.03 x 0.01 mm^3
Theta range for data collection	1.491 to 27.027°.
Index ranges	?<=h<=?,?<=k<=?,?<=l<=?
Reflections collected	?
Independent reflections	3315[R(int) = ?]
Completeness to theta =27.027°	99.0%
Absorption correction	Multi-scan
Max. and min. transmission	0.957 and 0.736
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3315/ 2/ 183
Goodness-of-fit on F^2	0.986
Final R indices [I>2sigma(I)]	R1 = 0.0644, wR2 = 0.1516
R indices (all data)	R1 = 0.0940, wR2 = 0.1661
Largest diff. peak and hole	4.489 and -2.338 e.$Å^{-3}$

Kinetic isotope effect (KIE) studies.



Scheme 3.30 Kinetic isotope effect (KIE).

Nitrogen source **85e** (0.15 mmol, 1.0 equiv.) was dissolved in a mixture of 1,2-dichloroethane and 1,1,1,3,3,3-hexafluoro-2-isopropanol (1/1, v/v) (0.5 mL). 1,2-Diiodobenzene (**87g**) (4 mol%), benzene (6.0 equiv.) and benzene-d_6 (6.0 equiv.), peracetic acid 35 wt% (1.5 equiv.) and trifluoroacetic acid (5.0 equiv.) were added in the order. The mixture was stirred at room temperature for the time indicated and then washed with water, extracted with CH_2Cl_2 (10 mL x 3), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (*n*-hexane/EtOAc, 95/5 v/v). The kinetic isotope effect was measured from the ^{1}H-NMR spectra given belove.

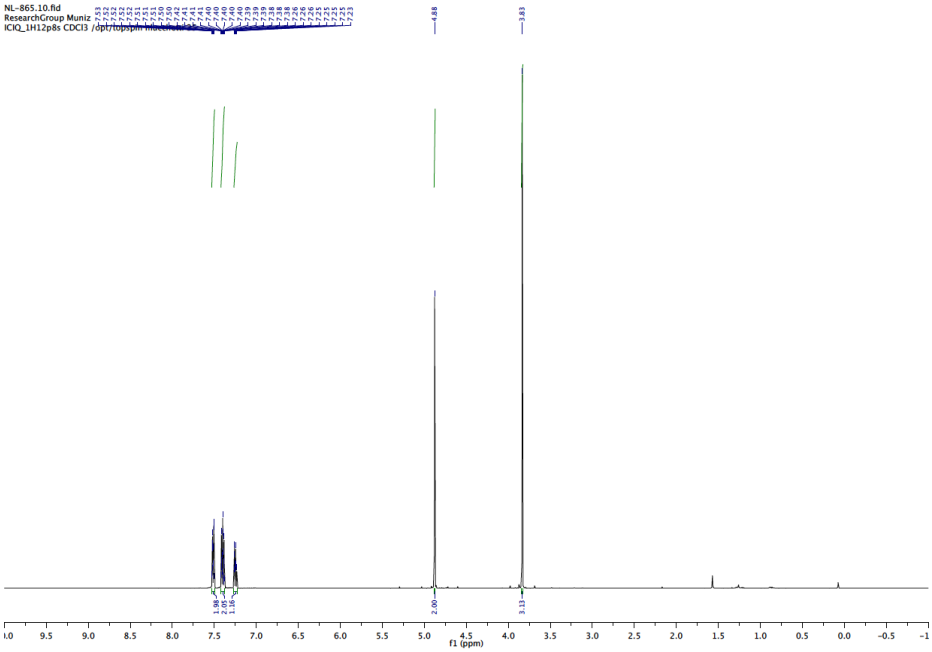


Figure 3.6 ^{1}H-NMR spectrum of the crude reaction mixture using C_6H_6/C_6D_6, 1/1.

Chapter IV

Title

This doctoral thesis is a collaboration with F. Hoffmann-La Roche Ltd. The content of this Chapter has not been included in this version of the document since is confidential. The following parts have been removed from the confidential version:

- Paragraph 1.4.3 (pagg. 17-18);
- Chapter IV, from pag. 119 to pag. 179;
- The last paragraph of Chapter V (pagg. 181-182).

Chapter V

Overall Conclusions and Outlook

5.1 Conclusions

The first example of reductive elimination at an iodine(III) centre using diaryliodonium salts and imides as nitrogen sources has been reported. The study of the kinetic profile of the transformation by ^{19}F-NMR allowed the calculation of the energetic parameters, which are in complete agreement with the experimental data. The developed protocol was of broad scope for the synthesis of congested 2,6-disubstituted anilines, including also amides and lactams as amino coupling partners. The synthetic utility was demonstrated by the short two-step-synthesis of the *N*,*N*'-diarylated pyrrolidinone carboxamide. This compound belongs to a family of binding inhibitors of the chemo-attractant peptide chemerin to the G-protein coupled receptor ChemR23. The outlook of the project will be the search for suitable catalytic conditions, which allow performing the transformation under milder and friendly conditions. Main issue will be the compatibility of the reactive diphenyliodonium phthalimidate intermediate with the reaction medium and the oxidative environment.

The subsequent step in the search for new metal-free approaches for the syntheses of anilines was the use of 1,2-diiodobenzene as precatalyst. The mechanism of the reaction, despite of the previous iodonium(III) salts, involved an electrophilic nitrogen intermediate. Interestingly, in sharp contrast with the reported proposal of Antonchick we could assume the active role of both iodine centres in the bis(iodo)arene. This was confirmed by the isolation and characterisation by X-ray diffraction of the oxidised iodine(III) intermediate, which showed a distorted five-membered ring. Next, it was utilised in control experiments to clarify the pathway of the transformation. The turnover numbers (TON) and the regioselectivities exhibited by the new catalytic system were superior to all the other reported protocols.

NEW PERSPECTIVES IN AROMATIC AMINATIONS USING HYPERVALENT IODINE(III) REAGENT

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