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The Development of Powerful Electron-Transfer Reagents

A thesis submitted to the University of Strathclyde in part fulfilment of regulations for the degree of Doctor of Philosophy in Chemistry.

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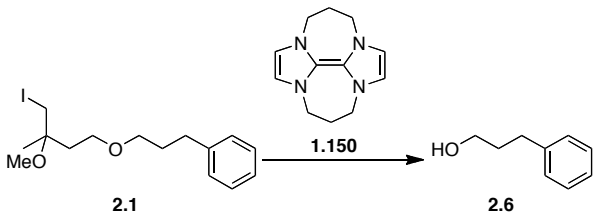
Abstract

This thesis discusses the investigation into powerful electron-transfer reagents conducted in the research group of Professor John Murphy at the University of Strathclyde between October 2006 and March 2010. **Chapter one** discusses the principal themes and areas of chemical research that are contained within this thesis, providing useful background information. Section 1.1 introduces electron-transfer using metals and metal-based reagents, including the use of dissolving group 1 (and 2) metal reductions, transition metals and lanthanides. Section 1.2 discusses organic electron-transfer reagents, focussing on the development of more powerful reagents. Section 1.3 focuses on *N*-heterocyclic carbenes (NHCs), including their structure and properties, their use as organocatalysts and their employment as ligands. Finally, section 1.4 introduces the theme of electron-transfer using nickel complexes, including the formation of aldehydes using nickel(I) salen and the employment of nickel(0) and NHCs in the reduction of organic substrates.

Chapters two, **three** and **four** discuss the results obtained during the development of powerful electron-transfer reagents. **Chapter two** reveals the surprising isolation of alcohols (*e.g.*, **2.6**) following the reduction of alkyl halides (*e.g.*, **2.1**) using a powerful organic electron-donor **1.150** (scheme i). The substrate scope is revealed, followed by mechanistic studies that investigate the mechanism that leads to alcohol formation. Several pathways were ruled out, allowing a single mechanism to be postulated as the most likely route for this transformation.

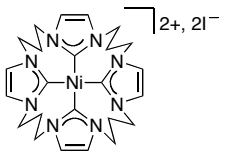
Scheme i: the isolation of alcohol **2.6** from alkyl iodide **2.1** using organic electron donor **1.150**.



Chapter three discusses a novel, nickel(II) crown carbene complex **3.1** that, when activated, is a powerful electron-donor (figure i). The activated nickel complex, formed by treatment with sodium amalgam, is a powerful reductant that reduces carbonyl-containing compounds, both activated and non-activated sulfones and

sulfonamides and the central aromatic ring of anthracene (and substituted analogues) in a Birch reduction. Extensive investigations into the active species using control experiments, cyclic voltammetry and computational analysis reveal the active species to be a nickel(II) ion bound to a di-anion ligand.

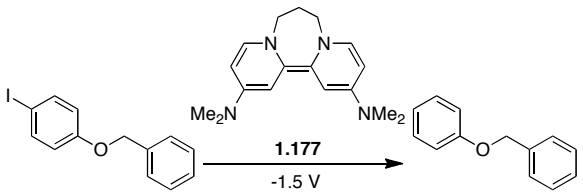
Figure i: the structure of nickel(II) crown carbene complex **3.1**.



3.1

Chapter four describes attempts to formulate a catalytic, reductive procedure using electrochemical cycling to generate the catalytic electron-donor **1.177** (scheme ii). The screening of various proton sources is discussed, as well as the synthetic procedures used and the challenges still ahead.

Scheme ii: the reduction of aryl halide **4.4** using electrochemically generated donor **1.177**.



4.4 **4.5**

Finally, **Chapter five** contains the experimental procedures and data for all synthesised compounds discussed within this thesis.

Abbreviations

AcOH	acetic acid
AIBN	azobisisobutyronitrile
ANC	active nickel complex
Ar	aryl
Ag/AgCl/KCl (sat.)	silver/silver(I) chloride reference electrode in a saturated potassium chloride solution (E° = -0.199 V vs. NHE)
b	broad
BMEA	*bis*methoxyethylamine
b.p.	boiling point
CHD	1,4-cyclohexadiene
CI	chemical ionisation
d	doublet
DBB	1,4′-di-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dec	decomposed
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyltetrahydropyrimidi-2-one
DMSO	dimethyl sulfoxide
e.g.	*exempli gratia*
EI	electron impact
ESI	electrospray ionisation
EWG	electron-withdrawing group
h	hour(s)
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
ICy	1,3-dicyclohexylimidazolylidene
IMes	1,3-dimesitylimidazolylidene
i.e.	*id est*
ir	irreversible
IR	infrared
KHMDS	potassium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital

M	molarity *or* generic metal
m	multiplet
Me	methyl
Mes	mesityl (1,3,5-trimethylphenyl)
min(s)	minute(s)
m.p.	melting point
Ms	methanesulfonyl
mV	millivolts
m/z	mass-to-charge ratio
Na/Hg	sodium amalgam
NHC	*N*-heterocyclic carbene
NHE	normal hydrogen electrode
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet
R	alkyl group
rpm	rotations per minute
r.t.	room temperature
s	singlet
sat	saturated
SCE	saturated calomel electrode (E° = -0.242 V vs. NHE)
SED	super electron-donor
SET	single electron-transfer
soln	solution
SOMO	singly occupied molecular orbital
t	triplet
TBAHFP	*tetra*-butylammonium hexafluorophosphate
TBATFB	*tetra*-butylammonium tetrafluoroborate
*t*BuOH	*tert*-butyl alcohol
TMAHFP	*tetra*-methylammonium hexafluorophosphate
TMATFB	*tetra*-methylammonium tetrafluoroborate
TDAE	*tetrakis*(dimethylamino)ethylene
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidide
TON	turnover numbers
TTF	tetrathiafulvalene
vs.	versus

Contents

Chapter 1

Introduction

This chapter serves as an introduction to the themes and topics that will be discussed in detail in the Results sections of this thesis (chapters 2, 3 and 4). Section 1.1 is entitled "electron-transfer using metals and metal-based reagents" and introduces the use of such reagents that mediate electron-transfer reactions. These reagents range from alkali metals to lanthanides, and are capable of mediating a wide range of organic transformations. Section 1.2 covers the theme of neutral, organic electron donors, where the development of powerful organic electron donors is detailed starting with tetrathiafulvalene and covering the most relevant and interesting discoveries that have so far been disclosed. Particular attention is paid to the "super organic electron donor" reagents developed by Murphy over the last decade. Section 1.3 discusses the chemistry of *N*-heterocyclic carbenes, including their important role as ligands. This section also discusses the origin and development of the crown carbene metal complexes by Murphy, which has recently been disclosed. Finally, section 1.4 introduces the role of nickel complexes in electron transfer.

Section 1.1

Electron-transfer using metals and metal-based reagents

Group 1 and Group 2 metals

The elements of group 1 and group 2 consist of highly reactive metals. These metals have long been used as powerful reductants,[1] in particular lithium, sodium and potassium. The reactivity and electropositivity increases as the group is descended. For example, comparison of the reaction with water of each metal is indicative of the increased reactivity on descending the group. Lithium reacts slowly in water, while potassium ignites. However, in terms of electron transfer, one of the best methods for comparison comes from the measured redox potential. The standard reduction potential, E°, provides an indication of how powerful the

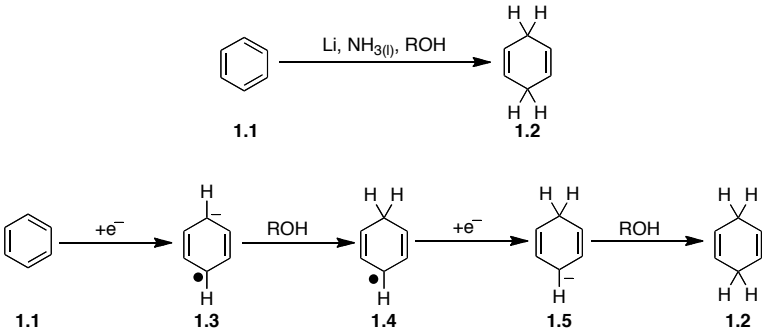
reductant under analysis is. The more negative the measured potential, the more powerful the reductant. The main difficulty when it comes to comparison is that redox potentials can vary dependent on solvent, due to variations in the solvation of the cation. However, data are available that allow a general guide to be considered, as shown in table 1.1.[1]

Table 1.1: Standard reduction potentials, E°, in water (vs. ferrocene).[1]

Half reaction (acidic solution)	Standard reduction potential, E° (V)
$Li^{+}_{(aq.)} + e^{-} \rightarrow Li_{(s)}$	-3.045
$K^{+}_{(aq.)} + e^{-} \rightarrow K_{(s)}$	-2.925
$Na^{+}_{(aq.)} + e^{-} \rightarrow Na_{(s)}$	-2.714
$Al^{3+}_{(aq.)} + 3e^{-} \rightarrow Al_{(s)}$	-1.66
$Zn^{2+}_{(aq.)} + 2e^{-} \rightarrow Zn_{(s)}$	-0.763
$Fe^{2+}_{(aq.)} + 2e^{-} \rightarrow Fe_{(s)}$	-0.44
$Sn^{2+}_{(aq.)} + 2e^{-} \rightarrow Sn_{(s)}$	-0.14

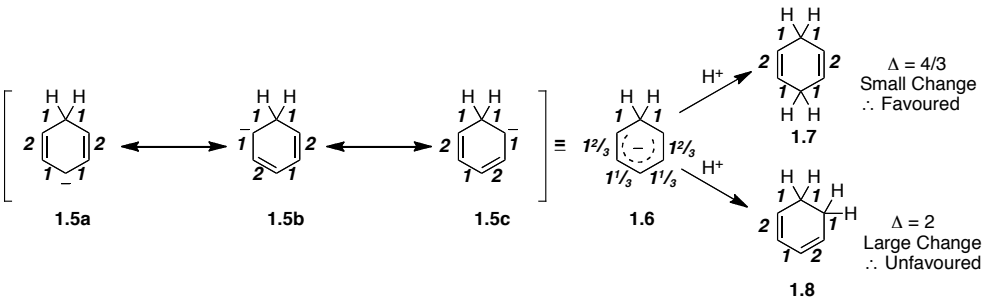
Perhaps the most well known use of alkali metals as electron donors in organic synthesis is the Birch reduction.[2] The Birch reduction was discovered in the 1940's by Arthur J. Birch, who used a solution of "dissolved metal" to reduce a number of naphthalene and benzene derivatives. The choice of sodium in liquid ammonia, together with an alcohol proton source, proved to be highly successful. The discovery came during a period of post-doctoral research in Oxford in the laboratory of Sir Robert Robinson, where Birch was tasked with synthesising cortical hormones.[3] During the Second World War, rumours from the Polish underground that the Luftwaffe pilots were being dosed with cortical hormones reached the RAF. These hormones were allegedly used to gain an advantage over allied forces during battle. The RAF wanted them too.[4] It was during the attempted synthesis of the steroid analogues that Birch discovered the reduction of aromatic rings by dissolving metals. Birch acknowledges that the "real clue"[4] came from Wooster,[5] who had earlier claimed to have isolated the 1,4-dihydro derivative of anisole by reaction with sodium in liquid ammonia. An example of the Birch reduction, and its proposed mechanism, is shown in scheme 1.1.

Scheme 1.1: the first example of the Birch reduction and the proposed mechanism.[6]



The mechanism involves the oxidation of lithium to Li^+, which creates a radical anion of benzene **1.3**. The radical anion **1.3** is protonated by the alcohol to form intermediate radical **1.4**, which can then accept a further electron to form a second anion **1.5**. Once more, this intermediate anion is protonated by the added alcohol to afford the product cyclohexadiene **1.2**. Initially, it may seem peculiar that the 1,4-product forms, rather than the thermodynamically more stable, conjugated 1,3-diene. One explanation is the principle of least motion,[7] which proposes that the product formed will be that which occurs *via* the reaction pathway in which the least change on atomic position and electronic configuration occurs. Structure **1.5** has three resonance forms that delocalise the negative charge. If each bond is assigned a value (1 for a single bond, 2 for a double bond, scheme 1.2) then an average bond value can be determined (**1.6**). Thus, when protonating structure **1.5**, the smallest change occurs to form the 1,4-product (**1.2**), rather than the conjugated 1,3-diene (**1.8**).

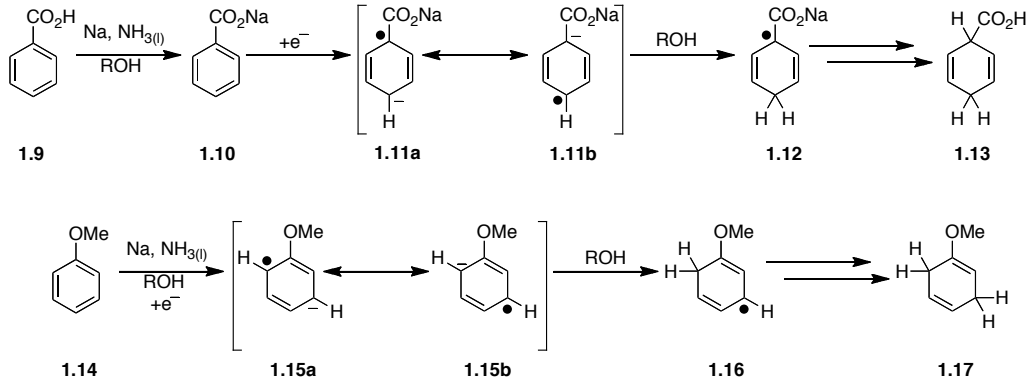
Scheme 1.2: illustration of the principle of least motion to explain why 1,4-product **1.2** (or **1.7**) is favoured during the Birch reduction.



One final question that must be answered concerning the Birch reduction is what is the regioselective outcome when the aromatic ring is substituted? The general

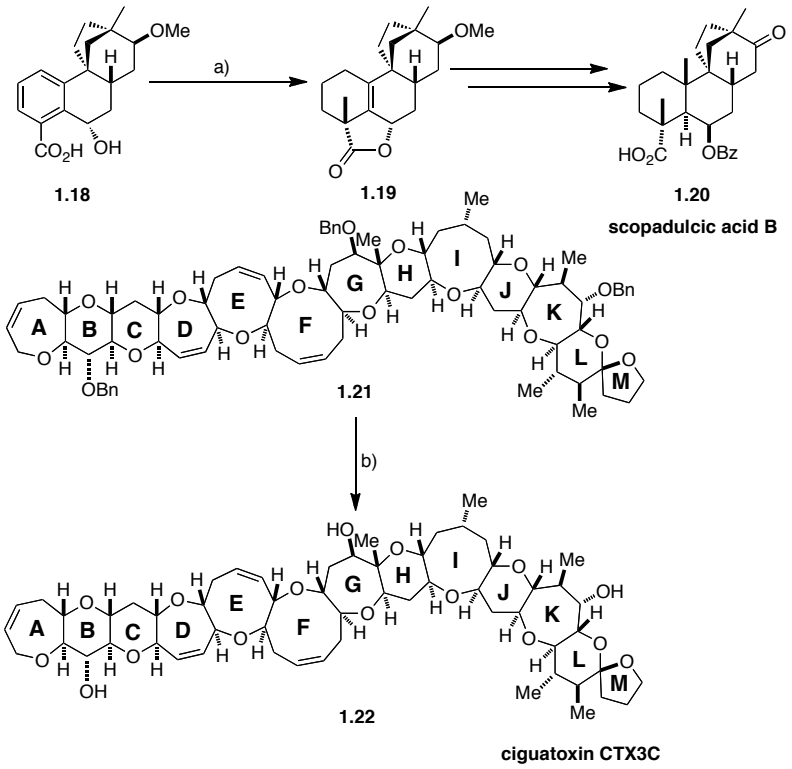
principle is that electron-withdrawing substituents promote *ipso*, *para* reduction, while electron-donating groups promote *ortho*, *meta* reduction.[8] The reason behind this rule relates to the distribution of electron density in the intermediate radical anions following addition of the initial electron. When an electron-withdrawing group is present, electron density is stabilised in the *ipso*- and *para*-positions on the ring. The use of an electron-donating group serves to stabilise electron density at the *ortho*- and *meta*-positions. The mechanisms for the reaction of benzoic acid (**1.9**) and anisole (**1.14**) under Birch reduction conditions are shown in scheme 1.3.

Scheme 1.3: the mechanism for the Birch reduction of benzoic acid **1.9** and anisole **1.14**.



The Birch reduction has seen widespread application in the area of natural product synthesis (scheme 1.4). Overman *et al.*[9] utilised the Birch reduction to construct the key tetracyclic intermediate (**1.19**) en route to the synthesis of (±)-scopadulcic acid B **1.20**, a promising compound in the treatment of peptic ulcers and herpes virus infections. Crucially, the absence of a proton source and the inclusion of iodomethane provided the correct diastereomer by methylation of the final anion. An alternative application of dissolving metal reduction is highlighted from a recent synthesis of ciguatoxin CTX3C **1.22** by Inoue and Hirama.[10] The synthesis of this potent toxin, commonly found in several species of reef fish and toxic by ingestion, includes the use of sodium in liquid ammonia for the global deprotection of the benzyl protection groups on structure **1.21**. The authors state that the isolation of CTX3C **1.22** required carefully controlled Birch reduction where the protected compound was only exposed to the solvated electrons for 10 minutes at -90 °C.

Scheme 1.4: the use of the Birch reduction in the synthesis of (±)-scopadulcic acid B **1.20** by Overman *et al.* and the application of dissolving metal techniques in the global deprotection to afford ciguatoxin CTX3C **1.22** by Inoue and Hirama.

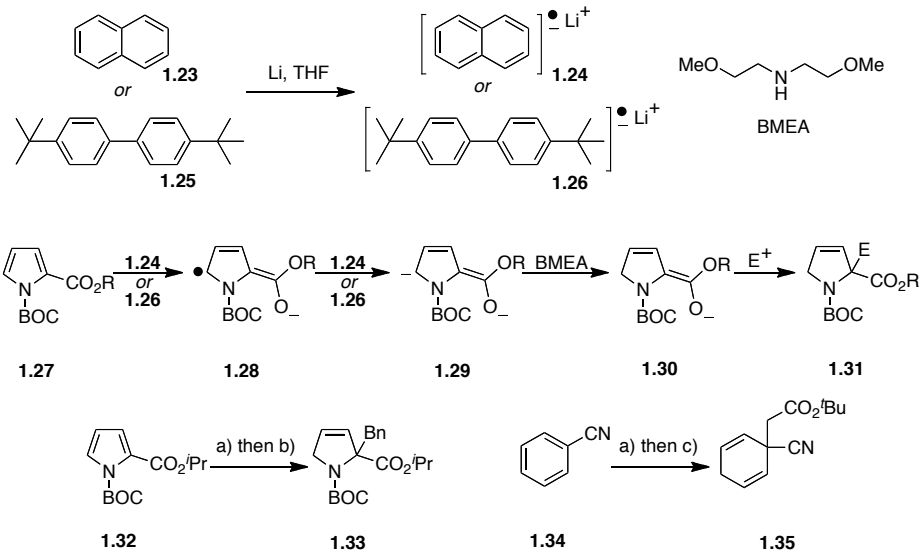


Reaction conditions: a) (i) Li, NH_3, THF, MeI, (ii) H_2, Rh/Al_2O_3; b) Na, NH_3, THF, EtOH, -90 °C, 10 min; **1.22**, 7%.

Recently, Donohoe revealed a significant alternative to the classic Birch conditions that achieves the reduction of aromatic molecules under ammonia-free conditions.[11] Initial attempts focussed on the use of naphthalene and lithium, forming the naphthalene radical anion **1.24** *in situ*, which could donate electrons to the electron-deficient protected pyrrole **1.27**. Trapping of the intermediate dianion **1.29** with either two equivalents of electrophile or, alternatively, a single equivalent of electrophile and protonation resulted in the reduced products. However, compared with the classical ammonia based methodology, the yields were considerably lower. Donohoe solved this issue by switching the electron carrier from naphthalene to the substantially more bulky 1,4′-di-*tert*-butylbiphenyl (DBB) (**1.25**, with radical anion **1.26**).[12] This caused a substantial increase in yield for most substrates, which was proposed to be a result of an increase in reducing power with DBB over naphthalene, as well as the increased steric emcumbrance hindering any side-reactions, such as radical anion-radical anion coupling. The use of

*bis*methoxyethylamine (BMEA) as a proton source is crucial, according to the authors, as the intermediate dianion **1.29** is capable of removing the proton on BMEA, whereas the intermediate monoanion **1.30** is unable to. The monoanion **1.30** is then primed to react with the added electrophile. Donohoe has shown the widespread utility of this system. The use of Li/DBB has allowed the reduction of nitrogen **(1.32**) and oxygen heterocycles, as well as carbocyclic molecules (**1.34**).

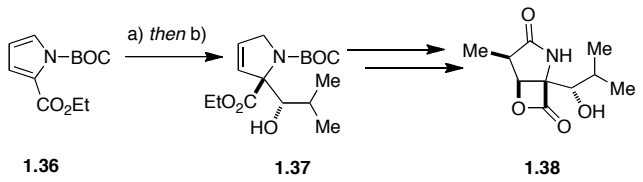
Scheme 1.5: the ammonia-free Birch reduction developed by Donohoe.



Reaction conditions: a) Li, DBB, BMEA, THF, -78 °C; b) BnBr, **1.33**, 80%; c) $BrCH_2CO_2tBu$, **1.35**, 80%.

More recently, Donohoe has shown the synthetic utility of the ammonia-free Birch reduction conditions in the total synthesis of the 20S proteasome inhibitor, *clasto*-Lactacystin β-lactone (**1.38**).[13] After initial protection of the commercially available pyrrole ester, Birch reduction under ammonia-free conditions and quenching with isobutyraldehyde *via* an aldol reaction, allowed the isolation of the key intermediate **1.37**. Crucially, transmetallation with $MgBr_2.Et_2O$ was required to achieve a high yield and diastereoselectivity.

Scheme 1.6: the application of the ammonia-free Birch reduction in the synthesis of *clasto*-Lactacystin β-lactone.

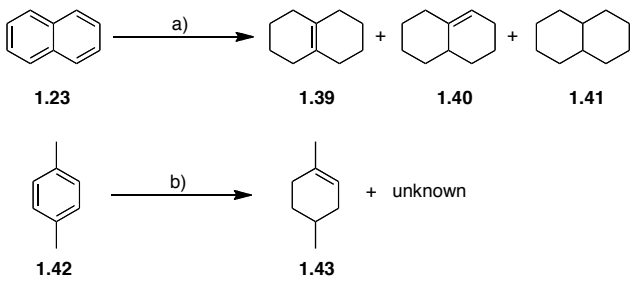


1.36 **1.37** **1.38**

Reaction Conditions: a) Li, DBB, THF, -78 °C, BMEA; b) $MgBr_2.Et_2O$ *then* isobutyraldehyde; **1.37**, 74%, 20:1 dr.

An alternative to the classic Birch conditions is the Benkeser reaction, which employs an amine in place of ammonia. Benkeser[14] reported "the absorption of large quantitites of lithium by various aromatic compounds" using ethylamine as solvent. These conditions are significantly more reducing than those of Birch, with reduction to the monoolefin generally occurring. For example, exposure of naphthalene to lithium in ethylamine for 10 h resulted in a mixture of $\Delta^{9,10}$- (**1.39**) and $\Delta^{1,9}$-octalin (**1.40**) (ratio of 50:1) and a small amount of decalin (**1.41**). The method can also employ an alcohol to alter the extent of reduction and stop at the diene stage, thus providing an alternative to the Birch reduction.[15] Reggel, Friedel and Wender also reported[16] the use of lithium in ethylenediamine as a wide-ranging metal-amine reducing system that was capable of reducing aromatic rings, reducing phenols, cleaving ethers and reducing ketones and olefins. The authors highlight the significant advantage of the high boiling point of ethylenediamine (117 °C). Later, Benkeser[17] announced a new reducing system that employed calcium together with a mixture of methylamine and ethylenediamine (generally 1:1 ratio) that was effective in reducing aromatic substrates to mono- and dialkenes. Although Benkeser-type reductions in low molecular weight amines are considerably less selective than Birch-type conditions, generally resulting in a mixture of isomeric products, the significant advantage of liquid-phase solvents at standard temperature implies that they are worthy of consideration by the synthetic chemist.

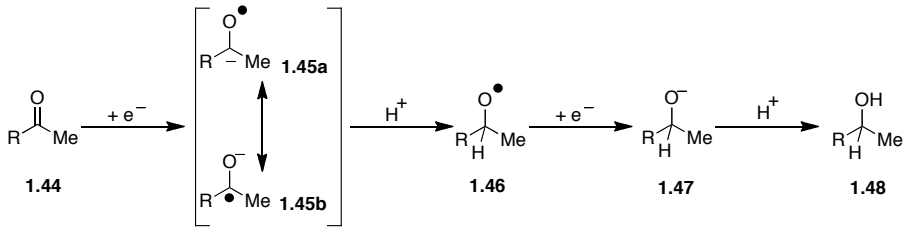
Scheme 1.7: the Benkeser conditions for the reduction of aromatic substrates.



Reaction conditions: a) Li, $EtNH_2$, 10 h, **1.39** + **1.40,** 71% (50:1), **1.41**, 5%; b) Ca, $MeNH_2/H_2N(CH_2)_2NH_2$ (1:1) 22 h, **1.43**, 84%.

The dissolving metal conditions synonymous with the Birch reduction have also found application in the reduction of carbonyl compounds. Known as the Bouveault-Blanc reduction,[18] carbonyl-containing compounds are reduced to alcohols (although more recently aluminium hydrides and borohydrides have become more widely used due to their practical convenience). The reaction employs dissolving sodium in ethanol to form ketyl radical anions **1.45** *via* electron transfer. The intermediate radical anions are protonated and accept a second electron to form an alkoxide **1.47**, which is in turn protonated to the alcohol product **1.48** (scheme 1.8). Clearly the use of a protic solvent such as ethanol is crucial.

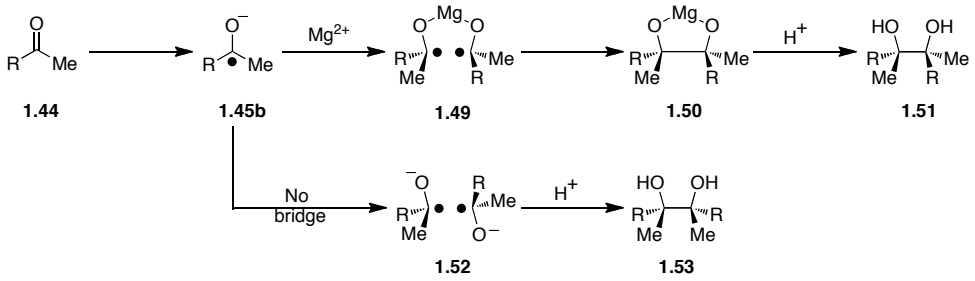
Scheme 1.8: the Bouveault-Blanc reduction.



In aprotic solvents, for example benzene or diethyl ether, no protons are readily available resulting in a significant increase in the concentration of the ketyl radical anions (**1.45**). Once the concentration reaches a particular level, dimerisation occurs to form the 1,2-diol. This is called the pinacol coupling.[19] Several group 1 or group 2 metals are effective for this transformation. For example, Na, Li or Mg can all be used efficiently (whilst use of alternatives, such as main group metals (*e.g.*, Al), transition metals (*e.g.*, Ti or V) or lanthanides (*e.g.*, Sm), are also possible).[20] The mechanism (scheme 1.9) once more involves initial electron transfer to the

carbonyl unit, forming the crucial ketyl radical anion **1.45b**, which is then primed to dimerise. In the presence of a divalent metal, *e.g.* Mg, dimerisation will be controlled by the pseudo-metal bridge, resulting in formation of the *dl* isomer **1.51**, due to steric reasons. Alternatively, when two ketyl radicals couple *via* a non-bridged pathway, the formation of the *meso* product (**1.53**) is favoured.[20]

Scheme 1.9: the mechanism for the pinacol coupling showing formation of *dl*- and *meso*-isomers.

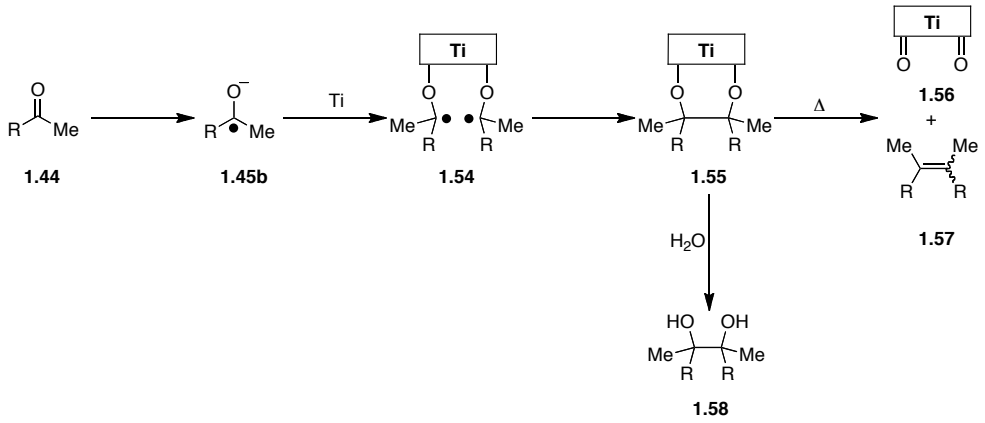


Transition metals

Transition metals are commonly employed as oxidation or reduction reagents and, as such, their associated chemistry is considerable. A few select items will be discussed here.

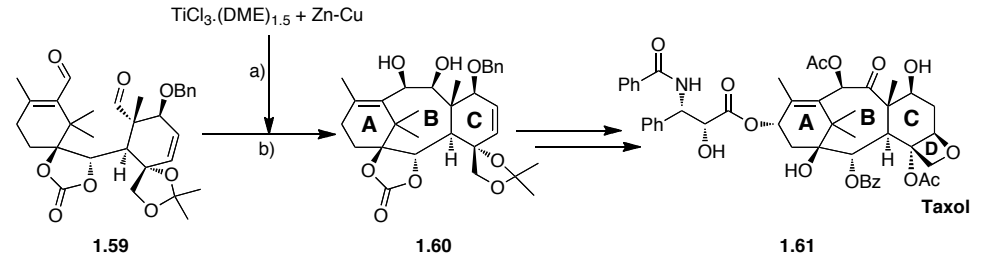
As mentioned above, titanium is commonly employed in the pinacol coupling for the construction of 1,2-diols. A common extension of this methodology is the formation of olefins *via* the McMurry reaction. The McMurry reaction was disclosed almost simultaneously by Mukaiyama,[21] Tyrlik[22] and McMurry[23] in the early 1970's. The reaction utilises low valent titanium compounds to reduce carbonyl-containing species, forming ketyl radical anions **1.45b**, which dimerise (**1.54** → **1.55**) in a similar fashion to the pinacol coupling.[24] However the crucial difference between the McMurry reaction and the pinacol coupling is that heating of the reaction mixture induces deoxygenation, resulting in the formation of the olefin products **1.57** (scheme 1.10).

Scheme 1.10: the mechanism for the McMurry reaction.



The McMurry reaction has shown widespread application in the synthesis of natural and non-natural products. One such example is the synthesis of Taxol (**1.61**) by K. C. Nicolaou *et al.* in 1995.[25] The crucial cyclisation to form the ABC ring system was completed using a highly optimised McMurry/pinacol coupling that employed 11 equivalents of $TiCl_3.(DME)_{1.5}$ and 26 equivalents of Zn-Cu couple in DME, furnishing the required *syn*-1,2-diol **1.60** in a yield of 25% (scheme 1.11).

Scheme 1.11: the formation of the ABC ring system in Taxol *via* the McMurry reaction.

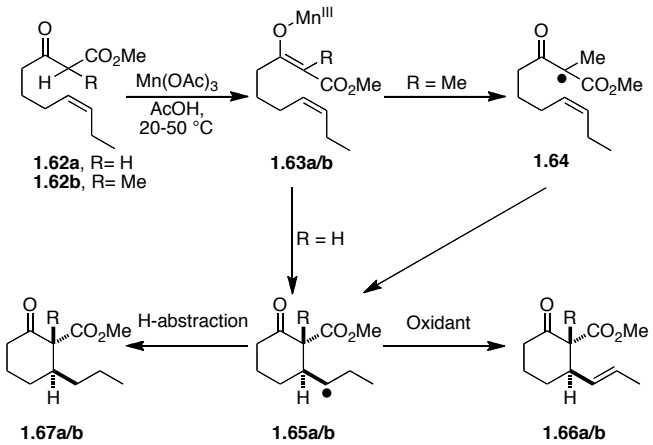


Reaction conditions: a) i) DME, reflux, 3.5 h ii) 70 °C; b) **1.59** (added over 1 h), 70 °C, 0.5 h; **1.60**, 25%.

Manganese is another transition metal that has seen widespread application in electron transfer, specifically in oxidative free-radical cyclisations.[26] $Mn(OAc)_3$ is commonly used as a one-electron oxidant. The cyclisation of **1.62** to **1.66** in scheme 1.12 serves to illustrate the key mechanistic points. $Mn(OAc)_3$ deprotonates β-ketoester **1.62** to Mn(III)-enolate **1.63**, which involves formal loss of the α-proton in **1.62**. When R = H, cyclisation directly from Mn(III)-enolate **1.63** to cyclohexanone-radical **1.65** occurs. When R = Me, loss of Mn(II) from **1.63** occurs to afford radical **1.64**. The difference in mechanism when R = H or Me is due to a

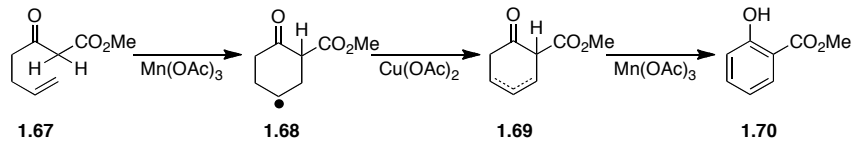
difference in the rate-determining step for each process. When R = H, the formation of Mn(III)-enolate **1.63a** is fast, with the cyclisation onto the alkene rate-limiting. When R = Me, formation of the Mn(III)-enolate **1.63b** is slow and limiting, while loss of Mn(II) to form radical **1.64** and subsequent cyclisation to form **1.65b** is rapid. The methyl group would slow down the formation of **1.63b** since it is inductively electron donating and decreases the acidity of the α-proton, while also increasing the rate of loss of Mn(II) due to the stabilising effect on the radical in **1.64**. Following formation of **1.65**, hydrogen abstraction to form **1.67** is possible. However, further oxidation to alkene **1.66** is more likely. Primary and secondary radicals (*e.g.* **1.65**) are not oxidised efficiently by Mn(III). As such, it is necessary to include $Cu(OAc)_2$ as a co-oxidant. Heiba and Dessau found that the rate of oxidation of secondary radicals by $Cu(OAc)_2$ is 350 times faster than that of Mn(III).[27] The two reagents can be employed together with only catalytic quantities of $Cu(OAc)_2$ required. The Cu(I) by-products are re-oxidised by excess Mn(III) *in situ*.[26] With no co-oxidant in place, hydrogen abstraction by primary or secondary radicals dominates, resulting in saturated products (*e.g.* **1.67**).[26]

Scheme 1.12: the Mn(III)-mediated free-radical cyclisation of **1.62** to **1.66** (or **1.67**).



One issue regarding free-radical oxidative cyclisations mediated by Mn(III) is over-oxidation.[26,28] This occurs when a second acidic proton is present in the substrate, *e.g.* in β-ketoester **1.67**. Here, formation of the Mn(III)-enolate and cyclisation onto the alkene unit would afford radical **1.68**, which would be oxidised to a mixture of cyclohexenes **1.69**. At this stage, removal of the acidic α-proton by two equivalents of Mn(III) would afford an intermediate cyclohexadienone that upon tautomerisation would form phenol **1.70** (scheme 1.13).

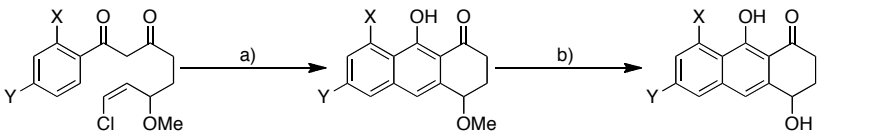
Scheme 1.13: an example of over-oxidation under Mn(III) conditions to afford phenol **1.70**.



1.67 **1.68** **1.69** **1.70**

Manganese(III)-based oxidative free-radical cyclisations have seen widespread application in the field of total synthesis.[26] Once such example is the synthesis of (±)-okicenone, an antitumour antibiotic, and (±)-aloesaponol III by Snider and Zhang in 1993.[29] Both natural products differ only by the substitution pattern on the aromatic ring. The tricyclic core is completed in the penultimate synthetic step, with treatment of **1.71** with $Mn(OAc)_3$ resulting in cyclisation and aromatisation. Finally, demethylation of **1.72** with boron tribromide furnished (±)-okicenone **1.73a** and (±)-aloesaponol III **1.73b** (scheme 1.14).

Scheme 1.14: the synthesis of (±)-okicenone **1.73a** and (±)-aloesaponol III **1.73b** by Mn(III)-mediated free-radical oxidative cyclisation.



X = Me, Y = OMe, **1.71a**
X = OMe, Y = Me, **1.71b**

X = Me, Y = OMe, **1.72a, 42%**
X = OMe, Y = Me, **1.72b, 31%**

X = Me, Y = OMe, **1.73a, 67%**
X = OMe, Y = Me, **1.73b, 70%**

Reaction Conditions: a) $Mn(OAc)_3.2H_2O$, AcOH, 120 °C, 6 min; b) BBr_3, DCM, -78 °C – r.t., 2-3 h.

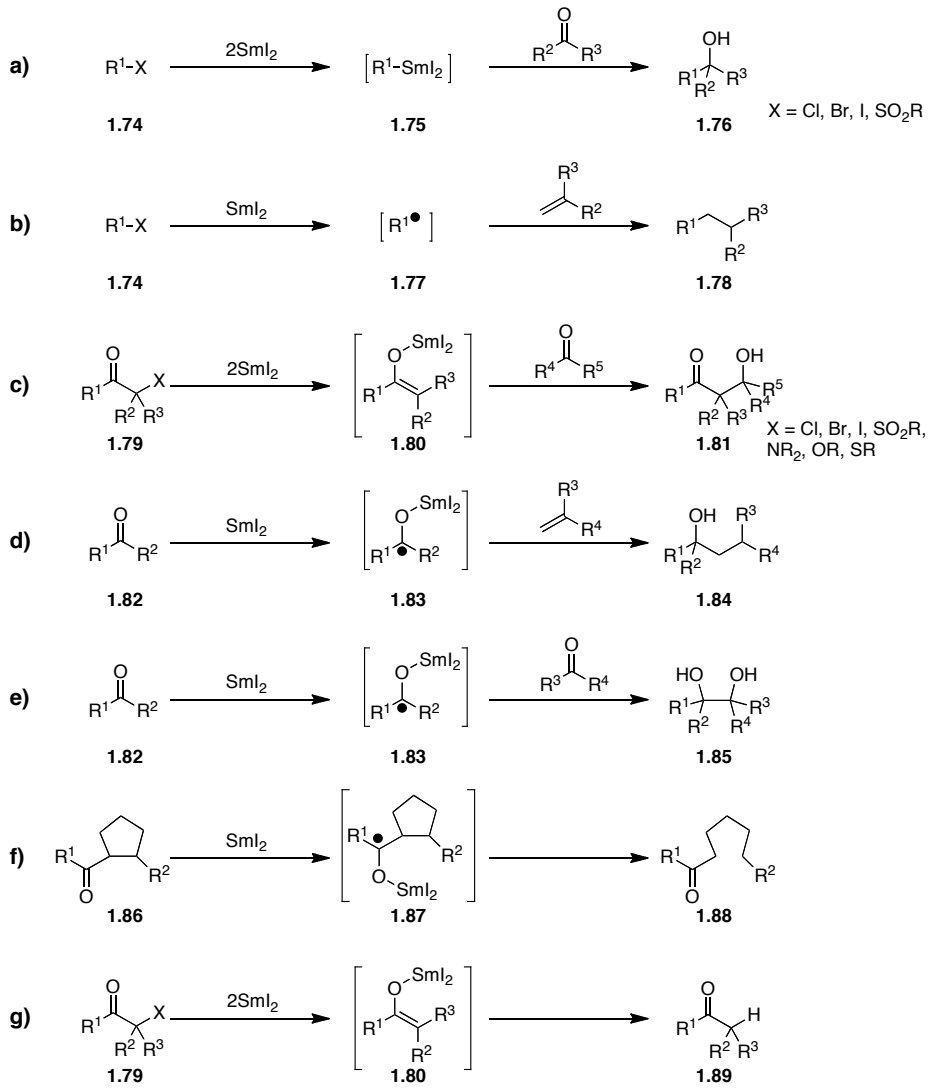
Lanthanide metals

The electron transfer chemistry of the lanthanide metals is dominated by samarium(II) iodide. Several reviews[30] have been published on the diverse and wide-ranging chemistry of SmI_2 and only a small representation of the transformations mediated by SmI_2 will be discussed here.

Samarium(II) diiodide has been developed as a mild, ether-soluble, one electron-reducing agent with applications in many diverse synthetic organic transformations.[30a] This has firmly established its place as a major reagent in organic synthesis.[30c] Preparation of SmI_2 is most convenient by reaction of samarium metal with 1,2-diiodoethane in THF at room temperature, forming a

characteristic deep blue solution.[30a] Applications of samarium diiodide include, but are not exclusive to, the Barbier reaction, radical cyclisation (or addition) to alkenes/alkynes, Reformatsky-type reactions, aldol-type reactions, carbonyl addition to alkenes/alkynes, pinacol coupling, fragmentation and reductive substitutions (scheme 1.15).[30]

Scheme 1.15: examples of the types of reaction typically exploited using samarium diiodide;[30e,31] a) Barbier reaction;[31a] b) radical-alkene/alkyne reaction;[31b] c) Reformatsky reaction;[31a] d) carbonyl-alkene/alkyne reaction;[31c] e) pinacol coupling;[31d] f) fragmentation reaction;[30e] g) reductive substitution.[30e]



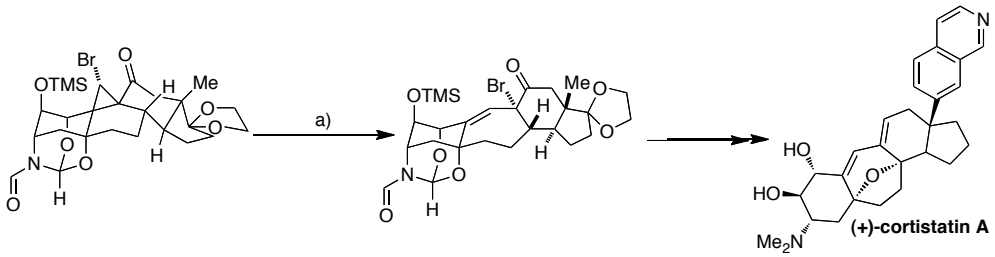
One interesting concept in the chemistry of samarium diiodide is that the inclusion of various additives or co-solvents within the reaction mixture can greatly increase the rate and reactivity of SmI_2 reactions.[32] For example it has been shown that ethers coordinated to Sm(II) provide a substantial rate enhancement.[33] The addition of

diethylene glycol to samarium diiodide in THF allowed the reduction of heptan-3-one to take place 255 times faster than in THF alone, whereas the addition of methanol increases the rate by a factor of only seventy. The authors also state the use of triethylene glycol results in a rate decrease, due to the probable full occupation of the samarium coordination sphere.

Flowers has also shown that the measured redox potential of samarium diiodide in THF was -1.33 V (vs. $Ag/AgNO_3$ reference electrode).[34] Upon addition of hexamethylphosphoramide (HMPA), Flowers observed a significant increase (shift to a more negative value) in the redox potential. When four equivalents of HMPA were added, the measured redox potential was -2.05 V (vs. $Ag/AgNO_3$). Any further increase in HMPA relative to samarium diiodide resulted in no further increase in the redox potential. Similarly, and more recently, Flowers revealed that the redox potential of samarium dibromide ($SmBr_2$) could be greatly increased from -2.07 V to -2.63 V (both vs. $Ag/AgNO_3$) upon addition of fifty equivalents of HMPA.[35] Once again, any further increase in the number of equivalents of HMPA relative to $SmBr_2$ gave no change in redox potential. The change in redox potential to more negative values can be ascribed to the ligation of HMPA as a strong donor ligand. HMPA perturbs the outer orbitals of the samarium(II) ion through ligand field effects, raising the energy level of the highest occupied molecular orbital (HOMO) and producing a more powerful reductant.[36] It is clear from the study of samarium(II) ions that the use of electron-rich additives or ligands with metal ions has the capability to greatly increase the reactivity of that metal ion.

Samarium diiodide has shown widespread application in the field of natural product synthesis, a fact discussed recently in two reviews.[30d,e] The mild and selective nature of samarium diiodide, coupled with the promise for access to a multitude of reaction types, makes samarium diiodide highly attractive to synthetic chemists. A recent example of the use of samarium diiodide in natural product synthesis comes from Baran and co-workers in the construction of (+)-cortistatin A **1.92**, a potent cell proliferation inhibitor.[37] Here a cascade sequence was used to convert cyclopropyl bromide **1.90** to bromoketone **1.91** *via* a sequential radical-opening of the three-membered ring, extrusion of the bromine radical and trapping of the organosamarium enolate by an external electrophilic bromine source (scheme 1.16).

Scheme 1.16: the use of samarium diiodide in the synthesis of (+)-cortistatin A **1.92**.



1.90 **1.91** **1.92**

Reaction conditions: a) SmI_2 (2.2 eq.), DMPU/THF (1:9), 23 °C, 5 min *then* 2,4,4,6-tetrabromo-2,5-cyclohexadienone (1.1 eq.), 23 °C, 5 h; **1.91** not isolated but identified by analysis of the products from subsequent reactions.

Section 1.2

Organic electron-transfer reagents

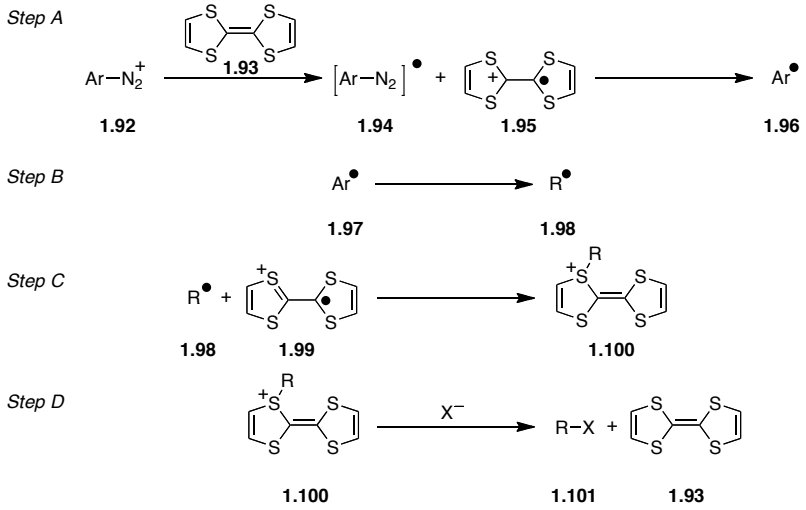
With the highly attractive prospect of organic redox reagents providing a lucrative and worthwhile target for researchers around the world, the use of alternatives to traditional metal reagents has become increasingly popular. For example, a replacement for alkali metals in the Birch reduction[2] would be a highly attractive achievement. Metals are clearly important but the use of many metals requires the monitoring of waste streams for evidence of contamination, while other metal salts cause problems such as corrosion.[38] The use of complexed metals on solid supports can overcome these problems, provided that leaching is not observed, however complexation of certain neutral metals, *e.g.* alkali metals, is not easy. The research documented in this thesis is part of a larger project that seeks to develop effective organic reducing agents that can vie with powerful metal reductants. The use of organic systems can lead to greater selectivity, enhanced solubility and more robust attachment to solid supports, which can avoid the problems of leaching. In this second section of the introduction, the advancement of organic reducing agents and the capabilities in the reduction of organic compounds will be discussed. The recent advances in this interesting area of chemistry, including that of the Murphy group at the University of Strathclyde, will then be highlighted.

Early organic electron-transfer reagents

In terms of reduction *via* organic electron transfer reagents, an important reagent in their development is tetrathiafulvalene **1.93**. Tetrathiafulvalene (TTF) employs four sulfur atoms that donate electron-density providing an electron-rich donor that is highly effective in the reduction of arenediazonium salts, which themselves are excellent electron acceptors.[39] One mechanism that TTF reacts by is termed the Radical-Polar Crossover reaction, where, in effect, the radical and ionic (polar) reactions occur consecutively in the same pot (scheme 1.17).[39] In step A, TTF **1.93** transfers an electron to an arenediazonium salt (**1.92**), forming an intermediate radical **1.94**, which fragments generating nitrogen and forming an organic radical **1.96**. In step B, the lifetime of the organic radical is crucial. Provided the radical lifetime is sufficient, further chemistry can occur such as cyclisation, fragmentation

or atom-abstraction. Combination with the TTF radical cation **1.99** occurs in step C to form intermediate **1.100**, after which time the radical process is complete and the "crossover" to polar chemistry occurs. The final step (step D) of nucleophilic substitution generates the product **1.101** and releases TTF **1.93**, meaning the process could be made catalytic.[39]

Scheme 1.17: the Radical-Polar Crossover reaction

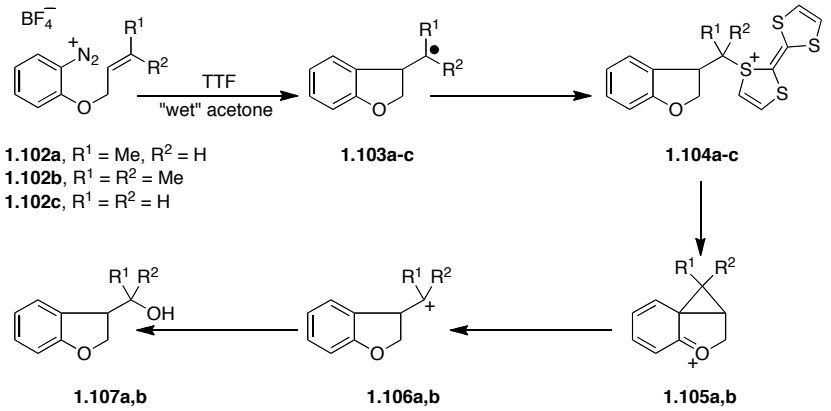


An alternative mechanism has also been proposed, with cationic, rather than radical intermediates involved.[40] The initial step would be spontaneous loss of nitrogen from **1.92** forming an aryl cation. However, this proposal can be rejected as NMR studies have shown that arenediazonium salts do not spontaneously decompose into their aryl cations at room temperature in acetone. Also, if the aryl cation was present, then the role of the sulfide (*i.e.*, TTF) would be to trap the cations following cyclisation, indicating that any sulfide could be used. Based on this, separate reactions involving TTF and dimethyl sulfide with arenediazonium salts showed that no reaction occurred with dimethyl sulfide, while immediate effervescence was evident using TTF. This showed the importance of TTF as an electron transfer agent and led to the aryl cation mechanism being rejected.[40]

An example of the Radical-Polar Crossover reaction is shown in scheme 1.18. Here, arenediazonium salt **1.102** was reacted with TTF **1.93** forming an intermediate aryl radical which cyclises to form alkyl radical **1.103**. This alkyl radical can trap the radical cation of TTF **1.95** forming polar intermediate **1.104**. Now, elimination of TTF **1.93** *via* neighbouring group participation[41] occurs forming **1.105**, followed by

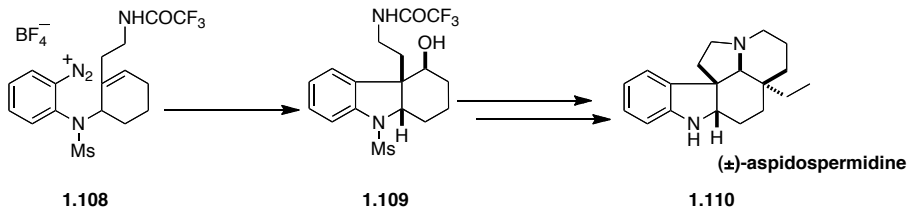
quenching of cation **1.106** with water resulting in formation of alcohol product **1.107**. Importantly, acetone should be used as the reaction solvent and the source of water.[39] Furthermore, the use of terminal alkenes (*e.g.* **1.102c**, R^1=R^2=H) results in no product alcohol **1.107c** being isolated. Instead the reaction stops at the polar sulfonium salt **1.104c** stage, indicating that at least one alkyl substituent is required to achieve conversion by substitution to product **1.107**.

Scheme 1.18: the Radical-Polar Crossover reaction for the formation of alcohols **1.107**.



The Radical-Polar Crossover reaction and TTF have been employed in the total synthesis of (±)-aspidospermidine **1.110**[42,43] (scheme 1.19), a compound closely related to the important anti-cancer agents vinblastine and vincristine. The TTF-induced cyclisation of arenediazonium salt **1.108** to form tricyclic alcohol **1.109** was completed in good yield to afford a single isomer of the required alcohol **1.109**. Crucially, the use of a radical cyclisation generated the *cis*-stereochemistry at the fused ring junction in **1.109**.

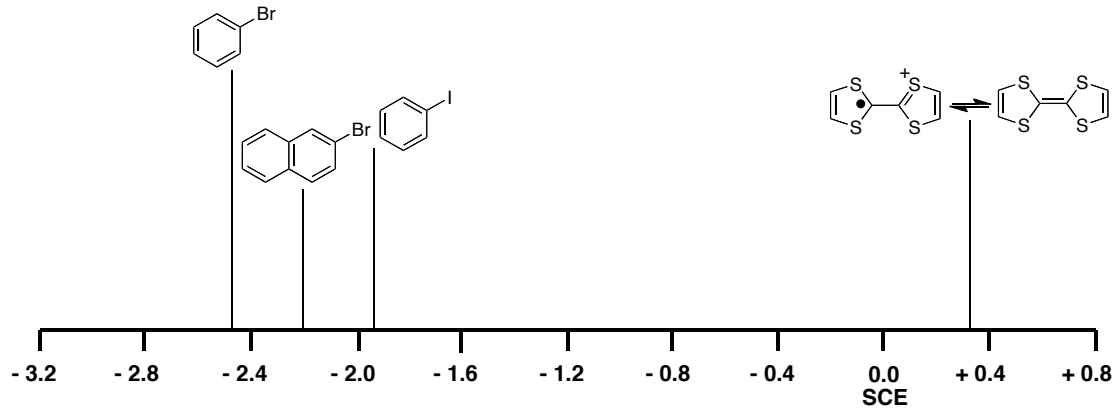
Scheme 1.19: the use of the Radical-Polar Crossover reaction in the synthesis of (±)-aspidospermidine.



Reaction conditions:[44] a) TTF, acetone, H_2O, 2 days; **1.109**, 45%.

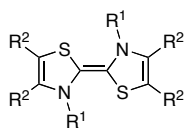
However, one major limitation when considering TTF as an effective electron donor is that the measured redox potential for the first electron is only +0.321 V (vs. SCE, in MeCN).[45] This is clearly sufficient when suitable electron acceptors such as arenediazonium salts are used,[39-43] however, TTF is ineffective for the reduction of more challenging substrates such as aryl halides. For example, the reduction potential of a common aryl halide, bromobenzene, is -2.43 V (vs. SCE in DMF), while the considerably less challenging iodobenzene has a reduction potential of -1.91 V (vs. SCE in DMF).[46] Both halides are beyond the scope of TTF. Clearly, the limited reactivity of TTF indicates that a more powerful reductant is required.

Figure 1.1: reactivity scale comparing TTF and common aryl halides vs. SCE.



In an effort to extend the limit of reactivity towards the level of common aryl halides, the next contribution took the form of incorporating nitrogen into the donor molecule. The highly π-electron-donating ability of nitrogen would provide a more powerful electron donor. Diazadithiafulvalenes **1.111** were studied in 1995 to determine their ability as electron transfer reagents.[47] Each molecule incorporated an electron-withdrawing group at the 4,4′ and 5,5′ positions (R^2 in figure 1.2) to moderate the strong donating properties and high reactivity of the basic system towards molecular oxygen (figure 1.2).

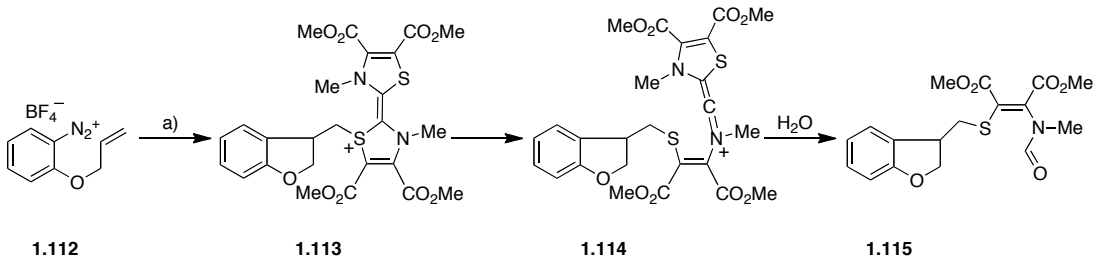
Figure 1.2: generic structure of diazadithiafulvalenes.



1.111

Diazadithiafulvalenes have been shown to be powerful single electron donors, with a measured redox potential of -0.02 V (vs. SCE in MeCN)[47] where R^1 = Me, R^2 = CO_2Me, a value considerably more negative (hence more reducing) than TTF (see figure 1.1, above). However, Koizumi and co-workers have shown that diazadithiafulvalenes undergo a side-reaction with arenediazonium salts forming unwanted by-products and thus inhibiting the required reaction.[48] In the Radical-Polar Crossover reaction, the presence of nitrogen leads to formation of intermediate keteniminium salts **1.114** that are rapidly trapped with water, furnishing ring-opened products **1.115** (scheme 1.20). This is due to the greater ability of nitrogen to stabilise positive charge in **1.114**.

Scheme 1.20: ring-opening side-reaction of diazadithiafulvalenes with arenediazonium salts.



1.112 **1.113** **1.114** **1.115**

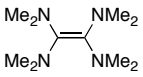
Reaction conditions: a) **1.111** (R^1 = Me, R^2 = CO_2Me), acetone; **1.115,** 70%.

The study of diazadithiafulvalenes provided a key piece of information towards the synthesis of powerful organic electron donors. Since diazadithiafulvalenes proved to be more powerful electron donors than TTF, it highlighted the fact that substitution of sulfur for nitrogen benefited electron donor ability. Nitrogen is better at stabilising an adjacent positive charge compared with sulfur. Also, with both TTF and diazadithiafulvalenes, donation of an electron results in an aromatic radical cation. A nitrogen atom within the radical cation unit would have better orbital overlap, due to the similar size between nitrogen and carbon orbitals, and thus the corresponding radical-cation would have greater aromaticity.

The role of nitrogen within organic electron donors was further expanded with the development of 1,1,2,2-*tetrakis*-(dimethylamino)ethylene (TDAE) **1.116** (figure 1.3). Médebielle and co-workers have extensively developed the electron-transfer chemistry of TDAE in the synthesis of fluorinated molecules.[49] Furthermore, the redox potential of TDAE was measured at -0.62 V (vs. SCE in *N,N*-

dimethylformamide)[50] – a significantly more negative potential than any previously discussed organic electron donor.

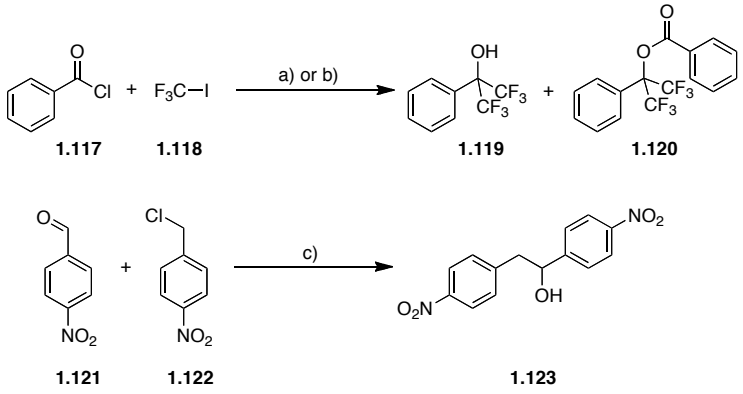
Figure 1.3: the structure of 1,1,2,2-*tetrakis*-(dimethylamino)ethylene (TDAE) **1.116**.



1.116

Médebielle and co-workers have found that the use of iodotrifluoromethane **1.118** as a trifluoromethyl anion precursor is possible when used with TDAE. Use of *N,N*-dimethylformamide as solvent led to coupling of benzoyl chloride **1.117** with the trifluoromethyl anion to afford alcohol **1.119** and ester **1.120** products.[51] Alcohol **1.119** results from double addition of trifluoromethyl anion on benzoyl chloride **1.117**, whereas ester **1.120** results from attack of the alkoxide equivalent of alcohol **1.119** on benzoyl chloride **1.117** starting material. Importantly, the authors state that when 1,2-dimethoxyethane was used as solvent, near complete conversion to ester **1.120** was observed. In 2003, Médebielle and co-workers followed their initial work by revealing the synthesis of diarylethanol derivatives (e.g. **1.123**) using TDAE to generate a nitrobenzyl carbanion of **1.122**, which coupled to aldehyde **1.121** to generate alcohol **1.123**.[52] The importance of an electron-withdrawing group in the *para*-position is also clear as the authors state that the analogous reaction using benzyl chloride resulted in no conversion and complete recovery of starting materials. It is likely that the electron-withdrawing group is crucial to stabilise the intermediate benzyl anion. This mild and original method avoids the use of organometallic/transition metal reagents to facilitate this coupling. The authors also indicate the possible advantages of this methodology towards pharmaceutical-based targets.

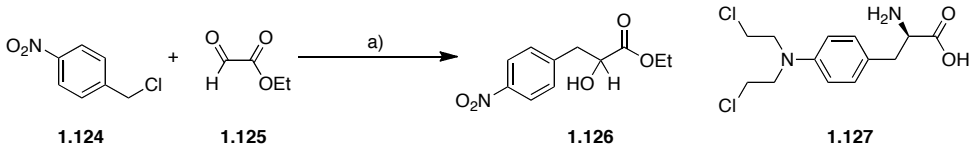
Scheme 1.21: the use of TDAE and iodotrifluoromethane in coupling reactions with benzoyl chlorides.



Reaction conditions: a)TDAE, DMF, -20 °C to r.t., 2 h; **1.119**, 5%, **1.120**, 44% b) TDAE, DME, -20 °C to r.t., 2 h; **1.120**, >98%; c) TDAE, DMF, -20 °C, 1 h then r.t, 2 h; **1.123**, 85%.

This methodology has also been extended to the coupling of an α-carbonyl ester **1.125** with a *para*-nitrobenzyl chloride **1.124** to form a 2-hydroxy-3-arylpropionic acid ethyl ester derivative **1.126** (scheme 1.22).[53] The products from these reactions could be considered as precursors to Melphalan analogues **1.127**, a nitrogen mustard derivative and important anti-cancer agent that is used in the treatment of patients with breast and ovarian cancers.

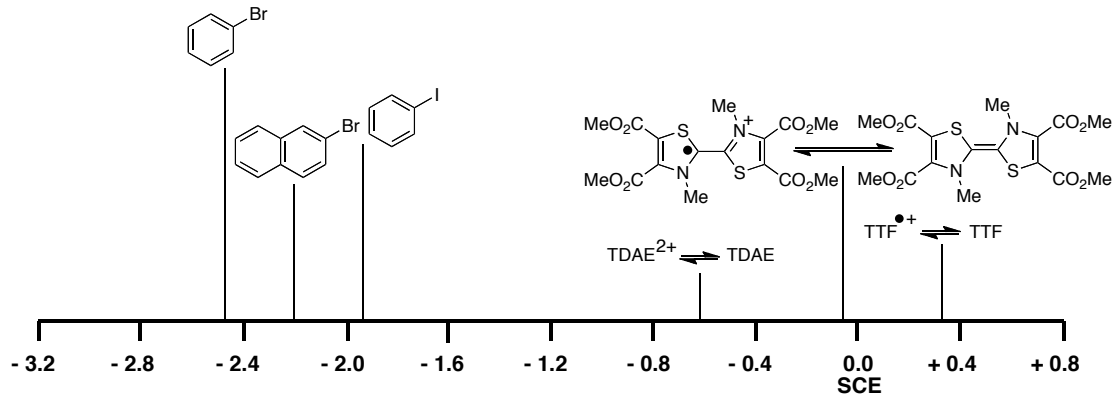
Scheme 1.22: the synthesis of an α-carbonyl ester derivative and the structure of Melphalan **1.127**, an anti-cancer agent.



Reaction conditions: a) DMF, -20 °C, 1 h then r.t., 2 h; **1.126**, 60%.

At this stage, following the above discussion of the development of neutral organic electron donors, it is useful to show the relative reducing power of each reagent (figure 1.4). Clearly, there is still considerable scope for a more powerful organic reductant, with TDAE possessing the most negative, and hence most reducing, redox potential. Furthermore, each of the electron donors revealed thus far has limited reactivity with common organic molecules, such as non-activated halides. An electron donor capable of this role would be a considerable advance in the chemistry of neutral organic electron donors.

Figure 1.4: reactivity scale comparing TTF, diazadithiafulvalenes and TDAE, with common aryl halides.

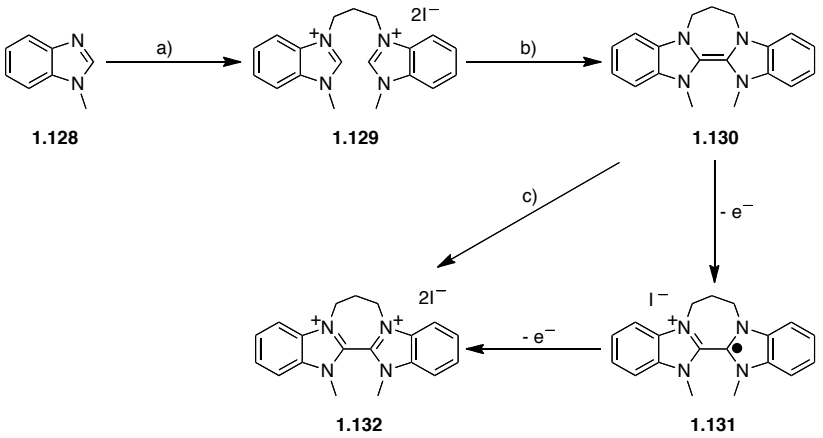


Super Electron Donors

Tetrathiafulvalene has shown that aromatic stabilisation energy is a key factor in an electron-transfer reagent, while TDAE has shown that the presence of nitrogen atoms with the electron donor are also greatly beneficial, due to the increased π-donation ability of nitrogen over sulfur. Murphy and co-workers combined these two fundamental ideas in 2005[54] and published the first example of a Super-S.E.T. reagent (Super-S.E.T. reagents are defined as reagents that are capable of reducing aryl halides). The structure of such a Super-S.E.T. reagent is benzimidazole-derived donor **1.130** (scheme 1.23), where it is clear that the two fundamental ideas outlined above are acting in concert. The synthesis of donor **1.130** is straightforward, with methylation of benzimidazole to form *N*-methylbenzimidazole **1.128** and alkylation with 1,3-diiodopropane in refluxing acetonitrile - affording diiodide precursor salt **1.129**. Treatment of the diiodide salt **1.129** with base affords donor **1.130** as a bright yellow, air- and moisture-sensitive solid (scheme 1.23). As a result, isolation and characterisation of donor **1.130** was carried out under an inert atmosphere. It is also possible to generate the active donor **1.130** *in situ* in solution and perform chemistry without isolation of the active species. The structure of donor **1.130** was confirmed by NMR studies, which indicated a characteristic peak at 123.1 ppm in the ^{13}C NMR corresponding to the central quaternary carbon. Further confirmation came from reaction of donor **1.130** with iodine, forming dication **1.132**, following loss of two electrons. The iodine was easily reduced, readily forming dication **1.132**, which was isolated and identified by NMR, supporting the formation

of donor **1.130**. Finally, ^{1}H NMR analysis of dication **1.132** indicated that the protons on the carbons bonded to the nitrogen atoms in the bridge are diastereotopic, a result of the helical twist imparted to the molecule due to positive charge repulsion.

Scheme 1.23: the synthesis of benzimidazole-derived donor **1.130**.

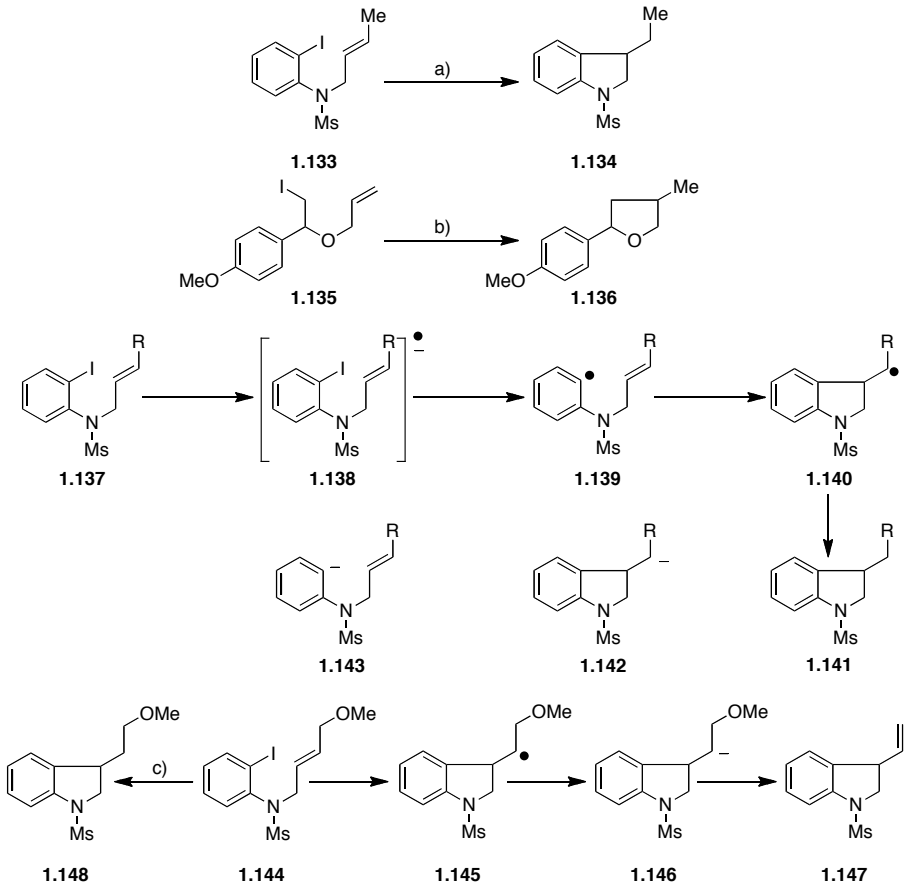


Reaction conditions: a) 1,3-diiodopropane, MeCN, reflux, 72 h; b) base; c) iodine, Et_2O.

Ames and co-workers[55] measured the reduction potential of donor **1.132** (with two bromides for counter-ions) as -0.76 V for the first electron and – 0.82 V for the second electron (both vs. SCE in *N*,*N*-dimethylformamide), meaning that donor **1.130** is the most powerful organic electron-donor discussed thus far. Murphy and co-workers examined the reactivity of the benzimidazole-derived donor **1.130** on a range of aryl and alkyl iodides.[54] In the first case, aryl iodides underwent smooth reduction and cyclisation to afford indoline products in excellent yields (for example, **1.133** to **1.134**, scheme 1.24). Similarly, aliphatic iodides reacted with donor **1.130** to form saturated cyclic products (e.g., **1.135** to **1.136**, scheme 1.24). A radical mechanism[54] was proposed following extensive investigation, with support for an aryl radical intermediate **1.139** over an aryl anion intermediate **1.143** coming from the non-incorporation of DMF into the isolated products (which would be expected with an aryl anion such as **1.143**). The aryl radical intermediate **1.139** is primed to cyclise in a 5-*exo*-trig manner to afford alkyl radical intermediate **1.140**, which can abstract a hydrogen atom to afford the product indoline **1.141**. In addition, substrate **1.144** was examined to investigate the intermediacy of alkyl anions, such as **1.142**. Donation of a single electron to **1.144** would result in loss of iodide and cyclisation as described above, resulting in alkyl radical **1.145**. If such a species abstracted a further electron, alkyl anion **1.146** would be formed resulting in elimination of

methoxide to form styrene **1.147**.[56] However, no styrene **1.147** was observed, with excellent conversion to indoline **1.148** occuring, lessening the likelihood of intermediate alkyl anions and resulting in the proposed radical mechanism (scheme 1.24).[54] A similar mechanism for the reduction of alkyl iodides is also probable.

Scheme 1.24: the reactivity of donor **1.130** and the proposed radical mechanism.

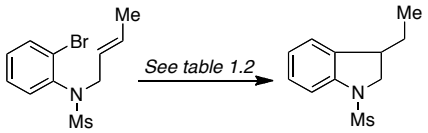


Reaction conditions: a) Salt **1.129** (1.2 eq.), KHMDS, toluene/DMF (2:1), 100 °C, Ar; **1.134**, 88%; b) Salt **1.129** (4.0 eq.), KHMDS, THF *then* toluene, 100 °C, Ar; **1.136**, 83%; c) Salt **1.129** (1.6 eq.), KHMDS, toluene/DMF (2:1), 100 °C, Ar; **1.148**, 90%.

The scope of benzimidazole-derived donor **1.130** was fully investigated and, as such, aryl bromides were closely examined to determine whether they would also be suitable substrates for donor **1.130**. This would allow donor **1.130** to be a more widely applicable reagent. Bromide **1.149** was synthesised using classic methods[57] and was subsequently tested with donor **1.130** under two different sets of conditions (table 1.2). It is clear in each case that low yields of cyclised product **1.134** were isolated, leading to the conclusion that donor **1.130** was insufficiently powerful to

reduce unactivated aryl bromides efficiently, even with extended reaction times. It was noted by the author that the reactions were performed under relatively dilute conditions and that more concentrated conditions had proved successful with other substrates.[57] However, it is clear that harsh and forceful conditions are required for the reduction of aryl bromides, highlighting their incompatibility with donor **1.130**. As such, a more powerful and more reactive organic electron donor would be required in order to achieve the reduction of challenging organic substrates.

Table 1.2: the reaction of an aryl bromide **1.149** with benzimidazole-derived donor **1.130**.



1.149 **1.134**

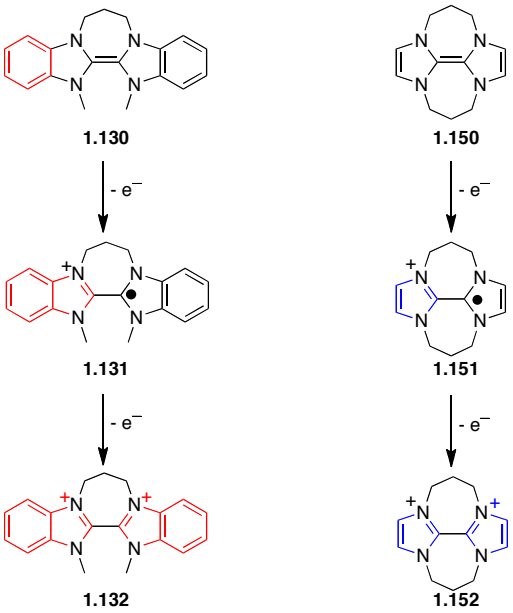
Equivalents of salt 1.129*	Equivalents of KHMDS*	Reaction time	Other conditions	Yield of 1.134 (%)
2.0	4.0	36 h	120 °C, DMF	30
4.0	8.0	7 days	120 °C, DMF	27

By collating and comparing the results highlighted for donor **1.130**, it is clear that a new, more powerful electron donor would be an important synthetic tool. Throughout the discussion of TTF, TDAE *etc.*, it was clear that both π-electron donation by neighbouring nitrogen atoms (to stabilise increasing positive charge after electron donation) and aromatisation following electron transfer were crucial factors in contributing to the strength of an electron donor. With electron donors such as TTF and benzimidazole-derived donor **1.130**, the driving force for electron transfer is the aromatisation energy gained on forming the radical cation by-product **1.131** (or dication **1.132**). In donor **1.130**, on transferring an electron to form **1.131** (or a second electron to form **1.132**), there is a considerable gain in aromatisation by forming the benzimidazole heterocycle (figure 1.5). Nevertheless, there does also exist aromaticity present within the donor prior to donation of an electron and formation of radical cation **1.131** (or dication **1.132**). This existing aromaticity lessens the aromatic energy gain achieved following electron transfer.

* Relative to one equivalent of bromide **1.149**.

In 2007, Murphy and co-workers[58] further developed the super electron donors to include the analogous imidazole-derived donor **1.150** (figure 1.5). The second generation of super electron donor also incorporates a second three-carbon bridge. Comparison of donor **1.150** with benzimidazole-derived donor **1.130** in terms of aromaticity gained reveals a major difference. Formation of radical cation **1.151** (or dication **1.152**) results in a substantial aromaticity gain since there is no inherent aromaticity within the original donor structure **1.150**. The generation of this new aromaticity results in a substantial energy gain for donor **1.150**. This was considered to mean that donor **1.150** would be a considerably more powerful organic electron donor than had been previously discovered.

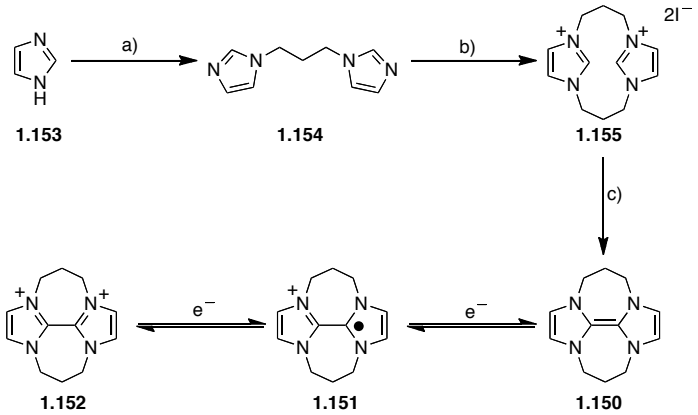
Figure 1.5: the contrast between the aromaticity gained in donor **1.130** and donor **1.150** after donation of one or two electrons.



Previously, several groups have studied donor **1.150**. Ames and co-workers[55] studied a range of biaryl molecules, both with and without a carbon bridge, and found that the redox potential on moving from **1.152** (bromide counter-ions) to donor **1.150** was -1.20 V (vs. SCE in *N,N*-dimethylformamide) or, alternatively, -1.18 V and -1.37 V (ir) (vs. SCE in acetonitrile). Also, Thummel and co-workers[59] showed that the redox potential for the reversible conversion of **1.152** to **1.150** was -1.14 V (vs. SCE in dimethyl sulfoxide). Clearly these values show that imidazole-derived donor **1.150** is a substantially more powerful electron donor than benzimidazole-derived donor **1.130**. The synthesis of donor **1.150** had been reported previously,[59,60,61]

although a large-scale synthesis to provide substantial quantities of **1.150** was unavailable prior to the report by Murphy and co-workers.[58] Imidazole-derived donor **1.150** was synthesised starting from alkylation of two equivalents of imidazole **1.153** with 1,3-dibromopropane to form the three-carbon-bridged *bis*imidazole precursor **1.154**. A second alkylation with 1,3-diiodopropane under dilute conditions generated the required diiodide salt **1.155**, as a stable crystalline solid. Donor **1.150** can either be prepared *in situ* using sodium hydride in *N*,*N*-dimethylformamide, or, alternatively, using sodium hydride in liquid ammonia. Evaporation of the ammonia solvent and extraction using diethyl ether afforded **1.150** as an air- and moisture-sensitive pure yellow solid (scheme 1.25).

Scheme 1.25: the synthesis of imidazole-derived donor **1.150**.

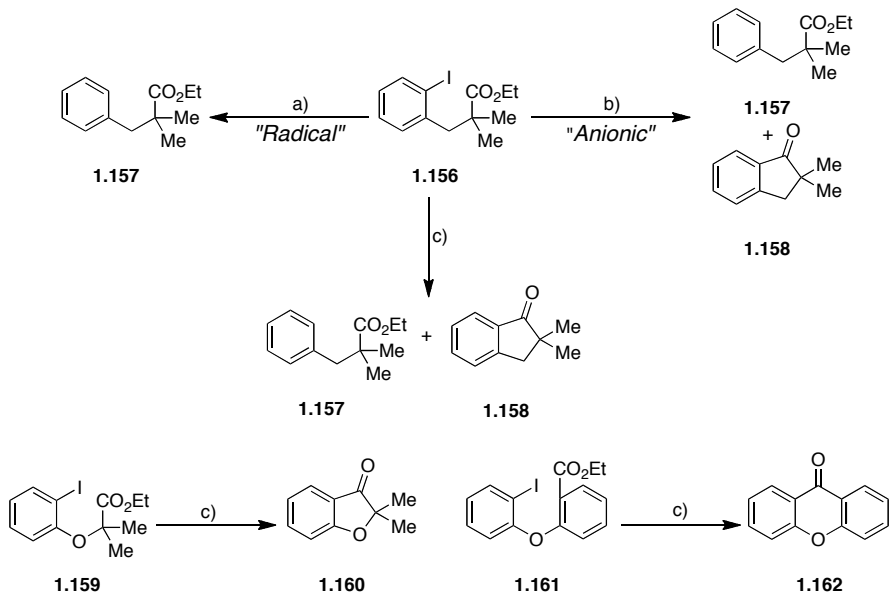


Reaction conditions: a) 1,3-dibromopropane, NaH, DMF, 0 °C to r.t., 18 h; **1.154**, 72%; b) 1,3-diiodopropane, MeCN, reflux, 24 days; **1.155**, 51%; c) NaH, NH_3, -78 °C, 6 h, r.t., 12 h, Ar; **1.150**, 98%.

Initial investigations into the scope of donor **1.150** revealed remarkable reactivity. Cyclic voltammetry indicated that two electrons were transferred from donor **1.150** almost concurrently to form dication **1.152**.[62] This led to the likelihood of aryl anion formation upon reduction of a suitable electron acceptor. However, to allow confirmation of aryl anions, a suitable diagnostic test was required.[58] Substrate **1.156** was chosen as a suitable candidate (scheme 1.26). When iodide **1.156** was exposed to the classical radical methodology of tris(trimethylsilylsilane) and AIBN in toluene, no cyclisation occurred and only reduced product **1.157** was isolated. This indicates that radical intermediates will not cyclise to form the ketone product **1.158**. Iodide **1.156** was also tested using anionic conditions. Thus, following exposure of **1.156** to caesium fluoride and trimethyl(tributylstannyl)silane,[63] ketone **1.158** was

formed in 68% yield, together with a small amount of reduced product **1.157**. As such, the isolation of indanone **1.158** is indicative of intermediate aryl anions (scheme 1.26). Murphy and co-workers[58] then exposed iodide **1.156** to imidazole-derived donor **1.150**, resulting in a mixture of reduced product **1.157** (70%) and indanone **1.158** (16%). It is likely that protonation of the intermediate aryl anion (forming product **1.157**) acts in competition to formation of indanone **1.158**. To achieve a higher yield of cyclised product, the reaction was repeated on modified substrates **1.159** and **1.161**, where the inclusion of an oxygen linker should allow a more facile cyclisation. This was indeed the case, with the products **1.160** (51%) and **1.162** (45%) isolated in improved yield following exposure to donor **1.150** (scheme 1.26). Products **1.158**, **1.160** and **1.162** can only result from intermediate aryl anions; thus, donor **1.150** is the first neutral organic reagent capable of producing aryl anions following donation of two electrons.[58] The authors also state that the yields of products **1.158**, **1.160** and **1.162** are representative of the *minimum* amount of aryl anion formed during each reaction.

Scheme 1.26: the generation of anions using donor **1.150**.

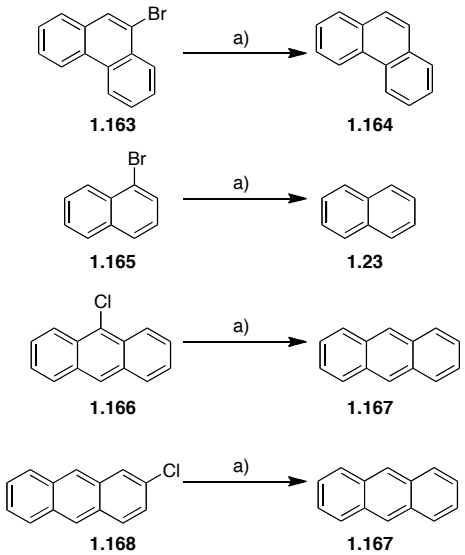


Reaction conditions: a) $(Me_3Si)_3SiH$, AIBN, toluene, 90 °C, 15 h, Ar; **1.157**, 70%; b) Bu_3Sn-$SiMe_3$, CsF, DMF, 100 °C, 2.5 h, Ar; **1.157**, 14%, **1.158**, 68%; c) donor **1.150** (1.6 eq.), DMF, 18 h, r.t., N_2; **1.157**, 70%, **1.158**, 16%; **1.160**, 51%; **1.162**, 45%.

Due to the high-level of reactivity exhibited by donor **1.150** thus far, further, more stringent examinations of the reactivity of **1.150** (scheme 1.27) were conducted. Previously, the benzimidazole-derived donor **1.130** was unsuccessful in reducing

aryl bromides (see table 1.2).[54] It was proposed that the increased reducing power that had been shown by donor **1.150** in the generation of aryl anions could lead to successful reduction of more challenging aryl halides.[58] To this end, 9-bromophenanthrene **1.163** was cleanly reduced to afford phenanthrene **1.164** (96%). Similarly, 1-bromonaphthalene **1.165**, 9-chloroanthracene **1.166** and 2-chloroanthracene **1.168** were all reduced under similar conditions to afford naphthalene **1.23** (86%) and anthracene **1.167** (99% and 97% respectively). The benzimidazole-derived donor **1.130** was unsuccessful in effecting these transformations, further indicating the substantial difference in reactivity between these two donors.

Scheme 1.27: the reduction of aryl bromides and chlorides using donor **1.150**.

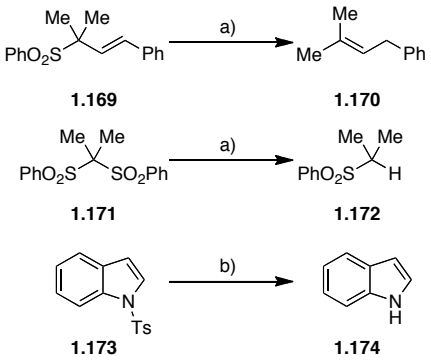


Reaction conditions: a) salt **1.155** (1.5 eq.), NaH, DMF, Ar, 100 °C, 18 h; **1.164**, 96%; **1.23**, 86%; **1.167**, 99% (from **1.166**); **1.167**, 97% (from **1.168**).

The repertoire for donor **1.150** was expanded further still in 2007.[64] Activated sulfones, bissulfones and sulfonamides proved to be a highly compatible set of functional groups with donor **1.150** (scheme 1.28). For example, activated monosulfone **1.169** was cleanly reduced using three equivalents of donor **1.150**, at 110 °C in *N*,*N*-dimethylformamide to afford alkene **1.170** in good yield (79%). Under the same conditions, bissulfone **1.171** was cleaved to the corresponding monosulfone **1.172** in excellent yield (97%). Furthermore, by doubling the amount of donor **1.150** used from three to six equivalents, sulfonamides were also cleaved. *N*-Toluenesulfonylindole **1.173** was deprotected cleanly to afford indole **1.174**

(91%). The use of donor **1.150** as a neutral, easily prepared reagent in conventional glassware and apparatus has several advantages such as close control of starting concentration (in contrast to electrochemistry where the concentration of active reducing agent is unknown as it is produced *in situ*) and use of higher temperatures.

Scheme 1.28: the reduction of activated sulfones, bissulfones and sulfonamides using donor **1.150**.



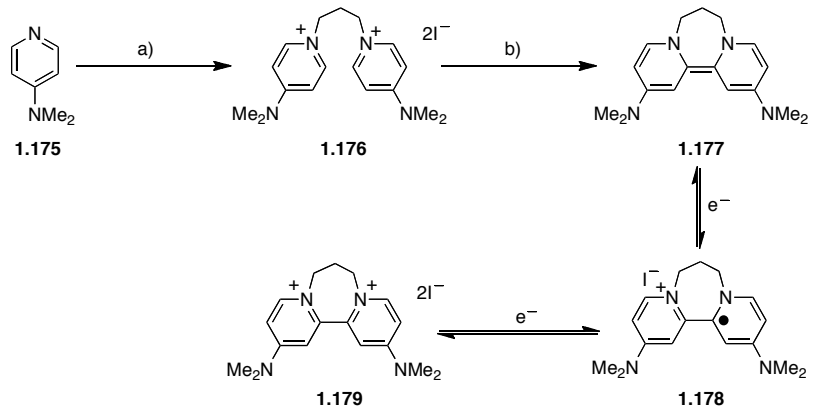
Reaction conditions: a) salt **1.155** (3.0 eq.), NaH, DMF, Ar, 18 h, 110 °C; **1.170**, 79%; **1.172**, 97%; b) salt **1.155** (6.0 eq.), NaH, DMF, Ar, 4 h, 110 °C; **1.174**, 91%.

Donor **1.150** has been shown to be an exceptionally powerful electron donor. However, the main disadvantage is that synthesis of disalt **1.155** requires an extended reaction time of 24 days.[58] Although the synthesis can be done on a large scale, thus lessening the effect of such a lengthy reaction time, Murphy and co-workers[65] provided an alternative to donor **1.150**. Based on 4-dimethylaminopyridine (DMAP), donor **1.177** contains the key principles of aromatic stabilisation after electron donation and π-stabilisation by nitrogen atoms that were detailed above. The DMAP-derived donor **1.177** has proved to be an excellent super electron donor that is capable of a wide range of synthetically useful transformations, which will be detailed below.[65,66,67,68]

Thus the 3rd generation of super electron-donor was disclosed in 2008.[65] The synthesis of donor **1.177** is extremely straightforward, with alkylation of two equivalents of 4-DMAP **1.175** by 1,3-diiodopropane furnishing salt **1.176** in high yield (scheme 1.29). Once more, salt **1.176** can be used to form donor **1.177** *in situ* by treatment with base, *e.g.* sodium hydride, or, alternatively, treated with sodium hydride in liquid ammonia to isolate pure donor **1.177** as a dark purple solid. Cyclic voltammetry revealed that donor **1.177** has a measured redox potential of -1.13 V

(vs. Ag/AgCl/KCl (sat.) in *N*,*N*-dimethylformamide)[65] thus was considered to be as powerful a reductant as imidazole-derived donor **1.150**. In contrast to donor **1.150** however, both electrons from donor **1.177** are transferred at the same potential forming dication **1.179** (scheme 1.29), making the DMAP-derived donor **1.177** a powerful double electron-donor (the cyclic voltammogram of donor **1.150** revealed a small shoulder on both the oxidation and reduction waves, indicating that the second electron is slightly more challenging to lose than the first).

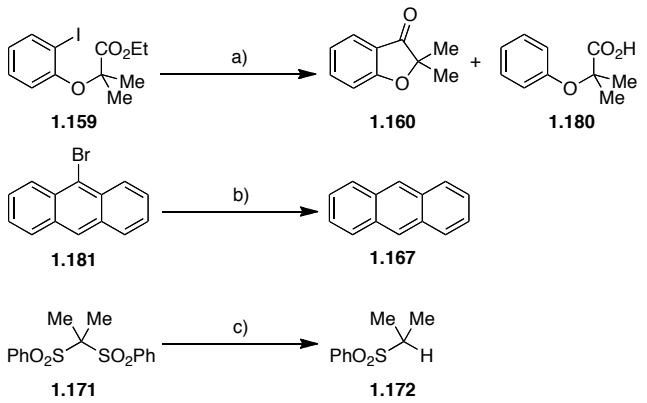
Scheme 1.29: the synthesis of DMAP-derived donor **1.177**.



Reaction conditions: a) 1,3-diiodopropane, MeCN, reflux, 48 h; **1.176**, 98%; b) NaH, NH_3, -33 °C, 6 h, r.t., 12 h, Ar; **1.177**, 83%.

The reactivity of donor **1.177** was also revealed.[65] As expected, a similar level of reactivity to imidazole-derived donor **1.150** was evident. Due to the double electron-transfer, donor **1.177** is capable of generating aryl anions when exposed to iodide **1.159**, resulting in cyclisation to form ketone **1.160** (83%). Murphy states that with at least 83% of aryl anions generated by exposure of iodide **1.159** to donor **1.177**, this is the highest yield of aryl anions formed by an organic electron donor. Further reactivity was also revealed.[65] For example, 9-bromoanthracene **1.181** was smoothly reduced to form anthracene **1.167** in an excellent 96% yield. Similarly, activated sulfones were also compatible with the DMAP-derived donor **1.177**. Reduction was achieved in excellent yields for each sulfone investigated (*e.g.*, the conversion of bissulfone **1.171** to monosulfone **1.172**).

Scheme 1.30: the reactivity of DMAP-derived donor **1.177** with various substrates.



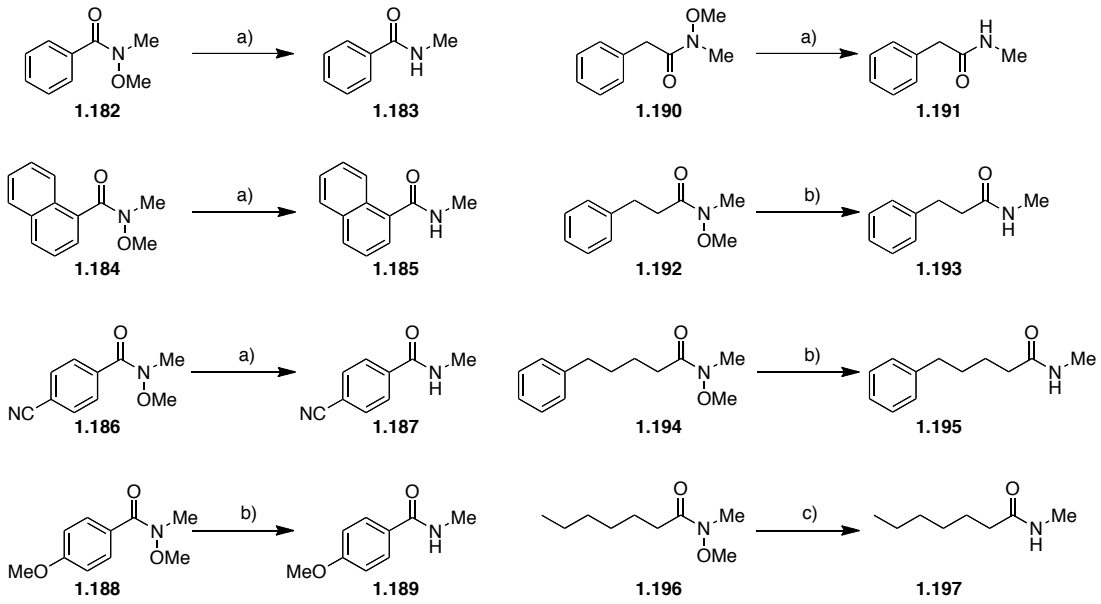
Reaction conditions: a) donor **1.177** (1.5 eq.), DMF, r.t., 18 h *then* KOH, H_2O, MeOH, 50 °C, 12 h; **1.160**, 83%; **1.180**, 8%; b) donor **1.177** (1.5 eq.), DMF, r.t., 18 h; **1.167**, 96%; c) donor **1.177** (3.0 eq.), DMF, 100 °C, 18 h; **1.172**, 96%.

Donor **1.177** has also been extensively applied to the reductive cleavage of N-O bonds in Weinreb amides.[66] Tuning of the reaction conditions allowed complete reductive cleavage to be achieved. For example, while 1.5 equivalents of donor **1.177** at room temperature was effective in the reductive cleavage of substrates containing electron-neutral (**1.182** to **1.183**, **1.184** to **1.185**) or electron-deficient (**1.186** to **1.187**) aromatic systems, heating to 100 °C was required to effect the same cleavage in substrates containing electron-rich aromatic systems (**1.188** to **1.189**). Furthermore, when conjugation with a π-system was removed or distant, reductive cleavage became more challenging.[66] In the extreme case with no aromatic moiety present in the substrate (**1.196**), five equivalents of donor **1.177** were required, together with heating to 100 °C, to achieve a 43% yield of amide **1.197**. Cutulic and co-workers state that the LUMO orbital, calculated using Spartan®,* rests upon the aromatic moiety in every case. When the aromatic ring is conjugated with a Weinreb amide, the LUMO energy is lowest (*e.g.*, **1.182**, LUMO 2.93 eV) and the LUMO spans both aromatic and amide components of the substrate, resulting in facile reduction to amide **1.183**. When methylene groups separate the aromatic and amide components (*e.g.*, **1.192** and **1.194**), the LUMO energy rises and reductive cleavage to form amide products is more challenging, which is reflected in the isolated yields of amides **1.193** and **1.195** (77% and 60% respectively). Thus, Cutulic and co-workers have clearly shown that the LUMO

* Calculated using equilibrium geometry, Hartree-Fock, 6-31G**.

energy correlates with the ease of N-O bond cleavage.[66] They propose that in the presence of an aromatic ring, initial electron transfer occurs to the arene moiety with subsequent intramolecular transfer to the Weinreb amide. When an aryl ring is not present or is distant from the Weinreb amide component, intramolecular electron transfer is significantly more challenging (or not possible in the case of **1.196**), alongside the initial electron transfer, and isolated yields of amide products **1.193**, **1.195**, and **1.197** are lower. The authors also propose an alternative rationale involving π-stacking between the aromatic component and the Weinreb amide, enhancing the likelihood of initial electron transfer to the arene unit.

Scheme 1.31: the reactivity of donor **1.177** with Weinreb amides.

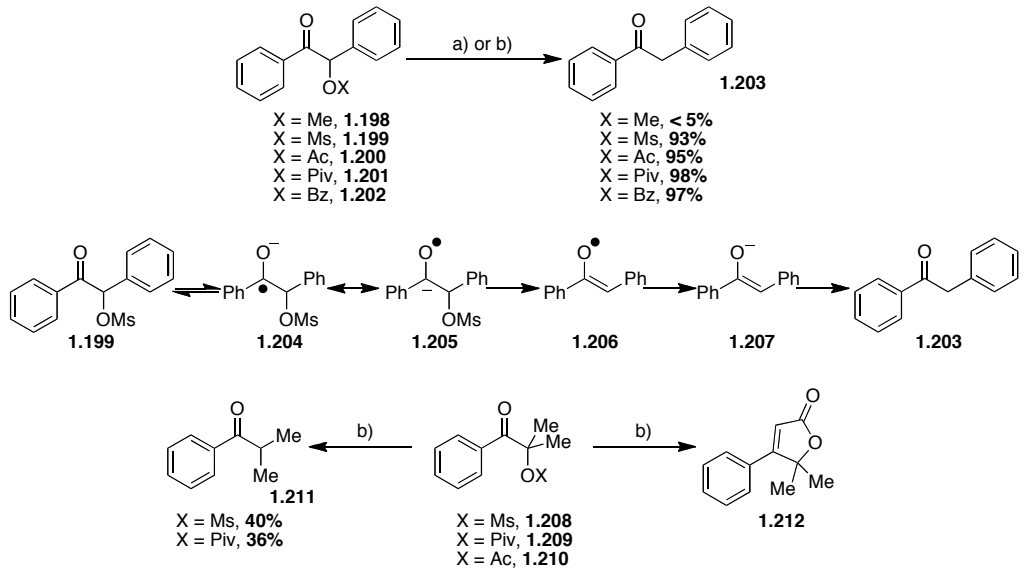


Reaction conditions: a) donor **1.177** (1.5 eq.), DMF, r.t., 18 h; **1.183**, 80%; **1.185**, 92%; **1.187**, 87%; **1.191**, 76%; b) donor **1.177** (1.5 eq.), DMF, 100 °C, 18 h; **1.189**, 81%; **1.193**, 77%; **1.195**, 60%; c) donor **1.177** (5.0 eq.), DMF, 100 °C, 18 h; **1.197**, 43%.

A further substrate class that was extensively investigated were protected acyloin derivatives.[67] Electron-rich groups (**1.198**) proved incompatible under these conditions, despite high reaction temperatures. However, when electron-withdrawing functionality (*e.g.*, **1.199** - **1.202**) was employed, efficient reduction was observed at room temperature (scheme 1.32). The proposed mechanism involves electron transfer to the LUMO of the substrate (*e.g.*, **1.199**), which was calculated as residing principally upon the aroyl component. The intermediate ketyl radical anion **1.205** will cleave the C-O bond in the α-position to afford the enolyl radical **1.206**.

Enolyl radical **1.206** can then accept a second electron to generate enolate **1.207**, which will then form the product desoybenzoin **1.203** (scheme 1.32). The electron-withdrawing nature of the O-X group is important for lowering the LUMO energy of the substrate and also in stabilising the leaving group as an anion.[67] The substrate scope encompasses a wide variety of benzoin derivatives (*e.g.*, **1.199** – **1.202**) and analogues. However, the absence of an aryl group α to the carbonyl component alters the mechanism. For example, substrates **1.208** – **1.210** were examined. Mesylate **1.208** and pivalate **1.209** both afforded the expected ketone product **1.211** in low yield. In the case of acetate **1.210**, deprotonation by donor **1.177** occurred, resulting in cyclisation and subsequent dehydration to afford the butenolide product **1.212** (scheme 1.32). The authors state that the isolation of **1.212** could be due to a significant *gem*-dialkyl effect and reactive rotamer effect, resulting in an accelerated ring closure.[67] The presence of a α-aryl unit would hinder these phenomena resulting in a smooth reductive cleavage to desoxybenzoin **1.203**.

Scheme 1.32: the reactivity of donor **1.177** with α-protected hydroxyketones.



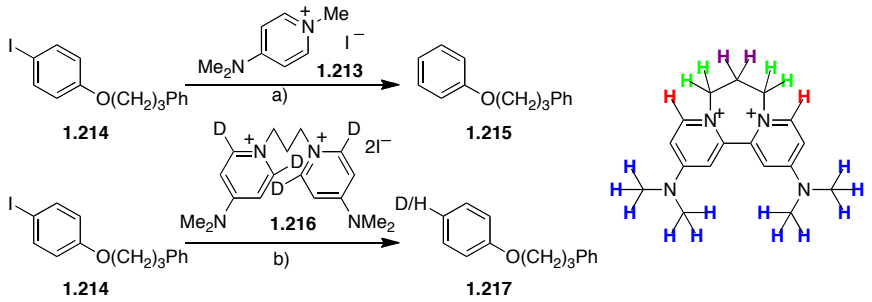
Reaction conditions: a) donor **1.177** (1.5 eq.), DMF, 100 °C, 18 h; **1.203**; from **1.198**, <5%;* b) donor **1.177** (1.5 eq.), DMF, r.t., 18 h; **1.203**; from **1.199**, 93%; from **1.200**, 95%; from **1.201**, 98%; from **1.202**, 97%; **1.211**; from **1.208**, 40%; from **1.209**, 36%; **1.212**, 86%.

Recently, Garnier and co-workers have revealed a convenient *in situ*, one-pot procedure where a close analogue of donor **1.177** is prepared *in situ* from

* Tentative identification, estimated as 5% maximum from the ^{1}H NMR spectrum of the unpurified reaction mixture.

methylated DMAP salt **1.213** and used to reduce aryl iodides (*e.g.*, **1.214**).[68] This novel procedure required just 1.5 equivalents of 4-DMAP methiodide **1.213** to achieve 84% reduction of iodide **1.214** (scheme 1.33). This same publication also reveals the likely source of protons used to quench intermediate anions when donor **1.177** is used. After much experimentation, Garnier and co-workers[68] revealed that the most likely source of protons came from the pyridinium α-CH protons (red, scheme 1.33) of the disalt **1.179** formed after double electron-transfer. Protons at the *N*-alkyl- (green and blue, scheme 1.33) and central methylene-positions (purple) were ruled out due to experiments such as the reaction of iodide **1.214** with modified donor **1.216**. These experiments showed that following work-up, 40% deuterium incorporation was observed, supporting the α-CH position as the likely proton source. These extensive deuterium-labelling investigations have assisted in solving a persistent question concerning the reactivity of anions of super electron-donors.[68]

Scheme 1.33: the application of a one-pot, *in situ* procedure for the reduction of iodide **1.214** and the key experiment to identify the likely site of proton source.

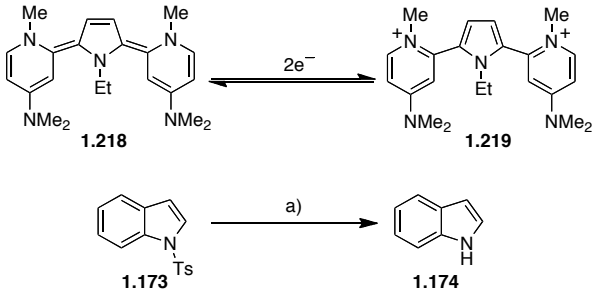


Reaction conditions: a) NaH, DMF, 16 h, Ar, r.t.; **1.215**, 84%; b) KHMDS, DMF, Ar, r.t., 18 h; **1.217**, 89%, **40% D incorporation**.

In an effort to achieve even greater levels of reactivity, Farwaha[69] within the Murphy group has prepared the next generation of super electron donor **1.218** (scheme 1.34), which features an extended π-system, as well as the key features of π-donating nitrogen atoms and the potential for aromaticity that were discussed at length above. This novel, electron-rich donor is a significantly more powerful donor than has been previously synthesised, with a measured reduction potential of -1.46 V (vs. Ag/AgCl/KCl (sat.) in *N*,*N*-dimethylformamide (-1.50 vs. SCE)). Calibration with ferrocene revealed that two electrons were transferred simultaneously, forming dication **1.219**. Donor **1.218** has been shown[69] to reduce activated sulfonamides, for example *N*-tosylindole **1.173**, forming indole **1.174** in 87% yield. This procedure

is effective using just three equivalents of donor **1.218** (compared with six equivalents of donor **1.150**).[64] Efforts are now under way to synthesise more complex, extended π-system donors, based on donor **1.218**

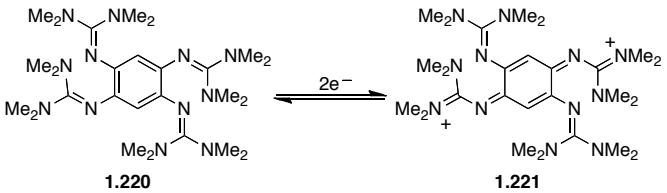
Scheme 1.34: novel, electron-rich, extended π-system donor **1.218** and its reaction with *N*-tosyl-indole **1.173**.



Reaction conditions: a) **1.219** (3 equiv.), Na/Hg, DMF, Ar, 3 h, r.t. *then added to* **1.173**, DMF, Ar, 18 h, 100 °C; **1.174**, 87%.

Other notable contributions to the chemistry of organic electron donors have come from the groups of Himmel[70] and Vaid.[71,72] Himmel and co-workers synthesised a novel organic electron-donor incorporating a benzene unit and four guanidine "arms" (figure 1.6).[70] The authors revealed that molecule **1.220** readily oxidised when exposed to air, with the electron-donor ability of **1.220** confirmed by cyclic voltammetry analysis. The CV curve displayed a two-electron wave at -0.32 V vs SCE in acetonitrile, a value significantly less negative than the donors developed by Murphy and co-workers discussed previously. However, Himmel suggests **1.120** as a mild reducing agent, but no experimental details regarding its reactivity with organic molecules were provided.

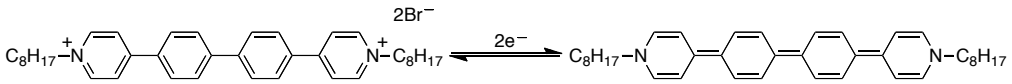
Figure 1.6: the guanidine derived donor developed by Himmel.



Vaid and co-workers have also made a significant contribution to the family of known organic electron-donors.[71] The synthesis and isolation of an "extended viologen" **1.223** was the first example of its kind and, at the time, was the most

reducing neutral organic molecule that had been reported (figure 1.7). The cyclic voltammogram of **1.223** indicated a reversible two-electron wave at -1.48 V (vs. Fc/Fc^+ in THF, approx. -0.93 V vs. SCE). However, once more there is no experimental evidence of the reducing ability of **1.223** with organic substrates. Interestingly, the structure of **1.223** remains to be confirmed beyond doubt, with ^1H NMR and ESR providing conflicting information regarding a singlet or triplet diradical structure.

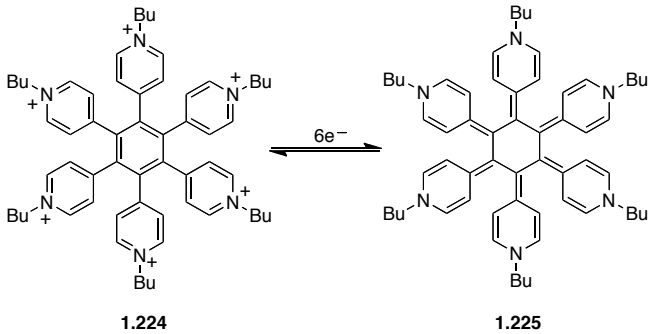
Figure 1.7: the structure of "extended viologen" **1.223** developed by Vaid and co-workers.



1.222 **1.223**

More recently, Vaid and co-workers have synthesised a six-electron organic redox system based on a benzene ring bonded to six pyridinium units (figure 1.8).[72] Treatment with sodium amalgam afforded **1.225** – structurally classified as a [6]-radialene. Cyclic voltammetry revealed two reversible waves at -1.14 V and -1.33 V (vs. Fc/Fc^+ in THF). Further studies revealed that the peak at -1.14 V corresponded to a four-electron transfer, a process which is without precedent for a molecule with its electroactive centres in communication. The peak at -1.33 V corresponds to the final two electrons on moving from **1.224** to **1.225**.

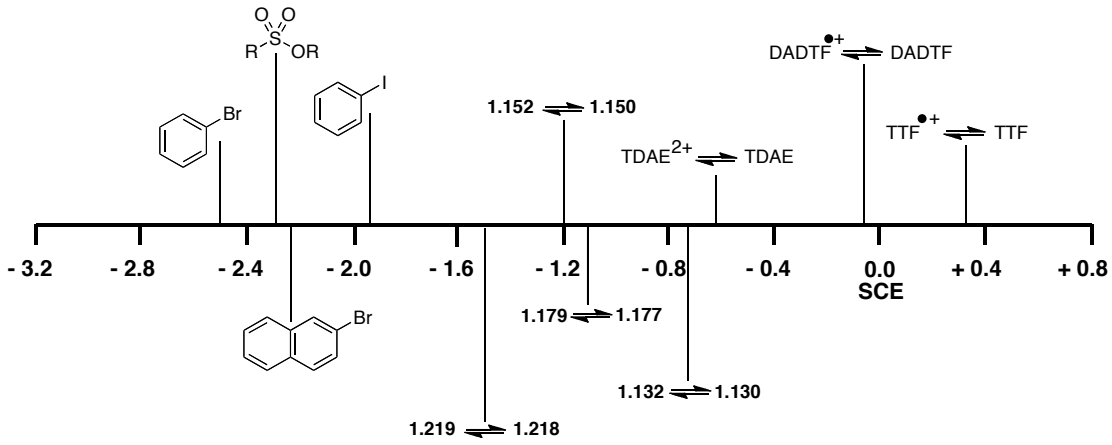
Figure 1.8: the six-electron donor (**1.225**) developed by Vaid and co-workers.



1.224 **1.225**

In summary, chapter 1.2 has discussed the recent advances in the field of organic electron donors in terms of their reactivity. Figure 1.9 shows a representation of the redox potential for the donors discussed in this chapter, together with some common organic functionalities that are compatible with these donors.

Figure 1.9: reactivity scale comparing TTF, diazadithiafulvalenes and all organic electron donors synthesised by the Murphy group, together with common organic functionalities that are compatible with these donors.

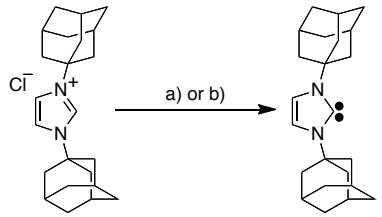


Section 1.3

N-Heterocyclic carbenes and their role as multidentate ligands

In recent years, *N*-heterocyclic carbenes (NHCs) have received great interest from chemists worldwide. They were first identified by Öfele[73] and Wanzlick[74] independently in the 1960's but were not isolated and confirmed until 1991 when Arduengo published his research into this area.[75] Arduengo reported that the deprotonation of 1,3-di-1-adamantylimidazolium chloride **1.226** afforded the corresponding carbene **1.227** (scheme 1.35), which was stable in the absence of air and moisture.

Scheme 1.35: the isolation of the first stable carbene **1.227** by Arduengo in 1991.



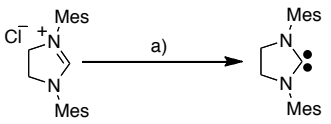
1.226 **1.227**

Reaction conditions: a) NaH, DMSO (cat.), THF, r.t.; **1.227**, 100%; b) KO*t*Bu, THF, r.t.; **1.227**, 96%.

Throughout the latter part of the twentieth century, research worldwide focussed on analysing the reasons behind the stability of such carbenes. In 2000, Bertrand and co-workers published an extensive review of carbenes, covering their stability and reactivity.[76] They state that steric interactions play a part in the overall stability of NHCs, but that these are not the principal factors governing their stability. The same can be said of the aromatic stabilisation energy, although an additional stabilisation of ~25 kJ mol^{-1} occurs with unsaturated imidazol-2-ylidenes relative to their saturated analogues. Thus, although unsaturated imidazol-2-ylidenes are more stable than their saturated analogues, fully saturated NHCs are still sufficiently stable to be isolated. Arduengo[77] isolated a stable, fully saturated imidazol-2-ylidene **1.229** by deprotonation of the precursor salt **1.228** using potassium hydride in tetrahydrofuran (scheme 1.36). According to Bertrand,[76] the principal factor concerning the stabilisation of *N*-heterocyclic carbenes is the interaction of the

electron-deficient carbene centre with the π-donating, σ-attracting amino substituents.

Scheme 1.36: a stable, saturated *N*-heterocyclic carbene **1.229**.



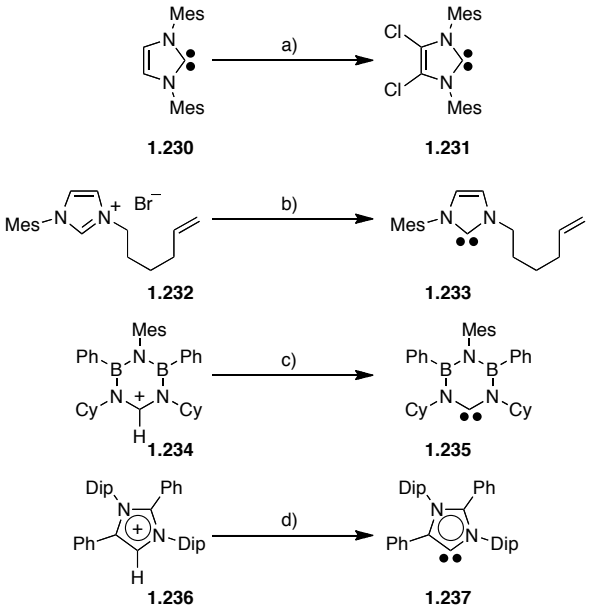
1.228 **1.229**

Reaction conditions: a) KH, THF, r.t.; **1.229**, 72%.

Since the preliminary investigations numerous examples of stable carbenes have been revealed. In 1997, Arduengo[78] revealed an air-stable NHC **1.231** derived from chlorination at the C4 and C5 positions of the parent structure **1.230** (scheme 1.37). Arduengo states that carbene **1.231** is tolerant of prolonged exposure to acidic solvents such as chloroform and also stable to air when either neat or as a benzene solution for a period of 1-2 days. The increased stability of **1.231** over the parent compound **1.230** is likely to be a result of the influence of the chlorine atoms. The π-electron donating and σ-electron-withdrawing ability of chlorine act in concert together with the inherent nitrogen components to deliver such a stable carbene as **1.231**. Fürstner[79] has also shown the remarkable progress in terms of carbene stability by isolating a stable carbene **1.233** in the presence of an olefin (scheme 1.37). It is well known that cyclopropanation of olefins is a prototype carbene reaction with a low activation barrier.[79] Solid-state analysis confirmed the close proximity of the olefin unit with the NHC moiety. Furthermore, the authors also state that NHCs can be generated despite being in close proximity to acidic C-H functionalities, such as those bearing ester or nitrile groups. More recently, Bertrand and co-workers have shown that stable, cyclic diamino carbenes can be synthesised that incorporate atoms other than just carbon and nitrogen.[80] Carbene **1.235** is stable at room temperature both in solution and in the solid state and is produced by deprotonation of cation **1.234** (scheme 1.37). X-ray crystallography reveals a planar, six-membered ring skeleton is in place, with a highly delocalised π-system, as suggested by measured bond distances. Bertrand has also extended the family of stable carbenes to include "abnormal" derivatives, so called due to the carbene site residing at C5 rather than the common case of C2.[81] Termed αNHCs, such compounds have been suggested as being even stronger electron-donors than

classical NHCs. Bertrand and co-workers isolated αNHC **1.237** as a green powder after treatment of salt **1.236** with base (scheme 1.37). Suitable crystals were grown from hexane, indicating that **1.237** was planar, confirming π-delocalisation. Carbene **1.237** is stable at room temperature both in the solid state and as a benzene solution.

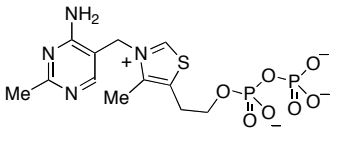
Scheme 1.37: the isolation of various stable carbenes.



Reaction conditions: a) CCl_4, THF, r.t., 20 min; **1.231**, 85%; b) KO*t*Bu, THF, 0 °C; **1.233**, 98%; c) LiTMP, THF -78 °C; **1.235**, 64%; d) KHMDS, THF, -78 °C, 30 min then r.t., 2 h; **1.237**, 68%.

The advent of organocatalysis has seen the increasing application of *N*-heterocyclic carbenes in this rapidly developing field. Much of today's interest in NHC chemistry stems from chemists' desires to mimic nature, *i.e.* to develop biomimetic processes. Thiamine pyrophosphate **1.238** (figure 1.10) is nature's acyl anion equivalent, or "active aldehyde".[82] Thiamine pyrophosphate **1.238** is involved in various biochemical processes including linking glycolysis and the citric acid cycle.

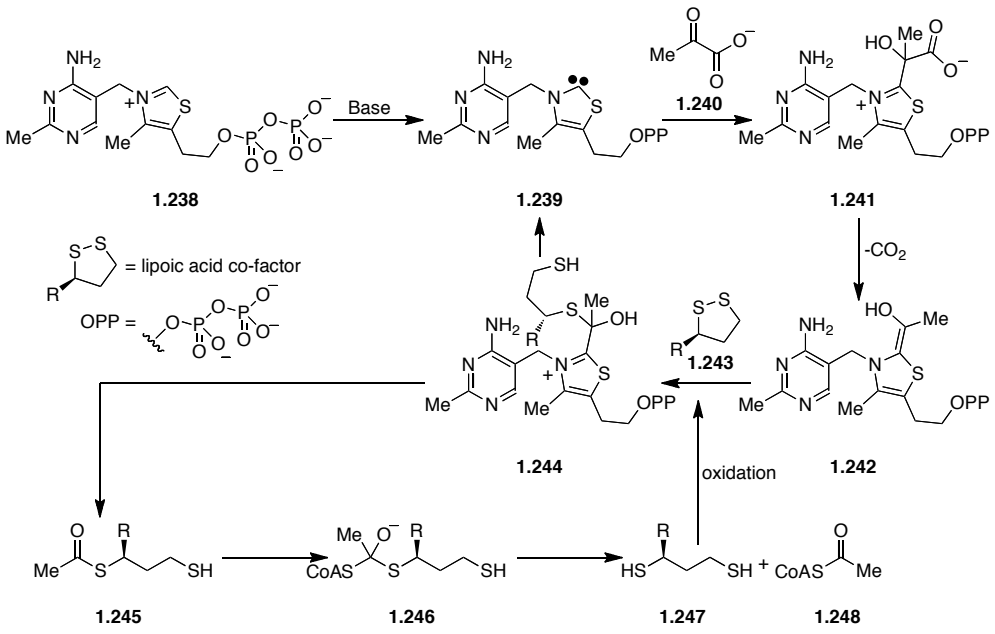
Figure 1.10: the structure of the key biochemical compound thiamine pyrophosphate **1.238**.



1.238

Thiamine pyrophosphate **1.238** is used to form the key co-factor, acetyl co-enzyme A **1.248**, from pyruvic acid **1.240** *via* a catalysis reaction. Pyruvate anion **1.240** is produced during glycolysis, it then reacts with **1.238** to generate co-factor **1.248**, which enters the citric acid cycle. In 1958, Breslow revealed the mechanism that catalyses such a process.[83] Each component of **1.238** was discussed in turn to determine whether it is the likely catalytic site. The result is a mechanism analogous to the classic mechanism of Lapworth for the cyanide-promoted benzoin condensation.[84] Crucially the "active aldehyde" intermediate **1.242** proposed by Breslow reacts as a nucleophile rather than an electrophile. It is the Umpolung reactivity of **1.242** that has been the focus of chemists worldwide. The mechanism for the formation of acetyl co-enzyme A **1.248** is shown below (scheme 1.38).

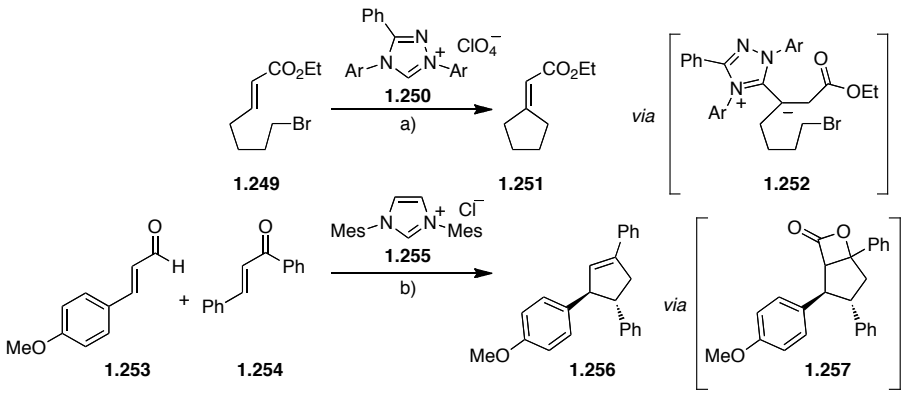
Scheme 1.38: the mechanism for the conversion of pyruvic acid **1.240** to acetyl co-enzyme A **1.248**, catalysed by thiamine pyrophosphate **1.238**, linking glycolysis and the citric acid cycle.



Several reviews document the remarkable role NHCs play in the field of organocatalysis.[85] *N*-Heterocyclic carbenes have been described as catalysing many different chemical transformations including the benzoin condensation, the Stetter reaction, transesterification, ring-opening polymerisation, homoenolate generation and nucleophilic aromatic substitution.[85] Both inter- and intramolecular variations have been disclosed, amongst those asymmetric processes.[85a,c] It is now even possible to purchase pure *N*-heterocyclic carbene catalysts that can be used without prior deprotonation.[85a,d] An interesting example of an NHC-catalysed

process includes the work of Fu and co-workers (scheme 1.39).[86] Here, cyclisation of an alkyl halide **1.249** to afford the exo cyclic alkene **1.251** was catalysed by a triazolium-derived carbene (from salt **1.250**). Attack of the NHC at the β-position of **1.249** and subsequent tautomerisation results in the β-position becoming nucleophilic (structure **1.252**), and cyclising in an S_N2 process to afford product **1.251**. The conditions are effective with alkyl bromides, chlorides and tosylates. Nair and co-workers published a further interesting example of an NHC-catalysed reaction in 2006 (scheme 1.39).[87] The synthesis of 1,3,4-trisubstituted cyclopentene **1.256** in excellent yield, from α,β-unsaturated aldehyde **1.253** and ketone **1.254** *via* NHC-mediated generation of homoenolates, was more remarkable due to the isolation of a single diastereomer. The mechanism involves initial attack of the NHC on aldehyde **1.253** forming a homoenolate, which can then attack ketone **1.254**. Cyclisation to form the five-membered ring present in **1.256**, followed by a second cyclisation to form an intermediate β-lactone **1.257** followed. Formation of **1.256** occurs *via* decarboxylation and loss of CO_2. The presence of the key β-lactone intermediate **1.257** was confirmed by IR analysis on the reaction mixture where a characteristic adsorption band at 1822 cm^{-1} was observed. This band disappeared after 45 minutes indicating loss of CO_2 and formation of **1.256**.

Scheme 1.39: NHC-catalysed processes from Fu[86] and Nair.[87]



Reaction conditions: a) 10 mol% **1.250** (Ar = *p*-anisyl), K_3PO_4 (2.5 eq.), glyme, 80 °C, 8 h; **1.251**, 94%; b) 6 mol% **1.255**, 12 mol% DBU, THF, r.t., 8 h; **1.256**, 88%.

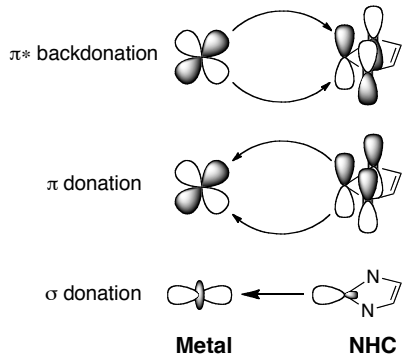
N-Heterocyclic carbenes are also commonly employed as ligands in organometallic processes. NHCs are a sub-set of Fischer carbenes, so called after E. O. Fischer who disclosed the structure of this general class of complex in 1964,[88] and are all singlet carbenes with both electrons present in the carbon sp^2 orbital. Several

reviews document the factors governing the nature of metal-NHC bonds.[89] Originally it was proposed that NHCs were simple σ-donor ligands *via* the lone pair on carbon C2 but that hypothesis has now been abandoned.[89] A recent review[89d] reveals that significant contributions towards metal-NHC bonding come from π*-backdonation, where the NHC acts as a π-acceptor for electron density from filled metal d-orbitals, and π-donation, where the NHC acts as a π-donor to empty metal d-orbitals. In general, electron-rich metals (those that have a higher d-electron count) will contribute more to π*-backdonation, whereas, those metals that are electron-poor (a lower d-electron count) will contribute less and the π-component of the metal-NHC bond will be made up by π-donation from the NHC. Cavallo and co-workers, who examined 36 model metal-NHC complexes using computational methods, have elegantly demonstrated this.[90] A summary of their data (table 1.3) reveals the average percent σ- and π-contributions to the orbital interaction energy (ΔE_{oi}) of the metal-NHC bond. It is noteworthy that the maximum amount of π contribution is 20%. Thus, the overall picture for metal-NHC bonding can be described as consisting of a strong σ-component, with a much smaller contribution consisting of both π*-backdonation from metal to NHC and π-donation from NHC to metal. This is shown below (figure 1.11).

Table 1.3: the average percent σ and π contributions to the orbital interaction energy (ΔE_{oi}) of the metal-NHC bond.

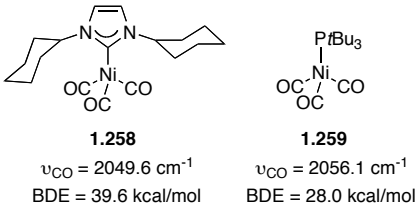
Source of contribution	**d electron count**				
	0	4	6	8	10
(ΔE_{oi} σ) - σ contribution	90	88	86	85	80
(ΔE_{oi} π) - π contribution	10	12	14	15	20
(ΔE_{oi} π) - π*-backdonation (M to NHC)	65	70	77	82	90
(ΔE_{oi} π) - π-donation (NHC to M)	35	30	23	18	10

Figure 1.11: orbital interactions in the metal-NHC bond.



N-Heterocyclic carbenes have frequently been described as phosphine mimics but there is increasing evidence that NHCs surpass phosphines in both catalyst activity and scope.[89c] In 2005, Crabtree[91] stated that "NHCs have a chemistry that is original, novel, useful and much more complex than was originally supposed" and that NHCs should be considered as "broadly catalytically useful ligands comparable with cyclopentadienyls and phosphines." Nolan and co-workers also compared phosphines and NHCs when investigating the steric and electronic properties of NHCs in 2005.[92] After synthesising complexes of the general formula Ni[NHC](CO)$_3$ and analysing the carbonyl stretching frequency, comparison with representative phosphine analogues (Ni(PR$_3$)(CO)$_3$) clearly demonstrated that NHC ligands are better σ-donors than even the most basic phosphine (P*t*Bu$_3$). For example, compare Ni(CO)$_3$(ICy) **1.258** and Ni(CO)$_3$(P*t*Bu$_3$) **1.259**, that have carbonyl stretching frequencies of 2049.6 cm^{-1} and 2056.1 cm^{-1} respectively. The greater electron-donating NHC ligands result in the metal centre being more electron-rich. This in turn leads to a greater degree of back-donation from the filled metal d-orbitals to the CO antibonding orbital, weakening and lengthening the CO bond causing it to show at lower wavenumbers. The authors also revealed that the calculated metal-ligand bond strength differed by 11.6 kcal/mol when Ni(CO)$_3$(ICy) **1.258** and Ni(CO)$_3$(P*t*Bu$_3$) **1.259** were analysed by DFT calculation (figure 1.12). This indicates the increased strength of the metal-NHC interaction over that in metal-phosphine complexes. Thus, NHCs as ligands should form complexes that complement and even surpass metal-phosphine analogues.

Figure 1.12: the comparison of $Ni(CO)_3(ICy)$ **1.258** and $Ni(CO)_3(PtBu_3)$ **1.259** carbonyl stretching frequencies and the computed bond dissociation energies for the metal-ligand bond.

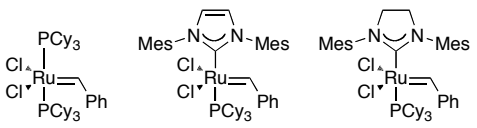


1.258 υ_{CO} = 2049.6 cm^{-1}, BDE = 39.6 kcal/mol

1.259 υ_{CO} = 2056.1 cm^{-1}, BDE = 28.0 kcal/mol

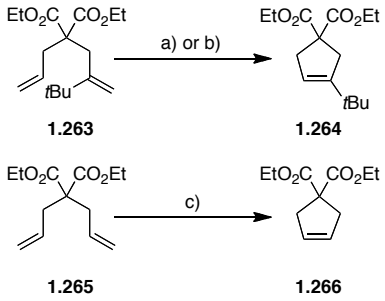
The scientific literature[93] contains numerous examples of monodentate metal-NHC complexes and, as such, this review will not discuss all of them. One particular catalyst family however has highlighted the impressive ability of *N*-heterocyclic carbenes as ligands - Grubbs' metathesis catalysts. The first generation of catalyst incorporated two phosphine ligands bound to the ruthenium centre **1.260** (figure 1.13).[94] However, greatly increased activity and scope was observed when one phosphine ligand was exchanged for an *N*-heterocyclic carbene in catalyst **1.261** (figure 1.13).[95] For example, cyclisation of diene **1.263** to afford cyclopentene **1.264** occurs readily using second-generation catalyst **1.261**, whereas no reaction was observed using first generation catalyst **1.260** (scheme 1.40). Furthermore, use of a saturated *N*-heterocyclic carbene provided another active catalyst **1.262** (figure 1.13).[96] Here the use of the more basic saturated imidazoline moiety led to greater activity at low catalyst loadings. Just 0.05 mol% of **1.262** was required to facilitate the quantitative ring closure of diethyl diallylmalonate **1.265** to cyclopentene **1.266** in refluxing dichloromethane over 1 h (scheme 1.40). Comparison with the parent diphosphine catalyst **1.260** revealed that catalyst **1.262** was two orders of magnitude more active, leading to obvious advantages in terms of economics and toxicity. The evolution of Grubbs' metathesis catalysts to incorporate NHCs and the improvement that has been discovered thus far not only demonstrates the differences between phosphines and NHCs as ligands, but also indicates the importance of NHCs within chemistry in general.

Figure 1.13: the structure of olefin metathesis catalysts.



1.260 **1.261** **1.262**

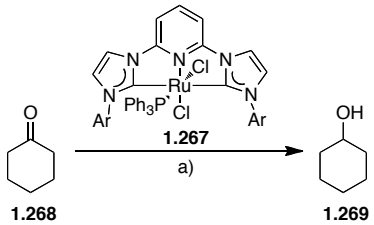
Scheme 1.40: the application of catalysts in olefin metathesis.



Reaction conditions: a) 5 mol% **1.260**, CD_2Cl_2, reflux, 1 h; **1.264**, 0%; b) 5 mol% **1.261**, CD_2Cl_2, reflux, 1 h; **1.264**, 100%; c) 0.05 mol% **1.262**, DCM, reflux, 1 h; **1.266**, 100%.

Multidentate *N*-heterocyclic carbene complexes are of increasing interest from not only a structural point of view but also in terms of catalysis.[97] The rest of this section will concentrate on selected examples of such complexes in line with the theme of this thesis. Danopoulos and co-workers revealed an air-stable crystalline Ru-NHC pincer complex **1.267** (scheme 1.41) – described as the first example of a chelating *bis*carbene.[98] Complex **1.267** was employed in the hydrogenation of various C=O and C=N groups by transfer hydrogenation from isopropanol in the presence of alkoxide base. Despite reactivity being sluggish at room temperature, elevated temperatures resulted in high turnover numbers (TON) for the reduction of cyclohexanone **1.268**, although no yields are stated. It is also noteworthy that a low catalyst loading of just 0.01 mol% **1.267** was effective for such a hydrogenation.

Scheme 1.41: *bis*carbene complex **1.267** and its employment in the catalytic transfer hydrogenation of cyclohexanone **1.268**.

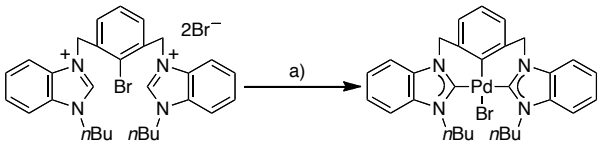


Reaction conditions: a) 0.01 mol% **1.267** (Ar = 2,6-iPr$_2$C$_6$H$_3$), KO*t*Bu, *i*PrOH, 55 °C, 20 h; **TON = 8800**.

Hahn and co-workers have investigated palladium pincer NHC complexes and their role in C-C coupling reactions.[99] Complex **1.271** was synthesised from the precursor benzimidazolium salt **1.270** by deprotonation with *n*-butyllithium in THF at

-78 °C to afford the free carbene intermediate. Addition of $[Pd_2(dba)_3]$ at this temperature afforded a red palladium(0) *bis*carbene solution that was then heated at reflux for 12 h. This initiated oxidative addition of palladium into the C-Br bond of the bridging aryl unit, forming complex **1.271**. NMR analysis of complex **1.271** revealed a resonance of δ 189 ppm in the ^{13}C NMR spectra, as expected of a metallated carbene carbon. Confirmation of the structure by X-ray crystallography indicated a distorted square-planar geometry, with the carbene-Pd-carbene bond angle found to be distorted severely to 169.5°. The stability of complex **1.271** to air, moisture and excess heating led to **1.271** being tested in catalysis.[99] It was found that complex **1.271** proved to be effective for the Heck and Suzuki couplings of electron-poor aryl bromides, with low catalyst loadings of just 0.01 mol% required to achieve 100% conversion over 24 h.

Scheme 1.42: the synthesis of Pd pincer-NHC complex **1.271**.



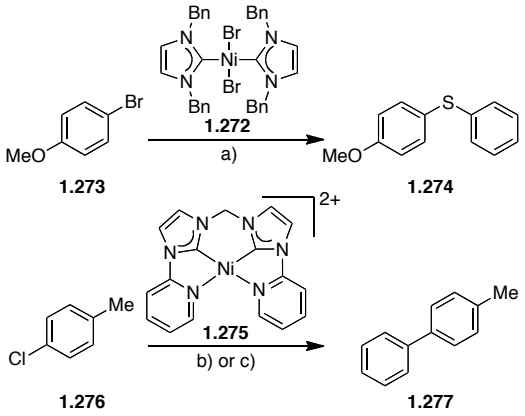
1.270 **1.271**

Reaction conditions: a) *n*BuLi, THF, -78 °C, 30 min; $Pd_2(dba)_3$, slowly warm to r.t.; reflux, 12 h; **1.271**, 71%.

Nickel-*bis*carbene complexes have also been employed in cross-coupling reactions. Zhang and co-workers disclosed the first example of a highly active nickel-NHC catalyst for the coupling of C-S bonds.[100] A wide range of aryl bromides and iodides proved compatible in coupling with thiophenol using Ni-NHC catalyst **1.272**, with excellent yields observed. For example, electron-rich 4-bromoanisole was coupled to thiophenol using just 3 mol% **1.272** to afford the product **1.274** under these conditions (scheme 1.43). Chen and co-workers have also described an interesting Ni-NHC complex capable of efficiently catalysing the Suzuki coupling reactions of aryl chlorides and bromides under mild conditions.[101] The ligand incorporates two internal NHCs, each of which is bonded to an external pyridine unit. Complex **1.275** was characterised by X-ray crystallography that clearly showed the nickel(II) ion coordinated to two NHCs and two pyridine units. The authors examined the Suzuki coupling of phenylboronic acid with numerous aryl halides and found that while complex **1.275** is capable of effecting C-C coupling, a dramatic improvement in yield

and reaction rate is realised upon addition of two equivalents of triphenylphosphine (scheme 1.43). For example, in the absence of triphenylphosphine, **1.277** was isolated in 15% yield in 24 h, whereas addition of triphenylphosphine afforded product **1.277** in an excellent 95% yield in just 10 h.[101]

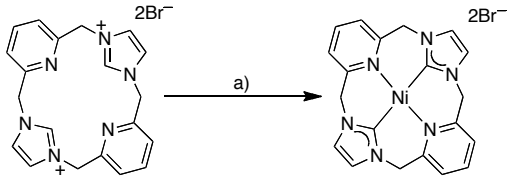
Scheme 1.43: the use of Ni-NHC complexes in cross-coupling reactions.



Reaction conditions: a) 3 mol% **1.272**, thiophenol, KO*t*Bu, DMF, 100 °C, 16 h: **1.274**, 89%; b) 3 mol% **1.275**, phenylboronic acid, K_3PO_4, toluene, 80 °C, N_2; **1.277**, 15%; c) 3 mol% **1.275**, PPh_3, phenylboronic acid, K_3PO_4, toluene, 80 °C, N_2; **1.277**, 95%.

In 2002, Baker and co-workers reported a macrocyclic, nickel-NHC complex, closely related to complex **1.275**.[102] The cyclophane structure of ligand **1.278** incorporates two NHCs and two pyridine units, with each *trans* to its partner. After treatment with sodium acetate and nickel(II) bromide in dimethyl sulfoxide at 85 °C, air-stable complex **1.279** was isolated (scheme 1.44). The ligand had previously been synthesised and used to form a silver(I) complex, however, complexation was only achieved to the NHC units in that case.[103] Here, X-ray analysis of complex **1.279** revealed the nickel ion lies in a quasi-planar, saddle-shaped, four-coordinate array complexed to two *trans* NHCs and two *trans* pyridine nitrogens.

Scheme 1.44: the synthesis of Ni-cyclophane complex **1.279**.

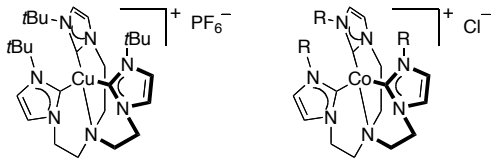


1.278 **1.279**

Reaction conditions: a) $NiBr_2$, NaOAc, DMSO, 85 °C, 3 days, N_2; **1.279**, 52%.

Tridentate, *N*-heterocyclic carbene complexes are less common than bidentate complexes.[97] Meyer and co-workers disclosed the first example of a 1:1 transition metal, mononuclear complex of a polydentate, *tris*-carbene tripodal ligand in the synthesis of complex **1.280** (figure 1.14).[104] The use of bulky *tert*-butyl groups on the external NHC nitrogen is crucial in order to obtain complex **1.280**. Use of less bulky groups, *e.g.* methyl, leads to a trinuclear complex. The role of the bridging nitrogen atom in stabilising the complex structurally is clear as it leads to the formation of three six-membered metallacycles, while also fixing the copper(I) ion in an ideal trigonal planar geometry with an average carbene-Cu-carbene angle of 119.99°. Similarly, the same authors synthesised a tripodal cobalt(I) *tris*-carbene complex **1.281** that was effective in the activation of dioxygen (figure 1.14, R = 2,6-dimethylphenyl).[105] The active oxygen complex proved to be nucleophilic, reacting with benzoyl chloride and forming phenyl benzoate quantitatively.

Figure 1.14: tripodal, *tris*-carbene complexes of copper(I) **1.280** and cobalt(I) **1.281** synthesised by Meyer and co-workers.

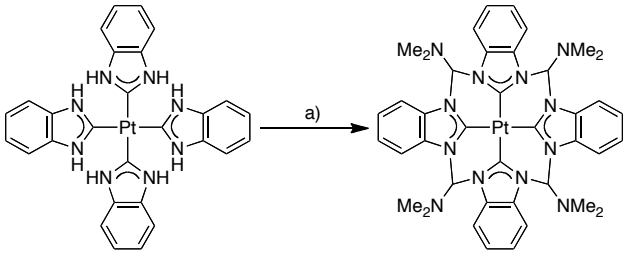


1.280 **1.281**

In comparison to mono-, bi- and tridentate *N*-heterocyclic carbene ligands, there are significantly fewer examples of tetradentate ligands and complexes. Hahn and co-workers constructed a tetracoordinated, tetracarbene platinum(II) complex **1.282** (scheme 1.45) by a controlled template synthesis around the central platinum(II) centre.[106] Cyclisation to complex **1.283** was achieved by reaction with phosgene in

N,N-dimethylformamide. Both complexes **1.282** and **1.283** exhibited near perfect square-planar geometries after analysis by X-ray crystallography, while complex **1.283** can be described as a cyclic tetracarbene complex with crown ether topology.

Scheme 1.45: the formation of cyclic tetracarbene complex **1.283** from **1.282**.

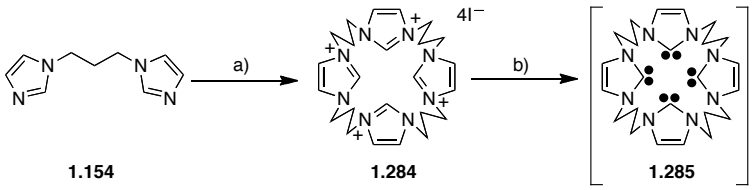


1.282 **1.283**

Reaction conditions: a) phosgene, DMF; **1.283**, 60%.

Murphy and co-workers published the synthesis of a macrocyclic, imidazolium salt **1.284** in 2007, together with its employment as a macrocylic, tetracarbene ligand **1.285** complexed to a series of transition metals.[107,108] The synthesis involved treatment of *bis*imidazole precursor **1.154** with 1,3-diiodopropane under dilute conditions in refluxing acetonitrile. After recrystallisation from methanol, macrocylic salt **1.284** was isolated in a respectable yield of 19% as light yellow microcrystals (scheme 1.46). X-ray crystallography revealed the tetracationic structure shown (with four iodide counter-ions), with each imidazolium unit separated by three-carbon methylene linkers.

Scheme 1.46: the synthesis of macrocylic salt **1.284**.



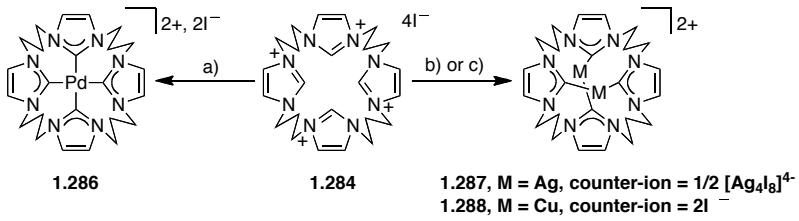
1.154 **1.284** **1.285**

Reaction conditions: a) 1,3-diiodopropane, MeCN, reflux, 24 days; **1.284**, 19%; b) base.

Macrocyclic salt **1.284** was used as a cyclic "crown carbene" ligand **1.285** (after deprotonation, scheme 1.46) to encapsulate metal salts. In 2007, the first three members of this family of complexes were revealed.[107] Palladium(II) complex **1.286** was synthesised using palladium(II) iodide and sodium acetate in dimethyl sulfoxide,

to afford square-planar complex **1.286** as a white solid (scheme 1.47, figure 1.15 – left-hand side image). The geometry of complex **1.286** is clearly evident from the X-ray crystal structure. Two bimetallic complexes were also revealed. The use of silver(I) oxide allowed isolation of bimetallic silver(I) complex **1.287** that contained two silver(I) ions encapsulated within the ligand core (scheme 1.47). Each silver(I) ion is bound to two NHC units of the ligand in a linear fashion, while also interacting with the other silver(I) ion. A further interesting feature is the counter ion $[Ag_4I_8]^{4-}$, shared between two cationic complexes **1.287**. The third complex containing copper(I) ions is also bimetallic and was synthesised in an analogous manner to silver(I) complex **1.287** (scheme 1.47, figure 1.15 – right-hand side image). In complex **1.288**, each copper(I) ion is clearly evident within the X-ray structure, with the copper(I)-copper(I) interaction also visible.

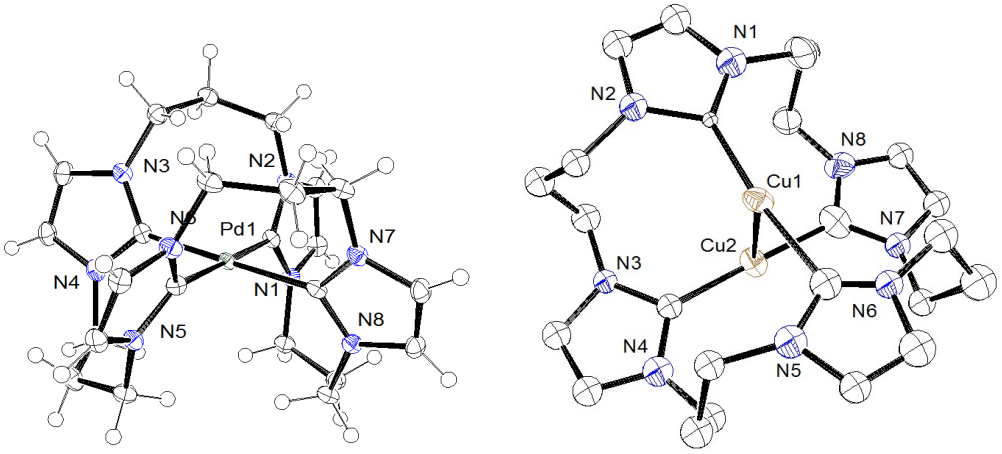
Scheme 1.47: the synthesis of palladium(II) complex **1.286**, bimetallic silver(I) complex **1.287** and bimetallic copper(I) complex **1.288** using macrocyclic salt **1.284**.



1.286 **1.284** **1.287, M = Ag, counter-ion = 1/2 $[Ag_4I_8]^{4-}$**
1.288, M = Cu, counter-ion = 2I⁻

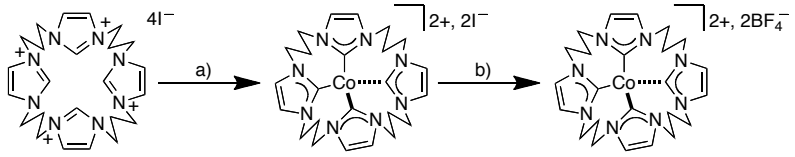
Reaction conditions: a) PdI_2, NaOAc, DMSO, reflux, 18 h; **1.286**, 87%; b) Ag_2O, NaOAc, DMSO, r.t., 18 h; **1.287**, 21%; c) Cu_2O, NaOAc, DMSO, 90 °C, 3 h; **1.288**, 53%.

Figure 1.15: the X-ray crystal structure for palladium(II) complex **1.286** (left-hand-side image) and bimetallic copper(I) complex **1.288** (right-hand-side image) – hydrogen atoms and counter-ions are omitted for clarity.



A fourth member of the crown carbene family was revealed in 2009.[109] Due to the considerable σ-donating ability of NHCs, Murphy proposed that an electron-rich tetracarbene ligand should greatly increase the electron-density of the metal-ion, in turn increasing the reactivity of the metal complex in terms of electron transfer. Cobalt(II) complex **1.289** was the first such example that supported this hypothesis. Synthesis of complex **1.289** was straightforward, with heating of a methanol solution of cobalt(II) chloride hexahydrate, macrocyclic salt **1.284** and sodium hydroxide at 60 °C, affording complex **1.289** as bright blue needles after recrystallisation (scheme 1.48).

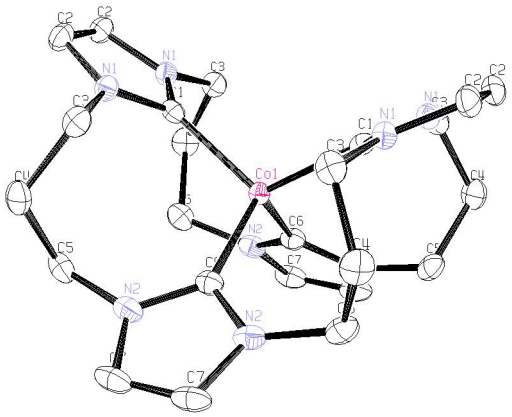
Scheme 1.48: the synthesis of cobalt(II) complex **1.289** and the ion-exchange reaction to afford tetrafluoroborate analogue **1.290**.



1.284 **1.289** **1.290**

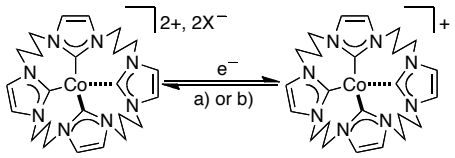
Reaction conditions: a) $CoCl_2.6H_2O$, NaOH, MeOH, 60 °C, 18 h; **1.289**, 60%; b) complex **1.289**, $AgBF_4$, MeCN, r.t., 18 h; **1.290**, 78%.

Figure 1.16: X-ray crystal structure of cobalt(II) complex **1.289** – hydrogen atoms and iodide counter-ions are omitted for clarity.



X-ray crystallography revealed complex **1.289** had a tetrahedral geometry with the cobalt(II) ion fully surrounded at the ligand core (figure 1.16).[109] Complex **1.289** was then examined by cyclic voltammetry to determine its redox properties. To achieve a satisfactory result, complex **1.289** underwent counter-ion exchange to afford complex **1.290** (scheme 1.48). The removal of redox-active iodide counter-ions in exchange for electrochemically inactive tetrafluoroborate ions was deemed necessary to avoid iodide contamination during the analysis. Cyclic voltammetry indicated that complex **1.289**/**1.290** was a powerful, single electron-donor, exhibiting a reversible one electron-transfer at -1.15 V (vs. Ag/AgCl/KCl (sat.) in DMF (-1.19 V vs. SCE)). It is most likely that the structurally analogous cobalt(I) complex **1.291** is formed after accepting one electron. Thus, this activated cobalt(I) complex **1.291** can be compared to the neutral, organic electron-donors derived from imidazole (**1.150**) and DMAP (**1.177**) that were discussed earlier, and, as expected, exhibits a similar level of reactivity.

Scheme 1.49: the generation of the activated cobalt(I) complex **1.291** from cobalt(II) complex **1.289**/**1.290**.

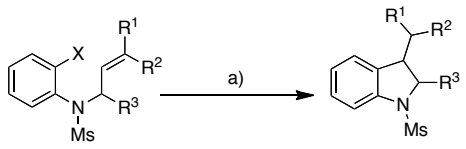


1.289 or **1.290** **1.291**

Reaction conditions: a) cyclic voltammetry; b) Na/Hg, DMF, 4 h, r.t.

The reducing ability of complex **1.291** was also revealed.[109] After activation by sodium amalgam, reaction with an array of aryl halides **1.292** resulted in the formation of indoline products **1.293** (table 1.4). Yields were highest when aryl iodides **1.292a-c** or bromides **1.292d-f** were examined, compared with aryl chlorides **1.292g-i**, reflecting the higher bond strength of the C-Cl bond.[110] Excess 1,4-cyclohexadiene (CHD) is crucial in many cases in order to quench the intermediate alkyl radical. When CHD was absent, there was significant evidence of dehydrocobaltation leading to *exo*-alkene products (which were isomerised to indoles upon treatment with acid).[109]

Table 1.4: the reductive cyclisation of aryl halides **1.292** to indolines **1.293** using active cobalt(I) complex **1.291**.



1.292 **1.293**

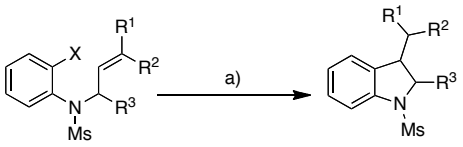
1.292	X	R^1	R^2	R^3	CHD (eq.)	1.293 (%)
a	I	Me	H	H	-	81
b	I	Me	Me	H	5	70
c	I	H	$(CH_2)_3$		5	77
d	Br	Me	H	H	-	74
e	Br	Me	Me	H	5	89
f	Br	H	$(CH_2)_3$		5	80
g	Cl	Me	H	H	-	23*
h	Cl	Me	Me	H	5	37*
i	Cl	H	$(CH_2)_3$		5	55*

Reaction conditions: a) cobalt(II) complex **1.289** (1.2 eq.), Na/Hg, DMF, 4 h, r.t. then added to **1.292** (with or without CHD as above), 18 h, 90 °C; * the remainder was isolated as starting material.

Due to the reversible nature of the **1.289**/**1.291** redox couple, as observed in the cyclic voltammogram, a catalytic method driven by applied potential was then explored (table 1.5).[109] A two-compartment cell equipped with a Pt wire counter electrode, Pt gauze working electrode and Ag/AgCl/KCl (sat.) reference electrode was employed, with an applied potential of -1.5 V. Aryl iodides **1.292a-c** reacted readily, forming indoline **1.293a-c** in good to excellent yields using just 10 mol% of

1.289. However, aryl bromide **1.292d** required heating to 90 °C to afford indoline **1.293d** – attempts to reduce bromide **1.292e** at room temperature were unsuccessful. Aryl chlorides were also attempted at high temperature, although only trace reduction was observed.

Table 1.5: the catalytic reductive cyclisation of aryl halides **1.292** to indolines **1.293**.



1.292 **1.293**

1.292	**X**	**R^1**	**R^2**	**R^3**	**CHD (eq.)**	**1.293 (%)**
a	I	Me	H	H	10	95
b	I	Me	Me	H	10	77*
c	I	H	$(CH_2)_3$		10	90
d†	Br	Me	H	H	-	77
e	Br	Me	Me	H	10	0*
g†	Cl	Me	H	H	-	trace‡

Reaction conditions: a) cobalt(II) complex **1.289** (0.1 eq.), TBAHFP/DMF (0.05 M), r.t., -1.5 V, 18 h; * the remainder was isolated as starting material; † the reaction was performed at 90 °C for 24 h; ‡ as observed in NMR and confirmed by GC-MS.

Section 1.4

Nickel in electron-transfer chemistry

Recently, nickel has been the focus of the organic chemistry community due to its combination of varied reactivity and low cost in comparison to palladium.[111] Its chemistry is vast and varied, encompassing many different bond-forming processes including cross-coupling chemistry.[112] In line with the theme of this thesis, this section will focus on the role of nickel macrocyclic complexes in electron transfer chemistry.

The predominantly stable oxidation state of nickel is the nickel(II) state, with numerous complexes containing the nickel(II) ion known.[113] Busch and co-workers have investigated a family of synthetic nickel macrocyclic complexes using electrochemistry, to establish the electronic and structural features that promote and retard their electron transfer reactions.[114] Each complex contained a nickel ion held in a square-planar geometry. The authors note that a pronounced shift in redox potential is observed when there is a change in macrocyclic ring size. An increase in ring size promotes the formation of nickel(I), while rendering the transition from nickel(II) to nickel(III) more challenging – illustrating the concept of optimum fit between the coordinated metal and the ligand "hole size". For example, note the change in redox values on moving from **1.294**, to **1.295**, to **1.296** (figure 1.14, table 1.6). Thirteen-membered ring ligand **1.294** or fourteen-membered ring ligand **1.295** provided the greatest challenge in forming the nickel(I) ion, whereas the fifteen-membered ring ligand **1.296** more easily accommodated the larger nickel(I) ion while exhibiting greater difficulty encompassing the smaller nickel(III) ion.[114] Ligand unsaturation was also shown to have a pronounced effect on the redox properties of nickel complexes. For example, the inclusion of an α-diimine functionality within the ligand infrastructure favours the formation of lower valent states (*e.g.*, formally nickel(I)) and causes the nickel(II) – nickel(III) process to occur at higher energy. Ligand **1.297** (with a fully saturated structure) promotes the formation of nickel(III) at low potential while reduction is challenging, whereas the inclusion of one or two imine functionalities (**1.298** or **1.299**) results in a significant increase in the oxidation potential and a lowering of the reduction value (table 1.6).[114] Thus, Busch and co-workers have shown that knowledge of the factors that govern the redox potentials

of certain complexes can lead to the synthetic design of a complex, which would enable it to fulfil a particular desired chemical function.

Figure 1.17: the structures of macrocyclic ligands studied by Busch and co-workers.

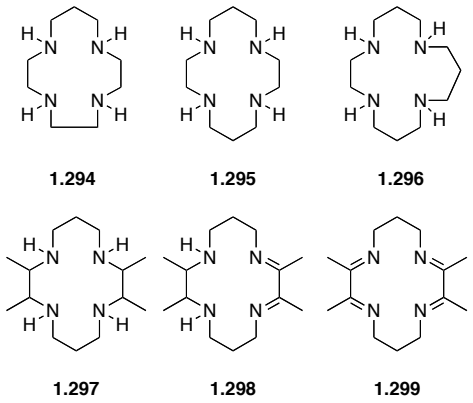


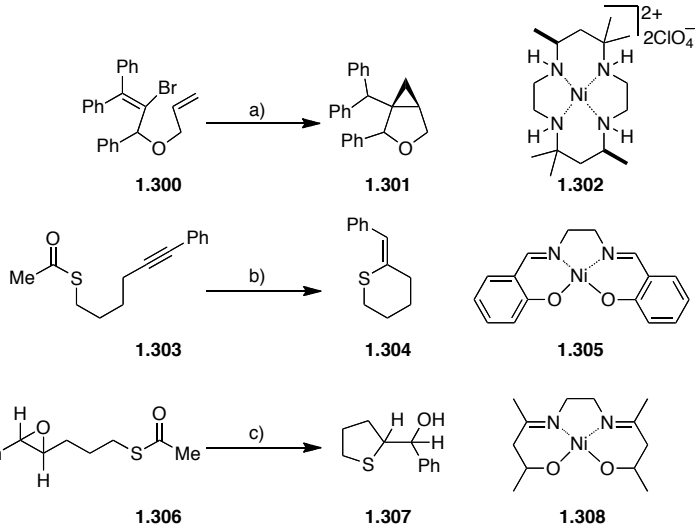
Table 1.6: the redox data for complexes formed using the ligands in figure 1.17.

Ligand	Oxidation Potential (V) $Ni(L)^{2+} \rightarrow Ni(L)^{3+}$	Reduction Potential (V) $Ni(L)^{2+} \rightarrow Ni(L)^{+}$
1.294	+0.7-0.9	-1.70
1.295	+0.67	-1.70
1.296	+0.90	-1.50
1.297	+0.71	-1.66
1.298	+0.86	-1.16
1.299	+1.00	-0.82

Radical cyclisations mediated by nickel(I) complexes have been studied by Ozaki and co-workers. For example, bicyclo[3.1.0]skeletons were prepared by single-electron reduction of vinyl halides (*e.g.*, **1.300**) to afford vinyl radicals, which cyclise twice to form the bicyclic structure **1.301** (scheme 1.50).[115] The process is relatively inefficient in terms of catalyst loading, with 30 mol% **1.302** required for conversion to bicycle **1.301**. Ozaki and co-workers also synthesised cyclic sulfides by nickel complex-catalysed electroreduction of unsaturated thioacetates and thiosulfonates (scheme 1.50).[116] The proposed mechanism involves reduction to an intermediate thiol, which then reacts with light or heat to furnish the corresponding thiyl radical, which could then cyclise onto the alkene/alkyne unit. For example, thioacetate **1.303** was reduced using nickel(II) salen **1.305** to form the six-membered cyclic sulfide **1.304**. Nickel(II) salen has a reported reduction potential of -1.70 (vs.

SCE)[116] – a value representative of such an electron-donating anionic ligand. An alternative method for the synthesis of cyclic sulfides involved the intramolecular ring-opening of epoxides by thiolates generated by nickel complex catalysed electroreduction of thioacetates (scheme 1.50).[117] Complex **1.308** also employs a dianionic ligand, resulting in a measured reduction potential of -2.10 V (vs. SCE). Thus, reduction of thioacetate **1.306** using electrochemically-generated nickel(I) **1.308** afforded five-membered cyclic sulfide **1.307** in good yield. These three examples serve to illustrate the wide-range of processes that are achievable using macrocyclic nickel complexes.

Scheme 1.50: examples of reductive cyclisations mediated by electrochemically-induced nickel(I) complexes.

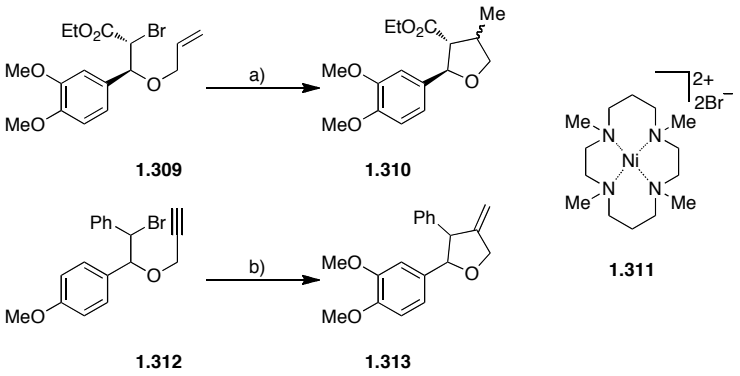


Reaction conditions: a) 30 mol% **1.302**, DMF, Et_4NClO_4 (0.1 M), 3 mA; **1.301**, 66%; b) 20 mol% **1.305**, DMF, Et_4NClO_4 (0.1 M), 3 mA; **1.304**, 61%; c) 30 mol% **1.308**, DMF, Et_4NClO_4 (0.1 M), 3 mA; **1.307**, 85%.

Similarly, Medeiros and co-workers examined the reductive cyclisation of alkyl bromides using nickel macrocyclic complexes.[118] While a variety of nickel complexes proved to be effective, the use of tetramethylcyclam in complex **1.311** proved to be the highest yielding in the reduction of bromide **1.309** to form tetrahydrofuran **1.310**.[118a] The authors also noted the importance of the sacrificial anode (counter electrode). When magnesium was used, the isolated yield of **1.310** was significantly lower (38%) than when aluminium (70%) or zinc (77%) was employed. The authors state that a major advantage that complex **1.311** has over other macrocyclic nickel complexes is that the catalytic cycle is rapid.[119] Thus, despite the reduction potential being measured at -0.86 V (vs. Ag/AgCl/3M KCl(aq.))

the rapid catalytic cycle, observed through the large cathodic peaks during CV,* leads to the possibility of quick synthetic electrolyses using a catalytic amount of complex **1.311**. Cyclisation onto alkyne units also occurs readily, as demonstrated by the formation of **1.313** from alkyne **1.312**.

Scheme 1.50: further examples of reductive cyclisation mediated by electrochemically-induced nickel(I) complexes.

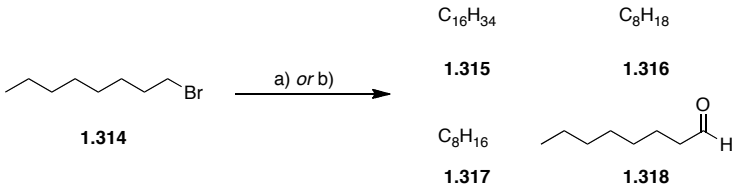


Reaction conditions: a) 20 mol% **1.311**, DMF, TBATFB (0.1 M), 30 mA; **1.310**, 77%; b) 10 mol% **1.311**, DMF, TBATFB (0.1 M), -0.9 V; **1.313**, 98%.

Peters and co-workers have also investigated the reduction of alkyl halides using nickel(II) salen **1.305** and electrochemistry.[120,121] They found that aldehydes (*e.g.*, **1.318**) were produced upon reduction of alkyl bromides and iodides (e.g., **1.314**) in *N,N*-dimethylformamide with electrochemically generated nickel(I) salen. Deliberate addition of water, as well as exposure to UV light and air were found to provide increased yields of aldehyde **1.318**. It is noteworthy that the aldehyde product **1.318** bears the same number of carbon atoms as the starting halide **1.314**. Modification of the reaction conditions greatly affected the product distribution, as can be seen in scheme 1.51. For example, under conditions a), just 33% of aldehyde **1.318** was produced, whereas when the ratio of substrate **1.314** to nickel(II) salen **1.305** was changed from 2:1 to 1:4 for conditions b), aldehyde **1.318** was isolated in significantly greater quantities (74%).[120]

* Complex **1.311** was analysed alongside an excess of substrate, during which time a large cathodic peak was observed. Peak current can be used to measure the rate at which the complex is regenerated. Thus, it follows that an increase in peak current means the complete catalytic cycle is rapid and electrochemically driven catalysis is a possibility.

Scheme 1.51: the reduction of alkyl bromide **1.314** using electrochemically generated nickel(I) salen.



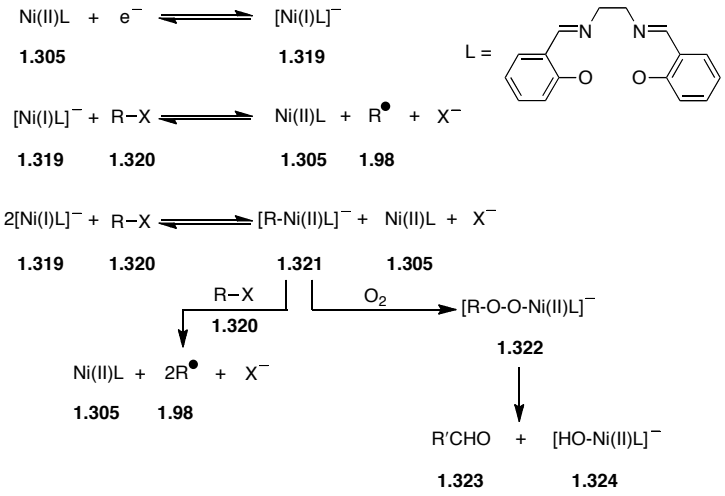
Reaction conditions	Product Distribution (%)				
	1.315	**1.316**	**1.317**	**1.318**	**Total**
a)	42	5	1	33	81
b)	2	2	1	74	79

Reaction conditions: a) **1.314** (4 mM), nickel(II) salen **1.305** (2 mM), DMF, TMATFB (0.1 M), water (0.75 M), -1.1 V, exposure to air on reaction completion; b) **1.314** (0.5 mM), nickel(II) salen **1.305** (2 mM), DMF, TMATFB (0.1 M), water (2 M), -1.1 V, exposure to air on reaction completion.

Mechanistic studies focussed on isotopic labelling of the reaction additives.[120,121] Experiments were conducted which included $H_2{}^{18}O$ as the water additive revealed that the product aldehyde contained 39-51% of oxygen-18. However, exposure of the reaction solution to air is crucial for the formation of the aldehyde product. Thus, further labelling studies involving $^{18}O_2$ revealed that the product aldehyde now contained 92% oxygen-18. Therefore, the authors proposed that the most likely source of the aldehydic oxygen was during exposure to air, with the positive result for inclusion of oxygen-18 during the $H_2{}^{18}O$ occurring due to hydration of the product aldehyde upon addition of water. The proposed mechanism is shown in scheme 1.52. Electrochemical generation of nickel(I) salen **1.319** is followed by reduction of the alkyl halide **1.320**, to form nickel(II) salen **1.305**, an alkyl radical **1.98** and a halide ion. At this stage, alkyl radical **1.98** can react *via* radical-radical coupling, disproportionation or hydrogen abstraction to form the by-products shown in scheme 1.51.[121] Alternatively, when a high ratio of nickel(II) salen **1.305** to alkyl halide **1.320** is used, following reduction to form nickel(I) salen **1.319**, alkylnickel(II) species **1.321** can form. This crucial intermediate can then react with atmospheric oxygen forming the peroxy species **1.322**. Oxygen-oxygen bond-breakage follows resulting in the formation of the product aldehyde **1.323**. The alternative pathway for alkylnickel(II) species **1.321** would be further reaction with alkyl halide **1.320**, forming alkyl radical **1.98**. The authors propose that a possible role for water is in

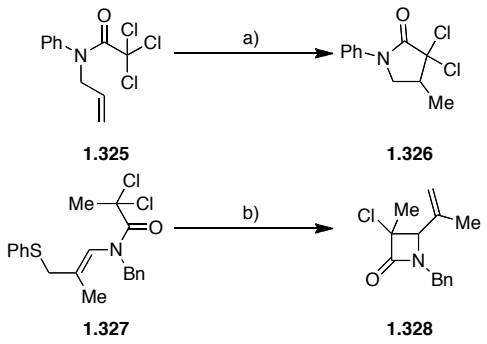
retarding this pathway and thus enhancing the formation of aldehyde **1.323** by limiting the amount of free alkyl radical **1.98** residing within the reaction mixture.[121] More recently, the authors extended this methodology to include secondary alkyl halides.[122] However, the yields of the corresponding ketone products were significantly lower than that of the aldehydes described above.

Scheme 1.52: the proposed mechanism for the formation of aldehydes from alkyl halides.



Zard and co-workers have developed a useful nickel powder/AcOH radical methodology that has been successfully applied to the formation of γ- (*e.g.*, **1.326**) and β-lactams (*e.g.*, **1.328**).[123] This mild method for the generation of radicals employs nickel powder (30 equiv.) and acetic acid (20 equiv.) in refluxing propan-2-ol to induce 5-*exo*-*trig*, 4-*exo*-*trig* or 5-*endo*-*trig* cyclisations. Although the initial one-electron reduction is fast, addition of the second electron occurs at a slower rate to allow cyclisation to occur. This methodology has been applied in the total synthesis of 3-demethoxyerythratidinone[124] and γ-lycorane.[125]

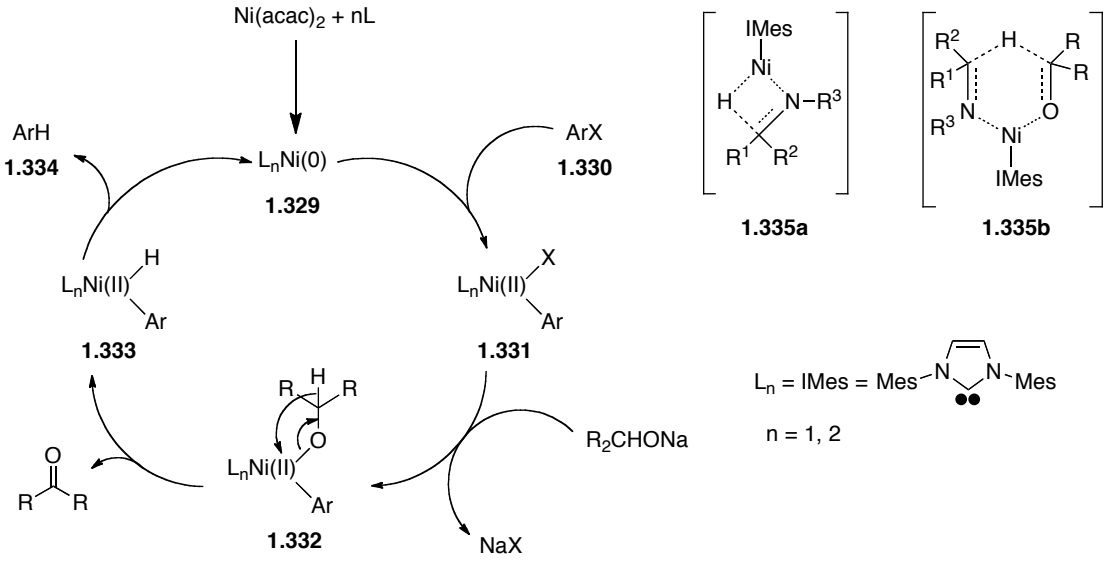
Scheme 1.53: the application of nickel powder/AcOH reducing system developed by Zard and co-workers.[123]



Reaction conditions: a) Ni powder, AcOH, propan-2-ol, *tert*-dodecanethiol, reflux; **1.326**, 76%; b) Ni powder, AcOH, propan-2-ol, reflux; **1.328**, 60%.

The reagents and systems described above have involved the nickel(I) oxidation state. However, Fort and co-workers have demonstrated the use of a nickel(0)/*N*-heterocyclic carbene catalytic reducing agent (scheme 1.54).[126] In their system, just 3-5 mol% of a nickel(0) source, together with 3-6 mol% of an *N*-heterocyclic carbene ligand and an excess of sodium alkoxide base, proved to be effective in the dehalogenation of aryl halides,[126a] including challenging aryl fluorides,[126b] as well as the transfer hydrogenation of imines.[126c] The authors state that the reduction of aryl fluorides was only achieved when a 1:1 ratio of nickel(0) to NHC was used, in contrast to a 1:2 ratio for less challenging aryl halides. Furthermore, the sodium alkoxide base must contain a β-hydrogen (*e.g.*, sodium isopropoxide or isopentoxide) as the hydrogen source. The proposed mechanism for the reduction of aryl halides[126a,b] involves first activation to nickel(0) and deprotonation of the imidazolium salt forming the active catalyst **1.329**. Oxidative addition with aryl halide **1.330** occurs forming **1.331**, which is then attacked by alkoxide, displacing the halide. Intermediate **1.332** then undergoes β-hydride elimination forming a nickel hydride intermediate **1.333**, that affords the reduced product (**1.334**) after reductive elimination, simultaneously generating the active catalyst and completing the catalytic cycle. In the transfer hydrogenation of imines, the mechanism differs and a full explanation was not provided. Instead, two transition states, **1.335a** and **b**, were proposed. Both involve hydride transfer from an activated nickel catalyst. Nolan and co-workers have demonstrated a similar system based on palladium(0).[127]

Scheme 1.54: the proposed mechanism for the nickel(0)/NHC-mediated reduction of aryl halides and the proposed transition states in the transfer hydrogenation of imines.



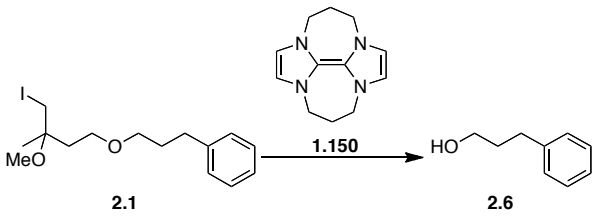
Section 1.5

Aims and objectives

The principal aim of the research documented within this thesis is the further development and understanding of powerful electron-transfer reagents. Chapter 1 introduced a variety of topics, with the main objective being to introduce the areas of research relevant to the discussion contained within the Results section of this thesis (chapters 2, 3 and 4).

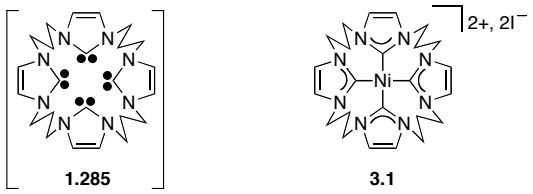
In chapter 1, section 1.2, the theme of organic electron donors was detailed extensively, including the most recent developments. The chemistry of donor **1.150** is further expanded in chapter 2, where the unusual isolation of a simple aliphatic alcohol (**2.6**) from alkyl iodide **2.1** is revealed (figure 1.18). The research reported in this chapter explores the reaction scope of this process, while also probing a mechanistic pathway that attempts to explain the isolation of alcohol **2.6**.

Figure 1.18: the initial isolation of alcohol **2.6** from alkyl iodide **2.1** using donor **1.150**.



Chapter 3 discusses the latest redox active member of the crown carbene complex family (that was revealed in chapter 1, section 1.3). The underlying aim of such complexes is that four highly electron-donating, *N*-heterocyclic carbene ligands would greatly increase the electron density of the complexed metal, in turn, providing a more powerful reductant complex. In addition, chapter 1, section 1.4, briefly discussed the role of nickel in electron transfer chemistry. In chapter 3, these two themes are combined in nickel(II) complex **3.1** (figure 1.19). The aim of this project was to develop extensively the reactivity of the activated complex against a range of organic substrates. Moreover, great importance has been placed on understanding the structure of the activated nickel complex that was performing such reactions.

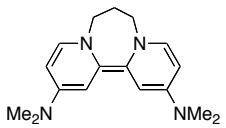
Figure 1.19: the *tetra-N*-heterocyclic carbene ligand **1.285**, and nickel(II) complex **3.1**.



1.285 **3.1**

Chapter 4 returns to the theme of organic electron donors. It would be highly advantageous to develop a catalytic method that would reduce simple organic substrates using substoichiometric quantities of electron donor that could be regenerated electrochemically. The outcomes of investigations, utilising donor **1.177** (figure 1.20), are presented in chapter 4.

Figure 1.20: the structure of donor **1.177**.



1.177

Chapter 2

The investigation into the isolation of alcohols from the reduction of alkyl iodides using a neutral, organic super electron donor

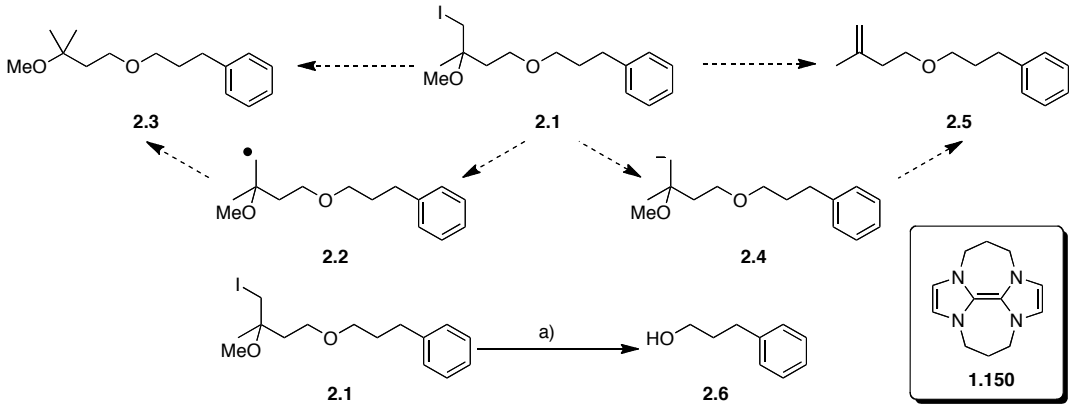
This chapter discusses the investigation into the unusual isolation of alcohols from alkyl iodides following exposure to the imidazole-derived donor **1.150**. This chapter focuses on an initial research programme undertaken during the first year of PhD study. This work can be divided into three principal sections. In section 2.1, the reaction discovery will be delineated and the reaction scope and development will be discussed. In section 2.2, the mechanistic possibilities for the reaction will be proposed and reviewed, in order to understand the likely mechanistic pathway that the process follows. Through experimentation and analysis of the results, one mechanism will be presented as the most likely pathway. Finally, in section 2.3, the conclusions from this chapter will be discussed, as well as potential future work.

Section 2.1

Introduction to the reaction and investigations on the scope of the reaction

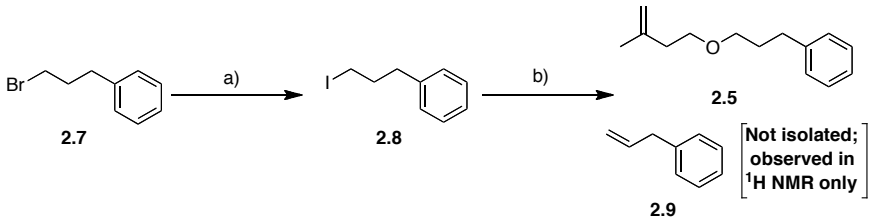
During the course of the initial investigations into the imidazole-derived donor **1.150**, mechanistic studies focussed upon alkyl iodides in order to determine whether the super electron donor reagent was transferring one or two electrons. If just a single electron were transferred, the resulting product would abstract a hydrogen atom forming dimethyl product **2.3**, *via* alkyl radical **2.2**. The transfer of two electrons would form an alkyl anion **2.4**, which, due to the alpha positioning of the methoxy-leaving group, could follow an elimination process to form the disubstituted alkene **2.5**. However, when alkyl iodide **2.1** was treated with 1.5 equivalents of the imidazole-derived donor **1.150**, neither expected product from the transfer of one or two electrons was observed. Instead, 3-phenylpropanol **2.6** was isolated in 49% yield.[128] This new and unexpected reactivity for donor **1.150** warranted further investigation.

Scheme 2.1: the expected outcome following the transfer of one or two electrons from donor **1.150** to substrate **2.1** and the experimental outcome.



Reaction conditions: a) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) iodide **2.1**, Ar, 18 h, r.t.; **2.6**, 49%.

Scheme 2.2: the synthesis of alkyl iodide **2.8** and the initial alkylation reaction attempt.



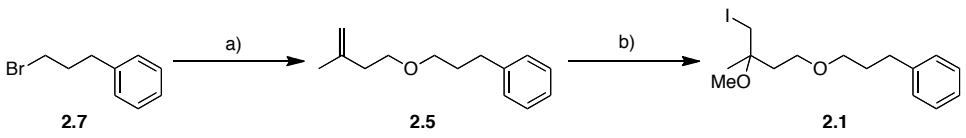
Reaction conditions: a) NaI, acetone, reflux, 64 h; **2.6**, 97%; b) 3-methyl-3-butenol, NaH, THF, r.t., Ar, 18 h; **2.5**, 25%.

Initially, alkyl iodide **2.1** was re-synthesised in order to repeat the reaction as a platform to build upon. The synthesis of the alkyl iodide precursor **2.5** followed the classical Williamson ether synthesis,[129] where an alcohol is deprotonated with a suitable base then exposed to an alkyl halide resulting in the alkylated product. Thus, it was envisaged that by treating 3-methyl-3-butenol with sodium hydride to form the corresponding alkoxide, then addition of 1-iodo-3-phenylpropane **2.8** would result in formation of the correct product **2.5**. As such, 1-iodo-3-phenylpropane **2.8** was synthesised from the bromo analogue **2.7** using sodium iodide in refluxing acetone in excellent yield. Iodide **2.8** was then reacted under the alkylation conditions shown, with, after stirring overnight at room temperature and chromatography, ether **2.5** isolated in 25% yield. The low yield was disappointing and was probably a result of significant elimination from 1-iodo-3-phenylpropane **2.6**

to form the alkene by-product **2.9**. This by-product was observed in the ^{1}H NMR spectrum of the crude reaction product (but was not isolated) and the identification based on the appearance of a characteristic signal at δ 5.12-5.17 ppm, corresponding to the terminal CH_2 of the alkene. In any case, formation of by-products such as **2.9** results in incomplete reaction and the low yield disclosed here.

The low yield from the alkylation was of considerable concern and steps were taken to address this, and, hopefully, obtain a higher yield of the ether product **2.5**. In the first alkylation attempt, tetrahydrofuran was used as solvent. It was envisaged that changing the solvent to *N*,*N*-dimethylformamide would assist the polar transition states and intermediates that would be present in the reaction medium and increase the reaction yield. In addition, the alkyl halide was changed from iodide **2.8** to the corresponding bromide **2.7**. It was proposed that the bromide would be less labile in terms of elimination and this step would lessen the formation of the unwanted alkene by-product **2.9**. Application of these two minor changes had an appreciable affect on the yield of product **2.5** isolated following chromatography, with ether **2.5** formed in 51% yield.

Scheme 2.3: the improved alkylation reaction to form ether **2.5** and the subsequent iodination to form alkyl iodide **2.1**.



2.7 **2.5** **2.1**

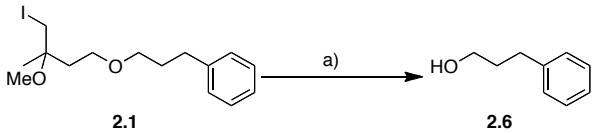
Reaction conditions: a) 3-methyl-3-butenol, NaH, DMF, Ar, r.t., 18 h; **2.5**, 51%; b) *N*-iodosuccinimide, MeOH, DCM, -78 °C to r.t., Ar, 18 h; **2.1**, 71%.

Following the formation of ether **2.5**, the synthesis of the alkyl iodide substrate **2.1** was achieved in one further step by iodination using *N*-iodosuccinimide and quenching with methanol, resulting in the isolation of the appropriate product **2.1** in 71% yield as a colourless oil.

With the alkyl iodide **2.1** now in hand, the reduction reaction was repeated in order to observe formation of the alcohol product **2.6**. Using the previously utilised conditions of 1.5 equivalents of imidazole-derived donor salt **1.155** and sodium hydride (15.0 equivalents) in *N*,*N*-dimethylformamide, 3-phenylpropanol **2.6** was

isolated in a good 70% yield. Thus, the formation of alcohols from alkyl iodides occurs readily after exposure to the imidazole-derived donor **1.150**.

Scheme 2.4: the isolation of alcohol **2.6** following exposure of alkyl iodide **2.1** to imidazole-derived donor **1.150**.

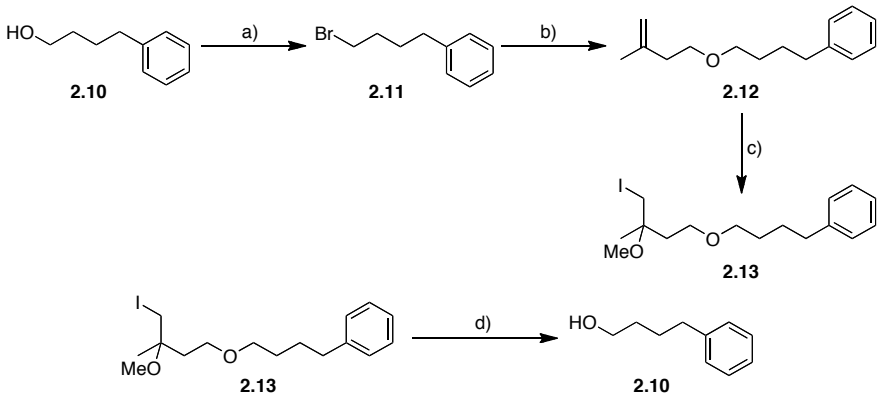


2.1 **2.6**

Reaction conditions: a) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) iodide, **2.1**, Ar, 18 h, r.t.; **2.6**, 70%.

With the confirmed result of alcohol **2.6** formation from alkyl iodide **2.1** in hand, further substrates were proposed, synthesised and subsequently tested to observe this fragmentation. It was suggested that the left-hand-side of the parent alkyl iodide **2.1** was kept constant and the right-hand-side modified, with the aim of providing a variety of alcohols. The general synthesis for each substrate followed that of alkyl iodide **2.1** discussed above. The next substrate synthesised differed from alkyl iodide **2.1** by one methylene unit on the right-hand-side. Bromination of 4-phenylbutanol **2.10** afforded 4-phenyl-1-bromobutane **2.11** in good yield (60%). Alkylation under the optimised conditions furnished the ether intermediate **2.12** (37%), which was iodinated and quenched with methanol to afford the appropriate substrate **2.13** (75%). After exposure to donor **1.150** and purification by chromatography, 4-phenylbutanol **2.10** was isolated as a colourless oil in 67% yield.

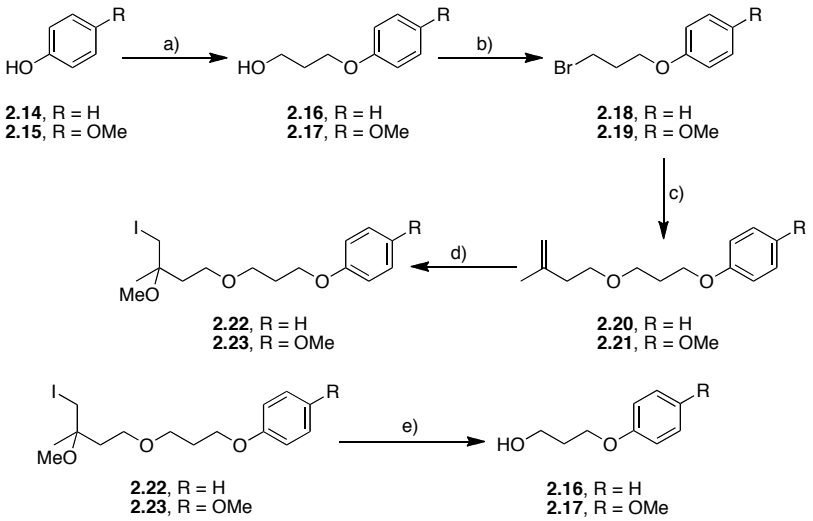
Scheme 2.5: the synthesis of the extended carbon chain alkyl iodide **2.13** and its reaction with the imidazole-derived donor **1.150**.



Reaction conditions: a) PBr_3, Et_2O, r.t., Ar, 18 h; **2.11**, 60%; b) 3-methyl-3-butenol, NaH, r.t., Ar, 18 h; **2.12**, 37%; c) *N*-iodosuccinimide, MeOH, DCM, -78 °C to r.t., Ar, 18 h; **2.13**, 75%; d) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) iodide **2.13**, Ar, 18 h, r.t.; **2.10**, 67%.

Further substrates were also envisaged to fully determine any possible role for the right-hand-side of the substrate in the mechanism. The synthesis of two phenoxy substrates (**2.22** and **2.23**) was completed in an analogous fashion to the previously synthesised alkyl iodides. There was the requirement for an additional synthetic step however, with alkylation of either phenol **2.14** or 4-methoxyphenol **2.15** with 3-bromopropanol in potassium carbonate and *N,N*-dimethylformamide needed to furnish the precursor alcohols (**2.16** and **2.17**). Each alkylation proceeded smoothly with the rest of the synthesis following the now typical pattern. Thus, after bromination, alkylation and iodination, each substrate was now in hand and subsequently tested using the imidazole-derived donor **1.150**. Each alcohol was recovered in good yield, indicating that the mechanism could accommodate a phenoxy group. This was of interest due to the fact that a non-aromatic C-O bond is cleaved to form the alcohol product, clearly indicating the non-participation of the right-hand-side of the molecule in the reaction pathway.

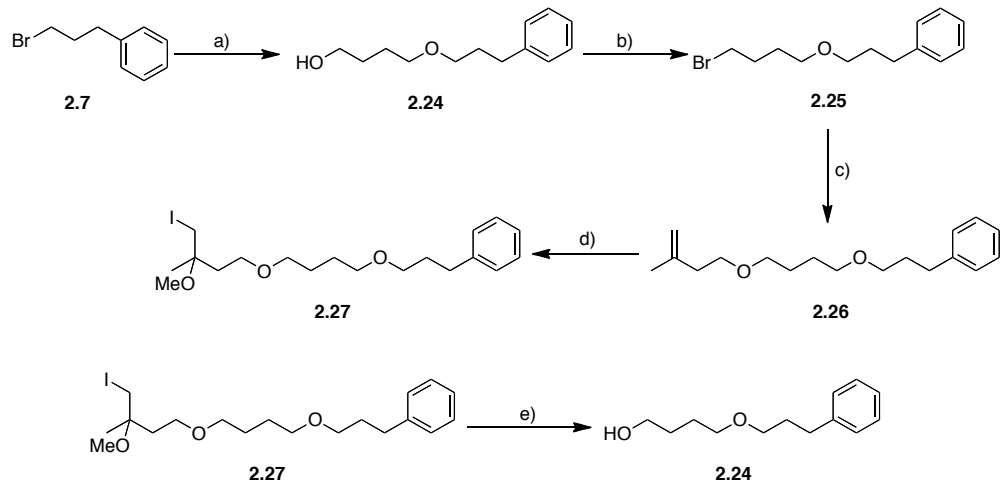
Scheme 2.6: the synthesis of the phenoxy-containing substrates **2.22** and **2.23** and their subsequent reaction with imidazole-derived donor **1.150**.



Reaction conditions: a) 3-bromopropanol, K_2CO_3, DMF, r.t., Ar, 64 h; **2.16**, 76%; **2.17**, 83%; b) PBr_3, Et_2O, r.t., Ar, 18 h; **2.18**, 64%; **2.19**, 49%; c) 3-methyl-3-butenol, NaH, DMF, 18 h, r.t., Ar; **2.20**, 15%; **2.21**, 20%; d) *N*-iodosuccinimide, MeOH, DCM, -78 °C to r.t., Ar, 18 h; **2.22**, 63%; **2.23**, 77%; e) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) **2.22** or **2.23**, Ar, 18 h, r.t.; **2.16**, 77%; **2.17**, 63%.

With the results shown above in scheme 2.6 indicating that the imidazole-derived donor **1.150** was capable of forming alcohols in the presence of an oxygen atom next to the aromatic ring, it was proposed to examine whether an oxygen atom could be tolerated elsewhere within the molecule to provide the expected alcohol product. Alkyl iodide **2.27** was proposed due to the fact that with two oxygen atoms in place in the alkyl chain, the reaction could have a choice over which C-O bond to cleave. The synthesis of alkyl iodide **2.27** broadly followed the synthesis of the earlier alkyl iodides. Alkylation of 3-phenyl-1-bromopropane **2.7** with 1,4-butanediol over 11 days gave the precursor alcohol **2.24**. Bromination, alkylation and iodination followed to furnish the appropriate alkyl iodide **2.27** as a clear and colourless oil. Under the optimised conditions for the reduction of alkyl iodides with the imidazole-derived donor **1.150**, the expected alcohol **2.24** with one ether linkage still intact was isolated in 70% yield following purification on silica. No lower molecular weight alcohol (*e.g.*, 3-phenylpropanol **2.6**) was identified in the ^{1}H NMR of the crude reaction mixture, and, owing to the high yield, it is clear that only one C-O bond is broken in the reaction. Evidently, the C-O bond that was closer to the iodide cleaved preferentially.

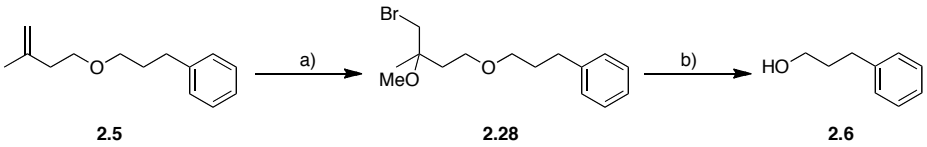
Scheme 2.7: the synthesis of the double oxygen-containing substrate **2.27** and the subsequent reaction with the imidazole-derived donor **1.150**.



Reaction conditions: a) 1,4-butandiol, NaH, DMF, r.t., 4 days then 80 °C, 7 days; **2.24**, 67%; b) PBr_3, Et_2O, r.t., Ar, 18 h; **2.25**, 56%; c) 3-methyl-3-butenol, NaH, r.t., Ar, 18 h; **2.26**, 33%; d) *N*-iodosuccinimide, MeOH, DCM, -78 °C to r.t., Ar, 18 h; **2.27**, 84%; e) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) iodide **2.27**, Ar, 18 h, r.t.; **2.24**, 70%.

One final compound that was synthesised and subsequently examined was the bromide analogue of the original alkyl iodide, which was prepared by bromination of the intermediate ether using *N*-bromosuccinimide. This furnished the alkyl bromide substrate **2.28** in moderate yield (47%) following quenching with methanol. Subsequent testing of alkyl bromide **2.28** by exposure to the imidazole-derived donor **1.150** resulted in isolation of the expected 3-phenylpropanol **2.6** in 69% yield, proving that the process is also compatible with alkyl bromides.

Scheme 2.8: the synthesis of alkyl bromide **2.28** and the subsequent reaction with the imidazole-derived donor **1.150**.



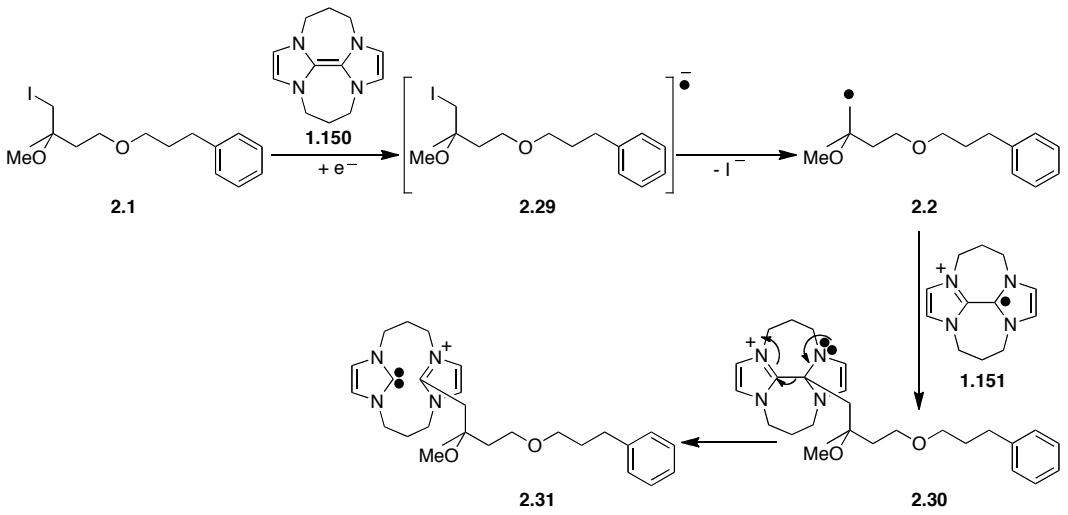
Reaction conditions: a) *N*-bromosuccinimide, MeOH, DCM, -78 °C to r.t., Ar, 18 h; **2.28**, 47%; d) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) bromide **2.28**, Ar, 18 h, r.t.; **2.6**, 69%.

Section 2.2

Investigations into the mechanistic pathway for this process

Following the successful isolation of a range of alcohols after exposure of alkyl iodides to the imidazole-derived donor **1.150**, it was necessary to attempt to gain an understanding of the mechanistic pathway of this reaction. The results shown in section 2.1 allow some conclusions to be drawn, notably that the right-hand-side of the molecule is not involved in the mechanism since each isolated alcohol is recovered in high yield. Also, following the isolation of alcohol **2.24** from the reduction of alkyl iodide **2.27** using donor **1.150**, it is clear that the cleavage of the C-O bond is focussed upon one particular molecular fragment, since no cleavage of the alternative C-O bond within alkyl iodide **2.27** was observed (see scheme 2.7). Finally, since no alkene (*e.g.*, **2.5**) was observed following the reduction of these alkyl iodides, it was believed that the initial electron transfer occurs with the donor donating only one electron, forming an alkyl radical **2.2** (rather than an alkyl anion), and this intermediate alkyl radical can then react further to generate the alcohol products.

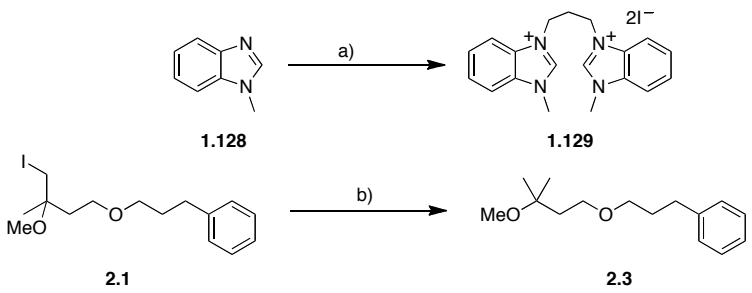
Scheme 2.9: the mechanistic proposal for the initial electron transfer and subsequent formation of key imidazolium intermediate **2.31**.



The initial mechanistic rationale that has been proposed is shown in scheme 2.9. Electron transfer from the HOMO of the imidazole-derived donor **1.150** to the low-lying σ^* orbital of the carbon-iodine bond in alkyl iodide **2.1** results in formation of

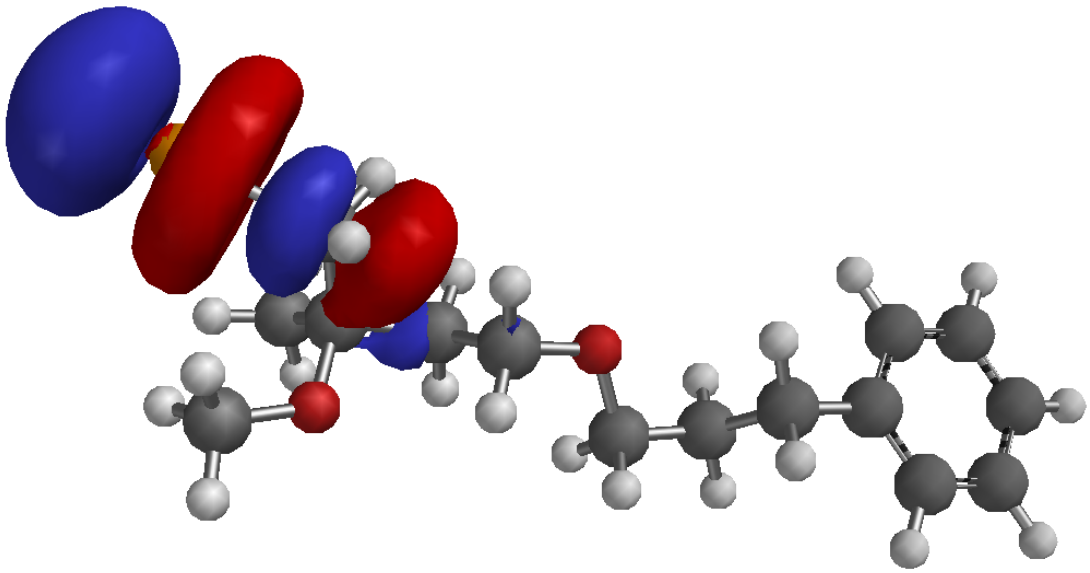
the radical anion intermediate **2.29**, which would rapidly fragment to form the alkyl radical **2.2** and iodide ion. This radical can then undergo a coupling reaction with the imidazole-derived donor radical cation **1.151** (formed after initial transfer of a single electron) to form the intermediate **2.30**, which can rearrange to form the key imidazolium *N*-heterocyclic carbene intermediate **2.31**. The initial electron transfer to the alkyl iodide carbon-iodine bond can be supported by the isolation of the simple reduced compound **2.3**. Product **2.3**, resulting from abstraction of a hydrogen atom by the alkyl radical intermediate **2.2**, has been observed (by ^{1}H NMR) as a minor by-product in the crude reaction mixture during the isolation of alcohols from alkyl iodides presented here. Although it wasn't isolated, its presence indicates that the initial mechanistic step would be a single electron transfer. Pleasingly, when alkyl iodide **2.1** was exposed to the benzimidazole-derived donor **1.130** – a known single electron donor,[54] the reduced product **2.3** was isolated in 40% yield (scheme 2.10). Further support for an initial single electron transfer step in the mechanism for this process came from simple molecular modelling of the alkyl iodide **2.1** starting material. Using Spartan®, the LUMO of iodide **2.1** was confirmed to be the σ^* orbital of the carbon-iodine bond (the iodine atom is coloured orange and is partially obscured by the orbital density). Thus, it has been established that the initial steps of the mechanism involve electron transfer to the C-I bond of the alkyl iodide **2.1** from the HOMO of the imidazole-derived donor **1.150**.

Scheme 2.10: synthesis of benzimidazole-derived donor precursor salt **1.129** and the reduction of alkyl iodide **2.1** to form reduced compound **2.3** using benzimidazole-derived donor **1.130**.



Reaction conditions: a) 1,3-diiodopropane, MeCN, reflux, 96 h; **1.129**, 95%; b) benzimidazole-derived donor salt **1.129** (4.0 equiv.), NaH (40.0 equiv.), toluene/DMF (2:1), r.t., Ar, 4 h *then added to substrate* ii) iodide **2.1**, Ar, 72 h, reflux; **2.3**, 40%.

Figure 2.1: the LUMO orbital of alkyl iodide **2.1**.* Atom(s) colouring: orange = iodide, red = oxygen, grey = carbon, white = hydrogen. Large areas of red and blue are orbital density.



After the initial electron transfer, four mechanistic possibilities were proposed for the generation of alcohol products, all *via* the key intermediate **2.31**. The first two of these, mechanisms A and B, are closely related and initially involve a further rearrangement to form a new carbon-oxygen interaction **2.32**. This mechanistic step is clearly dependent on the electrophilicity of the carbon in the C2 position of the imidazolium component of the key intermediate **2.31**. This has also been supported through Spartan® molecular modelling to provide the lowest energy conformation of oxonium intermediate **2.32**, pointing to formation of a weak C-O interaction. Previous work within the Murphy group had established that the imidazole-derived donor **1.150** is essentially planar, with the planarity remaining when one or two electrons were transferred.[58] In this case, it would be expected that the planarity would be lost due to the formation of the monocation and no formal C-C bond between each central C2 carbon on the imidazole/imidazolium rings in intermediate **2.31**. Loss of planarity would allow the two five-membered rings to exist in a staggered conformation to each other, and, as such, permit the six-membered oxonium-containing ring in **2.32** to sit comfortably. The calculated structure is shown in figure 2.2, with the C-O interaction displayed centrally, between the red oxygen atom and grey carbon immediately to its left. The calculated distance of

* Calculated using Spartan®, single-point energy, Hartree-Fock, 6-31G*

2.941 Å between the two atoms clearly represents what would be a weak interaction.

Scheme 2.11: the formation of the cyclic oxonium intermediate **2.32** for mechanisms A and B

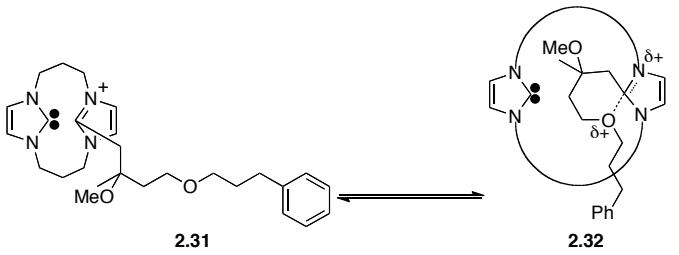
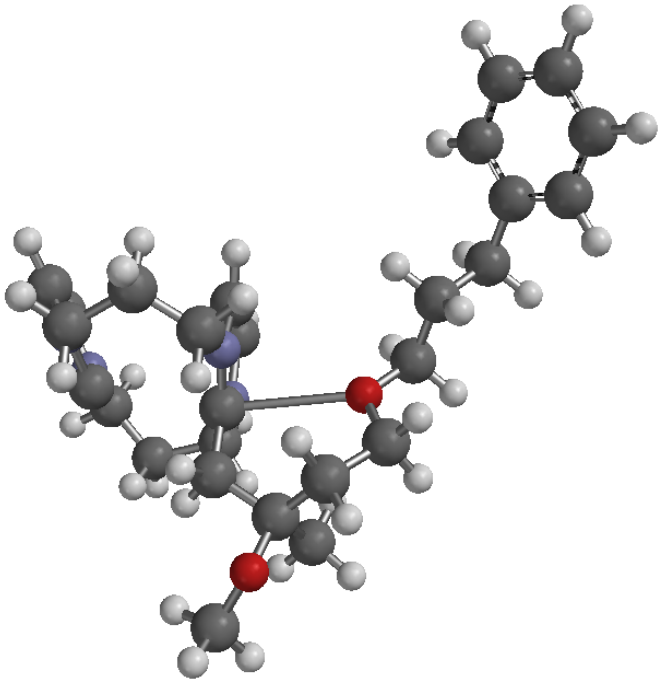


Figure 2.2: Spartan representation of key cyclic oxonium intermediate **2.32**.* Oxygen atoms are coloured red, nitrogen blue and carbon black. Hydrogen atoms omitted for clarity.

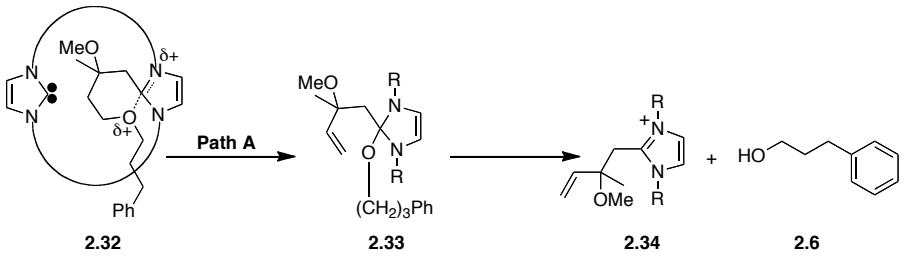


Following formation of the cyclic oxonium intermediate **2.32**, two mechanisms have been proposed. In mechanism A (scheme 2.12), base (perhaps the *N*-heterocyclic carbene on the other five-membered ring) could deprotonate at the carbon adjacent to the quaternary centre, forming alkene **2.33**. Elimination of the alkoxide moiety on alkene **2.33** is possible to form alcohol **2.6** as required, as well as the salt by-product **2.34**. In mechanism B (scheme 2.13), deprotonation can occur at the carbon adjacent to both the quaternary centre and the heterocycle in intermediate **2.32**

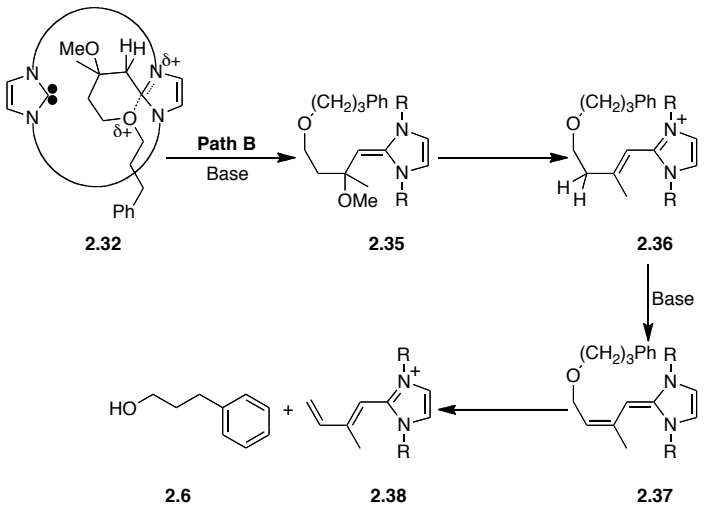
* Calculated using Spartan®, equilibrium geometry, Hartree-Fock, 6-31G*

forming an enediamine intermediate **2.35**. Elimination of methoxide from the enediamine intermediate **2.35** occurs first, forming a conjugated alkene **2.36**, which deprotonates once more (perhaps by eliminated methoxide, forming methanol) to form the second enediamine intermediate **2.37**. This intermediate is primed to expel the alcohol product **2.6**, forming salt by-product **2.38** also (scheme 2.13).

Scheme 2.12: proposed mechanism A for the formation of alcohol **2.6** from the reaction of imidazole-derived donor **1.150** with alkyl iodide **2.1**.

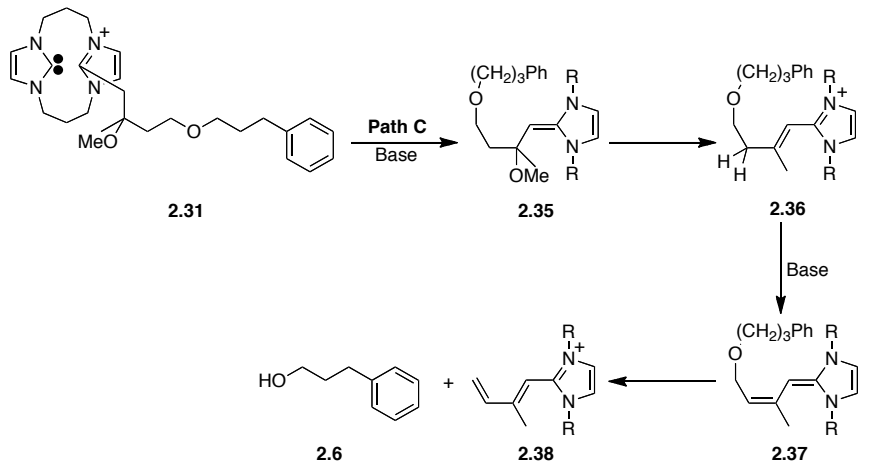


Scheme 2.13: proposed mechanism B for the formation of alcohol **2.6** from the reaction of imidazole-derived donor **1.150** with alkyl iodide **2.1**.



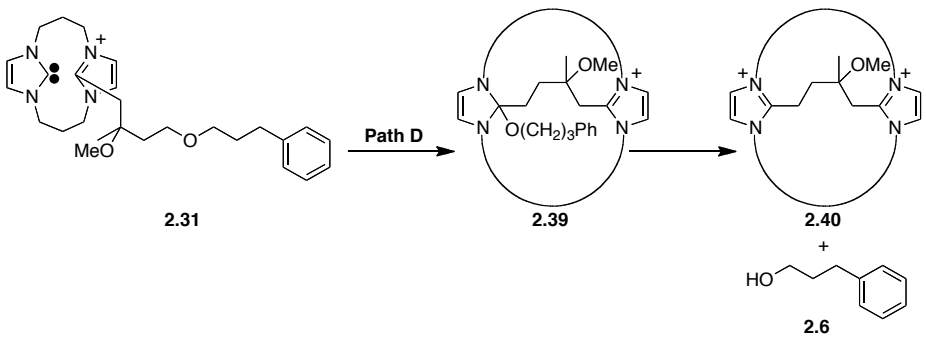
The third mechanistic possibility once more involves formation of the enediamine intermediate **2.35** (scheme 2.14). However, formation of the cyclic oxonium intermediate **2.32** is not required, with deprotonation of **2.31** leading directly to the enediamine intermediate **2.35**. Thus, mechanism C is then analogous to mechanism B (scheme 2.13) with elimination to form the alkene imidazolium intermediate **2.36**, followed by a second deprotonation and finally rearrangement to eliminate the alcohol product **2.6** (scheme 2.14).

Scheme 2.14: proposed mechanism C for the formation of alcohol **2.6** from the reaction of imidazole-derived donor **1.150** with alkyl iodide **2.1**.



The final proposed mechanism once more stems from key imidazolium-*N*-heterocyclic carbene intermediate **2.31** and would involve unusual reactivity of an *N*-heterocyclic carbene.[130] Mechanism D would involve insertion of the carbene moiety of **2.31** into the C-O bond to form the bridged intermediate **2.39** shown (scheme 2.15). Intermediate **2.39** is primed to expel the alcohol product **2.6** and rearomatise to form the imidazolium by-product **2.40**. This does seem unlikely, although it could not be ruled out at this stage as a possible route to the observed alcohol **2.6**.

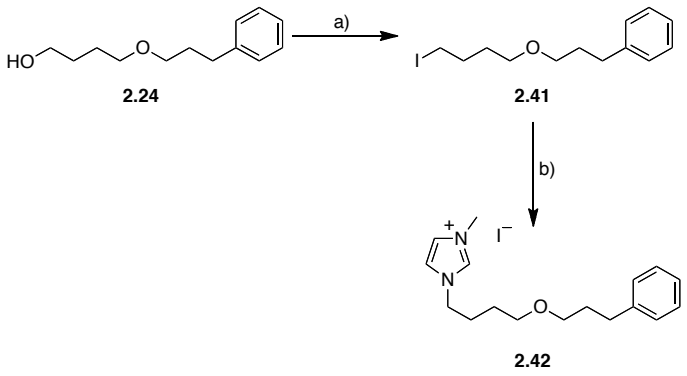
Scheme 2.15: proposed mechanism D for the formation of alcohol **2.6** from the reaction of imidazole-derived donor **1.150** with alkyl iodide **2.1**.



In order to ascertain which of these mechanistic routes was the most probable, several experiments were undertaken. Initially, the most intriguing mechanistic possibility was examined. This would be insertion of the *N*-heterocyclic carbene into the C-O bond of the imidazolium intermediate **2.31**, and subsequent cleavage to

form the product alcohol **2.6** (mechanism D, scheme 2.15, above). With the initial stages of the mechanism being established as occurring *via* an electron-transfer mechanism, the substrate that was required to test this insertion hypothesis did not need to contain an electron acceptor component. However, it was considered important to construct a molecule that was as closely related to the parent structure **2.1** as possible. With this in mind, imidazolium iodide **2.42** was synthesised by initial iodination of alcohol **2.24** (alcohol synthesised by alkylation of 1-bromo-3-phenylpropane **2.7** with 1,4-butanediol and used in synthesis of alkyl iodide **2.27**), followed by salt formation with *N*-methylimidazole, which proceeded in excellent yield (94%).

Scheme 2.16: the synthesis of imidazolium iodide **2.42** as a test substrate for mechanism D.

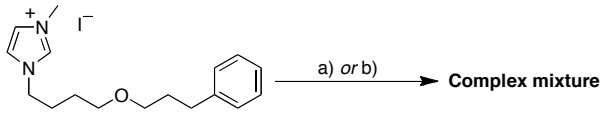


Reaction conditions: a) iodine, triphenylphosphine, imidazole, DCM, r.t., Ar, 20 h; **2.41**, 86%; b) *N*-methylimidazole, MeCN, reflux, 90 h, Ar; **2.42**, 94%.

This approach aimed to generate the *N*-heterocyclic carbene *in situ*, with the close proximity of the C-O bond in **2.42** providing the newly formed and highly reactive carbene with the best possible opportunity to attack and break the C-O bond. The first attempt focussed on the use of potassium *tert*-butoxide as base, with tetrahydrofuran as solvent, a commonly applied set of reaction conditions for *N*-heterocyclic carbene methodology.[131] However, when imidazolium iodide **2.42** was exposed to these conditions overnight, a complex mixture was observed upon work-up. Analysis by ^{1}H and ^{13}C NMR, IR, LCMS and GCMS gave no indication that the target alcohol **2.6** had been formed. The second attempt involved a change of base from potassium *tert*-butoxide to sodium hydride, and also a change of solvent from tetrahydrofuran to *N*,*N*-dimethylformamide. However, once more NMR, IR and mass spectrometry observed a complex mixture, with no trace of the target alcohol

2.6. These two results indicated that the mechanism that affords the alcohol products when alkyl iodides are exposed to the imidazole-derived donor **1.150** was not consistent with the insertion of an *N*-heterocyclic carbene into the C-O bond,[79] thus, mechanism D (scheme 2.15) can be ruled out.

Scheme 2.17: test reactions to observe the insertion of a carbene into the C-O bond of imidazolium iodide **2.42** as proposed in mechanism D.

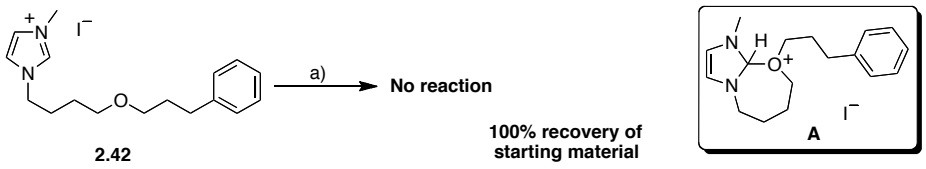


2.42

Reaction conditions: a) KO*t*Bu, THF, -10 C to r.t., Ar, 16 h, complex mixture; b) NaH, DMF, r.t., 20 h, Ar, complex mixture.

Of the three remaining mechanisms, both A and B involve cyclisation to form the more complex oxonium intermediate **2.32**. For example, in mechanism A, cyclisation to form oxonium intermediate **2.32** is required to activate the oxygen to allow elimination of the target alcohol product **2.6**. Now with imidazolium iodide **2.42** substrate in hand, it was believed that examination of this substrate under conditions similar to those required for reduction of alkyl iodides might allow for observation of the related oxonium intermediate **A** (scheme 2.18). Thus, imidazolium iodide **2.42** was dissolved in *N*,*N*-dimethylformamide and stirred under argon at room temperature for 18 h (scheme 2.18). On work-up and analysis by ^{1}H NMR, the starting material **2.42** was recovered in 100% yield, indicating that oxonium intermediate **A** is not occurring under these conditions to an extent that would allow its isolation. This, along with the weak nature of the C-O interaction shown in figure 2.2, casts doubt on the formation of **2.32** in mechanisms A and B, leaving mechanism C as the likely route to the alcohol products. However, it cannot be ruled out that a rapid equilibrium exists between the oxonium intermediate **2.32** and its precursor **2.31**. Thus it is possible, under the reaction conditions that the oxonium intermediate **2.31** is present in small amounts. As such, further investigations were required in order to fully support mechanism C, as well as to discount mechanisms A and B.

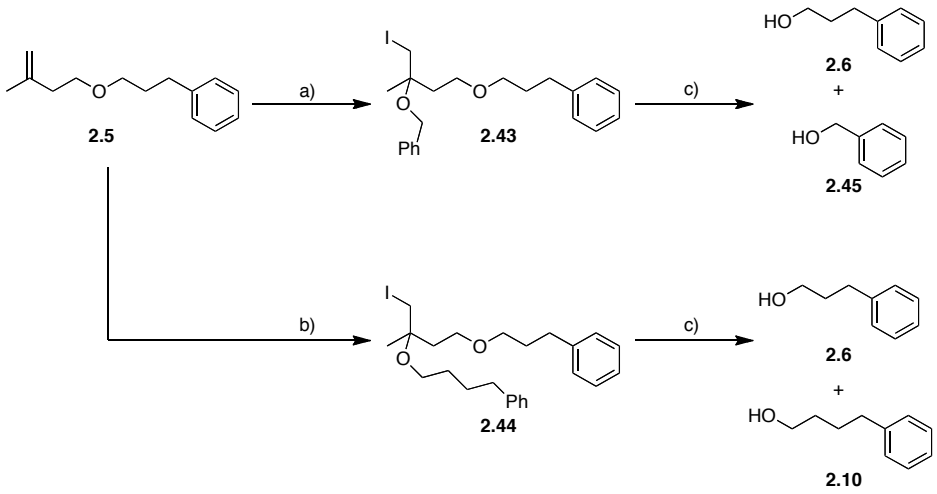
Scheme 2.18: the attempted isolation of the oxonium intermediate **A** proposed for mechanisms A and B, related to intermediate **2.32** shown in figure 2.2.



Reaction conditions: a) DMF, r.t., Ar, 18 h; 100% recovery of starting material **2.42**.

It was proposed that further insight into the most probable route to form the alcohol products (*e.g.*, **2.6**) would be gained by changing the labile alcohol group bound to the quaternary centre in substrate **2.1**. It is entirely possible that elimination of methoxide is occurring, generating methanol in the reaction mixture, at some point in the reaction process. The use of higher molecular weight alcohols could possibly lead to these eliminated alcohol products being observed after work-up. With this target in mind, alkyl iodide substrates containing a longer chain ether component as part of the quaternary carbon centre were synthesised. In an analogous fashion to those alkyl iodides previously discussed, the use of either benzyl alcohol **2.45**, in the case of **2.43**, or 4-phenylbutanol **2.10**, in the case of **2.44**, in place of methanol allowed each compound to be isolated (scheme 2.19). Thus, reaction of these substrates with the imidazole-derived donor **1.150** indicated that both alcohols were being cleaved during the course of the reaction. Substrate **2.43**, with a benzyl ether in place instead of the methyl ether, furnished a mixture of the expected 3-phenylpropanol **2.6** and benzyl alcohol **2.45** in a ratio of 1.5:1.0 (based on the ^{1}H NMR of the mixture after chromatography). The deviation from the expected equimolar ratio expected from this reaction could be explained by the slight volatility of the benzyl alcohol **2.45**, which could be lost on concentration of solvents after work-up or purification. Due to this, attention now turned to substrate **2.44**, containing a 4-phenylbutyl ether component in place of the methyl ether. Under the standard conditions of 1.5 eq. imidazole-derived donor precursor salt **1.155**, 15.0 eq. sodium hydride in *N*,*N*-dimethylformamide solvent and on work-up and chromatography, a 1:1 ratio of 3-phenylpropanol **2.6** and 4-phenylbutanol **2.10** was isolated, indicating a 1:1 relationship between the product alcohol and the eliminated alkoxide by-product (scheme 2.19).

Scheme 2.19: the synthesis of long-chain quaternary ether substrates **2.43** and **2.44** and the reaction of each with the imidazole-derived donor **1.150**.



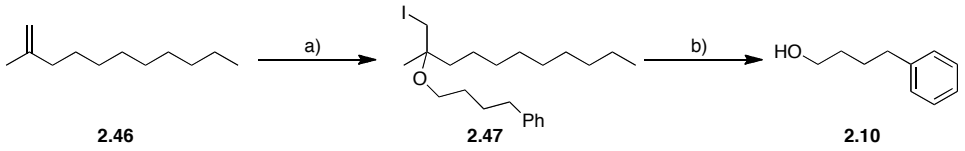
Reaction conditions: a) *N*-iodosuccinimide, benzyl alcohol, DCM, -78 °C to r.t., Ar, 18 h; **2.43**, 72%; b) *N*-iodosuccinimide, 4-phenylbutanol, DCM, -78 °C to r.t., Ar, 18 h; **2.44**, 61%; c) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) Ar, 18 h, r.t.; **2.6**/**2.45**, 1.5:1.0; **2.6**/**2.10**, 1.0:1.0.

These two results prove that loss of the alkoxy group bonded to the quaternary centre, *e.g.*, methoxide in **2.1**, plays a role in the mechanism of this reaction. This lends support to mechanism C, which involves loss of the methoxide in a key step prior to loss of the target alcohol product **2.6**. However, unfortunately these results do not rule out either of the other two remaining mechanisms. For example in mechanisms B and C, loss of methoxide occurs during formation of the second enediamine intermediate, *i.e.*, prior to generation of the alcohol product **2.6**. Each mechanism suggests that elimination of methoxide must occur for generation of the product alcohol to happen (schemes 2.13 and 2.14). However, there remains the possibility that elimination of methoxide occurs after loss of the main chain alkoxide group. If this is the case then mechanism A cannot be discounted from consideration. Thus it is incorrect to rule out any of the three remaining mechanisms.

An alternative approach was then considered in order to support one mechanism over the others. In each of the proposed mechanisms still under consideration, there are two leaving groups that are ultimately expelled during the course of the reaction, the product alcohol **2.6** and the alkoxide attached to the quaternary carbon atom (in mechanism A, elimination of methoxide is possible after the expulsion of

the product alcohol **2.6**). It was considered that rather than changing the group attached to the quaternary centre (such as substrates **2.43** and **2.44**, scheme 2.19), could it be possible to block the elimination of the product alcohol **2.6** by choice of test substrate? If the alkoxide group on the quaternary carbon were eliminated despite there being no possibility of elimination from the main chain, it would provide further insight into the likely mechanism for the formation of the product alcohol **2.6**. With this goal in mind, the synthesis of a suitable substrate was attempted. The clearest method for blocking elimination of the main chain alkoxide was to replace the ether linkage with a straight chain carbon moiety. For this reason, 2-methylundec-1-ene **2.46** was converted to the alkyl iodide **2.47** using the now standard conditions, using 4-phenylbutanol **2.10** as the quenching alcohol. The choice of this alcohol, over methanol, would allow isolation of 4-phenylbutanol **2.10** indicating fragmentation had occurred. The synthesis of **2.47** occurred in good yield (74%) to furnish the product as a slightly orange clear oil.

Scheme 2.20: the synthesis of straight-chain substrate **2.47** and its reaction with the imidazole-derived donor **1.150**.



2.46 **2.47** **2.10**

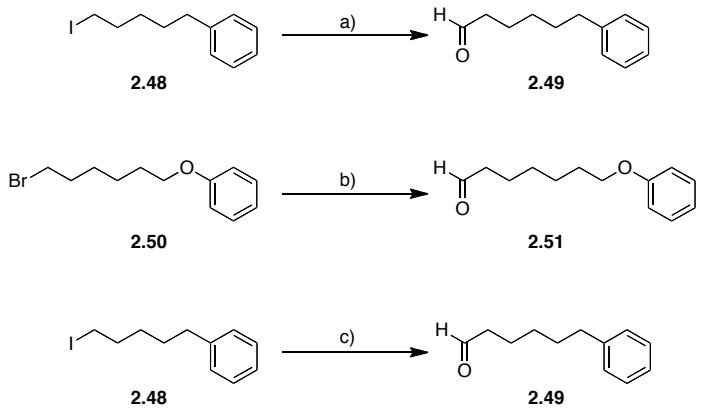
Reaction conditions: a) *N*-iodosuccinimide, 4-phenylbutanol, DCM, -78 °C to r.t., Ar, 18 h; **2.47**, 74%; b) i) imidazole-derived donor precursor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) Ar, 18 h, r.t.; **2.10**, 55%.

Long-chain alkyl iodide **2.47** was exposed to the imidazole-derived donor **1.150** in *N*,*N*-dimethylformamide for 18 h and, after work-up and purification on silica gel, 4-phenylbutanol **2.10** was isolated as a clear oil in a pleasing 55% yield. Clearly elimination of the β-alkoxide occurs during the reduction of these alkyl halides and this result indicates that the mechanism requires elimination of the β-alkoxide group. As such, it is reasonable to assume that the main chain alcohol (*e.g.*, **2.6**) is formed following elimination of the β-alkoxide group. This would support mechanisms B and C over mechanism A, however further evidence would be required in order to rule out mechanism A. One further point regarding mechanisms B and C is that the rearrangement to form the weak C-O interaction in oxonium intermediate **2.32**, which is necessary for mechanism B, would be in rapid equilibrium with the previous

intermediate **2.31**. Therefore, the low concentration and unstable nature of **2.32** (or related intermediate **A**, scheme 2.18) would lower the possibility of successful isolation. In addition, it must also be considered that the likely mechanism for the formation of alcohols (*e.g.*, **2.6**) would follow the least complex path, lending support to mechanism C (scheme 2.14).

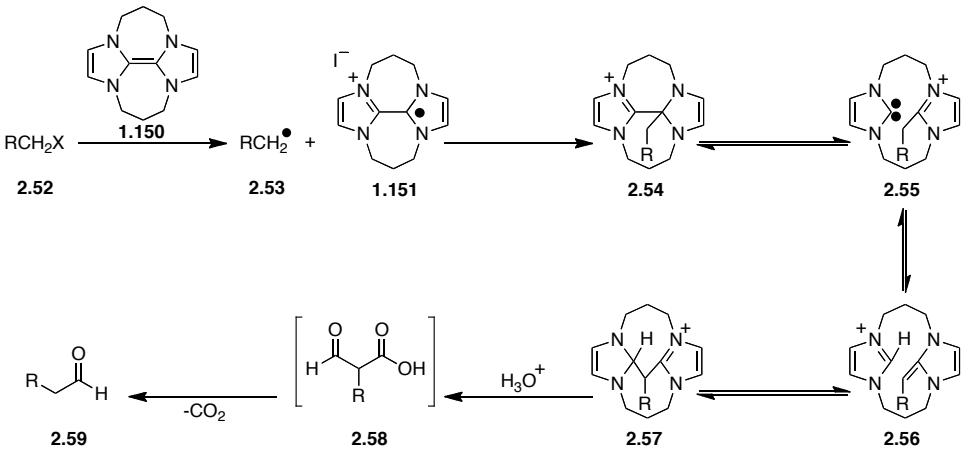
At this stage and upon reflection on the likely mechanism, it became clear that the isolation of alcohols was closely related to the isolation of aldehydes from simple alkyl iodides and bromides that had been recently investigated within the Murphy group. It was proposed that comparison of these two areas of research could further support mechanism C for the isolation of alcohols as discussed above. Schoenebeck[132] had shown that reaction of donor **1.150** with simple, long-chain alkyl iodide **2.48** resulted in isolation of the corresponding, one-carbon extended aldehyde **2.49** after application of an acidic work-up following completion of the reaction, albeit in low yield (scheme 2.21). Similarly, when straight-chain alkyl bromide **2.50** was tested using a large excess of imidazole-derived donor **1.150** and an acidic work-up, the corresponding one-carbon extended aldehyde **2.51** was isolated in good yield (61%). When a neutral work-up was used the yield of aldehyde was insignificant, suggesting that acidic conditions are required to liberate the aldehyde from a protected form. Experimental studies into the source of the aldehyde unit determined that the solvent, *N,N*-dimethylformamide, was not involved in providing the aldehyde moiety. Use of *N,N*-dimethylacetamide as solvent resulted in isolation of the aldehyde **2.49** only, in place of the expected ketone product were the solvent to be the carbon source (scheme 2.21).

Scheme 2.21: the isolation of aldehydes from the reaction of alkyl halides with the imidazole-derived donor **1.150**.



Reaction conditions: a) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) **2.48**, Ar, 18 h, r.t., iii) acidic work-up; **2.49**, 19%; b) i) imidazole-derived donor salt **1.155** (5.0 equiv.), NaH (50.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) **2.50**, Ar, 18 h, r.t., iii) acidic work-up; **2.51**, 61%; c) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMA, r.t., Ar, 4 h *then added to substrate* ii) **2.48**, Ar, 18 h, r.t., iii) acidic work-up; **2.49**, 32%.

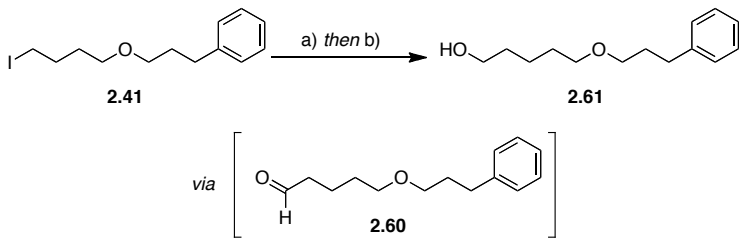
Scheme 2.22: the proposed mechanism for the liberation of aldehydes from alkyl halides.



The proposed mechanism for the formation of aldehydes is shown above (scheme 2.22). Formation of intermediate **2.55** is analogous to formation of intermediate **2.31** in the liberation of alcohols (*e.g.*, mechanism C, scheme 2.14). The primary difference between the two systems was the presence of a leaving group (alkoxide) in the alkyl iodide substrates (such as **2.1**), β to the iodide. It was proposed that it was the elimination of the leaving group that leads to further reactions of the intermediate enediamine-imidazolium species **2.31** (see scheme 2.14) and results in the isolation of the alcohol products. The key feature of each mechanism for both the isolation of aldehydes and the isolation of alcohols, and the feature that allows

proposal of a direct relationship, is the coupling of the intermediate alkyl radical (following loss of the halide after initial electron transfer) with the donor radical cation **1.151**. It was proposed that the overlap between each set of results could be confirmed by the testing of an ether substrate **2.41**, similar to those that had liberated alcohols above, which had a simple primary alkyl iodide in place, with no labile β-groups (scheme 2.23). Substrate **2.41** had previously been synthesised during the construction of the imidazolium iodide **2.41** substrate described previously. Thus, for direct comparison with both the results from Schoenebeck[132] and those described above, the simple alkyl iodide **2.41** was exposed to 1.5 eq. of donor **1.150** in *N,N*-dimethylformamide for 18 h, then diluted with 2M hydrochloric acid and worked up using the standard procedure. Analysis of the resulting clear oil revealed that aldehyde **2.60** was present. The product mixture was immediately reduced to the corresponding alcohol using sodium borohydride, which allowed isolation of 5-(3-phenylpropoxy)pentan-1ol **2.61** in an overall yield for the two steps of 32%, a result that compares favourably with the previous work described by Schoenebeck.[132] Notably, no 3-phenylpropanol **2.6** was observed at any stage.

Scheme 2.23: the isolation of 5-(3-phenylpropoxy)pentan-1-ol **2.61** following reduction of a simple alkyl iodide **2.41** to form 5-(3-phenylpropoxy)pentan-1-al **2.60** and reduction with sodium borohydride.

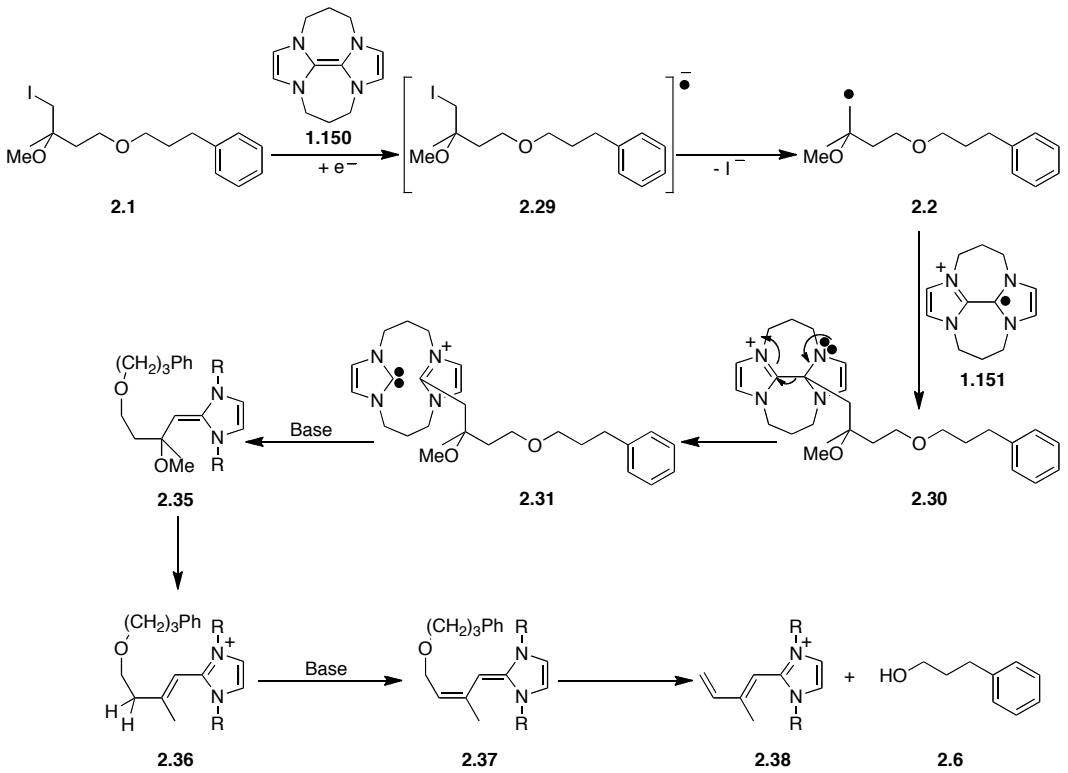


Reaction conditions: a) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) **2.41**, Ar, 18 h, r.t., iii) acidic work-up; b) $NaBH_4$, MeOH, r.t., 18 h, Ar; **2.61**, 32% (over two steps).

Thus, the isolation of 5-(3-phenylpropoxy)pentan-1-ol **2.61** provides a clear indication of the considerable overlap between the two mechanisms for the generation of alcohols and aldehydes, depending on the complexity of the substrate. In the absence of an alkoxide-leaving group attached to the quaternary centre, the alternative mechanism is followed (scheme 2.22), furnishing aldehyde products. When an alkoxide leaving group is present, the mechanism is more complex. For example, in mechanism A, the alkoxide leaving group is eliminated after the main

chain alcohol (scheme 2.12). Since alcohol **2.6** was not observed following the reduction of substrate **2.41**, where no leaving group is present, it follows that in order to isolate alcohols (*e.g.*, **2.6**) elimination of the alkoxide leaving group must occur prior to formation of the product alcohol. In mechanism C, this is the case, with elimination of the methoxide group allowing formation of advanced intermediates **2.36** and **2.37**, leading to the eventual elimination of alcohol **2.6**. Thus, since elimination of the alkoxide must occur for isolation of main chain alcohols, the most likely mechanism for the formation of alcohol **2.6** is mechanism C (scheme 2.24 below).

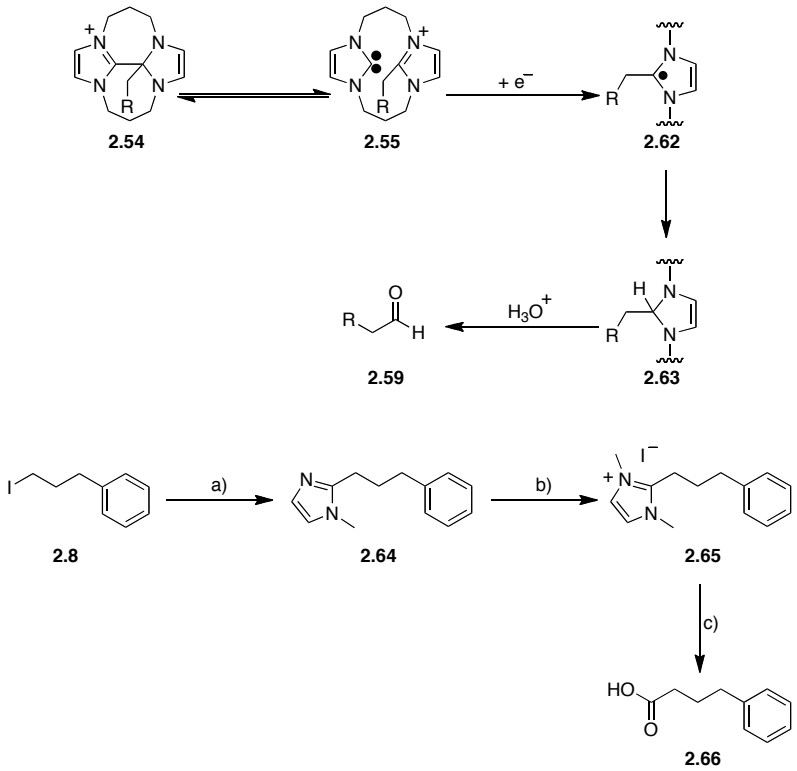
Scheme 2.24: the proposed mechanism (mechanism C) for the formation of alcohol **2.6** following the reaction of the imidazole-derived donor **1.150** with alkyl iodide **2.1**.



Two further points were also considered. First of all, an alternative mechanism for the formation of aldehydes would be the reduction of an intermediate imidazolium salt **2.55** to form the imidazolyl radical **2.62**, which could abstract a hydrogen atom and subsequently be hydrolysed to form the aldehyde product **2.59** (scheme 2.25). To examine this possibility, a simplified analogue of this intermediate was synthesised by alkylation of 3-phenyl-1-iodopropane **2.8** with *N*-methylimidazole, followed by salt formation to form **2.65** by treatment of the substituted imidazole **2.64**

with iodomethane in acetonitrile. This allowed isolation of the imidazolium iodide salt **2.65** in high yield (82%). With this substrate in hand, the mechanism was examined by exposure of the imidazolium iodide **2.65** to the imidazole-derived donor **1.150** under the standard conditions, followed by acidic work-up. However, no aldehyde was observed, with the only observed species being identified as 4-phenylbutyric acid **2.66**. This compound results from slow hydrolysis of the imidazolium unit on work-up. The low isolated yield (2%) is indicative of the challenging nature of this process. However, inspection of the proposed mechanism (scheme 2.22) reveals that the hydrolysis step in that case occurs on an intermediate (**2.57**) that is relatively more activated than the simple substrate (**2.65**) examined in this experiment. Thus it could be expected that higher conversion to the acid-aldehyde intermediate **2.58** (which would decarboxylate to the required product) would be achieved under the reaction conditions. As such, the isolation of 4-phenylbutyric acid **2.66** in low yield supports the proposed mechanism for the formation of aldehydes (scheme 2.22) and would appear to rule out the reductive route outlined in scheme 2.25.

Scheme 2.25: the alternative mechanism for the formation of aldehydes from reaction of alkyl halides with the imidazole-derived donor **1.150**, and the synthesis and reaction of a simple imidazolium salt **2.65** with donor **1.150**.

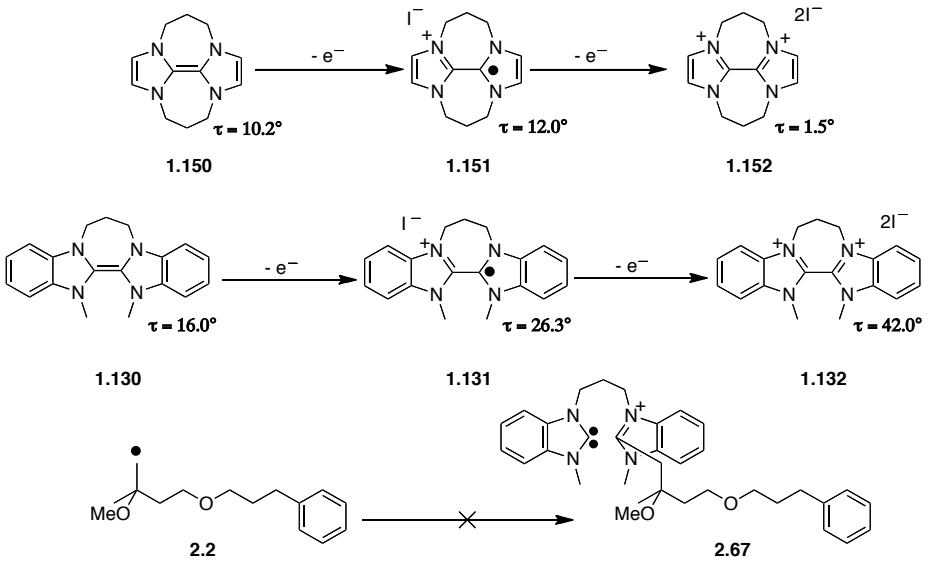


Reaction conditions: a) 1-methylimidazole, *n*-butyllithium (2.4 M), THF, -43 °C to r.t., 19 h, Ar; **2.64**, 91%; b) MeI, MeCN, reflux, 24 h, Ar; **2.65**, 82%; c) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) **2.65**, Ar, 18 h, r.t., iii) acidic work-up; **2.66**, 2%.

Secondly, why does the reaction of alkyl iodide **2.1** with the benzimidazole-derived donor **1.130** not yield alcohol **2.6**, but instead results only in the simple reduced ether product **2.3** (scheme 2.10)? The reasons behind this stem from the planarity of the imidazole-derived donor **1.150** compared with the benzimidazole-derived donor **1.130**.[58] The structure of donor **1.150** becomes slightly less planar on loss of one electron to form the radical cation **1.151**, with the angle between the planes of the imidazole rings (τ) increasing from 10.2° to 12.0°. Loss of another electron to form the dication **1.152** results in almost complete planarity being achieved, with τ = 1.5°. Thus, on loss of one or two electrons, the imidazole-derived donor **1.150** (and related cations) maintains planarity. It is this planarity in the radical cation **1.151** that is believed to allow it to couple with the intermediate alkyl radical **2.2** and form the crucial imidazolium *N*-heterocyclic carbene intermediate **2.31**. The high degree of planarity results in the radical cation **1.151** being less hindered and more

available for reaction. With the benzimidazole-derived donor **1.130**, the mechanism for formation of alcohol **2.6** from alkyl iodide **2.1** would be analogous to that proposed for the imidazole-derived donor **1.150**. However, the isolation of the simple reduced ether **2.3** instead of alcohol **2.6** indicates a significant difference. Once more it is important to consider the radical cation **1.131** and dication **1.132** on loss of one or two electrons. The structure of the benzimidazole-derived donor **1.130** becomes significantly less planar as electrons are removed, with the angle between the two imidazole rings measured at 26.3° for radical cation **1.131** and 42.0° for dication **1.132**.[58] The significant deviation from planarity in the radical cation **1.131** would result in substantial hindrance, meaning that **1.131** is unavailable for coupling with the alkyl radical **2.30**. Thus the crucial benzimidazolium intermediate **2.67** cannot be formed and the formation of alcohol **2.6** is blocked in the reaction of alkyl iodide **2.1** with donor **1.130**.

Figure 2.3: the angle between the planes of the imidazole rings for the imidazole-derived donor **1.150** and the benzimidazole-derived donor **1.130**.

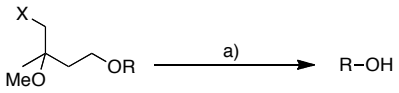


Section 2.3

Conclusions

The data described above in sections 2.1 and 2.2 details the investigations into the mechanism for the isolation of alcohols following the exposure of alkyl iodides to the imidazole-derived donor **1.150**. It has been shown that a range of alcohols can be isolated under the developed reaction conditions (table 2.1).

Table 2.1: the isolation of alcohols (**2.69**) from alkyl iodides (**2.68**) using imidazole-derived donor **1.150**.



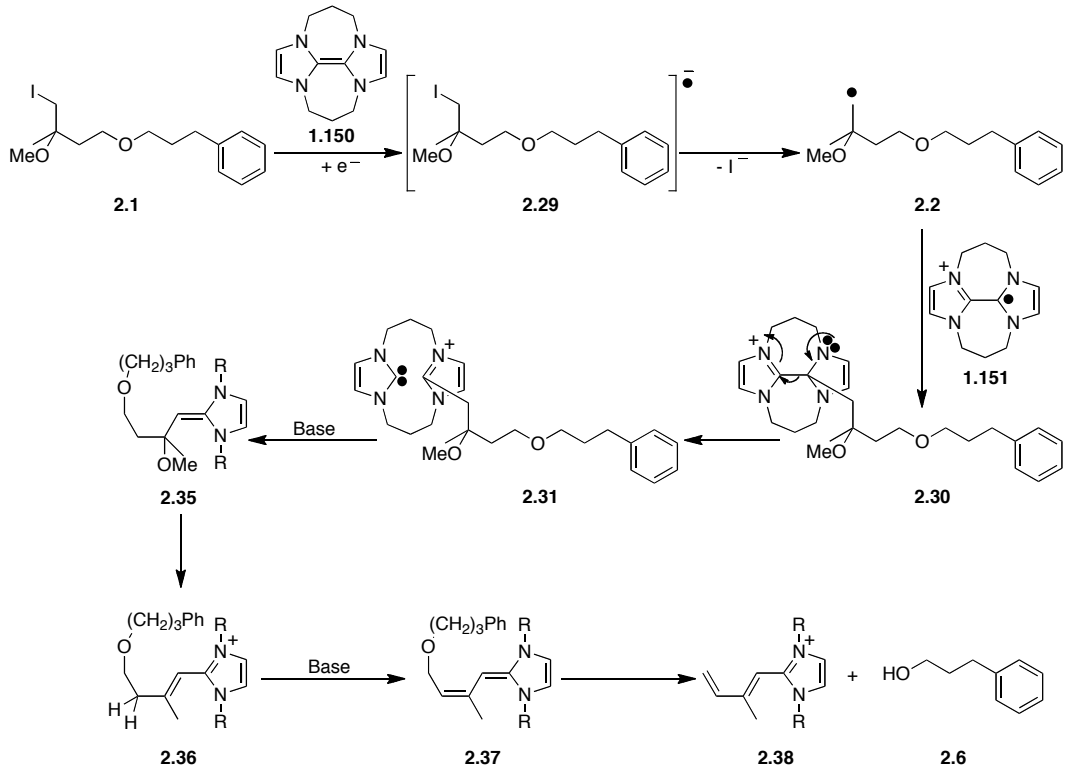
2.68 **2.69**

Entry	X	ROH	Yield (%)
A	I	$Ph(CH_2)_3OH$ (**2.6**)	70
B	I	$Ph(CH_2)_4OH$ (**2.10**)	67
C	I	$PhO(CH_2)_3OH$ (**2.16**)	77
D	I	*p*-$MeOC_6H_4O(CH_2)_3OH$ (**2.17**)	63
E	I	$Ph(CH_2)_3O(CH_2)_4OH$ (**2.24**)	70
F	Br	$Ph(CH_2)_3OH$ (**2.6**)	69

Reaction conditions: a) i) imidazole-derived donor salt **1.155** (1.5 equiv.), NaH (15.0 equiv.), DMF, r.t., Ar, 4 h *then added to substrate* ii) Ar, 18 h, r.t.

Investigations into the mechanism resulted in the proposed pathway shown (scheme 2.26). It has been shown that insertion of an *N*-heterocyclic carbene into the C-O bond does not occur under the reaction conditions. Furthermore, it has been shown that elimination of the β-alkoxy group is a requirement to generate the alcohol product.

Scheme 2.26: the proposed mechanism for the formation of alcohols from alkyl iodides using donor **1.150**.



The overlap between the isolation of alcohols and the isolation of aldehydes has been discussed, with the key radical-radical coupling step identified as the link between the two reactions. The main reasons for the isolation of different products have been suggested to be the use of an acidic work-up in the formation of aldehydes, and the presence of the β-alkoxy substituent in those substrates that liberate alcohol. The presence of this substituent allows further reaction of the intermediates within the reaction mixture.

This work has recently been published.[133]

Chapter 3

The development of a novel, crown carbene complex of nickel and its reactivity as a powerful electron-donor

This chapter serves as an introduction to the discovery, development and application of a novel crown carbene complex containing a nickel ion at its core. Chapter 1 provided an introduction to nickel electron transfer chemistry, as well as the origin of the crown carbene complexes that have previously been synthesised. This chapter provides a full account of the research into the nickel(II) crown carbene complex **3.1** conducted during this Ph.D. programme, together with the initial investigations performed by Park.[134]

The results presented here will be split into four sections. The first section will discuss the synthesis of the nickel(II) crown carbene complex **3.1** and the initial analyses into its promise as an electron-donor. The second section will discuss at length the synthetic applications of the nickel(II) crown carbene complex **3.1** towards common organic molecules when it is chemically activated. The third section will reveal the results of investigations towards the active species within the synthetic applications. Finally, the fourth section will discuss future work and conclusions that have been drawn thus far.

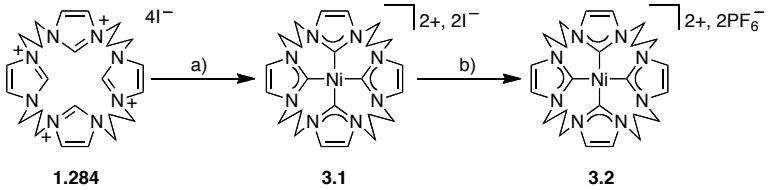
Section 3.1

The synthesis of the nickel(II) crown carbene complex 3.1

The initial synthesis of the nickel(II) crown carbene complex **3.1** followed that of Park within the Murphy group.[134] The synthesis is straightforward, with heating of a dimethyl sulfoxide solution of *tetrakis*trimethylene tetraimidazolium tetraiodide **1.284**, nickel(II) acetate tetrahydrate and four equivalents of sodium acetate at 90 ºC for 18 h affording a 79% yield of the nickel(II) complex diiodide salt **3.1** as yellow plate-like crystals (scheme 3.1). Since the initial small-scale synthesis by Park, complex **3.1** has been re-synthesised numerous times on scales ranging from 3-5 mmol. A further increase in scale would of course be possible, however, due to the low

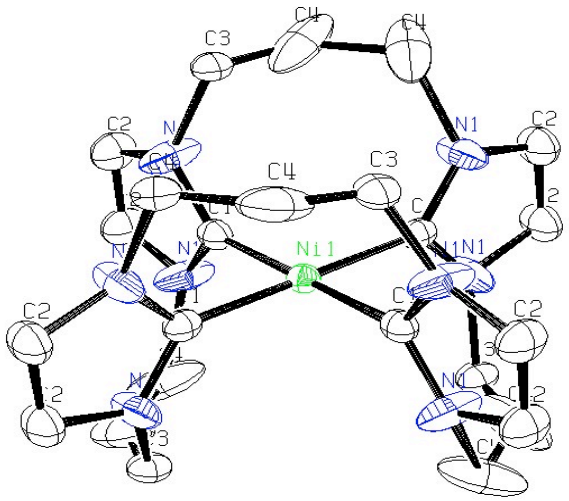
solubility of complex **3.1**, any increase in scale beyond this level would be impractical due to the requirement for large volumes of solvent during recrystallisation (typically, on a scale of 3.19 mmol, approximately 600-800 ml of methanol are required for recrystallising). From a practical point of view, it was more advantageous to prepare multiple batches on a smaller scale more often, rather than one large-scale batch. After the initial synthesis, Park obtained an X-ray crystal structure clearly indicating that the nickel(II) ion was centred within the ligand core, surrounded by the four *N*-heterocyclic carbene (NHC) units of the ligand in a square planar geometry (figure 3.1). Iodides were present as counter-ions but have been omitted, along with hydrogen atoms, for clarity.

Scheme 3.1: The synthesis of the nickel(II) complex, diiodide **3.1** and dihexafluorophosphate **3.2**.



Reaction conditions: a) tetrameric salt **1.284**, nickel(II) acetate, sodium acetate, DMSO, 90 ºC, 18 h; **3.1**, 79%; b) NH_4PF_6, MeOH, reflux, 48 h; **3.2**, 56%.

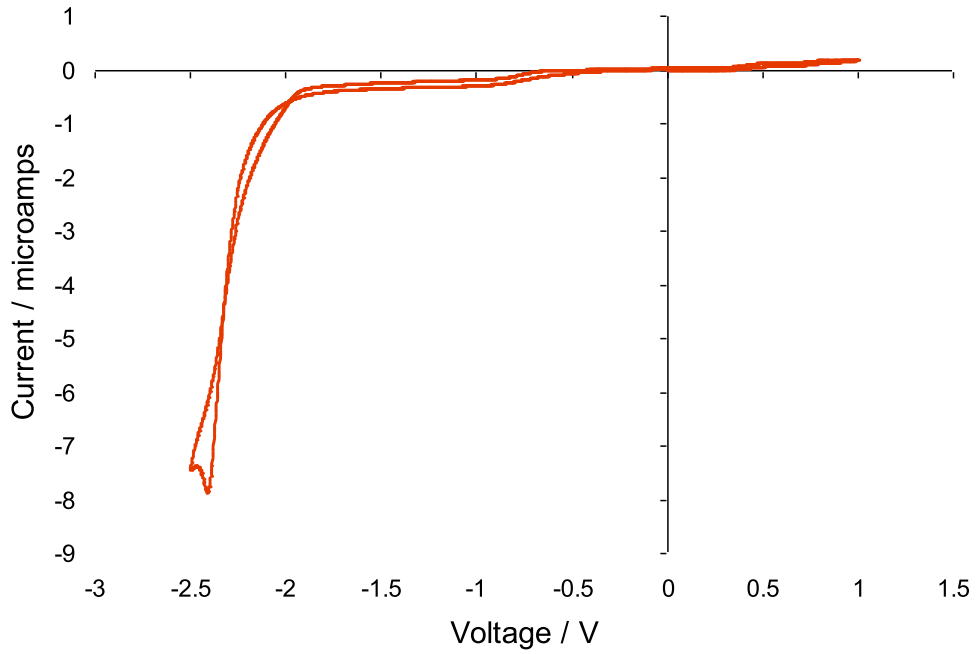
Figure 3.1: X-ray crystal structure of the nickel(II) complex, diiodide **3.1** (hydrogen atoms and iodide counter-ions omitted for clarity).[135]



In an effort to understand the electron transfer ability of nickel(II) complex **3.1**, analysis by cyclic voltammetry was performed. Cyclic voltammetry provides an indication of the potential at which the complex accepts and subsequently donates an electron. The more negative the recorded reduction potential, the more powerful a reductant the resulting molecule will be. Thus, analysis of a compound's reduction potential provides an early indication of how powerful that electron-donor may be, as well as what substrates may be susceptible to the electron-donor.

To allow the analysis to take place, a counter-ion exchange to hexafluorophosphate was performed. Using excess ammonium hexafluorophosphate in refluxing methanol, the dihexafluorophosphate analogue **3.2** was isolated in 56% yield as a fine yellow powder (scheme 3.1). Thus, using a Ag/AgCl/KCl (sat.) reference electrode, a platinum wire counter electrode and a platinum working electrode, with a 0.1 M *tetra*-butylammonium hexafluorophosphate (TBAHFP) in *N,N*-dimethylformamide supporting electrolyte, the cyclic voltammogram of the nickel(II) complex, dihexafluorophosphate **3.2** recorded by Park is shown (figure 3.2).[134] The reduction peak is clearly evident at -2.4 V (-2.36 V vs SCE); thus the nickel crown carbene complex **3.1**, when activated, should provide a very powerful electron donor.

Figure 3.2: Cyclic voltammogram of the nickel(II) complex, dihexafluorophosphate salt **3.2**. Conditions used were a platinum working electrode, platinum counter electrode, Ag/AgCl/KCl (sat.) reference electrode, 0.1M TBAHFP/DMF electrolyte, 50 mV/s scan rate.



Section 3.2

Investigations into the reactivity of the active nickel complex with typical organic substrates

The nickel(II) complex **3.1**, when activated, has been shown to be a powerful electron donor, according to the cyclic voltammogram (figure 3.2) shown in section 3.1. However, on a preparative scale within the laboratory, a method was required that could form the active nickel complex on a large scale. The method chosen was exposure to a freshly prepared sodium amalgam. This would provide a source of electrons that would reduce the nickel(II) complex **3.1** to form the active nickel complex, but, once the active nickel complex was formed, it could be readily removed from the sodium amalgam to a separate flask containing the substrate. Typically the amount of sodium amalgam used did not vary from 1%, formed from 100 mg of sodium dissolved in 10.0 g of mercury. The photographs shown in figure 3.3 chart the formation of the active nickel complex over time. Initially, a freshly prepared sodium amalgam is present along with some *N*,*N*-dimethylformamide solvent under a heavy Ar flow. The second photograph shows the addition of the correct quantity of nickel(II) complex **3.1** at time zero. This was done by simply removing the septum and quickly pouring the fine powder into the flask, with the Ar flow increased to eliminate the presence of air. The third photograph indicates that complex **3.1** has begun to dissolve, forming a light green/yellow solution after approximately 2 to 5 min, which over time darkens and changes colour to orange (photograph 4). Finally, in photograph 5, a solution of active nickel complex is present, which is clearly indicated by the presence of this dark red solution. During a typical experiment, the formation of the dark red colour occurs within 1 to 1.5 h, although the solution is stirred over the sodium amalgam for a total of 4 h to ensure that complete formation to the active nickel complex occurs. After the 4 h formation period, the dark red active donor solution in *N*,*N*-dimethylformamide was removed from the formation flask by cannula into a separate flask containing the substrate that is to be investigated. No sodium amalgam is transferred along with the active nickel solution. This ensures that the reactivity observed is entirely the result of the active nickel solution and the role of the sodium amalgam is as a reducing agent for the nickel complex **3.1**.

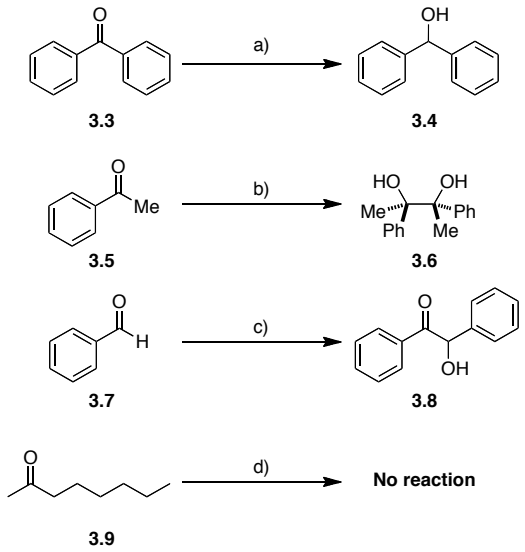
Figure 3.3: the formation of the active nickel complex, upon exposure of nickel(II) complex **3.1** to 1% sodium amalgam, over a period of 4 h.

1 **2** **3**

4 **5**

So, with a method of forming the active nickel complex developed, the next stage focussed upon understanding the level of reactivity that could be achieved using the active nickel complex. The first set of substrates that were investigated was aldehydes and ketones. Previously, Park had investigated the relationship between the active nickel complex and such compounds, concluding that reduction readily occurred.[136] Exposure of benzophenone **3.3** to the active nickel complex afforded clean formation of diphenylmethanol **3.4** in moderate yield. Similarly, acetophenone **3.5** was also reduced. However, instead of the expected 2-phenylethanol product, the product of a pinacol coupling was isolated (**3.6**), exclusively as the *dl*-isomer.[136] In addition, benzaldehyde **3.7** and 2-octanone **3.9** were also exposed to the active nickel complex. With benzaldehyde **3.7**, no reduction was observed, either directly to benzyl alcohol or *via* a pinacol coupling. Instead, benzoin **3.8** was isolated as the exclusive reaction product. In the case of 2-octanone **3.9**, no reaction was observed at all. Each of these last two results was intriguing and the initial investigations conducted, upon starting this project, focussed upon providing an explanation.

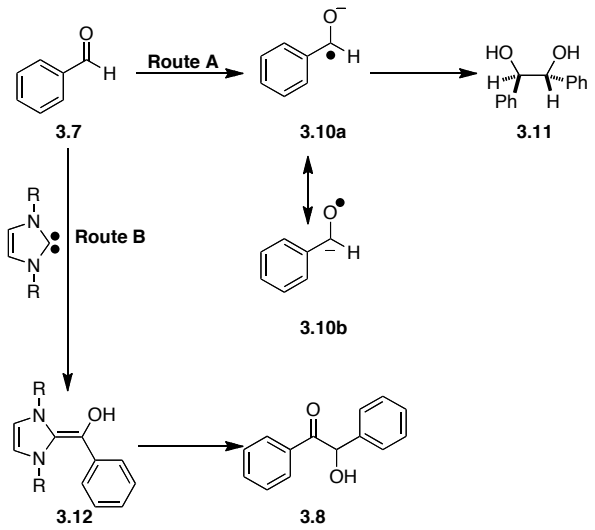
Scheme 3.2: initial investigations by Park into the reduction of carbonyl-containing compounds using the active nickel complex.[136]



Reaction conditions: a) i) nickel(II) complex **3.1** (2.0 eq.), Na/Hg, DMF, r.t., 4 h *then added to substrate* ii) **3.3**, 1.5 h, r.t., Ar; **3.4**, 65%; b) i) nickel(II) complex **3.1** (1.2 eq.), Na/Hg, DMF, r.t., 4 h *then added to substrate* ii) **3.5**, 18 h, r.t., Ar; **3.6**, 69%; c) i) nickel(II) complex **3.1** (1.0 eq.), Na/Hg, DMF, r.t., 4 h *then added to substrate* ii) **3.7**, 18 h, r.t., Ar; **3.8**, 70%; d) i) nickel(II) complex **3.1** (1.0 eq.), Na/Hg, DMF, r.t., 4 h *then added to substrate* ii) **3.9**, 18 h, r.t., Ar; no reaction.

First of all, the rationalisation behind the isolation of benzoin **3.8** from benzaldehyde **3.7** was probed. The reduction potential for benzaldehyde **3.7** has been reported at just -1.32 V vs. Ag/AgI.[137] Thus it should be well within the capabilities of the active form of nickel(II) complex **3.1** to effect such a reduction. One possible rationale for the isolation of benzoin **3.8** is as follows. Electron transfer to benzaldehyde **3.7** would result in formation of a ketyl radical (**3.10**) en route to formation of reduced product (*e.g.*, **3.11**). However, it is highly likely that such a process would be reversible and, if this were the case, equilibrium would exist between benzaldehyde **3.7** and its ketyl radical **3.10**. It is well known that the benzoin condensation can be catalysed by *N*-heterocyclic carbenes[85] and Park proposed that a carbene unit on the ligand decomplexed from the nickel ion and facilitated the benzoin condensation of benzaldehyde **3.7**, *via* Breslow intermediate **3.12**.[83] This would suggest that the active nickel complex is not stable, and that decomplexation would compete with electron transfer (this point will be discussed further in chapter 3.3). If this was the case, substrate compatibility and reaction scope might be compromised, and thus efforts were undertaken to further understand the reactivity of the active nickel complex.

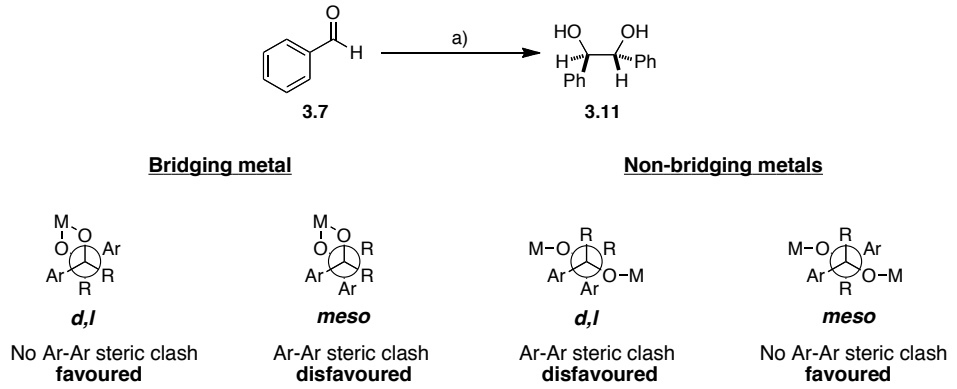
Figure 3.4: the mechanism for the formation of the pinacol product (route A) and benzoin (route B).



The reaction of benzaldehyde **3.7** with the active nickel complex was repeated under the conditions used by Park. In this case, no benzoin **3.8** was observed or isolated, and exclusive formation of the product from a pinacol coupling occurred (**3.11**), with the product isolated in moderate yield (64%, scheme 3.3). Thus it is clear that benzaldehyde **3.7** was reduced using the active nickel complex, in line with the previous reaction of acetophenone **3.5** with the active nickel complex. An alternative explanation for the isolation of benzoin **3.8** from the initial attempt could be that a small amount of *tetrakis*trimethylene tetraimidazolium tetraiodide **1.284** could have been present as a contaminant within the batch of nickel(II) complex **3.1** used by Park. Thus, if the initial electron transfer to benzaldehyde **3.7** is reversible, the presence of an *N*-heterocyclic carbene (from deprotonation of the imidazolium salt **1.284**) could catalyse the benzoin condensation to form **3.8**. When the pinacol product **3.11** was isolated, the nickel(II) complex used was of high purity, as observed from NMR and mass spectrometry. A further point to note is that, once again, exclusive formation of the *dl*-isomer of **3.11** was observed.[138] The pinacol coupling was briefly covered in chapter 1, with the mechanism shown in scheme 1.9. Although the precise mechanism is not fully understood, formation of the *dl*-isomer is likely to occur through chelation of two ketyl radicals to a bridging metal-ion.[20,139] The *trans* relationship of the bulky aryl groups favours formation of the *dl*-isomer, whilst unfavourable steric interactions between the two aryl rings disfavours formation of the *meso*-isomer (scheme 3.3). Conversely, formation of the *meso*-isomer is believed to occur *via* a non-bridging chelating metal mechanism (where,

on the other hand, steric interactions between the aryl rings hinder formation of the *dl*-isomer). In each mechanistic intermediate that leads to formation of the *meso*-isomer (scheme 3.3), the "M-O" components are *trans* to each other, as they would be considered the largest unit around the central carbon atom. Although selective formation of one isomer over the other is rare, the literature contains several examples.[20,139,140] This perhaps points to a role for the nickel complex in the mechanism for formation of **3.6** and **3.11**, with complexation of ketyl radicals to a single molecule of nickel complex prior to dimerisation. However, it will be shown in section 3.3 that complexation to the nickel ion is unlikely. Alternatively, the residual sodium ions, present in solution as a byproduct from the sodium amalgam, could play a role in the mechanism. Guo, Liu and co-workers have shown that excellent stereocontrol is possible using lithium in neat bromobenzene.[140b] However, a detailed mechanism was not proposed beyond bromobenzene acting as an electron shuttle. Furthermore, according to the classical mechanistic intermediates discussed above and shown in scheme 3.3, monovalent sodium ions should favour *meso*-isomer formation. Thus, aromatic aldehydes and ketones are generally susceptible to reduction using the active nickel complex, with little experimental evidence indicating decomplexation leading to competing side-reactions. A full explanation regarding the observed stereochemical outcome on conversion of **3.5** to **3.6** and **3.7** to **3.11** remains to be determined.

Scheme 3.3: the reduction of benzaldehyde **3.7** using the active nickel complex, and the proposed mechanistic intermediates for the pinacol coupling.

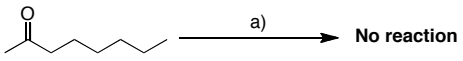


Reaction conditions: a) nickel(II) complex **3.1**, Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.7**, Ar, r.t. 18 h; **3.11**, 64%.

Attention now switched to providing a likely explanation for the lack of reduction when 2-octanone **3.9** was employed as the substrate with the active nickel complex

(scheme 3.4). To offer complete assurance that the active nickel complex could not facilitate the reduction of 2-octanone **3.9**, the experiment was repeated using the conditions employed by Park[136] (in addition, it was necessary that, in the event of no reduction, the starting material was recovered to observe whether side-reactions were competing with the reduction process). Once more, no reduction was observed and the starting material **3.9** was isolated in a recovered yield of 89% (this low mass recovery is possibly due to the slight volatility of 2-octanone **3.9** – reported b.p. 173°C).[141] With the confirmation of this result, efforts now focussed on an explanation. Spartan® molecular modelling (equilibrium geometry, Hartree-Fock, 6-31-G**) was used to compare benzophenone **3.3**, which was successfully reduced using the active nickel complex (scheme 3.2), and 2-octanone **3.9**. The LUMO orbitals for each are shown below (figure 3.5). In each compound the LUMO is centred over the carbonyl moiety, however, with benzophenone **3.3**, the LUMO is also further delocalised across both phenyl rings. The effect this has is evident when examining the calculated LUMO energy levels for each compound. Benzophenone **3.3** has a calculated LUMO energy level of 2.28 eV, which clearly equates to a realistic and achievable reduction for the active nickel complex, based on the isolation of 1,1-diphenylmethanol **3.4** shown above (scheme 3.2). In the case of 2-octanone **3.9**, the LUMO energy level is considerably higher at 4.47 eV. Clearly this would represent a much higher activation barrier for the active nickel complex to overcome to achieve a successful reduction of 2-octanone **3.9**, thus it is likely that for this reason the reduction of 2-octanone **3.9** is too challenging for the active nickel complex.

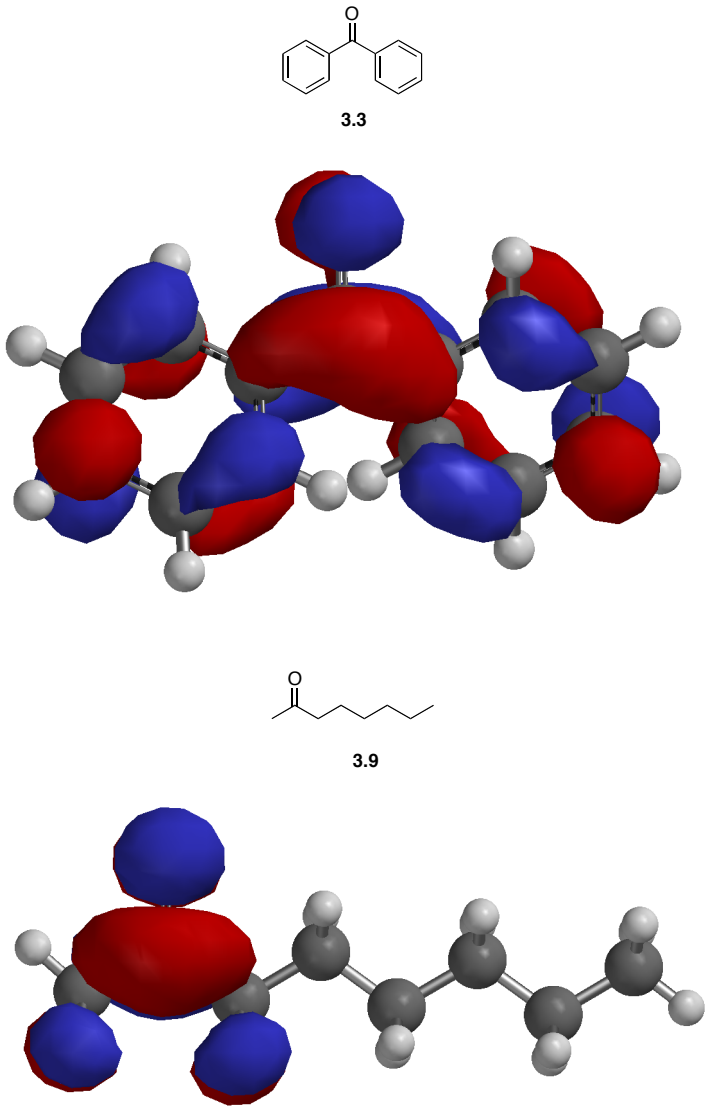
Scheme 3.4: the attempted reduction of 2-octanone **3.9** using the active nickel complex.



3.9

Reaction conditions: a) nickel(II) complex **3.1**, Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.9**, Ar, r.t. 18 h; 89% recovered starting material **3.9**.

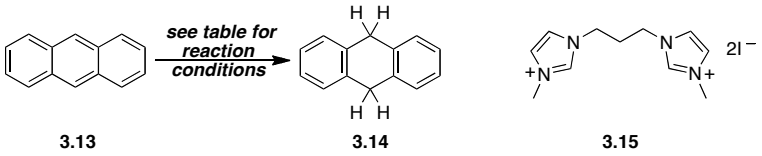
Figure 3.5: LUMO orbitals calculated for benzophenone **3.3** and 2-octanone **3.9** using the Spartan molecular modelling programme (equilibrium geometry, Hartree-Fock, 6-31G**). Areas of red and blue colour represent LUMO orbitals.



Following on from the conclusion of the investigations into carbonyl-containing compounds, the next set of substrates that were of interest were those that could undergo a Birch reduction. The large and negative reduction potential for the nickel(II) complex **3.1** points to the active nickel complex existing as a significantly powerful reductant. As such, it was proposed that the Birch reduction of anthracene **3.13** could be achieved using the active nickel complex (the Birch reduction has been briefly reviewed in chapter 1). Previously Park had investigated the Birch reduction of anthracene.[136] These results are detailed below. The initial conclusions focussed on the screening of suitable proton sources for the reduction, such as *tert*-

butanol and diimidazolium salt **3.15**, which had been synthesised earlier in the Murphy group.

Table 3.1: the initial investigations by Park into the Birch reduction of anthracene **3.13**.[136]



3.13 **3.14** **3.15**

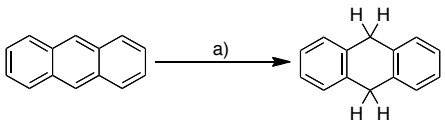
Attempt	Equivalents of nickel(II) complex	H^+/H-atom source	Comment	Conv. (%)*
1	2	*t*-Butanol	-	9%
2	2	Cyclohexadiene	Cyclohexadiene added 10 min after ANC	57%
3	3	Cyclohexadiene	Cyclohexadiene added 10 min after ANC	33%
4	2	Diimidazolium salt **3.15**	-	67%
5	2	Diimidazolium salt **3.15**	-	64%

From these results, a strong starting point was clear. A proton source would be required to achieve the successful reduction of the central ring of anthracene **3.13**. According to Park, the most suitable proton source screened thus far was the diimidazolium salt **3.15**, providing reduction to dihydroanthracene **3.14** in 67% conversion. However, Park also proposed that cyclic voltammogram evidence pointed to an incompatibility between the diimidazolium salt **3.15** and anthracene **3.13** as a substrate since the reduction potential of the diimidazolium salt **3.15** was measured at -2.16 V (ir., vs Ag/AgCl/KCl (sat.) in *N*,*N*-dimethylformamide), compared with -1.90 V (vs Ag/AgCl/KCl (sat.) in *N*,*N*-dimethylformamide) for anthracene **3.13**.[136] This could mean that competing electron transfer between the active nickel complex and the diimidazolium salt **3.15** could hinder the reduction of anthracene **3.13**, or, alternatively, the anthracene radical anion could donate an electron to the diimidazolium salt **3.15**.

* Calculated from the ^{1}H NMR spectrum of the crude reaction product by comparison of the central aromatic C-H in anthracene **3.13** (δ 8.50 ppm) and the CH_2 of dihydroanthracene **3.14** (δ 3.98 ppm).

In any case, in an attempt to understand the criteria, the conditions that afforded the highest conversion for Park were repeated in order to examine thoroughly the requirements for improving the reaction. The reaction was repeated in triplicate. In the first instance (*attempt 1*), the familiar dark red colour for the active nickel complex did not occur during the 4 h formation time. Instead, the reaction mixture formed an olive green solution, which, upon carrying through and on exposure to anthracene **3.13**, gave no reduction at all with only anthracene **3.13** observed in the ^{1}H NMR. The second and third attempts proved more successful, with dihydroanthracene **3.14** observed each time. The second attempt (*attempt 2*) afforded a conversion to 10% dihydroanthracene **3.14**, while the third attempt (*attempt 3*) was even more promising with 50% of the product mixture comprising dihydroanthracene **3.14**.

Scheme 3.5: the attempted reduction of anthracene **3.13** (*attempts 1-3*) – initial attempts at anthracene **3.13** reduction.



3.13 **3.14**

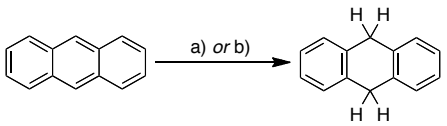
Reaction conditions: a) i) nickel(II) complex **3.1**, Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate and diimidazolium salt* ii) **3.13**, salt **3.15**, Ar, r.t. 18 h; *attempt 1*, 0% conversion; *attempt 2*, 10% conversion; *attempt 3*, 50% conversion.*

However, the conversion observed for attempt three was still not of the required standard and efforts continued to achieve a more successful set of reaction conditions. The next two attempts focussed on increasing the number of equivalents of active nickel complex present in the reaction mixture. In line with *attempt 3* that afforded a 50% conversion to dihydroanthracene **3.14**, the number of equivalents of nickel(II) complex **3.1** was increased from two to four (*attempt 4*). Unfortunately, no conversion to dihydroanthracene **3.14** was observed. A further attempt once more used four equivalents of nickel(II) complex **3.1**. However, in this reaction, two equivalents were added initially to the mixture of anthracene **3.13** and diimidazolium salt **3.15** and allowed to react for 5 min, before a second batch of active nickel complex (which had been prepared in a separate flask over a separate

* Calculated from the ^{1}H NMR spectrum of the crude reaction product by comparison of the central aromatic C-H in anthracene **3.13** (δ 8.50 ppm) and the CH_2 of dihydroanthracene **3.14** (δ 3.98 ppm).

amalgam) was then added (*attempt 5*). Nonetheless, only a 20% conversion was observed to dihydroanthracene **3.14** using this method. Thus it appears that increasing the number of equivalents to higher levels is detrimental to the process. A further point to note is that when a higher number of equivalents was used, the volume of *N*,*N*-dimethylformamide solvent required was increased also to allow dissolution of the nickel(II) complex **3.1**. Complex **3.1** is not very soluble in the reaction solvent; typically for every 100 mg of nickel(II) complex **3.1** used, 10 ml of *N*,*N*-dimethylformamide was also used. Clearly the use of large quantities of complex **3.1** and reaction solvent is unfavourable.

Scheme 3.6: the attempted reduction of anthracene **3.13** (*attempts 4* and *5*) – the use of higher equivalencies.



3.13 **3.14**

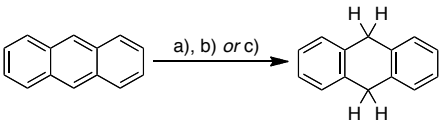
Reaction conditions: a) i) nickel(II) complex **3.1** (4 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate and diimidazolium salt* ii) **3.13**, **3.15**, Ar, r.t. 18 h; *attempt 4*, 0% conversion; b) i) nickel(II) complex **3.1** (2 x 2 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *batch 1 added to substrate and diimidazolium salt, 5 min pause, then batch 2 added to substrate* ii) **3.13**, **3.15**, Ar, r.t. 18 h; *attempt 5*, 20% conversion.*

The next attempt to achieve reduction of anthracene **3.13** to dihydroanthracene **3.14** focussed on the cyclic voltammetry analyses recorded by Park.[136] As stated above, it is likely that the similar reduction potentials for anthracene **3.13** and the diimidazolium salt **3.15** would inhibit the reaction owing to competing electron transfer. If this is the case, complete reduction might not be achieved. To avoid this, the next three experiments focussed on addition of the proton source after a pre-defined time. It was believed that by allowing the reduction of anthracene **3.13** to occur in the absence of a competing acceptor, the proton source could be added at a later time to protonate the intermediate radical anion and form the product **3.14**. As such, following the standard procedure and adding the proton source 5 min after addition of the active nickel complex gave, following work-up, a conversion to dihydroanthracene **3.14** of 44% by ^{1}H NMR (*attempt 6*). Encouraged by this, the

* Calculated from the ^{1}H NMR spectrum of the crude reaction product by comparison of the central aromatic C-H in anthracene **3.13** (δ 8.50 ppm) and the CH_2 of dihydroanthracene **3.14** (δ 3.98 ppm).

reaction was repeated except the proton source **3.15** was added 30 min after addition of the active nickel complex to anthracene **3.13** (*attempt 7*). However, instead of an increase in conversion to dihydroanthracene **3.14** that was expected, a decrease was observed (30%). It appears that there are still unfavourable interactions between the proton source **3.15**, anthracene **3.13** and the active nickel complex that are inhibiting the reaction and preventing complete reduction to dihydroanthracene **3.14** to occur. One final reaction that was attempted was the use of excess *tert*-butanol as the proton source added after 5 min (*attempt 8*). Although Park had worked extensively developing the chemistry with *tert*-butanol, no attempt had been made where *tert*-butanol had been added after the active nickel complex. Unfortunately, no reduction to dihydroanthracene **3.14** was observed using this method. Thus it appears that the use of proton sources as late-additives to the reaction mixture is incompatible with the reaction components, as the conversions recorded are less than the benchmark set by Park (67%).[136]

Scheme 3.7: the attempted reduction of anthracene **3.13** (*attempts 6-8*) – the late addition of proton source to the reaction mixture.



3.13 **3.14**

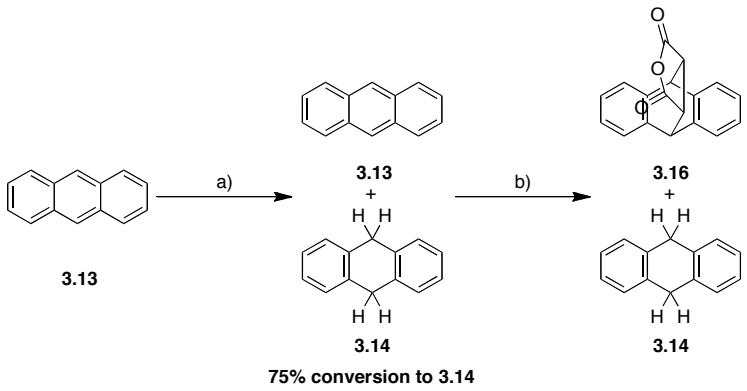
Reaction conditions: a) i) nickel(II) complex **3.1** (2 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.13**, Ar, r.t. 5 min *diimidazolium salt **3.15** added* iii) Ar, r.t. 18 h; *attempt 6*, 44% conversion; b) i) nickel(II) complex **3.1** (2 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.13**, Ar, r.t. 30 min *diimidazolium salt **3.15** added* iii) Ar, r.t. 18 h; *attempt 7*, 30% conversion; c) i) nickel(II) complex **3.1** (2 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.13**, Ar, r.t. 5 min *tert-butanol added* iii) Ar, r.t. 18 h; *attempt 8*, 0% conversion.*

At this point, a literature search revealed a possible solution to this problem. Until now, both Park and the results described in detail here had focussed on combining the proton source and anthracene **3.13** together when the active nickel complex was added, or, adding the proton source after exposing anthracene **3.13** to the active nickel complex. Classic Birch methodology developed by Rabideau[142] had utilised an inverse quench of the entire reaction mixture into a saturated aqueous solution of

* Calculated from the ^{1}H NMR spectrum of the crude reaction product by comparison of the central aromatic C-H in anthracene **3.13** (δ 8.50 ppm) and the CH_2 of dihydroanthracene **3.14** (δ 3.98 ppm).

ammonium chloride. The high concentration of available protons present meant that any suitable species would protonate rapidly. Using this methodology, together with 2.5 equivalents of nickel(II) complex **3.1** (that had been exposed to a 1% sodium amalgam for 4 h and the resulting dark red active nickel complex solution added to anthracene **3.13**), a higher conversion to 9,10-dihydroanthracene **3.14** was observed than had been previously recorded. The product mixture contained 75% 9,10-dihydroanthracene **3.14** and 25% anthracene **3.13**.*

Scheme 3.8: the optimised conditions for the Birch reduction of anthracene **3.13** using the inverse quench into saturated ammonium chloride solution.



Reaction conditions: a) i) nickel(II) complex **3.1** (2.5 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.13**, Ar, r.t. 1 h *then added to* iii) sat. $NH_4Cl_{(aq)}$, r.t., 5 min; 75% conversion; b) maleic anhydride, chlorobenzene, reflux, 18 h; **3.14,** 55%**, 3.16,** 14%.

Since the product mixture formed following an inverse quench with saturated ammonium chloride provided the highest conversion thus far to 9,10-dihydroanthracene **3.14**, the mixture was derivatised to allow separation of the two product components (the identical polarities of the anthracene **3.13** and 9,10-dihydroanthracene **3.14** had meant that percentage conversions from the ^{1}H NMR of the crude reaction mixture were used up till now). Following purification on silica gel to isolate the two-component mixture, derivatisation with maleic anhydride in chlorobenzene at reflux allowed separation of the two products, 9,10-dihydroanthracene **3.14** in 55% yield, as well as the maleic anhydride adduct **3.16** in 14% yield. The isolation of 9,10-dihydroanthracene **3.14** was the first example of a Birch reduction using an active nickel-containing complex as the electron-donating agent. Although Yus has previously reported the Birch reduction of aromatic

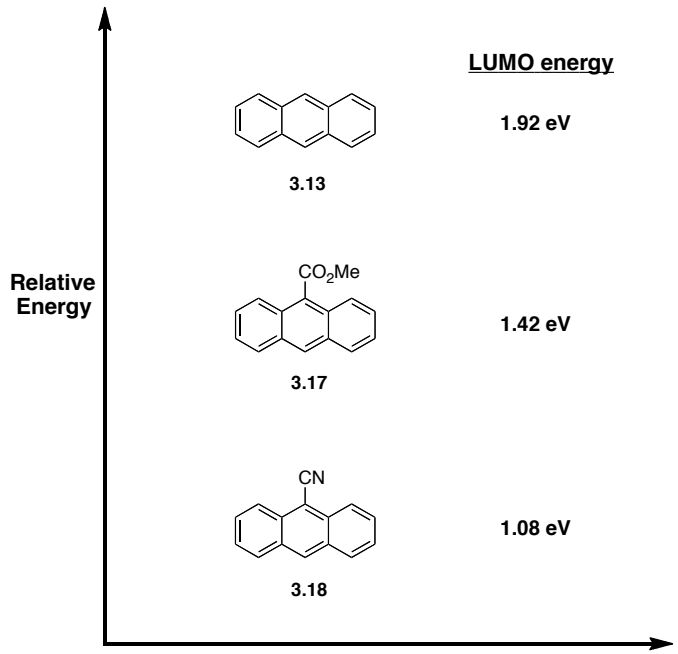
* Calculated from the ^{1}H NMR spectrum of the crude reaction product by comparison of the central aromatic C-H in anthracene **3.13** (δ 8.50 ppm) and the CH_2 of dihydroanthracene **3.14** (δ 3.98 ppm).

compounds using a system that contains nickel, there is uncertainty over the mechanism. It is likely that the active component used in these systems was either excess lithium metal in an electron transfer process, or, alternatively, reduction by an *in situ* formed nickel(0) catalyst and molecular hydrogen.[143]

With these newly optimised conditions in hand, and in order to expand this methodology to other substrates, it was proposed that substitution at the 9-position of anthracene **3.13** would provide a series of suitable compounds. Furthermore, substitution with an electron-withdrawing group would lower the LUMO energy level, and, as a consequence, the reduction potential for the electron-poor anthracene should be less negative. In turn, this could lead to an increased possibility of complete conversion to the reduced, substituted dihydroanthracene. This hypothesis was supported by a series of calculations on anthracene **3.13**, methyl anthracene-9-carboxylate **3.17** and 9-anthracenecarbonitrile **3.18** using Spartan®* (figure 3.6). The LUMO energy level of anthracene **3.13** was calculated at 1.92 eV, while the energy level for the LUMO of methyl anthracene-9-carboxylate **3.17** was just 1.42 eV. Furthermore, substitution at the 9-position with a nitrile group in 9-anthracenecarbonitrile **3.18** lowered the LUMO energy level still further to 1.08 eV. From these results, it is likely that substitution of anthracene at the 9-position would result in substrates that would be more easily reduced.

* Calculated using equilibrium geometry, Hartree-Fock, 6-31G**

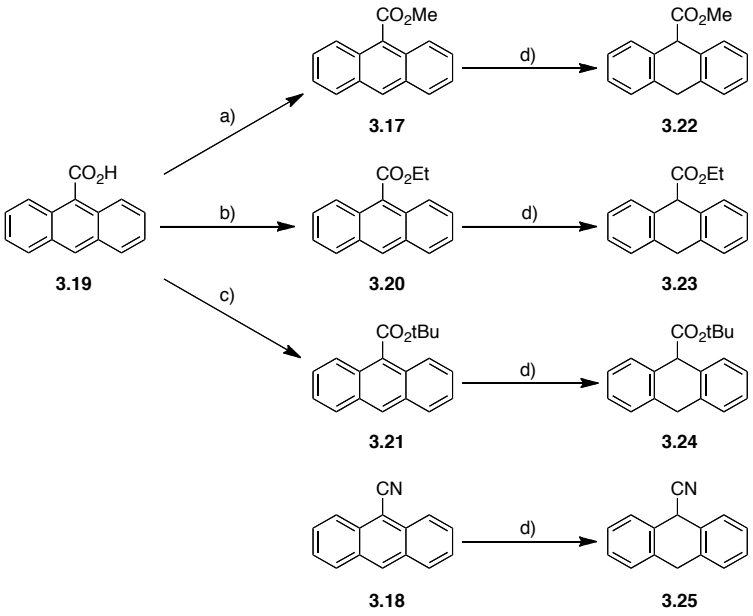
Figure 3.6: relative energies of anthracene **3.13**, methyl anthracene-9-carboxylate **3.17** and 9-anthracenecarbonitrile **3.18**.



In order to test this hypothesis, a series of anthracene esters was synthesised from the commercially available 9-anthracenecarboxylic acid **3.19** using classical esterification methodology. Treatment of 9-anthracenecarboxylic acid **3.19** with dimethyl sulfate and sodium methoxide in methanol afforded methyl anthracene-9-carboxylate **3.17** in 50% yield. In a similar manner, ethyl anthracene-9-carboxylate **3.20** and *tert*-butyl anthracene-9-carboxylate **3.21** were synthesised from 9-anthracenecarboxylic acid **3.19** using trifluoroacetic anhydride in toluene, followed by addition of the appropriate alcohol, to afford the ethyl analogue **3.20** in 78% yield and the *tert*-butyl analogue **3.21** in 88% yield. Once synthesised, each ester, along with the commercially available 9-anthracenecarbonitrile **3.18**, was exposed to the optimised conditions described above. In every case, complete conversion was observed, with no evidence of the starting material present in the ^{1}H NMR of the crude reaction mixture. Both the methyl and ethyl esters were cleanly reduced to afford methyl 9,10-dihydroanthracene-10-carboxylate **3.22** and ethyl 9,10-dihydroanthracene-10-carboxylate **3.23** in moderate yield (54% and 59% yield respectively). However, *tert*-butyl anthracene-9-carboxylate **3.21** and 9-anthracenecarbonitrile **3.18** were reduced in excellent yields to afford *tert*-butyl 9,10-dihydroanthracene-10-carbonitrile **3.24** (85%) and 9,10-dihydroanthracene-10-

carbonitrile **3.25** (78%). These results are further evidence of the reducing power of the active nickel complex.

Scheme 3.9: the synthesis of anthracene esters and the reduction of 9-substituted anthracene analogues to form 9,10-dihydroanthracene analogues using the active nickel complex.

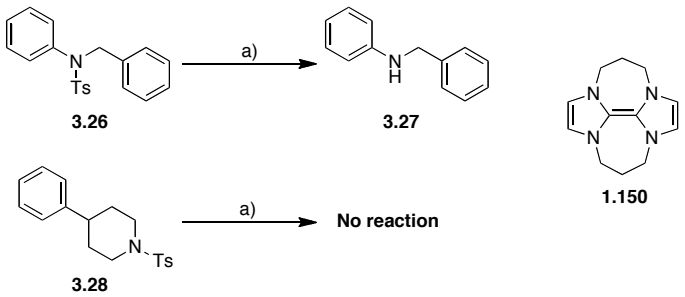


Reaction conditions: a) i) NaOMe, MeOH, r.t., 30 min, ii) reflux, dimethyl sulfate, 20 h; **3.17**, 50%; b) i) trifluoroacetic anhydride, toluene, 0 °C to r.t., 30 min, ii) ethanol, r.t., 18 h; **3.20**, 78%; c) i) trifluoroacetic anhydride, toluene, 0 °C to r.t., 30 min, ii) *tert*-butanol, r.t., 18 h; **3.21**, 88%; d) i) nickel(II) complex **3.1** (2.5 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) Ar, r.t. 1 h *then added to* iii) sat. $NH_4Cl_{(aq)}$, r.t., 5 min; **3.22**, 54%; **3.23**, 59%; **3.24**, 85%; **3.25**, 79%.

The final set of compounds that was investigated were those that contained the sulfone functionality. Previously within the Murphy group,[64] it had been shown that activated sulfones, bissulfones and sulfonamides could be cleanly reduced using the imidazole-derived donor **1.150** (discussed also in chapters 1 and 2). In each example, high reaction temperatures were required, with 100 °C being optimum. Furthermore, in every case multiple equivalents of the donor species were required to achieve each transformation, with, in the case of activated sulfonamides (*e.g.*, **3.26**), six equivalents needed. It was proposed that the large and negative reduction potential displayed by the active nickel complex might provide a means to achieve these transformations under less forceful conditions. In addition, the reduction of alkylarenesulfonamides (*e.g.*, **3.28**) could not be achieved using donor **1.150**, despite the use of excess equivalents and high temperatures. Computational

studies[64] revealed that this was due to the large activation energy associated with the initial electron transfer, due to the instability of the radical anion. The radical anion does not spontaneously dissociate to form the radical and anion components, unlike the radical anion for similar activated sulfonamides. It was anticipated that the highly reactive active nickel complex could facilitate reductions of non-activated alkylarenesulfonamides.

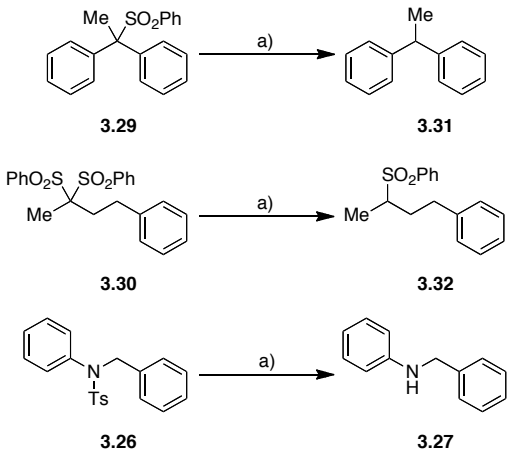
Scheme 3.10: the reduction of sulfonamides using imidazole-derived donor **1.150**.[64]



Reaction conditions: a) imidazole-derived donor **1.150** (6.0 equiv.), DMF, 100 °C, 18 h, Ar; **3.27**, 97%.

The initial investigations focussed upon an activated sulfone **3.29**, bissulfone **3.30** and sulfonamide **3.26**, both in order to determine substrate compatibility and to optimise the procedure.[144] Pleasingly, activated sulfone-containing compounds proved to be susceptible to the active nickel complex. For example, activated monosulfone **3.29** was effectively reduced to afford 1,1-diphenylethane **3.31** in a yield of 70%. Similarly, bissulfone **3.30** was also reduced to afford the corresponding monosulfone **3.32**, once more in 70% yield. The active nickel complex also proved to be effective in the cleavage of sulfonamides. Activated sulfonamide **3.26** was reduced cleanly to the corresponding secondary amine **3.27** in an excellent 97% yield. In each case, room temperature was sufficient to achieve these transformations (no thermal activation, in contrast to imidazole-derived donor **1.150**), as well as only a small excess of the nickel(II) complex **3.1** being required. This is clear evidence that the active nickel complex is a considerably more powerful electron donor than the previously synthesised neutral organic electron donors.

Scheme 3.11: the reaction of activated sulfone-containing compounds with the active nickel complex.



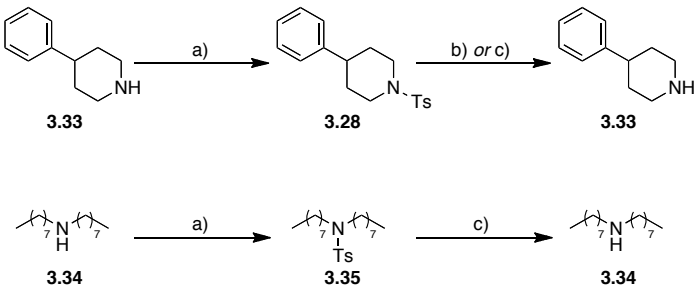
Reaction conditions: a) i) nickel(II) complex **3.1** (2.0 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.29**, **3.30** or **3.26**, Ar, r.t. 18 h; **3.31**, 70%; **3.32**, 70%; **3.27**, 97%.

Attention now turned to providing a more stringent examination of the reactivity of the active nickel complex. This was realised through reaction with non-activated alkylarenesulfonamides. Furthermore, any success with this substrate class would address the shortcomings of the neutral organic electron donors (**1.150** and **1.177**). With this objective in mind, two alkylarenesulfonamides were prepared by exposure of the alkyl secondary amine to *para*-toluenesulfonyl chloride and triethylamine in dichloromethane, providing *N*-toluenesulfonyl-4-phenylpiperidine **3.28** and *N*-toluenesulfonyl-di-*N*-octylamine **3.35** in good yields (89% and 93% respectively). Initially, *N*-toluenesulfonyl-4-phenylpiperidine **3.28** was selected as the test substrate due to the fact it had proven resistant under exposure to the imidazole-derived donor **1.150**. Under the conditions successful for the cleavage of activated sulfonamides (two equivalents of nickel(II) complex **3.1** at room temperature), moderate conversion was observed with approximately 60% conversion to 4-phenylpiperidine **3.33** product.* In an effort to move towards complete N-S bond scission and complete conversion to product, the reaction was repeated using four equivalents of the nickel(II) complex **3.1** with the reaction temperature held at room temperature as before. Now, complete conversion was observed with, after work-up and purification, 4-phenylpiperidine **3.33** isolated in a good 66% yield. With this result in hand, attention now focussed on *N*-toluenesulfonyl-di-*N*-octylamine **3.35**. Pleasingly, when this substrate was exposed to the newly optimised conditions for

* Conversion adjudged by analysis of the ^{1}H NMR of the crude reaction mixture.

alkylarenesulfonamides, di-*N*-octylamine **3.34** was isolated in an excellent 95% yield following purification. These two results with non-activated, alkylarenesulfonamides are a strong indication of the power of the active nickel complex and its increased reactivity relative to the neutral organic electron donors.

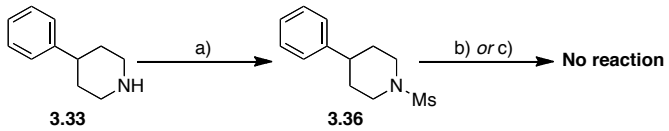
Scheme 3.12: synthesis of non-activated alkylarenesulfonamides **3.28** and **3.35** and their reaction with the active nickel complex.



Reaction conditions: a) *para*-toluenesulfonyl chloride, Et_3N, DCM, 20 h, r.t., Ar; **3.28**, 89%; **3.35**, 93%; b) i) nickel(II) complex (2.0 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.28**, Ar, r.t. 18 h; 60% conversion to **3.33**; c) i) nickel(II) complex (4.0 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.28** or **3.35**, Ar, r.t. 18 h; **3.33**, 66%; **3.34**, 95%.

In a further effort to fully understand the limits of reactivity associated with the active nickel complex, it was proposed that a methanesulfonamide should be tested in order to determine whether reduction of this group could be achieved. As such, *N*-methanesulfonyl-4-phenypiperidine **3.36** was synthesised from methanesulfonyl chloride and triethylamine in dichloromethane, providing the product in 83% yield. The methansulfonamide **3.36** was then exposed to the newly optimised conditions for non-activated, alkylarenesulfonamides described above. However, after work-up and purification, no evidence of reduction was observed and the starting material **3.36** was recovered in 93% yield. The reaction was then repeated once more. This time, after the usual formation of the dark red active nickel complex, the active solution was added to methanesulfonamide **3.36** at 90 °C and then held at this temperature for the duration of the 18 h reaction time. Once more, after work-up no conversion to product **3.33** was observed and the starting material **3.36** was again recovered in high yield (93%). Thus the active nickel complex is not capable of reducing non-activated alkyl sulfonamides.

Scheme 3.13: synthesis of *N*-methanesulfonyl-4-phenylpiperidine **3.36** and its reaction with the active nickel complex.

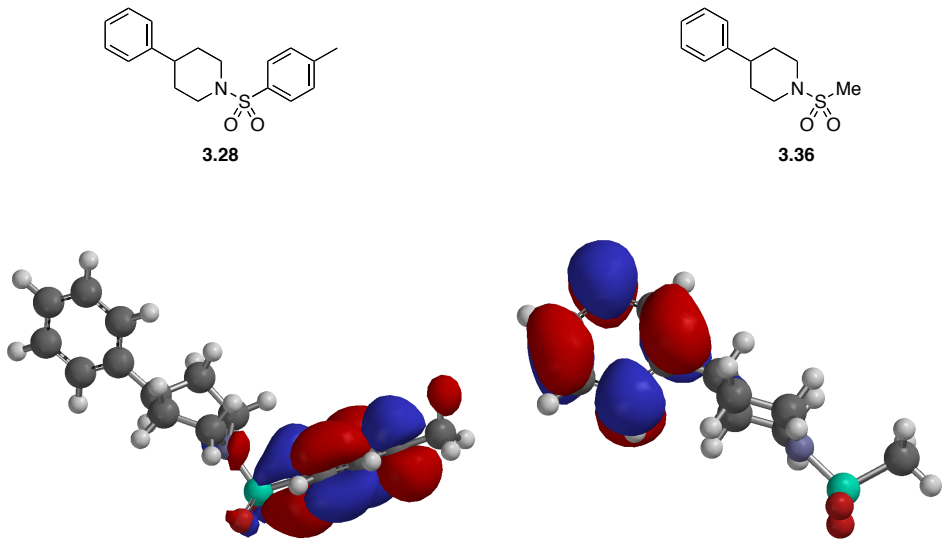


Reaction conditions: a) methanesulfonyl chloride, Et_3N, DCM, 20 h, r.t., Ar; **3.36**, 83%; b) i) nickel(II) complex **3.1** (4.0 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.36**, Ar, r.t. 18 h; recovered **3.36**, 93%; c) i) nickel(II) complex **3.1** (4.0 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate at 90 °C* ii) **3.36**, Ar, 90 °C, 18 h; recovered **3.36**, 93%.

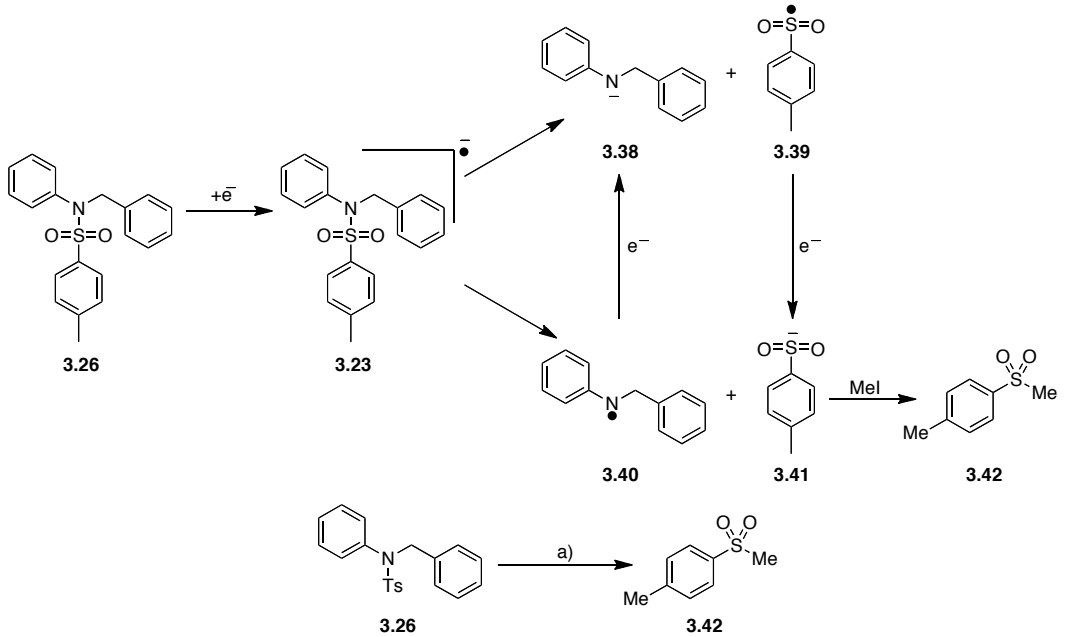
This latter set of observations can be rationalised by examination of both *N*-toluenesulfonyl- and *N*-methanesulfonyl-4-phenylpiperidine (**3.28** and **3.36**) using Spartan®.* First of all, the energy level for the LUMO of the toluenesulfonamide **3.28** was calculated at 2.90 eV, whereas using the same calculation of the methanesulfonamide analogue **3.36**, the LUMO energy level was found to be 3.40 eV. This is a relatively large increase in energy and represents a substantial barrier to be overcome for the reduction of *N*-methanesulfonyl-4-phenylpiperidine **3.36**. These results are further emphasised by inspection of the orbital images calculated during these computational calculations. The LUMO orbital for the toluenesulfonamide **3.28** is centred upon the phenyl ring of the amine-protecting group (figure 3.7). Thus addition of an electron into this molecule would involve transfer to the aromatic system of this phenyl ring. Since this is close to the point of N-S bond scission, reaction would be expected to occur, which is the case resulting in isolation of 4-phenylpiperidine **3.33**. In the case of the methanesulfonamide analogue **3.36**, the LUMO is now centred over the phenyl ring at the 4-position of the piperidine (figure 3.7). Since this is distant from the site of the proposed N-S bond scission and somewhat isolated, it would be unlikely for reduction to occur, which was what was observed experimentally.

* Calculated using equilibrium geometry, Hartree-Fock, 6-31G**

Figure 3.7: LUMO orbitals for *N*-toluenesulfonyl-4-phenylpiperidine **3.28** and *N*-methanesulfonyl-4-phenylpiperidine **3.36**.



Scheme 3.14: the proposed mechanism for the reductive cleavage of the sulfonyl group and the supporting experimental result.



Reaction conditions: a) i) nickel(II) complex **3.1** (4.0 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.26**, Ar, r.t. 18 h, iii) MeI, Ar, r.t., 48 h; **3.42**, 72%.

It is worth considering the likely mechanism for the reductive cleavage of the sulfonyl group by the active nickel complex. The mechanism shown (scheme 3.14) begins with addition of an electron to, for example, a sulfonamide (e.g., **3.26**),

resulting in formation of a radical anion **3.37**. This radical anion can fragment in two possible ways, resulting in both anion **3.38** and radical **3.39**, or radical **3.40** and anion **3.41**. Both of these two sets of reaction intermediates would be interchangeable by electron transfer. Support for this mechanism comes from trapping the intermediate sulfinate anion **3.41** with iodomethane to form methyl sulfone **3.42**. Thus, when activated sulfonamide **3.26** was exposed to the optimised conditions and then quenched by addition of a large excess of iodomethane and stirred an additional 48 h; methyl sulfone **3.42** was recovered (72%), supporting this reductive cleavage mechanism.

Thus it is clear that the active nickel complex is an extremely powerful electron donor, as evident from the results displayed in this chapter. The next path for the investigation to follow would be to explore the nature of the active nickel complex.

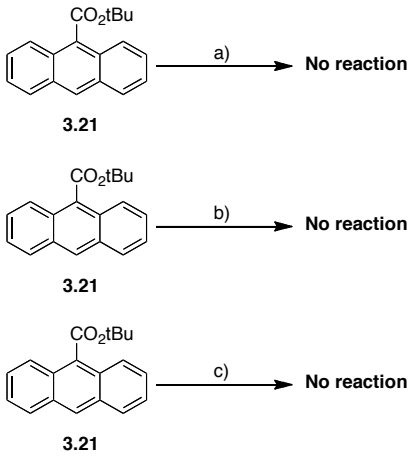
Section 3.3

Understanding the nature of the active nickel crown carbene complex

In sections 3.1 and 3.2, the synthesis and reactivity (when activated) of the nickel(II) complex **3.1** was revealed. However, it was considered important to determine the structure of the active nickel complex. The initial investigation focussed upon the use of three key control experiments to determine which components of the reaction mixture were crucial in enabling the level of reactivity outlined in the previous section. Initially, the role of the ligand **1.285** was examined from the standpoint of whether or not it was necessary. It was proposed that the tetra-*N*-heterocyclic carbene ligand **1.285** would be crucial for controlling the stability of the active nickel complex. The role of the tetra-*N*-heterocyclic carbene ligand **1.285** was examined in the Birch reduction of *tert*-butyl anthracene-9-carboxylate **3.21**. By using a simple nickel(II) salt, in place of the usual nickel(II) complex **3.1** that was previously successfully employed, and repeating the reaction under the previously optimised standard conditions, no reduction to the corresponding *tert*-butyl-9,10-dihydroanthracene-10-carboxylate **3.24** was observed. Thus, in the absence of the ligand, the starting material **3.21** was recovered almost quantitatively in 96% yield. Also, it is worth revealing that upon addition of the anhydrous nickel(II) chloride salt to anhydrous *N,N*-dimethylformamide over a sodium amalgam (the addition was performed under anhydrous and oxygen free conditions in a nitrogen-filled glovebox), an immediate precipitation of a black powder was evident, which was assumed to be nickel(0). Clearly the ligand **1.285** is crucial in controlling not only the stability and oxidation state of the complex, but also the overall reactivity of the active nickel complex. The second experiment that was attempted was a strict control with neither a nickel(II) salt nor the tetra-*N*-heterocyclic carbene ligand **1.285** present. This was done to ascertain whether an unusual role for the *N,N*-dimethylformamide solvent could be proposed following its exposure to sodium amalgam. After exposure of *tert*-butyl anthracene-9-carboxylate **3.21** to the optimised conditions (in the absence of nickel, ligand or complex), no reduction was observed. Again the starting material **3.21** was recovered almost quantitatively (98%). The third and final experiment that was attempted investigated whether the ligand **1.285** itself could effect transformations such as those shown in the previous section. Thus in an effort to achieve this level of reactivity, *tetrakis*trimethylene

tetraimidazolium tetraiodide **1.284** was used in place of the nickel(II) complex **3.1**, under the standard conditions employed successfully thus far. In any case, no reduction to **3.24** was observed, with the starting material **3.21** recovered in high yield (96%). This is clear, strong experimental evidence for the role of the nickel ion within the active nickel complex. In the absence of the central nickel ion, either the electron was not accepted by the ligand **1.285** or, if an electron was accepted, the species formed was not sufficiently activated to achieve this transformation. Clearly the nickel ion is crucial to achieve a highly reactive electron donor.

Scheme 3.15: Control reactions using **3.21** to examine the structure of the active nickel complex.



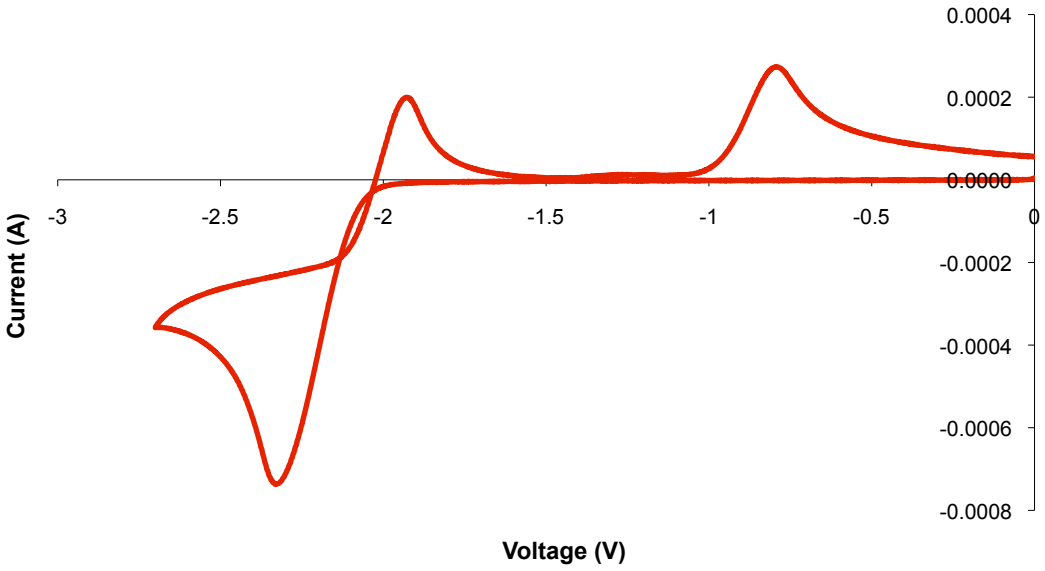
Reaction conditions: a) i) nickel(II) chloride (anhydrous), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.21**, Ar, r.t. 1 h, iii) sat. $NH_4Cl_{(aq.)}$ quench, 96% recovered starting material **3.21**; b) Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.21**, Ar, r.t. 1 h, iii) sat. $NH_4Cl_{(aq.)}$ quench, 98% recovered starting material **3.21**; c) salt **1.284**, Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.21**, Ar, r.t. 1 h, iii) sat. $NH_4Cl_{(aq.)}$ quench, 96% recovered starting material **3.21**.

The next stage of investigation focussed on the cyclic voltammogram of nickel(II) complex **3.2** that was revealed in chapter 3.1 (figure 3.2). The problem that presented itself on closer inspection of figure 3.2 was that calibration, to determine how many electrons were being transferred, wasn't possible due to the solvent reduction wave masking the reduction peak of complex **3.2**. The effect of the applied potential on the solvent is to cause a great increase in current, which, if measured to an even more negative potential, would result in a large, negative "spike". Any wave that occurs at a potential close to this solvent decomposition potential will be masked by this effect. Calibration with ferrocene, a known single electron-donor/acceptor based on the Fc/Fc^+ relationship, is crucial to establish the

number of electrons that are accepted by the compound of interest and thus, how many electrons will be donated when the complex reacts with a suitable substrate.

In an effort to facilitate this calibration, it was proposed to change the working electrode to glassy carbon. It was hoped that this should shift the solvent reduction potential to a more negative value, whilst leaving the reduction peak of nickel(II) complex **3.2** untouched, thus revealing the entire reduction wave. This hypothesis was effective, with the new cyclic voltammogram (figure 3.8) revealing the entire reduction wave at -2.4 V (vs. Ag/AgCl/KCl (sat.)). Calibration of this reduction peak with ferrocene revealed a single electron-transfer was occurring. Thus, when activated by applied potential, the nickel(II) complex is a very powerful, single electron-acceptor.

Figure 3.8: Cyclic voltammogram of the nickel(II) complex **3.2**. Conditions used were a glassy carbon working electrode, platinum counter electrode, Ag/AgCl/KCl (sat.) reference electrode, 0.1M TBAHFP/DMF electrolyte, 50 mV/s scan rate.

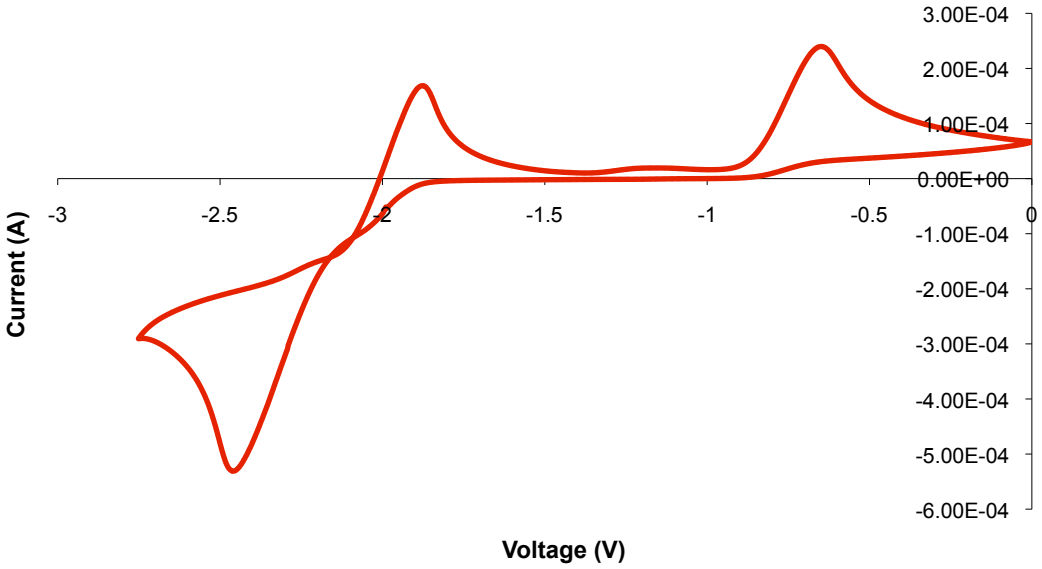


Closer inspection of the cyclic voltammogram for nickel(II) complex **3.2** shown in figure 3.8 revealed that two new oxidation peaks were also now present. These peaks were not present in the previous example (figure 3.2) where solvent decomposition was apparent. It is likely that the change in working electrode has revealed not only the reduction peak, but also the two oxidation waves also. When the cyclic voltammetry was stopped after cycling from 0 V to -1.3 V, then back to 0 V once more, the oxidation wave at -0.7 V was entirely absent. Similarly, when the cyclic voltammetry was cycled from 0 V to -2.1 V, then back to 0 V, the second

oxidation peak at -1.9 V was also absent. Thus, it is clear that the two oxidation waves that are present are likely to be the result of a chemical change occurring following the one-electron reduction. The rate of this chemical change must be so high as to make the reverse electrochemical process ineffective, resulting in the cyclic voltammogram shown (figure 3.8). Indeed, attempts to avoid this chemical change by increasing the scan rate from the standard 50 mV/s to considerably higher values did not remove either of these two waves. Thus, cycling at 100, 200, 400 and 800 mV/s was not successful in eliminating or decreasing these two oxidation peaks (when the scan rate was increased to even higher values of 16 V/s and 32 V/s, the resulting graph became staggered and non-smooth. It was deemed that scan rates at this level were too high to record a usable voltammogram).

One issue with this cyclic voltammogram (figure 3.8) was the irreversible nature of the reduction peak at -2.4 V (vs. Ag/AgCl/KCl (sat.)). As stated above, it is likely that a chemical change occurs at this potential, the rate of which is far greater than the rate of the reverse process. A literature search uncovered a paper by Enders concerning radical anion formation under electrochemical conditions using triazol-5-ylidene carbenes.[145] The paper details the analysis of the radical anion derived from the triazol-5-ylidene carbene, where cyclic voltammetry found a single electron reversible reduction occurred. However, the author states that the initial single sweep cyclic voltammogram formed an irreversible wave, with several sweeps being required to afford the reversible one-electron wave representative of the carbene/radical anion relationship. We were interested to understand whether this "several sweep" technique could effect a degree of reversibility in the cyclic voltammogram of nickel(II) complex **3.2**. Using the same set-up as was used previously, the cyclic voltammogram of complex **3.2** was recorded over a series of 100 scans (figure 3.9). However, it is clear that there is little difference in the cyclic voltammogram between 1 and 100 scans, with the reduction peak and the two oxidation peaks still clearly evident (compare figures 3.8 and 3.9). Thus no reversibility was observed using this technique. Each peak is smaller than the corresponding peak in the single scan cyclic voltammogram, but this is likely to be a result of a larger diffusion barrier at the working electrode surface.

Figure 3.9: Cyclic voltammogram of nickel(II) complex **3.2** recorded over 100 scans and displayed as an average of those 100 scans. Conditions used were a glassy carbon working electrode, platinum counter electrode, Ag/AgCl/KCl (sat.) reference electrode, 0.1M TBAHFP/DMF electrolyte, 50 mV/s scan rate, average of 100 scans.



A possible cause for the formation of the two oxidation peaks could be protonation of the reduced intermediate. Rapid protonation would integrate within the theory of a chemical change occurring at a rate far greater than the reverse redox process in the cyclic voltammogram and may explain the two oxidation peaks. Enders had rationalised that protonation was behind the irreversible nature of his system.[145] This hypothesis leads to consideration of any likely proton sources within the cyclic voltammetry cell. One such proton source would be the electrolyte. A literature search revealed precedent for the Hoffman elimination of *tetra*-butylammonium hexafluorophosphate after exposure to phenyl anions.[146] It is likely that within the analyte solution there would be basic species present and, as such, they could perhaps facilitate a process such as this. With this in mind, the electrolyte solution was switched from *tetra*-butylammonium hexafluorophosphate to *tetra*-methylammonium hexafluorophosphate – an electrolyte salt that does not contain β-hydrogens to the positively charged nitrogen atom so would be unable to undergo Hoffman-type elimination. In any event, the switch of electrolyte was unsuccessful as the cyclic voltammogram still provided the same three peaks at the same three positions. Thus it is unlikely that Hoffman elimination from *tetra*-butylammonium hexafluorophosphate electrolyte is the sole source of protons in the analyte solution. However, an alternative source of protons could also be present in the analyte

solution. Both electrolytes used thus far were commercially obtained and used without any further purification. Any water that is present from the commercial synthesis/purification of each electrolyte would also still be present in the analyte solution. As such, the water content of each salt was measured by Karl Fischer analysis. In the case of the *tetra*-butylammonium salt, the water content level was measured at 0.64% w/w, corresponding to a water mass of 1.58 mg per 10 ml of electrolyte solution. With the *tetra*-methylammonium salt, the water content was measured at 0.24% w/w, corresponding to a water mass of 0.62 mg per 10 ml of electrolyte solution.[147] Neither of these amounts is particularly large but they may play an important role in the protonation of the reduced intermediates during the cyclic voltammetry analysis.

The question that now presented itself was that since it appears unlikely that protonation of the reduced intermediate can be eradicated to allow a reversible redox process to occur within the cyclic voltammetry set-up, could deliberate addition of a suitable base hinder transfer of any available protons from the reaction mixture to the key nickel intermediates and change the make-up of the cyclic voltammogram? In an attempt to answer this, the first analysis of the nickel(II) complex **3.2** with addition of base was attempted. Using triethylamine (purified and dried by distillation), the cyclic voltammogram was recorded following the addition of three different concentrations of base. In each case (0.01 M, 0.1 M and excess), no change was observed in the cyclic voltammogram, indicating that the triethylamine was ineffective at scavenging any available protons. The second attempt focussed on the use of proton sponge[148] as the proton scavenger. In this attempt, a cyclic voltammogram was recorded for a 0.01 M solution of proton sponge, which revealed a reduction potential of -2.6 V (vs. Ag/AgCl/KCl (sat.)), close to the reduction potential of nickel(II) complex **3.2** (no cyclic voltammogram was recorded for triethylamine as it is not redox active under these conditions). In any case, the analysis was undertaken using the same three concentrations used for the triethylamine experiments. Once more, no significant change was observed in the cyclic voltammogram, with all three principal peaks still present, indicating that proton sponge is also ineffective at scavenging available protons. Thus it appears that deliberate addition of base is ineffective in inhibiting the chemical change in the cyclic voltammogram.

The likelihood that protonation could explain the two oxidation peaks that were observed when the nickel(II) complex **3.2** was analysed by cyclic voltammetry was examined using computational methods.[149] As stated above, it was proposed that traces of a proton source (probably water) were reacting with the active nickel complex within the cyclic voltammetry cell. This protonation was occurring at a far higher rate than the oxidative wave of the cyclic voltammogram, thus the active nickel species has a very short lifetime within the cyclic voltammetry cell. The protonated species can be depicted as shown in figure 3.10. So, following electron transfer to the nickel(II) complex (*e.g.*, **3.43**), the reduced species **3.44** (with the electron residing in the empty p-orbital of the *N*-heterocyclic carbene) can abstract a proton, resulting in two protonated species, **3.45** and **3.46**, differing only by the site of protonation. Each of these intermediates can be considered substantially less electron-rich than the parent active nickel complex. As such, they would be expected to undergo oxidation at a lower (less negative) potential to form **3.47** or **3.48**. This could explain the two oxidation peaks at -1.9 V and -0.5 V. Using the B3LYP calculation,[149] the relative energies of intermediates **3.45**-**3.48** to nickel(I) complex **3.44** were calculated (using water as the source of protons). Protonation on the peripheral carbon to form intermediate **3.45** is higher in energy by 17.7 kcal/mol, while protonation on a nitrogen atom is considerably less favourable. The calculated energy differerence between **3.44** and **3.46** was 52.5 kcal/mol. Clearly protonation is an unfavourable process but it must be considered that protonation on carbon might be possible under the conditions of analysis. However, protonation is not the complete picture. After protonation, each intermediate (**3.45** or **3.46**) must release an electron to form the oxidised intermediates **3.47** and **3.48**. The energy difference for each of these processes is also significant, with the oxidation of **3.45** to **3.47** being calculated at 105.4 kcal/mol and oxidation of **3.46** to **3.48** at 92.0 kcal/mol. Overall, protonation on carbon (from **3.44** to **3.47**) has an energy difference of 123.1 kcal/mol, while protonation on nitrogen (from **3.44** to **3.48**) has an energy difference of 144.5 kcal/mol. Thus, it is very unlikely that protonation is occurring during the cyclic voltammogram analysis and resulting in the two, unidentified oxidative peaks. This information is summarised in table 3.2 below.

Figure 3.10: the proposed protonation of intermediates within the cyclic voltammetry analysis of nickel(II) complex **3.2**.

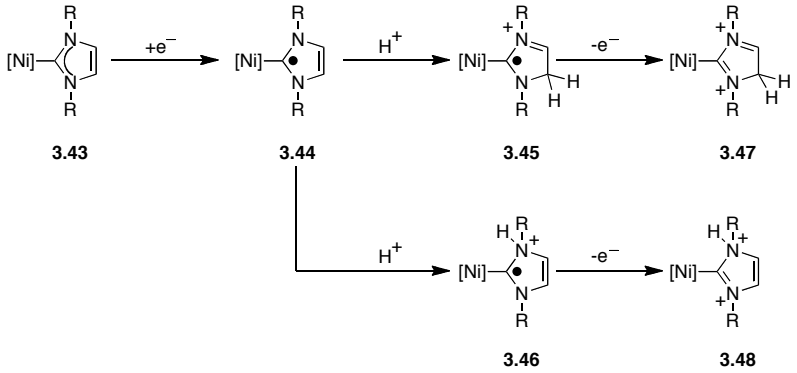


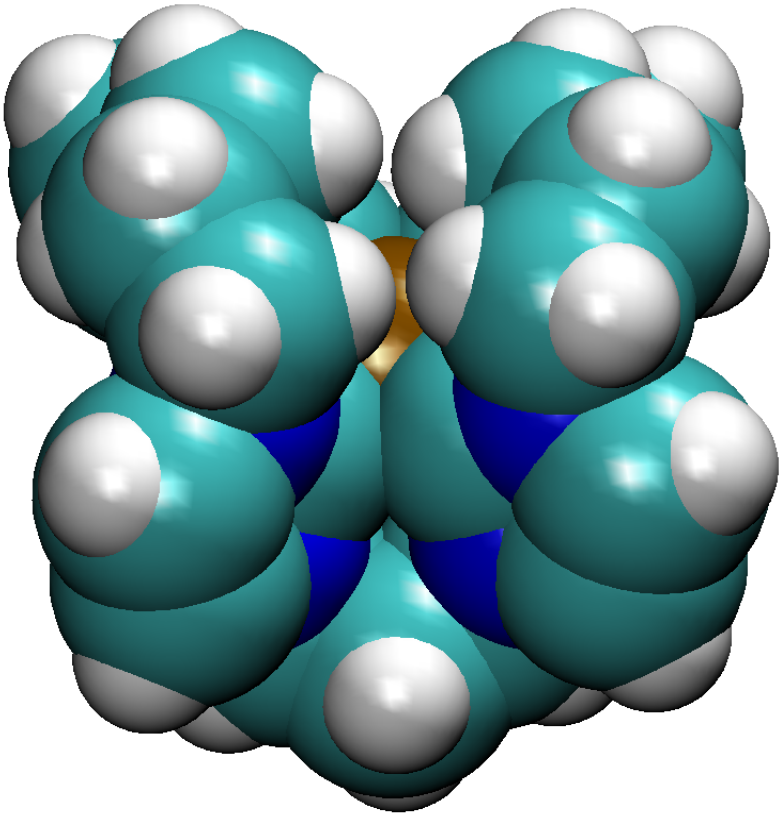
Table 3.2: computational values for the protonation of **3.44** and oxidation of **3.45** and **3.46** during cyclic voltammetry analysis of nickel(II) complex **3.1**.

Process	Energy difference, ΔGs (kcal/mol)
3.44 + H^+ → **3.45**	17.7
3.44 + H^+ → **3.46**	52.5
3.45 – e^- → **3.47**	105.4
3.46 – e^- → **3.48**	92.0
Overall, **3.44** → **3.47**	123.1
Overall, **3.44** → **3.48**	144.5

An alternative explanation for the two oxidative peaks would be the incorporation of a solvent molecule into the activated nickel complex during the cyclic voltammogram analysis, forming unknown products that were then responsible for the oxidation peaks. Once more, computational methods were used in order to determine whether this was feasible.[149] Both a single *N,N*-dimethylformamide solvent molecule and two solvent molecules were introduced in close proximity to the activated complex and their behaviour modelled. In each attempt, the solvent molecule was immediately ejected by the activated complex, which reorganised to form the original structure. The closest interaction observed was a very weak hydrogen bond between the peripheral hydrogen atoms on the methylene bridge that links the NHC units of the ligand, and the solvent carbonyl, calculated at approx. 2.6 Å. The reasons behind the non-incorporation of foreign molecules are clear when a space-filled model of the activated nickel complex is examined (figure 3.11). The nickel ion is completely encapsulated and is barely visible, let alone accessible for interaction with foreign molecules, as the ligand conformation topologically resembles the cover of a tennis

ball. This means that the exclusive isolation of the *dl*-isomer (**3.6** or **3.11**) from acetophenone **3.5** or benzaldehyde **3.7** cannot be explained *via* chelation to the central nickel ion, and the mechanism for stereocontrol of such pinacol products from the reduction of aldehydes and ketones remains uncertain.

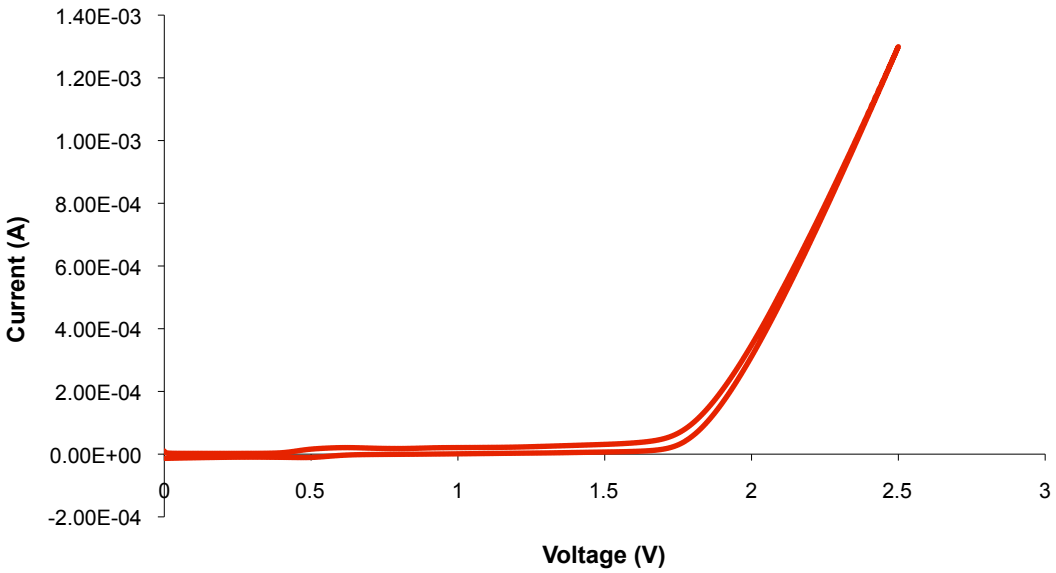
Figure 3.11: the space-filled model for the activated nickel complex.[149]



The cyclic voltammogram of nickel(II) complex **3.2** is interesting from a reductive point of view as it is clear how tough it is to donate an electron to the nickel(II) complex. However, it is also worth considering the oxidative process. It is likely that oxidation from Ni(II) → Ni(III) would occur within the potential limits for the cyclic voltammetry set-up.[114] However, it was proposed that the steric bulk of the tetra-*N*-heterocyclic carbene ligand **1.285** might have a significant role to play in inhibiting the oxidation of the complex. In any case, when nickel(II) complex **3.2** was analysed by cyclic voltammetry to a potential of +2.5 V, no significant oxidation activity was observed (figure 3.12). This is unusual and does indeed point to a possible role for the ligand in controlling the oxidation state of the nickel ion within the complex, due to the ligand resisting any change in shape that would be required to incorporate a higher oxidation state metal. Indeed, computational calculations

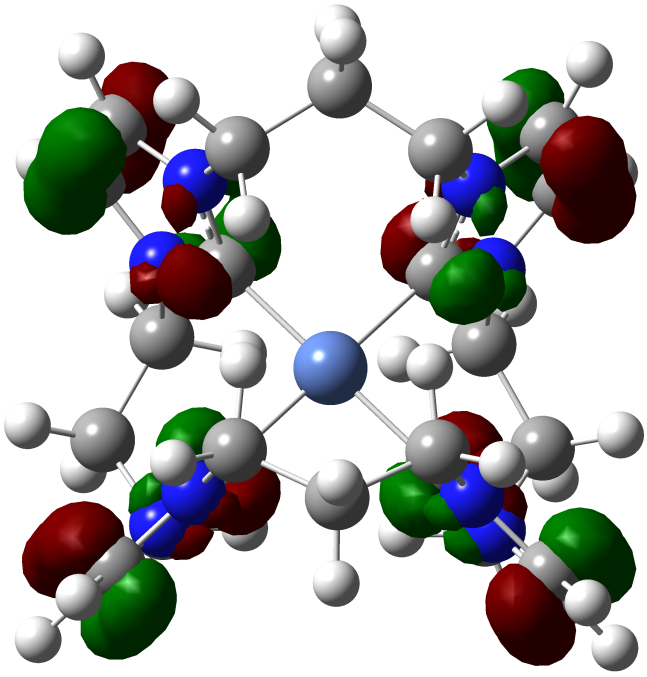
reveal that the oxidation to form the formal nickel(III) state is higher in energy than the nickel (II) state by 155.4 kcal/mol, clearly indicating how unlikely such an oxidation would be.[149]

Figure 3.12: Cyclic voltammogram of the nickel(II) complex **3.2**. Conditions used were a glassy carbon working electrode, platinum counter electrode, Ag/AgCl/KCl (sat.) reference electrode, 0.1M TBAHFP/DMF electrolyte, 50 mV/s scan rate.



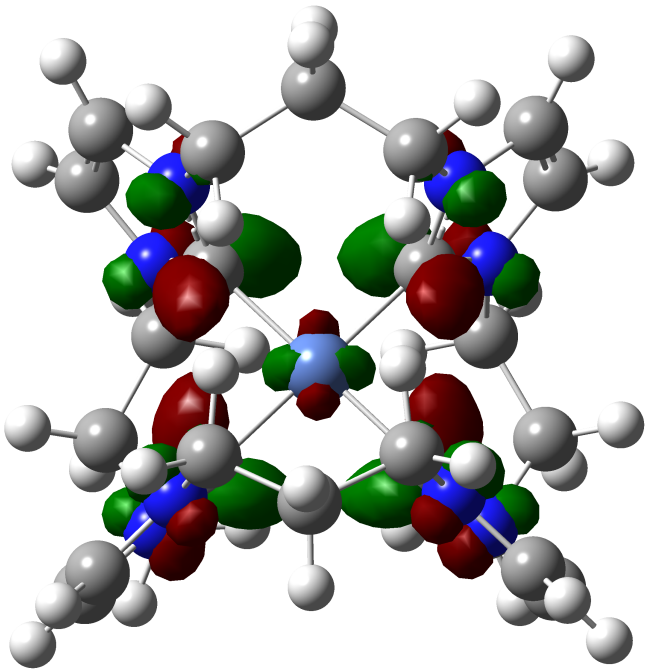
Computational calculations were also used to model the structure of active nickel complex formed during the cyclic voltammetry analysis. The nickel(II) complex **3.2** and the product upon addition of one electron to the nickel(II) complex **3.2** (*i.e.*, the active nickel complex) were examined. The stable nickel(II) complex **3.2** was investigated first, with both the HOMO and the LUMO calculated. The HOMO showed that the molecular orbital was situated entirely over the ligand, centred upon the C2, C4 and C5 carbons of the *N*-heterocyclic carbene units of the ligand macrocycle. There is no contribution from the central nickel ion (figure 3.13).

Figure 3.13: HOMO of the nickel(II) complex **3.2**.[149] Colour scheme: light blue – nickel; dark blue – nitrogen; grey – carbon; white – hydrogen; areas of red and green represent molecular orbitals. Iodide counter-ions are omitted for clarity.



More importantly, examination of the LUMO for the nickel(II) complex **3.2** revealed that the orbital was not centred upon the central nickel(II) ion of the complex (figure 3.14). It was expected that the role of the ligand would be to increase the electron density on the central nickel ion, making it more electron-rich, and subsequently more reactive as an electron-donor from its reduced state. If this was the case, the LUMO would be the $d_{x^2-y^2}$ orbital of the nickel(II) ion. From the outset, it was believed that the role of the macrocyclic ligand would be to stabilise the nickel complex to permit an electron to reside in this high-energy orbital. Instead, the LUMO was delocalised over the entire complex, predominantly upon the ligand system at the C2 carbon, with only a small contribution from the orbital of the nickel ion. It is this molecular orbital that would be distorted upon addition of an electron, thus it would be expected that the SOMO after addition of a single electron would appear similar to the LUMO shown in figure 3.14.

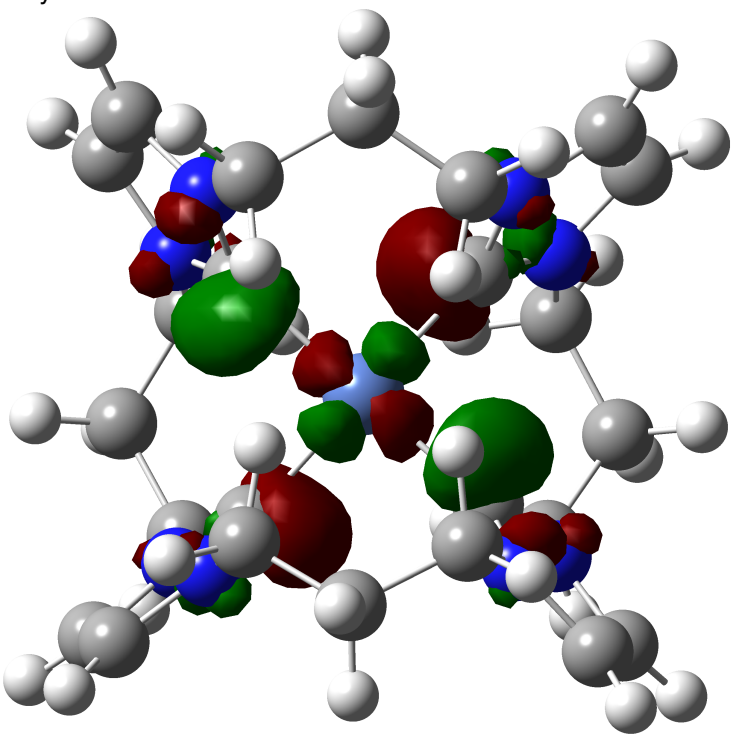
Figure 3.14: LUMO of the nickel(II) complex **3.2**.[149] Colour scheme: light blue – nickel; dark blue – nitrogen; grey – carbon; white – hydrogen; areas of red and green represent molecular orbitals. Iodide counter-ions are omitted for clarity.



Examination of the calculated SOMO for the activated nickel complex following addition of one electron revealed that the molecular orbital is delocalised over the entire complex (similar to the LUMO diagram, figure 3.14). The molecular orbital appears to be centred upon the C2 carbons of each *N*-heterocyclic carbene unit upon the macrocyclic ligand, with, once more a small contribution from the central nickel ion (figure 3.15). It is tempting to suggest that the SOMO is centred upon the empty p-orbital of the carbene carbon (each *N*-heterocyclic carbene would be a singlet carbene, thus the sp^2 orbital would be filled and the p-orbital empty). However, there is a considerable degree of distortion evident in the calculated SOMO structure that could cast some doubt on this claim. The small contribution from the central nickel ion is important. The role of the nickel ion as the central component to this delocalised "penta-centre" relationship means that the nickel ion acts as a "crossroads", faclilitating the delocalisation of the additional electron across all four *N*-heterocyclic carbene centres. This is only a small contribution from the nickel ion however, thus, the most appropriate way in which to describe the active nickel complex is as a central nickel(II) ion complexed to a radical anion ligand. Metal-NHC radical anion complexes are not unknown within the literature. Busch and co-workers have shown through EPR studies the existence of nickel(II)

ions bound to ligand anion radicals,[114] while Enders and co-workers have observed the formation of an NHC radical anion during cyclic voltammetry studies.[145] More recently, Arnold and co-workers have reported the first, stable, chemically-generated, radical anion NHC complex of potassium.[150] A novel role for NHC radicals has also been recently reported. The generation of delocalised NHC boryl radicals and their application in the Barton-McCombie reaction has provided a new application for NHCs.[151] Thus, the formation of a radical anion ligand when the nickel(II) complex **3.2** is activated is not surprising. One further point it is important to consider is whether the active nickel complex is stable to loss of an *N*-heterocyclic carbene unit, at least from a computational point of view. Any attempts to remove the *N*-heterocyclic carbene unit resulted in immediate recomplexation to give the SOMO structure shown below (figure 3.15).

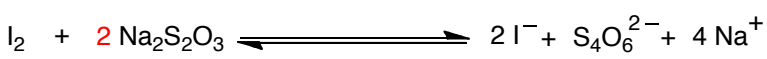
Figure 3.15: Computational calculations on the active nickel complex – SOMO after addition of one electron.[149] Colour scheme: light blue – nickel; dark blue – nitrogen; grey – carbon; white – hydrogen; areas of red and green represent molecular orbitals. Iodide counter-ions are omitted for clarity.

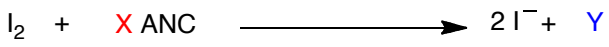


The computed image for the active nickel species formed during the cyclic voltammogram is shown above (figure 3.15). However, there remained the possibility that the active nickel species formed by stirring over sodium amalgam differed from that which was activated electrochemically. That is to say that the

species formed from chemical activation of complex **3.1** differed from the species formed during electrochemical activation of complex **3.2**. In order to examine this possibility, a titration was proposed to determine the number of moles of activated nickel complex that would react with an easily reducible molecule. Iodine was chosen as the electron acceptor as the active nickel complex would easily reduce iodine and it also provided an appropriate colour change when titrated with sodium thiosulfate. The key equations are shown in figure 3.16. Importantly, two moles of thiosulate are required to reduce one mole of iodine, thus two electrons are required to reduce iodine. This relationship will be used to determine how many moles of the active nickel complex are required to reduce iodine, and hence, the number of electrons transferred by the chemically activated nickel complex. In a control titration, addition of nickel(II) complex **3.1** to a known concentration of iodine and subsequent titration with sodium thiosulfate, revealed that no reaction occurred between complex **3.1** and iodine. As a result, the following analysis is an entirely valid method of determining how many electrons the chemically activated nickel complex transfers.

Figure 3.16: the equations relating to the titration of iodine with sodium thiosulfate and the active nickel complex.





The active nickel complex was prepared by stirring a known mass of nickel(II) complex **3.1** over 1% sodium amalgam in *N,N*-dimethylformamide (this provides an excess of electrons for complex **3.1**). This was performed in a glovebox to ensure an air- and moisture-free environment. After 4 h, and once the characteristic deep red colour had formed, a 10 ml aliquot of the active nickel complex was added to 10 ml of an excess iodine solution in *N,N*-dimethylformamide to quench the activated complex. This was repeated a further two times, resulting in three quenched solutions that were then removed from the glovebox. The concentration of iodine solution used was determined by titration with a known concentration of aqueous sodium thiosulfate. Once the iodine concentration was known, the three quenched solutions were then titrated with sodium thiosulfate to determine the number of

moles of unreacted iodine that remained after reaction with the active nickel complex. This allowed the number of moles of iodine that reacted with the active nickel complex to be determined. The results are displayed in table 3.3, while a detailed summary of the calculated results for these titrations is shown in appendix 1. It is clear that the molar relationship between iodine and the active nickel complex is 1:1, meaning that since two electrons are required to reduce iodine (figure 3.16), the **chemically activated nickel complex is a two-electron donor**. The entire titration was performed in duplicate to ensure the validity of the result. Thus, the active nickel species chemically generated by the sodium amalgam differs from the active nickel species generated electrochemically and observed in the cyclic voltammogram.

Table 3.3: the results from the quench of the active nickel complex with iodine, and subsequent titration with sodium thiosulfate.*

Titration No.	**Moles of 3.1 (mmol)**	**[$Na_2S_2O_3$] used (mM)**	**∴ [I_2] used (mM)**	**∴ Total moles of I_2 (mmol)**	**Vol. of $Na_2S_2O_3$ used for quench soln (ml)**	**∴ Moles I_2 after quench (mmol)**	**∴ No. moles I_2 reacted with ANC (mmol)**
1	**0.100**	10.537	17.632	0.176	15.5 (R)† 15.2 15.3	0.080	**0.096**
2	**0.104**	9.977	16.163	0.162	12.2 (R)† 12.5 12.4	0.062	**0.100**

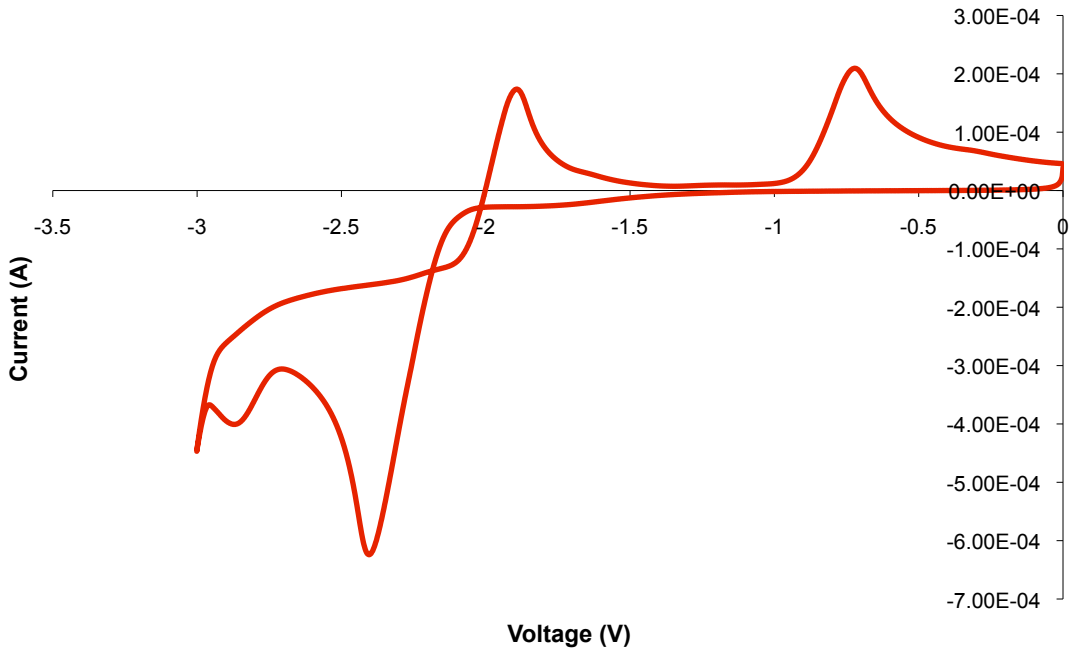
Thus, the chemically activated nickel complex is a two-electron donor and, as such, it follows that it must accept two electrons from the sodium amalgam to form the activated species. Some tentative evidence for the nickel(II) complex **3.2** accepting a second electron can be seen when the cyclic voltammogram is extended to -3.0 V – the potential at which the system starts to reduce the *N*,*N*-dimethylformamide solvent (figure 3.17). Moving from 0 V to -3 V and then back to 0 V, the first

* A full account of this titration and a detailed account of the calculations involved is shown in appendix 1

† (R) = rough titration. This value was not used in the calculation.

reduction wave at -2.4 V corresponds to the first electron being accepted by nickel(II) complex **3.2**. At more negative potentials, this peak starts to decrease in size and a new, previously unseen peak begins to appear at -2.80 V. It is possible that this new peak is nickel(II) complex **3.2** accepting a second electron, which would correspond with the titration results with iodine disclosed above (table 3.3). Unfortunately, due to solvent reduction occurring at -3.0 V, the full picture for this peak has not been revealed so it is difficult to confidently assign this peak as the second reduction wave to form the chemically activated nickel complex. Moreover, it still remains challenging to fully describe the cyclic voltammogram of nickel(II) complex **3.2**.

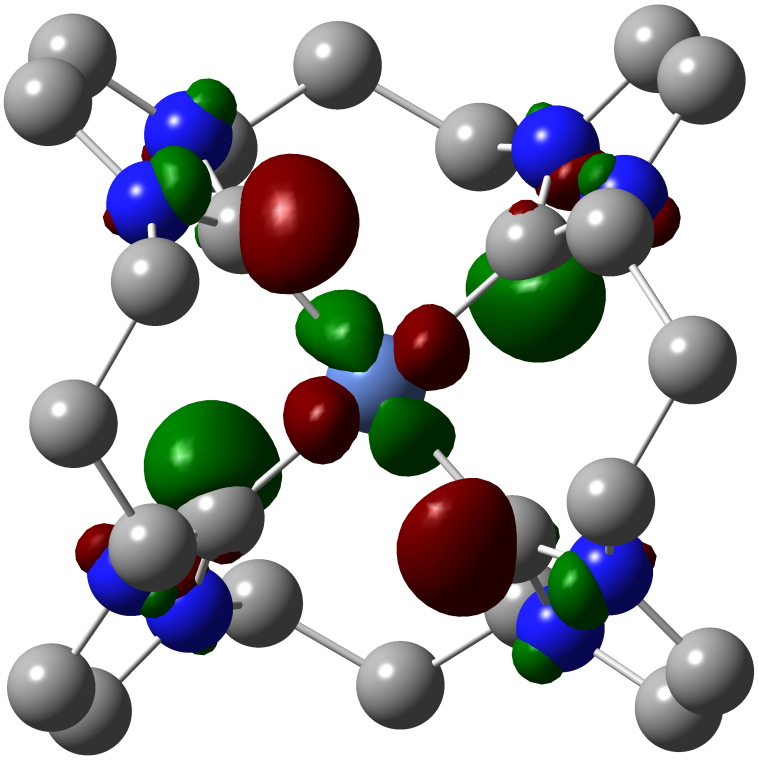
Figure 3.17: Cyclic voltammogram of the nickel(II) complex **3.2** to -3.0 V. Conditions used were a glassy carbon working electrode, platinum counter electrode, Ag/AgCl/KCl (sat.) reference electrode, 0.1M TBAHFP/DMF electrolyte, 50 mV/s scan rate.



The structure of the highly reactive, chemically generated active nickel complex was determined using computational methods and is shown in figure 3.18. Thus, the HOMO of the formally nickel(0) complex, after addition of two electrons into the nickel(II) complex **3.1**, is situated on the molecular orbital dispersed across the entire ligand system. Once again, the orbital is centred upon the C2 carbons of each *N*-heterocyclic carbene unit upon the macrocyclic ligand, with only a small contribution from the central nickel ion. This is similar to the description of the SOMO above (figure 3.15). Again, the small contribution from the central nickel ion

is important, delocalising the additional electrons as a chemical "crossroads". So, the structure of the chemically activated nickel complex is as shown in figure 3.18 and can best be described as a nickel(II) ion complexed to a dianion macrocyclic ligand. Furthermore, the energy barrier was calculated for the reduction of nickel(II) complex **3.1** following addition of one electron and two electrons.[149] The value for addition of a single electron to complex **3.1** was calculated at -42.7 kcal/mol. This corresponds to the energy liberated to form the electrochemically activated complex in the cyclic voltammogram. More importantly, the value for the addition of a further electron was -22.5 kcal/mol – meaning that the total energy liberated generating the chemically activated nickel complex is -65.2 kcal/mol.

Figure 3.18: Computational calculations on the chemically generated active nickel complex – HOMO after addition of two electrons.[149] Colour scheme: light blue – nickel; dark blue – nitrogen; grey – carbon; white – hydrogen; areas of red and green represent molecular orbitals. Iodide counter-ions are omitted for clarity.



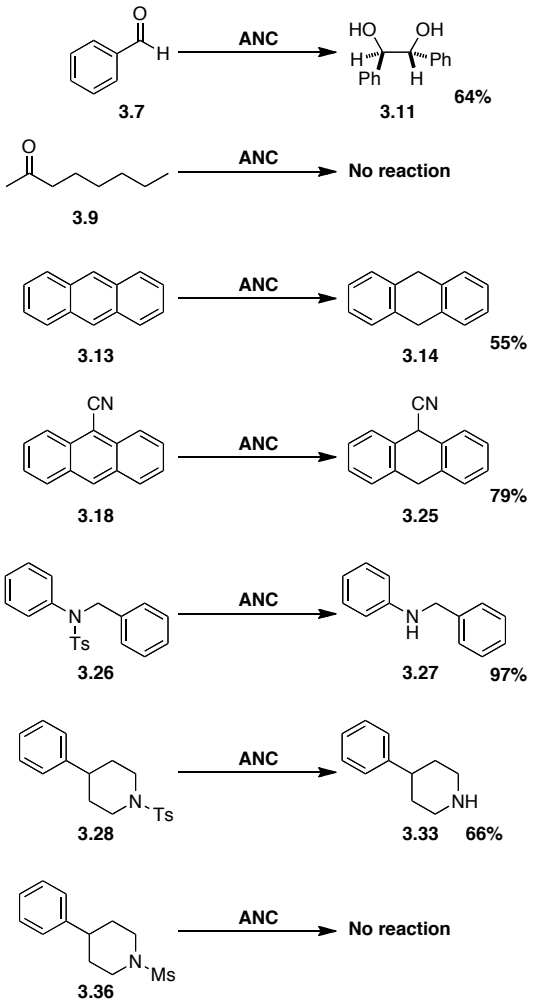
Thus, the structure of the chemically activated nickel complex is shown in figure 3.18. It is this species that is responsible for the impressive level of reactivity demonstrated in the reduction of organic compounds shown in section 3.2.

Section 3.4

Conclusions and future work

From the data presented in sections 3.1 to 3.3, it is clear that the active nickel complex is an extremely powerful electron donor. The complex is capable of reducing aldehydes and ketones, anthracene and its substituted analogues, as well as both activated and non-activated arenesulfonamides. Each of these transformations was achieved in good to excellent yield. Computational calculations have been used to probe the reasoning behind the variation in reactivity disclosed in this account. For example, calculations revealed the likely reasons behind the inactivity of the active nickel complex with *N*-methanesulfonyl-4-phenylpiperidine **3.36**, compared with the *N*-toluenesulfonyl- analogue **3.28**.

Scheme 3.16: results from the reaction of the active nickel complex with various substrates.



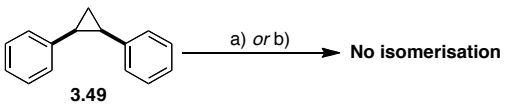
In addition, through extensive cyclic voltammetry studies and further computational analysis, the structure of the active nickel complex has been investigated, resulting in the proposal detailed in section 3.3. It is clear that the active nickel complex that is present during the cyclic voltammogram analysis differs from the chemically activated nickel complex. After addition of a single electron (*i.e.*, in the cyclic voltammogram), the activated complex is a nickel(II) ion bound to a radical anion ligand. More importantly, the chemically activated nickel complex that is responsible for the chemistry summarised in scheme 3.16, receives a second electron from the sodium amalgam forming a nickel(II) dianion complex. The structure of this complex is shown in figure 3.18 on page 141.

Future work must involve further analysis of the cyclic voltammogram of complex 3.2 in order to determine what each peak represents. It is clear that the addition of a second electron is masked by the solvent decomposition wave. It may be that a different set of conditions, where the working electrode or solvent was modified, may resolve this. More importantly, the two oxidation peaks should be identified. Further computational analysis may help the understanding of the cyclic voltammogram process. In addition, the exclusive isolation of the *dl*-isomers (**3.6** and **3.11**) from the reduction of acetophenone **3.5** and benzaldehyde **3.7** should be further probed by computational methods. Although the space-filled model for the activated nickel complex (figure 3.11) excludes a role for the nickel ion to act as a divalent scaffold to induce reactivity, it might be possible that an alternative site of the active nickel complex could fulfil such a role.

Future work should also focus upon expanding the reactivity of the active nickel complex. One such area for potential research would be in the isomerisation of cyclopropanes under reductive conditions. Recently, Cahard[152] and Cutulic within the Murphy group have shown that through use of donor **1.177** under UV conditions, isomerisation between the *cis*- and *trans*-cyclopropane occurred. This is evidence of electron transfer occurring from donor **1.177** into the π-system of the aromatic ring, which is a remarkable achievement. Initial investigations with the active nickel complex focussed on the use of thermal activation to achieve a similar transformation with cyclopropane **3.49**. However, when the reaction was attempted both at room temperature and at elevated temperature (100 °C), no isomerisation was evident. Future work should involve the development of a UV protocol for the

reaction. This would involve screening a solution of the active nickel complex to understand whether it can absorb at the correct wavelength for UV-activation to occur. If this is successful, a procedure to test the complex under UV conditions with the diphenylcyclopropane substrates (*e.g.*, **3.49**) should be identified.

Scheme 3.17: the attempted isomerisation of *cis*-diphenylcyclopropane **3.49** using the active nickel complex.



Reaction conditions: a) i) nickel(II) complex **3.1** (1.2 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate* ii) **3.49**, Ar, r.t. 18 h, 92% recovery of starting material **3.49**; b) i) nickel(II) complex **3.1** (1.2 equiv.), Na/Hg, DMF, Ar, r.t., 4 h *then added to substrate at 100 °C* ii) **3.49**, Ar, 100 °C, 18 h, 94% recovery of starting material **3.49**.

Chapter 4

Towards the development of a catalytic reductive methodology employing a neutral organic electron donor in the reduction of aryl iodides

This chapter discusses the initial investigations towards the development of a catalytic, reductive methodology using the DMAP-derived donor **1.177** in the reduction of simple aryl iodides. By application of an appropriate potential, the organic electron donor can be generated *in situ* and, in theory, after reaction with the substrate be regenerated by the applied potential to react with further moles of substrate. Using such mediated electron-transfer has two significant advantages. The first is that large quantities of stoichiometric reductants can have unwanted effects on the environment and may be expensive. The use of catalytic quantities of the key reductant is obviously beneficial. Secondly, pure electrochemistry relies on high potentials being required to achieve substrate reduction. Use of a mediator results in a lower applied potential,[153] resulting in a significant economic advantage over pure electrochemistry.

Section 4.1 introduces previous studies, the methods used and discusses the synthesis of the required materials. Section 4.2 discusses the initial investigations towards the development of a catalytic procedure using organic electron donor **1.177**, with particular focus on the use of a proton source to quench the intermediate aryl anion following reduction of the aryl halide. Finally, section 4.3 examines the conclusions arrived at from this work and proposes future studies that should be attempted.

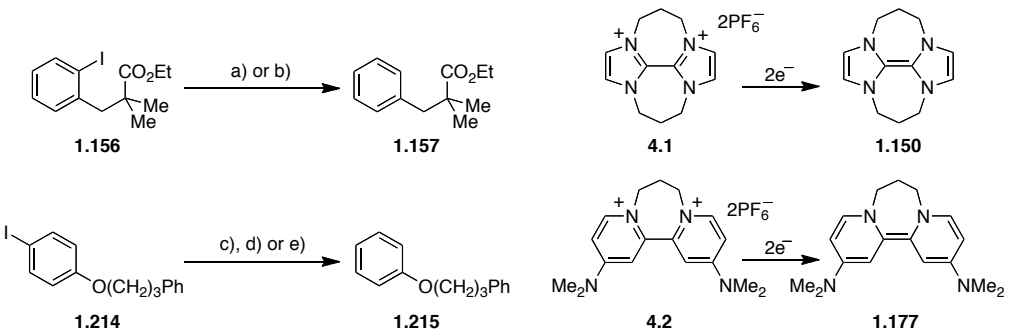
Section 4.1

The initial synthesis of the required materials and a discussion of apparatus used

Previously, Park had investigated the application of donors **1.150** and **1.177** to the catalytic reduction of aryl iodides using an applied potential to regenerate the active

donor.[154] After establishing that donor **1.150** could be electrochemically generated from the corresponding disalt **4.1** and used to reduce aryl iodide **1.156** when used stoichiometrically, initial catalytic results were disappointing with low yields of product **1.157** and low mass balance (scheme 4.1). It was proposed that donor **1.150** degraded after electron donation resulting in an inability to reform disalt **4.1**. This meant that donor **1.150** is unsuitable for application in catalysis. Donor **1.177** was also examined under catalytic conditions using substrate **1.214** (scheme 4.1).[154] Park found that when starting from pure donor **1.177** (as opposed to disalt **4.2**), low catalytic turnover was observed, resulting in low yields of product **1.215**. Higher conversions were observed however, on addition of *tert*-butanol as a proton source. Conversely, when disalt **4.2** was employed, no catalytic turnover was evident, with product **1.215** formed in just 24% yield despite stoichiometric quantities of disalt **4.2** being used.

Scheme 4.1: the initial investigations performed by Park towards the development of a catalytic, electrochemical reductive procedure.[154]



Reaction conditions: a) salt **4.1** (1.0 eq.), TBAHFP/DMF (0.1 M), -1.5 V, r.t., 6 h, N_2; **1.157**, 50%; b) salt **4.1** (0.5 eq.), TBAHFP/DMF (0.1 M), -1.5 V, r.t., 6 h, N_2; **1.157**, 18%; c) donor **1.177** (0.5 eq.), TBAHFP/DMF (0.1 M), -1.5 V, r.t., 18 h, N_2; **1.215**, 63.5%; d) donor **1.177** (0.5 eq.), *tert*-butanol (5.0 eq.), TBAHFP/DMF (0.1 M), -1.5 V, r.t., 18 h, N_2; **1.215**, 73%; e) salt **4.2** (1.0 eq.), TBAHFP/DMF (0.1 M), -1.5 V, r.t., 18 h, N_2; **1.215**, 24%.

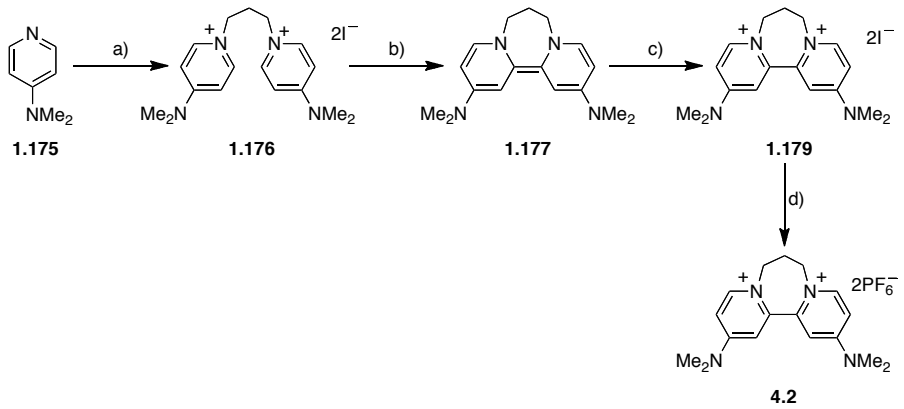
The reasons behind the disappointing reactivity with donor **1.177**, particularly when electrochemically generated from disalt **4.2**, are less obvious. Park had found that discolouration of the working electrode was evident following reduction of substrate **1.214** using disalt **4.2**.[154] Thus it is possible that donor **1.177** or disalt **4.2** foul the electrode, resulting in low catalytic turnover. An alternative possibility for the low level of catalysis displayed by **1.177**/**4.2** could be degradation of either species by intermediate aryl anions (formed after reduction of substrate **1.214**). Garnier[68,155] has shown that the *ortho*-protons in pyridinium disalts such as **4.2** are the primary

source of protons for quenching intermediate aryl anions during the reduction of aryl halides.

However, the reversible nature of the cyclic voltammogram for donor **1.177** provides an enticing basis for developing a catalytic procedure using an applied potential to generate the active donor **1.177** from disalt **4.2**. Furthermore, it was believed that through incorporation of an appropriate proton source into the reaction medium, intermediate basic aryl anions could be quenched, allowing a catalytic process to flourish and reduce aryl iodides using sub-stoichiometric quantities of disalt **4.2**. As such, the initial aim was to develop a catalytic procedure based on the use of catalytic quantities of disalt **4.2**, through the screening of various proton sources to hinder unwanted side-reactions. In addition, close attention was to be paid to the acidity of each proton source due to the likelihood of donor **1.177** being protonated and interrupting the catalytic cycle should a highly acidic proton source be employed.

Initially, large quantities of disalt **4.2** were required to use as the catalyst precursor. Alkylation of two moles of 4-dimethylaminopyridine (DMAP) with 1,3-diiodopropane formed salt **1.176** in quantitative yield. To allow isolation of disalt **4.2**, first pure donor **1.177** was formed by deprotonation with sodium hydride in liquid ammonia at low temperature. The resulting deep purple solid was then dissolved in acetonitrile and added to a solution of iodine in diethyl ether. After removal of the solvent, the resulting brown residue was checked by NMR and then used immediately in the next stage without further purification. Counter-ion exchange used hexafluorophosphoric acid in water afforded the corresponding dihexafluorophosphate salt **4.2** in moderate yield (46%).

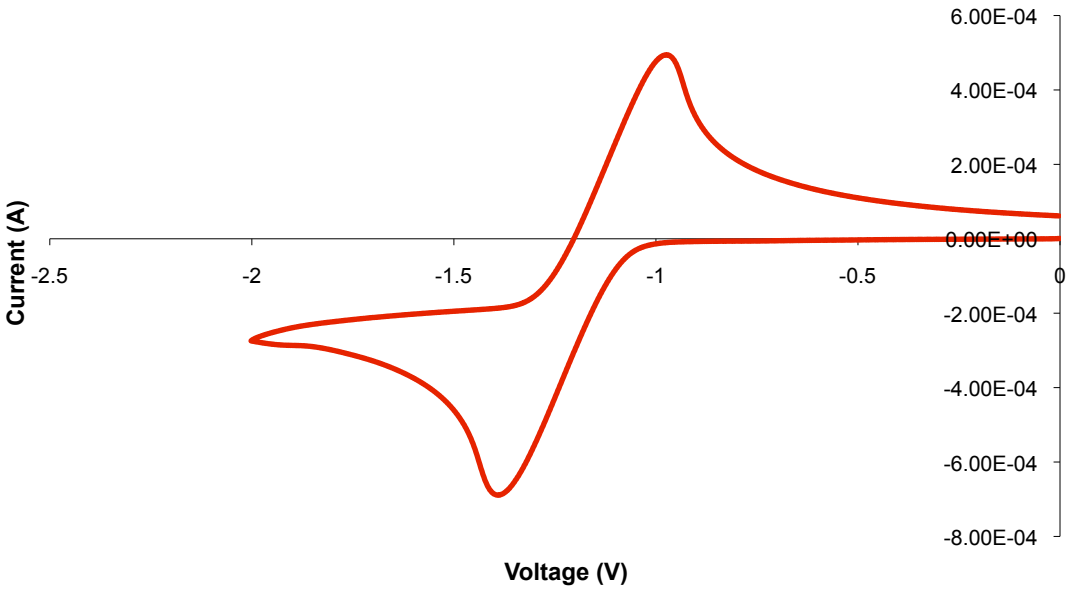
Scheme 4.2: the synthesis of disalt **4.2**.



Reaction conditions: a) 1,3-diiodopropane, MeCN, reflux, 48 h; **1.176**, 100%; b) NaH, liq. NH_3, -33 °C, 4 h *then* r.t., 14 h, Ar; **1.177**, 70%; c) iodine, MeCN, Et_2O, 30 min; d) HPF_6, H_2O; **4.2**, 46%.

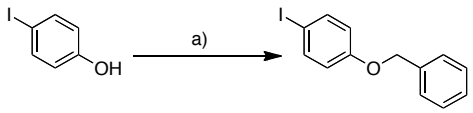
Disalt **4.2** was then examined by cyclic voltammetry, not only to further ensure its purity, but also to reaffirm the reversible nature of the electron transfer. The cyclic voltammogram revealed a reversible, two-electron peak occurring at – 1.17 V (vs. Ag/AgCl/KCl (sat.)), consistent with the previously published data.[65]

Figure 4.1: the cyclic voltammogram for disalt **4.2**. Conditions used were a glassy carbon working electrode, platinum counter electrode, Ag/AgCl/KCl (sat.) reference electrode, 0.1M TBAHFP/DMF electrolyte, 50 mV/s scan rate.



To examine the catalytic behaviour of disalt **4.2** when an appropriate potential was applied, substrate **4.4** was synthesised by alkylation of 4-iodophenol **4.3** with benzyl bromide using potassium carbonate in *N,N*-dimethylformamide. This procedure afforded iodide **4.4** in excellent yield.

Scheme 4.2: the synthesis of substrate **4.4** from 4-iodophenol **4.3** and benzyl bromide.

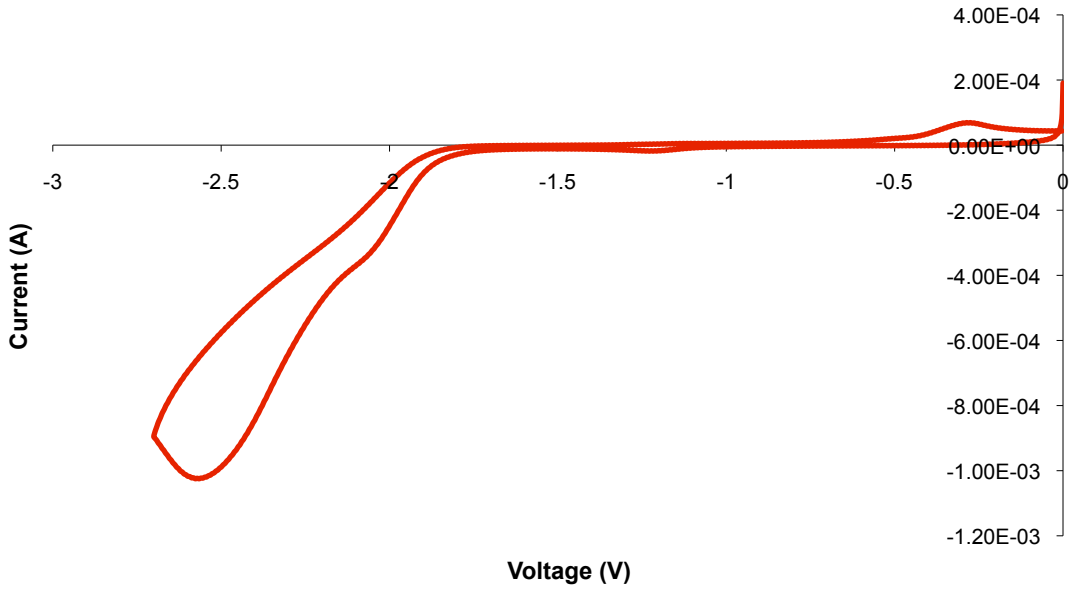


4.3 **4.4**

Reaction conditions: a) benzyl bromide, K_2CO_3, DMF, r.t., 72 h, Ar; **4.4**, 98%.

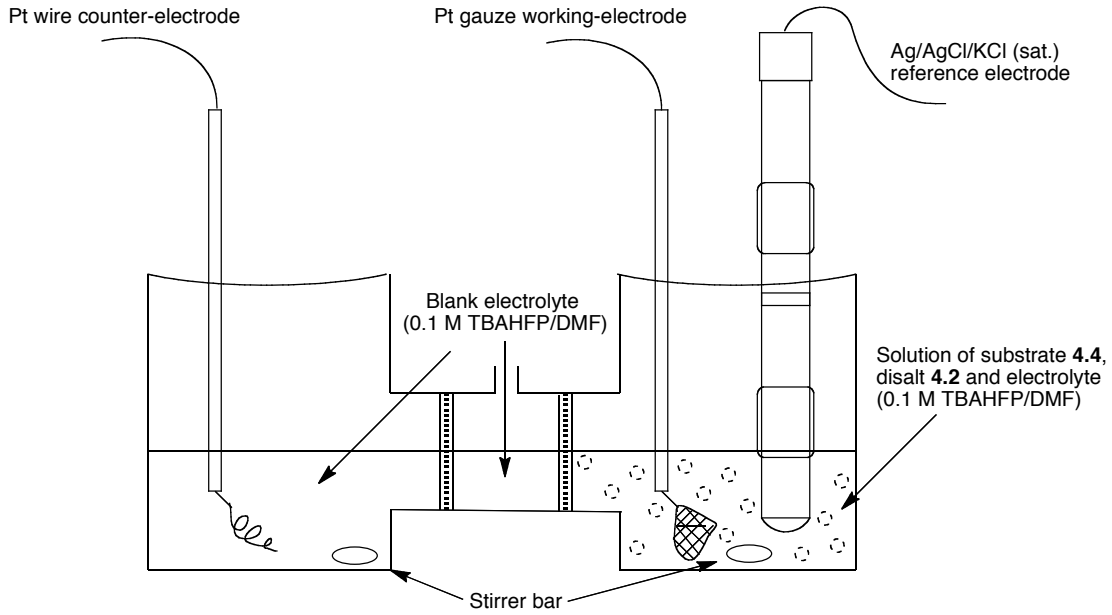
To ensure the compatibility of substrate **4.4** with both the catalyst and the catalytic conditions, the cyclic voltammogram was measured. It was crucial that the substrate could not be directly reduced by application of the potential required to generate the active donor **1.177** from disalt **4.2** (-1.5 V, explained below). Figure 4.2 shows the cyclic voltammogram measured for compound **4.4**. It is clear that reduction of substrate **4.4** only begins to occur electrochemically at approximately -1.8 V (vs. Ag/AgCl/KCl (sat.)). Thus, reduction of substrate **4.4** will not occur under an applied potential of -1.5 V and the substrate would be compatible for testing under catalytic conditions mediated by donor **1.177** generated from disalt **4.2** at -1.5 V.

Figure 4.2: the cyclic voltammogram for substrate **4.4**. Conditions used were a glassy carbon working electrode, platinum counter electrode, Ag/AgCl/KCl (sat.) reference electrode, 0.1M TBAHFP/DMF electrolyte, 50 mV/s scan rate.



With the synthesis of disalt **4.2** and substrate **4.4** in hand, the development of a catalytic procedure was attempted. As with previous attempts, the conditions used were a platinum counter-electrode and platinum-gauze working-electrode, together with a Ag/AgCl/KCl (sat.) reference electrode and the electrolyte used was 0.1 M *tetra*-butylammonium hexafluorophosphate in *N*,*N*-dimethylformamide. The applied potential was -1.5 V, a value chosen as it was significant enough to completely generate donor **1.177**, from disalt **4.2** (see figure 4.1). Finally, a three-compartment cell was used. Each main compartment was attached to a sinter, which led to a small chamber that also contained blank electrolyte. This small third chamber acted to minimise diffusion between the working and counter compartments. A schematic diagram of this apparatus is shown in figure 4.3. The results obtained using these conditions are detailed in section 4.2.

Figure 4.3: the apparatus used for the mediated electrochemistry investigations. All electrodes were connected to the Autolab potentiostat using electrical cable.

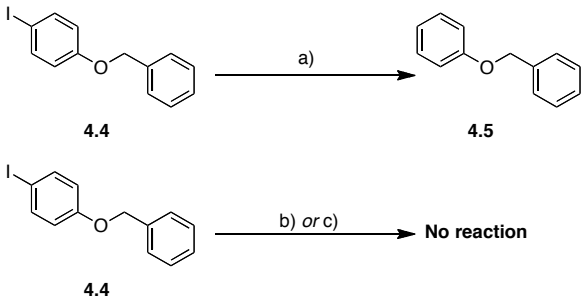


Section 4.2

Development of the reaction – the use of proton sources

Initially, control experiments were performed in order to establish the validity of the methodology in terms of whether the substrate **4.4** was reduced in the absence of donor **1.177**, or in the absence of applied potential to generate donor **1.177** from disalt **4.2**, or if donor **1.177** could reduce substrate **4.4** stoichiometrically (scheme 4.3).

Scheme 4.3: control reactions to test the validity of the proposed catalytic process.



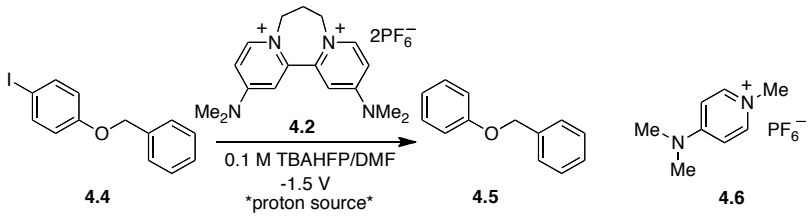
Reaction conditions: a) i) salt **1.176** (1.5 eq.), NaH (15.0 eq.), DMF, r.t., 4 h, Ar *then added to substrate* ii) iodide **4.4**, Ar, 18 h, r.t.; **4.5**, 75%; b) disalt **4.2** (0.1 eq.), TBAHFP/DMF (0.1 M), r.t., 24 h, Ar; recovered starting material **4.4**, 99%; c) TBAHFP/DMF (0.1 M), -1.5 V, r.t., 24 h, Ar; recovered starting material **4.4**, 97%.

First of all, the stoichiometric reduction of substrate **4.4** was examined. Using precursor salt **1.176** and sodium hydride to generate donor **1.177** *in situ*, substrate **4.4** was reduced to the corresponding (benzyloxy)benzene product **4.5** in good yield (scheme 4.3). The isolation of **4.5** not only provided evidence that donor **1.177** could reduce substrate **4.4** but also provided a sample of **4.5** that could be used to acquire data and compare all subsequent results with. Next, substrate **4.4** was exposed to a sub-stoichiometric amount of disalt **4.2** in a 0.1 M solution of electrolyte with no applied potential – a set of conditions designed to mimic the likely conditions required for a catalytic process. No reduction to product **4.5** was observed, with the starting material recovered in high yield (99%, scheme 4.3). The final control experiment involved the application of a potential (-1.5 V), in the electrolyte solution with no added donor **1.177** or disalt **4.2**. These conditions were used to determine the effect of the applied potential on the substrate. Although the

cyclic voltammogram had shown that the reduction potential of substrate **4.4** was significantly more negative than the applied potential (see figure 4.2), it was considered that it was necessary to check whether under the conditions of a different electrode and longer exposure to an applied potential, the substrate **4.4** could be reduced. In any case, no reduction to product **4.5** was observed, with once more high recovery of starting material **4.4** observed (97%, scheme 4.3).

Efforts now focussed on screening a variety of proton sources to determine their suitability in this reaction set-up (table 4.1).

Table 4.1: the screening of various proton sources for the catalytic reduction of substrate **4.4** to product **4.5** using disalt **4.2**.



Attempt No.	Catalyst loading (mol%)	Proton source (eq.)	^{1}H NMR ratio		Calculated yield (%)	
			4.4	4.5	4.4	4.5
1	10	-	85	15	81	15
2	10	*tert*-butanol (10)	85	15	78	14
3	10	*tert*-butanol (50)	87	13	82	12
4	10	$(CF_3)_2CHOH$	97	3	92	3
5	10	phenol	100	0	97	0
6	10	succinimide	100	0	97	0
7	10	diisopropylamine	88	12	80	10
8	10	salt **4.6**	89	11	82	10
9	20	-	74	26	72	26
10	20	*tert*-butanol (5)	74	26	62	22

Reaction conditions: disalt **4.2** (10 or 20 mol%), proton source (as above), 0.1 M TBAHFP in DMF, -1.5 V, 24 h, r.t., N_2.

The following discussion involves the ^{1}H NMR conversion only (based upon comparison of the integral at δ 5.05 ppm of **4.4** and at δ 5.10 ppm of **4.5**). For

completeness, the representative yields of starting material **4.4** and product **4.5** are shown in table 4.1. Initially, the reaction was attempted using no proton source, with just 10 mol% of disalt **4.2** used (*attempt 1*). This reaction would indicate whether disalt **4.2** could be used to generate donor **1.177** and turnover in a catalytic cycle. Pleasingly, the characteristic dark purple colour for donor **1.177**[65] was immediately observed once the appropriate potential of -1.5 V had been reached and a ^{1}H NMR conversion of 15% was observed for the conversion of **4.4** to **4.5**. Thus it is clear that some electrochemical regeneration is occurring. The next attempt included excess *tert*-butanol as proton source in order to quench the intermediate aryl anion formed following cleavage of the iodide on compound **4.4**. However, conversion to **4.5** remained much the same as in *attempt 1* at 15%. When the quantity of *tert*-butanol was increased from 10 equivalents to 50 equivalents, conversion to product **4.5** decreased to 13% (*attempt 3*). Attempts to use different proton sources unfortunately led to disappointing results. The use of 1,1,1,3,3,3-hexafluoroisopropanol resulted in a conversion of just 3% (*attempt 4*). It was immediately obvious that the additive had interfered in the catalytic cycle, as the dark purple colour representative of donor **1.177** did not appear for 3-4 h. This is due to the highly acidic nature of the proton source. The use of phenol (*attempt 5*) and succinimide (*attempt 6*) were completely unsuccessful in that no conversion to product **4.5** was observed in either attempt, again indicating that both are too acidic to be compatible with donor **1.177**. Curiously, the characteristic dark purple colour was present in these cases. Diisopropylamine was also utilised as a prospective proton source (*attempt 7*). However, conversion to product **4.5** was relatively low at 12% meaning it is possible that no catalysis was occurring and stoichiometric reduction of substrate **4.4** was responsible for such a conversion. As discussed in section 4.1, Garnier[68,155] had shown that the primary proton source in the reduction of aryl halides by donor **1.177** was the dication structure (*e.g.*, **4.2**). It is this situation that this study is aiming to resolve, as the deprotonation of disalt **4.2** interferes with the catalytic cycle. It was proposed that the use of salt **4.6**[156] as a proton source could address this problem. This would provide a readily available proton source that could protonate the intermediate aryl anion, meaning that disalt **4.2** would be principally participating in the catalytic cycle. Unfortunately, no real improvement in conversion to product **4.5** was observed (*attempt 8*). The final two attempts focussed on increasing the catalyst loading to 20 mol% in order to ascertain whether the lack of catalytic activity was due to a lack of available catalyst

(*attempts 9* and *10*). In each case 26% conversion to product **4.5** was observed. Disappointingly, the catalytic efficiency was lower when a higher "catalyst" loading was applied (*attempts 9* and *10*) with 20 mol% of **4.2** resulting in 26% conversion to product **4.5**, compared with 10 mol% of **4.2** affording a conversion to product **4.5** of 15% (*attempts 1* and *2*). The full results are shown in table 4.1 above.

Thus it is clear from the data in table 4.1 that attempts to introduce a proton source into the reaction mixture for the catalytic reduction of aryl halides have so far been unsuccessful. It is clear that selection of a suitable proton source depends not only on the ability of the additive to lose a proton to an aryl anion, but also in being of a specific acidity so as not to interfere in the catalytic cycle by protonation of the donor **1.177**. It is possible that the reasons behind the low conversions in *attempts 4-6* in table 4.1 are because the additives were too acidic. The most successful set of conditions was using either no proton source (*attempt 1*) or ten equivalents of *tert*-butanol (*attempt 2*), together with 10 mol% of disalt **4.2**. This represents a yield of 150% based on the amount of **4.2** used.

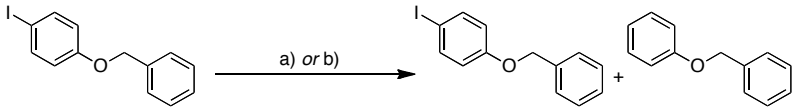
The development of a catalytic procedure using donor **1.177** is a significant challenge and should be the focus of future research.

Section 4.3

Conclusions and future work

In sections 4.1 and 4.2, the basis for the development of a catalytic procedure utilising disalt **4.2** (as the precursor for donor **1.177**) in the reduction of aryl iodide **4.4** was disclosed. Unfortunately, successful catalysis with multiple turnovers has not been achieved yet. The most successful result achieved thus far involved the use of either no proton source, or ten equivalents of *tert*-butanol, together with 10 mol% of disalt **4.2**, affording a 15% conversion to product **4.5** (scheme 4.4). This represents a yield of 150% based on the amount of **4.2** used. Attempts with other proton sources were unsuccessful. The likely reason for this is the inherent acidity of the proton sources used. If the proton source is too acidic it can interfere with the catalytic cycle between donor **1.177** and disalt **4.2**.

Scheme 4.4: the most successful catalytic reaction involving disalt **4.2** to generate donor **1.177**, and reduce substrate **4.4** to product **4.5**.



4.4 **4.4** **4.5**

Reaction conditions: a) disalt **4.2** (10 mol%), 0.1 M TBAHFP in DMF, -1.5 V, 24 h, r.t., N_2; 15% conversion to **4.5**; b) disalt **4.2** (10 mol%), *tert*-butanol (10 eq.), 0.1 M TBAHFP in DMF, 24 h, -1.5 V, r.t., N_2; 15% conversion to **4.5**.

Clearly, further experiments are required to develop a workable catalytic procedure with multiple turnovers for the reduction of aryl halides such as **4.4**. It is challenging to suggest further proton sources that may be compatible with donor **1.177** but the employment of a suitable proton source must be a future consideration. It is also worth considering different materials for the working electrode, a suggestion also offered by Park.[154] Although fouling of the working electrode was not observed directly during this work, during electrode cleaning the electrode burned with a flame, indicating that some organic material may have fouled the electrode. Thus alternative electrode materials may lead to a more successful catalytic process.

Chapter 5

Experimental procedures for chapters 2, 3 and 4

General Experimental

^{1}H NMR spectra were recorded at 400.13 MHz on a Bruker DPX 400 or AV400 spectrometer, or at 500.13 MHz on a Bruker DRX 500 spectrometer. ^{13}C NMR spectra were recorded at 100.6 MHz or 125.6 MHz on the same spectrometers using a broadband decoupled mode. JMOD spectra were used to determine the multiplicities of the carbon resonances. Experiments were carried out using deuterochloroform ($CDCl_3$) or dimethyl sulfoxide-d^6 (DMSO) unless otherwise stated and chemical shifts are reported in parts per million (ppm). Coupling constants *J* are reported in Hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Infrared spectra were recorded on a Perkin Elmer "spectrum One FT-IR" spectrometer. Melting points were recorded using a Gallemkamp 2C 7065 melting point apparatus. Mass spectra were carried out at the University of Wales, Swansea in the EPSRC National Mass Spectrometry centre. Accurate mass was obtained using electron impact (EI), chemical ionisation (CI) or electrospray ionisation (ESI) with a QUATTRO mass spectrometer. Low-resolution mass spectrometry was carried out at the University of Strathclyde using either Finnigan LCQ duo ESI or Finnigan Polaris Q GC-MS.

Column chromatography was performed using Prolabo 35-75 μm particle silica gel 60 (200-400 mesh). Reactions were followed using thin layer chromatography (TLC) carried out on Merck silica gel 60 F_{254} precoated aluminium plates. Visualisation was achieved under UVP mineralight UVG-11 lamp and/or by developing plates with methanolic vanillin or potassium permanganate solutions.

All reagents were obtained from commercial suppliers. Tetrahydrofuran, dichloromethane, hexane, diethyl ether and toluene were dried and deoxygenated with a Pure-Solv 400 solvent purification system (Innovative Technology Inc., USA). Acetonitrile was distilled over phosphorus pentoxide prior to use. *N,N*-Dimethylformamide was obtained from commercial suppliers as anhydrous (99.8%)

and used directly. Sodium amalgam was prepared fresh for each reaction, with sodium and mercury obtained from commercial suppliers.

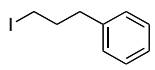
Karl Fischer analysis was performed using a Mettler Toledo DL39D coulometer.

Cyclic voltammetry was performed in a nitrogen-filled glovebox. A glassy carbon working electrode with a diameter of 7 mm was used (surface area of 38.48 mm^2). Prior to use, the electrode was cleaned using 1 micron alumina polish and distilled water on a Bueller polishing cloth and dried under compressed air. Alternatively, a Pt working electrode was used which was cleaned in the same way. The counter electrode consisted of a fine Pt wire, which was cleaned thoroughly prior to use by heating in a flame for 5 minutes and allowing to cool. Potentials are quoted with respect to the Ag/AgCl/sat. KCl reference electrode, in contact with a 0.1 M electrolyte solution in DMF. This electrode has a potential of +0.199 V vs. the standard hydrogen electrode (SHE) at 25 °C. For cyclic voltammetry, the electrolyte used was either tetrabutylammonium hexafluorophosphate or tetramethylammonium hexafluorophosphate as a 0.1 M solution in DMF, with the concentration of all substrate solutions 0.01 M. Ferrocene of equal concentration was used as an external reference. Under these conditions, ferrocene has a reversible peak at +0.55 V. Cyclic voltammograms were obtained using an Eco Chemie B. V. Autolab type III potentiostat/galvenstat system, with General Purpose Electrochemical System (GPES) software for data interpretation.

Electrochemically-mediated reductions were performed using the same apparatus as described above for cyclic voltammetry, with the exception of the working electrode. A Pt gauze working electrode was used, which was cleaned thoroughly prior to use by heating in a flame for 5 mins and allowing to cool. The potential was set at -1.5 V (within the amperometry programme) using the Eco Chemie B.V. Autolab type III system, for the duration of the reactions.

Experimental for Chapter 2

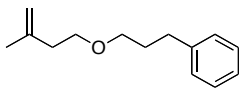
1-Iodo-3-phenylpropane **2.8**



2.8

1-Bromo-3-phenylpropane **2.7** (1.53 ml, 10.05 mmol, 1.0 equiv.) was dissolved in acetone (25 ml) and sodium iodide (7.53 g, 50.25 mmol, 5.0 equiv.) added. The white suspension was heated to reflux and stirred for 64 h before being cooled and the solvent removed under vacuum. The residue was suspended in diethyl ether (100 ml) and washed with water (100 ml), sodium thiosulfate solution (100 ml) and brine (100 ml), before being dried over sodium sulfate and concentrated to afford the title compound **2.8** as a clear colourless oil (2.52 g, 97%);[157] υ_{max} (neat/cm^{-1}) 3084, 3061, 3025, 2933, 2853, 1602, 1495, 1453; δ_H ($CDCl_3$, 400 MHz) 2.16-2.23 (2H, m, CH_2), 2.79 (2H, t, *J* 7.4, CH_2), 3.23 (2H, t, *J* 6.8, CH_2), 7.25-7.28 (3H, m, ArH), 7.33-7.37 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 6.8 (CH_2), 35.4 (CH_2), 36.8 (CH_2), 126.7 (CH), 129.0 (CH), 129.1 (CH), 141.0 (C); *m/z* (EI) 246 ([M]$^-$, 8%), 127 (25), 91 (100).

1-[3-(3-Methylbut-3-enyloxy)propyl]benzene **2.5**

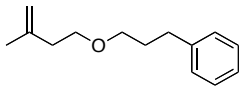


2.5

Sodium hydride (60% in oil, 326 mg, 8.13 mmol, 1.0 equiv.) was washed with hexane and dried, then suspended in dry tetrahydrofuran (15 ml). To this, 3-methyl-3-butenol (0.99 ml, 9.76 mmol, 1.2 equiv.) was added and the resultant orange suspension stirred under argon at room temperature for 1 h. The reaction mixture was cooled to 0 °C and a solution of 1-iodo-3-phenylpropane **2.8** (2.0 g, 8.13 mmol, 1.0 equiv.) in tetrahydrofuran (10 ml) added. The resultant reaction mixture was warmed to room temperature and stirred under argon for 18 h. Water (5 ml) was added to quench the reaction mixture and the solvent removed under vacuum. The residue was diluted with water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (4 x 100 ml) and brine (100 ml), then dried and concentrated *in vacuo*. Purification on silica gel eluting with

0-3% ethyl acetate in petroleum ether afforded the *title compound* **2.5** as a colourless oil (408 mg, 25%); [Found: $[M+NH_4]^+$, 222.1852. $C_{14}H_{20}O$ requires $[M+NH_4]^+$, 222.1856]; υ_{max} (neat/cm^{-1}) 3064, 3027, 2938, 2860, 1650, 1603, 1497, 1454; δ_H ($CDCl_3$, 500 MHz) 1.79 (3H, s, CH_3), 1.91-1.95 (2H, m, CH_2), 2.34 (2H, t, *J* 6.9, CH_2), 2.72 (2H, t, *J* 7.0, CH_2), 3.47 (2H, t, *J* 6.4, CH_2), 3.56 (2H, t, *J* 7.0, CH_2), 4.77 (1H, m, *H*CH=C), 4.81 (1H, m, HC*H*=C), 7.21-7.23 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 23.0 (CH_3), 31.5 (CH_2), 32.6 (CH_2), 38.1 (CH_2), 69.6 (CH_2), 70.2 (CH_2), 111.6 (CH_2), 126.0 (CH), 128.5 (CH), 128.7 (CH), 142.5 (C), 143.3 (C); *m/z* (CI) 222 ($[M+NH_4]^+$, 80%), 205 (100).

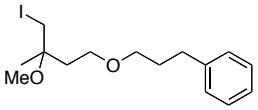
1-[3-(3-Methylbut-3-enyloxy)propyl]benzene **2.5** (improved synthesis)



2.5

Sodium hydride (60% in oil, 1.12 g, 27.86 mmol, 1.2 equiv.) was washed with hexane and dried, then suspended in dry *N,N*-dimethylformamide (20 ml). To this, 3-methyl-3-butenol (2.36 ml, 23.22 mmol, 1.0 equiv.) was added and the resultant orange suspension stirred under argon at room temperature for 1 h. The reaction mixture was cooled to 0 °C and 1-bromo-3-phenylpropane **2.7** (3.53 ml, 23.22 mmol, 1.0 equiv.) added. The resultant reaction mixture was warmed to room temperature and stirred under argon for 18 h. Water (5 ml) was added to quench the reaction mixture and the organic residue extracted with diethyl ether (3 x 75 ml). The combined organic layers were washed with water (4 x 75 ml) and brine (75 ml), then dried and concentrated *in vacuo*. Purification on silica gel eluting with 5% diethyl ether in petroleum ether afforded the *title compound* **2.5** as a colourless oil (2.43 g, 51%); the data were consistent with those described above; δ_H ($CDCl_3$, 500 MHz) 1.79 (3H, s, CH_3), 1.91-1.95 (2H, m, CH_2), 2.34 (2H, t, *J* 6.9, CH_2), 2.72 (2H, t, *J* 7.0, CH_2), 3.47 (2H, t, *J* 6.4, CH_2), 3.56 (2H, t, *J* 7.0, CH_2), 4.77 (1H, m, *H*CH=C), 4.81 (1H, m, HC*H*=C), 7.21-7.23 (3H, m, ArH), 7.28-7.32 (2H, m, ArH).

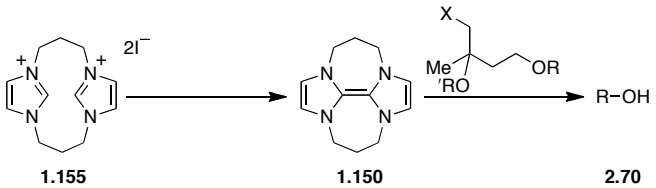
1-[3-(4-Iodo-3-methoxy-3-methylbutoxy)propyl]benzene **2.1**



2.1

1-[3-(3-Methylbut-3-enyloxy)propyl]benzene **2.5** (1.40 g, 6.85 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (30 ml) and anhydrous methanol (0.55 ml, 13.70 mmol, 2.0 equiv.) was added. The solution was cooled to –78 °C and *N*-iodosuccinimide (2.31 g, 10.28 mmol, 1.5 equiv.) added in one portion. The resultant suspension was stirred at –78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (20 ml) was added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (3 x 60 ml) and the combined organic layers then washed with water (3 x 50 ml) and brine (50 ml), dried with Na_2SO_4, filtered and concentrated. Purification on silica gel, eluting with 0-15% diethyl ether in petroleum ether, afforded the *title compound* **2.1** as a light brown oil (1.75 g, 71%); [Found: $[M+H]^+$, 363.0815. $C_{15}H_{23}IO_2$ requires $[M+H]^+$, 363.0862]; υ_{max} (neat/cm^{-1}) 3061, 3025, 2939, 2863, 1602, 1496, 1454, 1374; δ_H ($CDCl_3$, 500 MHz) 1.40 (3H, s, CH_3), 1.93-2.08 (4H, m, 2 x CH_2), 2.76 (2H, t, *J* 7.9, CH_2), 3.28 (3H, s, CH_3), 3.38 (1H, d, *J* 10.8, CH_2I), 3.43 (1H, d, *J* 10.8, CH_2I), 3.49 (2H, t, *J* 6.4, CH_2), 3.56 (2H, t, *J* 6.8, CH_2) 7.24-7.27 (3H, m, ArH), 7.33-7.37 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 16.4 (CH_2), 23.0 (CH_3), 31.5 (CH_2), 32.6 (CH_2), 36.8 (CH_2), 49.7 (CH_3), 66.9 (CH_2), 70.4 (CH_2), 74.1 (C), 125.9 (CH), 128.5 (CH), 128.7 (CH), 142.2 (C); *m/z* (CI) 363 ($[M+H]^+$, 20%), 222 (65), 91 (100).

General Procedure A - General procedure for the reduction of aliphatic halides

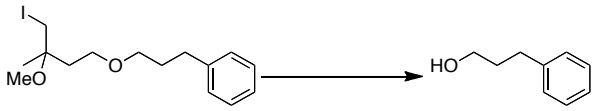


1.155 **1.150** **2.70**

Imidazole-derived salt **1.155** (319 mg, 0.68 mmol, 1.5 equiv.) was dried under vacuum at 100 °C for 1 h then cooled and purged with argon. Sodium hydride (60%

in mineral oil, 271 mg, 6.75 mmol, 15.0 equiv.) was added and the solid mixture washed with anhydrous hexane (2 x 20 ml) and dried under a stream of argon. *N,N*-Dimethylformamide (15 ml) was added, causing a yellow suspension to form, which was stirred under argon at room temperature for 4 h. After this time, the yellow donor suspension was centrifuged at 2000 rpm for 10 min to afford a yellow orange solution. This solution was added *via* cannula to the appropriate substrate (0.45 mmol, 1.0 equiv.). In general, a colour change to dark red was observed after less than 15 min, and the solution was stirred under argon at room temperature for 18 h. The dark solution was then diluted with water (50 ml) and then extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with water (4 x 50 ml) and brine (50 ml), dried and concentrated. Purification by silica gel chromatography eluting with 0-25% diethyl ether in petroleum ether afforded the corresponding alcohol **2.70** product.

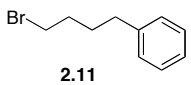
Reaction of donor **1.150** with 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propyl] benzene **2.1**



2.1 **2.6**

Using general procedure A, 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propyl]benzene **2.1** (163 mg, 0.45 mmol, 1.0 equiv.) afforded 3-phenylpropan-1-ol **2.6** as a colourless oil (42 mg, 70%);[158] [Found: $[M]^+$, 136.0883. $C_9H_{12}O$ requires $[M]^+$, 136.0883]; υ_{max} (neat/cm^{-1}) 3349, 3085, 3027, 2939, 2863, 1667, 1496, 1454; δ_H ($CDCl_3$, 500 MHz) 1.89-2.02 (2H, m, CH_2), 2.74 (2H, t, *J* 7.9, CH_2), 3.70 (2H, t, *J* 6.5, CH_2), 7.21-7.25 (3H, m, ArH), 7.28-7.34 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 32.1 (CH_2), 34.2 (CH_2), 62.3 (CH_2), 125.9 (CH), 128.3 (CH), 128.5 (CH), 141.8 (C); *m/z* (EI) 136 ($[M]^+$, 14%), 117 (55), 91 (100), 77 (42).

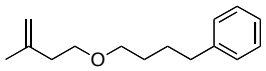
1-Bromo-4-phenylbutane **2.11**



2.11

4-Phenyl-1-butanol **2.10** (3.076 ml, 19.97 mmol, 1.0 equiv.) was dissolved in dry diethyl ether (20 ml) and cooled to -5 °C where phosphorus tribromide (0.939 ml, 9.99 mmol, 0.5 equiv.) was added (temperature maintained below 0 °C for duration of addition). The clear solution was stirred under argon for 18 h and the colour changed from colourless to orange during the reaction time. The orange solution was quenched by slowly pouring into water and the organic residue extracted with diethyl ether (100 ml), then washed with water (3 x 50 ml) and brine (50 ml), then dried and concentrated *in vacuo*. Purification by silica gel chromatography, eluting with 0-5% ethyl acetate in petroleum ether, afforded the *title compound* **2.11** as a colourless oil (2.55 g, 60%);[159] [Found: $[M]^+$, 212.0195. $C_{10}H_{13}Br$ requires $[M]^+$, 212.0195]; υ_{max} (neat/cm^{-1}) 3026, 2937, 2858, 1603, 1496, 1453; δ_H ($CDCl_3$, 500 MHz) 1.79-1.83 (2H, m, CH_2), 1.91-1.95 (2H, m, CH_2), 2.68 (2H, t, *J* 7.6, CH_2), 3.45 (2H, t, *J* 6.7, CH_2), 7.20-7.24 (3H, m, ArH), 7.28-7.34 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 29.8 (CH_2), 32.3 (CH_2), 33.7 (CH_2), 34.9 (CH_2), 125.9 (CH), 128.3 (CH), 128.5 (CH), 141.8 (C); *m/z* (EI) 214 ($[M]^+$, ^{81}Br, 100%), 212 (^{79}Br, 95), 133 (73), 132 (61).

1-[4-(3-Methylbut-3-enyloxy)butyl]benzene **2.12**

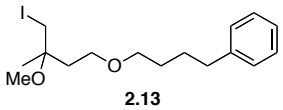


2.12

Sodium hydride (60% in mineral oil, 497 mg, 12.39 mmol, 1.2 equiv.) was washed with hexane and dried, then suspended in *N,N*-dimethylformamide (7 ml). To this, 3-methyl-3-butenol (1.05 ml, 10.32 mmol, 1.0 equiv.) was added and the resultant orange suspension stirred under argon at room temperature for 1 h. The reaction mixture was cooled to 0 °C and 1-bromo-4-phenylbutane **2.11** (2.2 g, 10.32 mmol, 1.0 equiv.) added. The resultant reaction mixture was warmed to room temperature and stirred under argon for 18 h. Water (5 ml) was added to quench, and the reaction mixture was extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with water (4 x 50 ml) and brine (50 ml), then dried and concentrated. Purification by silica gel chromatography eluting with 3-5% diethyl ether in petroleum ether afforded the *title compound* **2.12** as a colourless oil (822 mg, 37%); [Found $[M+NH_4]^+$, 236.2010. $C_{15}H_{22}O$ requires $[M+NH_4]^+$, 236.2009]; υ_{max} (neat/cm^{-1}) 3064, 3027, 2937, 2859, 1650, 1604, 1496, 1453, 888; δ_H ($CDCl_3$, 500 MHz) 1.60-1.73 (4H, m, 2 x CH_2), 1.78 (3H, s, CH_3), 2.32 (2H, t, *J* 7.0, CH_2), 2.66

(2H, t, *J* 7.7, CH_2), 3.47 (2H, t, *J* 6.9, CH_2), 3.54 (2H, t, *J* 6.2, CH_2), 4.75 (1H, m, *H*CH=C), 4.80 (1H, m, HC*H*=C), 7.18-7.21 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 22.8 (CH_3), 28.1 (CH_2), 29.4 (CH_2), 35.7 (CH_2), 37.8 (CH_2), 69.4 (CH_2), 70.8 (CH_2), 111.3 (CH_2), 125.7 (CH), 128.3 (CH), 128.5 (CH), 142.5 (C), 143.0 (C); *m/z* (CI) 236 ($[M+NH_4]^+$, 100%), 219 (94), 91 (40).

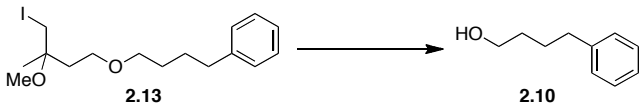
1-[4-(4-Iodo-3-methoxy-3-methylbutoxy)butyl]benzene **2.13**



2.13

1-[4-(3-Methylbut-3-enyloxy)butyl]benzene **2.12** (750 mg, 3.44 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (10 ml) and anhydrous methanol (0.56 ml, 13.76 mmol, 4.0 equiv.) added and cooled to -78 °C. *N*-Iodosuccinimide (1.16 g, 5.16 mmol, 1.5 equiv.) was added in one portion and the resultant suspension stirred for 1 h at -78 °C, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (20 ml) was added, causing a colour change from dark purple to colourless. The organic residue was extracted with dichloromethane (3 x 60 ml) and the combined organic layers washed with brine (3 x 50 ml), dried and concentrated. Purification by silica gel chromatography eluting with 10 % diethyl ether in petroleum ether afforded the *title compound* **2.13** as a pale red oil (977 mg, 75%); [Found: $[M+H]^+$, 377.0974. $C_{16}H_{25}IO_2$ requires $[M+H]^+$, 377.0972]; υ_{max} (neat/cm^{-1}) 3061, 3025, 2938, 2861, 1603, 1496, 1454, 1374; δ_H ($CDCl_3$, 500 MHz) 1.33 (3H, s, CH_3), 1.59-1.74 (4H, m, 2 x CH_2), 1.89-2.03 (2H, m, CH_2), 2.65 (2H, t, *J* 7.7, CH_2), 3.22 (3H, s, CH_3), 3.32 (1H, d, *J* 10.8, CH*H*I), 3.36 (1H, d, *J* 10.8, C*H*HI), 3.43 (2H, t, *J* 6.8, CH_2), 3.49 (2H, t, *J* 6.8, CH_2), 7.19-7.24 (3H, m, ArH), 7.27-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 16.2 (CH_2), 22.9 (CH_3), 28.0 (CH_2), 29.4 (CH_2), 35.7 (CH_2), 36.5 (CH_2), 49.5 (CH_3), 66.7 (CH_2), 70.9 (CH_2), 73.8 (C), 125.7 (CH), 128.3 (CH), 128.4 (CH), 142.4 (C); *m/z* (CI) 377 ($[M+H]^+$, 34%), 394 (50), 345 (100).

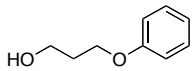
Reaction of donor **1.150** with 1-[4-(4-iodo-3-methoxy-3-methylbutoxy)butyl]benzene **2.13**



2.13 **2.10**

Using general procedure A, 1-[4-(4-iodo-3-methoxy-3-methylbutoxy)butyl]benzene **2.13** (169 mg, 0.45 mmol, 1.0 equiv.) afforded 4-phenylbutan-1-ol **2.10** as a colourless oil (45 mg, 67%);[160] [Found: $[M+NH_4]^+$, 168.1383. $C_{10}H_{14}O$ requires $[M+NH_4]^+$, 168.1383]; υ_{max} (neat/cm^{-1}) 3369, 3069, 3027, 2926, 2856, 1666, 1496, 1453; δ_H ($CDCl_3$, 500 MHz) 1.65-1.72 (4H, m, 2 x CH_2), 2.68 (2H, t, *J* 7.7, CH_2), 3.69 (2H, t, *J* 6.4, CH_2), 7.20-7.22 (3H, m, ArH), 7.28-7.34 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 27.5 (CH_2), 32.3 (CH_2), 35.7 (CH_2), 62.9 (CH_2), 125.8 (CH), 128.3 (CH), 128.4 (CH), 142.3 (C); *m/z* (CI) 168 ($[M+NH_4]^+$, 100%), 104 (30), 91 (18).

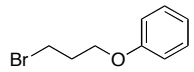
3-Phenoxypropan-1-ol **2.16**



2.16

Phenol **2.14** (5.00 g, 53.13 mmol, 1.0 equiv.) and potassium carbonate (36.00 g, 265.6 mmol, 5.0 equiv.) were stirred together in *N*,*N*-dimethylformamide (100 ml) and 3-bromopropanol (4.65 ml, 53.13 mmol, 1.0 equiv.) added. The resultant white suspension was stirred under an argon atmosphere at room temperature for 64 h. The reaction mixture was then diluted with water (200 ml) and extracted with diethyl ether (200 ml). The diethyl ether solution was washed with water (5 x 80 ml) and brine (100 ml), dried over sodium sulfate then concentrated. Purification by silica gel chromatography eluting with 20-33% ethyl acetate in petroleum ether afforded the title compound **2.16** as a colourless oil (6.16 g, 76%);[161] υ_{max} (neat/cm^{-1}) 3349, 3040, 2950, 1665, 1599, 1496; δ_H ($CDCl_3$, 400 MHz) 2.05-2.10 (2H, m, CH_2), 3.90 (2H, t, *J* 5.9, CH_2), 4.15 (2H, t, *J* 5.9, CH_2), 6.92-7.00 (3H, m, ArH), 7.27-7.33 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 32.0 (CH_2), 60.5 (CH_2), 65.7 (CH_2), 114.5 (CH), 120.9 (CH), 129.5 (CH), 158.7 (C); *m/z* (CI) 170 ($[M+NH_4]^+$, 100%), 153 (20), 152 (15).

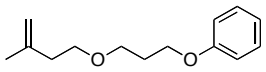
1-(3-Bromopropoxy)benzene **2.18**



2.18

3-Phenoxypropan-1-ol **2.16** (3.0 g, 19.71 mmol, 1.0 equiv.) was dissolved in dry diethyl ether (20 ml) and cooled to -5 °C where phosphorus tribromide (0.649 ml, 6.90 mmol, 0.35 equiv.) was added (temperature maintained below 0 °C for duration of addition). The clear solution was stirred under argon for 18 h at room temperature, during which time a colour change from colourless to orange was observed. The reaction mixture was quenched by slowly pouring into water and the organic residue extracted with diethyl ether (100 ml), then washed with water (3 x 50 ml) and brine (50 ml), dried and concentrated. Purification by silica gel chromatography, eluting with 0-5% ethyl acetate in petroleum ether afforded the title compound **2.18** as a colourless oil (2.69 g, 64%);[162] [Found: $[M]^+$, 213.9990. $C_9H_{11}{}^{79}BrO$ requires $[M]^+$, 213.9988]; υ_{max} (neat/cm^{-1}) 3039, 2928, 1600, 1498, 1387; δ_H ($CDCl_3$, 400 MHz) 2.35 (2H, quintet, *J* 6.2, CH_2), 3.64 (2H, t, *J* 6.4, CH_2), 4.14 (2H, t, *J* 5.8, CH_2), 6.92-7.00 (3H, m, ArH), 7.28-7.34 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 30.0 (CH_2), 32.4 (CH_2), 65.2 (CH_2), 114.5 (CH), 120.9 (CH), 129.5 (CH), 158.7 (C); *m/z* (EI) 216 ($[M]^+$, ^{81}Br, 12%), 214 ($[M]^+$, ^{79}Br, 12%), 94 (100).

1-[3-(3-Methylbut-3-enyloxy)propoxy]benzene **2.20**

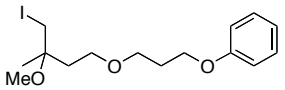


2.20

Sodium hydride (60% in mineral oil, 447 mg, 11.16 mmol, 1.2 equiv.) was washed with hexane and dried under a stream of argon, then suspended in *N,N*-dimethylformamide (10 ml). To this, 3-methyl-3-butenol (0.95 ml, 9.30 mmol, 1.0 equiv.) was added and the resultant orange suspension stirred at room temperature for 1 h. The reaction mixture was then cooled to 0 °C where 1-(3-bromopropoxy)benzene **2.18** (2.0 g, 9.30 mmol, 1.0 equiv.) was added and the resultant reaction mixture stirred under argon at room temperature for 18 h. Water was added to quench and the reaction mixture extracted with diethyl ether (3 x 50

ml). The combined organic layers were washed with water (4 x 50 ml) and brine (50 ml), dried and concentrated. Purification by silica gel chromatography eluting with 5% diethyl ether in petroleum ether afforded the *title compound* **2.20** as a colourless oil (303 mg, 15%); [Found: $[M+NH_4]^+$, 238.1800. $C_{14}H_{20}O_2$ requires $[M+NH_4]^+$, 238.1802]; υ_{max} (neat/cm^{-1}) 3065, 3029, 2934, 2858, 1650, 1601, 1497, 1470, 888; δ_H ($CDCl_3$, 500 MHz) 1.76 (3H, s, CH_3), 2.07 (2H, quintet, *J* 6.2, CH_2), 2.32 (2H, t, *J* 6.9, CH_2), 3.58 (2H, t, *J* 6.9, CH_2), 3.64 (2H, t, *J* 6.2, CH_2), 4.08 (2H, t, *J* 6.2, CH_2), 4.74 (1H, m, HC*H*=C), 4.79 (1H, m, *H*CH=C), 6.92-6.98 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 22.7 (CH_3), 29.7 (CH_2), 37.8 (CH_2), 64.7 (CH_2), 67.3 (CH_2), 69.5 (CH_2), 111.4 (CH_2), 114.5 (CH), 120.6 (CH), 129.4 (CH), 142.9 (C), 159.0 (C); *m/z* (CI) 238 ($[M+NH_4]^+$, 93%), 221 (64), 133 (100).

1-[3-(4-Iodo-3-methoxy-3-methylbutoxy)propoxy]benzene **2.22**

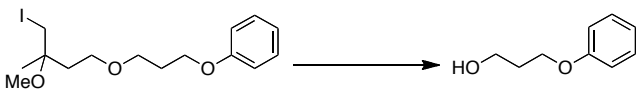


2.22

1-[3-(3-Methylbut-3-enyloxy)propoxy]benzene **2.20** (250 mg, 1.13 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (5 ml) and anhydrous methanol (0.18 ml, 4.54 mmol, 4.0 equiv.) added. The reaction mixture was cooled to -78 °C and *N*-iodosuccinimide (383 mg, 1.70 mmol, 1.5 equiv.) was added in one portion. The resultant suspension was stirred at -78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (10 ml) was added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (3 x 30 ml) and the organic layers combined and washed with brine (3 x 30 ml), dried and concentrated. Purification by silica gel chromatography eluting with 5-10% diethyl ether in petroleum ether afforded the *title compound* **2.22** as a colourless oil (271 mg, 63%); [Found: $[M+NH_4]^+$, 396.1028. $C_{15}H_{23}IO_3$ requires $[M+NH_4]^+$, 396.1030]; υ_{max} (neat/cm^{-1}) 3062, 3029, 2935, 2872, 1600, 1587, 1497, 1470; δ_H ($CDCl_3$, 500 MHz) 1.33 (3H, s, CH_3), 1.93-2.08 (4H, m, 2 x CH_2), 3.21 (3H, s, CH_3), 3.31 (1H, d, *J* 10.8, C*H*HI), 3.35 (1H, d, *J* 10.8, CH*H*I), 3.54 (2H, t, *J* 6.8, CH_2), 3.61 (2H, t, *J* 6.2, CH_2), 4.08 (2H, t, *J* 6.3, CH_2), 6.91-6.98 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 16.2 (CH_2), 22.8 (CH_3), 29.7 (CH_2), 36.5

(CH_2), 49.5 (CH_3), 64.7 (CH_2), 66.9 (CH_2), 67.5 (CH_2), 73.8 (C), 114.5 (CH), 120.6 (CH), 129.4 (CH), 159.0 (C); *m/z* (EI) 378 ([M]$^+$, 100%), 379 (17), 251 (58).

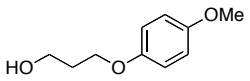
Reaction of donor **1.150** with 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propoxy] benzene **2.22**



2.22 **2.16**

Using general procedure A, 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propoxy]benzene **2.22** (170 mg, 0.45 mmol, 1.0 equiv.) afforded 3-phenoxypropan-1-ol **2.16** as a colourless oil (53 mg, 77%);[161] υ_{max} (neat/cm^{-1}) 3349, 3040, 2950, 1665, 1599, 1496; δ_H ($CDCl_3$, 500 MHz) 2.07 (2H, quintet, *J* 5.9, CH_2), 3.88 (2H, t, *J* 5.9, CH_2), 4.14 (2H, t, *J* 6.0, CH_2), 6.93-7.00 (3H, m, ArH), 7.28-7.33 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 32.0 (CH_2), 60.5 (CH_2), 65.7 (CH_2), 114.5 (CH), 120.9 (CH), 129.5 (CH), 158.7 (C); *m/z* (CI) 170 ([M+NH_4]$^+$, 100%), 153 (20), 152 (15).

3-(4-Methoxyphenoxy)propan-1-ol **2.17**

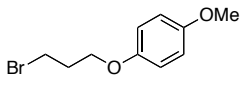


2.17

4-Methoxyphenol **2.15** (3.0 g, 24.17 mmol, 1.0 equiv.), 3-bromopropanol (2.11 ml, 24.17 mmol, 1.0 equiv.) and potassium carbonate (16.7 g, 120.8 mmol, 5.0 equiv.) were stirred together in *N*,*N*-dimethylformamide (30 ml) under argon at room temperature for 64 h. Water (20 ml) was added and the reaction mixture extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with water (5 x 50 ml) and brine (50 ml), then dried and concentrated. Purification by silica gel chromatography eluting with 25-50% ethyl acetate in petroleum ether afforded the title compound **2.17** as a white powder (3.66 g, 83%); m.p. 64-66 °C (lit. 65-66 °C);[163] [Found: [M+NH_4]$^+$, 200.1282. $C_{10}H_{14}O_3$ requires [M+NH_4]$^+$, 200.1281]; υ_{max} (KBr disc/cm^{-1}) 3348, 3089, 2970, 2832; δ_H ($CDCl_3$, 500 MHz) 2.04 (2H, quintet, *J* 5.9, CH_2), 3.78 (3H, s, CH_3), 3.88 (2H, t, *J* 5.9, CH_2), 4.09 (2H, t, *J* 5.9, CH_2), 6.82-

6.88 (4H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 32.0 (CH_2), 55.7 (CH_3), 60.8 (CH_2), 66.7 (CH_2), 114.6 (CH), 115.4 (CH), 152.9 (C), 153.9 (C); *m/z* (CI) 200 ($[M+NH_4]^+$, 100%), 183 (38), 124 (20).

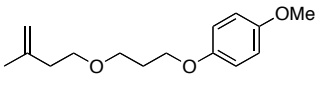
1-(3-Bromopropoxy)-4-methoxybenzene **2.19**



2.19

3-(4-Methoxyphenoxy)propan-1-ol **2.17** (3.0 g, 16.46 mmol, 1.0 equiv.) was dissolved in dry diethyl ether (25 ml) and cooled to -5 °C where phosphorus tribromide (0.78 ml, 8.23 mmol, 0.5 equiv.) was added (temperature maintained below 0°C for duration of addition). The clear solution was stirred under argon for 20 h, during which time a colour change from colourless to orange was observed. The orange solution was quenched by slowly pouring into water and the reaction mixture extracted with diethyl ether (3 x 50 ml). The organic layers were combined then washed with water (2 x 50 ml) and brine (50 ml), dried and concentrated. Purification by silica gel chromatography, eluting with 5% ethyl acetate in petroleum ether afforded the title compound **2.19** as a colourless oil (1.97 g, 49%);[164] [Found: $[M+NH_4]^+$, 262.0437. $C_{10}H_{13}{}^{79}BrO_2$ requires $[M+NH_4]^+$, 262.0437); υ_{max} (neat/cm^{-1}) 3044, 2998, 2952, 2833, 1592, 1508, 1441; δ_H ($CDCl_3$, 500 MHz) 2.31 (2H, m, CH_2), 3.62 (2H, t, *J* 6.5, CH_2), 3.78 (3H, s, CH_3), 4.07 (2H, t, *J* 5.8, CH_2), 6.82-6.88 (4H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 30.2 (CH_2), 32.5 (CH_2), 55.7 (CH_3), 66.0 (CH_2), 114.7 (CH), 115.5 (CH), 152.8 (C), 154.0 (C); *m/z* (CI) 264 ($[M+NH_4]^+$, ^{81}Br, 12%), 262 ($[M+NH_4]^+$, ^{79}Br, 12%) 244 (53), 124 (20).

1-[3-(3-Methylbut-3-enyloxy)propoxy]-4-methoxybenzene **2.21**

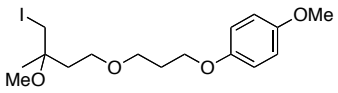


2.21

Sodium hydride (60% in mineral oil, 333 mg, 8.32 mmol, 1.2 equiv.) was washed with hexane and dried, then suspended in *N*,*N*-dimethylformamide (10 ml). To this, 3-methyl-3-butenol (0.70 ml, 6.94 mmol, 1.0 equiv.) was added and the resultant

orange suspension stirred under argon at room temperature for 1 h. The reaction mixture was cooled to 0 °C where 1-(3-bromopropoxy)-4-methoxybenzene **2.19** (1.70 g, 6.94 mmol, 1.0 equiv.) as a solution in *N*,*N*-dimethylformamide (5 ml) was added and the reaction mixture stirred under argon for 18 h. Water (5 ml) was added to quench, and the reaction mixture then extracted with diethyl ether (3 x 40 ml). The combined organic layers were then washed with water (4 x 40 ml) and brine (40 ml), then dried and concentrated. Purification by silica gel chromatography eluting with 0-3% diethyl ether in petroleum ether afforded the *title compound* **2.21** as a colourless oil (343 mg, 20%); [Found: $[M+NH_4]^+$, 268.1910. $C_{15}H_{22}O_3$ requires $[M+NH_4]^+$, 268.1907]; υ_{max} (neat/cm^{-1}) 3074, 2935, 1649, 1598, 1467, 1442, 890; δ_H ($CDCl_3$, 500 MHz) 1.75 (3H, s, CH_3), 2.02-2.05 (2H, m, CH_2), 2.31 (2H, t, *J* 6.9, CH_2), 3.56 (2H, t, *J* 6.9, CH_2), 3.62 (2H, t, *J* 6.2, CH_2), 3.78 (3H, s, CH_3), 4.02 (2H, t, *J* 6.2, CH_2), 4.73 (1H, m, *H*CH=C), 4.78 (1H, m, HC*H*=C), 6.81-6.87 (4H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 22.8 (CH_3), 29.8 (CH_2), 37.8 (CH_2), 55.7 (CH_3), 65.5 (CH_2), 67.4 (CH_2), 69.4 (CH_2), 111.4 (CH_2), 114.6 (CH), 115.6 (CH), 142.9 (C), 153.2 (C), 153.7 (C); *m/z* (CI) 268 ($[M+NH_4]^+$, 40%), 251 (60), 200 (100).

1-[3-(4-Iodo-3-methoxy-3-methylbutoxy)propoxy]-4-methoxybenzene **2.23**

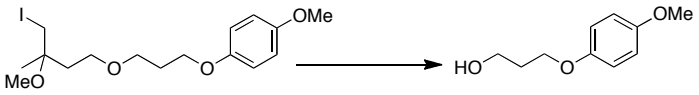


2.23

1-[3-(3-Methylbut-3-enyloxy)propoxy]-4-methoxybenzene **2.21** (250 mg, 1.00 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (5 ml) and anhydrous methanol (0.16 ml, 4.00 mmol, 4.0 equiv.) added. The reaction mixture was cooled to -78 °C and *N*-iodosuccinimide (337 mg, 1.50 mmol, 1.5 equiv.) was added in one portion. The resultant suspension was stirred at -78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (10 ml) was added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (3 x 30 ml) and the organic layers combined and washed with brine (3 x 30 ml), dried and concentrated. Purification by silica gel chromatography eluting with 0-20% diethyl ether in petroleum ether afforded the *title compound* **2.23** as a colourless oil (314 mg, 77%); [Found: $[M+NH_4]^+$, 426.1135. $C_{16}H_{25}IO_4$ requires $[M+NH_4]^+$, 426.1136]; υ_{max} (neat/cm^{-1})

3044, 2934, 2831, 1591, 1495, 1464; δ_H ($CDCl_3$, 500 MHz) 1.32 (3H, s, CH_3), 1.88-2.05 (4H, m, 2 x CH_2), 3.19 (3H, s, CH_3), 3.29 (1H, d, *J* 10.8, C*H*HI), 3.34 (1H, d, *J* 10.8, CH*H*I), 3.52 (2H, t, *J* 6.7, CH_2), 3.59 (2H, t, *J* 6.2, CH_2), 3.77 (3H, s, CH_3), 4.01 (2H, t, *J* 6.2, CH_2), 6.81-6.87 (4H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 16.1 (CH_2), 22.8 (CH_3), 29.8 (CH_2), 36.5 (CH_2), 49.5 (CH_3), 55.7 (CH_3), 65.6 (CH_2), 66.8 (CH_2), 67.6 (CH_2), 73.8 (C), 114.6 (CH), 115.4 (CH), 153.2 (C), 153.8 (C); *m/z* (CI) 426 ($[M+NH_4]^+$, 80%), 408 (65), 394 (100).

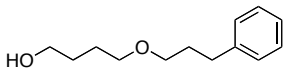
Reaction of donor **1.150** with 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propoxy]-4-methoxybenzene **2.23**



2.23 **2.17**

Using general procedure A, 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propoxy]-4-methoxybenzene **2.23** afforded 3-(4-methoxyphenoxy)propan-1-ol **2.17** as a white solid (53 mg, 63%); m.p. 63-65 °C (lit. 65-66 °C);[163] [Found: $[M+NH_4]^+$, 200.1282. $C_{10}H_{14}O_3$ requires $[M+NH_4]^+$, 200.1281]; υ_{max} (KBr disc/cm^{-1}) 3348, 3089, 2970, 2832; δ_H ($CDCl_3$, 500 MHz) 2.04 (2H, quintet, *J* 5.9, CH_2), 3.78 (3H, s, CH_3), 3.88 (2H, t, *J* 5.9, CH_2), 4.09 (2H, t, *J* 5.9, CH_2), 6.82-6.88 (4H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 32.0 (CH_2), 55.7 (CH_3), 60.8 (CH_2), 66.7 (CH_2), 114.6 (CH), 115.4 (CH), 152.9 (C), 153.9 (C); *m/z* (CI) 200 ($[M+NH_4]^+$, 100%), 183 (38), 124 (20).

4-(3-Phenylpropoxy)butan-1-ol **2.24**

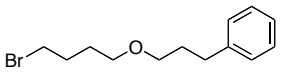


2.24

Sodium hydride (60% in mineral oil, 8.10 g, 200.9 mmol, 4.0 equiv.) was washed with hexane and dried, then suspended in *N*,*N*-dimethylformamide (100 ml) and cooled to 0 °C whereupon 1,4-butanediol (17.8 ml, 200.09, 4.0 equiv.) was added. The resultant orange suspension was warmed to room temperature and stirred under argon for 1 h, then cooled to 0 °C. To this, 1-bromo-3-phenylpropane **2.7** (7.64 ml, 50.22 mmol, 1.0 equiv.) was added drop-wise and the resultant

suspension stirred under argon at room temperature for 4 days. Due to slow rate of reaction, the mixture was heated at 80 °C for 7 days. After this time, the reaction mixture was cooled to room temperature and quenched with water (25 ml). The reaction mixture was concentrated to a reduced volume, then extracted with diethyl ether (3 x 100 ml) and the combined organic layers washed with water (4 x 150 ml) and brine (150 ml), dried and concentrated. Purification by silica gel chromatography eluting with 15-30% ethyl acetate in petroleum ether afforded the *title compound* **2.24** as a colourless oil (6.88 g, 67%); [Found: $[M+H]^+$, 209.1538. $C_{13}H_{20}O_2$ requires $[M+H]^+$, 209.1536]; υ_{max} (neat/cm^{-1}) 3390, 3026, 2939, 2861, 1603, 1496, 1454; δ_H ($CDCl_3$, 500 MHz) 1.69-1.74 (4H, m, 2 x CH_2), 1.91-1.95 (2H, m, CH_2), 2.71 (2H, t, *J* 7.9, CH_2), 3.46-3.50 (4H, m, 2 x CH_2), 3.67-3.70 (2H, m, CH_2), 7.20-7.22 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 26.9 (CH_2), 30.4 (CH_2), 31.2 (CH_2), 32.3 (CH_2), 62.8 (CH_2), 70.1 (CH_2), 70.9 (CH_2), 125.8 (CH), 128.3 (CH), 128.4 (CH), 141.9 (C); *m/z* (CI) 209 ($[M+H]^+$, 100%), 91 (13), 118 (33).

1-[3-(4-Bromobutoxy)propyl]benzene **2.25**

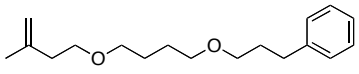


2.25

4-(3-Phenylpropoxy)butan-1-ol **2.24** (3.0 g, 14.40 mmol, 1.0 equiv.) was dissolved in dry diethyl ether (20 ml) and cooled to -5 °C where phosphorus tribromide (0.677 ml, 7.20 mmol, 0.5 equiv.) was added (temperature maintained below 0 °C for duration of addition). The clear solution was stirred under argon for 18 h at room temperature. A colour change from colourless to orange was observed during the reaction time. The orange solution was quenched slowly by addition to water and the organic residue extracted with diethyl ether (100 ml). The organic layer was washed with water (3 x 50 ml) and brine (50 ml), dried and concentrated. Purification by silica gel chromatography eluting with 0-5% ethyl acetate in petroleum ether afforded the *title compound* **2.25** as a colourless oil (2.15 g, 56%); [Found: $[M+NH_4]^+$, 288.0956. $C_{13}H_{19}{}^{79}BrO_2$ requires $[M+NH_4]^+$, 288.0956]; υ_{max} (neat/cm^{-1}) 3026, 2937, 2859, 1602, 1496, 1454; δ_H ($CDCl_3$, 400 MHz) 1.73-1.79 (2H, m, CH_2), 1.90-2.01 (4H, m, 2 x CH_2), 2.71 (2H, t, *J* 7.9, CH_2), 3.42-3.50 (6H, m,

3 x CH_2), 7.21-7.22 (3H, m, ArH), 7.28-7.33 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 28.4 (CH_2), 29.8 (CH_2), 31.3 (CH_2), 32.4 (CH_2), 33.8 (CH_2), 69.8 (CH_2), 70.0 (CH_2), 125.8 (CH), 128.3 (CH), 128.5 (CH), 142.0 (C); *m/z* (CI) 290 ($[M+NH_4]^+$, ^{81}Br, 100%), 288 ($[M+NH_4]^+$, ^{79}Br, 100%), 273 (10), 271 (10).

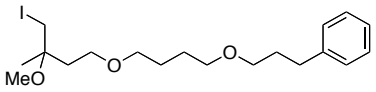
1-{3-[4-(3-Methylbut-3-enyloxy)butoxy]propyl}benzene **2.26**



2.26

Sodium hydride (60% in mineral oil, 177 mg, 4.43 mmol, 1.2 equiv.) was washed with hexane and dried, and then suspended in *N,N*-dimethylformamide (7 ml). To this, 3-methyl-3-butenol (0.38 ml, 3.69 mmol, 1.0 equiv.) was added and the resultant orange suspension stirred under argon at room temperature for 1 h. The reaction mixture was cooled to 0 °C where 1-[3-(4-bromobutoxy)propyl]benzene **2.25** (1.00 g, 3.69 mmol, 1.0 equiv.) as a solution in *N,N*-dimethylformamide (5 ml) was added and the reaction mixture stirred under argon for 18 h. Water (10 ml) was added to quench, and the reaction mixture then extracted with diethyl ether (3 x 50 ml). The combined organic layers were then washed with water (4 x 50 ml) and brine (50 ml), then dried and concentrated. Purification by silica gel chromatography eluting with 0-5% diethyl ether in petroleum ether afforded the *title compound* **2.26** as a colourless oil (334 mg, 33%); [Found: $[M+H]^+$, 277.2164. $C_{18}H_{28}O_2$ requires $[M+H]^+$, 277.2162]; υ_{max} (neat/cm^{-1}) 3075, 3027, 2940, 2859, 1649, 1603, 1496, 1454, 888; δ_H ($CDCl_3$, 500 MHz) 1.66-1.68 (4H, m, 2 x CH_2), 1.77 (3H, s, CH_3), 1.89-1.93 (2H, m, CH_2), 2.32 (2H, t, *J* 6.9, CH_2), 2.71 (2H, t, *J* 7.9, CH_2), 3.42-3.49 (6H, m, 6 x CH_2), 3.55 (2H, t, *J* 7.0, CH_2), 4.75 (1H, m, *H*CH=C), 4.79 (1H, m, HC*H*=C), 7.18-7.21 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 22.8 (CH_3), 26.5 (2 x CH_2), 31.3 (CH_2), 32.4 (CH_2), 37.8 (CH_2), 69.3 (CH_2), 69.9 (CH_2), 70.6 (CH_2), 70.7 (CH_2), 111.3 (CH_2), 125.7 (CH), 128.3 (CH), 128.5 (CH), 142.0 (C), 143.0 (C); *m/z* (CI) 277 ($[M+H]^+$, 100%), 294 (15), 191 (11), 91 (21).

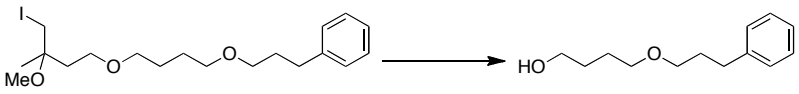
1-{3-[4-(4-Iodo-3-methoxy-3-methylbutoxy)butoxy]propyl}benzene **2.27**



2.27

1-{3-[4-(3-Methylbut-3-enyloxy)butoxy]propyl}benzene **2.26** (250 mg, 0.91 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (5 ml) and anhydrous methanol (0.18 ml, 4.52 mmol, 5.0 equiv.) added. The reaction mixture was cooled to -78 °C and *N*-iodosuccinimide (306 mg, 1.36 mmol, 1.5 equiv.) was added in one portion. The resultant suspension was continued at -78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (10 ml) was added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (3 x 30 ml) and the organic layers combined and washed with brine (3 x 30 ml), dried and concentrated. Purification by silica gel chromatography eluting with 10% diethyl ether in petroleum ether afforded the *title compound* **2.27** as a colourless oil (332 mg, 84%); [Found: $[M+NH_4]^+$, 452.1658. $C_{19}H_{31}IO_3$ requires $[M+NH_4]^+$, 452.1656]; υ_{max} (neat/cm^{-1}) 3061, 3025, 2860, 2799, 1496, 1454, 1374; δ_H ($CDCl_3$, 400 MHz) 1.34 (3H, s, CH_3), 1.65-1.68 (4H, m, 2 x CH_2) 1.89-2.00 (4H, m, 2 x CH_2), 2.71 (2H, t, *J* 7.9, CH_2), 3.22 (3H, s, CH_3), 3.33 (1H, d, *J* 10.8, C*H*HI), 3.36 (1H, d, *J* 10.8, CH*H*I), 3.42-3.46 (6H, m, 3 x CH_2), 3.51 (2H, t, *J* 7.0, CH_2), 7.20-7.22 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 16.3 (CH_2), 22.9 (CH_3), 26.5 (2 x CH_2), 31.3 (CH_2), 32.4 (CH_2), 36.5 (CH_2), 49.5 (CH_3), 66.7 (CH_2), 69.9 (CH_2), 70.6 (CH_2), 70.9 (CH_2), 73.9 (C), 125.8 (CH), 128.3 (CH), 128.5 (CH), 142.1 (C); *m/z* (CI) 435 ($[M+H]^+$, 100%), 403 (55).

Reaction of donor **1.150** with 1-{3-[4-(4-iodo-3-methoxy-3-methylbutoxy)butoxy] propyl}benzene **2.27**

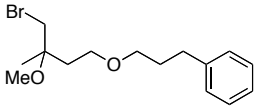


2.27 **2.24**

Using general procedure A, 1-{3-[4-(4-iodo-3-methoxy-3-methylbutoxy)butoxy] propyl}benzene **2.27** afforded 4-(3-phenylpropoxy)butan-1-ol **2.24** as a clear oil (66 mg, 70%); [Found: $[M+H]^+$, 209.1538. $C_{13}H_{20}O_2$ requires $[M+H]^+$, 209.1536]; υ_{max}

(neat/cm^{-1}) 3390, 3026, 2939, 2861, 1603, 1496, 1454; δ_H ($CDCl_3$, 500 MHz) 1.69-1.74 (4H, m, 2 x CH_2), 1.91-1.95 (2H, m, CH_2), 2.71 (2H, t, *J* 7.9, CH_2), 3.46-3.50 (4H, m, 2 x CH_2), 3.67-3.70 (2H, m, CH_2), 7.20-7.22 (3H, m, ArH), 7.28-7.32 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 26.9 (CH_2), 30.4 (CH_2), 31.2 (CH_2), 32.3 (CH_2), 62.8 (CH_2), 70.1 (CH_2), 70.9 (CH_2), 125.8 (CH), 128.3 (CH), 128.4 (CH), 141.9 (C); *m/z* (CI) 209 ([M+H]$^+$, 100%), 91 (13), 118 (33).

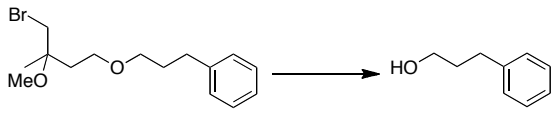
1-[3-(4-Bromo-3-methoxy-3-methylbutoxy)propyl]benzene **2.28**



2.28

1-[3-(3-Methylbut-3-enyloxy)propyl]benzene **2.5** (500 mg, 2.45 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (8 ml) and anhydrous methanol (0.40 ml, 9.80 mmol, 4.0 equiv.) was added. The solution was cooled to –78 °C and *N*-bromosuccinimide (655 mg, 3.68 mmol, 1.5 equiv.) added in one portion. The resultant suspension was stirred at –78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (20 ml) was added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (2 x 50 ml) and the combined organic layers then washed with water (3 x 50 ml) and brine (50 ml), dried with Na_2SO_4, filtered and concentrated. Purification on silica gel, eluting with 0-10% diethyl ether in petroleum ether, afforded the *title compound* **2.28** as a colourless oil (360 mg, 47%); [Found: [M+NH_4]$^+$, 332.1220. $C_{15}H_{23}BrO_2$ requires [M+NH_4]$^+$, 332.1220]; υ_{max} (neat/cm^{-1}) 3062, 3026, 2940, 2864, 1602, 1496, 1455; δ_H ($CDCl_3$, 500 MHz) 1.32 (3H, s, CH_3), 1.88-2.01 (4H, m, 2 x CH_2), 2.70 (2H, t, *J* 7.7, CH_2), 3.23 (3H, s, CH_3), 3.39-3.51 (6H, m, 3 x CH_2), 7.17-7.21 (3H, m, ArH), 7.24-7.31 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 21.9 (CH_3), 31.3 (CH_2), 32.4 (CH_2), 35.9 (CH_2), 39.6 (CH_2), 49.5 (CH_3), 66.4 (CH_2), 70.2 (CH_2), 74.8 (C), 125.8 (CH), 128.3 (CH), 128.5 (CH), 142.0 (C); *m/z* (CI) 317 ([M+H]$^+$, ^{81}Br 20%), 315 ([M+H]$^+$, ^{79}Br 22%), 205 (100).

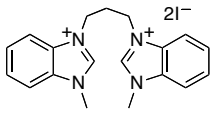
Reaction of donor **1.150** with 1-[3-(4-bromo-3-methoxy-3-methylbutoxy)propyl] benzene **2.28**



2.28 **2.6**

Using general procedure A, 1-[3-(4-bromo-3-methoxy-3-methylbutoxy) propyl]benzene **2.28** (142 mg, 0.45 mmol, 1.0 equiv.) afforded 3-phenylpropan-1-ol **2.6** as a colourless oil (42 mg, 69%);[158] [Found: $[M]^+$, 136.0883. $C_9H_{12}O$ requires $[M]^+$, 136.0883]; υ_{max} (neat/cm^{-1}) 3349, 3085, 3027, 2939, 2863, 1667, 1496, 1454; δ_H ($CDCl_3$, 500 MHz) 1.89-2.02 (2H, m, CH_2), 2.74 (2H, t, *J* 7.9, CH_2), 3.70 (2H, t, *J* 6.5, CH_2), 7.21-7.25 (3H, m, ArH), 7.28-7.34 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 32.1 (CH_2), 34.2 (CH_2), 62.3 (CH_2), 125.9 (CH), 128.3 (CH), 128.5 (CH), 141.8 (C); *m/z* (EI) 136 ($[M]^+$, 14%), 117 (55), 91 (100), 77 (42).

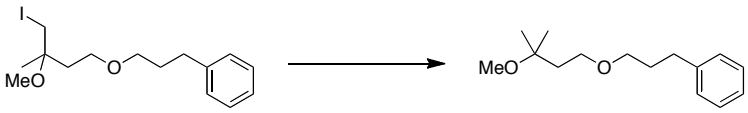
1,3-*bis*[3-Methyl-3*H*-benzimidazolium]propane diiodide (benzimidazole-derived salt) **1.129**



1.129

1-Methyl-*1H*-benzimidazole **1.128** (15.0 g, 113.5 mmol, 2.5 equiv.) and 1,3-diiodopropane (5.21 ml, 45.4 mmol, 1.0 equiv.) were dissolved in acetonitrile (60 ml) and heated under reflux for 96 h. After cooling, the resulting precipitate was collected by filtration and washed with dichloromethane (50 ml). The product salt was ground to a fine powder and washed with further dichloromethane (50 ml) and dried under vacuum to afford the title compound **1.129** as a white free-flowing powder (24.11 g, 95%); the data were consistent with those which had been previously recorded;[54] δ_H (DMSO, 400 MHz) 2.59-2.62 (2H, m, CH_2), 4.08 (6H, s, 2 x CH_3), 4.68 (4H, t, *J* 7.1, 2 x CH_2), 7.68-7.74 (4H, m, ArH), 8.03-8.10 (4H, m, ArH), 9.74 (2H, s, ArH); δ_C (DMSO, 100 MHz) 28.4 (CH_2), 33.8 (CH_3), 44.2 (CH_2), 113.9 (CH), 114.0 (CH), 126.9 (CH), 127.0 (CH), 131.2 (C), 132.2 (C), 143.2 (CH).

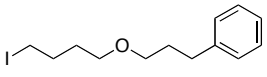
Reaction of donor **1.130** with 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propyl] benzene **2.1**



2.1 **2.3**

1,3-bis[3-Methyl-3*H*-benzimidazolium]propane diiodide **1.129** (672 mg, 1.2 mmol, 4.0 equiv.) was dried under vacuum at 100 °C for 1 h then cooled and sodium hydride (60% in mineral oil, 481 mg, 12.0 mmol, 40.0 equiv.) was added. The solid mixture was washed with hexane and dried, then *N*,*N*-dimethylformamide (5 ml) and toluene (10 ml) were added causing a yellow suspension to form, which was stirred under argon for 4 h at r.t. After this time, the yellow/orange suspension was centrifuged at 2000 rpm for 10 min to afford a yellow/orange solution which was added to 1-[3-(4-iodo-3-methoxy-3-methylbutoxy)propyl]benzene **2.1** (109 mg, 0.3 mmol, 1.0 equiv.) *via* cannula. The resultant solution was stirred under argon for 72 h at reflux. After this time, the reaction mixture was cooled and diluted with water (50 ml), then extracted with diethyl ether (3 x 50 ml), and the combined organic layers washed with water (4 x 50 ml) and brine (50 ml), dried over sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography, eluting with 5-10% ethyl acetate in petroleum ether afforded the *title compound* **2.3** as a light green oil (28 mg, 40%); [Found: $[M+H]^+$, 237.1851. $C_{15}H_{24}O_2$ requires $[M+H]^+$, 237.1849]; υ_{max} (neat/cm^{-1}) 3026, 2928, 2857, 1496, 1454; δ_H ($CDCl_3$, 400 MHz) 1.26 (6H, s, 2 x CH_3), 1.88 (2H, t, *J* 7.3, CH_2), 1.95-1.99 (2H, m, CH_2), 2.76 (2H, t, *J* 7.7, CH_2), 3.27 (3H, s, CH_3), 3.50 (2H, t, *J* 6.4, CH_2), 3.57 (2H, t, *J* 7.3, CH_2), 7.21-7.25 (3H, m, ArH), 7.32-7.38 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 25.5 (CH_3), 31.4 (CH_2), 32.4 (CH_2), 39.2 (CH_2), 49.2 (CH_3), 67.1 (CH_2), 70.2 (CH_2), 73.8 (C), 125.8 (CH), 128.3 (CH), 128.5 (CH), 142.1 (C); *m/z* (CI) 237 ($[M+H]^+$, 65%), 205 (68), 134 (47), 58 (50), 44 (100).

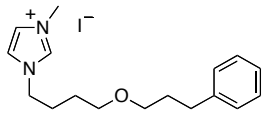
1-[3-(4-Iodobutoxy)propyl]benzene **2.41**



2.41

4-(3-Phenylpropoxy)butan-1ol **2.24** (1.0 g, 4.80 mmol, 1.5 equiv.) was dissolved in dichloromethane (10 ml) at 0 °C and triphenylphosphine (839 mg, 3.20 mmol, 1.0 equiv.), followed by imidazole (218 mg, 3.20 mmol, 1.0 equiv.) and iodine (1.22 g, 4.80 mmol, 1.5 equiv.) added. The dark solution was warmed to room temperature and stirred under argon for 20 h. After this time, the dark solution was diluted with dichloromethane (20 ml) and washed with sodium thiosulfate solution (2 x 50 ml) and brine (50 ml), then dried over sodium sulfate and concentrated onto silica. Purification on silica gel eluting with 10% ethyl acetate in petroleum ether afforded the *title compound* **2.41** as a colourless oil (873 mg, 86%); [Found: $[M+NH_4]^+$, 336.0824. $C_{13}H_{19}IO$ requires $[M+NH_4]^+$, 336.0819]; υ_{max} (neat/cm^{-1}) 3061, 3025, 2937, 2860, 1602, 1496, 1454; δ_H ($CDCl_3$, 400 MHz) 1.58-1.74 (2H, m, CH_2), 1.88-1.99 (4H, m, 2 x CH_2), 2.71 (2H, t, *J* 7.9, CH_2), 3.25 (2H, t, *J* 7.0, CH_2), 3.42-3.47 (4H, m, 2 x CH_2), 7.19-7.22 (3H, m, ArH), 7.28-7.33 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 6.9 (CH_2), 30.5 (CH_2), 30.7 (CH_2), 31.3 (CH_2), 32.4 (CH_2), 69.5 (CH_2), 70.0 (CH_2), 125.8 (CH), 128.3 (CH), 128.5 (CH), 141.9 (C); *m/z* (CI) 336 ($[M+NH_4]^+$, 67%), 319 (50), 208 (100).

4-(3-Methylimidazolium)butyl(3-phenylpropyl) ether **2.42**

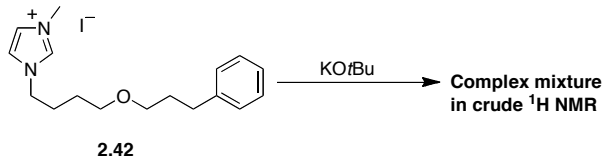


2.42

1-[3-(4-Iodobutoxy)propyl]benzene **2.41** (1.50 g, 4.71 mmol, 1.0 equiv.) and *N*-methylimidazole (0.38 ml, 4.71 mmol, 1.0 equiv.) were dissolved in acetonitrile (15 ml) and heated to reflux for 90 h. After this time, the reaction mixture was cooled and the solvent removed under reduced pressure. The resulting brown residue was washed with diethyl ether (3 x 30 ml) and dried under vacuum to afford the *title compound* **2.42** as a light brown, viscous oil (1.76 g, 94%); [Found: $[M-I]^+$, 273.1959. $C_{17}H_{25}IN_2O$ requires $[M-I]^+$, 273.1961]; υ_{max} (neat/cm^{-1}) 3434, 3082, 2941, 2861, 1570, 1453; δ_H (DMSO, 400 MHz) 1.45-1.50 (2H, m, CH_2), 1.74-1.85 (4H, m, 2 x CH_2), 2.60 (2H, t, *J* 7.7, CH_2), 3.32-3.38 (4H, m, 2 x CH_2), 3.84 (3H, s, CH_3), 4.18 (2H, t, *J* 7.2, CH_2), 7.14-7.19 (3H, m, ArH), 7.25-7.29 (2H, m, ArH), 7.70 (1H, m, ArH), 7.77 (1H, m, ArH), 9.11 (1H, s, ArH); δ_C (DMSO, 100 MHz) 25.8 (CH_2), 26.6 (CH_2), 30.9 (CH_2), 31.7 (CH_2), 35.8 (CH_3), 48.6 (CH_2), 69.2 (CH_2), 69.3 (CH_2), 122.2

(CH), 123.6 (CH), 125.7 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 141.7 (C); *m/z* (ESI) 273 ($[M-I]^+$, 100%), 274 (22).

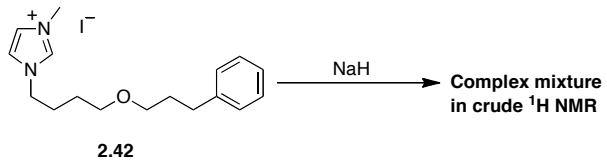
Reaction of 4-(3-methylimidazolium)butyl(3-phenylpropyl) ether **2.42** – attempt 1



2.42

Potassium *tert*-butoxide (35 mg, 0.306 mmol, 1.02 equiv.) was suspended in tetrahydrofuran (1 ml) at -10 °C and a solution of 4-(3-methylimidazolium)butyl(3-phenylpropyl) ether **2.42** (120 mg, 0.3 mmol, 1.0 equiv.) in tetrahydrofuran (5 ml) was added (temperature kept below 0 °C for duration of addition). On complete addition, the reaction mixture was warmed to room temperature and stirred under argon for 16 h. The solvent was removed under vacuum and the organic residue diluted with water (30 ml) and extracted with diethyl ether (50 ml). The diethyl ether solution was washed with water (2 x 50 ml) and brine (50 ml), dried over sodium sulfate and concentrated under vacuum to a yellow gum. Analysis by ^{1}H NMR revealed that a complex mixture had formed with no products of interest detectable.

Reaction of 4-(3-Methylimidazolium)butyl(3-phenylpropyl) ether **2.42** – attempt 2

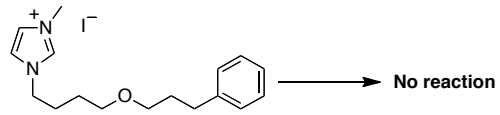


2.42

Sodium hydride (60% in mineral oil, 20 mg, 0,50 mmol, 1.0 equiv.) was washed with hexane (2 x 5 ml) and dried under argon. Once dry, *N,N*-dimethylformamide (1 ml) was added, followed by a solution of 4-(3-methylimidazolium)butyl(3-phenylpropyl) ether **2.42** in *N,N*-dimethylformamide (5 ml) *via* cannula and the mixture stirred under argon at room temperature for 20 h. After this time, the reaction mixture was diluted with water (30 ml) and then extracted with diethyl ether (2 x 50 ml) and the combined organic layers washed with water (3 x 50 ml) and brine (50 ml), then dried over sodium sulfate and concentrated under vacuum to afford a light green gum.

Analysis by ^{1}H NMR revealed that a complex mixture had formed with no products of interest detectable.

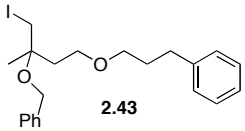
Reaction of 4-(3-Methylimidazolium)butyl(3-phenylpropyl) ether **2.42** – attempt 3



2.42

4-(3-Methylimidazolium)butyl(3-phenylpropyl) ether **2.42** (159 mg, 0.45 mmol, 1.0 equiv.) was dissolved in *N,N*-dimethylformamide (15 ml) under an argon atmosphere and stirred at room temperature for 18 h. The solvent was then removed by distillation and the crude residue analysed by ^{1}H NMR. The NMR revealed only starting material **2.42** was present (100% recovery); the data were consistent with that of 4-(3-methylimidazolium)butyl(3-phenylpropyl) ether **2.42** shown above; δ_H (DMSO, 400 MHz) 1.45-1.50 (2H, m, CH_2), 1.74-1.85 (4H, m, 2 x CH_2), 2.60 (2H, t, *J* 7.7, CH_2), 3.32-3.38 (4H, m, 2 x CH_2), 3.84 (3H, s, CH_3), 4.18 (2H, t, *J* 7.2, CH_2), 7.14-7.19 (3H, m, ArH), 7.25-7.29 (2H, m, ArH), 7.70 (1H, m, ArH), 7.77 (1H, m, ArH), 9.11 (1H, s, ArH).

1-{[4-(3-Phenylpropoxy)-1-iodo-2-methylbutan-2-yloxy]methyl}benzene **2.43**

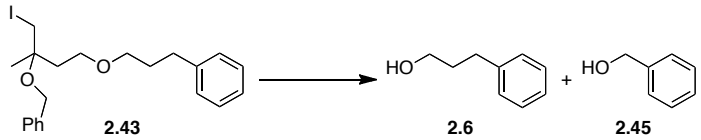


2.43

1-[3-(3-Methylbut-3-enyloxy)propyl]benzene **2.5** (1.0 g, 4.89 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (15 ml) and anhydrous benzyl alcohol **2.45** (2.02 ml, 19.56 mmol, 4.0 equiv.) was added. The solution was cooled to –78 °C and *N*-iodosuccinimide (1.65 g, 7.34 mmol, 1.5 equiv.) added in one portion. The resultant suspension was stirred at –78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (30 ml) was added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (3 x 50 ml) and the combined organic layers then washed with water (3 x 50 ml) and brine (70 ml), dried with Na_2SO_4, filtered and concentrated.

Purification on silica gel, eluting with 0-10% diethyl ether in petroleum ether, afforded the *title compound* **2.43** as a colourless oil (1.46 g, 72%); [Found: $[M+NH_4]^+$, 456.1400. $C_{21}H_{27}IO_2$ requires $[M+NH_4]^+$, 456.1394]; υ_{max} (neat/cm^{-1}) 3062, 3026, 2938, 2864, 1602, 1496, 1453; δ_H ($CDCl_3$, 500 MHz) 1.41 (3H, s, CH_3), 1.87-1.94 (2H, m, CH_2), 2.01-2.16 (2H, m, CH_2), 2.70 (2H, t, *J* 7.7, CH_2), 3.38-3.46 (4H, m, CH_2I, CH_2), 3.56 (2H, t, *J* 6.8, CH_2), 4.49 (2H, s, CH_2), 7.18-7.21 (3H, m, ArH), 7.26-7.31 (3H, m, ArH), 7.32-7.39 (4H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 16.6 (CH_2), 23.6 (CH_3), 31.3 (CH_2), 32.4 (CH_2), 37.2 (CH_2), 63.9 (CH_2), 66.7 (CH_2), 70.2 (CH_2), 74.4 (C), 125.7 (CH), 127.4 (CH), 127.5 (CH), 128.3 (CH), 128.3 (CH), 128.5 (CH), 138.7 (C), 142.0 (C); *m/z* (CI) 456 ($[M+NH_4]^+$, 75%), 311 (100).

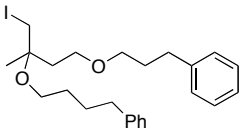
Reaction of donor **1.150** with 1-{[4-(3-phenylpropoxy)-1-iodo-2-methylbutan-2-yloxy] methyl}benzene **2.43**



2.43 **2.6** **2.45**

Using general procedure A, 1-{[4-(3-phenylpropoxy)-1-iodo-2-methylbutan-2-yloxy]methyl}benzene **2.43** (197 mg, 0.45 mmol, 1.0 equiv.) afforded a mixture of 3-phenylpropan-1-ol **2.6** and benzyl alcohol **2.45** as a colourless oil (48 mg); ^1H NMR showed a mixture of 3-phenylpropan-1-ol **2.6** and benzyl alcohol **2.45** in a 1.5:1 ratio (by comparison of the peaks at 3.68 ppm (CH_2OH of **2.6**) and at 4.70 ppm (CH_2OH of **2.45**).

1-{4-[4-(3-Phenylpropoxy)-1-iodo-2-methylbutan-2-yloxy]butyl}benzene **2.44**

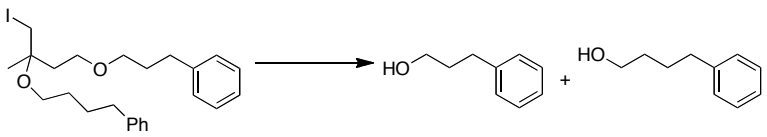


2.44

1-[3-(3-Methylbut-3-enyloxy)propyl]benzene **2.5** (500 mg, 2.54 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (8 ml) and 4-phenylbutanol **2.10** (0.755 ml, 4.90 mmol, 2.0 equiv.) was added. The solution was cooled to –78 °C and *N*-iodosuccinimide (828 mg, 3.68 mmol, 1.5 equiv.) added in one portion. The

resultant suspension was stirred at –78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (15 ml) was added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (3 x 50 ml) and the combined organic layers then washed with water (3 x 50 ml) and brine (50 ml), dried with Na_2SO_4, filtered and concentrated. Purification on silica gel, eluting with 0-10% diethyl ether in petroleum ether, afforded the *title compound* **2.44** as a colourless oil (717 mg, 61%); [Found: $[M+NH_4]^+$, 498.1860. $C_{24}H_{33}IO_2$ requires $[M+NH_4]^+$, 498.1861]; υ_{max} (neat/cm^{-1}) 3060, 3025, 2936, 2861, 1602, 1495, 1453; δ_H ($CDCl_3$, 500 MHz) 1.33 (3H, s, CH_3), 1.56-1.64 (2H, m, CH_2), 1.69-1.76 (2H, m, CH_2), 1.86-2.04 (4H, m, 2 x CH_2), 2.63-2.71 (4H, m, 2 x CH_2), 3.32-3.36 (4H, m, CH_2I, CH_2), 3.42 (2H, t, *J* 6.4, CH_2), 3.50 (2H, t, *J* 6.9, CH_2), 7.15-7.21 (6H, m, ArH), 7.27-7.31 (4H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 16.9 (CH_2), 23.4 (CH_3), 28.1 (CH_2), 29.9 (CH_2), 31.3 (CH_2), 32.4 (CH_2), 35.8 (CH_2), 37.1 (CH_2), 61.2 (CH_2), 66.7 (CH_2), 70.2 (CH_2), 73.5 (C), 125.7 (CH), 125.8 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 142.0 (C), 142.5 (C); *m/z* (CI) 498 ($[M+NH_4]^+$, 36%), 481 (52), 355 (100).

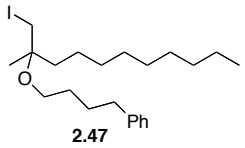
Reaction of donor **1.150** with 1-{4-[4-(3-phenylpropoxy)-1-iodo-2-methylbutan-2-yloxy]butyl}benzene **2.44**



2.44 **2.6** **2.10**

Using general procedure A, 1-{4-[4-(3-phenylpropoxy)-1-iodo-2-methylbutan-2-yloxy]butyl}benzene **2.44** (216 mg, 0.45 mmol, 1.0 equiv.) afforded a mixture of 3-phenylpropan-1-ol **2.6** and 4-phenylbutan-1-ol **2.10** as a colourless oil (93 mg); ^1H NMR showed a mixture of 3-phenylpropan-1-ol **2.6** and 4-phenylbutan-1-ol **2.10** in a 1:1 ratio (by comparison of the peaks at 1.66-1.77 ppm (CH_2CH_2 of **2.10**) and at 1.90-1.96 ppm (CH_2 of **2.6**).

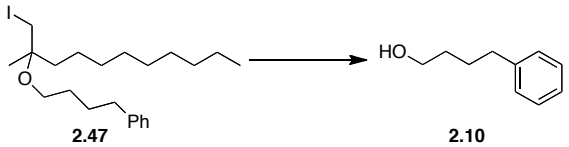
1-[4-(1-Iodo-2-methylundecan-2-yloxy)butyl]benzene **2.47**



2.47

2-Methyl-1-undecene **2.46** (500 mg, 2.97 mmol, 1.0 equiv.) was dissolved in dry dichloromethane (8 ml) at room temperature and 4-phenylbutan-1-ol **2.10** (1.04 ml, 5.94 mmol, 2.0 equiv.) added. The solution was cooled to -78 °C and *N*-iodosuccinimide (1.01 g, 4.46 mmol, 1.5 equiv.) added in one portion. The resultant suspension was stirred at -78 °C for 1 h, then warmed to room temperature and stirred under argon for 18 h. Sodium thiosulfate (10 ml) was then added, causing a colour change from dark purple to colourless. The reaction mixture was extracted with dichloromethane (2 x 50 ml) and the combined organic layers washed with water (3 x 50 ml) and brine (50 ml), then dried over sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography, eluting with 0-3% diethyl ether in petroleum ether, afforded the *title compound* **2.47** as a slightly orange clear oil (977 mg, 74%); [Found: $[M+NH_4]^+$, 462.2225. $C_{22}H_{37}IO$ requires $[M+NH_4]^+$, 462.2227]; υ_{max} (neat/cm^{-1}) 3026, 2925, 2855, 1604, 1495, 1454; δ_H ($CDCl_3$, 400 MHz) 0.88-0.91 (3H, m, CH_3), 1.27-1.29 (17H, m, 7 x CH_2, CH_3), 1.56-1.64 (4H, m, 2 x CH_2), 1.68-1.74 (2H, m, CH_2), 2.65 (2H, t, *J* 7.6, CH_2), 3.28-3.32 (4H, m, 2 x CH_2), 7.18-7.21 (3H, m, ArH), 7.27-7.30 (2H, m, ArH); δ_C ($CDCl_3$, 100 MHz) 14.1 (CH_3), 16.9 (CH_2), 22.7 (CH_2), 23.0 (CH_3), 23.8 (CH_2), 28.2 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.9 (CH_2), 30.0 (CH_2) 30.0 (CH_2), 31.9 (CH_2), 35.8 (CH_2), 37.4 (CH_2), 61.2 (CH_2), 74.2 (C), 125.7 (CH), 128.2 (CH), 128.5 (CH), 142.6 (C); *m/z* (CI) 462 ($[M+NH_4]^+$, 10%), 108 (30), 104 (100).

Reaction of donor **1.150** with 1-[4-(1-iodo-2-methylundecan-2-yloxy)butyl]benzene **2.47**

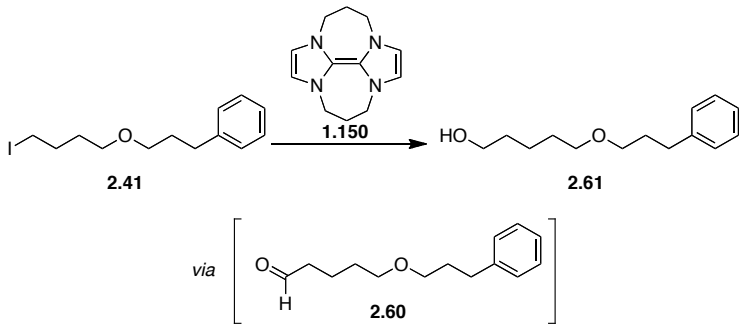


2.47 **2.10**

Using general procedure A, 1-[4-(1-Iodo-2-methylundecan-2-yloxy)butyl]benzene **2.47** afforded 4-phenylbutan-1-ol **2.10** as a colourless oil (36 mg, 55%);[159] δ_H

($CDCl_3$, 500 MHz) 1.65-1.72 (4H, m, 2 x CH_2), 2.68 (2H, t, *J* 7.7, CH_2), 3.69 (2H, t, *J* 6.4, CH_2), 7.20-7.22 (3H, m, ArH), 7.28-7.34 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 27.5 (CH_2), 32.3 (CH_2), 35.7 (CH_2), 62.9 (CH_2), 125.8 (CH), 128.3 (CH), 128.4 (CH), 142.3 (C).

Reaction of donor **1.150** with 1-[3-(4-iodobutoxy)propyl]benzene **2.41** to afford 5-(3-phenylpropoxy)pentanol **2.61**

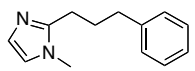


Imidazole-derived salt **1.155** (708 mg, 1.50 mmol, 1.5 equiv.) was dried under vacuum at 100 °C for 1 h then cooled and purged with argon. Sodium hydride (60% in mineral oil, 601 mg, 15.0 mmol, 15.0 equiv.) was added and the solid mixture washed with anhydrous hexane (2 x 20 ml) and dried under a stream of argon. *N,N*-Dimethylformamide (15 ml) was added, causing a yellow suspension to form, which was stirred under argon at room temperature for 4 h. After this time, the yellow donor suspension was centrifuged at 2000 rpm for 10 min to afford a yellow orange solution. This solution was added *via* cannula to 1-[3-(4-iodobutoxy)propyl]benzene **2.41** (319 mg, 1.00 mmol, 1.0 equiv.). A colour change to dark red was observed after less than 15 min, and the solution was stirred under argon at room temperature for 18 h. The dark solution was then diluted with hydrochloric acid (2M, 10 ml) and the solution stirred for 20 min. Water was then added (50 ml) and the aqueous mixture then extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with water (4 x 50 ml) and brine (50 ml), dried with sodium sulfate and concentrated to afford a clear oil (104 mg). ^{1}H NMR confirmed the presence of 5-(3-phenylpropoxy)pentanal **2.60**, which was used immediately in the next stage.

The oil was dissolved in methanol (2 ml) and a solution of sodium borohydride (23 mg, 0.62 mmol, 0.62 equiv.) in methanol (3 ml) was added drop wise at 0 °C. On complete addition, the reaction mixture was warmed to room temperature and

stirred for 18 h under argon. After 18 h, water (2 ml) was added causing a white precipitate to form and the methanol removed under vacuum. The residue was dissolved in diethyl ether (50 ml) and washed with water (4 x 40 ml) then brine (40 ml), dried over sodium sulfate and concentrated. Purification by silica gel chromatography eluting with 0-25% diethyl ether in petroleum ether afforded 5-(3-phenylpropoxy)pentan-1-ol **2.61** as a clear oil (71 mg, 32% over two steps); [Found: $[M+H]^+$, 223.1694. $C_{14}H_{22}O_2$ requires $[M+H]^+$, 223.1693]; υ_{max} (neat/cm^{-1}) 3369, 3026, 2936, 2861, 1497, 1455, 1115, 747, 700; δ_H ($CDCl_3$, 500 MHz) 1.42-1.49 (2H, m, CH_2), 1.59-1.66 (5H, m, 2 x CH_2, OH), 1.88-1.93 (2H, m, CH_2), 2.70 (2H, t, *J* 7.7, CH_2), 3.42-3.47 (4H, m, 2 x CH_2), 3.67 (2H, t, *J* 6.5, CH_2), 7.17-7.21 (3H, m, ArH), 7.27-7.31 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 22.5 (CH_2), 29.5 (CH_2), 31.3 (CH_2), 32.4 (CH_2), 32.5 (CH_2), 62.9 (CH_2), 70.0 (CH_2), 70.8 (CH_2), 125.8 (CH), 128.3 (CH), 128.5 (CH), 142.0 (C); *m/z* (CI) 223 ($[M+H]^+$, 100%), 118 (43).

1-Methyl-2-(3-phenylpropyl)-1*H*-imidazole **2.64**[165]

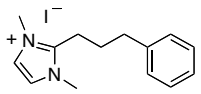


2.64

1-Methylimidazole (1.035 g, 1.0 ml, 12.61 mmol, 1.0 equiv.) was dissolved in dry tetrahydrofuran (15 ml) and cooled to -50 °C. Once cool, *n*-butyllithium (2.4 M, in hexane, 5.25 ml, 12.61 mmol, 1.0 equiv.) was added with the temperature kept below -43 °C. The reaction mixture was stirred for 20 min at low temperature and then a solution of 3-phenyl-1-iodopropane **2.8** (3.41 g, 13.87 mmol, 1.1 equiv.) in tetrahydrofuran (5 ml) was added drop-wise. The resulting light yellow solution was stirred under argon for 19 h while slowly warming to room temperature. After this time, the reaction mixture was diluted with diethyl ether (30 ml) and 2M HCl (30 ml) added. The solution was stirred for 10 min, and then the aqueous layer was separated. The organic layer was extracted with further 2M HCl (2 x 15 ml) and the combined aqueous acidic layers basified with 2M NaOH until pH 12. The now basic aqueous layer was extracted with chloroform (4 x 40 ml), and the organic layers combined and dried with sodium sulfate, filtered and concentrated *in vacuo* to a clear oil. The oil was dried under vacuum at 120 °C to afford the *title compound* **2.64** as a light yellow, clear oil (2.289 g, 91%); [Found: $[M+H]^+$, 201.1385. $C_{13}H_{16}N_2$ requires $[M+H]^+$, 201.1386]; υ_{max} (neat/cm^{-1}) 3374, 3026, 2943, 2859, 1603, 1497,

1455, 1282, 1123, 1081; δ_H ($CDCl_3$, 400 MHz) 2.11 (2H, quintet, *J* 7.6, CH_2), 2.67 (2H, t, *J* 7.6, CH_2), 2.74 (2H, t, *J* 7.4, CH_2), 3.50 (3H, s, CH_3), 6.77 (1H, d, *J* 1.2, ArH), 6.94 (1H, d, *J* 1.2, ArH), 7.17-7.21 (3H, m, ArH), 7.27-7.31 (2H, m, ArH); δ_C ($CDCl_3$, 125 MHz) 26.0 (CH_2), 29.1 (CH_2), 32.5 (CH_3), 35.3 (CH_2), 120.3 (CH), 125.9 (CH), 127.1 (CH), 128.4 (CH), 128.5 (CH), 141.7 (C), 148.1 (C); *m/z* (ESI) 201 ($[M+H]^+$, 100%), 223 (5).

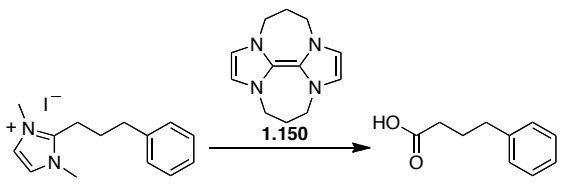
1,3-Dimethyl-2-(3-phenylpropyl)-1H-imidazolium iodide **2.65**



2.65

A solution of 1-methyl-2-(3-phenylpropyl)-1H-imidazole **2.64** (2.0 g, 9.99 mmol, 1.0 equiv.) in acetonitrile (20ml) was stirred at room temperature and iodomethane (3.11 ml, 49.93 mmol, 5.0 equiv.) was added. The reaction mixture was heated to reflux and stirred under argon for 24 h then slowly cooled to room temperature. Diethyl ether (50 ml) was added resulting in a light yellow precipitate forming. The solid was filtered and washed with further diethyl ether (2 x 50 ml) and dried under vacuum for 18 h to afford the *title compound* **2.65** as light yellow crystals (2.81 g, 82%); m.p. 136-139 °C; [Found: $[M-I]^+$, 215.1544. $C_{14}H_{19}IN_2$ requires $[M-I]^+$, 215.1543]; υ_{max} (KBr disc/cm^{-1}) 3073, 2923, 1633, 1445; δ_H (DMSO, 500 MHz) 1.90 (2H, quintet, *J* 8.0, CH_2), 2.70 (2H, t, *J* 8.0, CH_2), 3.02 (2H, t, *J* 8.0, CH_2), 3.77 (6H, s, 2 x CH_3), 7.17-7.20 (1H, m, ArH), 7.25-7.31 (4H, m, ArH), 7.60 (2H, s, ArH); δ_C (DMSO, 125 MHz) 22.6 (CH_2), 27.5 (CH_2), 34.7 (CH_2), 39.5 (CH_3), 122.8 (CH), 126.5 (CH), 128.7 (CH), 128.8 (CH), 141.2 (C), 147.1 (C); *m/z* (ES^+) 215 ($[M-I]^+$, 100%), 365 (6).

Reaction of 1,3-dimethyl-2-(3-phenylpropyl)-1H-imidazolium iodide **2.65** with donor **1.150**

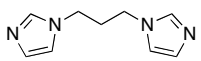


2.65 **2.66**

The imidazole-derived salt **1.155** (850 mg, 1.8 mmol, 3.0 equiv.) was dried under vacuum for 1 h at 100 °C then cooled to room temperature and purged with argon. Sodium hydride (60% in oil, 762 mg, 18.0 mmol, 30.0 equiv.) was added and the mixture washed with hexane (2 x 20 ml) and dried under an argon stream. Once dry, degassed anhydrous *N*,*N*-dimethylformamide (20 ml) was added and the resulting yellow mixture stirred under argon at room temperature for 4 h. After this time, the mixture was centrifuged at 2000 rpm for 10 min and the resulting orange liquid added to 1,3-dimethyl-2-(3-phenylpropyl)-1*H*-imidazolium iodide **2.65** (205 mg, 0.6 mmol, 1.0 equiv.) *via* cannula, causing a colour change to dark red. The reaction mixture was stirred under argon for 18 h at room temperature, then exposed to air and 2M HCl (20 ml) added and stirring continued for 30 min. The orange aqueous solution was extracted with diethyl ether (3 x 30 ml) and the organic layers combined and washed with 2M HCl (4 x 20 ml) and brine/2M HCl (20 ml + 10 ml), then dried with sodium sulfate, filtered and concentrated. Purification on silica gel eluting with 20-80% ethyl acetate/dichloromethane afforded 4-phenylbutyric acid **2.66** as a white solid (2 mg, 2 %); m.p. 46-48 °C (lit. 50-51 °C);[166] υ_{max} (neat/cm^{-1}) 3400-2400 (b), 3027, 2918, 2849, 1708, 1497, 1454, 1412; δ_H ($CDCl_3$, 500 MHz) 1.99 (2H, quintet, *J* 7.5, CH_2), 2.39 (2H, t, *J* 7.5, CH_2), 2.69 (2H, t, *J* 7.6, CH_2), 7.19-7.22 (3H, m, ArH), 7.27-7.31 (2H, m, ArH); *m/z* (ESI) 165 ([M+H]$^+$, 41%), 197 (100), 187 (3), 149 (20).

Experimental for Chapter 3

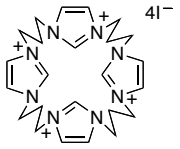
1,3-Bis(1-imidazolyl)propane **1.154**



1.154

Sodium hydride (60% in mineral oil, 63.0 g, 1.76 mol, 1.2 equiv.) was washed with hexane (2 x 150 ml) and dried under an argon stream. Once dry, *N,N*-dimethylformamide (300 ml) was added and the suspension cooled to 0 °C, where a solution of imidazole **1.153** (100.0 g, 1.47 mmol, 1.0 equiv.) in *N,N*-dimethylformamide (300 ml) was added. The reaction temperature was raised to room temperature and stirred for 1 h, then cooled to 0 °C once more. 1,3-Dibromopropane (74.1 ml, 0.73 mol, 0.5 equiv.) was added and the reaction warmed to room temperature and stirred under argon for 18 h. After this time, the reaction mixture was diluted with dichoromethane (2.5 L) and filtered, then concentrated to a viscous yellow oil by rotary evaporation and distillation of the residual *N,N*-dimethylformamide under reduced pressure. The crude reaction mixture was purified by distillation at approx. 0.2 mBar and 206-208 °C to give the title compound **1.154** as a viscous yellow oil (51.45 g, 40%) [note that initially imidazole distills at approximately 150 °C causing the condenser to block];[107] υ_{max} (neat/cm^{-1}) 3106, 2939, 1599, 1508, 1452; δ_H (400 MHz, $CDCl_3$) 2.29 (2H, quintet, *J* 6.8, CH_2), 3.91 (4H, t, *J* 6.8, 2 x CH_2), 6.89 (2H, s, ArH), 7.10 (2H, s, ArH), 7.44 (2H, s, ArH); δ_C (100 MHz, $CDCl_3$) 32.1 (CH_2), 43.5 (CH_2), 118.7 (CH), 130.4 (CH), 137.3 (CH); *m/z* (ESI) 275 ([2M+Na]$^+$, 53%), 353 (100), 177 (55).

*Tetrakis*trimethylene tetraimidazolium tetraiodide **1.284**

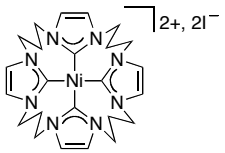


1.178

To a three-necked flask equipped with a mechanical stirrer and a condenser were added acetonitrile (4.0 L), 1,3-bis(1-imidazolyl)propane **1.154** (2.00 g, 11.36 mmol,

1.0 equiv.) and 1,3-diiodopropane (3.36 g, 1.31 ml, 11.36 mmol, 1.0 equiv.). The mixture was heated to reflux for 24 h, after which time a further equal quantity of the starting materials was added. One batch of starting materials was added every 24 h, until, after 20 days, a total of 40.0 g (277.0 mmol) of 1,3-bis(1-imidazolyl)propane and 67.2 g (227.0 mmol) of 1,3-diiodopropane had been added. During this period, a white solid precipitated gradually. After addition was complete, the mixture was refluxed for a further 4 days then filtered while hot to yield a crude white solid. After drying, the white solid was purified by recrystallising from hot methanol to afford the title compound **1.284** as a white crystalline solid (21.67 g, 20 %); m.p. 263 °C (lit. 264 °C);[107] υ_{max} (KBr disc/cm^{-1}) 3413, 3132, 3069, 1571, 1450; δ_H (400 MHz, DMSO) 2.50 (8H, m (including DMSO peak), CH_2), 4.28 (16H, t, *J* 6.8, CH_2), 7.86 (8H, s, ArH), 9.50 (4H, s, ArH); δ_C (100 MHz, DMSO) 28.0 (CH_2), 45.8 (CH_2), 122.6 (CH), 136.5 (CH); *m/z* (ESI) 966 ([M+Na-H]$^+$, 5%), 816 (30), 689 (100), 561 (30).

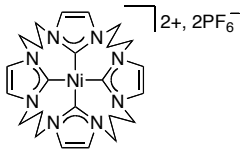
Nickel(II) *tetra*-NHC complex, diiodide **3.1**



3.1

*Tetrakis*trimethylene tetraimidazolium tetraiodide **1.284** (3.0 g, 3.18 mmol, 1.0 equiv.), nickel(II) acetate tetrahydrate (791 mg, 3.18 mmol, 1.0 equiv.) and sodium acetate (1.043 g, 12.72 mmol, 4.0 equiv.) were suspended in dimethylsulfoxide (100 ml) and heated to 90 °C for 18 h. After this time, the reaction mixture was cooled to room temperature and the solvent removed by distillation to give a yellow residue which was recrystallised from hot methanol to afford the *title compound* **3.1** as light yellow cubes (1.81 g, 79%); m.p. > 300 °C (dec.); [Found: [M-I]$^+$, 617.1140. $C_{24}H_{32}I_2N_8Ni$ requires [M-I]$^+$, 617.1143]; υ_{max} (KBr disc/cm^{-1}) 3153, 3092, 2958, 1470, 1406, 1261, 1195; δ_H (400 MHz, DMSO) 1.62-1.76 (4H, m, CH_2), 2.40-2.52 (4H, m (including DMSO peak), CH_2), 4.50-4.59 (8H, m, CH_2), 5.06-5.17 (8H, m, CH_2), 7.28 (8H, s, ArH); δ_C (100 MHz, DMSO) 31.6 (CH_2), 52.6 (CH_2), 124.1 (CH), 172.2 (C); *m/z* (ESI) 617 ([M-I]$^+$, 15%), 245 (100).

Nickel(II) *tetra*-NHC complex, dihexafluorophosphate **3.2**



3.2

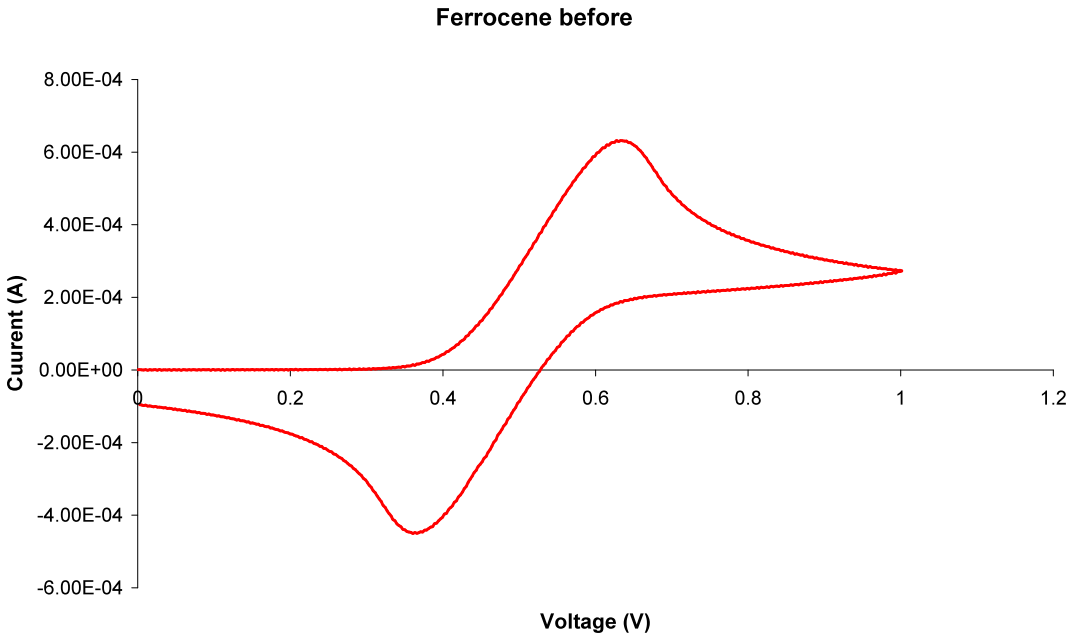
Nickel(II) tetra-NHC complex, diiodide **3.1** (300 mg, 0.40 mmol, 1.0 equiv.) was suspended in methanol (50 ml) and heated to reflux until all the material had dissolved. Ammonium hexafluorophosphate (328 mg, 2.01 mmol, 5.0 equiv.) was added and the reaction continued at reflux for 48 h, cooled to room temperature and filtered. The resulting off-white powder was recrystallised from hot methanol to afford the *title compound* **3.2** as light yellow microcrystals (177 mg, 56%); m.p. > 280 °C (dec.); [Found: $[M\text{-}PF_6]^+$, 635.1728. $C_{24}H_{32}F_{12}N_8NiP_2$ requires $[M\text{-}PF_6]^+$, 635.1740]; υ_{max} (KBr disc/cm^{-1}) 3183, 2932, 1474, 1414, 1185; δ_H (400 MHz, DMSO) 1.65-1.72 (4H, m, CH_2), 2.44-2.49 (4H, m (including DMSO peak), CH_2), 4.52-4.56 (8H, m, CH_2), 5.07-5.12 (8H, m, CH_2), 7.26 (8H, s, ArH); δ_C (100 MHz, DMSO) 32.1 (CH_2), 53.1 (CH_2), 124.6 (CH), 172.7 (C); *m/z* (ESI) 635 ($[M\text{-}PF_6]^+$, 100%), 489 (14), 245 (32).

Example of a typical cyclic voltammetry analysis

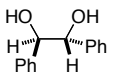
A standard 0.1 M solution of tetrabutylammonium hexafluorophosphate in *N,N*-dimethylformamide was prepared (hereafter referred to as TBAHFP/DMF) and used to prepare standard 0.01 M solutions of ferrocene and substrate(s). The solutions were vigorously degassed (or, alternatively, prepared within the glovebox) and transferred to the glovebox, together with two 50 ml beakers, a glassy carbon working electrode, a platinum wire counter electrode and a Ag/AgCl/KCl (sat.) reference electrode. The ferrocene solution was added to one beaker (with the second beaker upturned and used as a removable stand) and the three electrodes held in place so that all were submerged to the same depth within the solution, and all were equidistant from one another. Each electrode was connected using the appropriate wires and a cyclic voltammogram taken (example shown below). If not suitable, all connections were examined and any metal-metal contacts replaced. If suitable, the ferrocene was removed, the beaker and electrodes rinsed with

TBAHFP/DMF and the substrate solution added to the beaker. A cyclic voltammogram was taken once more and any further analyses performed. Once all data had been collected, the substrate solution was removed from the beaker and the cleaning process repeated. If any further substrates were to be examined, this was done at this time. If not, the ferrocene solution was re-examined (both $E_{1/2}$ values should be within ±0.02 V). The raw data were converted using "Excel" and plotted as a line graph for each substrate.

Example of a ferrocene cyclic voltammogram using the procedure detailed above.



dl-1,2-Diphenylethan-1,2-diol **3.11**

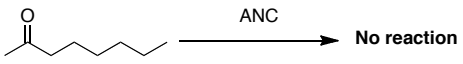


3.11

A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (40 ml), followed by ground nickel(II) complex **3.1** (373 mg, 0.5 mmol, 1.0 equiv.) added. The reaction mixture was stirred for 4 h under an argon atmosphere, during which time the reaction mixture turned dark red. After this time, the dark red solution of the active nickel complex was added to freshly distilled benzaldehyde **3.7** (53 mg, 0.5 mmol, 1.0 equiv.) rapidly *via* cannula and stirred

under argon at room temperature for 18 h. The reaction mixture was then partitioned between diethyl ether (100 ml) and water (100 ml), then the organic layer separated and the aqueous layer extracted with further diethyl ether (3 x 50 ml). The diethyl ether layers were combined then washed with water (2 x 100 ml) and brine (100 ml), then dried with sodium sulfate and concentrated. Purification by silica gel chromatography eluting with 0-10% diethyl ether in hexane afforded the title compound **3.11** as a white powder (34 mg, 64%); m.p. 116-117 °C (lit. 117-118 °C);[167] υ_{max} (KBr disc/cm^{-1}) 3393 (b), 2918, 1644, 1455, 1205, 1055; δ_H (400 MHz, $CDCl_3$) 2.81 (2H, bs, OH), 4.72 (2H, s, CH), 7.12-7.15 (4H, m, ArH), 7.22-7.25 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 79.1 (CH), 126.9 (CH), 127.9 (CH), 128.2 (CH), 139.9 (C); *m/z* (CI) 232 ([M+NH_4]$^+$, 100%), 214 (47), 124 (80), 105 (87).

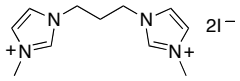
Attempted reduction of 2-octanone **3.9** using the active nickel complex



3.9

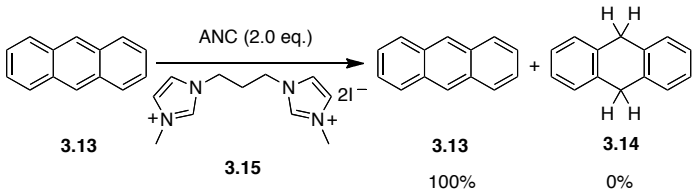
A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (45 ml), followed by ground nickel(II) complex **3.1** (436 mg, 0.58 mmol, 1.0 equiv.) added. The reaction mixture was stirred for 4 h under an argon atmosphere, during which time the reaction mixture turned dark red. After this time, the dark red solution of the active nickel complex was added to 2-octanone **3.9** (75 mg, 0.58 mmol, 1.0 equiv.) rapidly *via* cannula and stirred under argon at room temperature for 18 h. The reaction mixture was then partitioned between diethyl ether (100 ml) and water (120 ml), then the organic layer separated and the aqueous layer extracted with further diethyl ether (2 x 100 ml). The diethyl ether layers were combined then washed with water (3 x 100 ml) and brine (100 ml), then dried with sodium sulfate and concentrated. Purification by silica gel chromatography eluting with 0-10% ethyl acetate in hexane afforded recovered 2-octanone **3.9** as a colourless oil (67 mg, 89%) indicating no reduction had occurred; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0, CH_3), 1.27-1.32 (6H, m, 3 x CH_2), 1.54-1.60 (2H, m, CH_2), 2.13 (3H, s, CH_3), 2.42 (2H, t, *J* 7.5, CH_2); δ_C (125 MHz, $CDCl_3$) 14.0 (CH_3), 22.5 (CH_2), 23.8 (CH_2), 28.8 (CH_2), 29.8 (CH_2), 31.6 (CH_3), 43.8 (CH_2), 209.4 (C).

1,3-Bis(1-[3-methyl]imidazolyl)propane **3.15**



N-Methylimidazole (4.85 ml, 60.9 mmol, 2.5 equiv.) and 1,3-diiodopropane (2.82 ml, 24.36 mmol, 1.0 equiv.) were added to acetonitrile (50 ml) and brought to reflux for 40 h. After this time, the reaction mixture was cooled to room temperature and concentrated under vacuum. The resultant residue was stirred in petroleum ether (120 ml) for 1 h, then filtered and washed with a mixture of petroleum ether and dichloromethane (30 ml, 10:1) to afford the title compound **3.15** as an off-white powder (11.101 g, 99%); m.p.146-148 °C (lit. 148-149 °C);[60] υ_{max} (KBr disc/cm^{-1}) 3082, 3041, 1571, 1449; δ_H (500 MHz, DMSO) 2.37 (2H, quintet, *J* 7.0, CH_2), 3.86 (6H, s, 2 x CH_3), 4.22 (4H, t, *J* 7.2, 2 x CH_2), 7.73-7.76 (4H, m, ArH), 9.11 (2H, s, ArH); δ_C (125 MHz, DMSO) 30.0 (CH_2), 36.6 (CH_3), 46.2 (CH_2), 122.6 (CH), 124.2 (CH), 137.2 (CH); *m/z* (ESI) 333 ([M-I]$^+$, 5%), 205 (10), 123 (75), 103 (100).

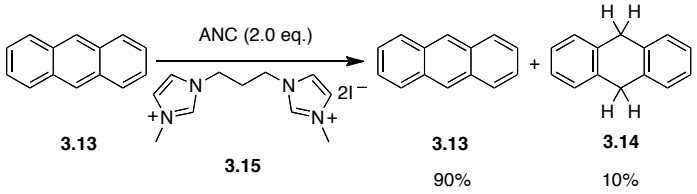
Attempted Birch reduction of anthracene **3.13** – Attempt 1



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N,N*-dimethylformamide (40 ml) added, followed by nickel(II) complex **3.1** (418 mg, 0.56 mmol, 2.0 equiv.). The resultant suspension was stirred under argon at room temperature for 4 h, during which time the reaction formed a dark green colour. After this time, the dark green solution was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) and 1,3-bis(1-[3-methyl]imidazolyl)propane **3.15** (645 mg, 1.40 mmol, 5.0 equiv.) rapidly *via* cannula and stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (150 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under

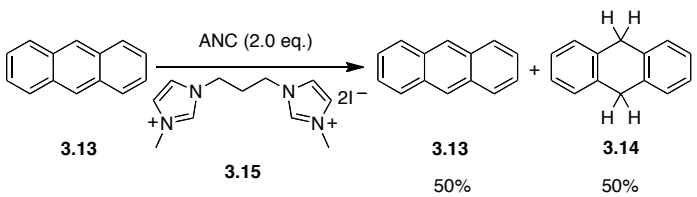
vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed only anthracene **3.13** starting material was present.

Attempted Birch reduction of anthracene **3.13** – Attempt 2



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (40 ml) added, followed by nickel(II) complex **3.1** (418 mg, 0.56 mmol, 2.0 equiv.). The resultant suspension was stirred under argon at room temperature for 4 h, during which time the reaction formed a dark red colour. After this time, the dark red solution was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) and 1,3-bis(1-[3-methyl]imidazolyl)propane **3.15** (645 mg, 1.40 mmol, 5.0 equiv.) rapidly *via* cannula and stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (150 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed a mixture of anthracene **3.13** starting material and the expected dihydroanthracene (**3.14**) product with 10% consisting of dihydroanthracene **3.14** (by comparison of the central aromatic CH peak of anthracene (δ 8.50 ppm) and the CH_2 peak of dihydroanthracene (δ 3.98 ppm) – not isolated).

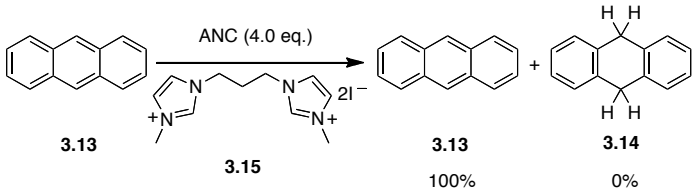
Attempted Birch reduction of anthracene **3.13** – Attempt 3



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (40 ml) added, followed by nickel(II) complex **3.1** (418 mg,

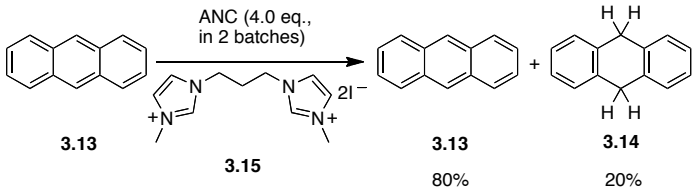
0.56 mmol, 2.0 equiv.). The resultant suspension was stirred under argon at room temperature for 4 h, during which time the reaction formed a dark red colour. After this time, the dark red solution was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) and 1,3-bis(1-[3-methyl]imidazolyl)propane **3.15** (645 mg, 1.40 mmol, 5.0 equiv.) rapidly *via* cannula and stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (150 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed a mixture of anthracene **3.13** starting material and the expected dihydroanthracene **3.14** product with 50% consisting of dihydroanthracene **3.14** (by comparison of the central aromatic CH peak of anthracene (δ 8.50 ppm) and the CH_2 peak of dihydroanthracene (δ 3.98 ppm) – not isolated).

Attempted Birch reduction of anthracene **3.13** – Attempt 4



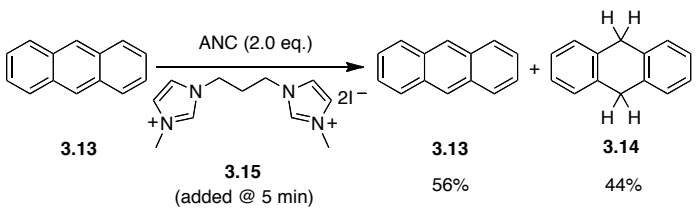
A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N,N*-dimethylformamide (80 ml) added, followed by nickel(II) complex **3.1** (834 mg, 1.12 mmol, 4.0 equiv.). The resultant suspension was stirred under argon at room temperature for 4 h, during which time the reaction formed a dark red colour. After this time, the dark red solution was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) and 1,3-bis(1-[3-methyl]imidazolyl)propane **3.15** (645 mg, 1.40 mmol, 5.0 equiv.) rapidly *via* cannula and stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (200 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (4 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed only anthracene **3.13** starting material was present.

Attempted Birch reduction of anthracene **3.13** – Attempt 5



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury, per flask) was freshly prepared in two separate flasks and *N,N*-dimethylformamide (40 ml) added to each, followed by nickel(II) complex **3.1** (418 mg, 0.56 mmol, 2.0 equiv. per flask). The resultant suspension was stirred under argon at room temperature for 4 h for each flask, during which time each reaction mixture formed a dark red colour. After this time, the dark red solution in the first flask was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) and 1,3-bis(1-[3-methyl]imidazolyl)propane **3.15** (645 mg, 1.40 mmol, 5.0 equiv.) rapidly *via* cannula, quickly followed by the dark red solution of the second flask [total nickel(II) complex **3.1** added (834 mg, 1.12 mmol, 4.0 equiv.) in 80 ml *N,N*-dimethylformamide], and stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (200 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (4 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed a mixture of anthracene **3.13** starting material and the expected dihydroanthracene **3.14** product with 20% consisting of dihydroanthracene **3.14** (by comparison of the central aromatic CH peak of anthracene (δ 8.50 ppm) and the CH_2 peak of dihydroanthracene (δ 3.98 ppm) – not isolated).

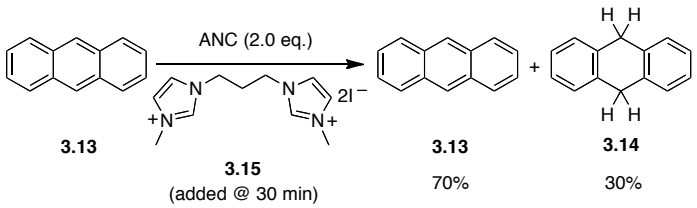
Attempted Birch reduction of anthracene **3.13** – Attempt 6



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N,N*-dimethylformamide (40 ml) added, followed by nickel(II) complex **3.1** (418 mg,

0.56 mmol, 2.0 equiv.). The resultant suspension was stirred under argon at room temperature for 4 h, during which time the reaction formed a dark red colour. After this time, the dark red solution was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) rapidly *via* cannula and stirred under argon. After 5 min, 1,3-bis(1-[3-methyl]imidazolyl)propane **3.15** (645 mg, 1.40 mmol, 5.0 equiv.) was swiftly added and the reaction mixture stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (150 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed a mixture of anthracene **3.13** starting material and the expected dihydroanthracene **3.14** product with 44% consisting of dihydroanthracene **3.14** (by comparison of the central aromatic CH peak of anthracene (δ 8.50 ppm) and the CH_2 peak of dihydroanthracene (δ 3.98 ppm) – not isolated).

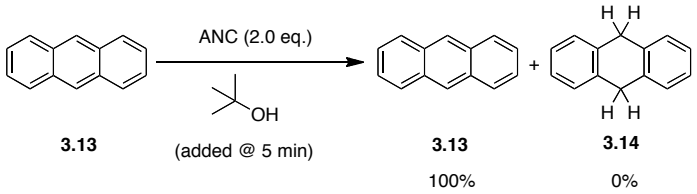
Attempted Birch reduction of anthracene **3.13** – Attempt 7



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N,N*-dimethylformamide (40 ml) added, followed by nickel(II) complex **3.1** (418 mg, 0.56 mmol, 2.0 equiv.). The resultant suspension was stirred under argon at room temperature for 4 h, during which time the reaction formed a dark red colour. After this time, the dark red solution was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) rapidly *via* cannula and stirred under argon. After 30 min, 1,3-bis(1-[3-methyl]imidazolyl)propane **3.15** (645 mg, 1.40 mmol, 5.0 equiv.) was swiftly added and the reaction mixture stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (150 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed a mixture of anthracene **3.13** starting material and the expected dihydroanthracene **3.14** product

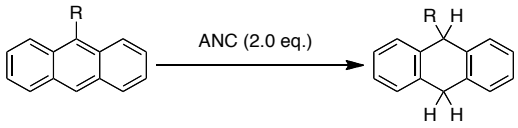
with 30% consisting of dihydroanthracene **3.14** (by comparison of the central aromatic CH peak of anthracene (δ 8.50 ppm) and the CH_2 peak of dihydroanthracene (δ 3.98 ppm) – not isolated).

Attempted Birch reduction of anthracene **3.13** – Attempt 8



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N,N*-dimethylformamide (40 ml) added, followed by nickel(II) complex **3.1** (418 mg, 0.56 mmol, 2.0 equiv.). The resultant suspension was stirred under argon at room temperature for 4 h, during which time the reaction formed a dark red colour. After this time, the dark red solution was added to anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) rapidly *via* cannula and stirred under argon. After 5 min, a solution of *tert*-butyl alcohol (0.131 ml, 1.40 mmol, 5.0 equiv.) in *N,N*-dimethylformamide (2 ml) was swiftly added and the reaction mixture stirred under argon at room temperature for 18 h. The reaction mixture was then added to water (150 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic extracts were washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture revealed only anthracene **3.13** starting material was present.

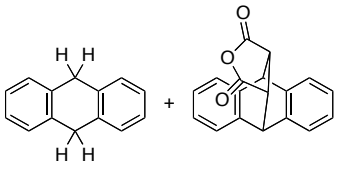
General Procedure B – General procedure for the reduction of anthracene **3.13** and analogues using the active nickel complex



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was prepared and *N,N*-dimethylformamide added, followed by nickel(II) complex **3.1** (2.5 equiv.). The resultant suspension was stirred under argon for 4 h, during which time the

suspension turned from colourless to dark red. The dark red solution was then added to the substrate (1.0 equiv., which had been dried under vacuum at room temperature for 2 h) rapidly *via* cannula and stirred under argon at room temperature for 1 h. After this time, the reaction mixture was quenched by addition to a saturated solution of ammonium chloride (150 ml) and, after 5 min, extracted with diethyl ether (2 x 150 ml). The combined organic layers were washed with water (2 x 100 ml) and brine (100 ml), then dried with sodium sulfate and concentrated. Purification by silica gel chromatography afforded the appropriate product.

9,10-Dihydroanthracene **3.14** and 9,10-dihydroanthracene-9,10-α,β-succinic acid anhydride **3.16**



3.14 **3.16**

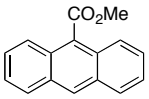
Using general procedure B, anthracene **3.13** (50 mg, 0.28 mmol, 1.0 equiv.) was reduced in *N*,*N*-dimethylformamide (50 ml) using nickel(II) complex **3.1** (523 mg, 0.71 mmol, 2.5 equiv.) to afford a mixture of 9,10-dihydroanthracene **3.14** and anthracene **3.13** with approximately 75% conversion to 9,10-dihydroanthracene **3.14** as adjudged by ^{1}H NMR. The mixture was dissolved in chlorobenzene (5 ml) and maleic anhydride (28 mg, 0.28 mmol, 1.0 equiv.) added. The reaction mixture was heated to reflux for 18 h, then cooled to room temperature and the solvent removed under vacuum. Purification by silica gel chromatography afforded 9,10-dihydroanthracene **3.14** (28 mg, 55%) and 9,10-dihydroanthracene-9,10-α,β-succinic acid anhydride **3.16** (10 mg, 14%) as white crystalline solids.

9,10-dihydroanthracene **3.14**: m.p. 105-107 °C (lit. 108-109 °C);[168] υ_{max} (KBr disc/cm^{-1}) 3060, 3027, 2953, 2839, 2807, 1477, 1450, 1426; δ_H (500 MHz, $CDCl_3$) 3.97 (4H, s, 2 x CH_2), 7.21-7.24 (4H, m, ArH), 7.31-7.33 (4H, m, ArH); δ_C (125 MHz, $CDCl_3$) 36.2 (CH_2), 126.1 (CH), 127.4 (CH), 136.1 (C); *m/z* (EI) 180 ([M]$^+$, 100%), 179 (85), 178 (60).

9,10-dihydroanthracene-9,10-α,β-succinic acid anhydride **3.16**: m.p. 256-257 °C (lit. 257-258 °C);[169] υ_{max} (KBr disc/cm^{-1}) 3075, 3026, 2968, 1863, 1782, 1463, 1229,

1213, 1070; δ_H (500 MHz, $CDCl_3$) 3.54 (2H, s, 2 x CH), 4.84 (2H, s, 2 x CH), 7.19-7.24 (4H, m, ArH), 7.34-7.37 (2H, m, ArH), 7.39-7.42 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 45.4 (CH), 48.0 (CH), 124.4 (CH), 125.2 (CH), 127.2 (CH), 127.7 (CH), 138.1 (C), 140.6 (C), 170.4 (C); *m/z* (CI) 294 ($[M+NH_4]^+$, 100%), 179 (96), 58 (56).

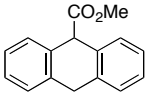
Methyl anthracene-9-carboxylate **3.17**[170]



3.17

Sodium methoxide (729 mg, 13.5 mmol, 1.5 equiv.) was suspended in methanol (20 ml) and 9-anthracenecarboxylic acid **3.19** (2.0 g, 9.0 mmol, 1.0 equiv.) added in one portion. The reaction mixture was stirred at room temperature for 30 min then heated to reflux. Once at reflux, dimethyl sulfate (1.7 ml, 18.0 mmol, 2.0 equiv.) was added slowly over 2 min and the reaction continued at reflux for 20 h, then cooled to room temperature. The methanol was removed under vacuum and the brown residue dissolved in ethyl acetate (100 ml) and washed with water (3 x 75 ml) and brine (100 ml), dried with sodium sulfate and concentrated. Purification by silica gel chromatography, eluting with 10% diethyl ether in petroleum ether afforded the title compound **3.17** as a light yellow powder (1.07 g, 50%); m.p. 109-110 °C (lit. 108.5-110 °C);[170] [Found: $[M]^+$, 236.0834. $C_{16}H_{12}O_2$ requires $[M]^+$, 236.0832]; υ_{max} (KBr disc/cm^{-1}) 3030, 3013, 2945, 1727, 1434, 1207, 1173, 1154, 1021; δ_H (500 MHz, $CDCl_3$) 4.19 (3H, s, CH_3), 7.49-7.52 (2H, m, ArH), 7.54-7.57 (2H, m, ArH), 8.03-8.05 (4H, m, ArH), 8.55 (1H, s, ArH); δ_C (125 MHz, $CDCl_3$) 52.6 (CH_3), 125.0 (CH), 125.5 (CH), 127.0 (CH), 128.5 (C), 128.6 (CH), 129.5 (C), 131.0 (C), 170.1 (C); *m/z* (EI) 236 ($[M]^+$, 100%), 205 (84), 176 (89).

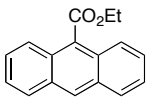
Methyl-9,10-dihydroanthracene-10-carboxylate **3.22**



3.22

Using general procedure B, methyl anthracene-9-carboxylate **3.17** (50 mg, 0.21 mmol, 1.0 equiv.) was reduced in *N*,*N*-dimethylformamide (40 ml) using nickel(II) complex **3.1** (391 mg, 0.53 mmol, 2.5 equiv.) to afford the *title compound* **3.22** as a white crystalline solid (27 mg, 54%); m.p. 91-93 °C; [Found: $[M]^+$, 238.0991. $C_{16}H_{14}O_2$ requires $[M]^+$, 238.088]; υ_{max} (KBr disc/cm^{-1}) 3068, 3021, 2954, 2931, 2852, 1725, 1480, 1454, 1436, 1276, 1226, 1203, 1011; δ_H (500 MHz, $CDCl_3$) 3.61 (3H, s, CH_3), 3.93 (1H, d, *J* 18.1, *H*CH), 4.34 (1H, d, *J* 18.1, HC*H*), 5.05 (1H, s, CH), 7.25-7.31 (4H, m, ArH), 7.35-7.37 (2H, m, ArH), 7.41-7.42 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 35.7 (CH_2), 52.4 (CH), 52.9 (CH_3), 125.5 (CH), 126.4 (CH), 127.5 (CH), 128.1 (CH), 133.8 (C), 136.7 (C), 172.4 (C); *m/z* (EI) 238 ($[M]^+$, 100%), 236 (58), 205 (55).

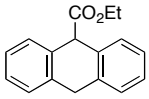
Ethyl anthracene-9-carboxylate **3.20**[171]



3.20

9-Anthracenecarboxylic acid **3.19** (2.0 g, 9.0 mmol, 1.0 equiv.) was suspended in toluene (40 ml) and trifluoroacetic anhydride (5.1 ml, 36.0 mol, 4.0 equiv.) added drop-wise at 0 °C. The reaction mixture was warmed to room temperature and stirred under argon for 30 min before ethanol (10 ml) was added and stirring continued for 18 h. The reaction mixture was then poured into a mixture of sodium bicarbonate (sat., 100 ml) and ethyl acetate (100 ml), and the organic phase separated. The organic phase was then washed with water (100 ml) and brine (100 ml), then dried and concentrated. Recrystallisation from ethanol afforded the title compound **3.20** as a light brown crystalline solid (1.75 g, 78%); m.p. 109-110 °C (lit. 108-109 °C);[172] [Found: $[M+NH_4]^+$, 268.1328. $C_{17}H_{14}O_2$ requires $[M+NH_4]^+$, 268.1332]; υ_{max} (KBr disc/cm^{-1}) 3053, 2979, 2928, 1711, 1623, 1214, 1021; δ_H (500 MHz, $CDCl_3$) 1.55 (3H, t, *J* 7.1, CH_3), 4.70 (2H, q, *J* 7.1, CH_2), 7.49-7.60 (4H, m, ArH), 8.03-8.07 (4H, m, ArH), 8.54 (1H, s, ArH); δ_C (125 MHz, $CDCl_3$) 14.5 (CH_3), 61.8 (CH_2), 125.0 (CH), 125.5 (CH), 126.9 (CH), 128.1 (CH), 128.4 (C), 128.6 (CH), 129.2 (C), 131.0 (C), 169.6 (C); *m/z* (CI) 268 ($[M+NH_4]^+$, 100%), 251 (32), 179 (41).

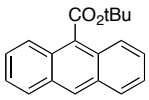
Ethyl-9,10-dihydroanthracene-10-carboxylate **3.23**



3.23

Using general procedure B, ethyl anthracene-9-carboxylate **3.20** (50 mg, 0.2 mmol, 1.0 equiv.) was reduced in *N*,*N*-dimethylformamide (40 ml) using nickel(II) complex **3.1** (372 mg, 0.5 mmol, 2.5 equiv.) to afford the *title compound* **3.23** as a light yellow waxy solid (30 mg, 59%); [Found: (ESI) $[M+NH_4]^+$, 270.1841. $C_{17}H_{16}O_2$ requires $[M+NH_4]^+$, 270.1849]; υ_{max} (neat/cm^{-1}) 3067, 3025, 2981, 2935, 2873, 1732, 1482, 1454, 1293, 1216, 1185, 1150, 1027; δ_H (500 MHz, $CDCl_3$) 1.17 (3H, t, *J* 7.1, CH_3), 3.92 (1H, d, *J* 18.1, *H*CH), 4.06 (2H, q, *J* 7.1, CH_2), 4.36 (1H, d, *J* 18.1, HC*H*), 5.00 (1H, s, CH), 7.25-7.28 (4H, m, ArH), 7.35-7.37 (2H, m, ArH), 7.41-7.43 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.0 (CH_3), 35.7 (CH_2), 53.1 (CH), 61.1 (CH_2), 126.4 (CH), 127.4 (CH), 127.9 (CH), 128.1 (CH), 133.9 (C), 136.7 (C), 171.9 (C); *m/z* (CI) 270 ($[M+NH_4]^+$, 100%), 253 (24), 179 (32).

tert-Butyl anthracene-9-carboxylate **3.21**[171]

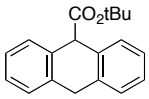


3.21

9-Anthracenecarboxylic acid **3.19** (1.90 g, 8.55 mmol, 1.0 equiv.) was dissolved in toluene (40 ml) under argon and cooled to 0 °C where trifluoroacetic anhydride (4.8 ml, 34.19 mmol, 4.0 equiv.) was added drop-wise. The reaction mixture was warmed to room temperature and stirred for 30 min before *tert*-butanol (10 ml) was added. The mixture was stirred under argon for 18 h at room temperature before being poured into a mixture of sodium bicarbonate (sat., 100 ml) and ethyl acetate (100 ml). The organic phase was removed and washed with water (100 ml) and brine (100 ml), then dried over sodium sulfate and concentrated. Purification by silica gel chromatography eluting with 0-2% ethyl acetate in petroleum ether afforded the title compound **3.21** as a yellow crystalline solid (2.11 g, 88%); m.p. 155-157 °C (lit. 158 °C);[171] [Found: $[M+NH_4]^+$, 296.1648. $C_{19}H_{18}O_2$ requires

$[M+NH_4]^+$, 296.1645]; υ_{max} (KBr disc/cm^{-1}) 3052, 2974, 2931, 1714, 1625, 1456, 1445; δ_H (400 MHz, $CDCl_3$) 1.82 (9H, s, CH_3), 7.50-7.51 (2H, m, ArH), 7.57-7.58 (2H, m, ArH), 8.02 (2H, d, *J* 8.4, ArH), 8.12 (2H, d, *J* 8.6, ArH), 8.50 (1H, s, ArH); δ_C (100 MHz, $CDCl_3$) 28.7 (CH_3), 83.1 (C), 125.1 (CH), 125.6 (CH), 126.9 (CH), 128.2 (C), 128.7 (CH), 128.8 (CH), 129.8 (C), 131.3 (C), 169.3 (C); *m/z* (EI) 278 ($[M]^+$, 20%), 222 (100), 205 (35), 176 (50), 57 (20).

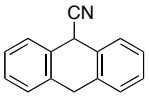
tert-Butyl-9,10-dihydroanthracene-10-carboxylate **3.24**



3.24

Using general procedure B, *tert*-butyl anthracene-9-carboxylate **3.21** (50 mg, 0.18 mmol, 1.0 equiv.) was reduced in *N*,*N*-dimethylformamide (35 ml) using nickel(II) complex **3.1** (335 mg, 0.45 mmol, 2.5 equiv.) to afford the *title compound* **3.24** as a white crystalline solid (43 mg, 85%); m.p. 55-58 °C; [Found: $[M+NH_4]^+$, 298.1797. $C_{19}H_{20}O_2$ requires $[M+NH_4]^+$, 298.1802]; υ_{max} (KBr disc/cm^{-1}) 3061, 3029, 3006, 2978, 2931, 1719, 1481, 1452, 1368, 1311, 1294, 1216, 1182, 1148; δ_H (500 MHz, $CDCl_3$) 1.33 (9H, s, CH_3), 3.91 (1H, d, *J* 18.2, *H*CH), 4.34 (1H, d, *J* 18.2, HC*H*), 4.90 (1H, s, CH), 7.24-7.30 (4H, m, ArH), 7.34-7.36 (2H, m, ArH), 7.40-7.41 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 27.9 (CH_3), 35.7 (CH_2), 54.2 (CH), 81.2 (C), 126.3 (CH), 127.9 (CH), 128.1 (CH), 134.3 (C), 136.5 (C), 171.1 (C); *m/z* (CI) 298 ($[M+NH_4]^+$, 92%), 242 (80), 179 (100).

9,10-Dihydroanthracene-10-carbonitrile **3.25**

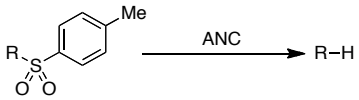


3.25

Using general procedure B, 9-anthracenecarbonitrile **3.18** (50 mg, 0.25 mmol, 1.0 equiv.) was reduced in *N*,*N*-dimethylformamide (45 ml) using nickel(II) complex **3.1** (467 mg, 0.625 mmol, 2.5 equiv.) to afford the *title compound* **3.25** as a light-yellow crystalline solid (41 mg, 79%); m.p. 109-111 °C; [Found: $[M]^+$, 205.0888. $C_{15}H_{11}N$

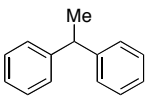
requires $[M]^+$, 205.0886]; υ_{max} (KBr disc/cm^{-1}) 3069, 3037, 3023, 2856, 2244, 1477, 1456, 1431; δ_H (500 MHz, $CDCl_3$) 3.94 (1H, d, *J* 17.9, *H*CH), 4.11 (1H, d, *J* 17.9, HC*H*), 5.05 (1H, s, CH), 7.33-7.40 (6H, m, ArH), 7.63-7.65 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 35.6 (CH_2), 37.1 (CH), 118.3 (C), 126.6 (CH), 127.1 (CH), 128.0 (CH), 128.3 (CH), 130.9 (C), 136.1 (C); *m/z* (EI) 205 ($[M]^+$, 100%), 204 (86), 203 (62), 178 (55).

General Procedure C – General procedure for the reductive cleavage of sulfones, bissulfones and sulfonamides using the active nickel complex



Nickel(II) complex **3.1** (2.0 – 4.0 equiv.) was added to *N*,*N*-dimethylformamide over a freshly prepared sodium amalgam (1%, 100 g sodium, 10.0 g mercury) and stirred under an argon flow for 4 h at room temperature. During this time, the reaction mixture a formed a dark red solution and the substrate was dried under vacuum at room temperature. After this time, the dark red active nickel complex solution was added to the substrate rapidly *via* cannula and the resulting solution stirred under argon at room temperature for 18 h. The reaction solution was poured into water (150 ml) and extracted with diethyl ether (2 x 150 ml). The combined organic layers were then washed with water (2 x 100 ml) and brine (100 ml), dried over sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography afforded the required reduced product.

1,1-Diphenylethane **3.31**

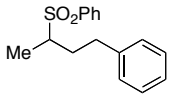


3.31

Using general procedure C, 1,1-diphenyl-1-(phenylsulfonyl)ethane **3.29**[144] (60 mg, 0.186 mmol, 1.0 equiv.) was reacted with nickel(II) complex **3.1** (277 mg, 0.372 mmol, 2.0 equiv.) that had been stirred over a sodium amalgam in *N*,*N*-dimethylformamide (30 ml). Purification by silica gel chromatography eluting with

100% hexane afforded the title compound **3.31** as a clear oil (24 mg, 70%);[64] υ_{max} (neat/cm^{-1}) 3061, 3026, 2967, 2930, 1599, 1493, 1450; δ_H (500 MHz, $CDCl_3$) 1.65 (3H, d, *J* 7.5, CH_3), 4.16 (1H, q, *J* 7.5, CH), 7.18-7.21 (2H, m, ArH), 7.23-7.24 (4H, m, ArH), 7.27-7.31 (4H, m, ArH); δ_C (125 MHz, $CDCl_3$) 21.9 (CH_3), 44.8 (CH), 126.0 (CH), 127.6 (CH), 128.4 (CH), 146.4 (C); *m/z* (EI) 182 ([M]$^+$, 32%), 167 (100), 165 (38), 152 (25).

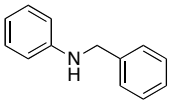
1-[3(Phenylsulfonyl)butyl]benzene **3.32**



3.32

Using general procedure C, 1-phenyl-3,3′-bis(phenylsulfonyl)butane **3.30**[144] (50 mg, 0.121 mmol, 1.0 equiv.) was reacted with nickel(II) complex **3.1** (180 mg, 0.242 mmol, 2.0 equiv.) that had been stirred over a sodium amalgam in *N*,*N*-dimethylformamide (25 ml). Purification by silica gel chromatography eluting with 0-20% ethyl acetate in hexane afforded the title compound **3.32** as a colourless oil (23 mg, 70%);[64] υ_{max} (neat/cm^{-1}) 3062, 3037, 2934, 1603, 1585, 1496, 1447, 1304, 1145, 1085; δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.9, CH_3), 1.70-1.77 (1H, m, *H*CH), 2.29-2.36 (1H, m, *H*CH), 2.57-2.63 (1H, m, *H*CH), 2.80-2.86 (1H, m, *H*CH), 3.02-3.06 (1H, m, CH), 7.10-7.12 (2H, m, ArH), 7.19-7.21 (1H, m, ArH), 7.26-7.31 (2H, m, ArH), 7.54-7.57 (2H, m, ArH), 7.64-7.67 (1H, m, ArH), 7.85-7.87 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 13.3 (CH_3), 30.7 (CH_2), 32.5 (CH_2), 59.1 (CH), 126.3 (CH), 128.3 (CH), 128.6 (CH), 128.9 (CH), 129.0 (CH), 133.6 (CH), 137.3 (C), 140.1 (C); *m/z* (EI) 275 ([M+H]$^+$, 4%), 132 (30), 117 (77), 91 (100).

N-Benzyl-*N*-phenylamine **3.27**

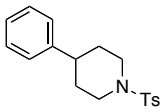


3.27

Using general procedure C, *N*-benzyl-4-methyl-*N*-phenylbenzenesulfonamide **3.26**[144] (50 mg, 0.148 mmol, 1.0 equiv.) was reacted with nickel(II) complex **3.1** (220

mg, 0.296 mmol, 2.0 equiv.) that had been stirred over a sodium amalgam in *N,N*-dimethylformamide (30 ml). Purification by silica gel chromatography eluting with 2-4% ethyl acetate in hexane afforded the title compound **3.27** as a clear yellow oil (27 mg, 97%);[64] υ_{max} (neat/cm^{-1}) 3419, 3052, 3026, 2922, 2852, 1602, 1505, 1324, 1268; δ_H (500 MHz, $CDCl_3$) 4.04 (1H, bs, NH), 4.35 (2H, s, CH_2), 6.65-6.67 (2H, m, ArH), 6.71-6.75 (1H, m, ArH), 7.17-7.21 (2H, m, ArH), 7.27-7.31 (1H, m, ArH), 7.34-7.40 (4H, m, ArH); δ_C (125 MHz, $CDCl_3$) 48.4 (CH_2), 112.9 (CH), 117.6 (CH), 127.3 (CH), 127.5 (CH), 128.7 (CH), 129.3 (CH), 139.5 (C), 148.2 (C); *m/z* (EI) 183 ([M]$^+$, 80%), 91 (100).

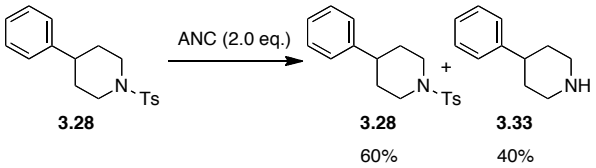
N-Toluenesulfonyl-4-phenylpiperidine **3.28**[64]



3.28

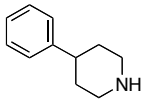
4-Phenylpiperidine **3.33** (800 mg, 4.96 mmol, 1.0 equiv.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triethylamine (1.66 ml, 11.96 mmol, 2.4 equiv.), followed by a solution of *p*-toluenesulfonyl chloride (1.14 g, 5.95 mmol, 1.2 equiv.) in dichloromethane (10 ml) added drop-wise. The reaction mixture was warmed to room temperature and stirred under argon for 20 h. After this time, the reaction mixture was poured into 2M hydrochloric acid (30 ml). The organic layer was separated and washed successively with 2M hydrochloric acid (2 x 30 ml), 2M sodium hydroxide (2 x 30 ml) and brine (50 ml). The dichloromethane solution was dried with sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography eluting with 10-100% ethyl acetate in hexane afforded the title compound **3.28** as a white powder (1.391 g, 89%); m.p. 150-151 °C (lit. 151-152 °C);[64] υ_{max} (KBr disc/cm^{-1}) 3025, 2943, 2922, 2840, 1595, 1493, 1450, 1341, 1334, 1164; δ_H (500 MHz, $CDCl_3$) 1.81-1.90 (4H, m, 2 x CH_2), 2.33-2.44 (3H, m, CH_2, CH), 2.46 (3H, s, CH_3), 3.93-3.96 (2H, m, CH_2), 7.14-7.16 (2H, m, ArH), 7.19-7.23 (1H, m, ArH), 7.29-7.32 (2H, m, ArH), 7.35 (2H, d, *J* 7.9, ArH), 7.68-7.70 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 21.6 (CH_3), 32.5 (CH_2), 41.8 (CH), 46.9 (CH_2), 126.6 (CH), 126.7 (CH), 127.8 (CH), 128.6 (CH), 129.6 (CH), 133.2 (C), 143.5 (C), 144.9 (C); *m/z* (CI) 316 ([M+H]$^+$, 58%), 162 (100).

Attempted reduction of *N*-toluenesulfonyl-4-phenylpiperidine **3.28**



Using general procedure C, *N*-(toluenesulfonyl)-4-phenylpiperidine **3.28** (50 mg, 0.159 mmol, 1.0 equiv.) was reacted with nickel(II) complex **3.1** (237 mg, 0.318 mmol, 2.0 equiv.) that had been stirred over a sodium amalgam in *N,N*-dimethylformamide (25 ml). The ^{1}H NMR spectrum of the crude reaction mixture revealed a mixture of *N*-toluenesulfonyl-4-phenylpiperidine **3.28** starting material and 4-phenylpiperidine **3.33** product in an approximate 60:40 ratio (based on the peaks at δ 3.93-3.96 ppm of **3.28** and at δ 3.19-3.21 ppm of **3.33**).

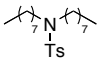
4-Phenylpiperidine **3.33**



3.33

Using general procedure C, *N*-(toluenesulfonyl)-4-phenylpiperidine **3.28** (50 mg, 0.159 mmol, 1.0 equiv.) was reacted with nickel(II) complex **3.1** (472 mg, 0.634 mmol, 4.0 equiv.) that had been stirred over a sodium amalgam in *N,N*-dimethylformamide (45 ml). Purification by dissolving the residue in dichloromethane (20 ml) and extraction with 0.5 M hydrochloric acid, followed by basification with 2M sodium hydroxide then extraction with dichloromethane (2 x 25 ml) and concentration, afforded the title compound **3.33** as an off-white crystalline solid (17 mg, 66%); m.p. 62-64 °C (lit. 60-63 °C);[173] [Found: $[M+H]^+$, 162.1274. $C_{11}H_{15}N$ requires $[M+H]^+$, 162.1274]; υ_{max} (KBr disc/cm^{-1}) 3293, 2931, 2917, 2848, 1644, 1543, 1451, 1413, 1370, 1247; δ_H (500 MHz, $CDCl_3$) 1.27 (1H, s, NH), 1.62-1.70 (2H, m, CH_2), 1.83-1.86 (2H, m, CH_2), 2.60-2.65 (1H, m, CH), 2.73-2.79 (2H, m, CH_2), 3.19-3.21 (2H, m, CH_2), 7.19-7.25 (3H, m, ArH), 7.30-7.33 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 34.6 (CH_2), 43.1 (CH), 47.2 (CH_2), 126.1 (CH), 126.8 (CH), 128.4 (CH), 146.8 (C); *m/z* (CI) 162 ($[M+H]^+$, 100%), 72 (43).

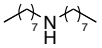
N-Toluenesulfonyl-di-*N*-octylamine **3.35**



3.35

Di-*N*-octylamine **3.34** (2.0 g, 8.28 mmol, 1.0 equiv.) and triethylamine (2.77 ml, 19.88 mmol, 2.4 equiv.) were dissolved in dichloromethane (20 ml) and cooled to 0 °C where a solution of *p*-toluenesulfonyl chloride (1.74 g, 9.11 mmol, 1.1 equiv.) in dichloromethane (10 ml) was added *via* cannula. The resultant mixture was warmed to room temperature and stirred under argon for 20 h. After this time, the cloudy solution was diluted with dichloromethane (80 ml) and washed successively with 2M hydrochloric acid (3 x 100 ml), 2M sodium hydroxide (3 x 100 ml) and brine (100 ml), then dried with sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography, eluting with first 2-4% diethyl ether in petroleum ether, then 10% ethyl acetate in petroleum ether, afforded the *title compound* **3.35** as a clear colourless oil (3.07 g, 93%); [Found: $[M+H]^+$, 396.2926. $C_{23}H_{41}NO_2S$ requires $[M+H]^+$, 396.2931]; υ_{max} (neat/cm^{-1}) 3029, 2927, 2856, 1599, 1494, 1465, 1343, 1159, 1092; δ_H (500 MHz, $CDCl_3$) 0.89 (6H, t, *J* 7.0, 2 x CH_3), 1.25-1.31 (20H, m, 10 x CH_2), 1.49-1.52 (4H, m, 2 x CH_2), 2.42 (3H, s, CH_3), 3.08-3.11 (4H, m, 2 x CH_2), 7.28 (2H, d, *J* 8.0, ArH), 7.68-7.70 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 14.1 (CH_3), 21.5 (CH_3), 22.6 (CH_2), 26.7 (CH_2), 28.6 (CH_2), 28.7 (CH_2), 29.2 (CH_2), 31.8 (CH_2), 48.2 (CH_2), 127.1 (CH), 129.5 (CH), 137.3 (C), 142.8 (C); *m/z* (CI) 396 ($[M+H]^+$, 100%), 242 (82), 142 (47).

Di-*N*-octylamine **3.34**

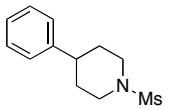


3.34

Using general procedure C, *N*-toluenesulfonyl-di-*N*-octylamine **3.35** (70 mg, 0.177 mmol, 1.0 equiv.) was reacted with nickel(II) complex **3.1** (527 mg, 0.708 mmol, 4.0 equiv.) that had been stirred over a sodium amalgam in *N*,*N*-dimethylformamide (50 ml). Purification by washing a diethyl ether (50 ml) solution of the crude product with a 0.5 M sodium hydroxide solution (2 x 25 ml) afforded the title compound **3.34** as a slightly yellow oil (41 mg, 95%);[174] [Found: $[M+H]^+$, 242.2844. $C_{16}H_{35}N$ requires

[M+H]$^+$, 242.2842]; υ_{max} (neat/cm^{-1}) 3114, 2954, 2916, 2848, 2814, 1469, 1129; δ_H (500 MHz, $CDCl_3$) 0.89 (6H, t, *J* 7.0, 2 x CH_3), 1.23-1.30 (20H, m, 10 x CH_2), 1.47-1.52 (4H, m, 2 x CH_2), 2.60 (4H, t, *J* 7.5, 2 x CH_2); δ_C (125 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 27.4 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 30.1 (CH_2), 31.8 (CH_2), 50.1 (CH_2); *m/z* (EI) 241 ([M]$^+$, 5%), 170 (10), 142 (100).

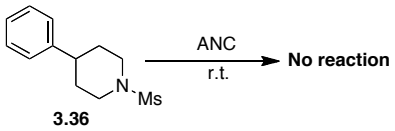
N-Methanesulfonyl-4-phenylpiperidine **3.36**



3.36

4-Phenylpiperidine **3.33** (800 mg, 4.96 mmol, 1.0 equiv.) was dissolved in dichloromethane (20 ml), cooled to 0 °C and triethylamine (2.07 ml, 14.88 mmol, 3.0 equiv.), followed by methanesulfonyl chloride (1.16 ml, 14.88 mmol, 3.0 equiv.), added drop-wise. The resulting yellow solution was warmed to room temperature and stirred under argon for 20 h. After this time, 2 M hydrochloric acid (40 ml) was added and the reaction mixture stirred for 10 min before the organic layer was separated and the aqueous layer washed with dichloromethane (2 x 30 ml). The combined organic layers were washed with sodium bicarbonate (sat., 50 ml) and brine (50 ml), before being dried with sodium sulfate, filtered and concentrated under vacuum. Purification by silica gel chromatography eluting with 20-30% ethyl acetate in petroleum ether afforded the *title compound* **3.36** as a white powder (986 mg, 83%); m.p. 129-131 °C; [Found: [M+H]$^+$, 240.1055. $C_{12}H_{17}NO_2S$ requires [M+H]$^+$, 240.1053]; υ_{max} (KBr disc/cm^{-1}) 3020, 2937, 2851, 1600, 1445, 1320, 1145; δ_H (500 MHz, $CDCl_3$) 1.85-1.90 (2H, m, CH_2), 1.96-1.99 (2H, m, CH_2), 2.60-2.65 (1H, m, CH), 2.76-2.83 (5H, m, CH_2, CH_3), 3.94-3.97 (2H, m, CH_2), 7.21-7.27 (3H, m, ArH), 7.32-7.35 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 32.8 (CH_2), 34.8 (CH_3), 42.0 (CH), 46.6 (CH_2), 126.7 (CH), 126.8 (CH), 128.7 (CH), 144.8 (C); *m/z* (ESI) 240 ([M+H]$^+$, 100%), 257 (41), 262 (23).

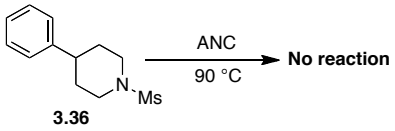
Attempted reduction of *N*-methanesulfonyl-4-phenylpiperidine **3.36** using the active nickel complex – attempt 1



3.36

A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N,N*-dimethylformamide (40 ml), followed by nickel(II) complex **3.1** (373 mg, 0.501 mmol, 4.0 equiv.) added. The reaction mixture was stirred under argon at room temperature 4 h, during which time the colour changed to dark red and *N*-methanesulfonyl-4-phenylpiperidine **3.36** (30 mg, 0.125 mmol, 1.0 equiv.) was dried under vacuum at room temperature. After this time, the dark red solution was added to the substrate **3.36** rapidly *via* cannula and stirred under argon at room temperature for 18 h. The reaction mixture was then partitioned between diethyl ether (150 ml) and water (150 ml) and the organic layer separated. The aqueous layer was extracted with further diethyl ether (150 ml) and the organic layers combined then washed with water (2 x 100 ml) and brine (100 ml). The diethyl ether solution was dried with Na_2SO_4 and concentrated under vacuum. Purification by silica gel chromatography eluting with 20% ethyl acetate in hexane afforded the starting material **3.36** as a white powder (28 mg, 93%); the data were consistent with those of *N*-methanesulfonyl-4-phenylpiperidine **3.36**.

Attempted reduction of *N*-methanesulfonyl-4-phenylpiperidine **3.36** using the active nickel complex – attempt 2

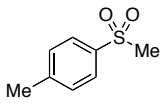


3.36

A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N,N*-dimethylformamide (40 ml), followed by nickel(II) complex **3.1** (373 mg, 0.501 mmol, 4.0 equiv.) added. The reaction mixture was stirred under argon at room temperature 4 h, during which time the colour changed to dark red and *N*-methanesulfonyl-4-phenylpiperidine **3.36** (30 mg, 0.125 mmol, 1.0 equiv.) was dried under vacuum at room temperature. After this time, the dark red solution was added

to the substrate, which had been heated to 90 °C, rapidly *via* cannula and stirred under argon at 90 °C for 18 h. The reaction mixture was then partitioned between diethyl ether (150 ml) and water (150 ml) and the organic layer separated. The aqueous layer was extracted with further diethyl ether (150 ml) and the organic layers combined then washed with water (2 x 100 ml) and brine (100 ml). The diethyl ether solution was dried with Na_2SO_4 and concentrated under vacuum. Purification by silica gel chromatography eluting with 20% ethyl acetate in hexane afforded the starting material **3.36** as a white powder (28 mg, 93%); the data were consistent with those of *N*-methanesulfonyl-4-phenylpiperidine **3.36**.

Trapping of intermediate sulfinate anion to support reductive cleavage mechanism – isolation of 1-methyl-(4-methylsulfonyl)benzene **3.42**

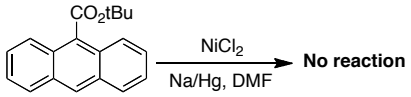


3.42

A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (40 ml) added, followed by nickel(II) complex **3.1** (400 mg, 0.537 mmol, 2.0 equiv.). The reaction mixture was stirred under an argon atmosphere for 4 h, during which time the reaction mixture formed a dark red solution and *N*-benzyl-4-methyl-*N*-phenylbenzenesulfonamide **3.26**[144] (90 mg, 0.269 mmol, 1.0 equiv.) was dried under vacuum at room temperature. After this time, the dark red solution was added rapidly *via* cannula to the substrate and stirred under argon at room temperature for 18 h. Iodomethane (0.834 ml, 13.4 mmol, 50.0 equiv.) was then added and stirring continued for 48 h under argon at room temperature. The reaction mixture was then partitioned between diethyl ether (150 ml) and water (150 ml) and the organic layer separated. The aqueous layer was extracted with further diethyl ether (150 ml) and the organic layers combined then washed with water (2 x 100 ml) and brine (100 ml). The diethyl ether solution was dried with Na_2SO_4 and concentrated under vacuum. Purification by silica gel chromatography eluting with 10% ethyl acetate in hexane afforded the title compound **3.42** as a white powder (33 mg, 72%); m.p. 83-85 °C (lit. 88 °C);[175] υ_{max} (KBr disc/cm^{-1}) 3010, 2926, 1320, 1301, 1290, 1148; δ_H (500 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 3.03 (3H, s, CH_3), 7.36 (2H, d, *J* 8.0, ArH), 7.82 (2H, d, *J* 8.0, ArH); δ_C (125

MHz, $CDCl_3$) 21.6 (CH_3), 44.6 (CH_3), 127.3 (CH), 129.9 (CH), 137.8 (C), 144.7 (C); *m/z* (EI) 170 ([M]$^+$, 20%), 155 (22), 107 (58), 91 (100), 83 (93).

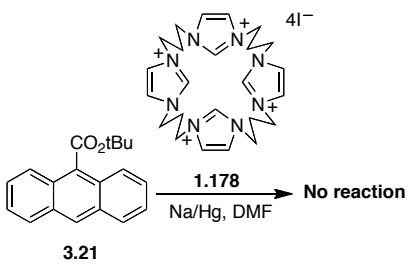
Control reaction to investigate active species – reaction with nickel(II) chloride



3.21

A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (20 ml), followed by nickel(II) chloride (58 mg, 0.45 mmol, 2.5 equiv.) added. The reaction mixture was stirred for 4 h under an argon atmosphere, during which time a black powder precipitated and *tert*-butyl anthracene-9-carboxylate **3.21** (50 mg, 0.18 mmol, 1.0 equiv.) was dried under vacuum at room temperature in a separate flask. After this time, the black suspension was added to the substrate **3.21** rapidly *via* cannula and stirred under argon at room temperature for 1 h. The reaction mixture was then quenched by addition to a saturated ammonium chloride solution (100 ml) and stirred for 5 min then extracted with diethyl ether (2 x 150 ml). The diethyl ether layers were combined then washed with water (2 x 100 ml) and brine (100 ml), then dried with sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography eluting with 5% diethyl ether in hexane afforded the starting material **3.21** as a light-yellow crystalline solid (49 mg, 98%); the data were consistent with those of *tert*-butyl anthracene-9-carboxylate **3.21**.

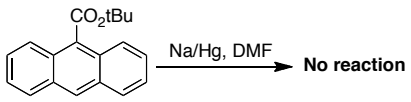
Control reaction to investigate active species – reaction with *tetrakis*trimethylene tetraimidazolium tetraiodide **1.178**



3.21

A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (20 ml), followed by *tetrakis*trimethylene tetraimidazolium tetraiodide **1.178** (425 mg, 0.45 mmol, 2.5 equiv.) added. The reaction mixture was stirred for 4 h under an argon atmosphere, during which time a yellow solution formed and *tert*-butyl anthracene-9-carboxylate **3.21** (50 mg, 0.18 mmol, 1.0 equiv.) was dried under vacuum at room temperature in a separate flask. After this time, the yellow solution was added to the substrate **3.21** rapidly *via* cannula and stirred under argon at room temperature for 1 h. The reaction mixture was then quenched by addition to a saturated ammonium chloride solution (100 ml) and stirred for 5 min then extracted with diethyl ether (2 x 150 ml). The diethyl ether layers were combined then washed with water (2 x 100 ml) and brine (100 ml), then dried with sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography eluting with 5% diethyl ether in hexane afforded the starting material **3.21** as a light-yellow crystalline solid (48 mg, 96%); the data were consistent with those of *tert*-butyl anthracene-9-carboxylate **3.21**.

Control reaction to investigate active species – reaction with *N*,*N*-dimethylformamide only

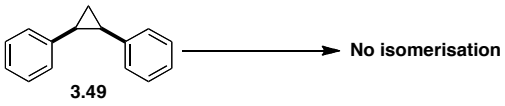


3.21

A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (20 ml) added. The reaction mixture was stirred for 4 h under an argon atmosphere, during which time *tert*-butyl anthracene-9-carboxylate **3.21** (50 mg, 0.18 mmol, 1.0 equiv.) was dried under vacuum at room temperature in a separate flask. After this time, the colourless solution was added to the substrate **3.21** rapidly *via* cannula and stirred under argon at room temperature for 1 h. The reaction mixture was then quenched by addition to a saturated ammonium chloride solution (100 ml) and stirred for 5 min, and then extracted with diethyl ether (2 x 150 ml). The diethyl ether layers were combined then washed with water (2 x 100 ml) and brine (100 ml), then dried with sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography eluting with 5% diethyl ether in hexane

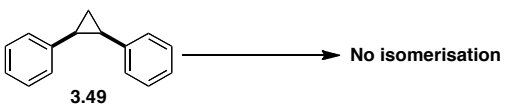
afforded the starting material **3.21** as a light-yellow crystalline solid (48 mg, 96%); the data were consistent with those of *tert*-butyl anthracene-9-carboxylate **3.21**.

Attempted isomerisation of *cis*-diphenylcyclopropane **3.49** – Attempt 1



A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (25 ml), followed by nickel(II) complex **3.1** (229 mg, 0.308 mmol, 1.2 equiv.) added. The reaction mixture was stirred under argon at room temperature for 4 h, during which time the colour changed to dark red and 1*R*,2*S*-diphenylcyclopropane **3.49**[176] (50 mg, 0.257 mmol, 1.0 equiv.) was dried under vacuum at room temperature. After this time, the dark red solution was added to the substrate **3.49** rapidly *via* cannula and stirred under argon at room temperature for 18 h. The reaction mixture was then partitioned between diethyl ether (100 ml) and water (100 ml) and the organic layer separated. The aqueous layer was extracted with further diethyl ether (2 x 75 ml) and the organic layers combined then washed with water (2 x 100 ml) and brine (100 ml). The diethyl ether solution was concentrated under vacuum. Purification by silica gel chromatography eluting with 100% hexane afforded the starting material **3.49** as a colourless, clear oil (46 mg, 92%); the data were consistent with those of 1*R*,2*S*-diphenylcyclopropane **3.49** which had been previously synthesised within our group; δ_H (500 MHz, $CDCl_3$) 1.38-1.42 (1H, m, CH), 1.47-1.52 (1H, m, CH), 2.50-2.53 (2H, m, CH_2), 6.96-6.98 (4H, m, ArH), 7.04-7.13 (6H, m, ArH); δ_C (125 MHz, $CDCl_3$) 11.4 (CH), 24.3 (CH_2), 125.6 (CH), 127.6 (CH), 129.0 (CH), 138.3 (C).

Attempted isomerisation of *cis*-diphenylcyclopropane **3.49** – attempt 2

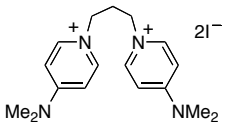


A sodium amalgam (1%, 100 mg sodium, 10.0 g mercury) was freshly prepared and *N*,*N*-dimethylformamide (25 ml), followed by nickel(II) complex **3.1** (229 mg, 0.308

mmol, 1.2 equiv.) added. The reaction mixture was stirred under argon at room temperature for 4 h, during which time the colour changed to dark red and 1*R*,2*S*-diphenylcyclopropane **3.49**[176] (50 mg, 0.257 mmol, 1.0 equiv.) was dried under vacuum at room temperature. After this time, the dark red solution was added to the substrate **3.49** (which was pre-heated to 100 °C) rapidly *via* cannula and stirred under argon at 100 °C for 18 h. The reaction mixture was then partitioned between diethyl ether (100 ml) and water (100 ml) and the organic layer separated. The aqueous layer was extracted with further diethyl ether (2 x 75 ml) and the organic layers combined then washed with water (2 x 100 ml) and brine (100 ml). The diethyl ether solution was concentrated under vacuum. Purification by silica gel chromatography eluting with 100% hexane afforded the starting material **3.49** as a colourless, clear oil (47 mg, 94%); the data were consistent with those of 1*R*,2*S*-diphenylcyclopropane **3.49** which had been previously synthesised within our group; δ_H (500 MHz, $CDCl_3$) 1.38-1.42 (1H, m, CH), 1.47-1.52 (1H, m, CH), 2.50-2.53 (2H, m, CH_2), 6.96-6.98 (4H, m, ArH), 7.04-7.13 (6H, m, ArH); δ_C (125 MHz, $CDCl_3$) 11.4 (CH), 24.3 (CH_2), 125.6 (CH), 127.6 (CH), 129.0 (CH), 138.3 (C).

Experimental for Chapter 4

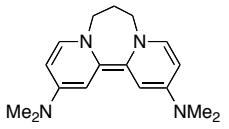
1,3-*bis*(*N′*,*N′*-Dimethyl-4-aminopyridinium)propane diiodide **1.176**[65]



1.176

4-Dimethylaminopyridine **1.175** (6.00 g, 49.11 mmol, 2.5 equiv.) and 1,3-diiodopropane (2.26 ml, 19.64 mmol, 1.0 equiv.) were dissolved in acetonitrile (100 ml) at room temperature then heated to reflux for 48 h. After this time, the reaction mixture was cooled to room temperature where a white precipitate formed. Diethyl ether (50 ml) was added and the white precipitate filtered and washed with further diethyl ether (25 ml) then dried under vacuum. This afforded the title compound **1.176** as a white powder solid (10.63 g, 100%); the data were consistent with those published previously;[65] δ_H (DMSO, 500 MHz) 2.32-2.35 (2H, m, CH_2), 3.19 (12H, s, 4 x CH_3), 4.23 (4H, t, *J* 7.0, 2 x CH_2), 7.04 (4H, d, *J* 7.5, ArH), 8.26 (4H, d, *J* 7.5, ArH); δ_C (125 MHz, DMSO) 31.5 (CH_2), 40.4 (CH_3), 40.5 (CH_3), 54.3 (CH_2), 108.3 (CH), 142.4 (CH), 156.4 (C).

N,*N*,*N′*,*N′*-Tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2-a;2′,1′-c][1,4]diazepine-2,12-diamine **1.177**[65]

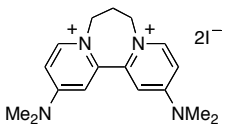


1.177

1,3-*bis*(*N′*,*N′*-Dimethyl-4-aminopyridinium)propane diiodide **1.176** (10.00 g, 18.51 mmol, 1.0 equiv.) was dried under vacuum at 100 °C for 1.5 h then cooled to room temperature, purged with argon and sodium hydride (60% in mineral oil, 7.42 g, 185.1 mmol, 10.0 equiv.) added in one portion. The mixture was washed with dry hexane (3 x 50 ml) and dried under a stream of argon, followed by application of vacuum, to a fine powder. Once dry, the flask was equipped with a dry ice condenser, which had been connected to both the argon inlet and ammonia inlet.

Ammonia (150 ml) was condensed onto the solid mixture, forming a purple suspension. The dry ice condenser was kept cold to allow a reflux of ammonia for 4 h, after which time, the cooling was stopped and the reaction mixture warmed to room temperature overnight (during which time the ammonia evaporated). The flask was moved to the glovebox and the solid residue extracted with diethyl ether (100 ml) by stirring for 1 h then being filtered. The diethyl ether solution was concentrated under vacuum to afford a dark purple residue. This process was repeated a further 4 times (total volume of diethyl ether used = 500 ml) with the diethyl ether solutions combined each time. Removal of all solvent by application of vacuum afforded the title compound **1.177** as a dark purple crystalline solid (3.67 g, 70%); the data were consistent with those published previously;[65] δ_H (C_6D_6, 500 MHz) 0.97-1.02 (2H, m, CH_2), 2.46 (12H, s, 4 x CH_3), 3.02 (4H, bs, 2 x CH_2), 4.91 (2H, bs, 2 x CH), 5.15 (2H, bs, 2 x CH), 5.63-5.64 (2H, m, 2 x CH); δ_C (125 MHz, C_6D_6) 23.9 (CH_2), 40.2 (CH_3), 52.0 (CH_2), 95.2 (CH), 95.6 (CH), 115.4 (C), 138.1 (CH), 143.1 (C).

N,N,N′,N′-Tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2a-2′,1′c][1,4]diazepinium-2,12-diamine diiodide **1.179**[65]

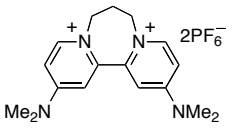


1.179

N,N,N′,N′-Tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2-a;2′,1′-c][1,4]diazepine-2,12-diamine **1.177** (3.66 g, 12.87 mmol, 1.0 equiv.) was dissolved in acetonitrile (100 ml) and slowly added to a solution of iodine (5.55 g, 21.88 mmol, 1.7 equiv.) in diethyl ether (200 ml) at room temperature in the glovebox. A yellow/brown precipitate immediately formed. The suspension was stirred at room temperature for 30 min, then removed from the glovebox and filtered. The resulting solid was washed thoroughly with diethyl ether (approx. 100 ml) and dried under vacuum to afford a brown powder **1.179** that was immediately used in the next stage without further purification (9.12 g, 132%); the data were consistent with those published previously;[65] δ_H (DMSO, 500 MHz) 2.40-2.41 (2H, m, CH_2), 3.29 (6H, s, 2 x CH_3), 3.34 (6H, s, 2 x CH_3), 3.92-3.98 (2H, m, 2 x CH), 4.54-4.57 (2H, m, 2 x CH), 7.23 (2H, dd, *J* 7.8, 2.5, ArH), 7.41 (2H, s, ArH), 8.45 (2H, d, *J* 7.5, ArH); δ_C (125 MHz,

DMSO) 29.2 (CH_2), 40.5 (CH_3), 40.7 (CH_3), 51.6 (CH_2), 108.6 (CH), 112.1 (CH), 143.4 (C), 144.1 (CH), 156.8 (C).

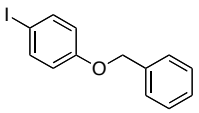
N,N,N′,N′-Tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2a-2′,1′c][1,4]diazepinium-2,12-diamine dihexafluorophosphate **4.2**[65]



4.2

N,N,N′,N′-Tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2a-2′,1′c][1,4]diazepinium-2,12-diamine diiodide **1.179** (7.0 g, 12.87 mmol, 1.0 equiv.) was added to distilled water (100 ml) and filtered to remove any residual iodine or iodide salts. The resulting aqueous solution was stirred vigorously while hexafluorophosphoric acid (5.69 ml, 38.61 mmol, 3.0 equiv.) was added causing a light yellow precipitate to form. The aqueous suspension was stirred for 10 min then filtered and washed with distilled water until the pH of the drops leaving the funnel was neutral. The yellow powder was dried under vacuum, then transferred to a round-bottomed flask and dried under high vacuum for 24 h to afford the title compound **4.2** as a light yellow powder (3.43 g, 46%); m.p. 276-278 °C (dec.) (lit. 282-287 °C (dec.);[65] υ_{max} (KBr disc/cm^{-1}) 3663, 3116, 2952, 1931, 1643, 1578, 1540, 1436, 843; δ_H (DMSO, 500 MHz) 2.40-2.41 (2H, m, CH_2), 3.28 (6H, s, 2 x CH_3), 3.31 (6H, s, 2 x CH_3), 3.91-3.98 (2H, m, 2 x CH), 4.52-4.54 (2H, m, 2 x CH), 7.23 (2H, dd, *J* 7.8, 3.0, ArH), 7.38 (2H, s, ArH), 8.42 (2H, d, *J* 8.0, ArH); δ_C (125 MHz, DMSO) 28.7 (CH_2), 40.0 (CH_3), 40.1 (CH_3), 51.1 (CH_2), 108.1 (CH), 111.5 (CH), 142.9 (C), 143.5 (CH), 156.4 (C); *m/z* (ESI) 597 ($[M+Na]^+$, 10%), 429 (75), 283 (84), 142 (100).

1-(Benzyloxy)-4-iodobenzene **4.4**

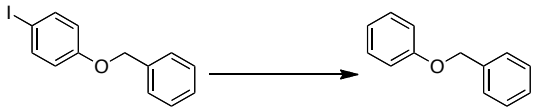


4.4

4-Iodophenol **4.3** (12.10 g, 55.0 mmol, 1.1 equiv.), potassium carbonate (20.73 g, 150.0 mmol, 3.0 equiv.) and *N,N*-dimethylformamide (80 ml) were stirred together in

a round-bottomed flask at room temperature and benzyl bromide (5.95 ml, 50.0 mmol, 1.0 equiv.) added. The reaction mixture was stirred under argon at room temperature for 72 h. After this time, the reaction mixture was diluted with water (150 ml) and extracted with diethyl ether (3 x 100 ml). The organic layers were combined and washed with water (4 x 100 ml) and brine (100 ml), then dried over sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography eluting with 10% diethyl ether in hexane afforded the title compound **4.4** as white needles (15.219 g, 98%); m.p. 59-61 °C (lit. 58 °C);[177] [Found: $[M]^+$, 309.9846. $C_{13}H_{11}IO$ requires $[M]^+$, 309.9849]; υ_{max} (KBr disc/cm^{-1}) 3089, 3063, 3032, 2907, 2861, 1568, 1454, 1400, 1382, 1225; δ_H ($CDCl_3$, 500 MHz) 5.05 (2H, s, CH_2), 6.76 (2H, d, *J* 9.0, ArH), 7.33-7.43 (5H, m, ArH), 7.55-7.58 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 70.1 (CH_2), 83.1 (C), 117.1 (CH), 127.4 (CH), 128.1 (CH), 128.7 (CH), 136.5 (C), 138.3 (CH), 158.6 (C); *m/z* (EI) 310 ($[M]^+$, 14%), 91 (100).

Stoichiometric reduction of 1-(benzyloxy)-4-iodobenzene **4.4** using donor **1.177** to afford (benzyloxy)benzene **4.5**

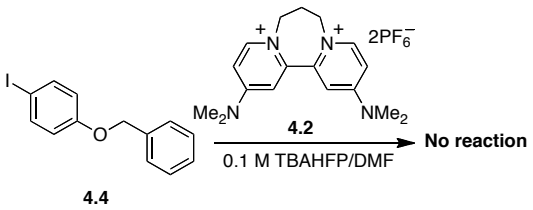


4.4 **4.5**

1,3-*bis*(*N′*,*N′*-Dimethyl-4-aminopyridinium)propane diiodide **1.176** (810 mg, 1.5 mmol, 1.5 equiv.) was dried under vacuum at 100 °C for 1 h then cooled and purged with argon. Sodium hydride (60% in mineral oil, 601 mg, 15.0 mmol, 15.0 equiv.) was added and the solid mixture washed with anhydrous hexane (2 x 20 ml) and dried under a stream of argon. *N*,*N*-Dimethylformamide (15 ml) was added, causing a dark purple suspension to form, which was stirred under argon at room temperature for 4 h. After this time, the dark purple donor suspension was centrifuged at 2000 r.p.m. for 10 min to afford a dark purple solution. This solution was added *via* cannula to 1-(benzyloxy)-4-iodobenzene **4.4** (310 mg, 1.0 mmol, 1.0 equiv.). The solution was stirred under argon at room temperature for 18 h. The dark solution was then diluted with water (50 ml) and then extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with water (4 x 50 ml) and brine (50 ml), dried and concentrated. Purification by silica gel chromatography

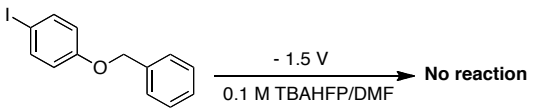
eluting with 0-2% diethyl ether in hexane afforded (benzyloxy)benzene **4.5** (138 mg, 75%); m.p. 37-38 °C (lit. 39-40 °C);[178] [Found: $[M]^+$, 184.0881. $C_{13}H_{12}O$ requires $[M]^+$, 184.0883]; υ_{max} (KBr disc/cm^{-1}) 3056, 3034, 2907, 2866, 1599, 1585, 1498, 1455, 1377, 1246, 1029; δ_H ($CDCl_3$, 500 MHz) 5.10 (2H, s, CH_2), 6.98-7.03 (3H, m, ArH), 7.31-7.38 (3H, m, ArH), 7.40-7.44 (2H, m, ArH), 7.46-7.49 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 70.0 (CH_2), 114.9 (CH), 121.0 (CH), 127.5 (CH), 128.0 (CH), 128.6 (CH), 129.5 (CH), 137.1 (C), 158.9 (C); *m/z* (EI) 184 ($[M]^+$, 22%), 91 (100).

Control reaction 1: absence of applied potential in the attempted reduction of 1-(benzyloxy)-4-iodobenzene **4.4**



1-(Benzyloxy)-4-iodobenzene **4.4** (150 mg, 0.48 mmol, 1.0 equiv.), *N,N,N′,N′*-tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2a-2′,1′c][1,4]diazepinium-2,12-diamine dihexafluorophosphate **4.2** (28 mg, 0.048 mmol, 0.1 equiv.) and tetrabutylammonium hexafluorophosphate (387 mg, 0.1 M solution) were dissolved in *N,N*-dimethylformamide (10 ml) and stirred under argon at room temperature for 24 h. After this time, the reaction mixture was diluted with water (100 ml) and extracted with diethyl ether (3 x 100 ml). All organic layers were combined and washed with brine (3 x 100 ml), dried over sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography eluting with 2% diethyl ether in hexane afforded the starting material 1-(benzyloxy)-4-iodobenzene **4.4** (148 mg, 99%); the data were consistent with those stated above; δ_H ($CDCl_3$, 500 MHz) 5.05 (2H, s, CH_2), 6.76 (2H, d, *J* 9.0, ArH), 7.33-7.43 (5H, m, ArH), 7.55-7.58 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 70.1 (CH_2), 83.1 (C), 117.1 (CH), 127.4 (CH), 128.1 (CH), 128.7 (CH), 136.5 (C), 138.3 (CH), 158.6 (C).

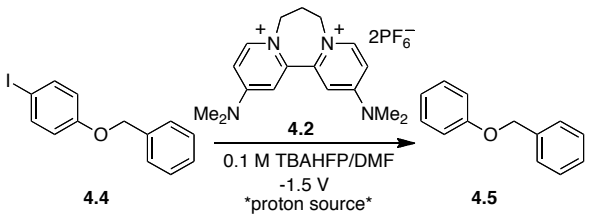
Control reaction 2: absence of *N,N,N′,N′*-tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2a-2′,1′c][1,4]diazepinium-2,12-diamine dihexafluorophosphate **4.2** in the attempted reduction of 1-(benzyloxy)-4-iodobenzene **4.4**



4.4

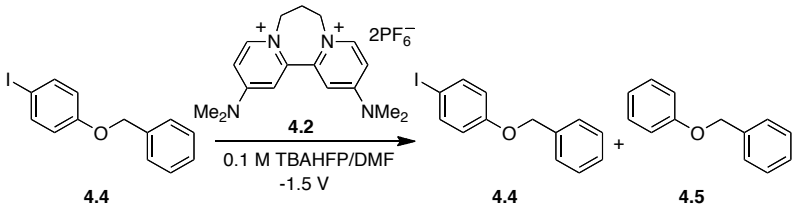
A 10 ml volumetric flask containing 1-(benzyloxy)-4-iodobenzene **4.4** (155 mg, 0.5 mmol, 1.0 equiv.) and tetrabutylammonium hexafluorophosphate (387 mg, 0.1 M solution) were transferred to the glovebox together with a three-compartment cell, Pt gauze working electrode, Pt wire counter-electrode and a Ag/AgCl/KCl (sat.) reference electrode. The Pt working-electrode and the reference electrode were suspended above the working compartment of the cell, while the Pt counter electrode was suspended above the counter compartment of the cell. The contents of the flask were dissolved in *N,N*-dimethylformamide (10 ml). The centre compartment of the cell was filled with blank electrolyte (0.1 M tetrabutylammonium hexafluorophosphate in *N,N*-dimethylformamide), followed by the addition of blank electrolyte (10 ml) to the counter compartment, then the contents of the volumetric flask to the working compartment. Using the programme “amperometry”, the cell was switched on at -1.5 V and held at this potential, with stirring of each compartment, for 24 h. After this time, the reaction mixture from each cell compartment was diluted with water (100 ml) and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with brine (3 x 100 ml), dried over sodium sulfate and concentrated under vacuum. Purification by silica gel chromatography eluting with 2% diethyl ether in hexane afforded the starting material 1-(benzyloxy)-4-iodobenzene **4.4** (150 mg, 97%); the data were consistent with those stated above; δ_H ($CDCl_3$, 500 MHz) 5.05 (2H, s, CH_2), 6.76 (2H, d, *J* 9.0, ArH), 7.33-7.43 (5H, m, ArH), 7.55-7.58 (2H, m, ArH); δ_C (125 MHz, $CDCl_3$) 70.1 (CH_2), 83.1 (C), 117.1 (CH), 127.4 (CH), 128.1 (CH), 128.7 (CH), 136.5 (C), 138.3 (CH), 158.6 (C).

General procedure D – Procedure for the catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4** using donor **1.177** (derived from disalt **4.2**)



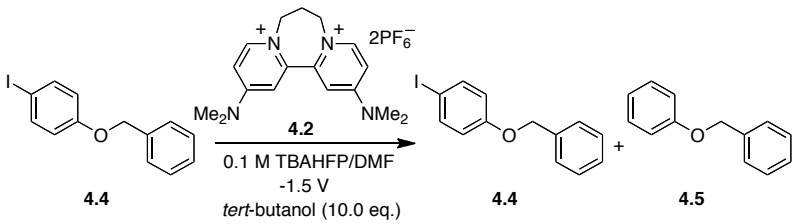
A 10 ml volumetric flask containing 1-(benzyloxy)-4-iodobenzene **4.4** (155 mg, 0.5 mmol, 1.0 equiv.), *N,N,N′,N′*-tetramethyl-7,8-dihydro-*6H*-dipyrido[1,2a-2′,1′c][1,4]-diaze-pinium-2,12-diamine dihexafluorophosphate **4.2** and tetrabutylammonium hexafluorophosphate (387 mg, 0.1 M solution) were transferred to the glovebox together with a three-compartment cell, Pt gauze working electrode, Pt wire counter electrode and a Ag/AgCl/KCl (sat.) reference electrode. The Pt working electrode and the reference electrode were suspended above the working compartment of the cell, while the Pt counter electrode was suspended above the counter compartment of the cell. The contents of the flask were dissolved in *N*,*N*-dimethylformamide (10 ml). The centre compartment of the cell was filled with blank electrolyte (0.1 M tetrabutylammonium hexafluorophosphate in *N*,*N*-dimethylformamide), followed by the addition of blank electrolyte (10 ml) to the counter compartment, then the contents of the volumetric flask to the working compartment. Using the programme "amperometry", the cell was switched on at -1.5 V and held at this potential, with stirring of each compartment, for 24 h. After this time, the reaction mixture from each cell compartment was diluted with water (100 ml) and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with brine (3 x 100 ml), dried over sodium sulfate and concentrated under vacuum. The resulting residue was purified by silica gel chromatography eluting with 2% diethyl ether in hexane and analysed by ^{1}H NMR to observe the conversion to product **4.5**.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 1* – 10 mol% disalt **4.2**



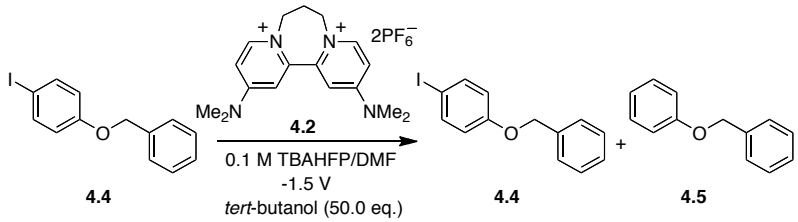
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (139 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (125.5 mg, 81%) and (benzyloxy)benzene **4.5** product (13.5 mg, 15%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 2* – 10 mol% disalt **4.2** and *tert*-butanol



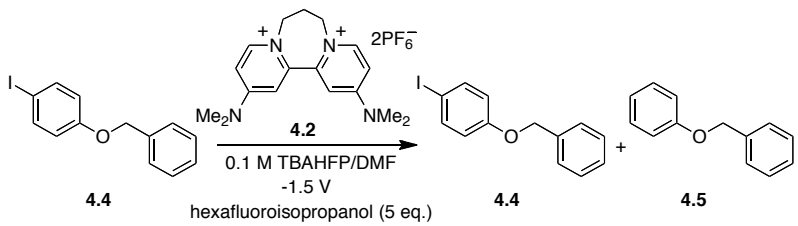
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) and *tert*-butanol (371 mg, 5.0 mmol, 10.0 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (134 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (120.9 mg, 78%) and (benzyloxy)benzene **4.5** product (13.1 mg, 14%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 3* – 10 mol% disalt **4.2** and *tert*-butanol



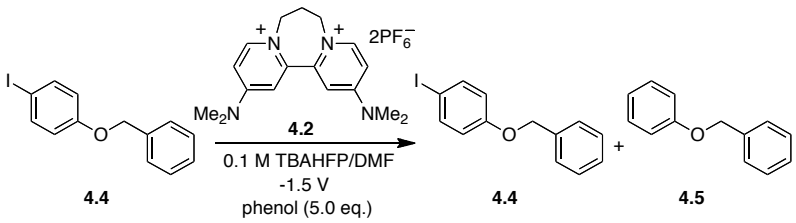
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) and *tert*-butanol (1.85 g, 25.0 mmol, 50.0 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (138 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (126.9 mg, 82%) and (benzyloxy)benzene **4.5** product (11.1 mg, 12%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 4* – 10 mol% disalt **4.2** and 1,1,1,3,3,3-hexafluoroisopropanol



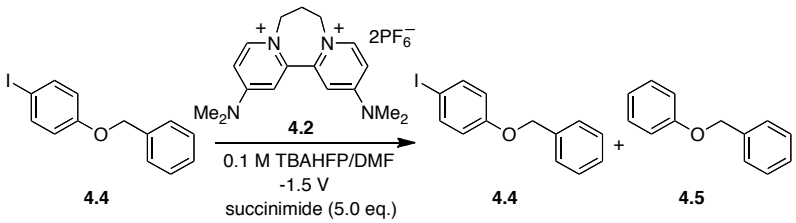
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) and 1,1,1,3,3,3-hexafluoroisopropanol (420 mg, 2.5 mmol, 5.0 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (146 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (143.2 mg, 92%) and (benzyloxy)benzene **4.5** product (2.8 mg, 3%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 5* – 10 mol% disalt **4.2** and phenol



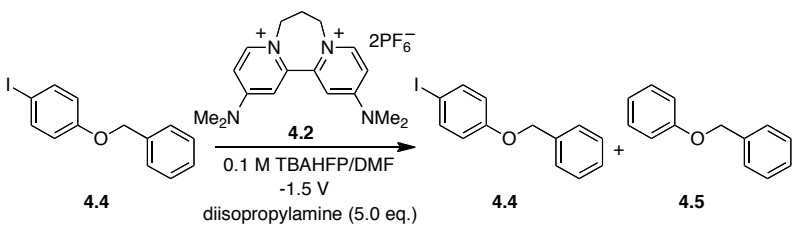
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reacted using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) and phenol (235 mg, 2.5 mmol, 5.0 eq.) to afford starting material **4.4** (151 mg, 97%) only; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 6* – 10 mol% disalt **4.2** and succinimide



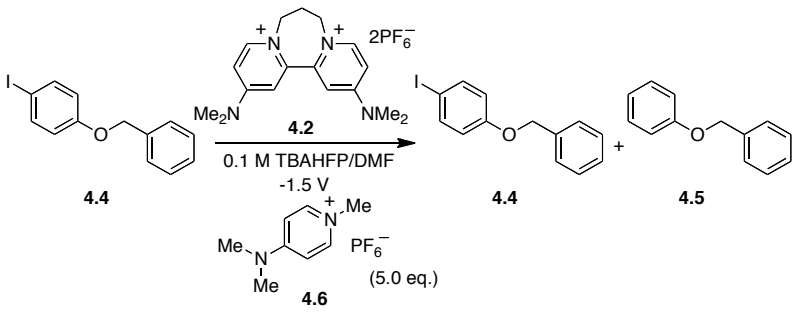
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reacted using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) and succinimide (248 mg, 2.5 mmol, 5.0 eq.) to afford starting material **4.4** (150 mg, 97%) only; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 7* – 10 mol% disalt **4.2** and diisopropylamine



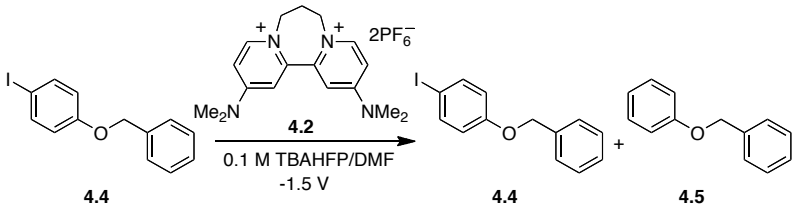
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) and diisopropylamine (253 mg, 2.5 mmol, 5.0 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (133 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (123.5 mg, 80%) and (benzyloxy)benzene **4.5** product (9.5 mg, 10.3%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 8* – 10 mol% disalt **4.2** and 4-(dimethylamino)-1-methylpyridinium iodide **4.6**



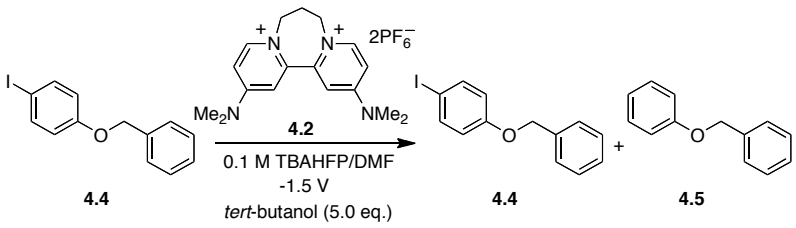
Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (29 mg, 0.05 mmol, 0.1 eq.) and 4-(dimethylamino)-1-methylpyridinium iodide (705 mg, 2.5 mmol, 5.0 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (137 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (127.8 mg, 82%) and (benzyloxy)benzene **4.5** product (9.2 mg, 10%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 9* – 20 mol% disalt **4.2**



Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (57 mg, 0.1 mmol, 0.2 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (135 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (111.4 mg, 72%) and (benzyloxy)benzene **4.5** product (23.6 mg, 26%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Catalytic reduction of 1-(benzyloxy)-4-iodobenzene **4.4**: *attempt 10* – 20 mol% disalt **4.2** and *tert*-butanol



Using general procedure D, 1-(benzyloxy)-4-iodobenzene **4.4** was reduced using disalt **4.2** (57 mg, 0.1 mmol, 0.2 eq.) and *tert*-butanol (185 mg, 2.5 mmol, 5.0 eq.) to afford a mixture of starting material **4.4** and (benzyloxy)benzene **4.5** as an inseparable mixture (115 mg, combined mass). Mixture consisted of starting material 1-(benzyloxy)-4-iodobenzene **4.4** (94.8 mg, 62%) and (benzyloxy)benzene **4.5** product (20.2 mg, 22%); mass and yield of each component calculated based upon comparison of the integral at δ 5.05 ppm of 1-(benzyloxy)-4-iodobenzene **4.4** and at δ 5.10 ppm of (benzyloxy)benzene **4.5**; the data were consistent with those stated above.

Appendix

Titration to determine the number of electrons transferred from the chemically activated nickel complex

Attempt 1

Initially, a known concentration of sodium thiosulfate was used to calculate the concentration of iodine used to quench the active nickel complex.

Concentration of sodium thiosulfate solution

Mass of sodium thiosulfate used = 523.0 mg

M.W. of sodium thiosulfate = 248.18

Volume of water used = 200 ml

$\therefore [Na_2S_2O_3]_{(aq)} = \frac{523/248.18}{0.2} = 10.537$ mM

Titration against iodine of unknown concentration

Volume of iodine solution used = 10 ml

Volume of sodium thiosulfate used:

1. 33.5 ml (rough)
2. 33.4 ml
3. 33.5 ml

Average volume = 33.45 ml

$\therefore [I_2]$, since $2\ Na_2S_2O_3 + I_2 \rightarrow 2I^- + S_4O_6^{2-} + 4\ Na^+$

$$\therefore [I_2] = \frac{\text{ave. vol. } Na_2S_2O_3 \times [Na_2S_2O_3]}{2 \times \text{vol. } I_2}$$

$$= \frac{0.033467 \times 10.537}{2 \times 0.01}$$

$\therefore [I_2] = 17.632$ mM

$\therefore$ No. of moles of I_2 per 10 ml aliquot $= 17.632 \times 0.01$

$= 0.176$ mmol

The experiment involves the addition of a 10 ml aliquot of the activated nickel complex to a 10 ml DMF solution of iodine of the above concentration. A bulk solution of active nickel complex was prepared to allow repetition of the titration.

*Concentration and number of moles of nickel(II) complex **3.1** used*

Mass of nickel(II) complex **3.1** = 261.4 mg

M.W. of nickel(II) complex **3.1** = 745.07

Volume of DMF used = 35 ml

$\therefore$ [Nickel(II) complex **3.1**] = $\frac{261.4/745.07}{0.035}$ = 10.024 mM

$\therefore$ No. of moles of nickel(II) complex **3.1** (and hence no. of moles of active nickel complex (ANC)) per 10 ml aliquot used = 10.024 mM x 0.01

= 0.100 mmol

Titration of sodium thiosulfate against quenched solution of ANC and iodine

Since, $2\ Na_2S_2O_3 + I_2 \rightarrow 2I^- + S_4O_6^{2-} + 4\ Na^+$

$\therefore$ 2 moles of thiosulfate are always required to react with iodine

Volume of sodium thiosulfate used:
1. 15.5 ml (rough)
2. 15.2 ml
3. 15.3 ml

Average volume = 15.25 ml

$\therefore$ No. of moles of i_2 = Total moles of I_2 – Moles of iodine titrated with $Na_2S_2O_3$ reacted with ANC

$\therefore$ = 0.176 – $\frac{[\text{ave. moles } Na_2S_2O_3 \text{ used in } I_2 \text{ titration}]}{2}$

= 0.176 – $\frac{[10.537 \times 0.01525]}{2}$

= 0.176 – 0.080

= 0.096 mmol

*Comparison of molar ratio of nickel(II) complex **3.1** and iodine*

Comparing the total number of moles of nickel(II) complex **3.1** (and hence ANC) and the number of moles of iodine that were calculated to react with the ANC, it is clear that:

0.100 mmol of ANC reacted with **0.096 mmol of iodine**

$\therefore$ the chemically activated nickel complex is a two electron donor

Attempt 2

Initially, a known concentration of sodium thiosulfate was used to calculate the concentration of iodine used to quench the active nickel complex.

Concentration of sodium thiosulfate solution

Mass of sodium thiosulfate used = 495.2 mg

M.W. of sodium thiosulfate = 248.18

Volume of water used = 200 ml

$\therefore [Na_2S_2O_3]_{(aq)} = \frac{495.2/248.18}{0.2} = 9.977$ mM

Titration against iodine of unknown concentration

Volume of iodine solution used = 10 ml

Volume of sodium thiosulfate used: 1. 31.8 ml (rough)

2. 32.4 ml

3. 32.4 ml

Average volume = 32.4 ml

$\therefore [I_2]$, since $2\ Na_2S_2O_3 + I_2 \rightarrow 2I^- + S_4O_6^{2-} + 4\ Na^+$

$$\therefore [I_2] = \frac{\text{ave. vol. } Na_2S_2O_3 \times [Na_2S_2O_3]}{2 \times \text{vol. } I_2}$$

$$= \frac{0.0324 \times 9.977}{2 \times 0.01}$$

$\therefore [I_2] = 16.163$ mM

$\therefore$ No. of moles of I_2 per 10 ml aliquot = 16.163 x 0.01

= 0.162 mmol

The experiment involves the addition of a 10 ml aliquot of the activated nickel complex to a 10 ml DMF solution of iodine of the above concentration. A bulk solution of active nickel complex was prepared to allow repetition of the titration.

*Concentration and number of moles of nickel(II) complex **3.1** used*

Mass of nickel(II) complex **3.1** = 272.1 mg

M.W. of nickel(II) complex **3.1** = 745.07

Volume of DMF used = 35 ml

$\therefore$ [Nickel(II) complex **3.1**] $= \frac{272.1/745.07}{0.035} = 10.434$ mM

$\therefore$ No. of moles of nickel(II) complex **3.1** (and hence no. of moles of active nickel complex (ANC)) per 10 ml aliquot used = 10.434 mM x 0.01

= 0.104 mmol

Titration of sodium thiosulfate against quenched solution of ANC and iodine

Since, $2\ Na_2S_2O_3 + I_2 \rightarrow 2I^- + S_4O_6^{2-} + 4\ Na^+$

$\therefore$ 2 moles of thiosulfate are always required to react with iodine

Volume of sodium thiosulfate used: 1. 12.2 ml (rough)

2. 12.5 ml

3. 12.4 ml

Average volume = 12.45 ml

∴ No. of moles of i_2 reacted with ANC = Total moles of I_2 – Moles of iodine titrated with $Na_2S_2O_3$

$$\therefore = 0.162 - \left[\frac{\text{ave. moles } Na_2S_2O_3 \text{ used in } I_2 \text{ titration}}{2}\right]$$

$$= 0.162 - \left[\frac{9.977 \times 0.01245}{2}\right]$$

$$= 0.162 - 0.062$$

$$= 0.100 \text{ mmol}$$

*Comparison of molar ratio of nickel(II) complex **3.1** and iodine*

Comparing the total number of moles of nickel(II) complex **3.1** (and hence ANC) and the number of moles of iodine that were calculated to react with the ANC, it is clear that:

0.104 mmol of ANC reacted with **0.100 mmol of iodine**

∴ the chemically activated nickel complex is a two electron donor

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